

Il profilo molecolare del paziente con mielofibrosi citopenica

Francesco Passamonti

Chair of Hematology, University of Milano

Division of Hematology, Fondazione I.R.C.C.S.

Ospedale Maggiore Policlinico of Milano



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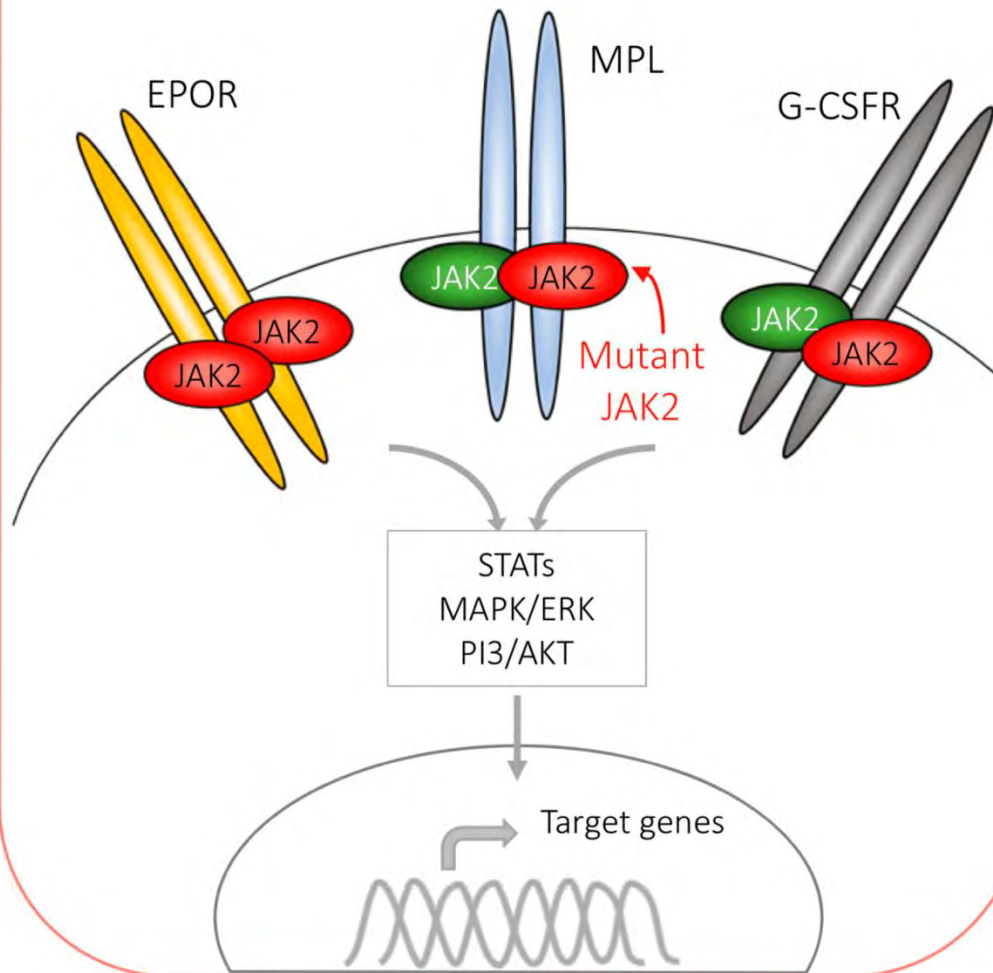


Regione
Lombardia

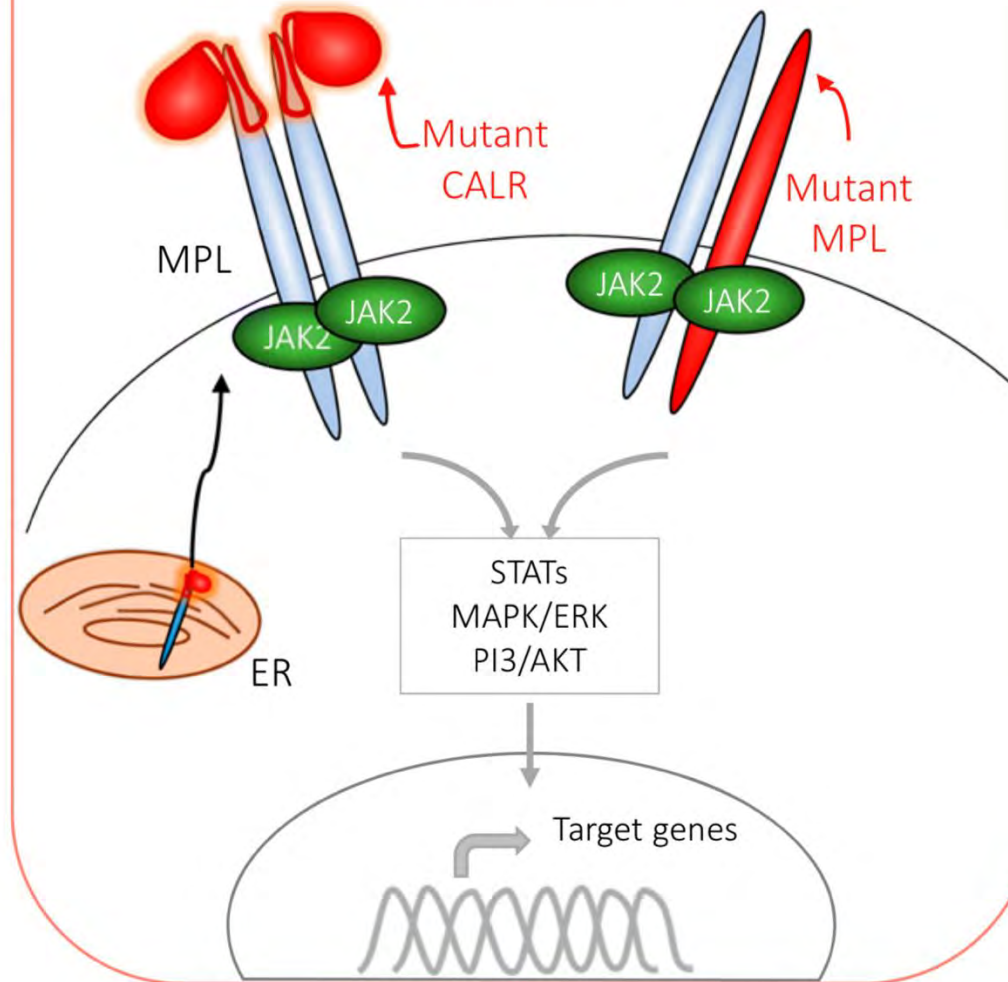
Disclosures

- FRANCESCO PASSAMONTI received honoraria during the last two years for lectures from Novartis, Bristol-Myers Squibb, Abbvie, GSK, AOP Orphan, Menarini Stemline, MSD, and for advisory boards from Novartis, Bristol-Myers Squibb/Celgene, GSK, Abbvie, Keros, Takeda, Sumitomo.

JAK2 mutations

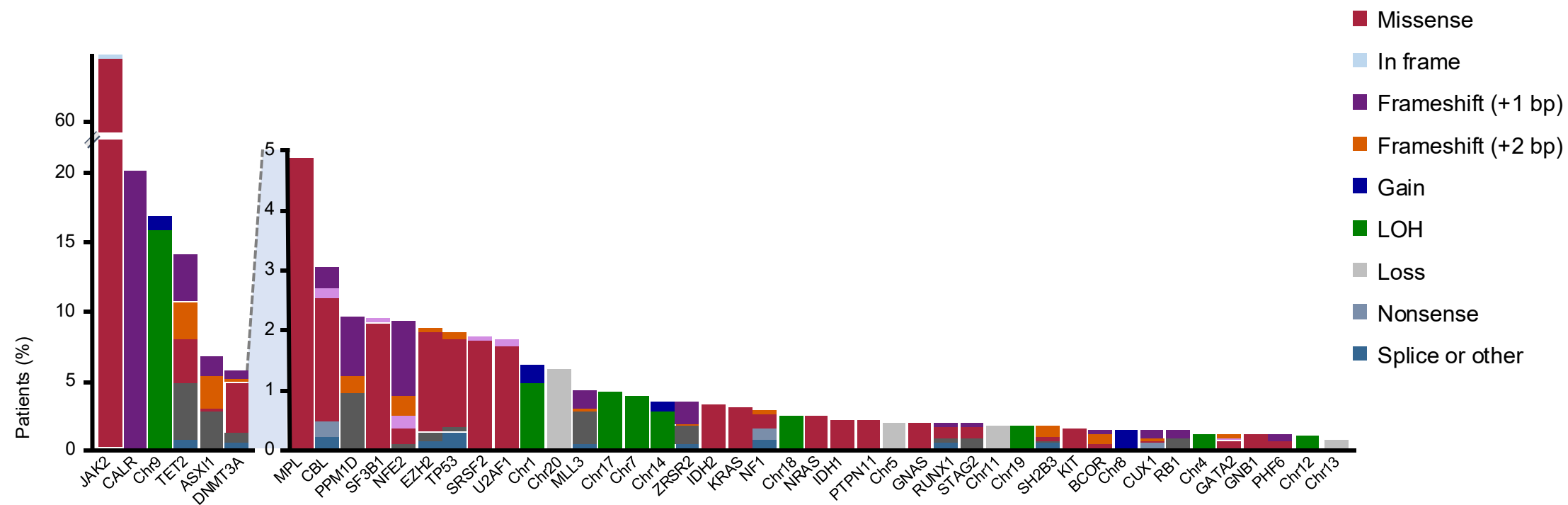


CALR and MPL mutations



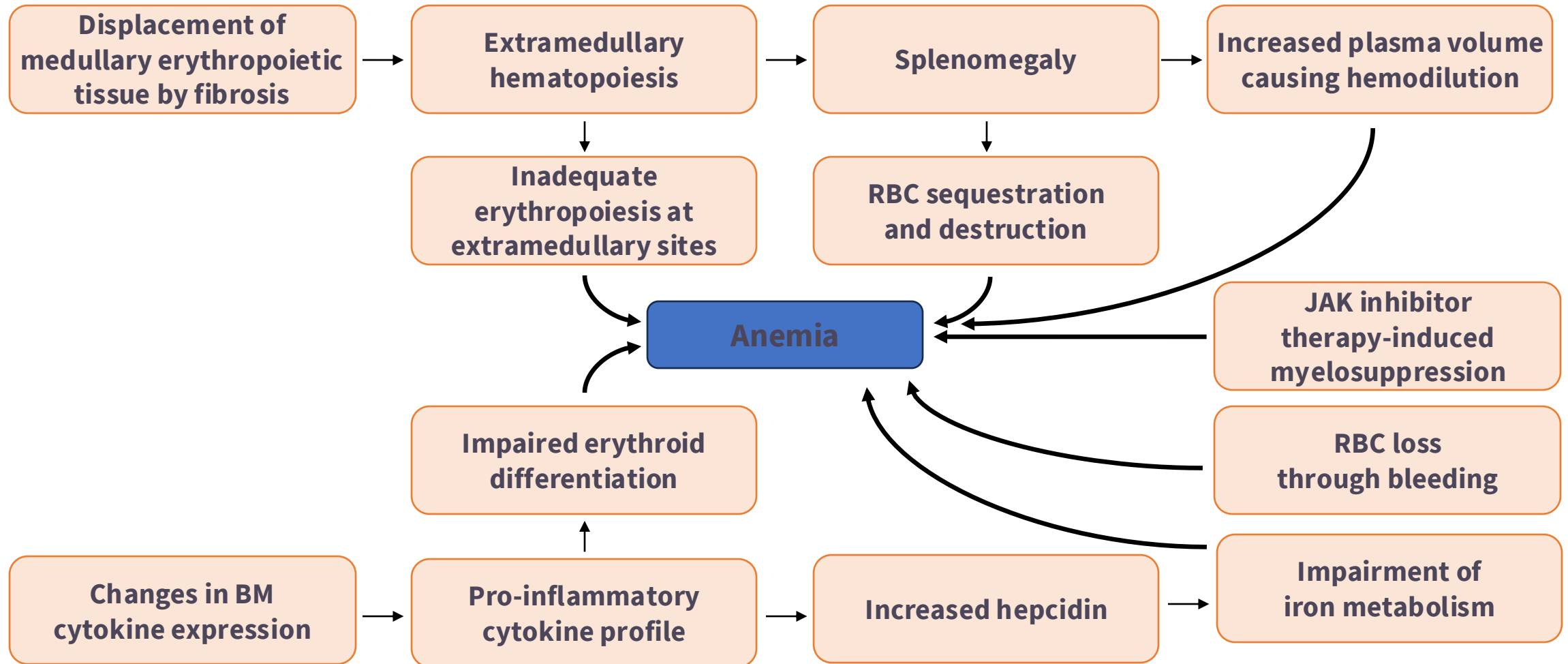
The Mutation Profile of Chronic-Phase MPN

Recurrently mutated genes and chromosomal abnormalities



Anemia in myelofibrosis

Anemia in myelofibrosis is multifactorial and has not been fully elucidated

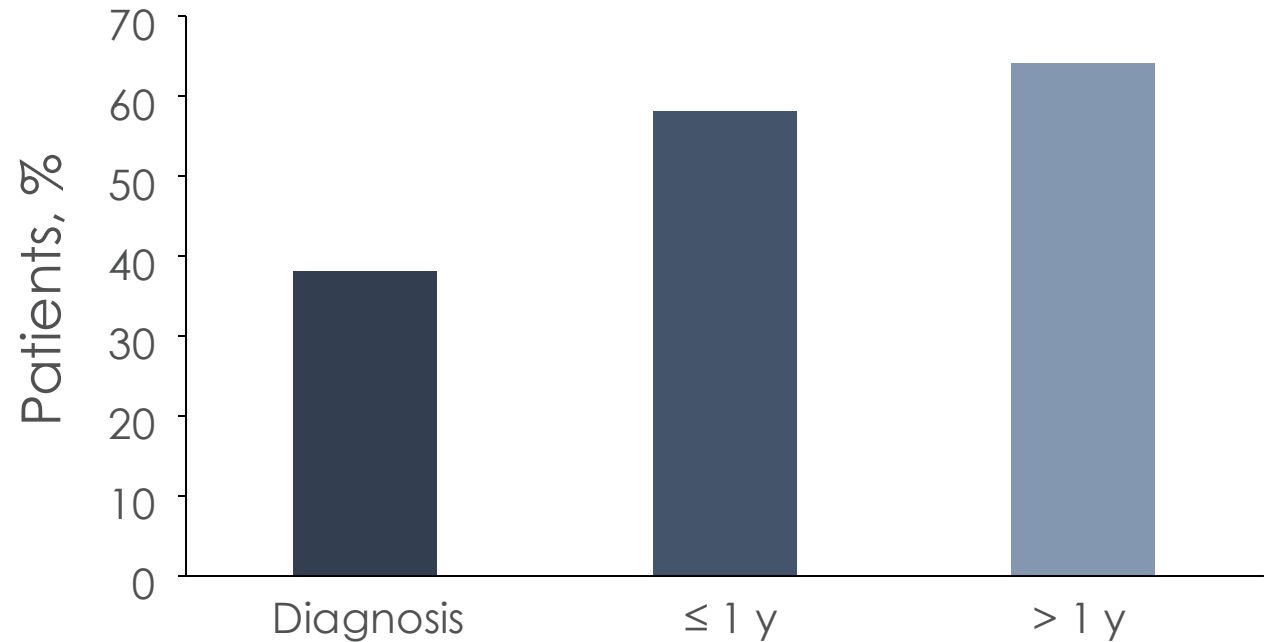


Adapted from Naymagon *et al.*¹ in accordance with the Creative Commons Attribution License (CC BY 4.0).

Anemia: a common manifestation of MF

- Anemia presents in ~30% to 50% of patients at diagnosis and in ~ 60% after 1 y^[1]
- ~46% of patients become dependent on RBC transfusions within 1 y of diagnosis^[1,2]
- Independent prognostic risk factor for leukemic transformation^[3,4]

Proportion of Patients With Anemia^[1]



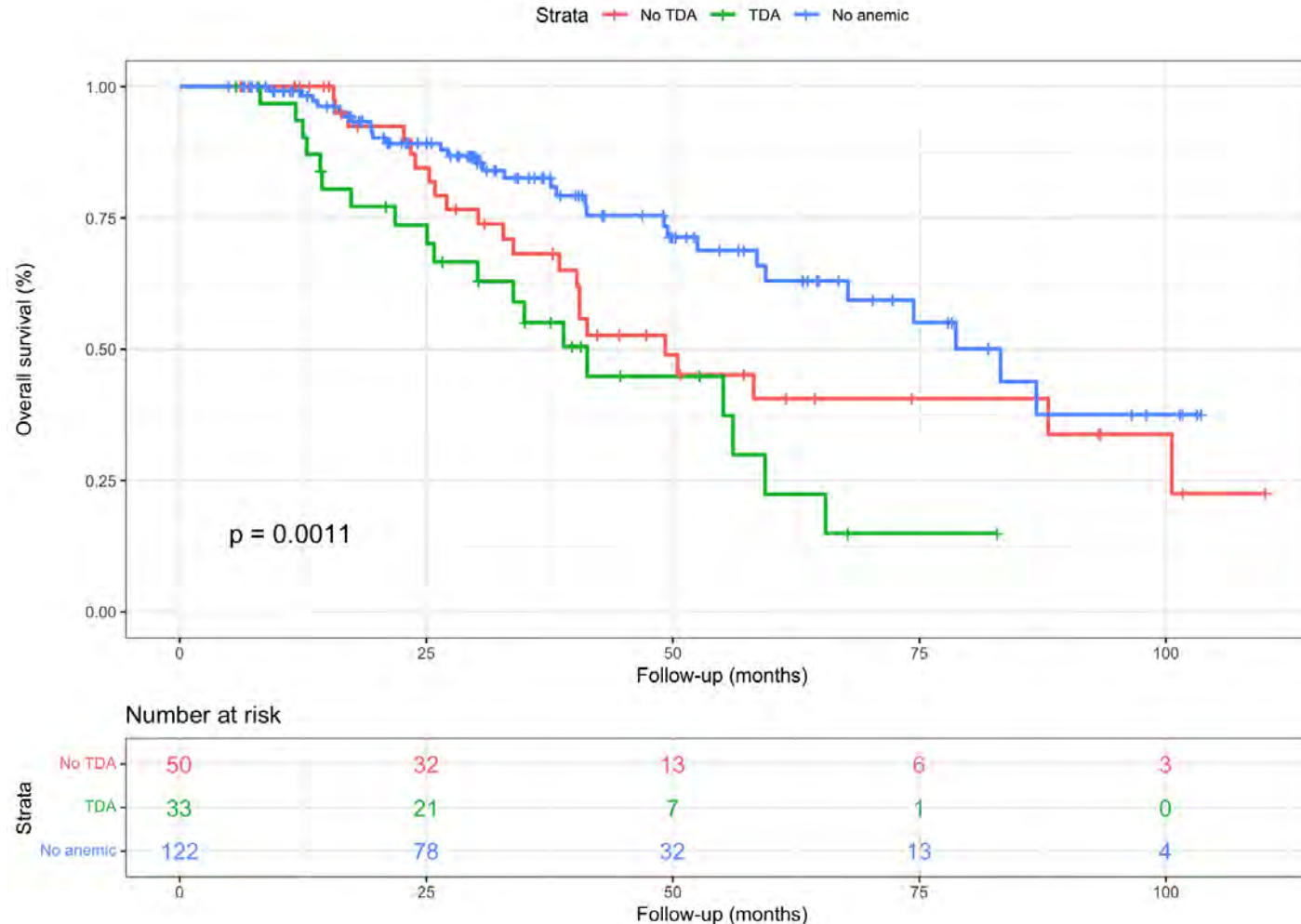
• MF, myelofibrosis; RBC, red blood cell.

- 1. Tefferi A, et al. Mayo Clin Proc. 2012;87:25-33; 2. Harrison CN, et al. Leukemia. 2016;30:1701-1707
3. Rago A, et al. Leuk Res. 2015;39:314-317; 4. Curto-Garcia N, et al. Future Oncol. 2018;14:137-150

The revised IWG-ELN criteria proposed three strata for anemia definition

- A hemoglobin level of <10 g/dL, irrespective of gender, is considered a suitable key inclusion criterion for clinical trials targeting anemia
- TDA is defined as the need for ≥ 3 units of red blood cells/12 weeks
 - Patients requiring ≥ 6 units, within the 12-week preenrollment period constitute a high transfusion burden subcategory
- Non-TDA includes anemic subjects who do not qualify for TDA
- Dispense RBC transfusions if Hb to be <8.5 g/dL

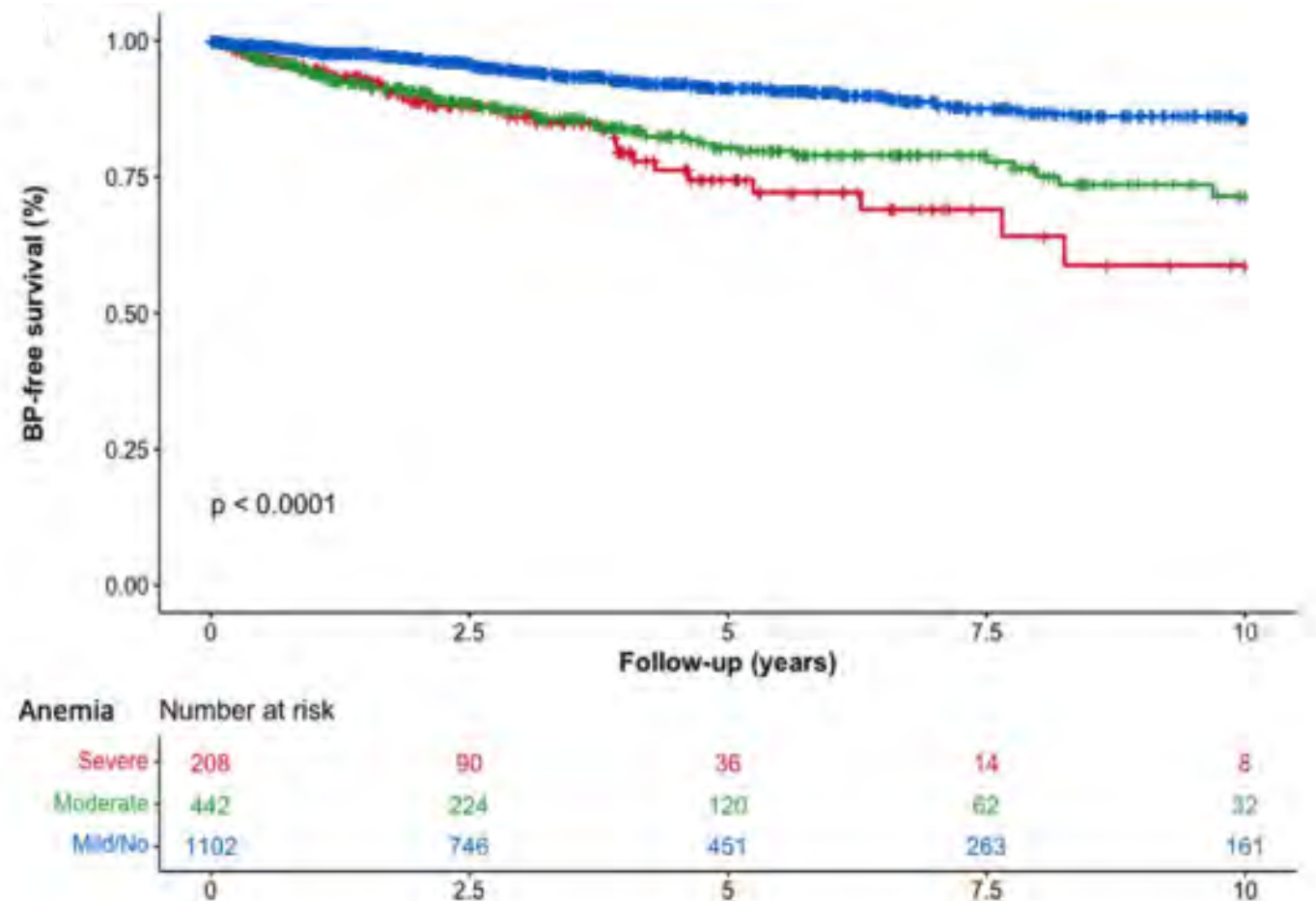
Actuarial survival curves according to baseline (at ruxolitinib start) anemia status



- Non-anemic
- Anemic but not transfusion-dependent (non-TDA)
- Transfusion-dependent (TDA)

A link between anemia and evolution to Blast-Phase MF

Association between blast phase-free survival (BP-FS) and anemia at time of MF diagnosis in 1,752 patients, according to severity¹



- BP-FS was associated with the presence and severity of anemia at MF diagnosis

Myelofibrosis Presents Across a Spectrum of Disease

Emerging Characterization of Phenotypic Extremes¹

Proliferative MF

Better/Lower AML risk

More often secondary

Lower risk of cytopenias,
pronounced splenomegaly

Mostly *JAK2*,
low somatic mutations

Often high

Prognosis

Etiology of MF

Clinical Presentation

Mutational Landscape

JAK2^{V617F} Allele Burden

^aSomatic mutations in DNA methylation genes (eg, *TET2* and *DNMT3A*), epigenetic modifiers (eg, *IDH1/2*, *EZH2*, and *ASXL1*) and RNA splicing (eg, *SRSF2* and *U2AF1*).^{2,3}

Cytopenic MF

Poor/Higher AML risk

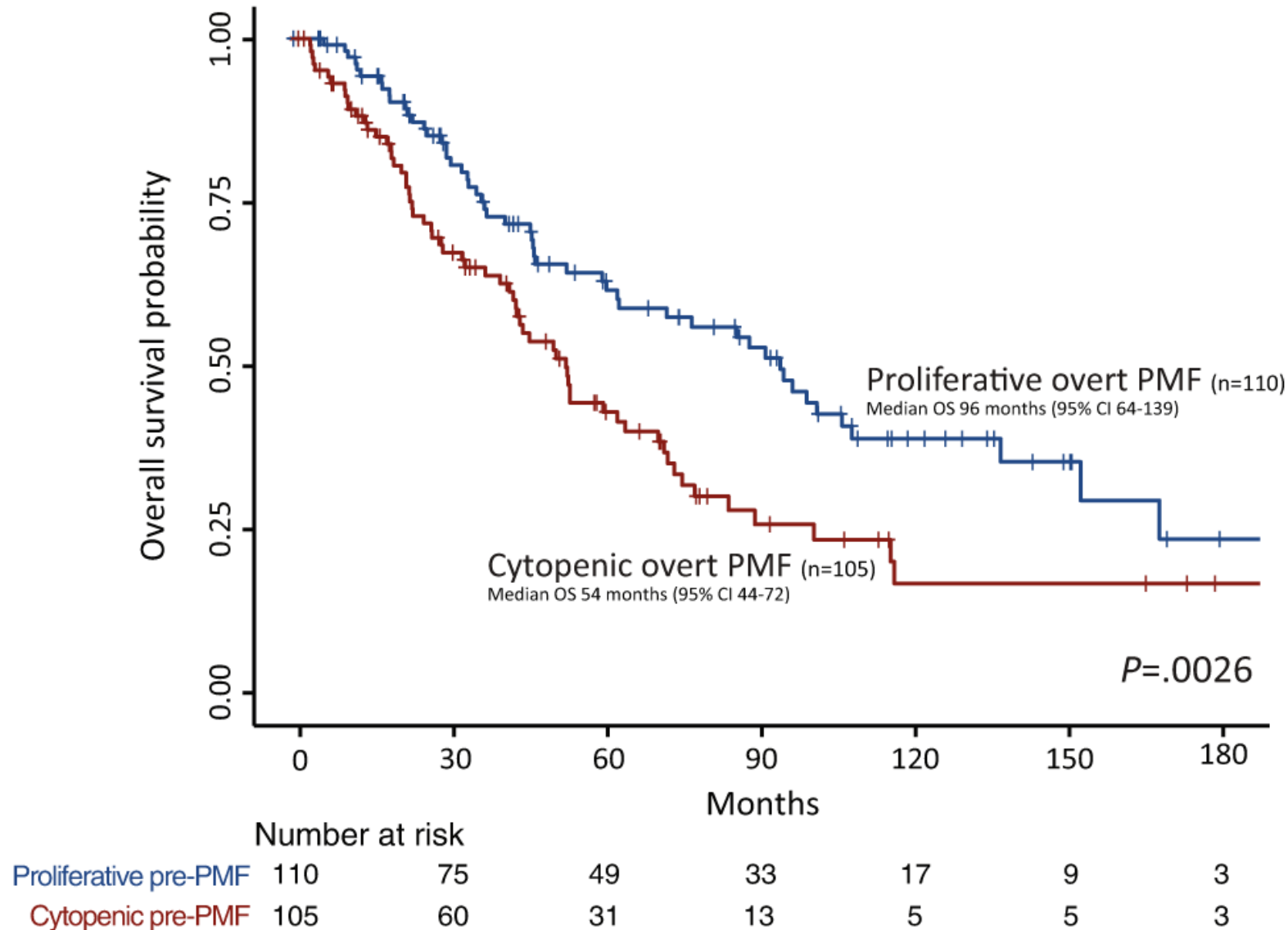
More often primary

Pronounced cytopenias, transfusion requirements, bleeding, infection, less pronounced splenomegaly

Variability in driver mutations
(*JAK2*, *CALR*, *MPL*, or triple-negative)
≥3 somatic mutations^a

Often low

Cytopenic MF is more aggressive vs. proliferative MF



Cytopenic MF is defined as any 1 of the following

- Leukocytes $<4 \times 10^9/L$
- Hemoglobin <11 g/dL and <10 g/dL for men and women, respectively
- Platelets $<100 \times 10^9/L$

Overt PMF with ≥ 2 cytopenias have a median OS of 43 months

Anemia and thrombocytopenia are often paired

Variable	Platelets $<50 \times 10^9/L$ (n=57)	Platelets $\geq 50 \times 10^9/L$ (n=834)	P-value
Age >65 years	75%	60%	0.019
Bleeding manifestations	19%	6%	<0.001
Constitutional symptoms	40%	34%	0.31
Hgb <80 g/L	35%	8%	<0.001
WBC $<4 \times 10^9/L$	26%	10%	<0.001
WBC $>25 \times 10^9/L$	14%	11%	0.47
Blasts $\geq 1\%$	57%	45%	0.069
Blasts $\geq 3\%$	21%	11%	0.022
Grade 3 bone marrow fibrosis	24%	11%	0.008
Unfavorable cytogenetics	17%	11%	0.35
JAK2 mutated	50%	64%	0.057
Int-2/High-risk IPSS	86%	60%	<0.001
Int-2/High-risk DIPSS+	100%	59%	<0.001

Prognostic Models of Myelofibrosis

Parameter	Included in IPSS ²	Included in DIPSS ³	Included in DIPSS-Plus ⁴
Age > 65 y	Yes (1 point)	Yes (1 point)	Yes ^a
Hgb < 10 g/dL	Yes (1 point)	Yes (2 points)	Yes ^a
WBC > 25 × 10 ⁹ /L	Yes (1 point)	Yes (1 point)	Yes ^a
PB blood blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes ^a
Constitutional symptoms	Yes (1 point)	Yes (1 point)	Yes ^a
Unfavorable karyotype ^b	No	No	Yes (1 point)
RBC transfusion dependence ^c	No	No	Yes (1 point)
Platelet count < 100 × 10 ⁹ /L	No	No	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

Risk group	Median Survival, Years		
	IPSS ²	DIPSS ³	DIPSS-Plus ⁴
Low	11.3	Not reached	15.4
Intermediate-1	7.9	14.2	6.5
Intermediate-2	4.0	4.0	2.9
High	2.3	1.5	1.3

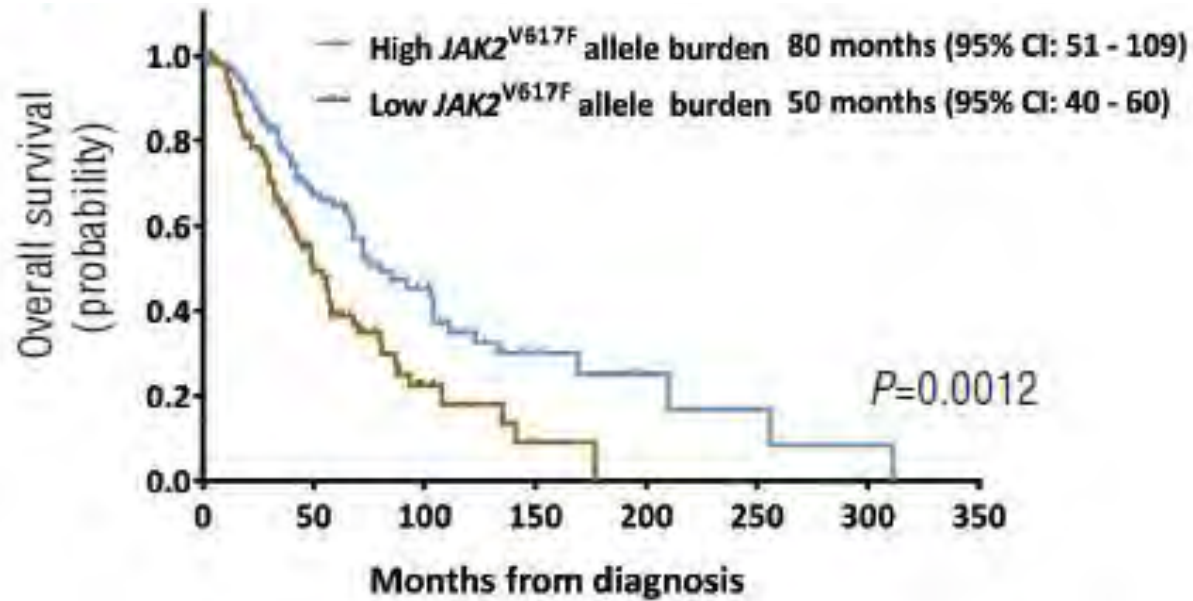
Prognostic impact of driver and high molecular risk nondriver mutations in primary mf

- Analysis of association between driver mutations and survival in patients with primary MF (N = 617)^[a]

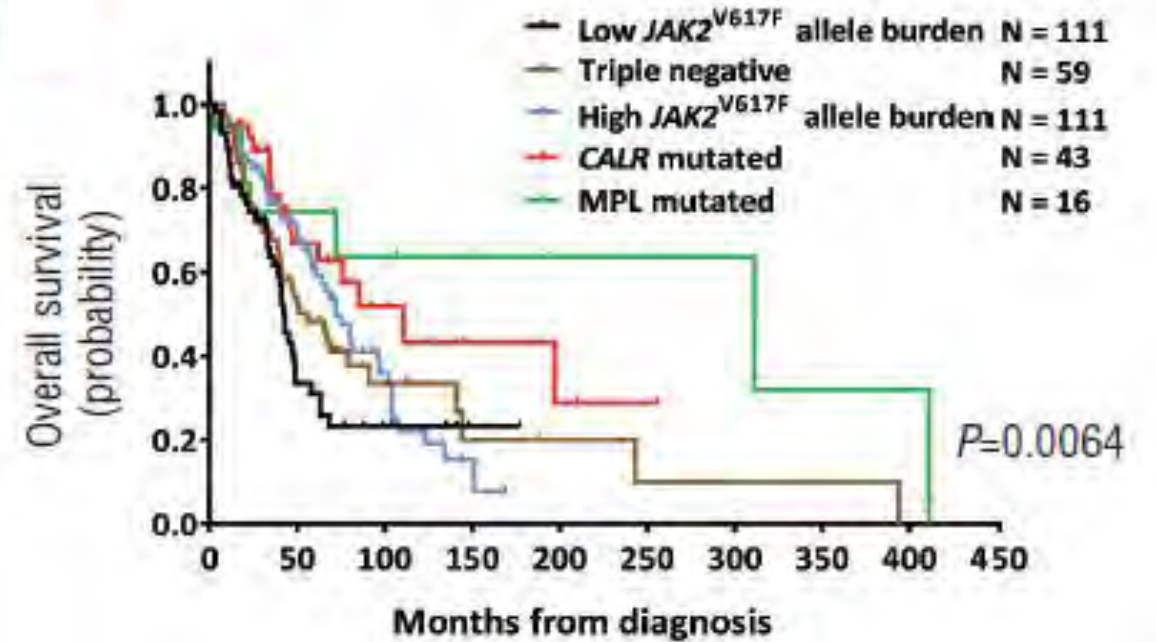
Driver Mutation	Patients, %	Median OS, y
<i>CALR</i> mutated	22.7	17.7
<i>JAK2</i> mutated	64.7	9.2
<i>MPL</i> mutated	4.0	9.1
Triple negative	8.6	3.2

- Analysis of association between set of nondriver mutations (*IDH*, *EZH2*, *ASXL1*, *SRSF2*) and survival in patients with primary MF (N = 797)^[b]
 - Presence of mutations predicted decreased survival; ≥ 2 mutations predicted worst survival

JAK2 VAFs <50% were associated with shorter survival

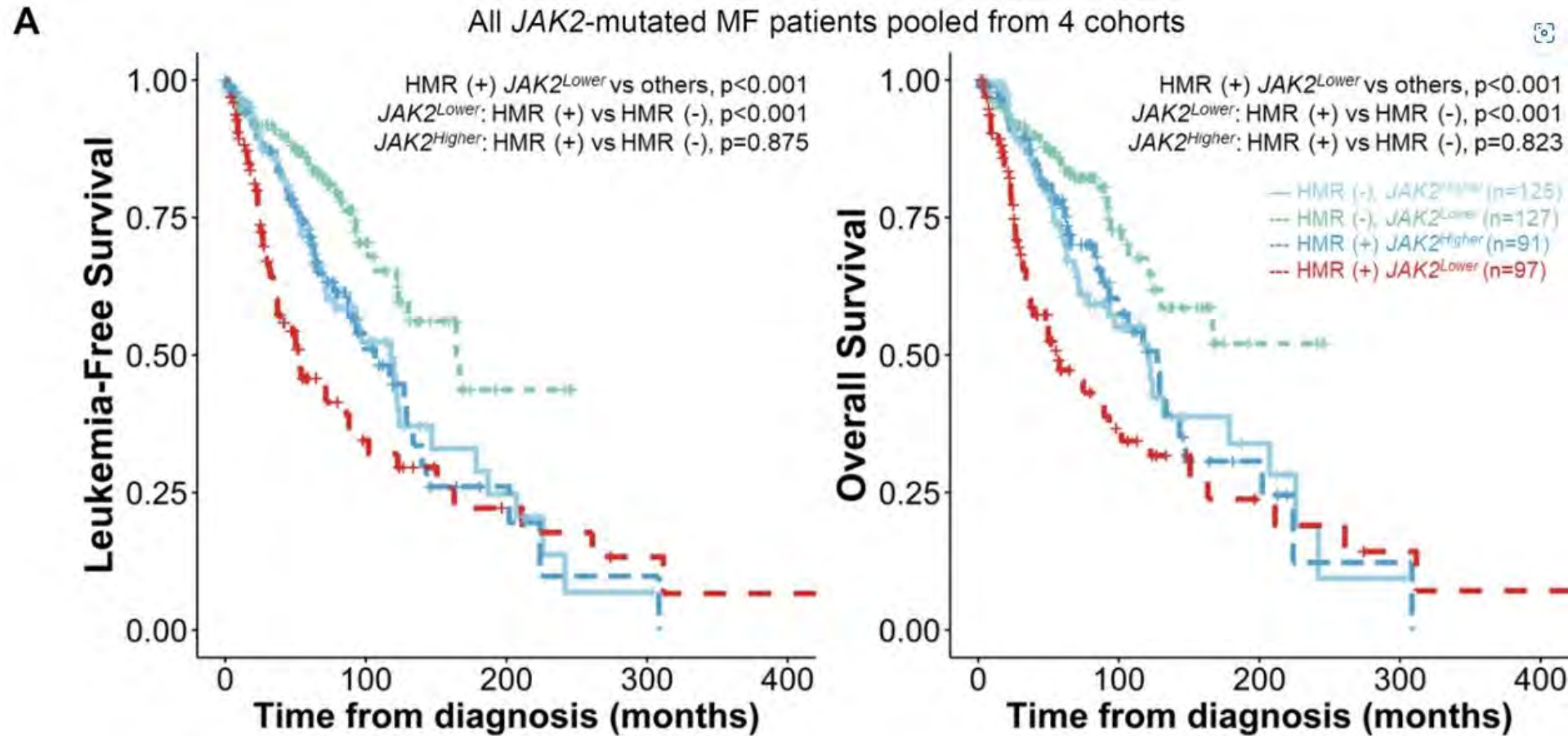


- JAK2 V617F $\geq 50\%$, mOS = 80 months (51-109)
- JAK2 V617F <50%, mOS = 50 months (40-60)

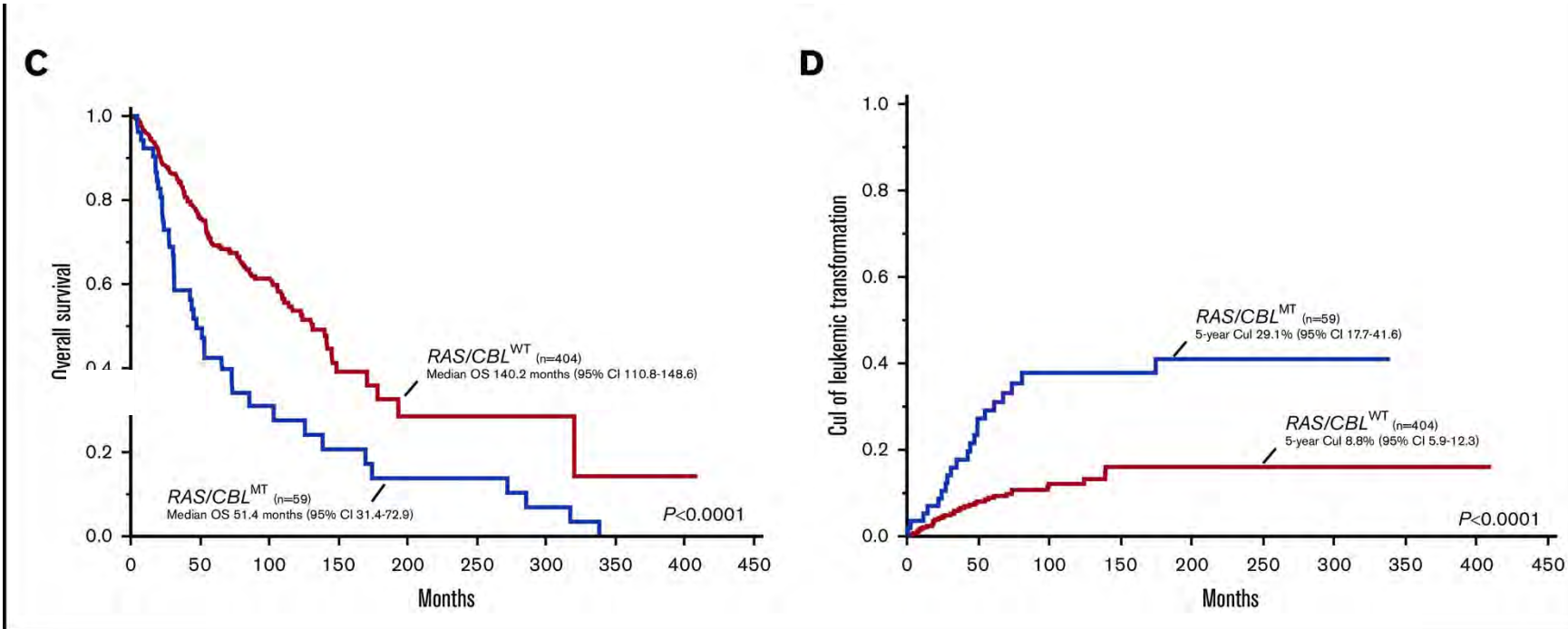


- JAK2 V617F $\geq 50\%$, mOS = 80 months (51-109)
- Triple negative, mOS = 56 months (35-77)
- JAK2 V617F <50%, mOS = 50 months (40-60)

HMR are detrimental only in the *JAK2V617F* low VAF



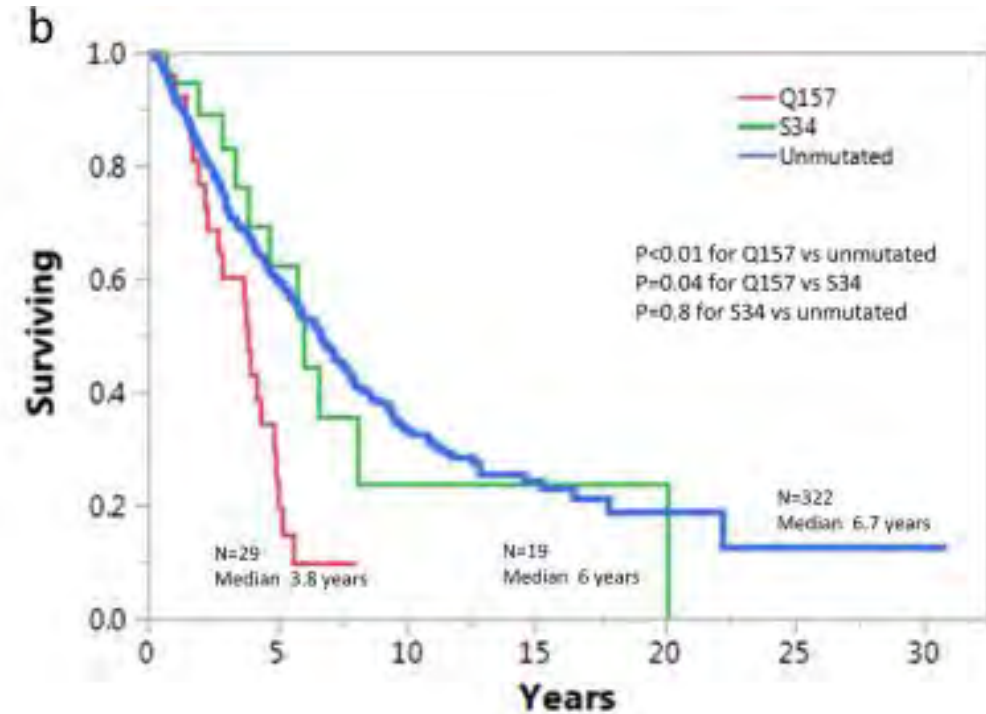
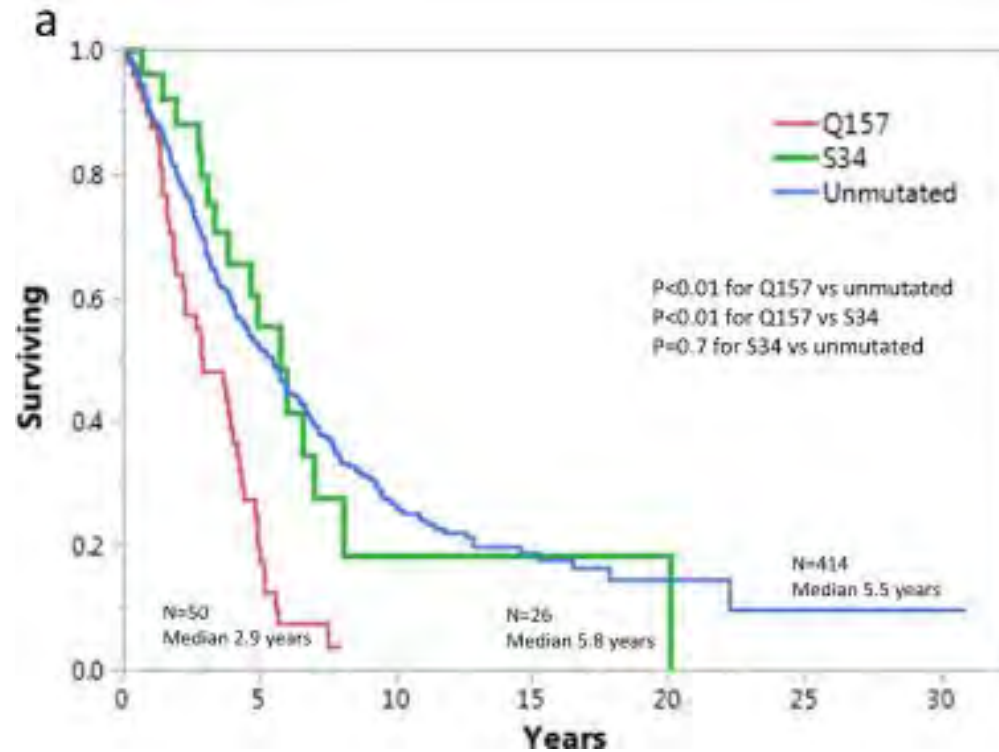
RAS/CBL+ adversely associated with cytopenic profile



U2AF1 associates with cytopenias and clusters with JAK2

Variables	All patients (n=250)	U2AF1 mutated (n=40)	U2AF1 wild-type (n=210)	P value
Constitutional symptoms; n (%)	86 (34.4)	18 (45)	68 (32.4)	0.12
Circulating blasts $\geq 1\%$; n (%)	143 (57.2)	14 (35)	115 (54.8)	0.07
Hemoglobin < 10 g/dl; n (%)	118 (47.2)	34 (85)	84 (40)	<0.0001
Transfusion requiring; n (%)	79 (31.6)	28 (70)	51 (24.3)	<0.0001
Leukocytes > $25 \times 10^9/l$; n (%)	40 (16)	8 (20)	32 (15.2)	0.45
Leukocytes < $4 \times 10^9/l$; n (%)	34 (13.6)	5 (12.5)	29 (13.8)	0.82
Platelets < $100 \times 10^9/l$; n (%)	53 (21.2)	22 (55)	35 (16.7)	<0.0001
JAK2V617F-positive; n (%) 'N' evaluable=249	145 (58.2)	32 (80)	113(54.1)	0.002

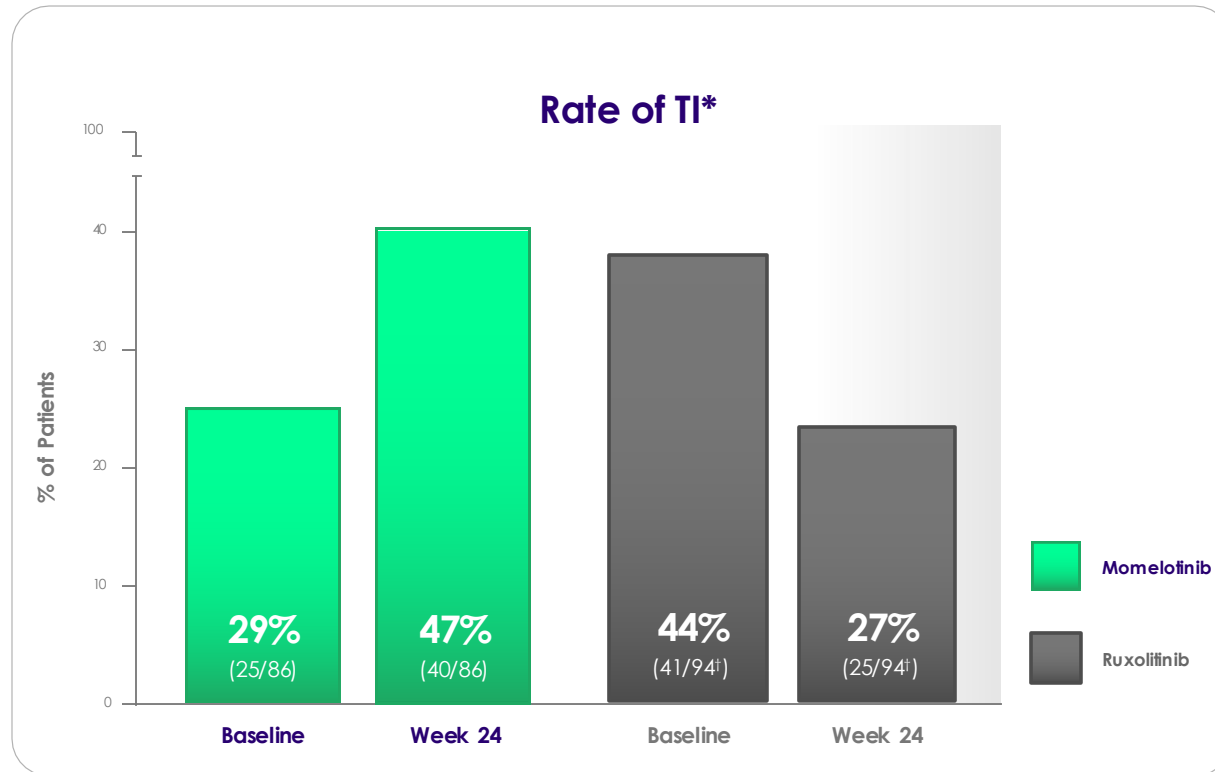
U2AF1Q157, worse marker associated to cytopenic MF



Current treatments to address MF-related anemia

		Examples
RBC transfusion	Supplementation of mature RBCs via transfusion to raise Hb levels	
ESAs	Activate pro-erythroid signaling to stimulate erythropoiesis	EPO
Androgens	Enhance erythropoiesis and alleviate MF-related anemia	Danazol
Splenectomy	Removal of spleen to address splenomegaly and RBC destruction	
IMiD agents	Immunomodulators with pleiotropic effects, including promoting erythropoiesis	Thalidomide, lenalidomide, pomalidomide
JAK inhibitors	Prevent overactive JAK/STAT signaling due to mutation; can exacerbate MF-related anemia	Ruxolitinib, fedratinib, pacritinib, momelotinib

Patients Receiving Mometotinib Had Numerically Higher Transfusion Independence Rates at Week 24



Graph adapted from Gupta V, et al. *Leuk Lymphoma*. 2024;65(7):965-977.

- Nearly half (47%) of patients on momelotinib were transfusion independent at Week 24*

These descriptive post hoc subgroup data for TI are not included in the momelotinib label and are not powered to detect treatment differences. Any differences in baseline characteristics of the treatment groups are not accounted for.

*TI rate at Week 24 was defined as the proportion of patients with no transfusion or Hb <8 g/dL between Weeks 12 and 24. ¹One patient who received ruxolitinib was excluded from this analysis due to a missing Hb value prior to randomisation.

Hb, haemoglobin; **TI**, transfusion independence.

Reference: Gupta V, et al. *Leuk Lymphoma*. 2024;65(7):965-977.

Ruxolitinib Plus Luspatercept ACE-536-MF-001 Study Design

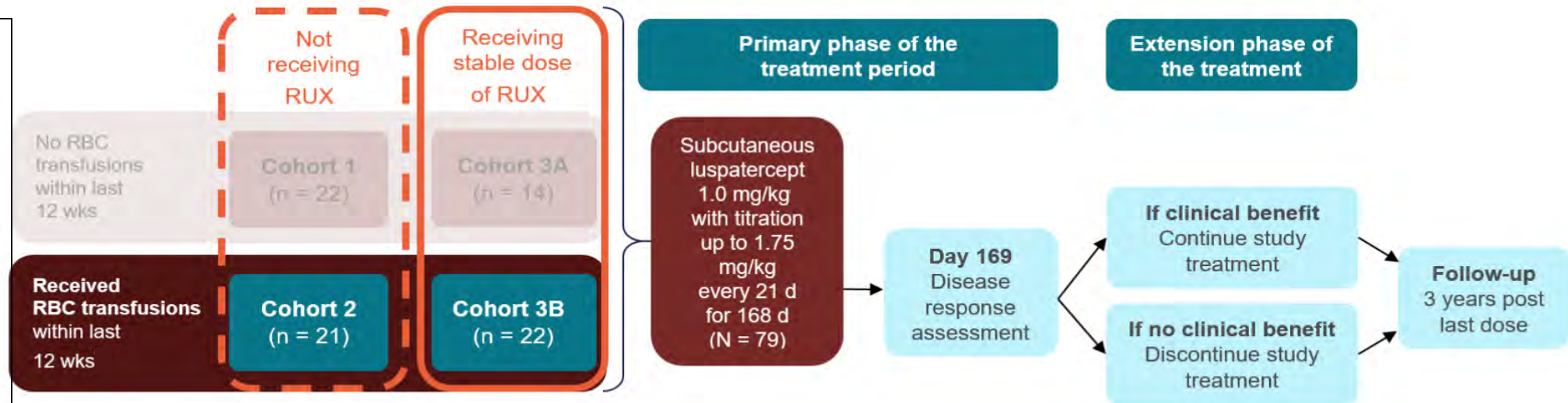
- The phase 2, multicenter, open-label ACE-536-MF-001 study evaluated the efficacy and safety of luspatercept in patients with MPN-associated MF and anemia with and without RBC TD

Key eligibility criteria

- PMF or post-ET/
post-PV MF
- Anemia
- ECOG performance
status ≤ 2

Key exclusion criteria

- Use of hydroxyurea,
androgenic
corticosteroids,
ESAs, or other drugs
with potential effect on
hematopoiesis ≤ 112 d
up to enrollment
- Blood myeloblasts $\geq 5\%$



Primary endpoints:

- TD patients: anemia response (84 consecutive days **without RBC transfusion**)
- NTD patients: 84 consecutive days with Hb increase of ≥ 1.5 g/dL from baseline without transfusion

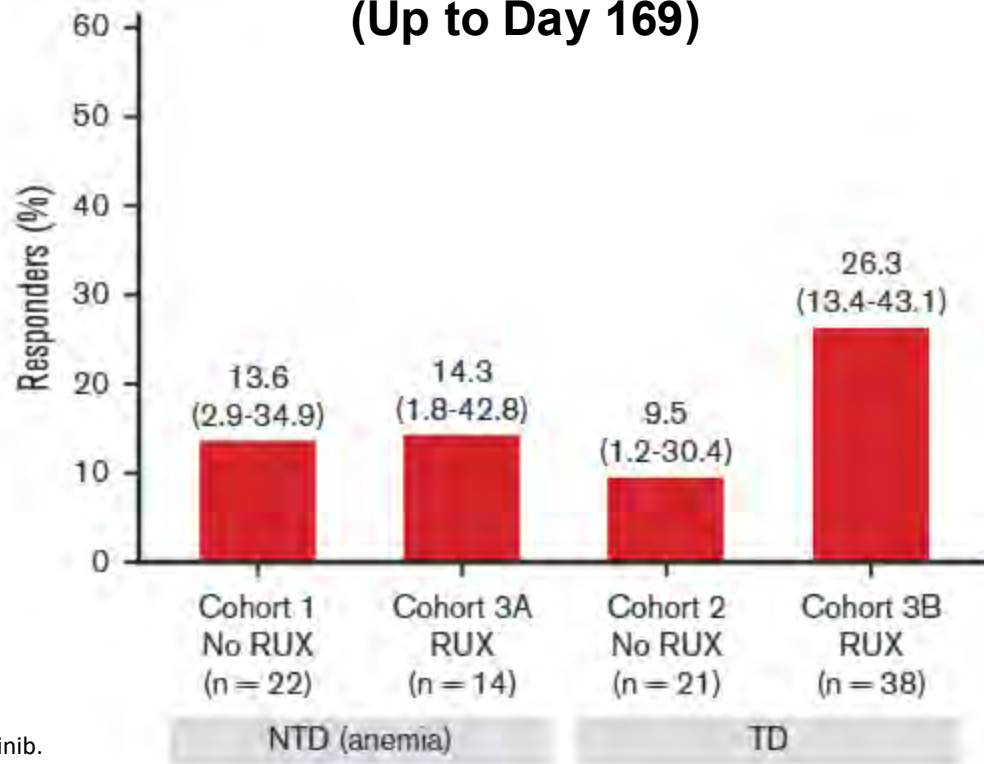
Secondary endpoints included:

- Time to and duration of anemia response
- Frequency of RBC transfusions and TD
- Symptom response
- Changes in mean Hb

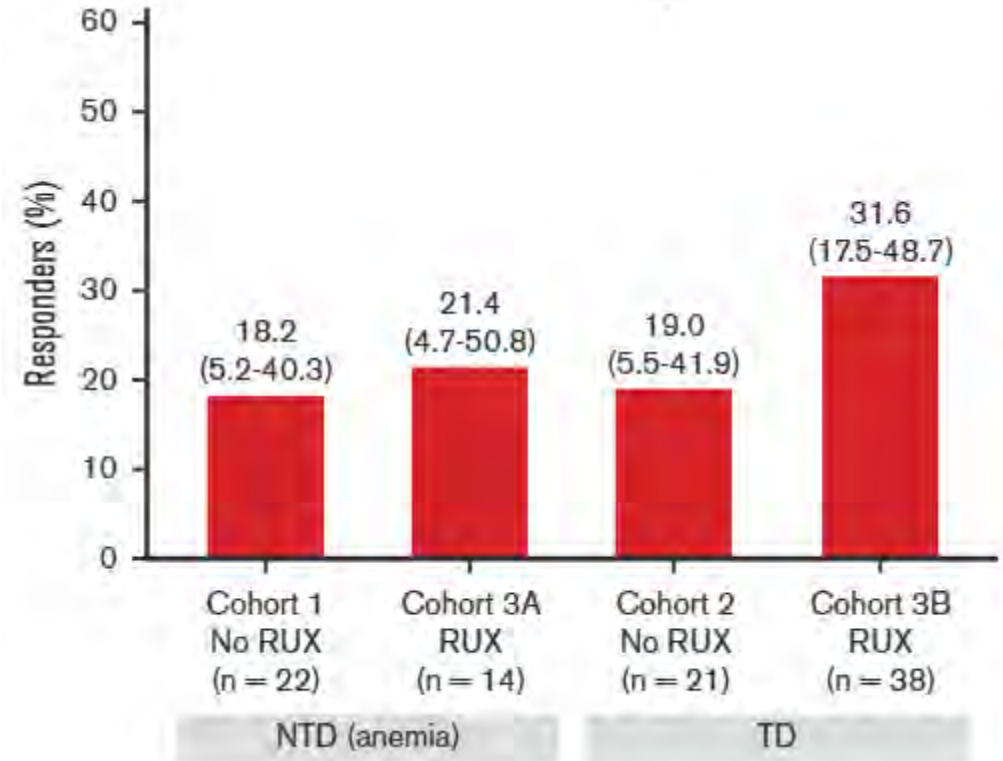
Luspatercept Induced TI in Approximately One-Third of TD Patients on RUX During the Entire Treatment Period

- Primary endpoints:
 - TD patients: anemia response defined as 84 consecutive days without RBC transfusion
 - NTD: anemia response defined as 84 consecutive days with ≥ 1.5 g/dL Hb increase from baseline without RBC transfusion

**Primary Treatment Period
(Up to Day 169)**



Entire Treatment Period

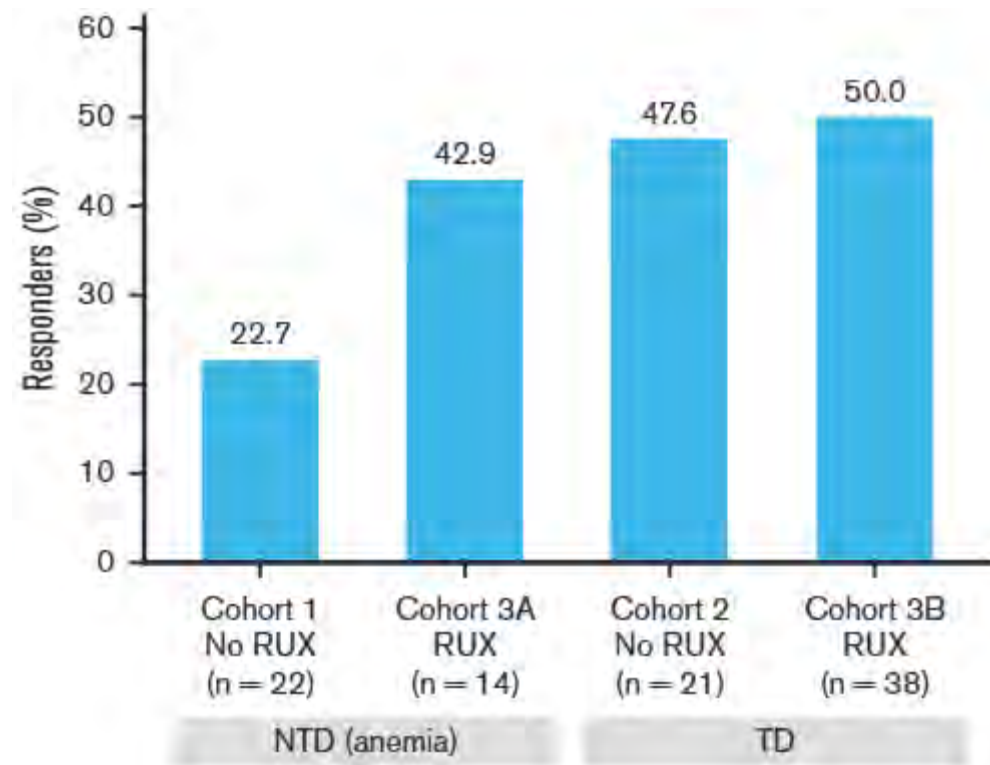


- RUX, ruxolitinib.
- Gerds AT, et al. Blood Adv. 2024;8:4511-4522.

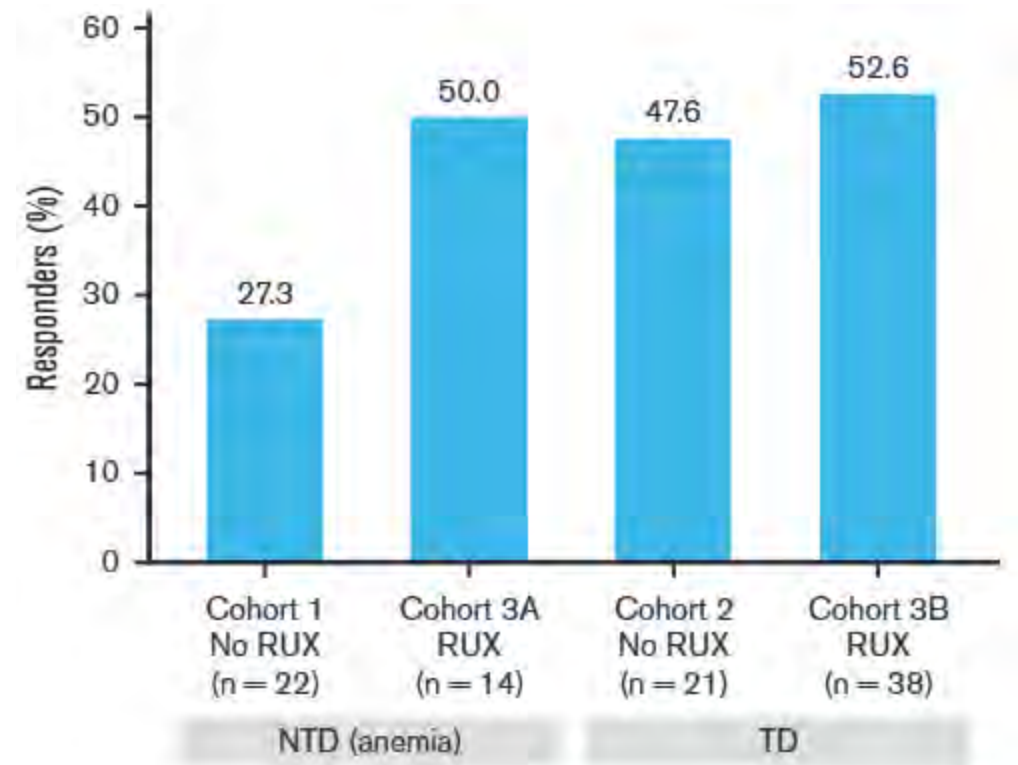
Luspatercept Induced a $\geq 50\%$ Reduction in Transfusion Burden in Approximately Half of TD Patients

- Secondary endpoints:
 - TD patients: $\geq 50\%$ reduction in RBC transfusion burden from baseline
 - NTD: mean Hb increase ≥ 1.5 g/dL Hb increase from baseline

**Primary Treatment Period
(Up to Day 169)**



Entire Treatment Period



The Phase 3 INDEPENDENCE Trial Will Assess the Role of Luspatercept for MPN-Associated MF

Screening Period (28 d)

Key Eligibility Criteria

- Age ≥ 18 y
- Diagnosis of PMF or post-ET MF or post-PV MF
- Require RBC transfusions (4-12 U/12 wk)
- Require continuous JAK2 inhibitor therapy as part of SoC therapy for ≥ 32 wk
- ECOG PS ≤ 2

Stratification factors

- RBC transfusion burden at baseline
- DIPSS score at baseline

Treatment (Estimated N = 309)

Luspatercept + BSC (n = 206)
1.33 mg/kg SC every 21 d with
titration up to 1.75 mg/kg

Luspatercept + BSC

Placebo + BSC (n = 103)
SC every 21 d

Placebo + BSC

Day 169
response assessment

Follow-Up

- **42-d follow-up period:**
AEs and hematology
- **Long-term follow-up period:**
serious AEs
- Transformation to blast phase
and other malignancies
- Survival and other
posttreatment MF therapies

Blinded core treatment period
(weeks 1-24)

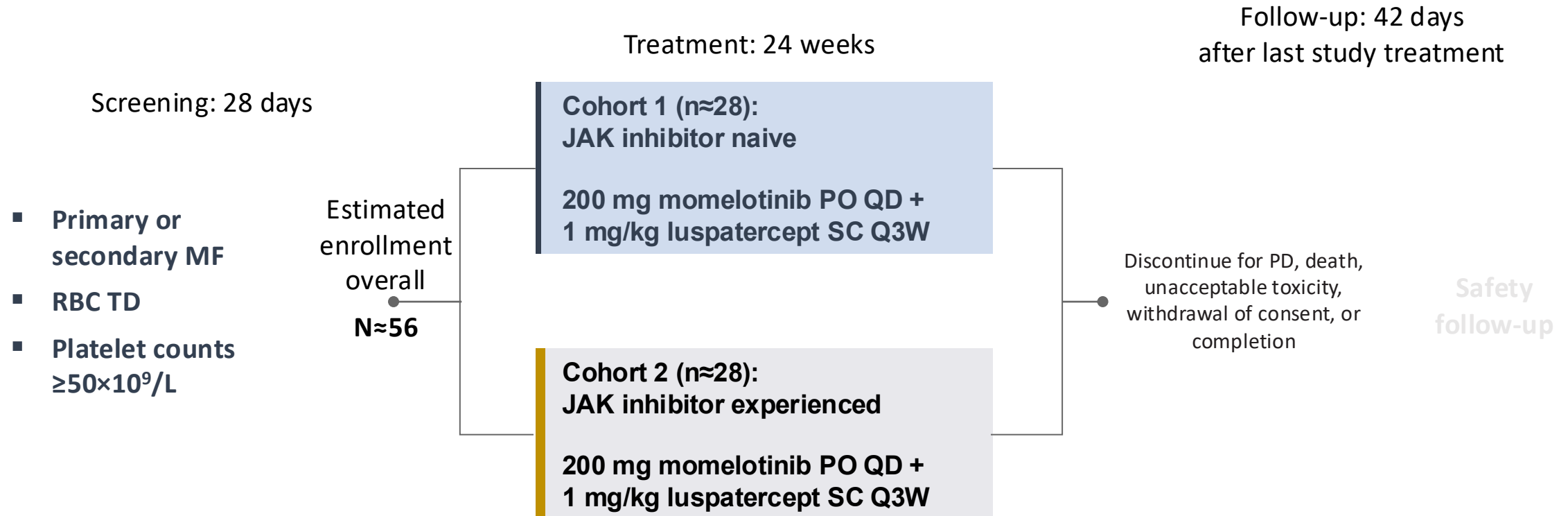
Blinded core treatment
period (weeks 25+)

Unblinded posttreatment follow-up period
(5 y after first dose or 3 y after last dose,
whichever occurs later)

Primary endpoint: proportion of patients who become RBC transfusion free over any consecutive 12-wk period

- BSC, best supportive care; DIPSS, Dynamic International Prognostic Scoring System; PS, performance status; SC, subcutaneous; SoC, standard of care.
- ClinicalTrials.gov. NCT04717414. Accessed May 22, 2025.

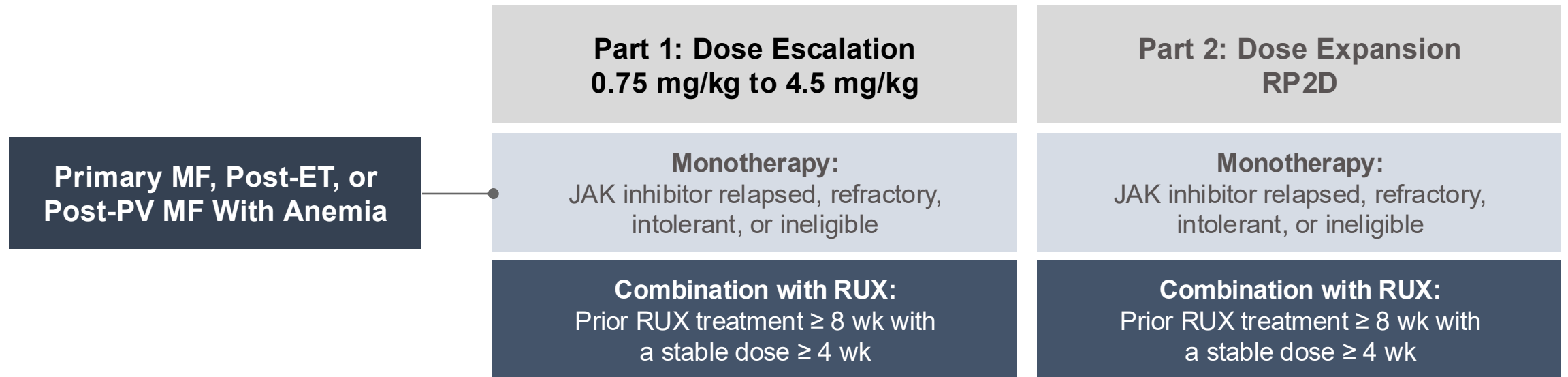
ODYSSEY: A Phase 2 Open-Label Study of Mometotinib Plus Luspatercept in TD MF



- The recommended starting dose of luspatercept is 1 mg/kg, given the acute and sustained increase in Hb levels associated with momelotinib vs decrease in Hb levels associated with ruxolitinib
- In the absence of safety concerns or rapid increase in Hb levels of ≥ 2 g/dL, up-titration to 1.33 mg/kg and up to a maximum of 1.75 mg/kg will be permitted

Elritercept With or Without RUX in Patients With MF

Phase 2 RESTORE Study Design



Key eligibility criteria:

- Transfusion dependent (TD6): received ≥ 6 RBC units/12 wk with ≥ 1 transfusion within 28 d before treatment
- Non-TD (non-TD6): BL Hb < 10 g/dL, with or without transfusions, but not meeting TD6
- Baseline platelet count ≥ $25 \times 10^9/L$

Primary endpoint:

- Evaluate the safety and tolerability of elritercept as monotherapy or in combination with RUX in patients with MF and anemia

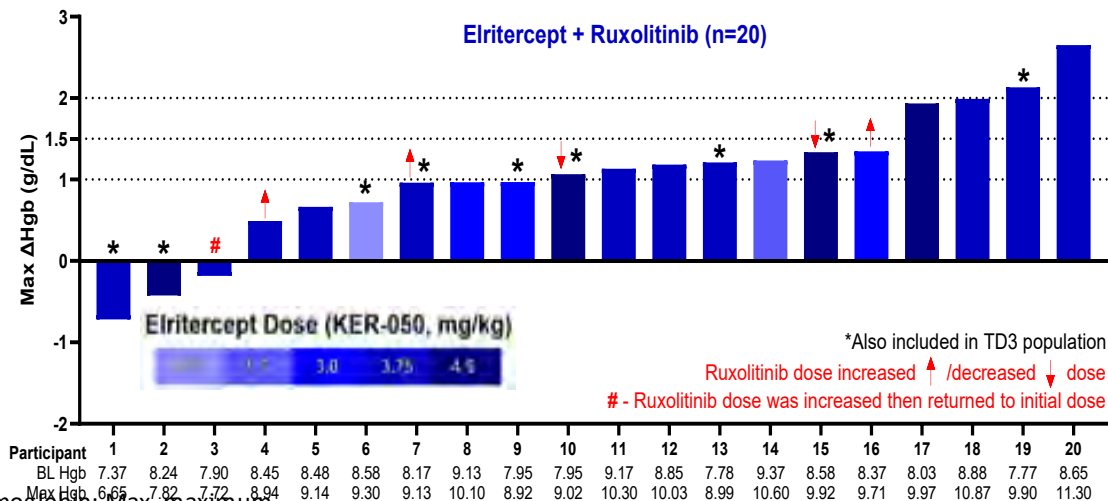
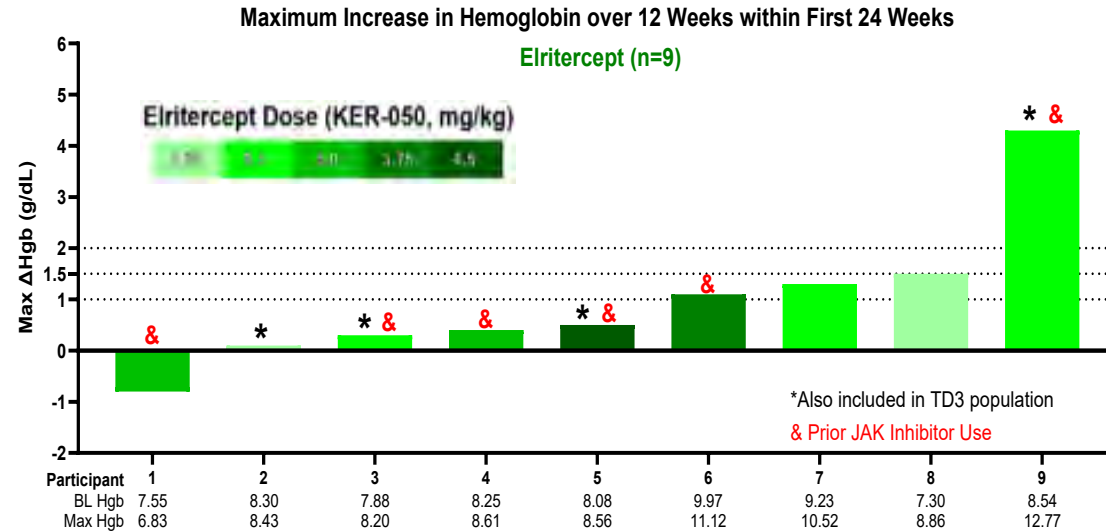
Secondary endpoints:

- Assess the effects of elritercept on anemia, spleen volume, symptom score, and exploratory biomarkers

- RP2D, recommended phase 2 dose.
- Harrison C, et al. Blood. 2024;144(suppl 1):997-998.

RESTORE

Hb Response in Monotherapy and Combination



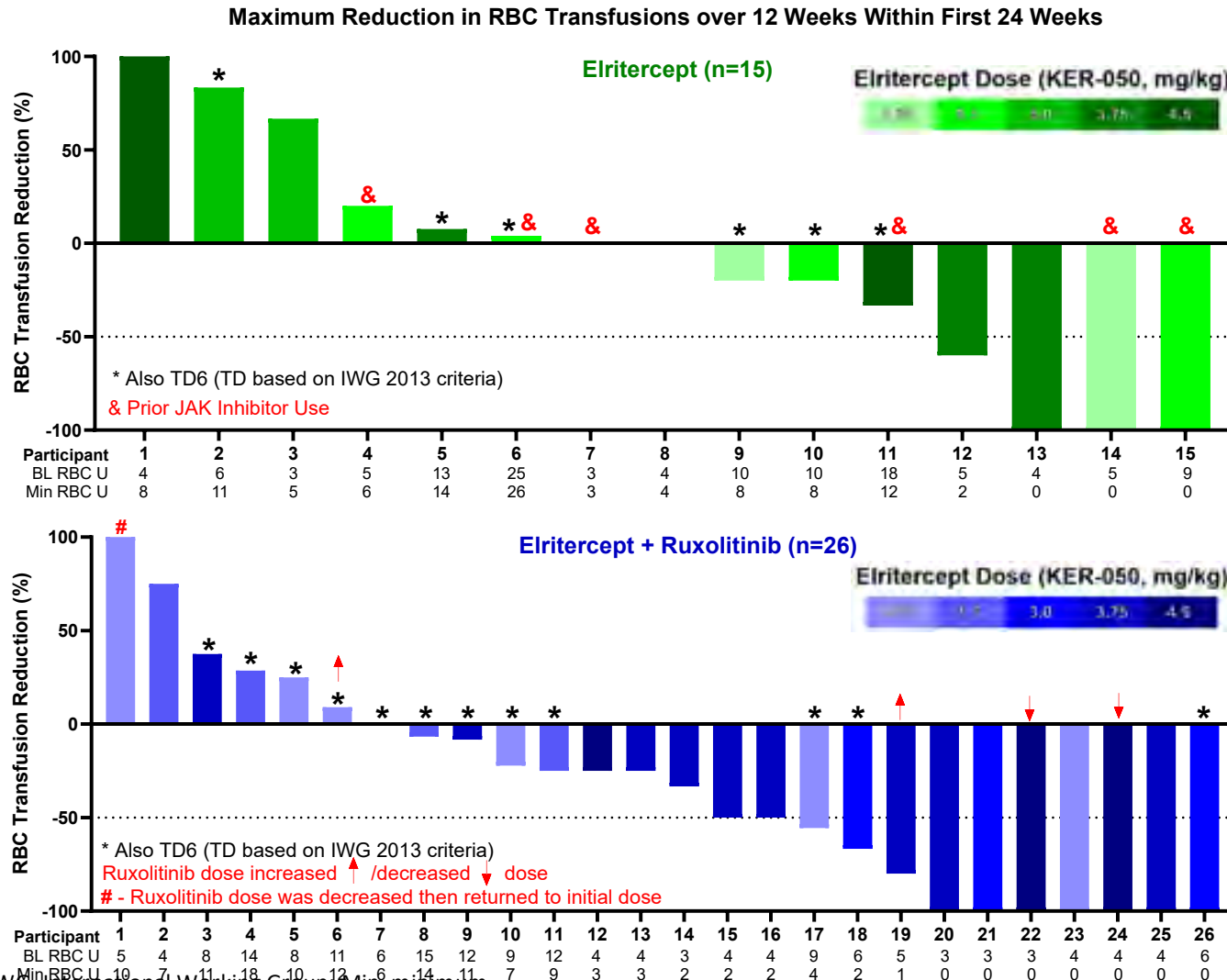
- In both the monotherapy and combination arms, increases in Hb were observed in non-TD6 participants over a 12-wk period within the first 24 wk:
 - 15/29 (51.7%) had an increase ≥ 1.0 g/dL
 - 6/29 (20.7%) had an increase ≥ 1.5 g/dL
 - 3/29 (10.3%) had an increase ≥ 2 g/dL
- For non-TD6 participants in the combination arm treated with a starting dose of elritercept of ≥ 3 mg/kg:
 - 10/18 (55.6%) had an increase ≥ 1.0 g/dL

• Hgb, hemoglobin, Max, maximum.

• Harrison C, et al. Blood. 2024;144(suppl 1):997-998.

RESTORE

Transfusion Burden Reduction in Monotherapy and Combination



- In both monotherapy and combination arms, reductions in transfusion burden were observed in TD3 participants over the first 24 wk of treatment:

- 16/41 (39%) had a reduction $\geq 50\%$
- 10/41 (24%) achieved TI

- For TD3 participants in the combination arm treated with a starting dose of elritercept of ≥ 3 mg/kg:

- 10/16 (62.5%) had a reduction $\geq 50\%$
- 6/16 (37.5%) achieved TI

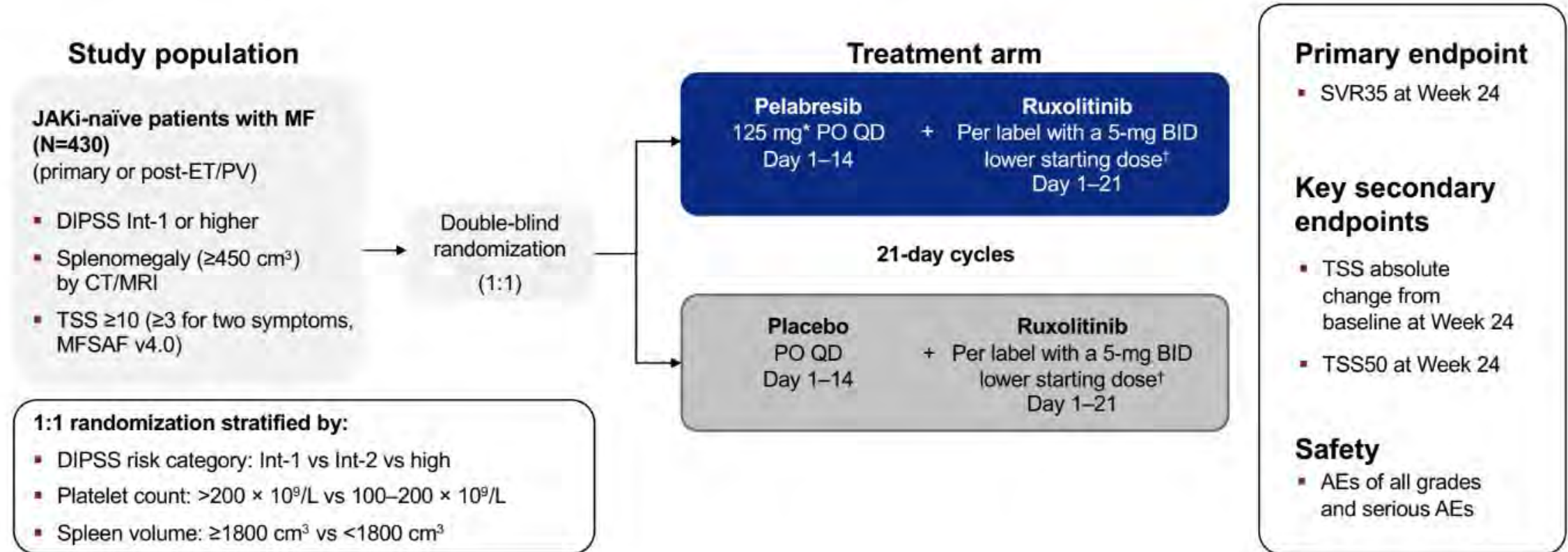
- Elritercept was generally well tolerated

- IWG, International Working Group, Min, minimum.
- Harrison C, et al. Blood. 2024;144(suppl 1):997-998.

Pelabresib Plus Ruxolitinib

Phase 3 MANIFEST-2 Study Design

- The phase 3, randomized, blinded MANIFEST-2 study evaluated the efficacy and safety of pelabresib and RUX with placebo and RUX in patients with MF who were not previously treated with JAK inhibitor

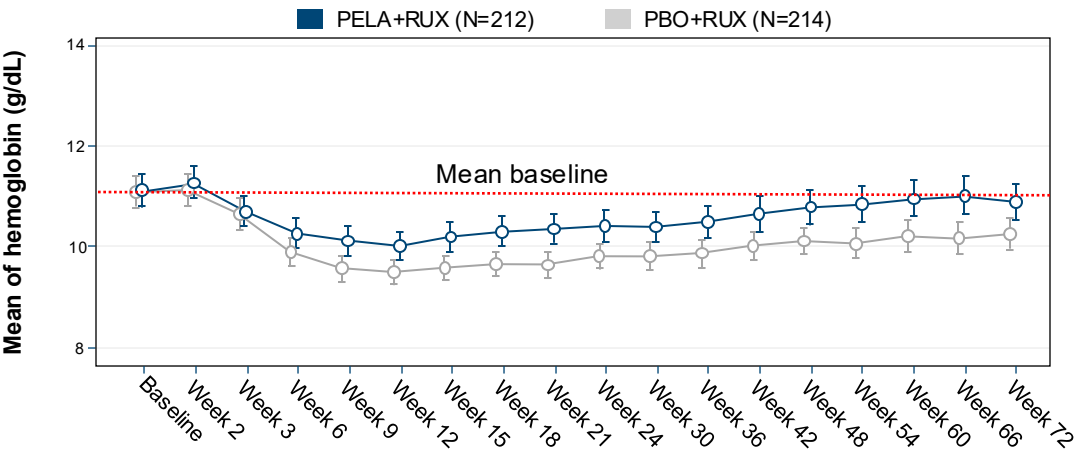


27.1% discontinued study treatment

- BID, twice daily; CT, computed tomography; Int, intermediate; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PO, by mouth; QD, once daily; SVR35, $\geq 35\%$ spleen volume reduction; TSS, total symptom score.
- Rampal RK, et al. Nat Med. 2025;31:1531-1538.

A numerically greater proportion of patients had a hemoglobin response, and fewer patients required RBC transfusions with PELA+RUX versus PBO+RUX

Hemoglobin levels in the PELA+RUX arm continued to rise, approaching baseline levels at Week 72 (safety population*)



Number of at-risk patients

PELA+RUX	212	204	209	199	193	189	186	185	184	181	171	168	162	156	148	144	139	136
PBO+RUX	214	206	211	209	207	205	204	199	196	195	185	179	175	170	161	152	145	139

ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Hemoglobin response, ^{†,‡} % (n/N) (95% CI)	16.4 (35/214) (11.4-21.31)	9.3 (20/216) (5.39-13.12)
Hemoglobin response, ^{†,‡} in patients with anemia (baseline <10 g/dL), % (n/n) (95% CI)	20.9 (14/67) (11.16-30.63)	16.9 (12/71) (8.18-25.62)

Fewer patients in the PELA+RUX arm versus the PBO+RUX arm required RBC transfusions[§] over 72 weeks:

- Weeks 0 to 24: 24.1% (35/145) versus 36.4% (59/162)
- Weeks 25 to 48: 19.3% (28/145) versus 30.9% (50/162)
- Weeks 49 to 72: 19.3% (28/145) versus 25.3% (41/162)

Data cutoff date: August 30, 2024. *Safety population received ≥1 dose of study drug. [†]Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the prior 12 weeks in the ITT population. [‡]Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. [§]RBC transfusions refer to number of patients who received any RBC transfusion during the first 24 weeks after Cycle 1 Day 1, during the 25-48 weeks after Cycle 1 Day 1 or during the 49-72 weeks after Cycle 1 Day 1. CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RBC, red blood cell; RUX, ruxolitinib.

Conclusions

- Anemia and transfusion dependency are frequent conditions in MF
- Anemia represents an unmet medical need
- MMB can reduce transfusion burden and increase hemoglobin levels
- New anti anemia agents are under investigation