Myeloproliferative Neoplasien, CML und MDS

ASH 2023

Christoph Lutz

Praxis für Hämatologie und Onkologie Koblenz

#628, Rampal et. al

Pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve patients with myelofibrosis: results of the MANIFEST-2 randomized, double-blind, Phase 3 study

Global, randomized, double-blind, active-control, Phase 3 study

Study population

JAKi-naïve patients with MF (N=430)
(primary or post-ET/PV)

- DIPSS Int-1 or higher
- Splenomegaly (≥450 cm^3) by CT/MRI
- TSS ≥10 (≥3 for two symptoms, MFSAF v4.0)

Double-blind randomization (1:1)

1:1 randomization stratified by:

- DIPSS risk category: Int-1 versus Int-2 versus high
- Platelet count: >200 × 10^9/L versus 100–200 × 10^9/L
- Spleen volume: ≥1800 cm^3 versus <1800 cm^3

Treatment arm

Pelabresib 125 mg* PO QD Day 1–14 + **Ruxolitinib** Per label with a 5-mg BID lower starting dose† Day 1–21

21-day cycles

Placebo PO QD Day 1–14 + **Ruxolitinib** Per label with a 5-mg BID lower starting dose† Day 1–21

Primary endpoint

- SVR35 at Week 24

Key secondary endpoints

- TSS absolute change from baseline at Week 24
- TSS50 at Week 24

Safety

- AEs of all grades and serious AEs

AE, adverse event; BID, twice daily; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PO, orally; PV, polycythemia vera; QD, once daily; SVR35, ≥35% reduction in spleen volume; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score. *The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD; †Ruxolitinib was started at 10 mg BID (baseline platelet count 100–200 × 10^9/L) or 15 mg BID (baseline platelet count >200 × 10^9/L) with a mandatory dose increase by 5 mg BID after one cycle and a maximum dose of 25 mg BID per label. Harrison CN, et al. *Future Oncol*. 2022;18(27):2987-29977.

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Baseline disease characteristics

Characteristic		Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Age — years	Median (min, max)	66 (19, 84)	66 (26, 88)
Sex — n (%)	Female / male	85 (39.7) / 129 (60.3)	94 (43.5) / 122 (56.5)
Race — n (%)	White / Asian / Black American Indian or Alaska Native Not reported / Unknown	160 (74.8) / 35 (16.4) / 2 (0.9) 1 (0.5) 15 (7.0) / 1 (0.5)	163 (75.5) / 42 (19.4) / 0 0 11 (5.1) / 0
Myelofibrosis subtype — n (%)	Primary myelofibrosis Post-polycythemia vera myelofibrosis Post-essential thrombocytopenia myelofibrosis	107 (50) 45 (21) 62 (29)	110 (50.9) 53 (24.5) 53 (24.5)
Dynamic International Prognostic Scoring System — n (%)	Intermediate-1 Intermediate-2 High-risk	128 (59.8) 75 (35) 11 (5.1)	127 (58.8) 74 (34.3) 15 (6.9)
Mutations — n (%)*	*JAK2* V617F *CALR* *MPL* Triple negative High-molecular risk mutations Missing	125 (67.2) 45 (24.2) 11 (5.9) 8 (4.3) 72 (38.7) 28 (13.1)	122 (64.6) 50 (26.5) 13 (6.9) 5 (2.6) 88 (46.6) 27 (12.5)
Hemoglobin — g/dL	Median (range) ≤10 — n (%)	10.9 (5.8–18.0) 70 (32.7)	11.0 (6.7–17.9) 76 (35.2)
Platelets — × 10^9/L	Median (min, max) >200 × 10^9/L	285 (99, 1303) 154 (72)	287 (66, 1084) 157 (72.7)
Peripheral blasts	Mean (SD)	0.8 (1.18)†	0.8 (1.25)‡
RBC transfusions — patient n (%)	Requiring RBC transfusion at baseline	35 (16)	25 (12)
ECOG performance status	0 1 ≥2 Missing	107 (50) 97 (45.3) 10 (4.7) 0	109 (50.5) 95 (44.0) 10 (4.6) 2 (0.9)
Spleen volume (central read) §	Median spleen volume (range) — cc	1308.89 (200.24–7117.03)	1382.97 (277.87–5540.45)
Total symptom score¶	Median total symptom score (range)	26.6 (7.3–66.4)	24.7 (9.0–68.4)

Data cut off: August 31, 2023. *CALR*, calreticulin; ECOG, Eastern Cooperative Oncology Group; *JAK*, Janus kinase; max, maximum; min, minimum; *MPL*, MPL proto-oncogene, thrombopoietin receptor; RBC red blood cell; SD, standard deviation. *Results do not originate from a validated programming environment. †n=208. ‡n=207. §Randomization of patients was based on local read. ¶Patients with baseline TSS values of <10 have at least 2 individual symptoms score ≥ 3 at baseline.

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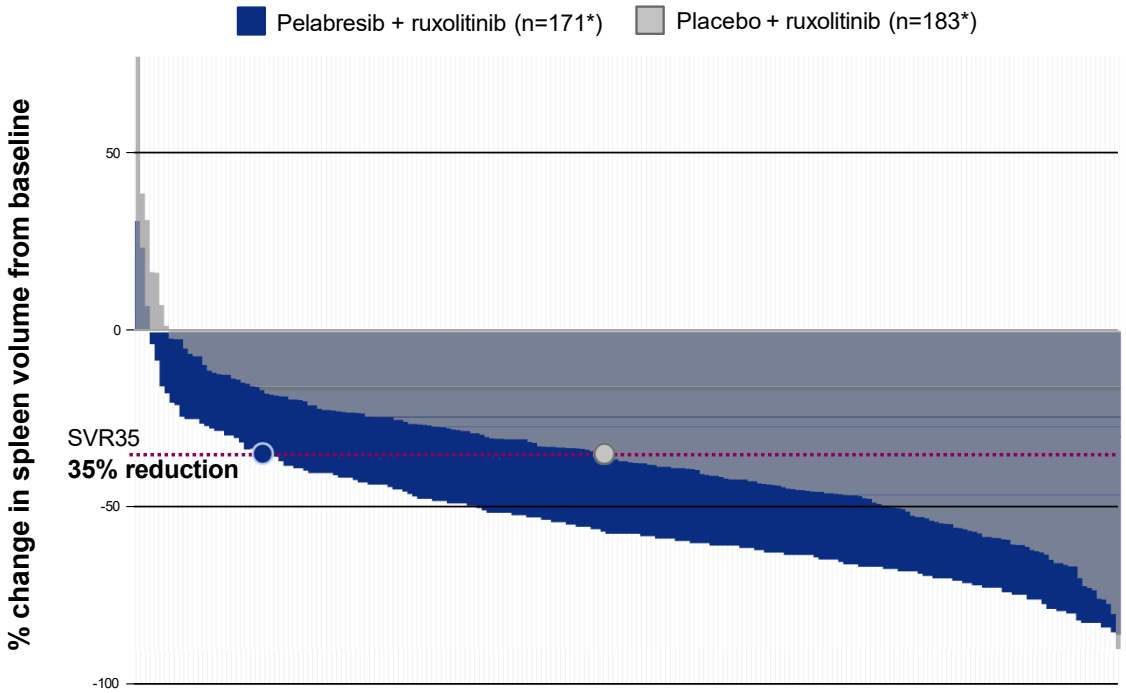
MANIFEST-2 study achieved its primary endpoint: SVR35 at Week 24

Significantly greater response in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib



ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
SVR35 at Week 24	65.9%	35.2%	
Difference† (95% CI)	30.4 (21.6, 39.3)		<0.001
Mean % change in spleen volume at Week 24‡	-50.6 (n=171)	-30.6 (n=183)	
95% CI	-53.2, -48	-33.7, -27.5	

Data cut off: August 31, 2023. CI, confidence interval; ITT, intent-to-treat; SVR35, ≥35% reduction in spleen volume. Spleen volume assessed by central read. *Waterfall plots represent patients who have baseline and Week 24 data. †Calculated by stratified Cochran–Mantel–Haenszel test; ‡Patients without Week 24 assessment are considered non-responders.

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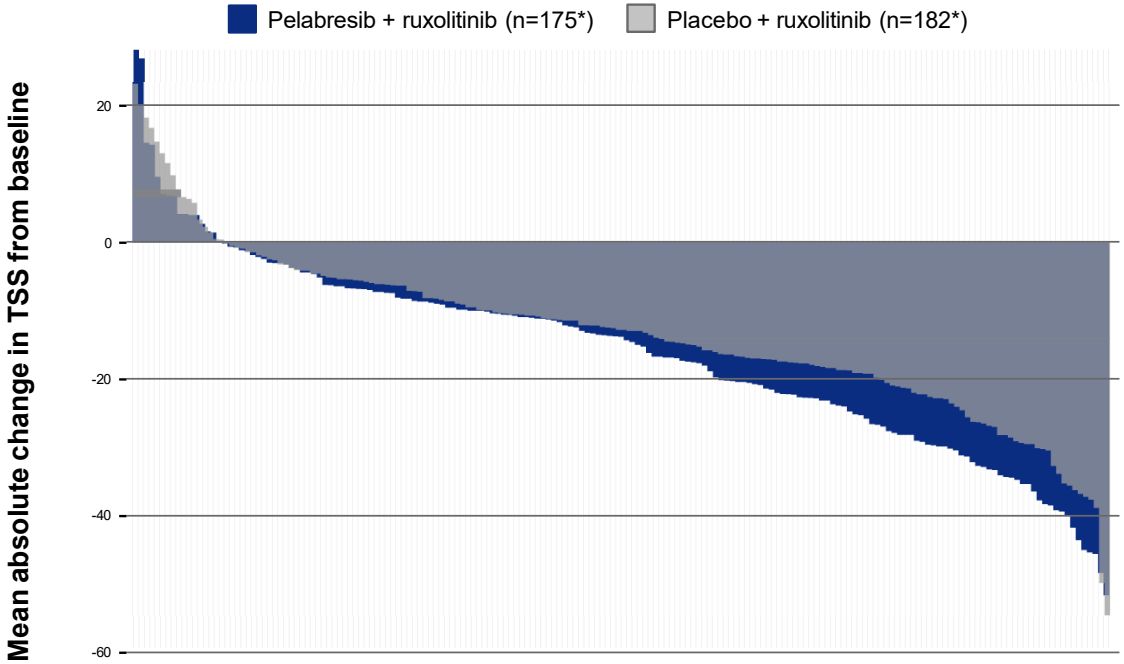
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

Absolute TSS at Week 24

Strong numerical improvements for patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib



ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
TSS change† from baseline at Week 24	-15.99	-14.05	
Mean difference‡ (95% CI)	-1.94 (-3.92, 0.04)		0.0545

- **Absolute change in TSS is a continuous endpoint** that estimates magnitude of symptom burden reduction with enhanced precision

Data cut off: August 31, 2023. ANCOVA, analysis of covariance; CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; FDA, Food and Drug Administration; ITT, intent-to-treat; TSS, total symptom score. *Waterfall plots represent patients who have baseline and Week 24 data. †Change from baseline determined by ANCOVA model using Multiple Imputation. ‡Least square mean difference from ANCOVA model using baseline DIPSS, baseline platelet count and baseline spleen volume as factors, and baseline TSS as covariate.

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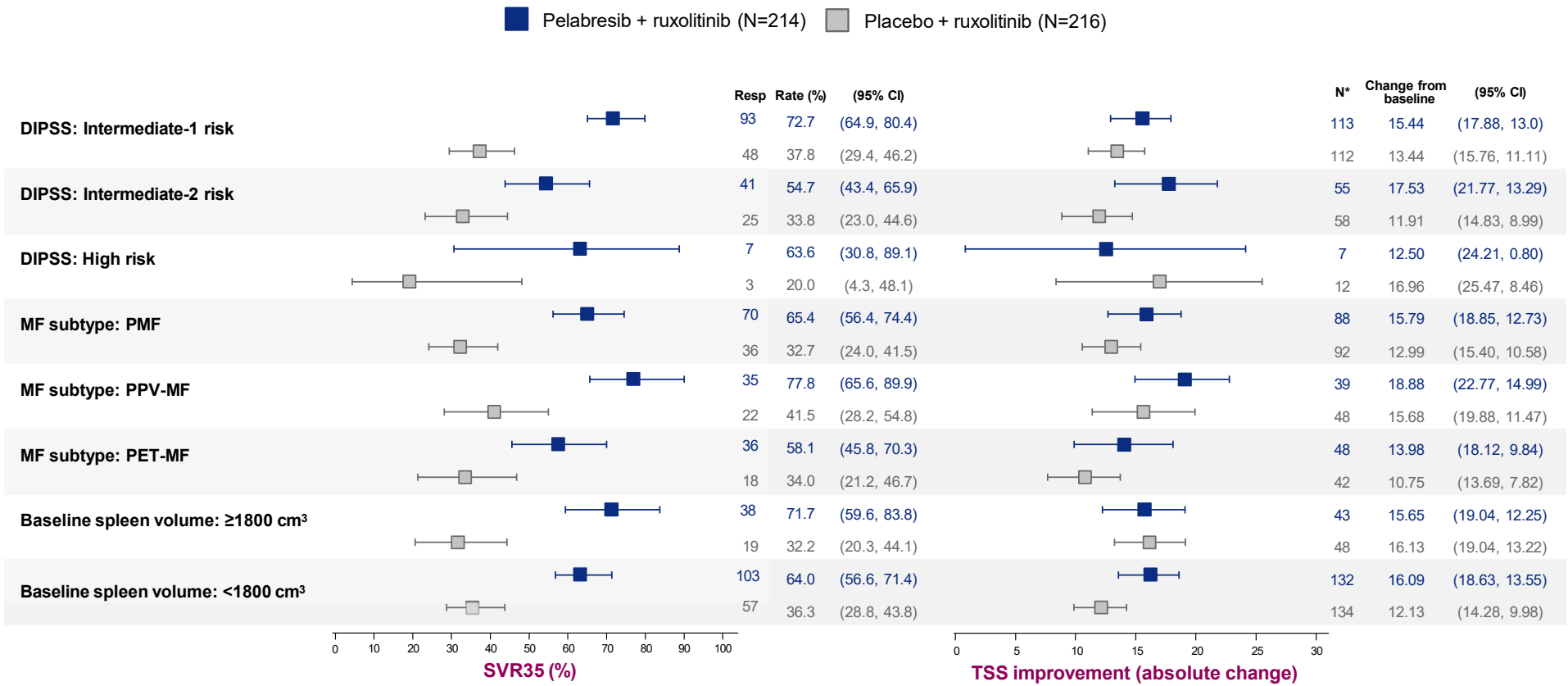
Prespecified subgroup analyses at Week 24

SVR35 outcomes consistently favored pelabresib + ruxolitinib over placebo + ruxolitinib across all predefined subgroups



Data cut off: August 31, 2023. CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; Resp, number of responders; SVR35, ≥35% reduction in spleen volume; TSS, total symptom score. *Number of patients with Week 24 observations.

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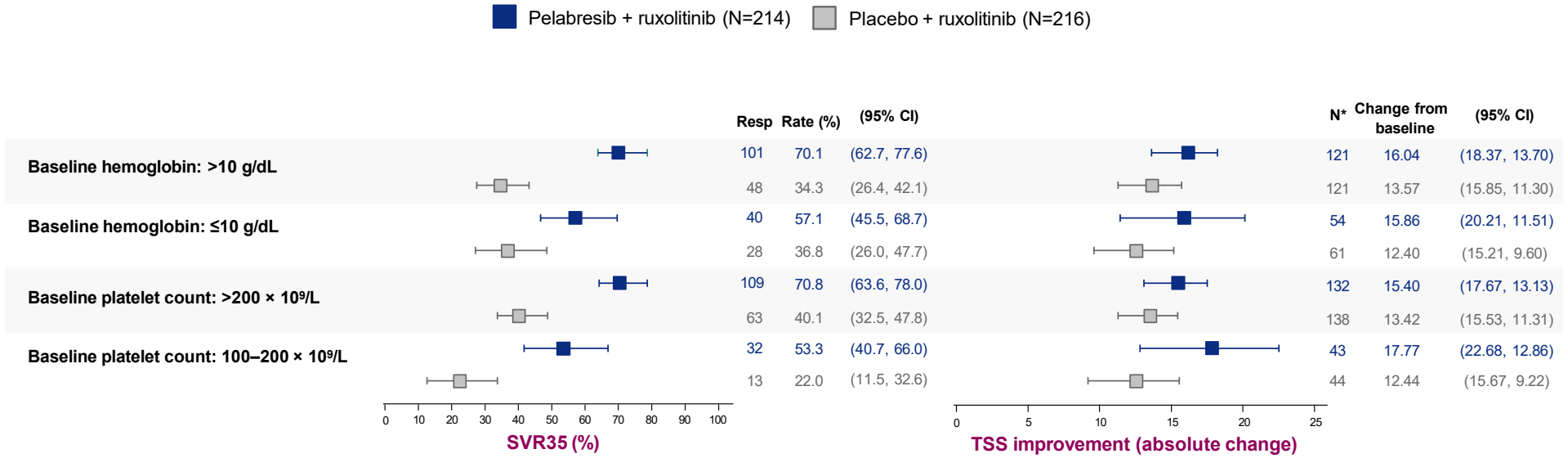
Prespecified hematological subgroup analyses at Week 24

SVR35 consistently favored the pelabresib + ruxolitinib combination over placebo + ruxolitinib across hematologic subgroups



Data cut off: August 31, 2023. CI, confidence interval; Resp, number of responders; SVR35, ≥35% reduction in spleen volume; TSS, total symptom score. *Number of patients with Week 24 observations.

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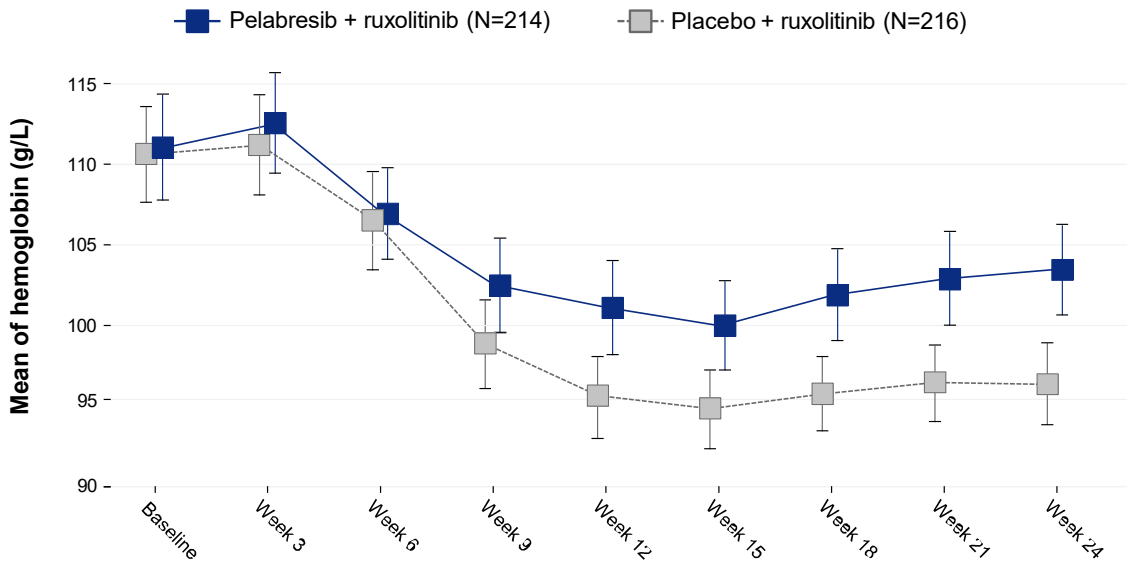
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

Hemoglobin response

A numerically greater proportion of patients achieved hemoglobin response with pelabresib + ruxolitinib versus placebo + ruxolitinib



Number of patients

Pelabresib + ruxolitinib	212	204	209	199	193	189	186	185	184
Placebo + ruxolitinib	214	206	211	209	207	205	204	199	196

ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Hemoglobin response* ≥1.5 g/dL mean increase (95% CI)	9.3% (5.45, 13.25)	5.6% (2.50, 8.61)
Patients requiring RBC transfusion during screening, n (%)	35 (16.4)	25 (11.6)
Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)	66 (30.8)	89 (41.2)

Preliminary Analyses from Data cut off: August 31, 2023. CI, confidence interval; RBC, red blood cell. *Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the previous 12 weeks prior to the laboratory assessment. Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. A similar effect was observed across DIPSS categories.

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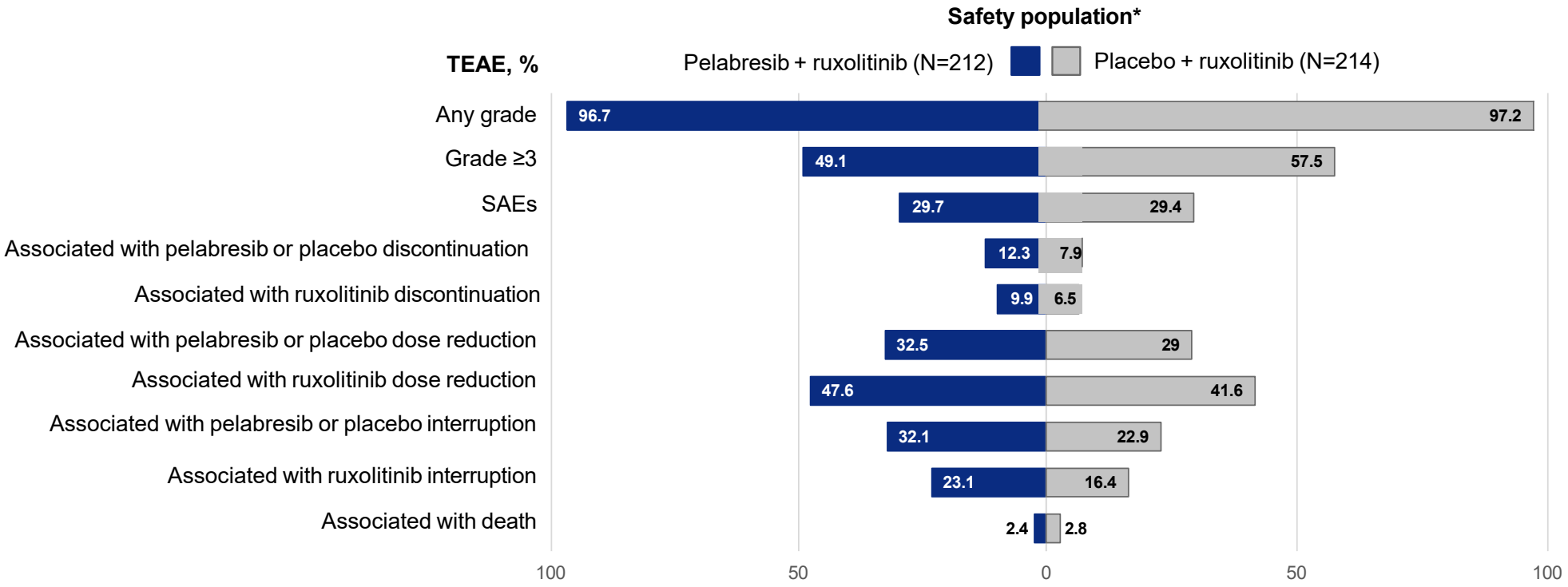
Summary of safety

The safety profile of the pelabresib + ruxolitinib combination was consistent with prior trials



Preliminary Analyses from Data cut off: August 31, 2023. TEAE, treatment-emergent adverse event; SAE, serious adverse event. *Safety population: received at least one dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blinded treatment period is defined as an adverse event that has a start date on or after the first dose of the pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first. MF, myelofibrosis.

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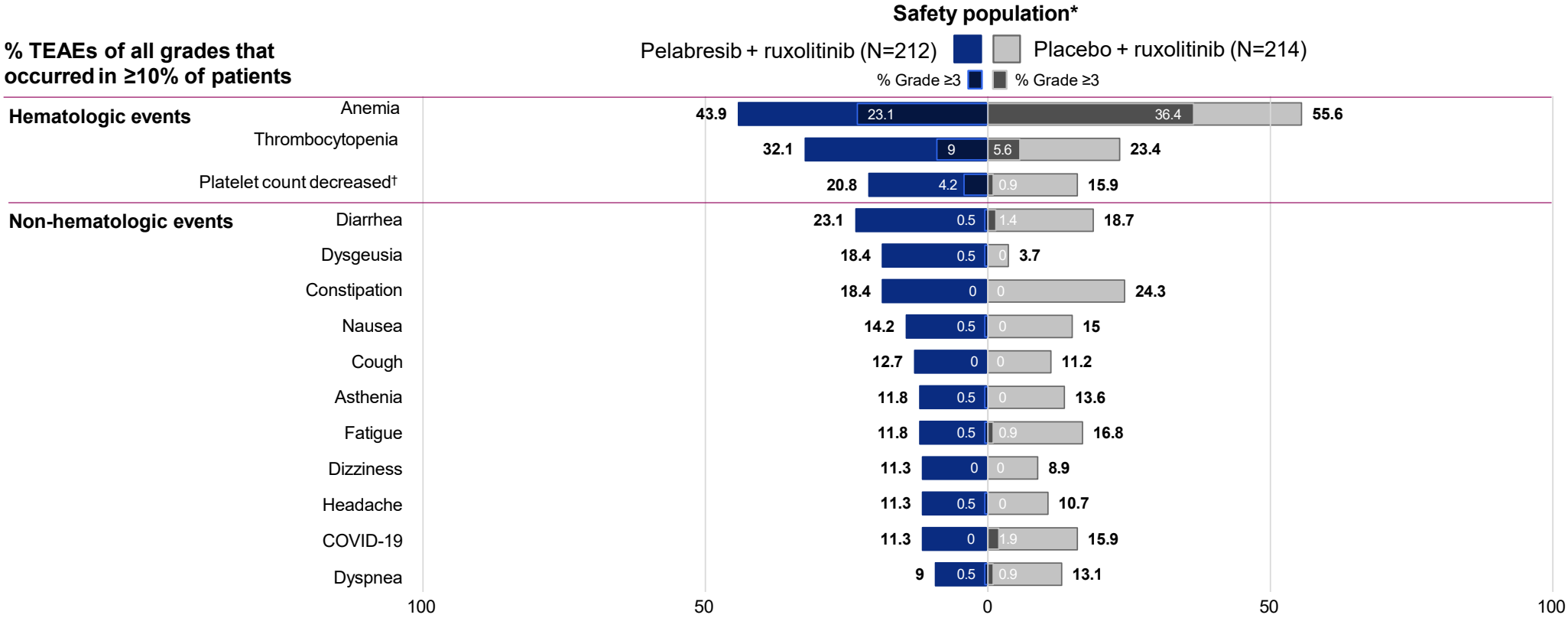
Treatment-emergent adverse events

Adverse events of anemia were reported less frequently with pelabresib + ruxolitinib combination than with placebo + ruxolitinib; no new safety signals were observed



Preliminary Analyses from Data cut off: August 31, 2023. TEAE, treatment-emergent adverse event. *Safety population: received at least one dose of study drug. †Platelet count decreased was classified under the system organ class of investigation. TEAEs are regardless of relationship to study drug. A TEAE for the double-blinded treatment period is defined as an adverse event that has a start date on or after the first dose of the pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first. MF, myelofibrosis; COVID-19, coronavirus disease 2019.

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#867, Jiang et. al

Safety and Efficacy of Tgrx-678, a Potent BCR-ABL Allosteric Inhibitor in Patients with Tyrosine Kinase Inhibitor (TKI) Resistant/Refractory Chronic Myeloid Leukemia (CML): Preliminary Results of Phase I Study

TGRX-678: A Selective and Potent BCR::ABL1 Inhibitor

Novel BCR::ABL1 tyrosine kinase inhibitor targeting the ABL myristoyl pocket (STAMP)

- **Increased permeability**

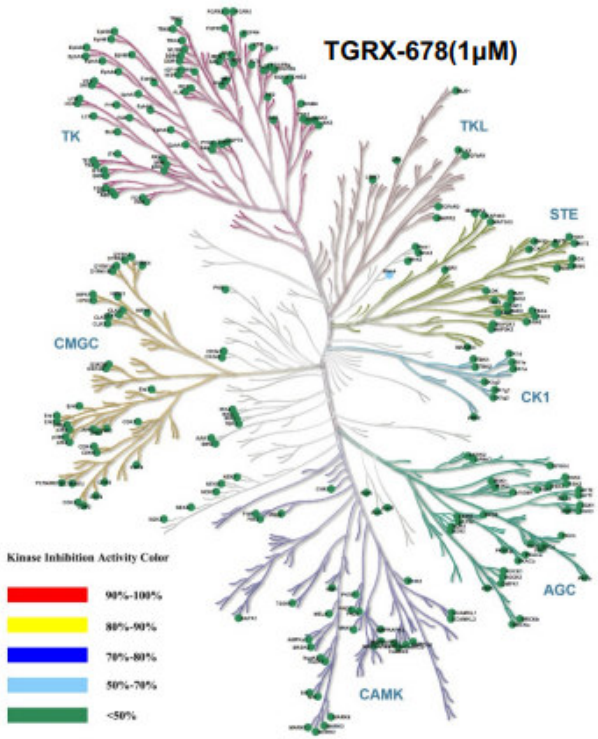
Caco-2 Permeability Assay	TGRX-678	Asciminib[a]
P_{app} (A→B) (cm/s x 10^{-6})	6.54±0.35	2.3
Efflux ratio (ER)	0.99±0.07	3

Caco-2 permeability assay: TGRX-678 has higher permeability and is unlikely a substrate of efflux transporter. (A test drug is usually considered a substrate of efflux transporters If ER > 2)

- **Enhanced bioactivity**

Ba/F3-BCR::ABL1	TGRX-678	Asciminib
Native	4.11±0.05	8.64±1.15
T315I	66.1±2.55	120±3.54

Cell proliferation assay IC_{50} (nM): TGRX-678 has higher potency against Ba/F3 cells expressing native or T315I-mutant BCR::ABL1.



Kinase	Inhi % at 1μM
WNK4	57.21
ALK	56.67
PRKCQ	47.27
PRKCD	33.26
LYNb	31.90
PRKCH	31.81
PKCβ2	29.34
MRCKα	28.54
VRK2	27.32
MAPKAPK5	27.10
EGFR	26.11
FER	25.96
CDK16/CycY	25.30
EPHA8	24.52
SIK	23.13
QIK	23.11
CK1ε	23.06
GPRK4	20.88
TRKB	20.48
FGFR2	19.82

Inhi.%
100
80
60
40
20
0

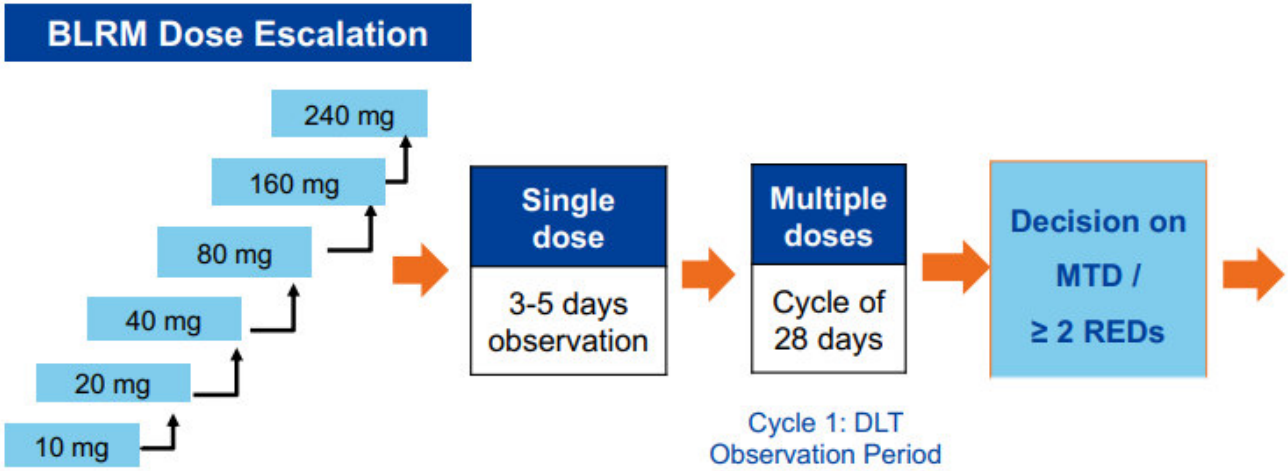
[a] *J. Med. Chem.* 2018, 61, 8120-8135

ASH 2023 Poster #2807

***Full length c-ABL1 was not inhibited by TGRX-678 most likely due to myristoylation-mediated auto-inhibition**

List of top 20 kinase inhibition among the ~300 kinase panel

Study Design



Dose Expansion	
Arm	**Cohort**
1	**≥ 2 prior TKIs, CP, no T315I mutation**
2	**≥ 1 prior TKI, CP, T315I mutation**
3	**≥ 1 prior TKI, AP**

- **Primary objectives**

  Safety and tolerability

- **Secondary objectives**

  Preliminary efficacy and pharmacokinetics

BLRM, Adaptive Bayesian logistic regression model; MTD, maximum toxicity dose; RED, recommended dose.

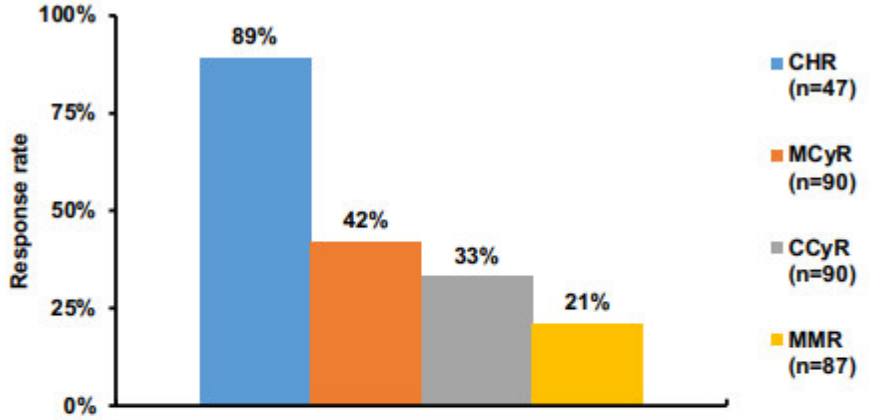
Patient Characteristics

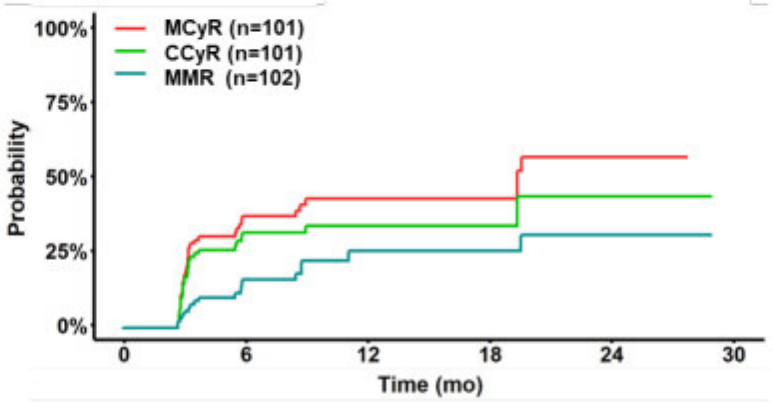
	Total (N = 150)	20 mg/d (N = 3)	40 mg/d (N = 27)	80 mg/d (N = 22)	160 mg/d (N = 7)	240 mg/d (N = 91)
Age, y, median (range)	**46 (19-74)**	45 (34-58)	46 (24-74)	50 (20-67)	44 (31-67)	46 (19-71)
Male, n (%)	**87 (58)**	1 (33)	18 (67)	15 (68)	3 (43)	50 (55)
ECOG, n (%)						
0	**79 (53)**	3 (100)	13 (48)	11 (50)	2 (29)	50 (55)
1	**71 (47)**	0	14 (52)	11 (50)	5 (71)	41 (45)
Disease phase at baseline, n (%)						
CP	**102 (68)**	2 (67)	23 (85)	15 (68)	4 (57)	58 (64)
AP	**48 (32)**	1 (33)	4 (15)	7 (32)	3 (43)	33 (36)
Median interval from diagnosis of CML to TGRX-678 therapy, mo	**92**	107	99	94	160	61
Cytogenetic status at baseline, n (%)						
No CyR	**98 (65)**	2 (67)	15 (56)	14 (64)	6 (86)	62 (68)
No PCyR	**35 (23)**	1 (33)	5 (19)	7 (32)	1 (14)	20 (22)
PCyR	**17 (11)**	0	7 (26)	1 (5)	0	9 (10)

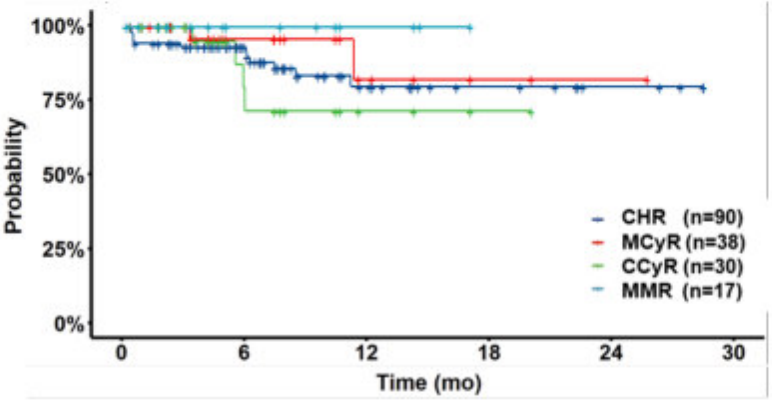
Patient Characteristics (cont.)

	Total (N = 150)	20 mg/d (N = 3)	40 mg/d (N = 27)	80 mg/d (N = 22)	160 mg/d (N = 7)	240 mg/d (N = 91)
Mutation at baseline, n (%)						
Single T315I mutation	**38 (25)**	0	5 (19)	4 (18)	4 (57)	25 (27)
T315I + additional mutation	**9 (6)**	0	2 (7)	0	0	7 (8)
Other mutation	**28 (19)**	1 (33)	4 (15)	5 (23)	1 (14)	17 (19)
No mutation	**75 (50)**	2 (67)	16 (59)	13 (59)	2 (29)	42 (46)
TKI-therapy lines, n (%)						
1L	**5 (3)**	0	0	0	0	5 (5)
2L	**32 (21)**	0	3 (11)	3 (14)	0	26 (29)
≥ 3L	**113 (75)**	3 (100)	24 (89)	19 (86)	7 (100)	60 (66)
Prior TKI used, n (%)						
Non 3G TKI	**83 (55)**	2 (67)	12 (44)	12 (55)	6 (86)	51 (56)
Ponatinib and / or HQP1351	**54 (36)**	1 (33)	11 (41)	7 (32)	1 (14)	34 (37)
Asciminib	**13 (9)**	0	4 (15)	3 (14)	0	6 (7)

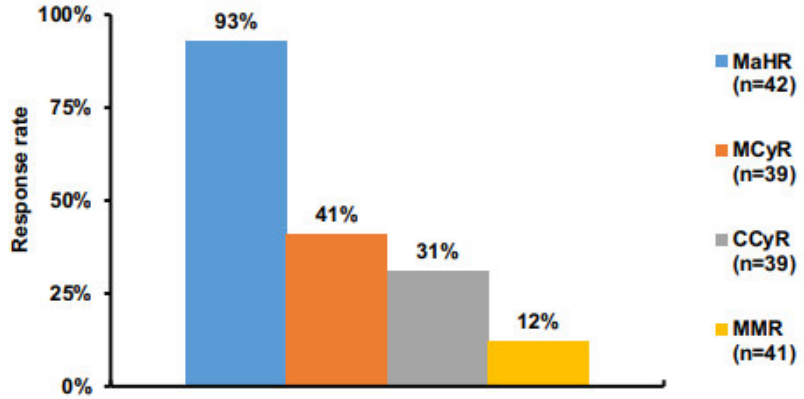
Responses in CP Patients (n = 102)

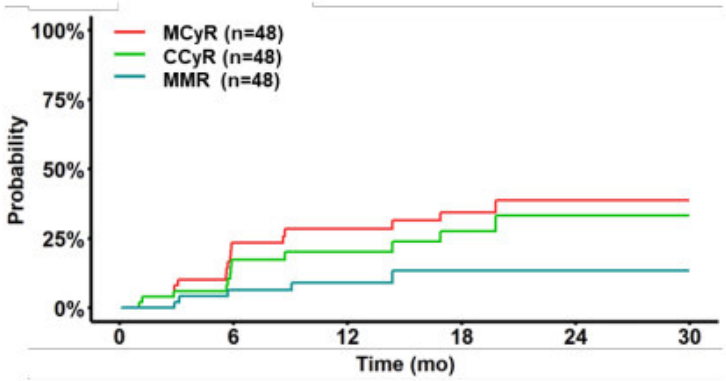


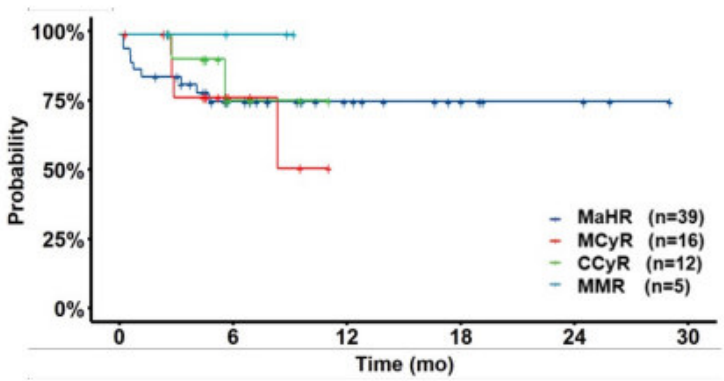




Responses in AP Patients (n = 48)

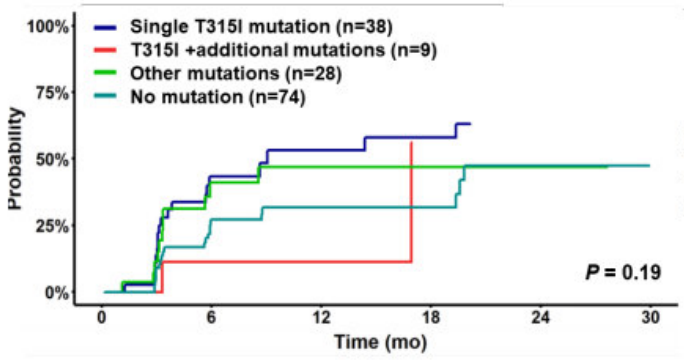




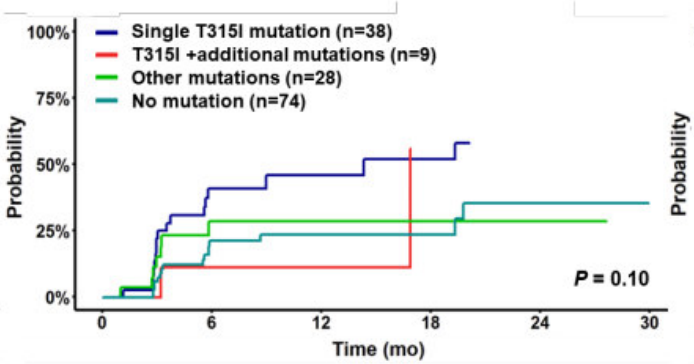


Responses by Baseline BCR::ABL1 Mutation Status

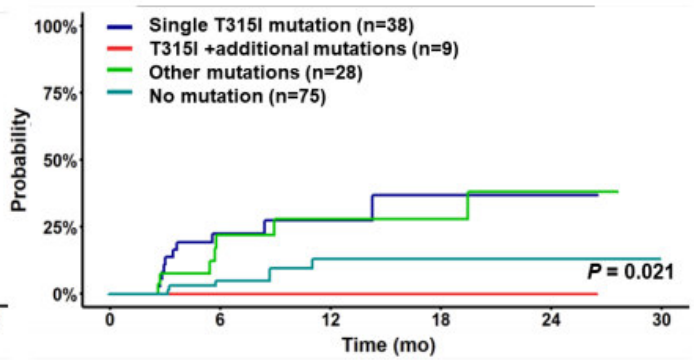
MCyR



CCyR

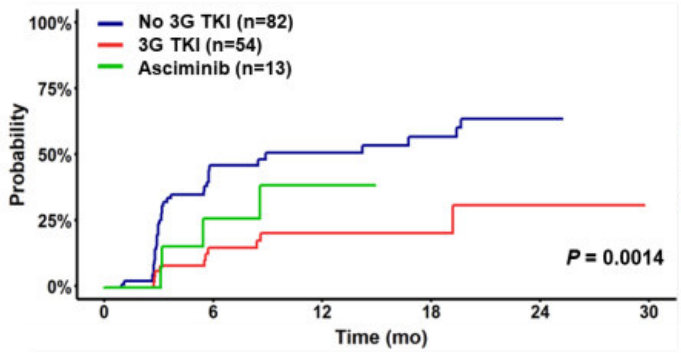


MMR

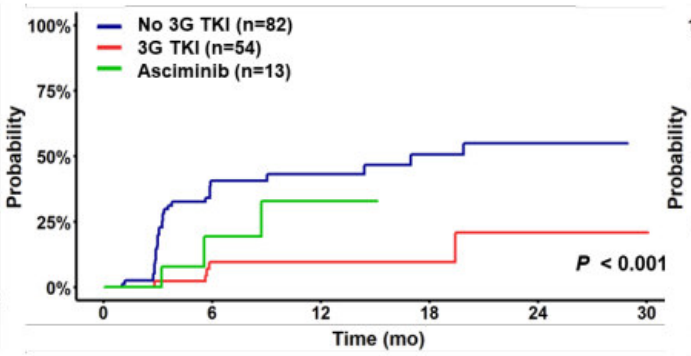


Responses by Prior TKIs

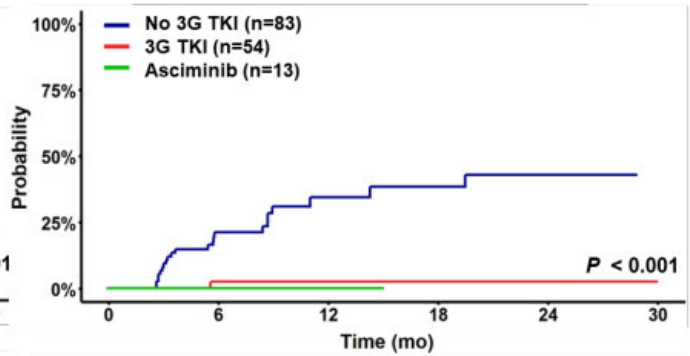
MCyR



CCyR



MMR



Safety

AEs	TGRX-678 n (%)
TRAEs	**144 (96)**
TRAEs ≥ 3 grade	**97 (65)**
SAEs	**25 (17)**
Drug-related SAEs	**14 (9)**
TEAEs leading to dose reduction	**17 (11)**
TEAEs leading to suspension	**70 (47)**
TEAEs leading to discontinuation	**5 (3)**

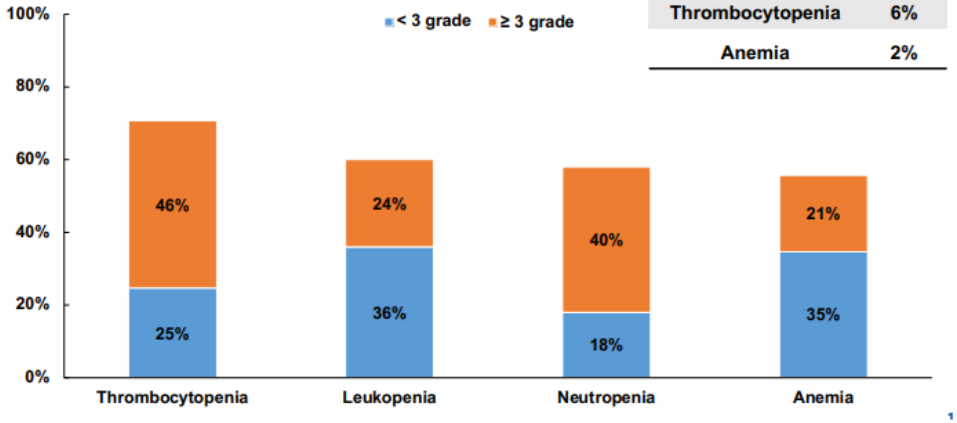
TEAEs: Treatment emergent adverse events; TRAEs: treatment-related adverse events; SAEs, serious adverse events

32 DLT-evaluable patients experienced 7 DLTs and MTD was not reached in the dose-determining analysis set

- Grade 4 thrombocytopenia: 1 patient in 40 mg/d and 4 patients in 80 mg/d
- Grade 3 alanine aminotransferase increased: 1 patient in 40 mg/d
- Grade 4 hepatic function abnormal: 1 patient in 240 mg/d

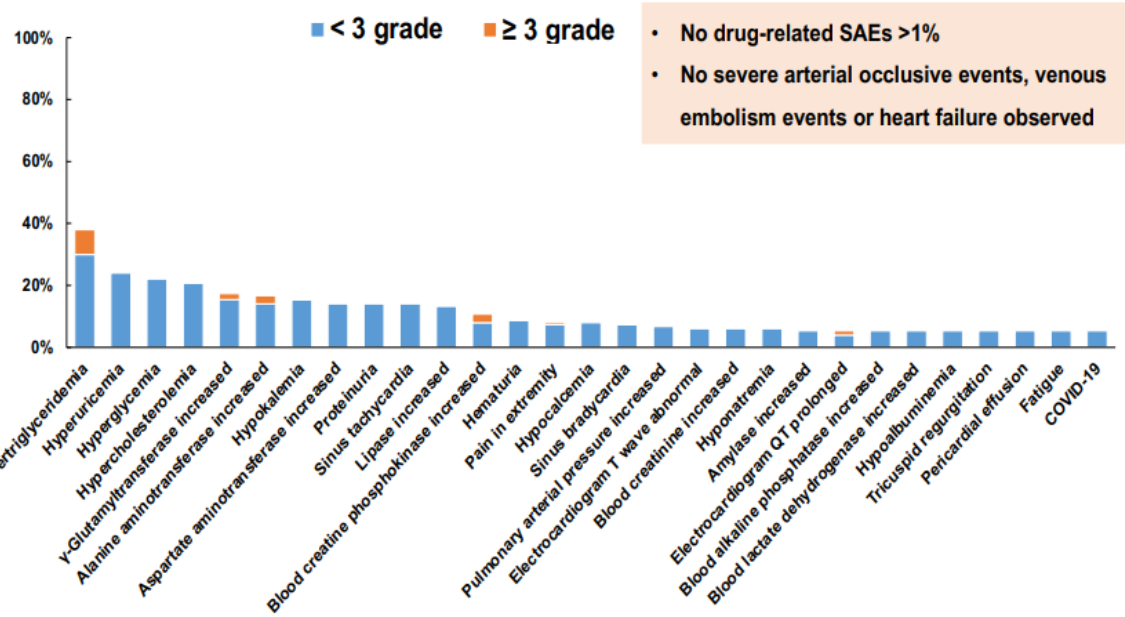
No clear safety correlation was observed among the doses.

Hematologic Adverse Events



SAEs	
Thrombocytopenia	6%
Anemia	2%

Non-hematologic Adverse Events (Incidence ≥ 5%)



- No drug-related SAEs >1%
- No severe arterial occlusive events, venous embolism events or heart failure observed

#869, Jiang et. al

Olverembatinib (HQP1351) Demonstrates Efficacy Vs. Best Available Therapy (BAT) in Patients (Pts) with Tyrosine Kinase Inhibitor (TKI)-Resistant Chronic Myeloid Leukemia Chronic-Phase (CML-CP) in a Registrational Randomized Phase 2 Study Qian Jiang et al., Peking, China

Study Design

Key study criteria

- Adults with CP-CML
- Resistance or intolerance to I, D, N
- ECOG PS ≤ 2
- Adequate organ function
- Excluded patients with conditions complicating TKI treatment or in CCyR at baseline

HQP1351CC203 (NCT04126681)

Randomized 2:1

N = 144*

Olverembatinib 40 mg QOD, n = 96

Best Available Therapy n= 48**

Primary Endpoints:

Event-free survival ***

[I], [D], [N], imatinib, dasatinib, nilotinib
CP-CML, CML in chronic phase;
ECOG PS, Eastern Cooperative Oncology Group performance status;
QOD, every other day.
BAT, best available therapy
*2 patients in BAT group had been randomized successfully but not dosed .
** **BAT includes interferon, hydroxyurea, and homoharringtonine or TKIs I, D, and N and combinations**
*** **Cross-over from BAT was allowed when meeting the event criteria**
Cut off Oct 17, 2023

Patients' Characteristics (N = 144)

	Olverembatinib (n = 96)	Best Available Therapy (n = 48)	P value
Age, yr, median (range)	48.5 (18-77)	49.0 (24-75)	0.12
Male, n (%)	70 (72.9)	30 (62.5)	0.25
Response at baseline, n (%)			1.00
CHR	34 (35.4)	18 (37.5)	
PCyR	11 (11.5)	5 (10.4)	
ECOG, n (%)			0.65
0	56 (58.3)	25 (52.1)	
1	39 (40.6)	22 (45.8)	
2	1 (1.0)	0	
Interval from diagnosis of CML to randomization, yr, median (range)	6.1 (0.3-19.2)	6.5 (0.6-17.5)	0.45

Best Available Therapy

	Best Available Therapy (n = 48), n (%)
Nilotinib	22 (47.8)
Dasatinib	16 (34.8)
Imatinib	2 (4.3)
Nilotinib + Hydroxyurea	2 (4.3)
Dasatinib + Interferon	2 (4.3)
Nilotinib + Interferon	1 (2.2)
Interferon + Hydroxyurea + Homoharringtonine	1 (2.2)

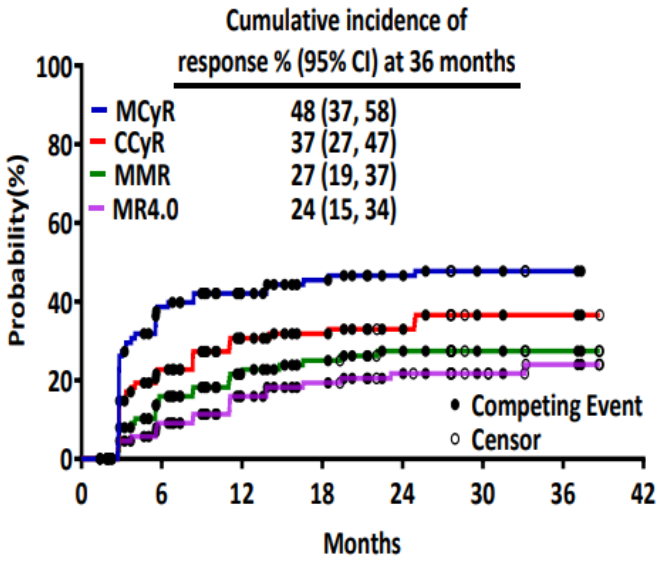
Patients' Disposition

	Olverembatinib (n = 96), n (%)	Best Available Therapy (n = 48), n (%)
Treatment duration, mo; median (range)	**21** (0.6-44.2)	**3** (0.2-40.5)
Study follow-up, mo; median (range)	**31** (1.3-46.0)	30 (0-45.8)
Continuing on treatment, n (%)	40 (**41.7**)	6 (**12.5**)
Discontinued, n (%)	56 (58.3)	42 (87.5)
AE	27 (28.0)	15 (31.3)
Treatment failure	13 (13.5)	22 (45.8)
Consent withdraw	9 (9.4)	1 (2.1)
Poor compliance	3 (3.1)	1 (2.1)
Death*	1 (1.0)	1 (2.1)
Lost to follow-up	0 (0)	1 (2.1)
Other**	3 (3.1)	1 (2.1)

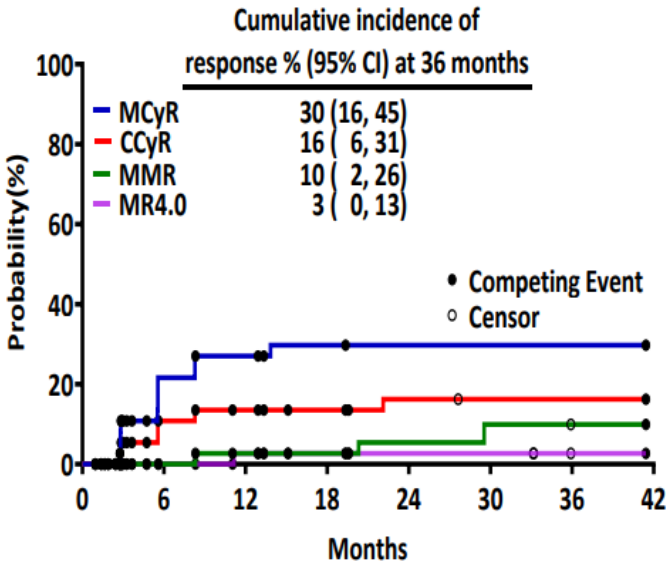
* **One subject with CCyR experienced "subarachnoid haemorrhage" resulted from a craniocerebral fracture due to a fall by accident. One subject died of uncleared reason.** ** **Other: withdraw based on the investigator's discretion**

35 patients in BAT arm crossed over to HQP1351 arm

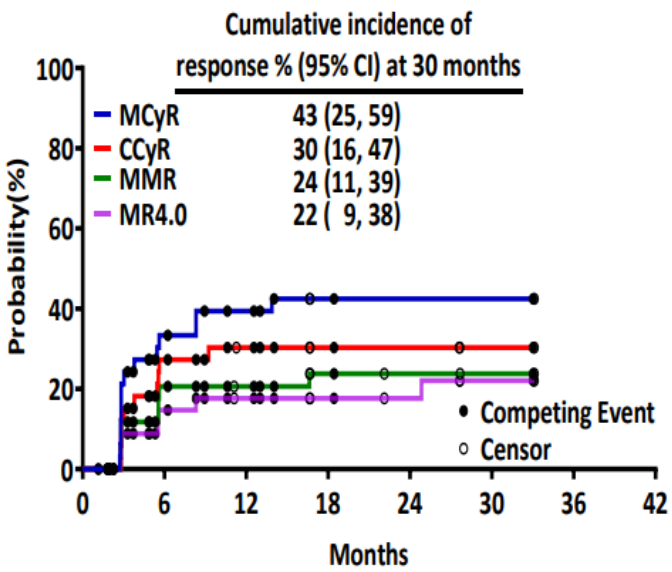
Olverembatinib



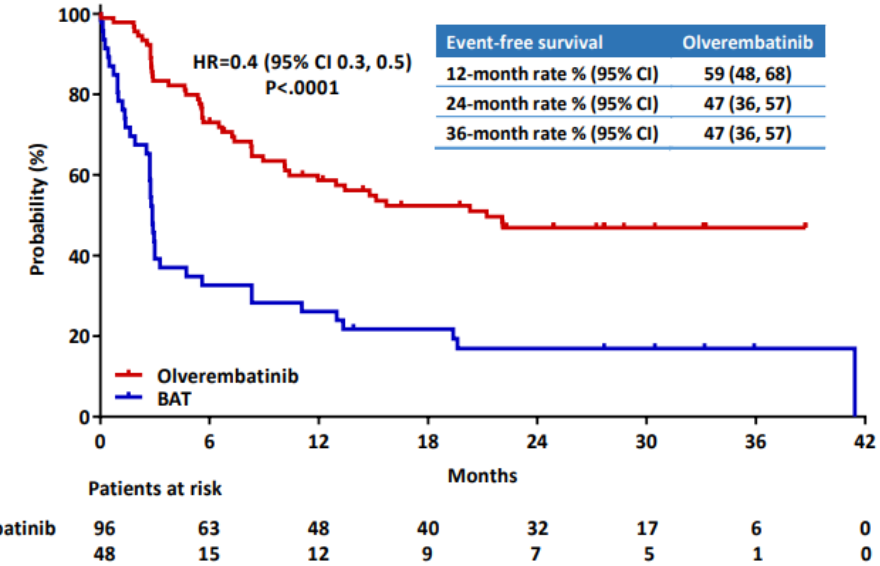
BAT



Switched from BAT



Event-Free Survival

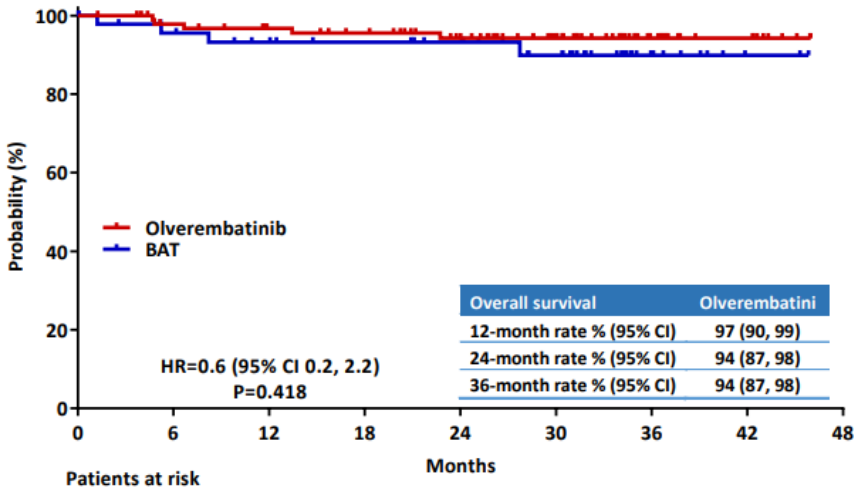


Event-free survival	Olverembatinib
12-month rate % (95% CI)	59 (48, 68)
24-month rate % (95% CI)	47 (36, 57)
36-month rate % (95% CI)	47 (36, 57)

Patients at risk

Olverembatinib	96	63	48	40	32	17	6	0
BAT	48	15	12	9	7	5	1	0

Overall Survival



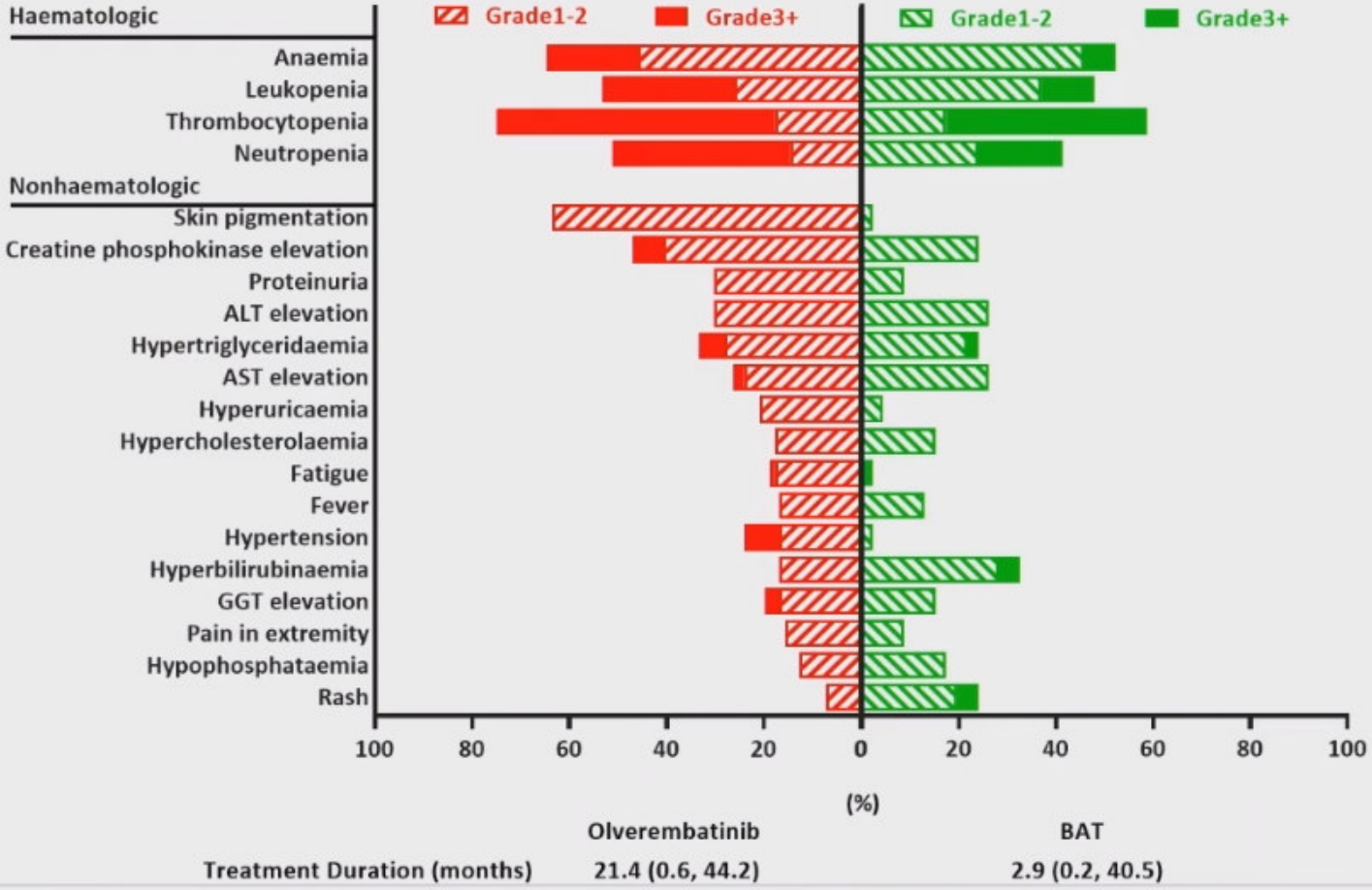
Overall survival	Olverembatini
12-month rate % (95% CI)	97 (90, 99)
24-month rate % (95% CI)	94 (87, 98)
36-month rate % (95% CI)	94 (87, 98)

Patients at risk

Olverembatinib	96	89	83	79	70	52	21	9	0
BAT	48	42	38	35	32	25	9	4	0

Among 48 patients in BAT group, 35(73%) patients were switched to Olverembatinib treatment.
Most switches (25/35, 71%) occurred on the first 3 months, and 6 switches (17%) occurred from 4 months to 12 months.

All Grade TRAEs (incidence ≥15%)



Jiang Q, et al. ASH abstract #869, 2023

#193, Guillermo Garcia-Manero et. al

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

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

[a]MDS patients with del(5q) were excluded; [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]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.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: study endpoints

Primary endpoint (weeks 1-24)

RBC-TI for ≥ 12 weeks **WITH CONCURRENT** mean Hb increase ≥ 1.5 g/dL

Secondary endpoints (weeks 1-24)

- HI-E response ≥ 8 weeks per IWG 2006 criteria
- RBC-TI
  - 24 weeks
  - ≥ 12 weeks
- Preplanned subgroup analysis of RBC-TI ≥ 24 weeks (weeks 1–48)

Safety assessment

- TEAEs, EOI[a]
- AML progression
- Rates of on- and post-treatment deaths

[a]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.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: patient baseline characteristics

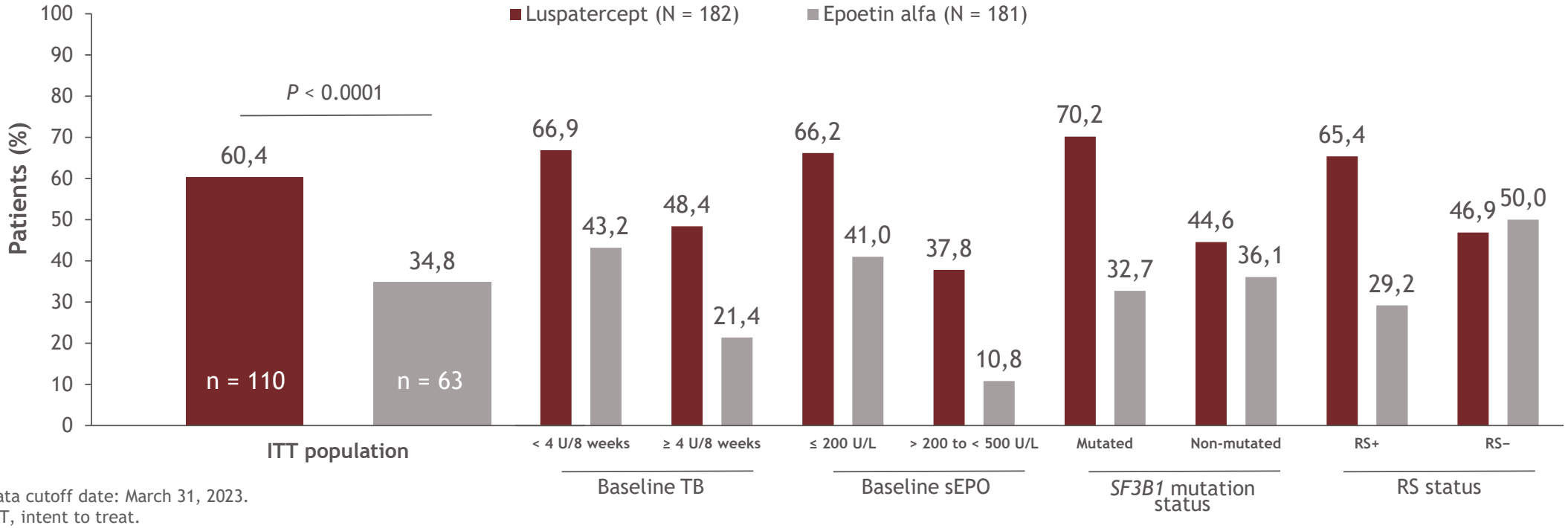
	Luspatercept (n = 182)	Epoetin alfa (n = 181)	Total (N = 363)
Age, median (range), years	74.0 (46-93)	74.0 (31-91)	74.0 (31-93)
Sex, female, n (%)	73 (40.1)	89 (49.2)	162 (44.6)
Hb, median (range), g/dL	7.80 (4.7-9.2)	7.80 (4.5-10.2)	7.80 (4.5-10.2)
Baseline TB, median (range), RBC U/8 weeks	3.0 (1-10)	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.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

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

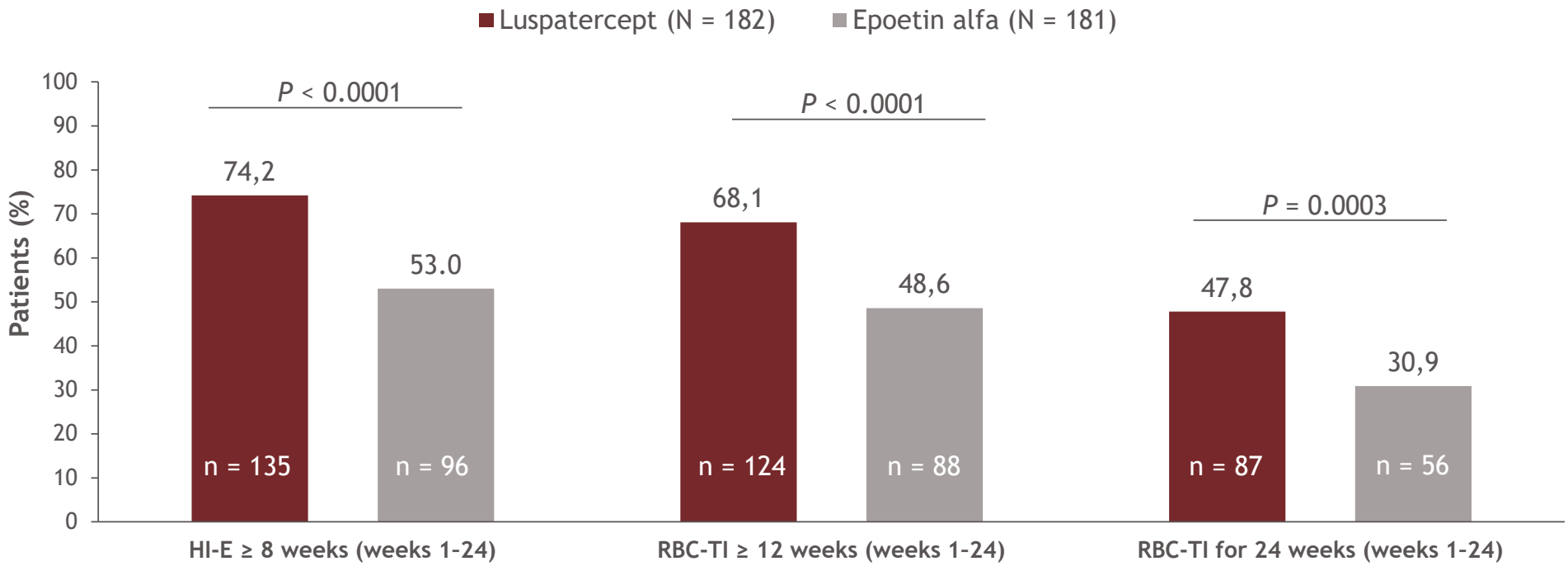


Data cutoff date: March 31, 2023.
ITT, intent to treat.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: secondary endpoints

- The proportions of patients achieving HI-E, RBC-TI ≥ 12 weeks, and RBC-TI for 24 weeks (weeks 1–24) were significantly greater in the luspatercept treatment arm than the epoetin alfa arm

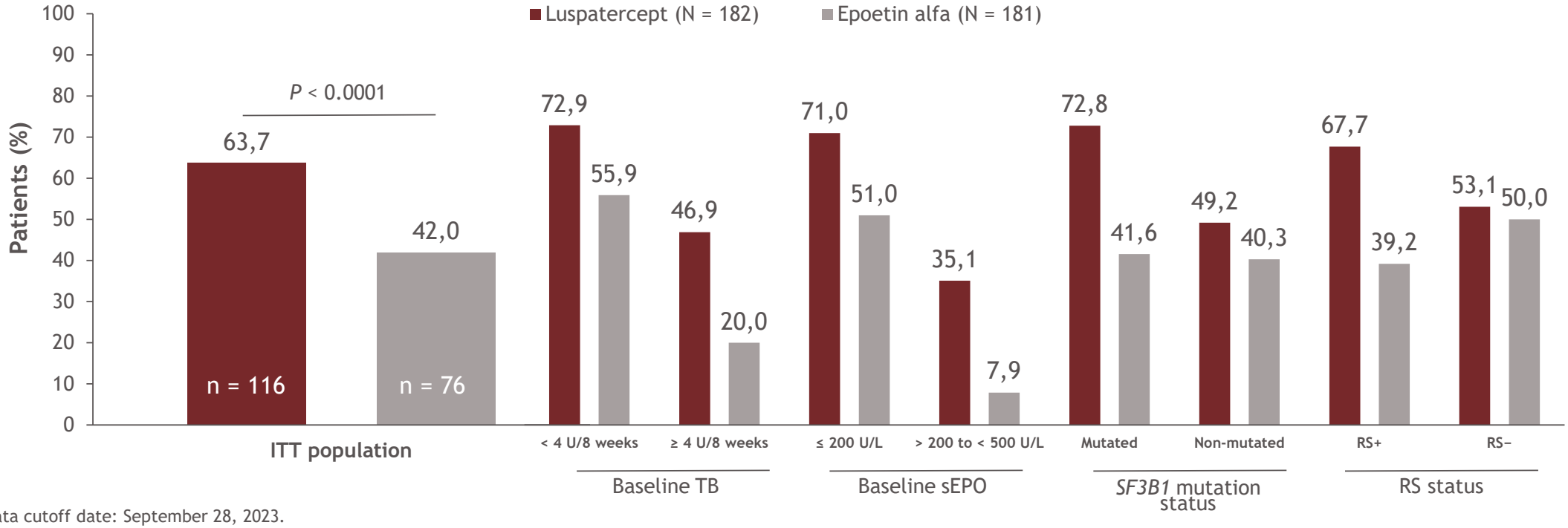


Data cutoff date: March 31, 2023.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: preplanned subgroup analysis of RBC-TI for ≥ 24 weeks (weeks 1-48)

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

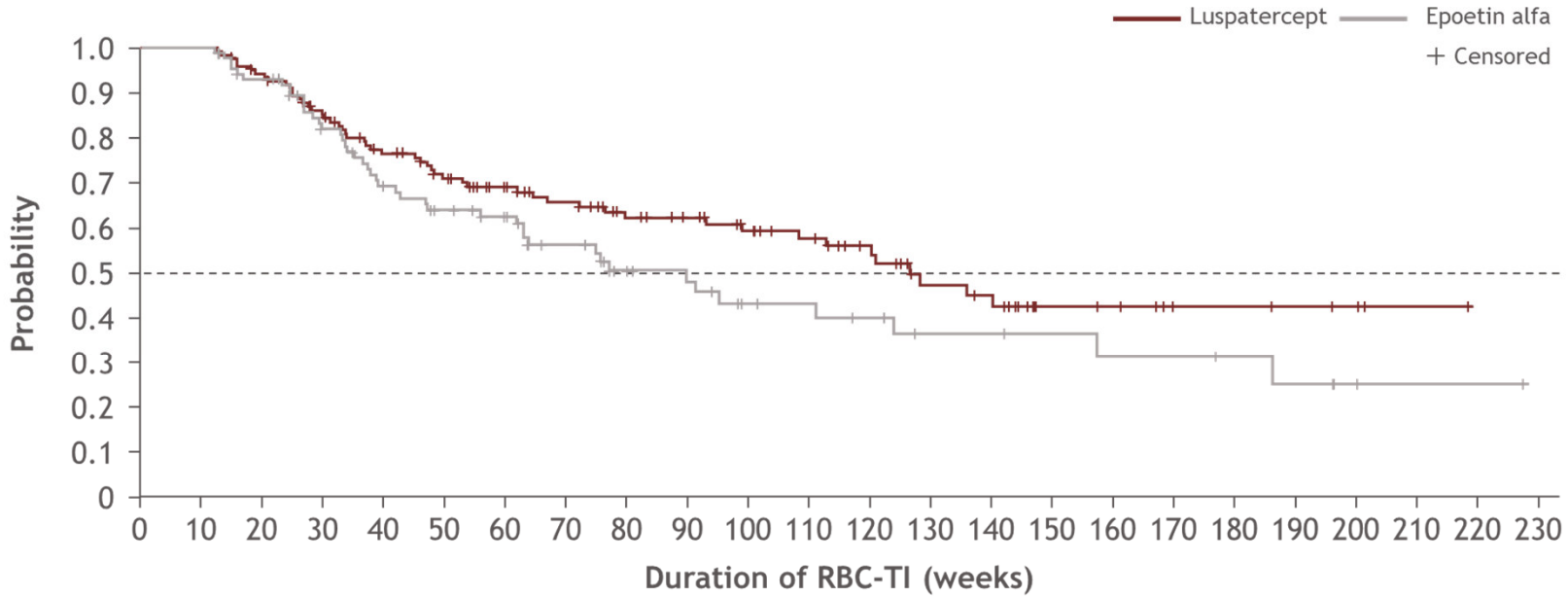


Data cutoff date: September 28, 2023.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

COMMANDS: duration of RBC-TI ≥ 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) *P* = 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

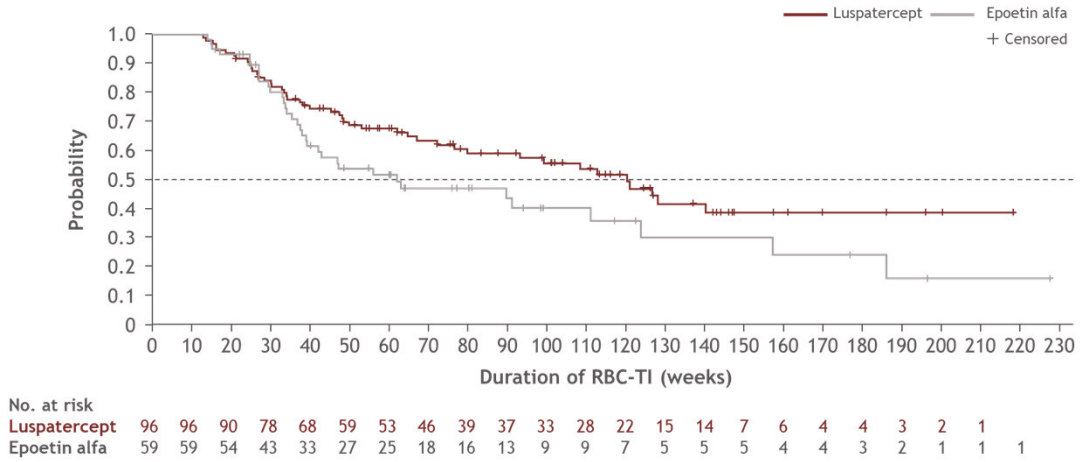
Data cutoff date: September 28, 2023.
CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not estimable.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

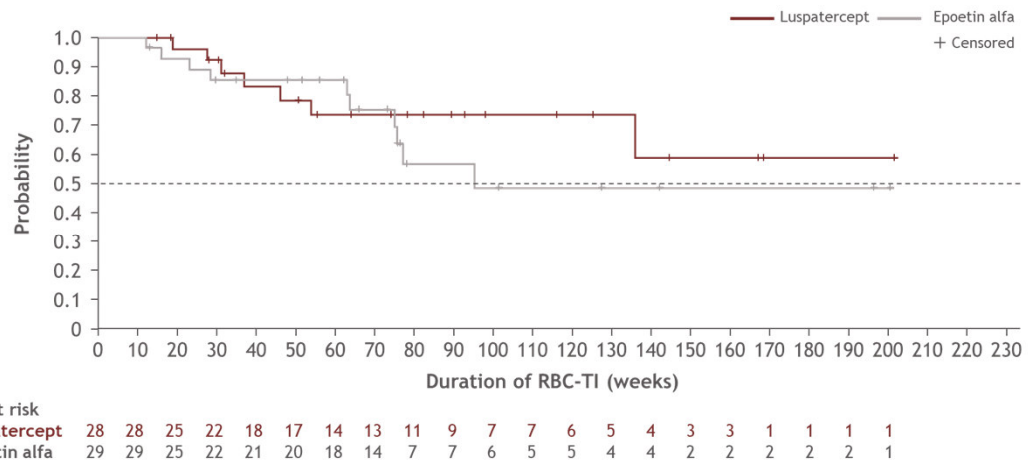
COMMANDS: duration of RBC-TI ≥ 12 weeks by RS subgroups (week 1–EOT)

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+



RS−



Data cutoff date: September 28, 2023.

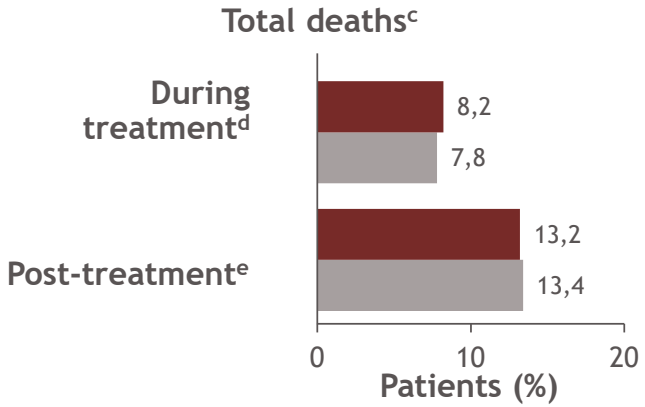
Garcia-Manero G, et al. ASH 2023 [Abstract #193]

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



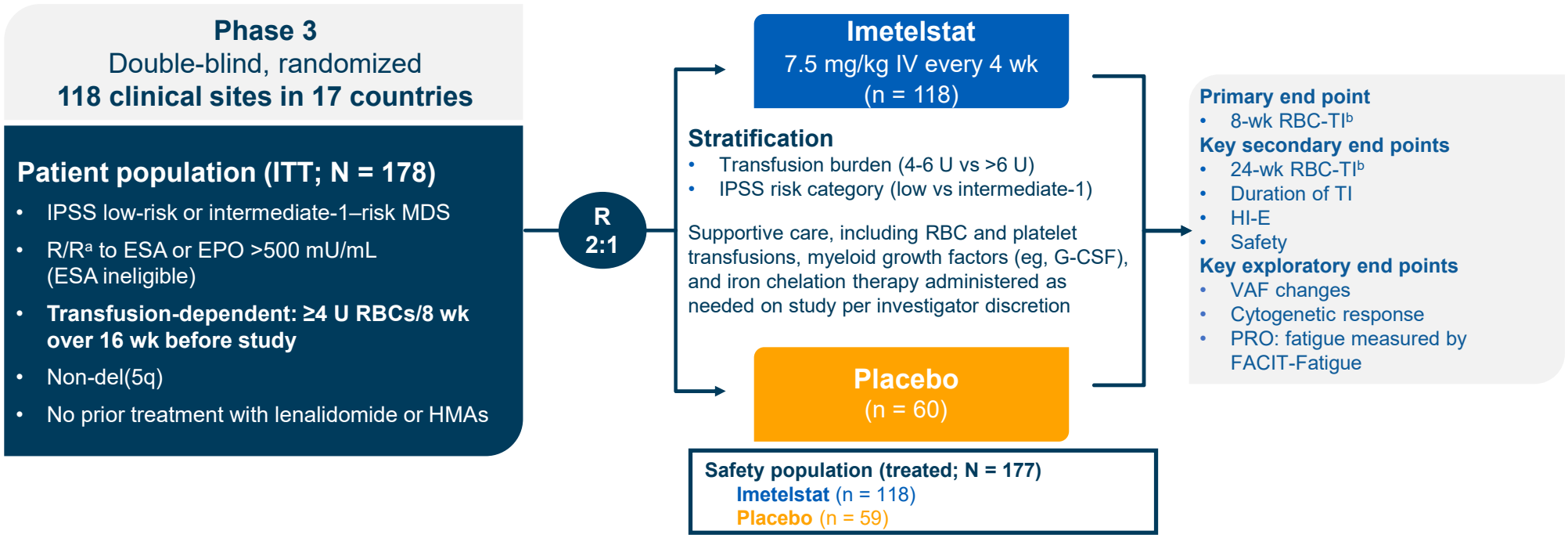
Data cutoff date: March 31, 2023.
[a]Assessed in the safety population; [b]Assessed in the ITT population; [c]Total number of deaths includes number of deaths during treatment period and post-treatment period; [d]Any death that occurred on or after first dose of treatment until 42 days after the last dose of treatment; [e]Any death that occurred after 42 days of the last dose date of treatment.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

#194, Komrokji RS et al: et. al

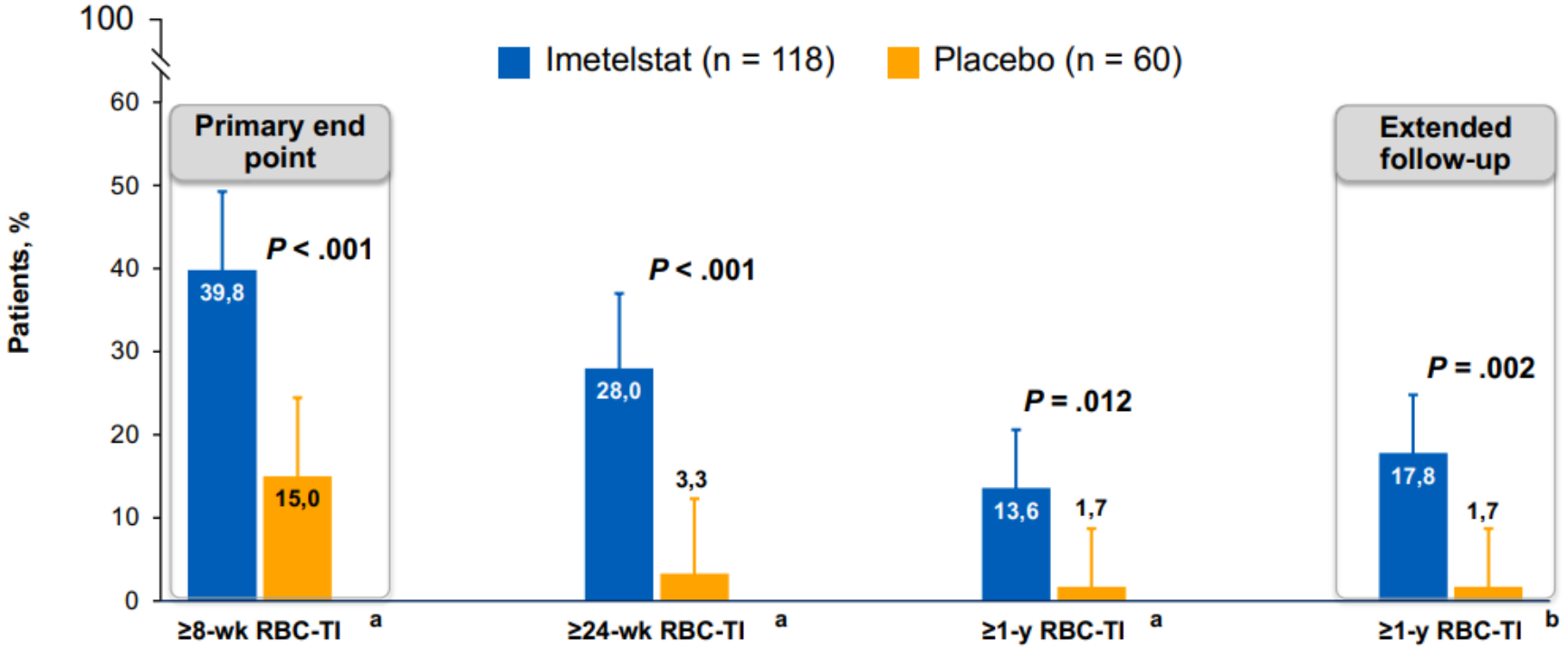
Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence (RBC-TI) across Different Risk Subgroups in Patients with Lower-Risk Myelodysplastic Syndromes (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis-Stimulating Agents (ESAs) in IMerge Phase 3 Study

IMerge Phase 3 Trial Design



[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 wk or transfusion dependence or reduction in Hb by ≥1.5 g/dL after HI-E from ≥8 weeks of ESA treatment. [b]Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).
del(5q), deletion on chromosome 5q; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement–erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; TI, transfusion independence, VAF, variant allele frequency.

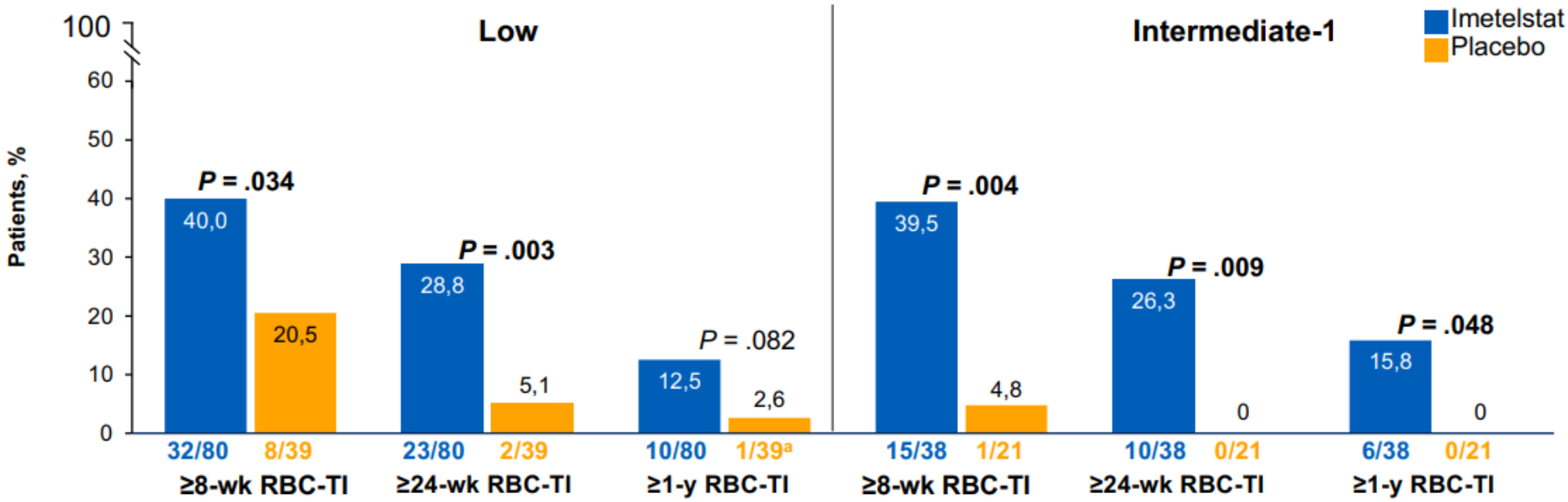
Overall Population: Higher Rates of Longer-Term Duration of RBC-TI With Imetelstat vs Placebo[1,2]



[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.
The *P* value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1–risk) applied to randomization.
IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
1. Zeidan A, et al. ASCO 2023. Abstr 7004. 2. Platzbecker U, et al. *Lancet*. Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

RBC-TI by IPSS Subgroup

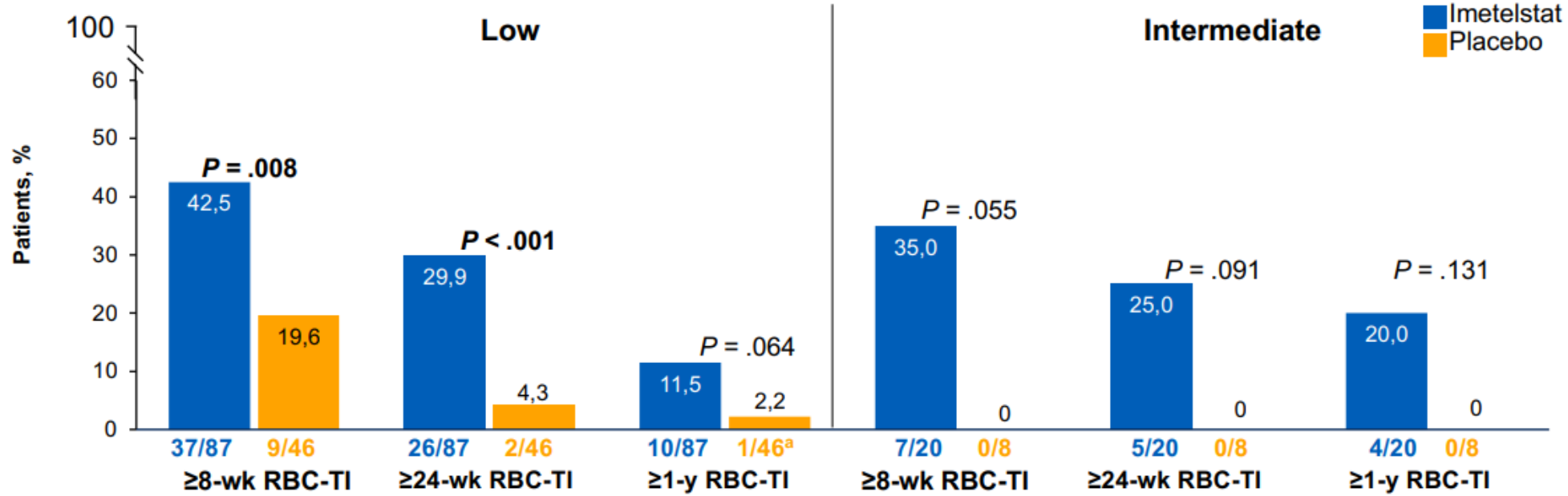
- Imetelstat treatment resulted in significantly higher 8- and 24-week RBC-TI response rates than did placebo, regardless of IPSS risk group



Data cutoff date: October 13, 2022. [a]For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period
Hb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

RBC-TI by IPSS-R Subgroup

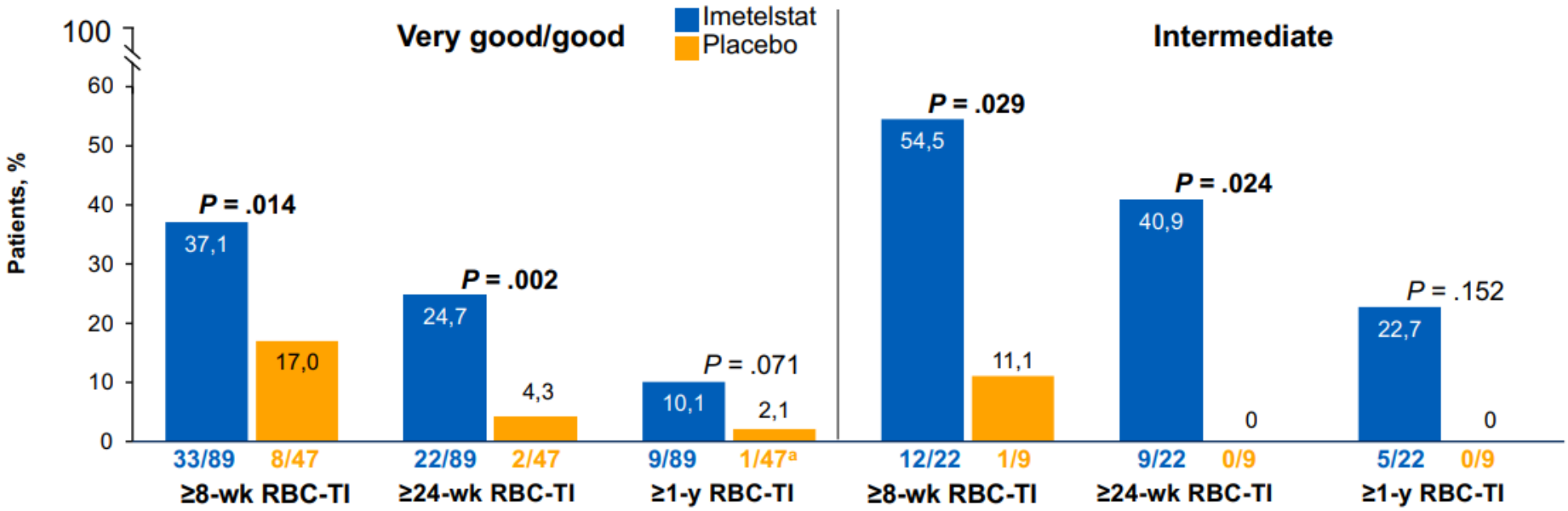
- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-R risk group
- Among imetelstat-treated patients reclassified as intermediate risk by IPSS-R, response rates were similar to those reclassified as low risk; no response was noted in placebo-treated patients reclassified as intermediate risk
- For the very low and high IPSS-R categories, the number of patients was too low (≤3 patients) in both groups to assess differences in RBC-TI response



Data cutoff date: October 13, 2022. [a]For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period
Hb, hemoglobin; IPSS-R, revised International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

RBC-TI by IPSS-R Cytogenetic Subgroup

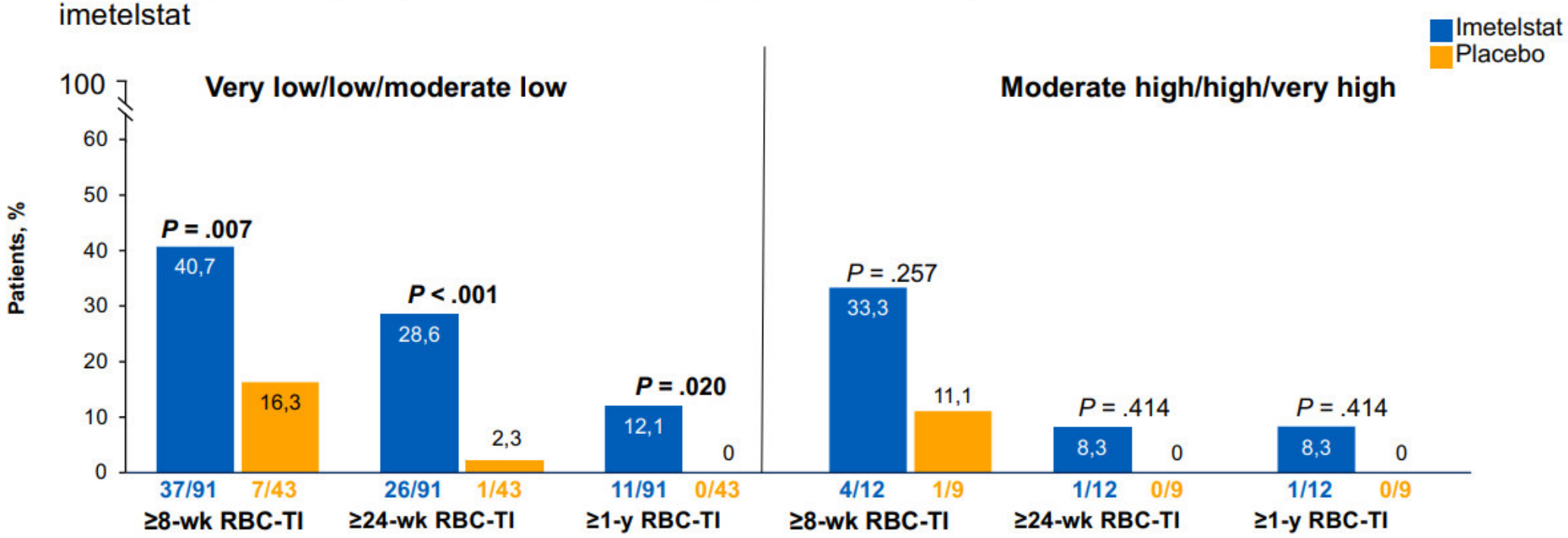
- Imetelstat treatment resulted in significantly higher 8- and 24-week RBC-TI rates than did placebo, regardless of IPSS-R cytogenetic risk group



Data cutoff date: October 13, 2022. [a]For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period
Hb, hemoglobin; IPSS-R, revised International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

RBC-TI by IPSS-M Subgroup

- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-M risk group
- 4 out of 12 patients (33%) reclassified as having higher risk MDS by IPSS-M had ≥8-week RBC-TI with imetelstat



Data cutoff date: October 13, 2022.

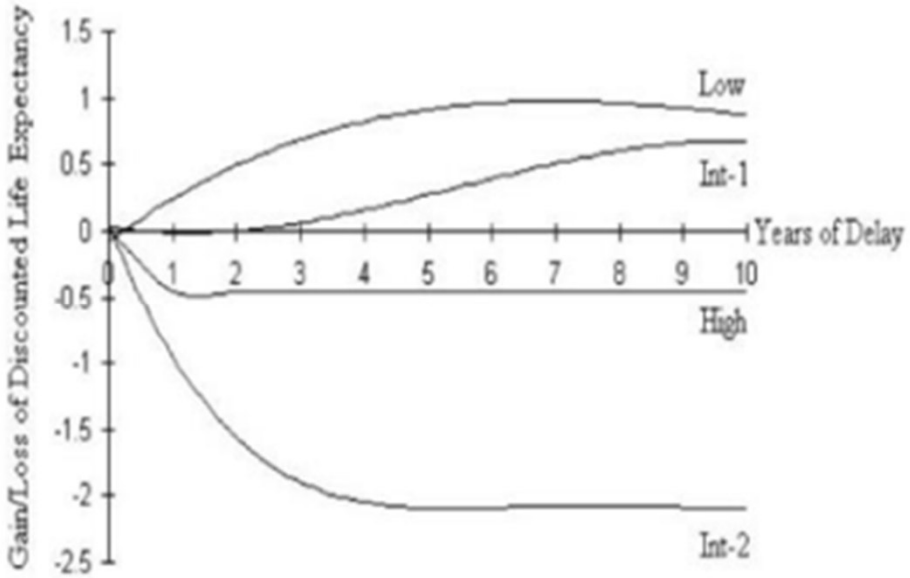
Hb, hemoglobin; IPSS-M, molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

#194, Tentori et. al

Clinical and genomic-based Decision Support System to define the optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic neoplasms

Transplantation strategy according to IPSS or IPSS-R

IPSS



Cutler CS et al Blood 2004;104(2):579-85

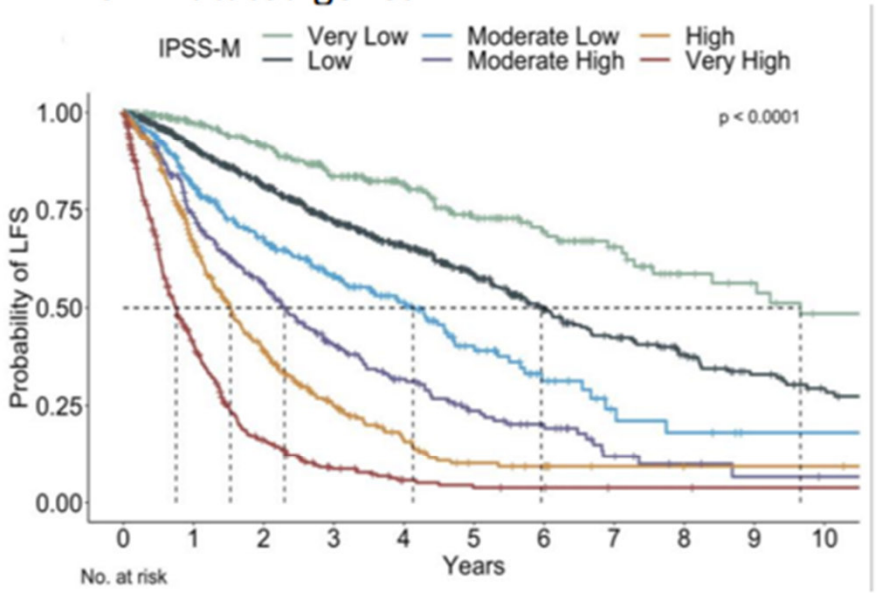
IPSS-R

	delay time (months)	*40*	*50-55*	*>60*
Years of life expectancy under policy 1: IPSS-R Low	***0***	16.4	16.1	15.1
	12	17.3	16.8	15.4
	24	17.9	17.3	15.6
	48	18.5	17.7	15.7
	60	18.7	17.9	15.7
Years of life expectancy under policy 2: IPSS-R intermediate	***0***	19.3	18.1	15.9
	12	17.9	17.1	14.9
	24	17.1	16.4	14.5
	48	16.3	15.7	14.2
	60	16.0	15.5	13.9

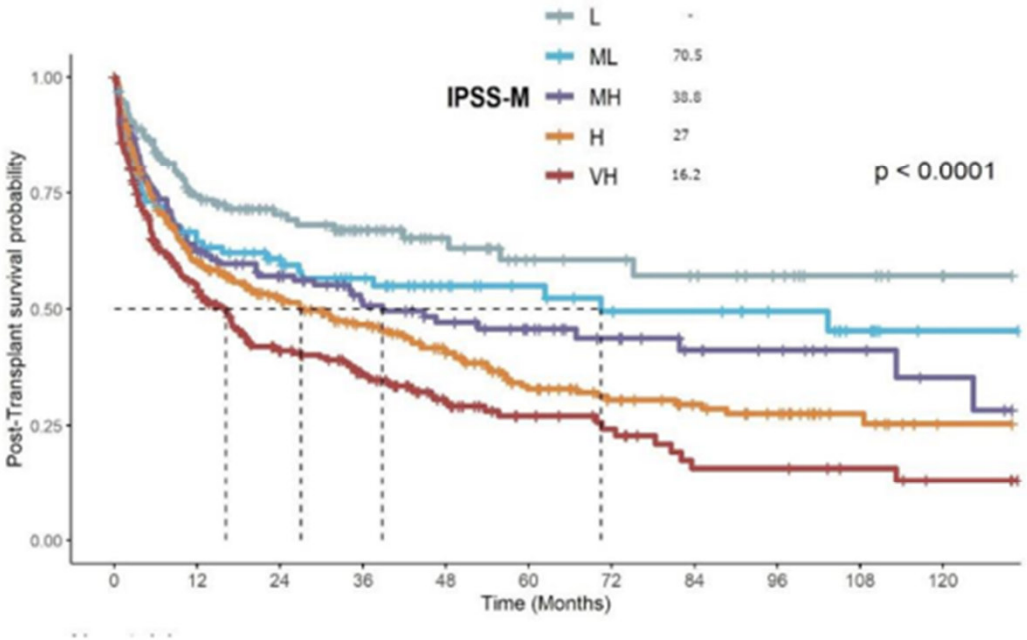
Della Porta MG et al Leukemia 2017;312449-57

Molecular IPSS (IPSS-M) for MDS prognostication

- Study Population: 2,957 patients
- The IPSS-M risk score consisted of:
  - hemoglobin, platelets and bone marrow blasts
  - IPSS-R cytogenetic category
  - 31 mutated genes



- IPSS-M validation by GenoMed4All network
- Survival of 964 pts who underwent HSCT



Bernard E at al. NEJM Evid 2022; 1 (7) DOI:https://doi.org/10.1056/EVIDoa2200008

Sauta E at al. J Clin Oncol. 2023;41:2827-2842

Clinical Characteristics of Patients (n=7118)

	MDS natural history (n=5380)	MDS receiving HSCT (n=1738)
Demographic		
Male sex	3309 (62)	1088 (61,7)
Age at diagnosis, y	73 (18 - 98)	59,9 (18 - 77)
IPSS-M risk group		
Very low	534 (10,1)	-
Low	1842 (34,2)	408 (24,1)
Moderate low	709 (12,9)	205 (12,1)
Moderate high	553 (10,5)	255 (15)
High	795 (14,5)	425 (24,2)
Very high	947 (17,9)	445 (24,6)

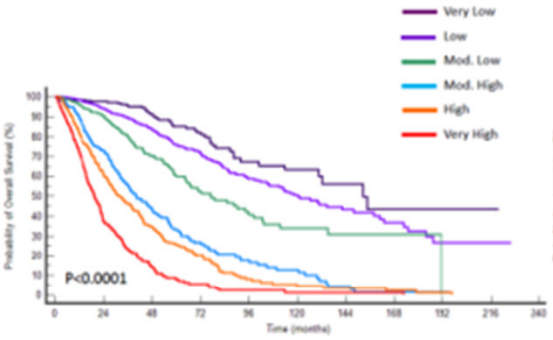
HSCT variables	N=1738
Time to HSCT, months	7,1 (1-226)
Donor Type	
HLA-identical sibling	531 (32.1)
Matched unrelated donor	650 (36.4)
Mismatched unrelated donor	388 (21.3)
Mismatched related donor	149 (9.1)
Cord blood	20 (1.1)
Disease status at HSCT	
Upfront HSCT	630 (37.6)
Complete response	503 (27.5)
Active disease	605 (34.9)
Conditioning regimen	
Standard conditioning regimen	1050 (60.6)
Reduced-intensity conditioning	688 (39.4)

Clinical Outcomes of MDS patients by IPSS-M

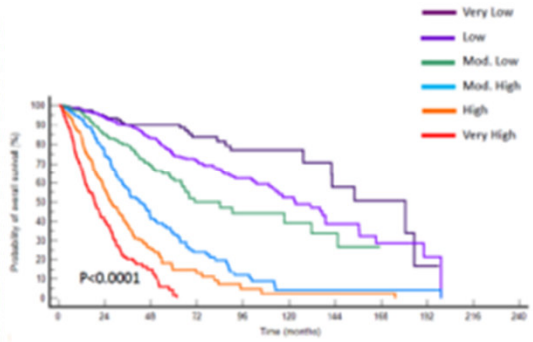
MDS natural history

Overall survival

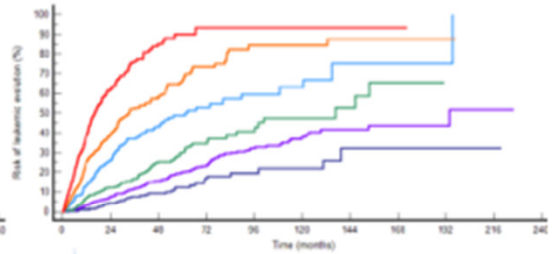
TRAINING COHORT

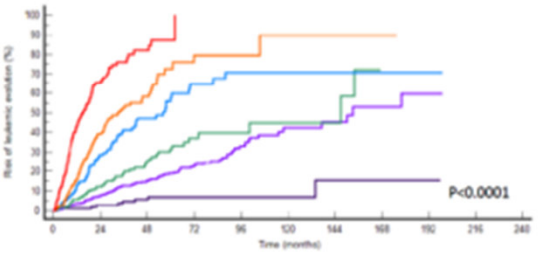


VALIDATION COHORT



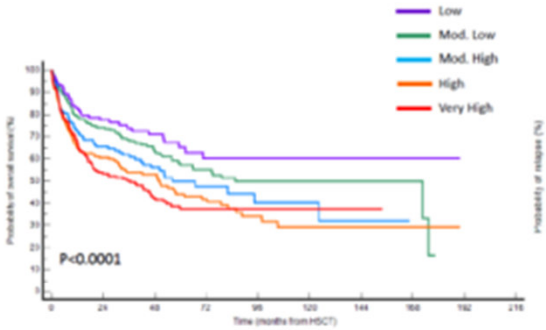
AML evolution

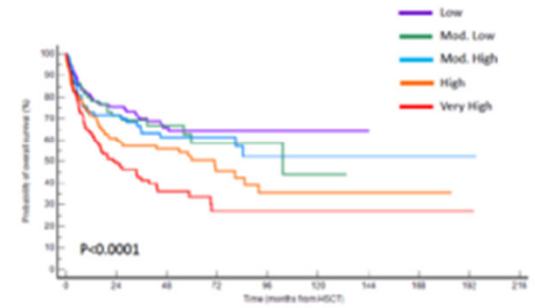




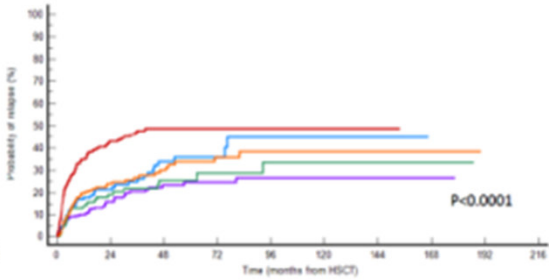
MDS who received HSCT

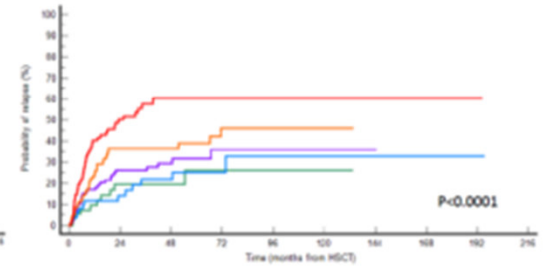
Post transplantation survival





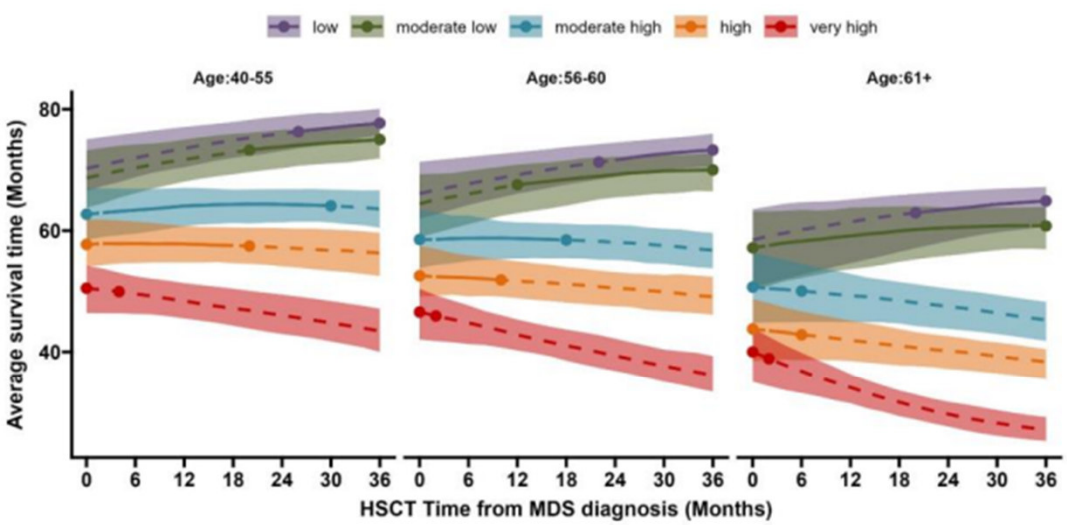
Risk of relapse



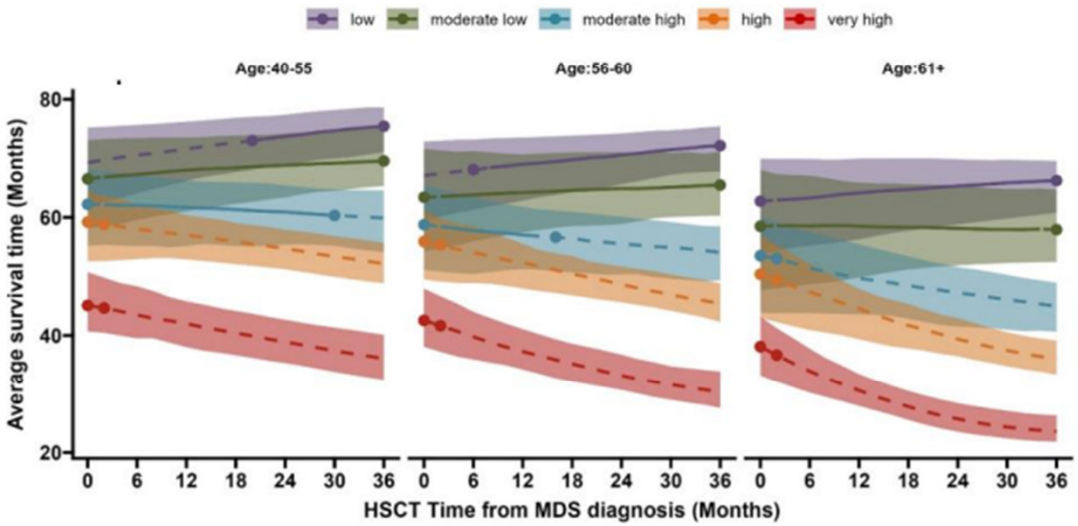


IPSS-M based transplantation policy

A – TRAINING COHORT



B – VALIDATION COHORT



- Under an IPSS-M based policy, in the training cohort, patients with either low- and moderate-low risk benefited from a delayed transplantation policy, while in those belonging to moderate-high, high- and very-high risk categories immediate transplantation was associated with a prolonged RMST

- All these results were confirmed in the validation cohort

Danke für die Aufmerksamkeit!

Übersicht

1. Myeloproliferative Neoplasien
    1. Abstract #628; Rampal et al.: Pelabresib in combination with ruxolitinib

2. Chronische myeloische Leukämie
    1. Abstract #867; Jiang et al.: Safety and Efficacy of Tgrx-678, a Potent BCR-ABL Allosteric Inhibitor in Patients with Tyrosine Kinase Inhibitor (TKI) Resistant/Refractory Chronic Myeloid Leukemia (CML): Preliminary Results of Phase I Study
    2. Yeung et al., Abstract #869; Jiang et al.: Olverembatinib (HQP1351) Demonstrates Efficacy Vs. Best Available Therapy (BAT) in Patients (Pts) with Tyrosine Kinase Inhibitor (TKI)-Resistant Chronic Myeloid Leukemia Chronic-Phase (CML-CP) in a Registrational Randomized Phase 2 Study Qian Jiang et al., Peking, China

3. MDS
    1. Abstract #193; Guillermo Garcia-Manero et al.: Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive patients
    2. Abstract #194; Platzbecker et. al.: Durable Continuous Transfusion Independence With Imetelstat in IMerge Phase 3 for Patients With Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic
    3. Abstract #197; Tentori et al.: Clinical and genomic-based Decision Support System to define the optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic neoplasms