



Strategie condivise
per la Mielofibrosi

23 giugno 2025 • Milano

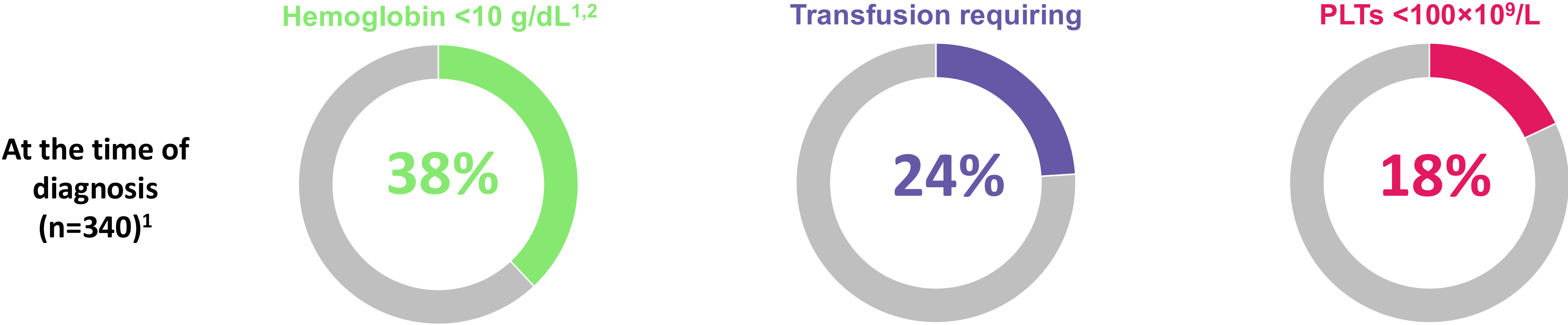
Unmet medical needs nei pazienti con mielofibrosi e anemia

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di CATANIA

Rates of Anemia and Thrombocytopenia Increase Over Time in Patients With Primary Myelofibrosis



The data shown are based on patients with primary myelofibrosis seen at the Mayo Clinic between November 4, 1977, and September 1, 2011.
PLT, platelet.
1. Tefferi A, et al. *Mayo Clin Proc.* 2012;87(1):25-33. 2. Cervantes F, et al. *Blood.* 2009;113(13):2895-901.

“Clinical needs” oriented current therapy for MF

Clinical need	Drugs / Intervention	
Anemia	• Corticosteroids • Danazol	• Thalidomide • Lenalidomide • Erythropoietin
Symptomatic splenomegaly	• Hydroxyurea	• Cladribine, IMiDs • Splenectomy
Extramedullary hematopoiesis	• Radiation therapy	
<i>Hyperproliferative (early) disease</i>	• Interferon, Hydroxyurea	
Risk of thrombosis	• Low-dose ASA	
Constitutional symptoms/ QoL	• Corticosteroids	
<i>Accelerated/blastic Phase</i>	• Hypomethylating agents	
Improved survival	• Allo SCT	

“Clinical needs” oriented current therapy for MF

Clinical need	Drugs / Intervention	
Anemia	• JAKi (Mometotinib) • Corticosteroids • Danazol	• Thalidomide • Lenalidomide • Erythropoietin
Symptomatic splenomegaly	• JAKi • Hydroxyurea	• Cladribine, IMiDs • Splenectomy
Extramedullary hematopoiesis	• Radiation therapy	
<i>Hyperproliferative (early) disease</i>	• Interferon, Hydroxyurea	
Risk of thrombosis	• Low-dose ASA	
Constitutional symptoms/ QoL	• JAKi • Corticosteroids	
<i>Accelerated/blastic Phase</i>	• Hypomethylating agents	
Improved survival	• Allo SCT • JAKi (Ruxolitinib)	

Modified from Barbui T, et al. J Clin Oncol. 2011;29:761-770.



Myelofibrosis Treatment Approach

Prognostication*
(IPSS/DIPSS/-plus) vs (MIPSS70s)

Allogeneic Stem Cell Transplant

Allogeneic HSCT is the only potentially curative treatment option but is applicable only to a minority of the patients^{1,2}

- The **EBMT** and **ELN** produced **consensus-based guidelines** for the indication and management of allogeneic HSCT in myelofibrosis¹
- Eligible patients should be **referred early** for discussions on transplant²

Patient selection¹

Intermediate-1 or 2 or high risk: DIPSS, MIPSS70, or MIPSS70-plus

Low- or intermediate-risk MTSS score^a

Biological age: allogeneic HSCT on an individual basis, balancing patient preferences and disease-associated and patient-associated features

Age and/or comorbidities

Timing of transplant

Spleen size/volume reduction

JAK inhibitors

Phase of disease

Donor type and stem cell source

Conditioning regimen

Mutational status

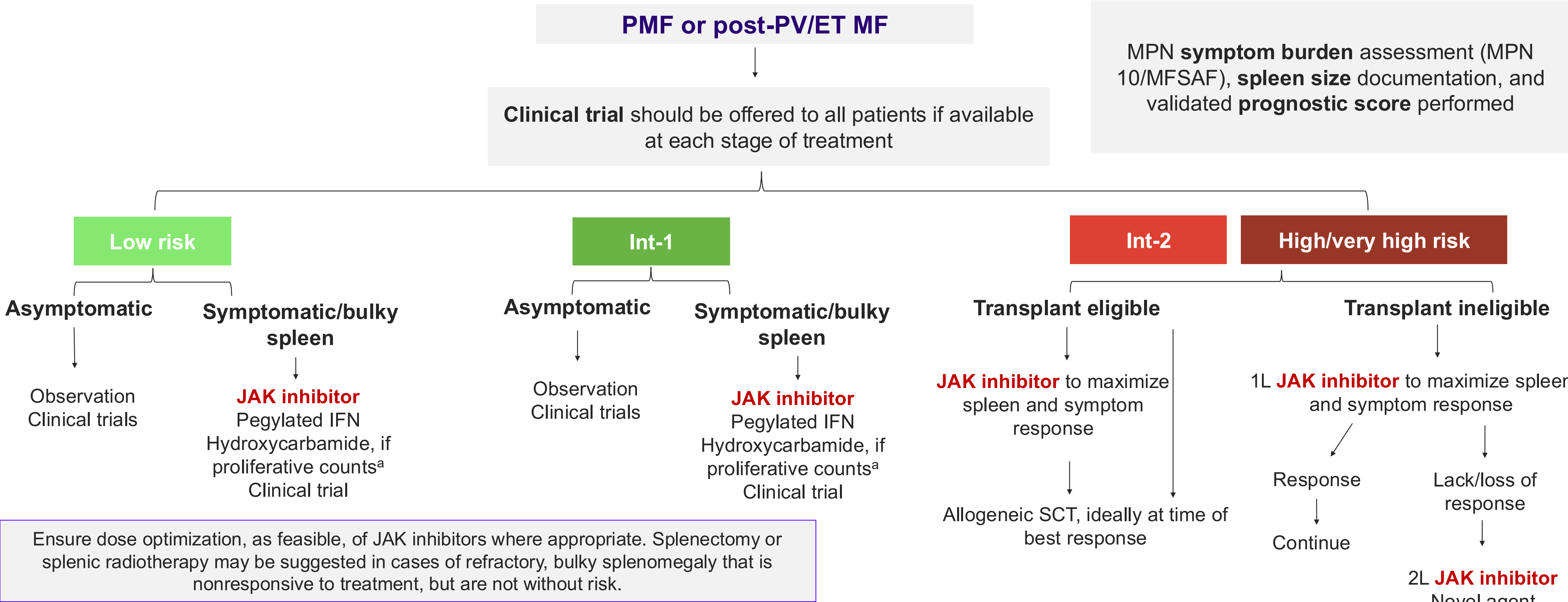
Patient/disease/treatment factors

Post-allogeneic HSCT outcomes

DIPSS, Dynamic International Prognostic Scoring System; EBMT, European Society for Blood and Marrow Transplantation; ELN, European LeukemiaNet; HSCT, hematopoietic stem cell transplant; JAK, Janus kinase; MIPSS, Mutation-Enhanced International Prognostic Score System; MTSS, Myelofibrosis Transplant Scoring System.

^a MTSS identifies patient risk level after allogeneic HSCT by including transplant-specific risk factors, such as donor source and Karnofsky index or the DIPSS.

British Society for Haematology Guidelines for Patients With Myelofibrosis



Speaker’s personal opinion adapted from McLornan DP, et al. Br J Haematol. 2024;204:136-150. Copyright © 2023 British Society for Haematology and John Wiley & Sons Ltd.

1L, first line; 2L, second line; ET, essential thrombocythemia; IFN, interferon; int, intermediate; JAK, Janus kinase; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera; SCT, stem cell transplant.

^a For example, white cell count of >50×10⁹/L.

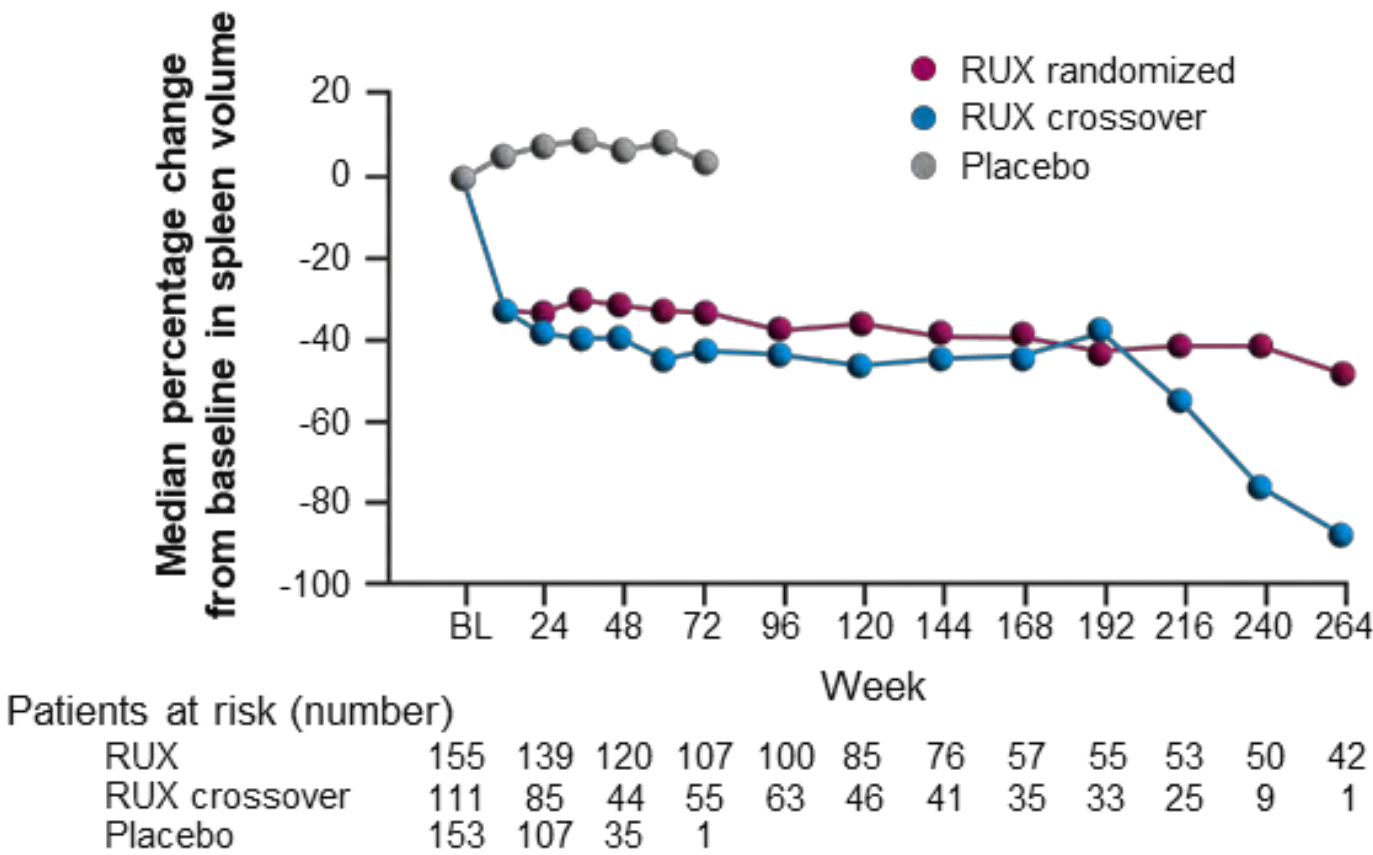


What Are the Benefits of Ruxolitinib in Myelofibrosis?

Splenomegaly

Evidence of therapeutic benefit based on SVR35

COMFORT-I Study: Randomized, double-blind, placebo-controlled, phase 3 study | 5-year analysis | n=309

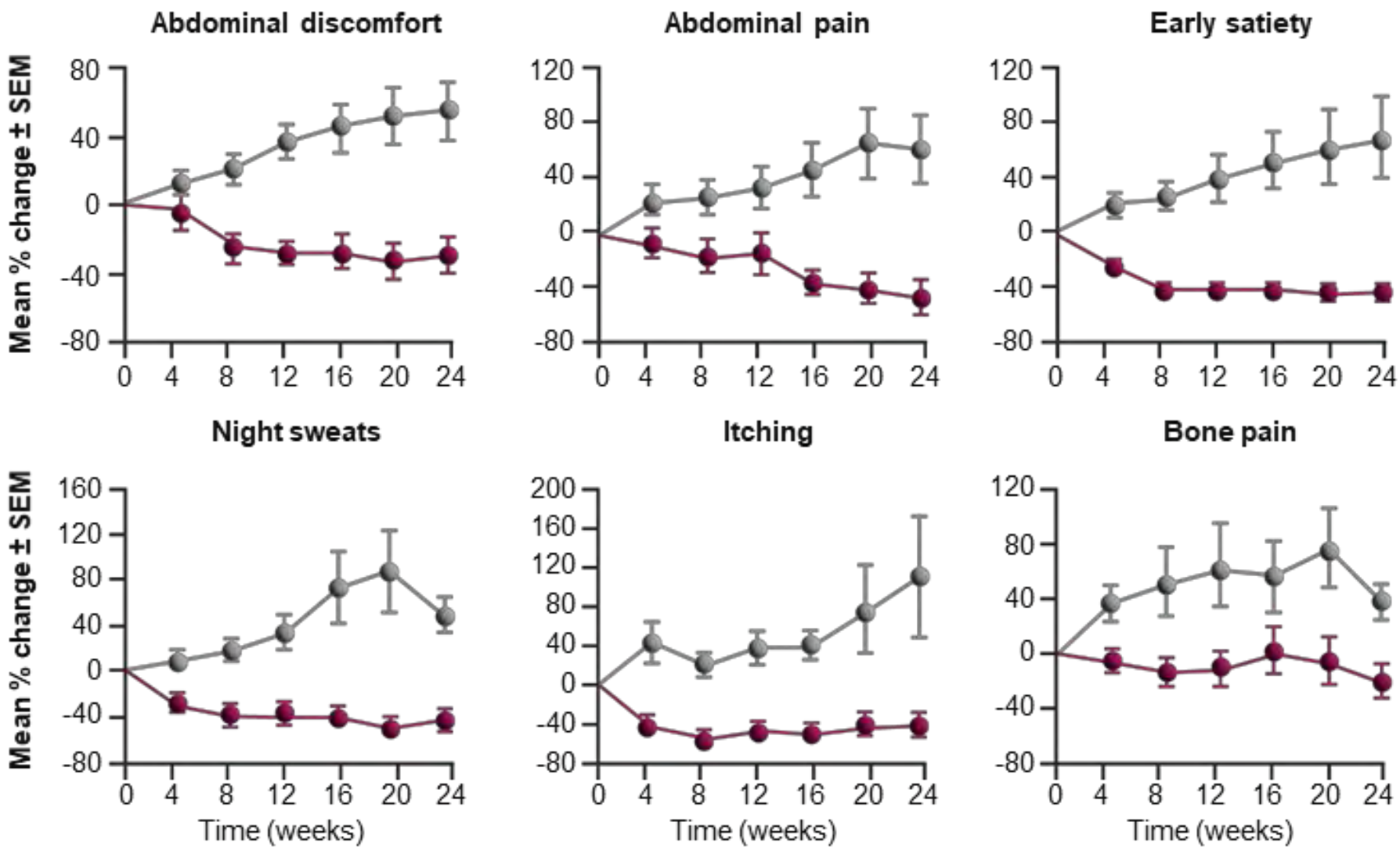


Among patients originally randomized to RUX, 59.4% (92/155) achieved a $\geq 35\%$ reduction in spleen volume at any time during the study
50% of patients maintained the response at 5 years

Symptoms

Evidence of therapeutic benefit based on TSS50

COMFORT-I Study

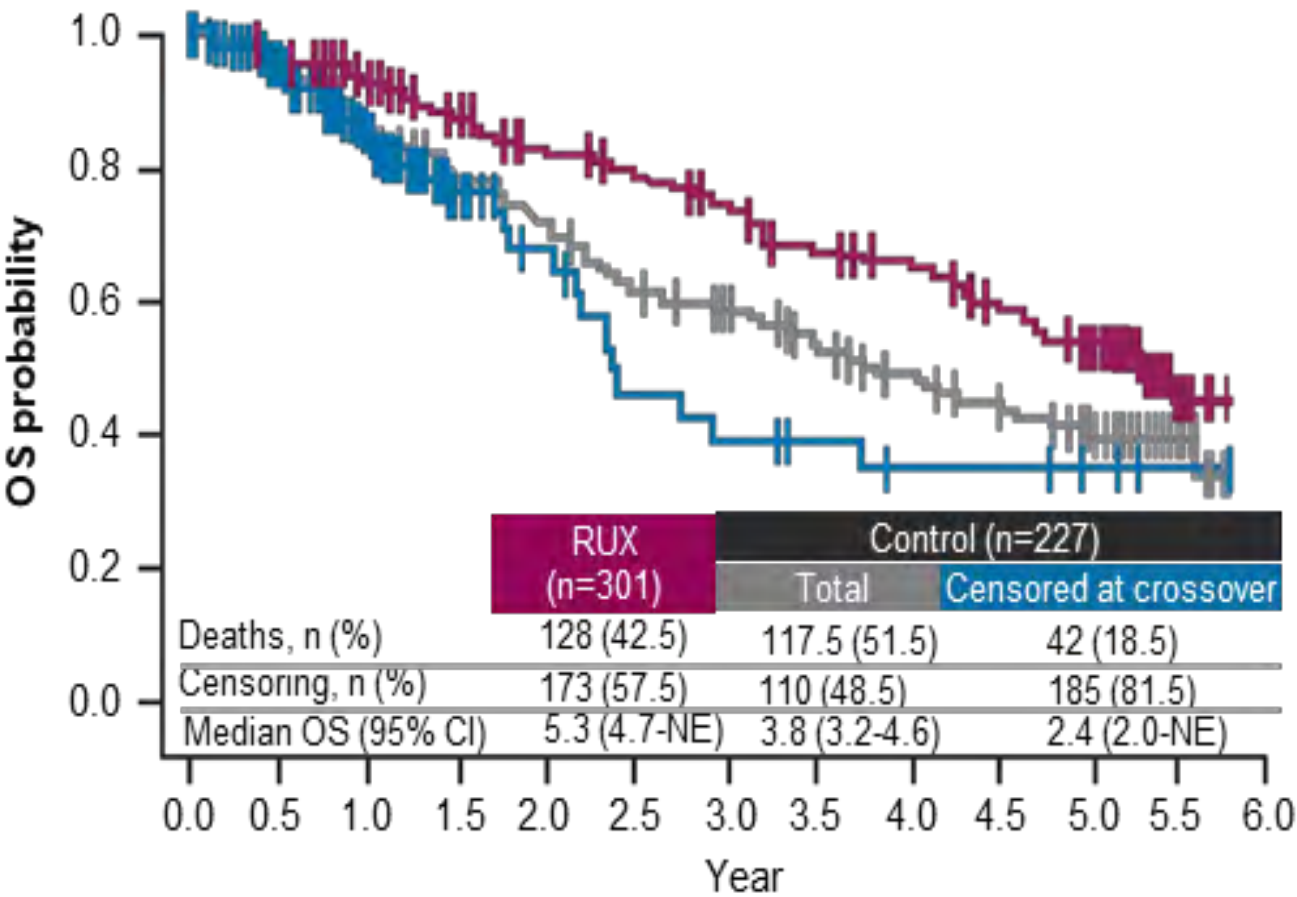


Individual symptom scores, as assessed by the modified MFSAF v2.0 at each 4-week timepoint in patients receiving RUX, showed **improvement relative to baseline**

Survival

Some evidence of survival benefit for ruxolitinib

COMFORT I and COMFORT-II Studies (Randomized, open-label, active-controlled, phase 3 study with crossover) | 5-year pooled analysis of overall survival

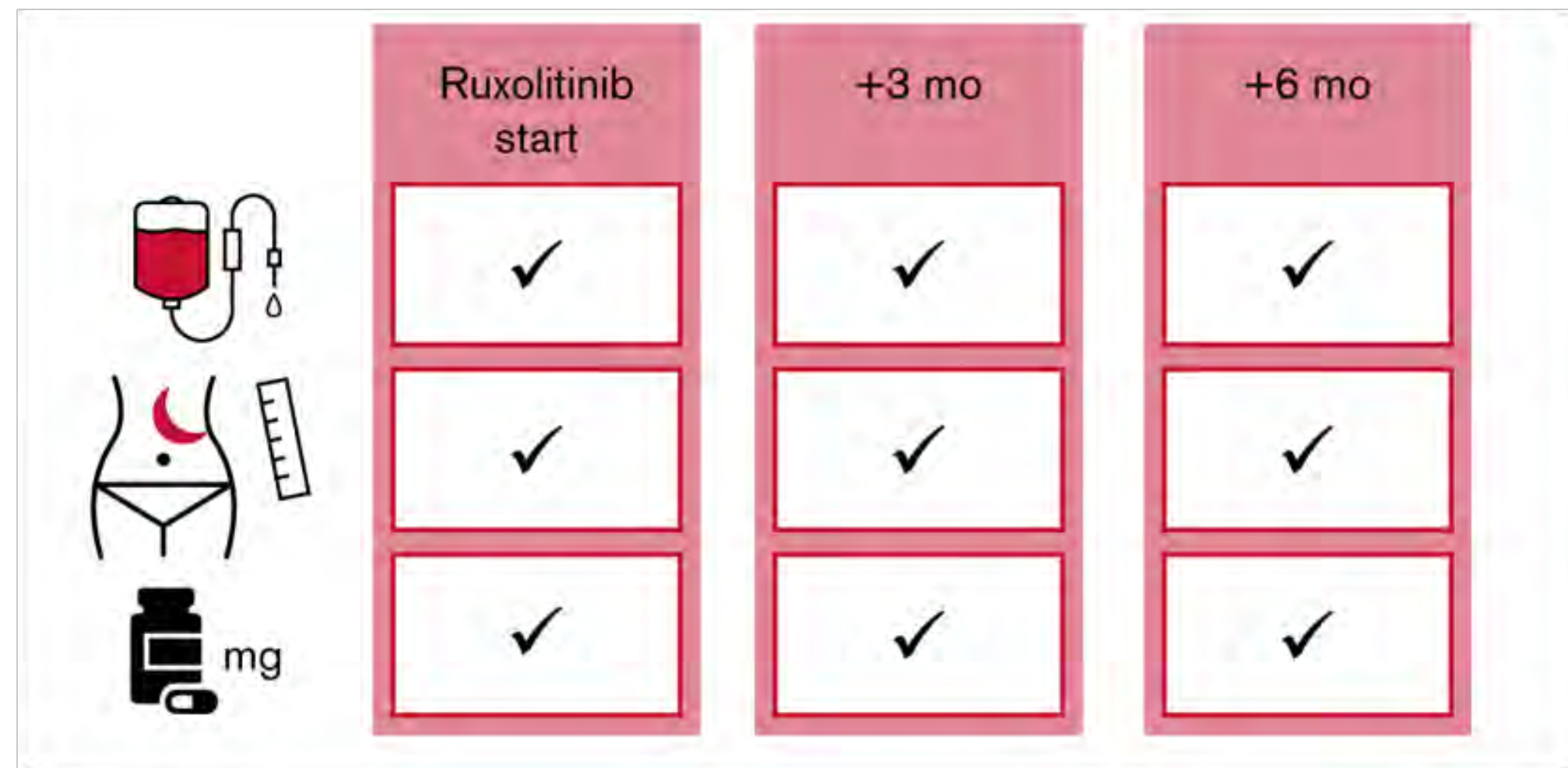


MFSAF, myelofibrosis symptom assessment form; RUX, ruxolitinib; SVR35, $\geq 35\%$ spleen volume reduction from baseline; TSS50, $\geq 50\%$ improvement in Total Symptom Score from baseline.

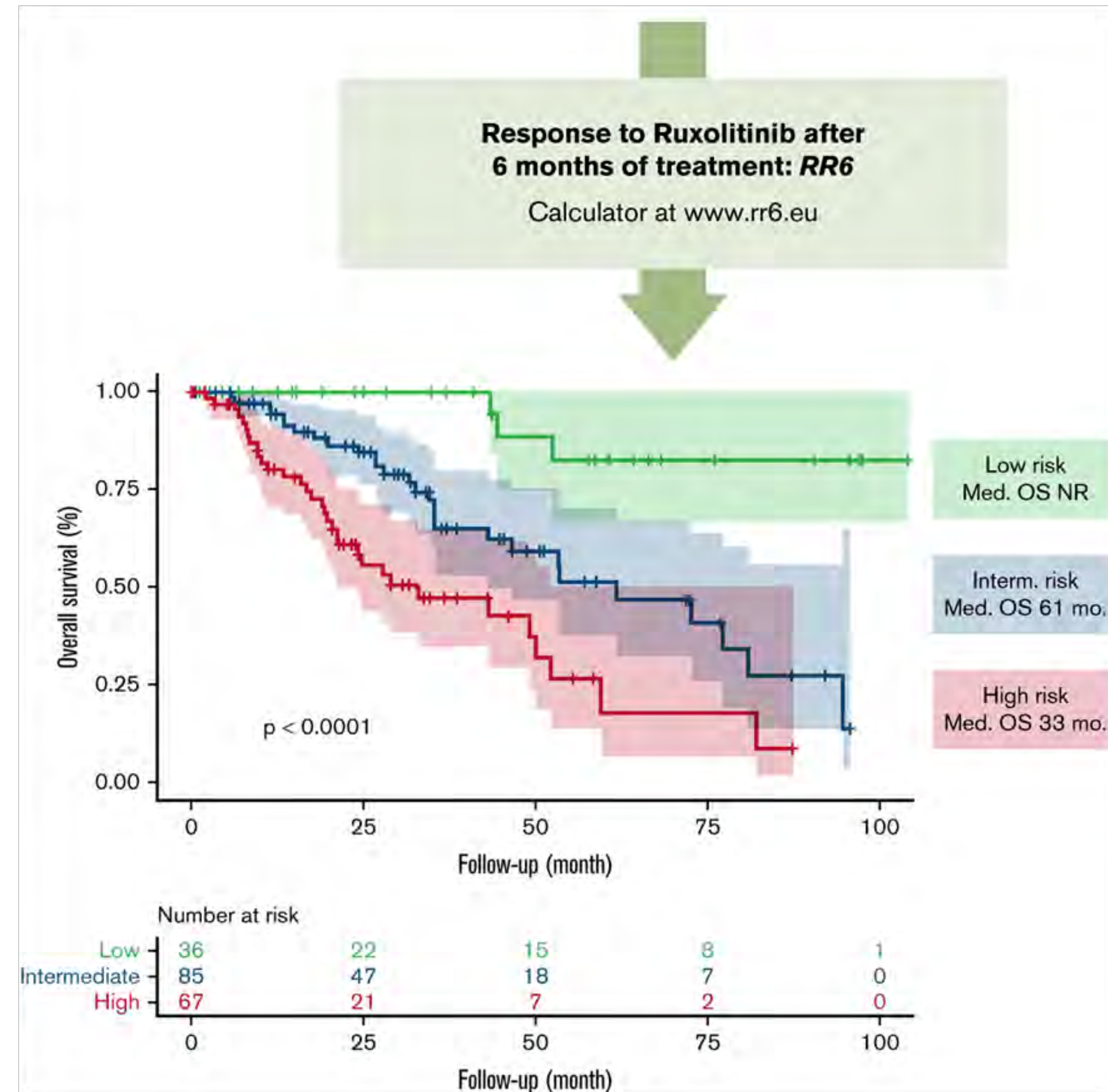
[1] JAKAFI (ruxolitinib). U.S. Prescribing Information. January 2023. [2] JAKAVI (ruxolitinib). Summary of Product Characteristics. May 2022. [3] Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55. [4] ClinicalTrials.gov COnTrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment: The COMFORT-I Trial. Available at: <https://clinicaltrials.gov/ct2/show/NCT00952289>. Accessed June 2, 2023. [5] Mesa RA, et al. *J Clin Oncol*. 2013;31(10):1285-1292. [6] Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):156. [7] ClinicalTrials.gov Controlled Myelofibrosis Study With Oral Janus-associated Kinase (JAK) Inhibitor Treatment-II: The COMFORT-II Trial. Available at: <https://clinicaltrials.gov/ct2/show/NCT00934544>. Accessed June 2, 2023.



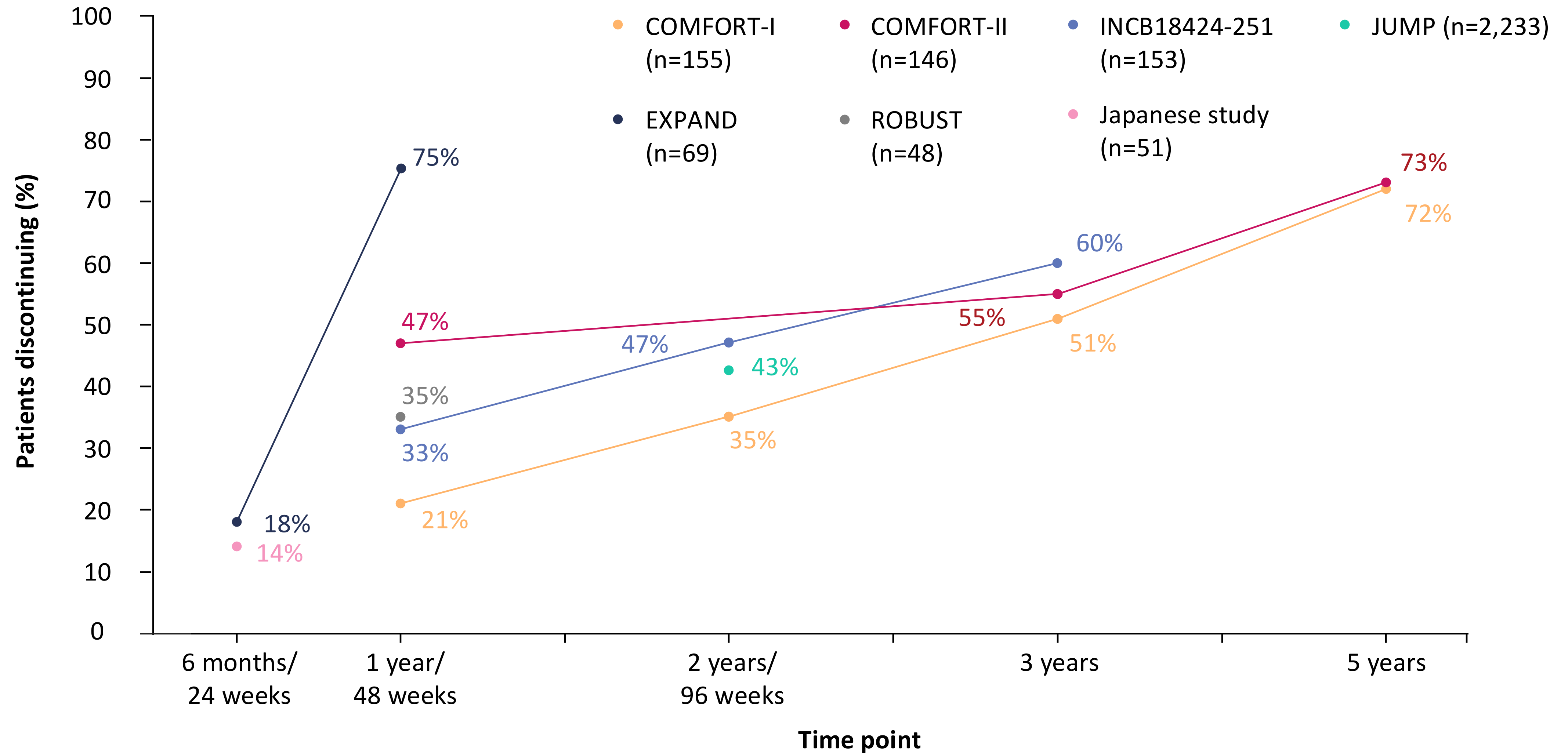
A prognostic model to predict survival after 6 months of ruxolitinib in patients with MF



RBC transfusion need at all time points (ie, baseline and months 3 and 6; HR, 2.32; 95% CI, 1.19-4.54; $P = .02$)

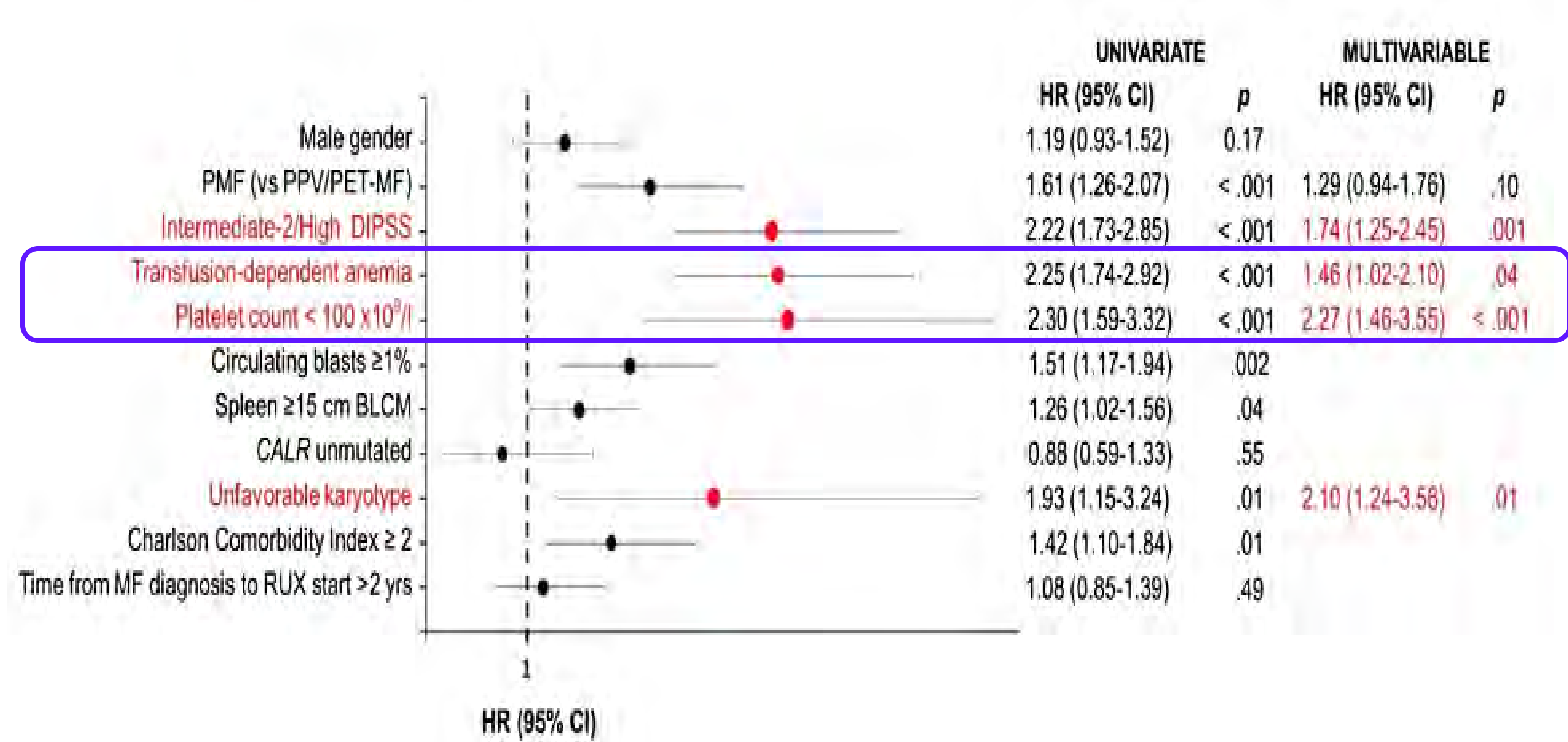


Rates of ruxolitinib discontinuation at various time points in clinical trials



Real-World Evidence on Ruxolitinib Use

Baseline Risk Factors for Ruxolitinib Discontinuation

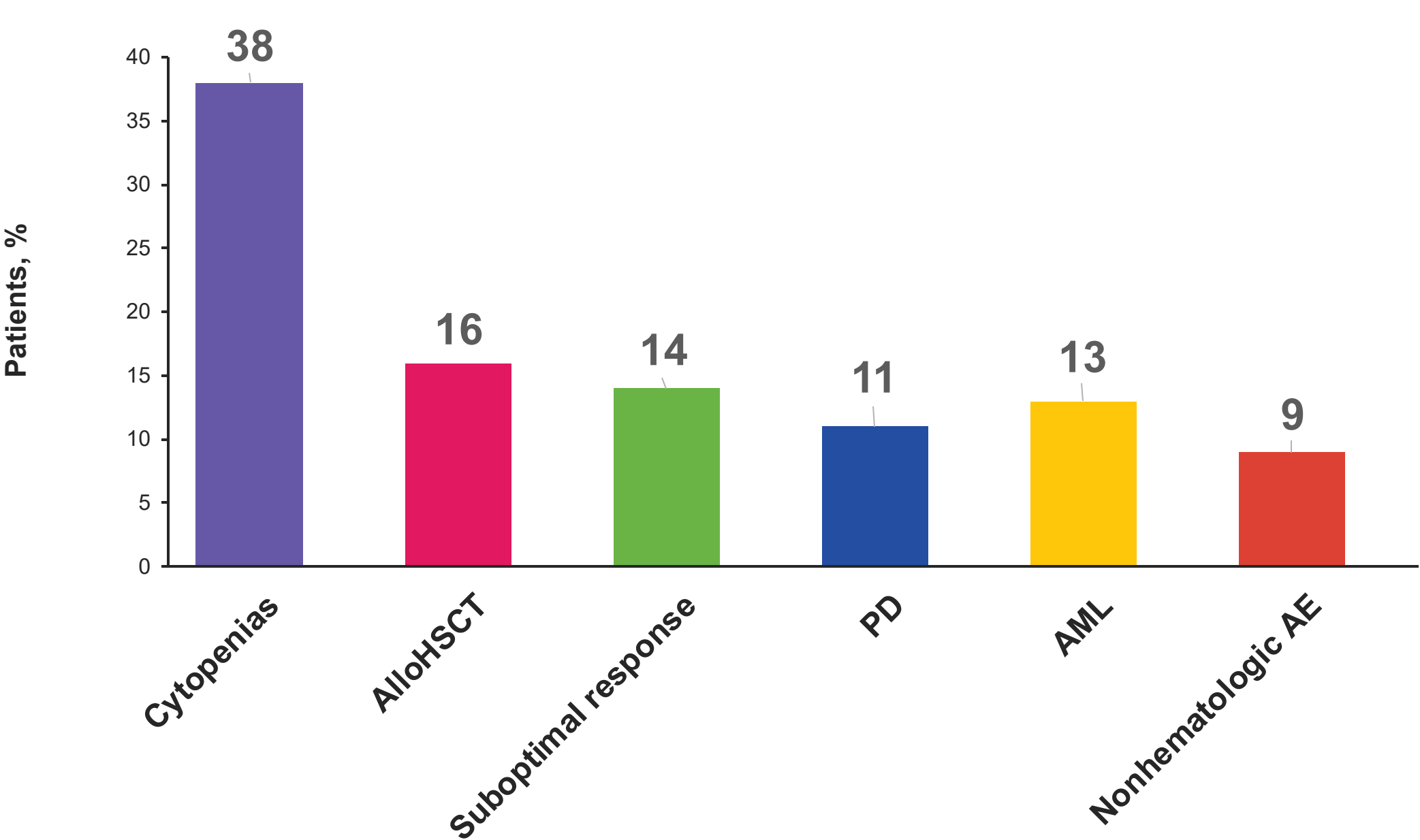


BLCM indicates below the left costal margin; PMF, primary myelofibrosis; PPV/PET-MF, postpolycythemia vera/postessential thrombocythemia myelofibrosis.

The 3 top clinical reasons for stopping ruxolitinib in patients with MF in chronic phase: inadequately controlled splenomegaly (including the lack or loss of a spleen response; 34.8%), **anemia/thrombocytopenia (17.4%)**, and infectious events (9.2%)

Palandri F et al. Cancer. 2020 Mar 15;126(6):1243-1252.

Real-World Study Showing Reasons for Ruxolitinib Discontinuation

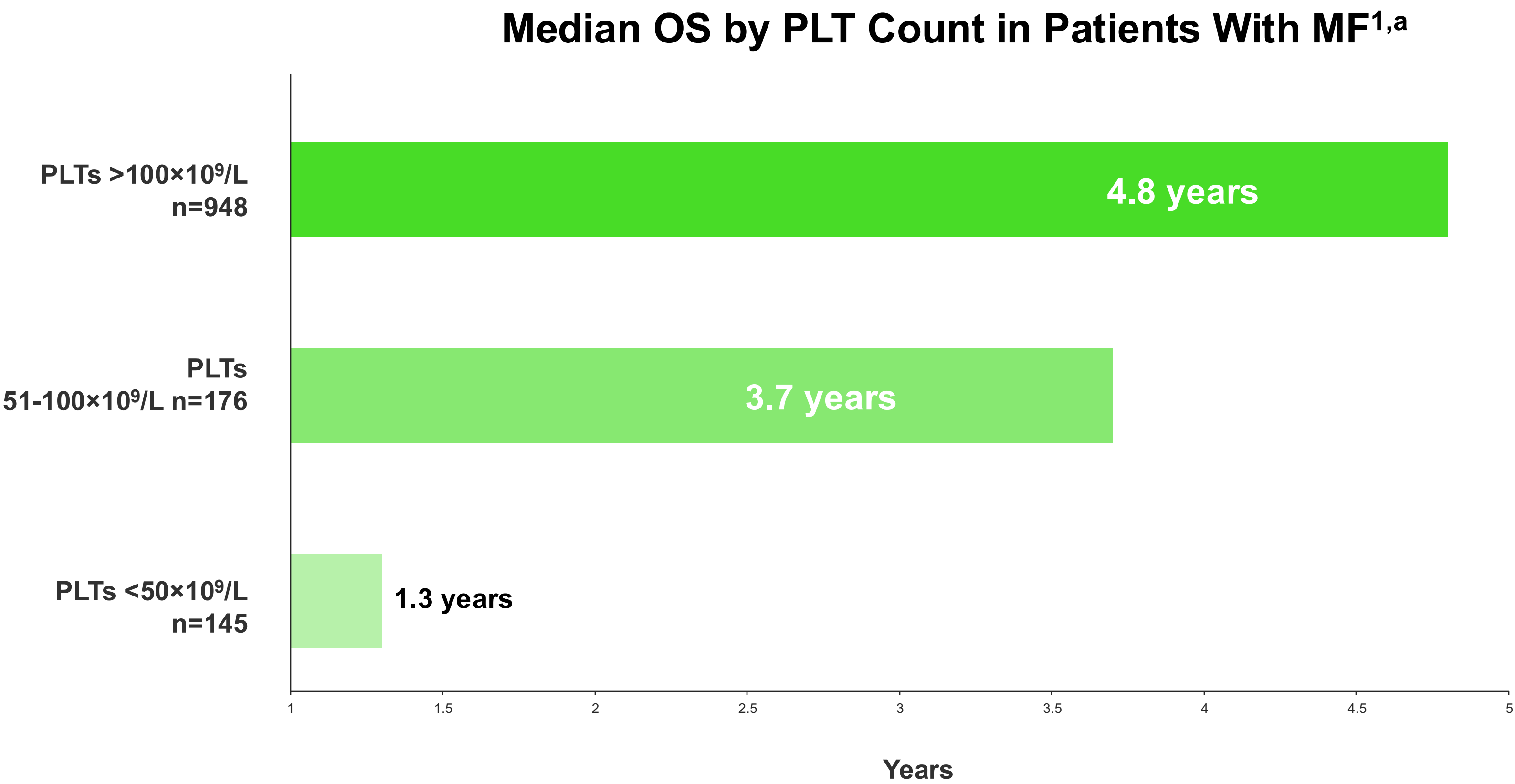


AE, adverse event; alloHSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukaemia; PD, progressive disease; PLT, platelet.

In a real-world analysis, the most common reason for ruxolitinib discontinuation was cytopenias (n=24; 38%). Most commonly due to anemia (n=21; 33%)

Kuykendall AT. Ann Hematol. 2018;97(3):435-441.

Thrombocytopenia at Diagnosis Is Independently Associated With Reduced Survival in Patients With Myelofibrosis



MF, myelofibrosis; OS, overall survival; PLT, platelet.

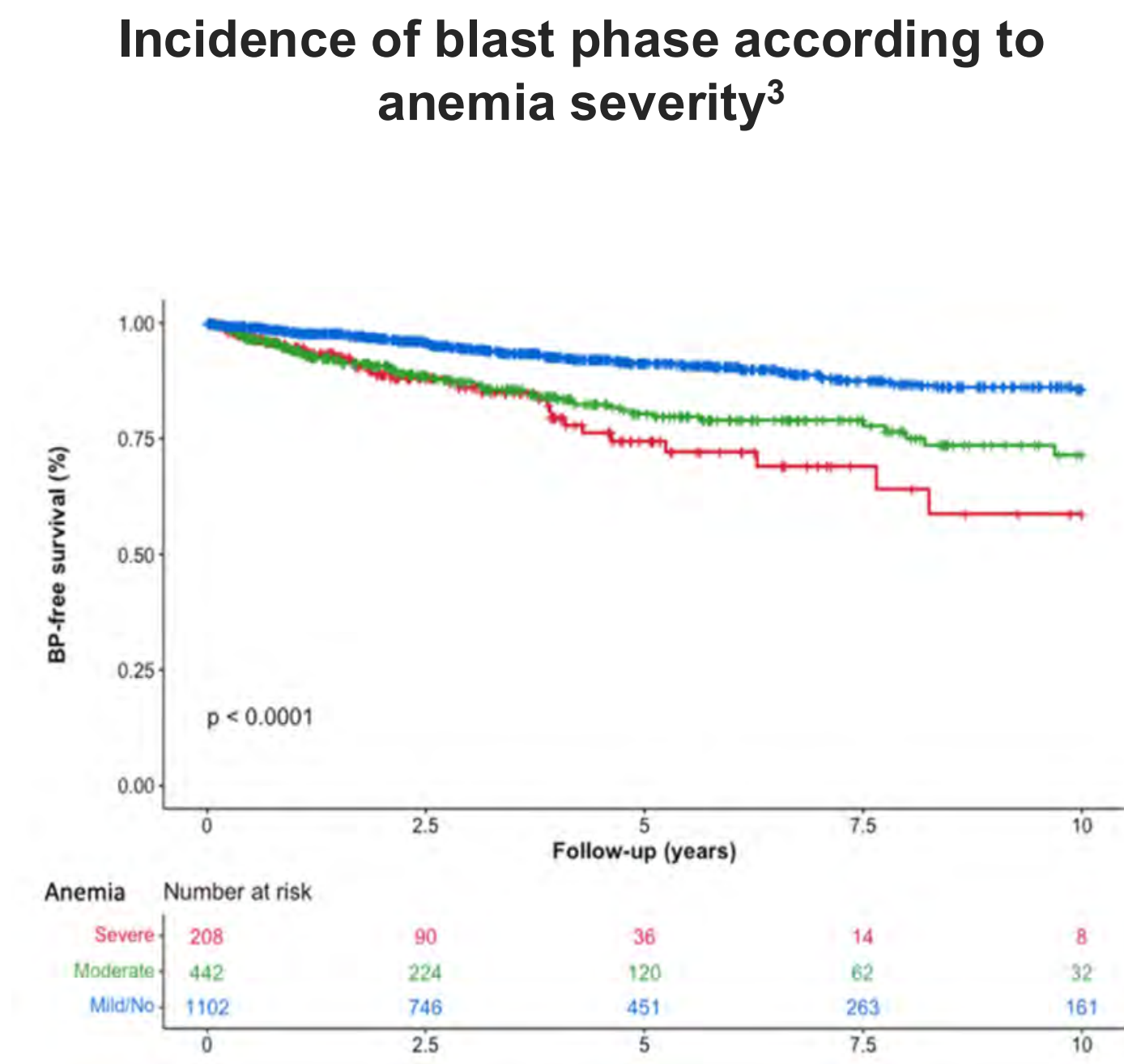
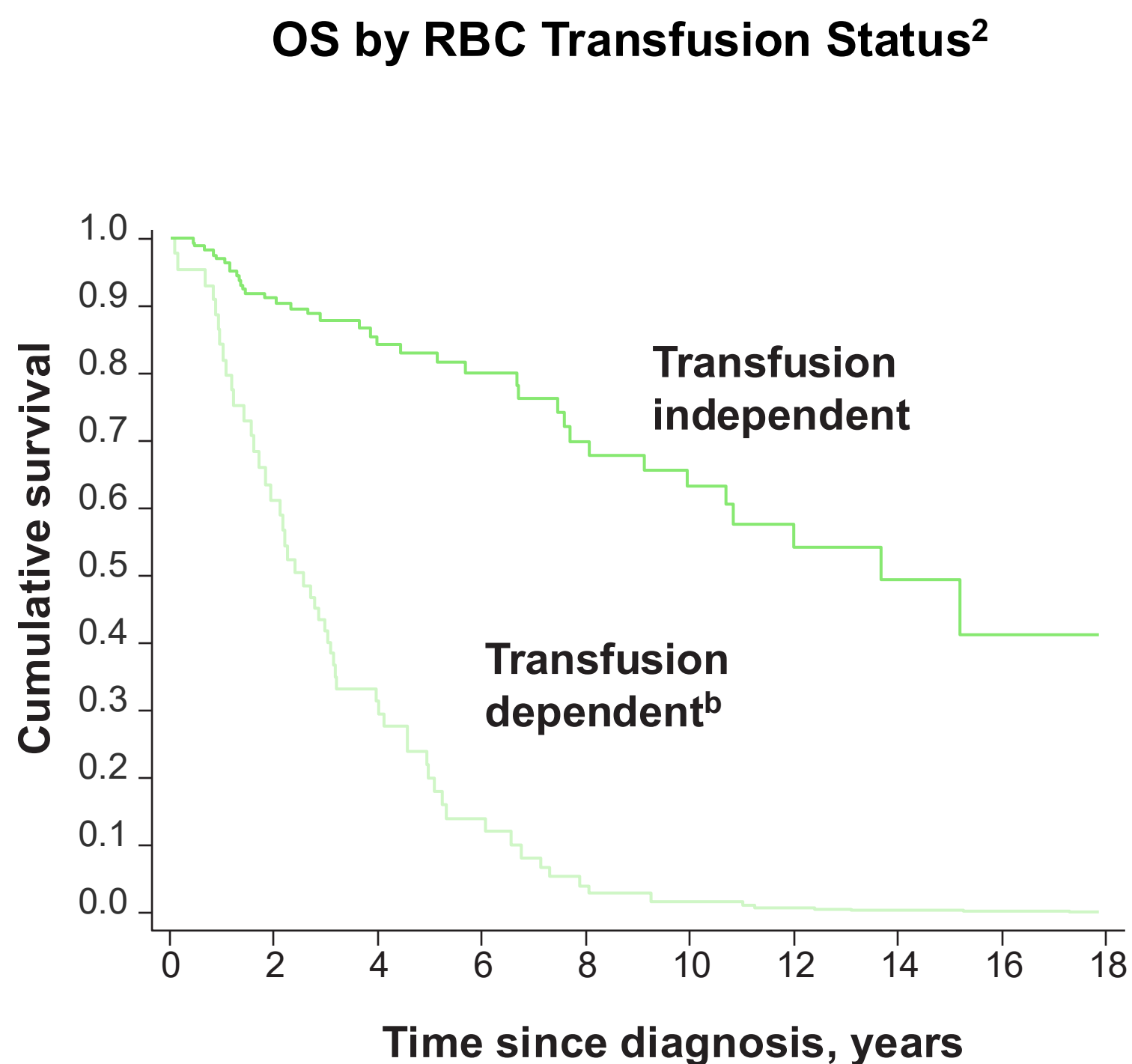
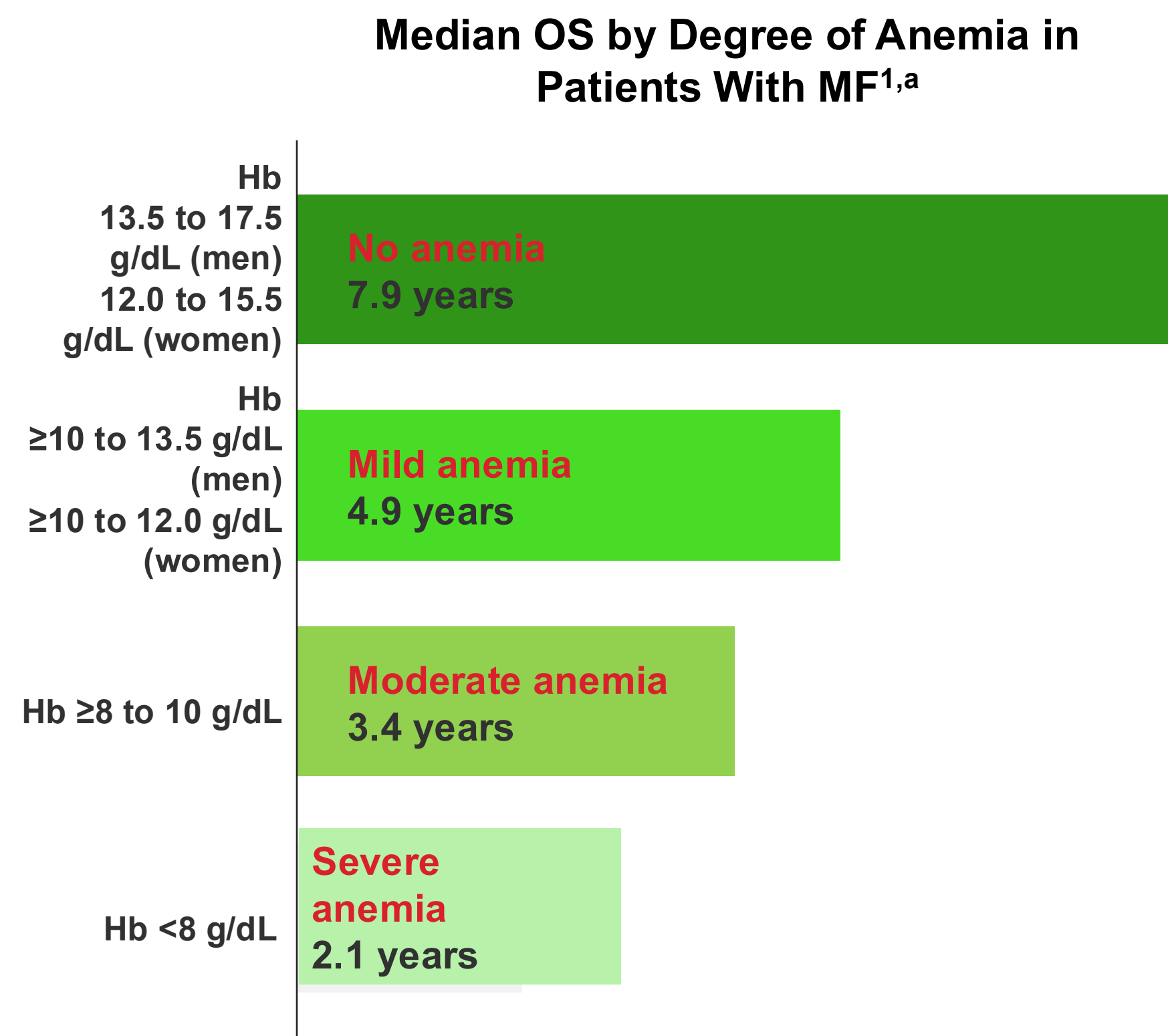
^a Data are based on ≈1100 patients with MF included in the Mayo Clinic, MN, USA, institutional databases. DIPSS risk distribution was 11% high, 43% intermediate-2, 34% intermediate-1, and 12% low

^a Includes patients with primary or secondary MF.

1. Masarova L, et al. Eur J Haematol. 2018;100(3):257-263.



Anemia is Independently Associated With Reduced Survival in Patients With Myelofibrosis



Hb, hemoglobin; MF, myelofibrosis; OS, overall survival; RBC, red blood cell.
^a Data are based on ≈1100 patients with MF included in the Mayo Clinic, MN, USA, institutional databases. DIPSS risk distribution was 11% high, 43% intermediate-2, 34% intermediate-1, and 12% low. ^b Transfusion dependency was defined as the onset of regular transfusion requirement to correct anemia (at least one unit per month)². ^c Includes patients with primary or secondary MF.

1. Nicolosi M, et al. Leukemia. 2018;32(5):1254-1258. 2. Elena C, et al. Haematologica. 2011;96(1):167-170. 3. Mora B et al. Eur J Haematol 2023;4(3):679-689



Prognostic Scores in Myelofibrosis

Risk factor	Prognostic Score System				
	IPSS ¹	DIPSS ²	DIPSS-Plus ³	MIPSS70 ⁴	MIPSS70-Plus ⁴
Age >65 years	✓	✓	✓		
Constitutional symptoms	✓	✓	✓	✓	✓
Hb <10 g/dL	✓	✓	✓	✓	✓
Leukocyte count >25×10 ⁹ /L	✓	✓	✓	✓	
Circulating blasts ≥1%	✓	✓	✓	✓	✓
Platelet count <100×10⁹/L			✓	✓	
RBC transfusion need			✓		
Unfavorable karyotype			✓		
Absence of CALR mutations				✓	✓
HMR category				✓	✓
≥2 HMR mutations				✓	✓
Bone marrow fibrosis grade ≥2				✓	

1. Cervantes F, et al. Blood. 2009;113(13):2895-2901. 2. Passamonti F, et al. Blood. 2010;115(9):1703-1708. 3. Gangat N, et al. J Clin Oncol. 2011;29(4):392-397.
 4. Guglielmelli P, et al. J Clin Oncol. 2018;36(4):310-318



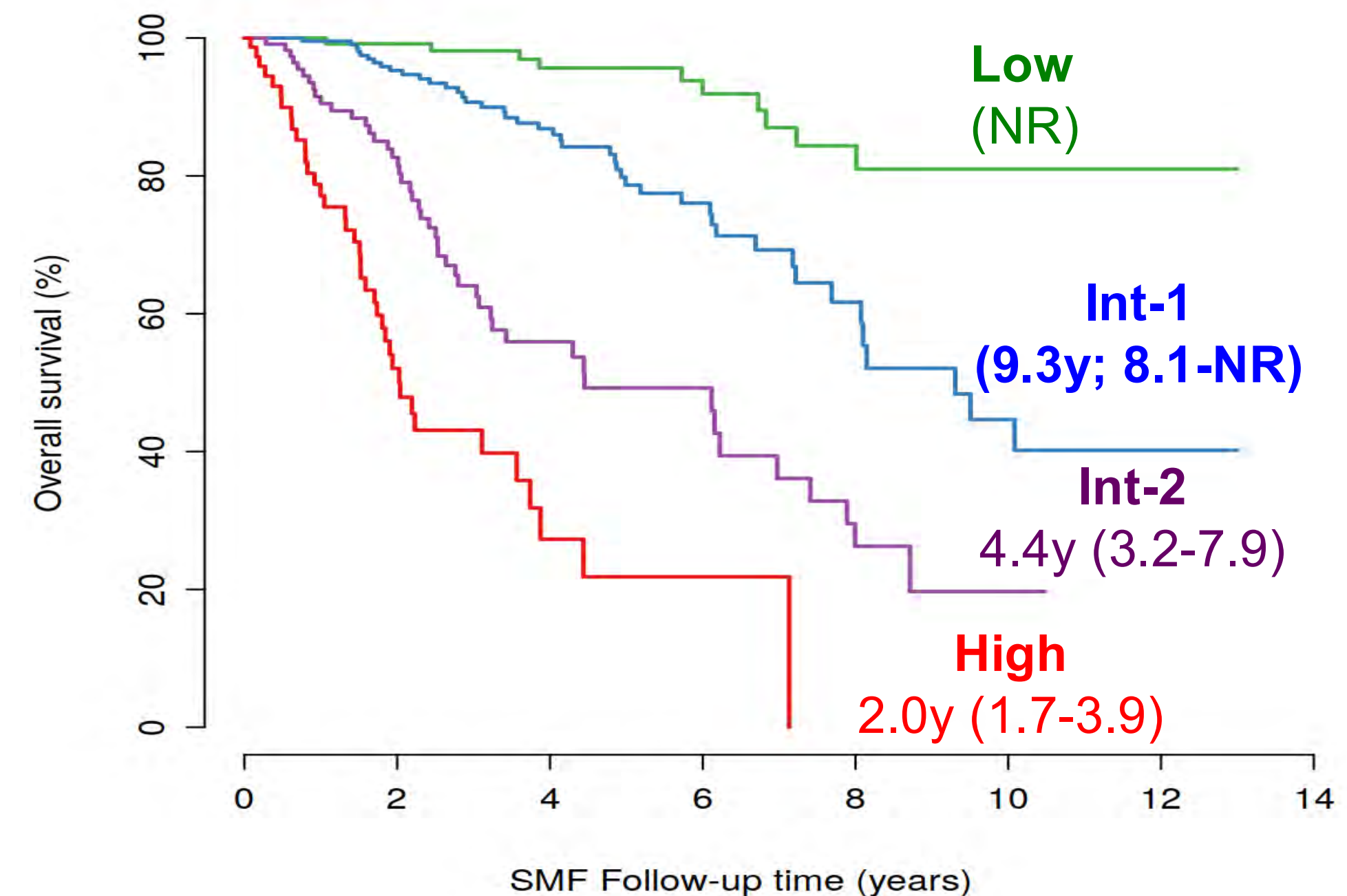
MYSEC (MYelofibrosis SECondary to PV and ET)-MF: a Molecular-Enriched Prognostic Model

A clinical-molecular prognostic model for predicting survival in secondary Myelofibrosis

- Includes 685 patients, 397 with PET-MF and 384 with PPV-MF

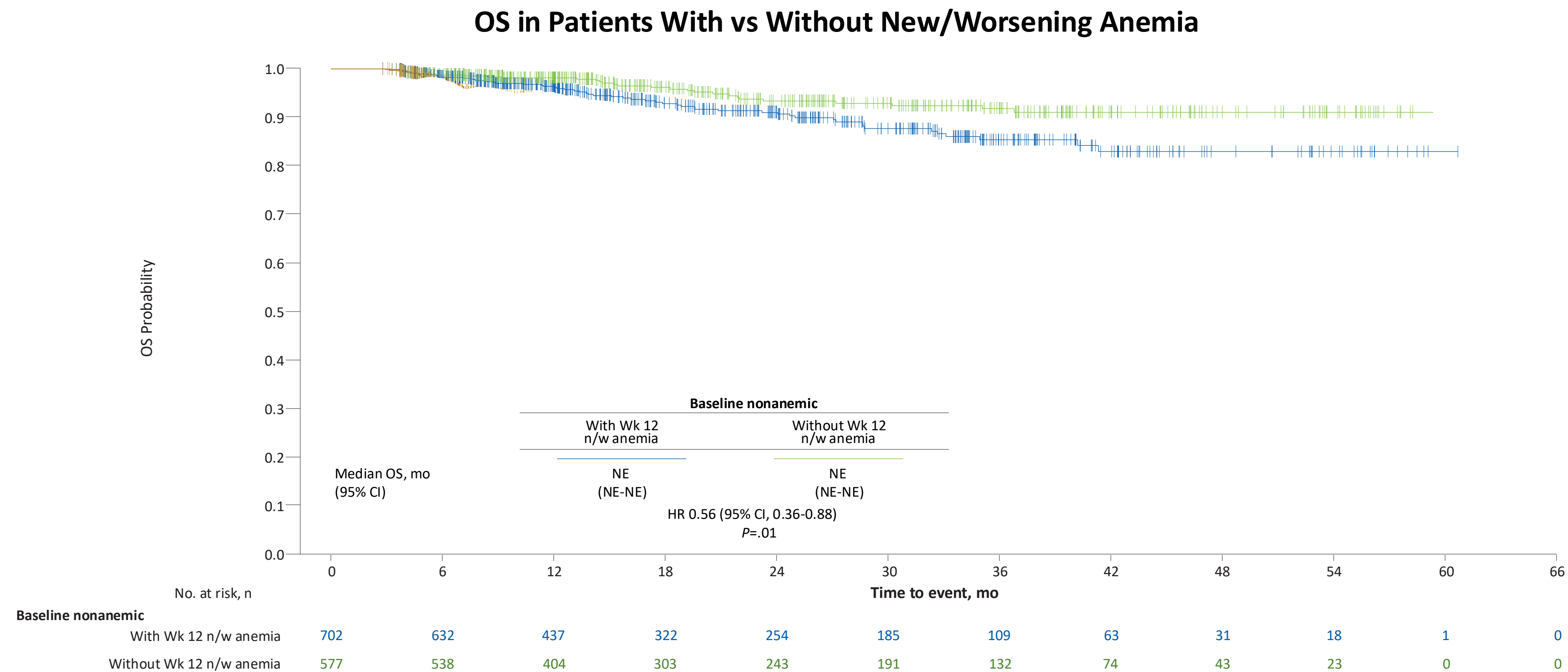
Covariate	HR (95% CI)	P value	Points
Age at MF dx*	1.07 (1.05-1.09)	<.0001	0.15
Hb <11 g/dL	2.3 (1.6-3.3)	<.0001	2
Plt <150x10⁹/L	1.7 (1.2-2.5)	.006	1
PB blasts ≥3%	2.9 (1.8-4.8)	<.0001	2
<i>CALR</i> wt	2.6 (1.2-5.3)	.001	2
Const. symptoms	1.5 (1.0-2.0)	.03	1

* continuous, 0.15 point/year



- Of the HMR mutations, *SRSF2* mutation was significant for reduced OS in PET-MF

Ruxolitinib: Post Hoc Analysis of the JUMP Expanded-Access Phase 3b Trial in Patients With and Without New/Worsening Anemia at Week 12 of Treatment



Reprinted from Gupta V, et al. Blood. 2023;142 (Suppl 1):5174. Copyright © 2023 The American Society of Hematology. Published by Elsevier Inc.

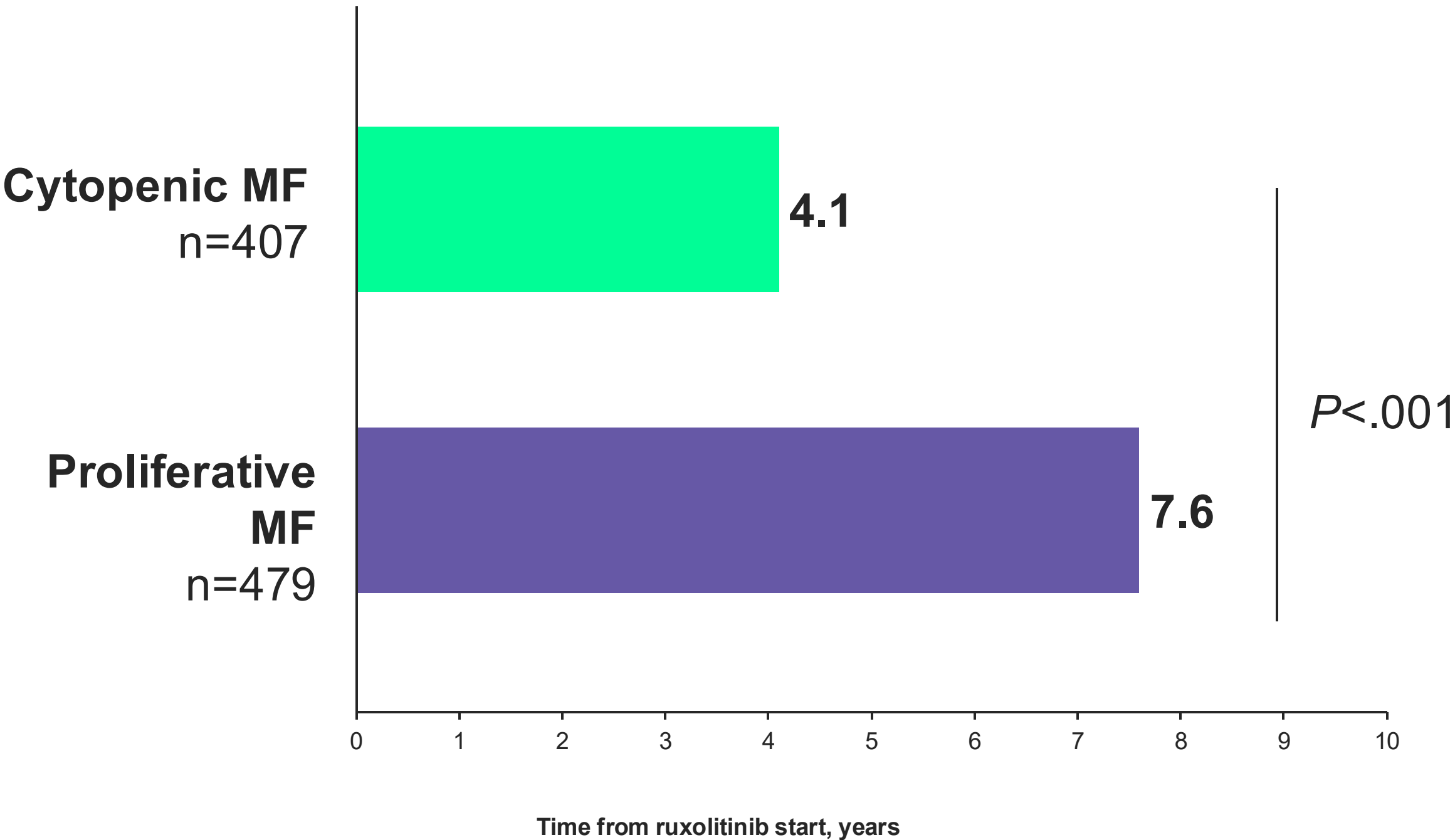
BID, twice daily; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; Hb, hemoglobin; HR, hazard ratio; Int, intermediate; MF, myelofibrosis; NE, not estimable; n/w, new or worsening; OS, overall survival; PLT, platelet; SLR, spleen length response; Wk, week.

^a Outcomes were stratified by the presence or absence of new or worsening anemia following ruxolitinib initiation, defined as Hb $\geq$ 1.5 g/dL decrease from baseline, or new transfusion requirement at weeks 4, 8, or 12. ^b Nonanemic defined as Hb >10 g/dL.



Ruxolitinib Retrospective Study (EU): Clinical Outcomes for Cytopenic vs Myeloproliferative MF at Baseline

Median OS in Patients With Cytopenic vs Proliferative MF Treated With Ruxolitinib^a



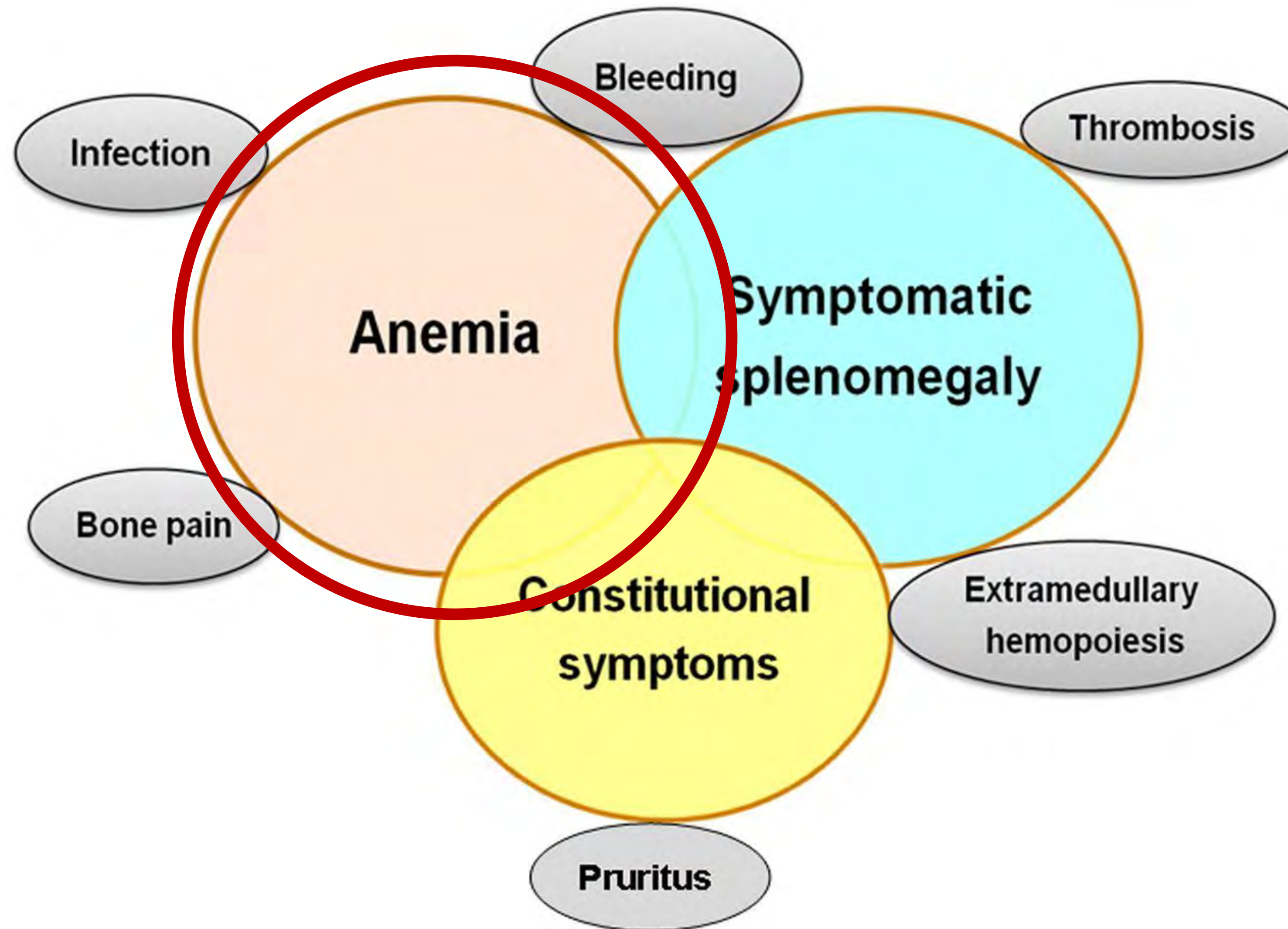
Retrospective study of outcomes in 886 ruxolitinib-treated patients with MF.

MF, myelofibrosis; OS, overall survival; RUX, ruxolitinib.

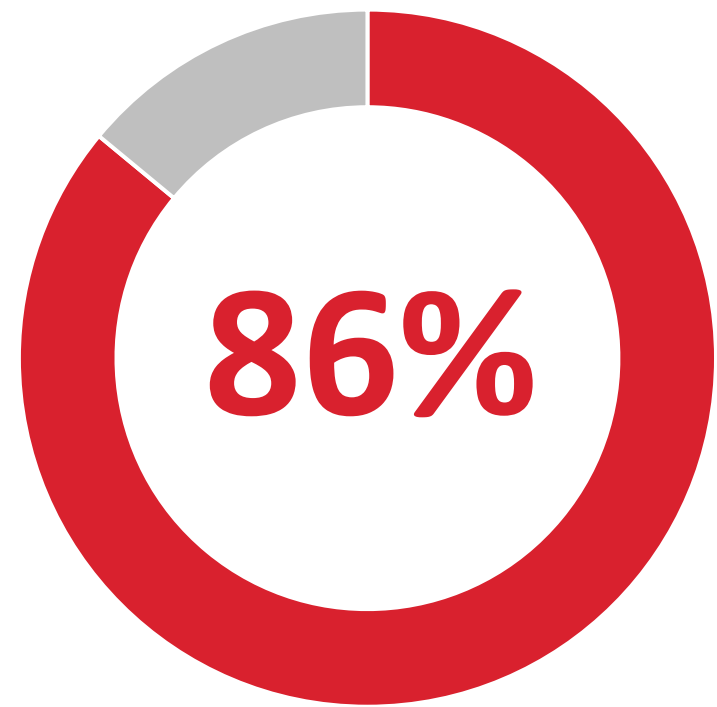
^a Cytopenias at ruxolitinib start were defined as follows: white blood cell <4×10⁹/L, hemoglobin <11 g/dL for men and <10 g/dL for women, and platelets <100×10⁹/L. The cytopenic phenotype was defined by the presence of at least 1 cytopenia. Patients not included in the cytopenic group were considered as having a proliferative phenotype.



Therapy of Myelofibrosis



Effects of Anemia Are Associated With a Significant Burden on Patients



of patients with MF would most like **fatigue/tiredness** improved.^{1,a} Patients with MF and anemia have **higher mean total symptom scores** than those without anemia
(29.6 vs 22.3; $P<.001$)²



- **Hemoglobin levels and transfusion dependency** significantly correlate with **worse quality of life**^{3,4}



Ability to work and productivity are typically impaired in patients with high symptom burden^{1,2}



RBC transfusions may cause⁵⁻⁷:

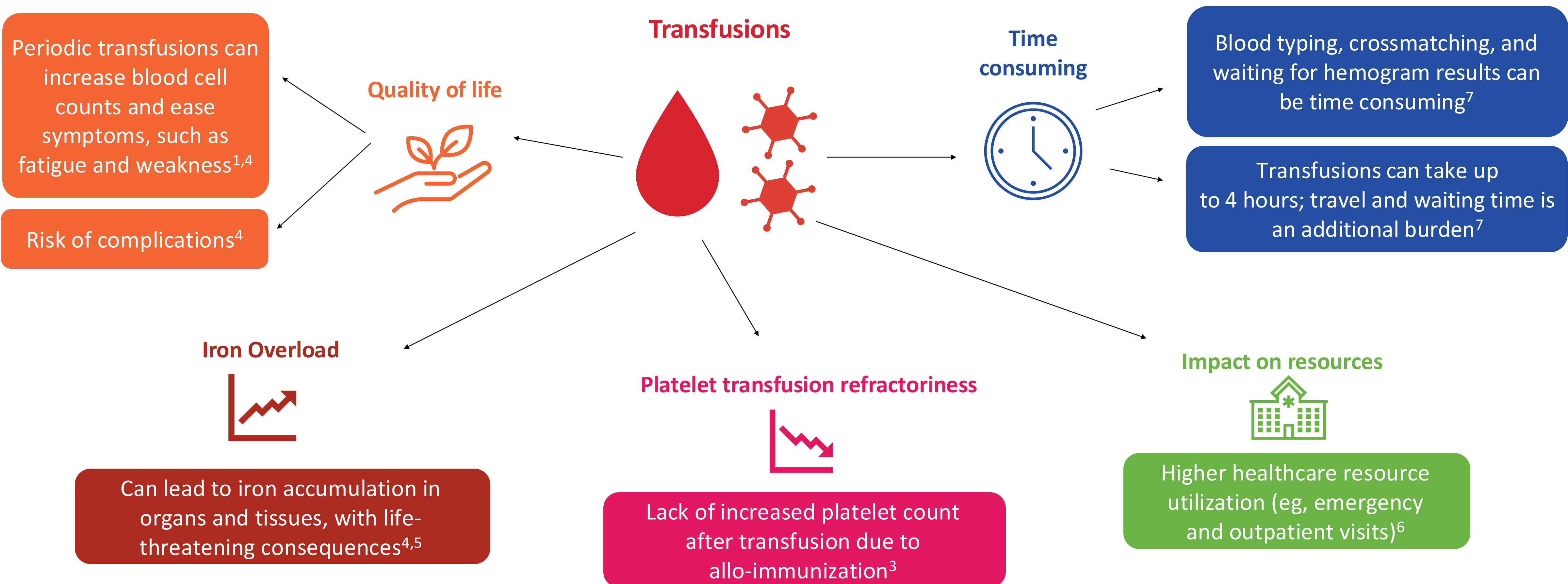
- **Iron overload**
- **Time burden** to receive treatment
- **Burden on healthcare resources**

MF, myelofibrosis; RBC, red blood cell.

^a The data shown are based on a global online survey of patients with MF and physicians conducted from April 2016 to October 2016.

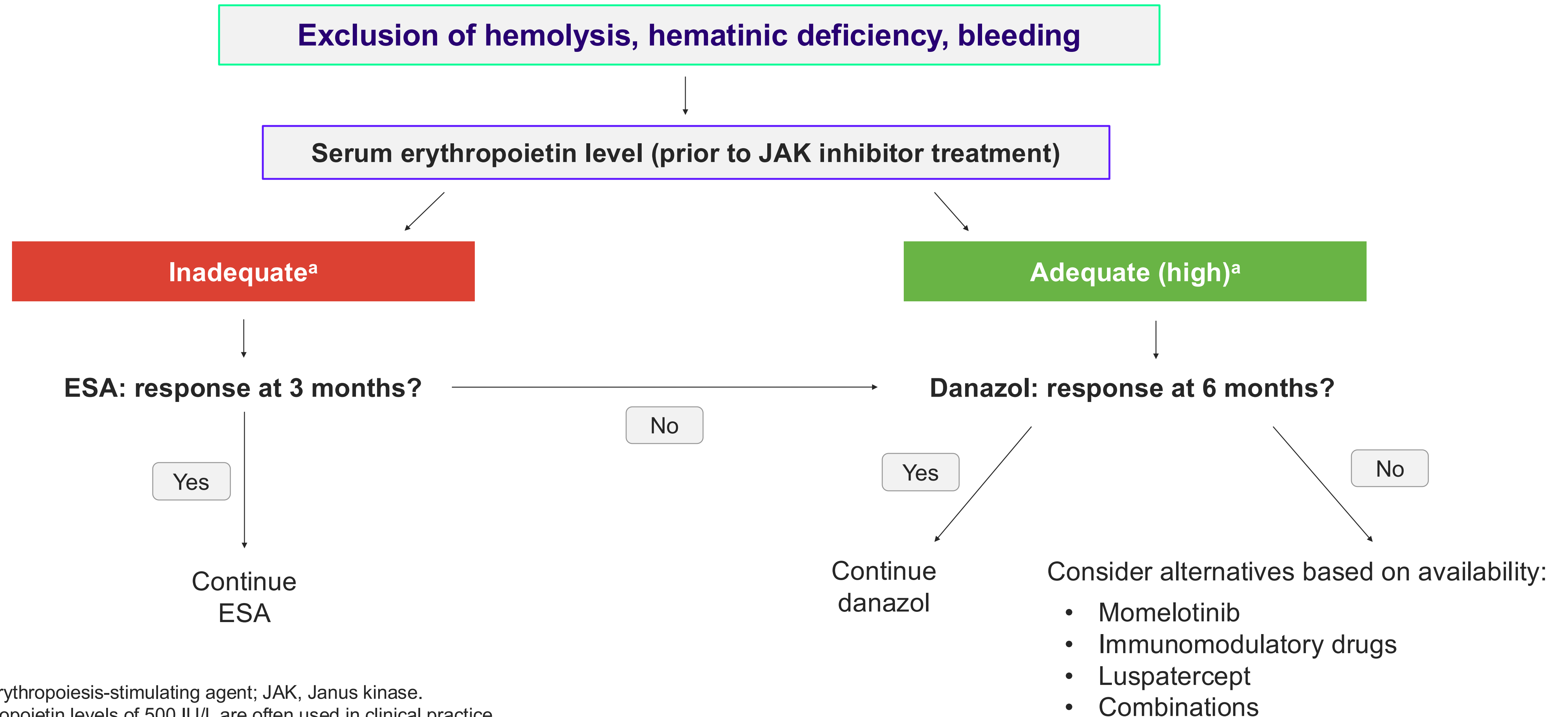
1. Harrison CN, et al. *Ann Hematol*. 2017;96(10):1653-1665.
2. Scotch AH, et al. *Leuk Res*. 2017;63:34-40.
3. Mesa RA, et al. *Cancer*. 2007;109(1):68-76.
4. Tefferi A, et al. *Clin Ther*. 2014;36(4):560-566.
5. Wood JC, *Am J Hematol*. 2007;82(12 suppl):1132-1135.
6. Shreay S, et al. *Support Care Cancer*. 2013;21(5):1335-40.
7. Gerds A, et al. ASH 2022. Poster 1729.

Red Blood Cell and Platelet Transfusions Can Improve Myelofibrosis-Related Cytopenias But May Pose Challenges¹⁻³



1. Mayo Clinic. Myelofibrosis. Accessed May 24, 2023. <https://www.mayoclinic.org/diseases-conditions/myelofibrosis/diagnosis-treatment/drc-20355062>. 2. Sastow D, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22(7):e507-e520. 3. Aclaina PS, et al. *J Blood Med*. 2020;11:19-26. 4. Oliva EN, et al. *Blood Rev*. 2021;50:100851. 5. Wood JC, *Am J Hematol*. 2007;82(12 suppl):1132-1135. 6. Gerds A, et al. ASH 2022. Poster 1729. 7. Shreay S, et al. *Support Care Cancer*. 2013;21(5):1335-40.

British Society for Haematology Guidelines for Patients With Myelofibrosis and Anemia

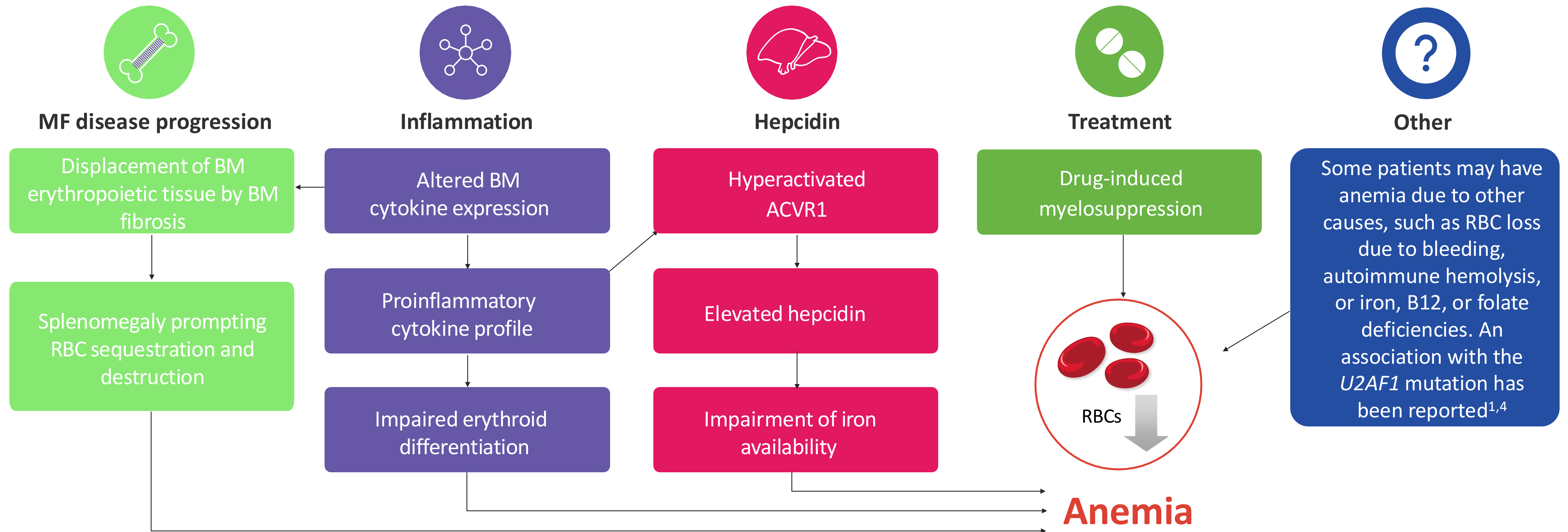


ESA, erythropoiesis-stimulating agent; JAK, Janus kinase.

^a Erythropoietin levels of 500 IU/L are often used in clinical practice.

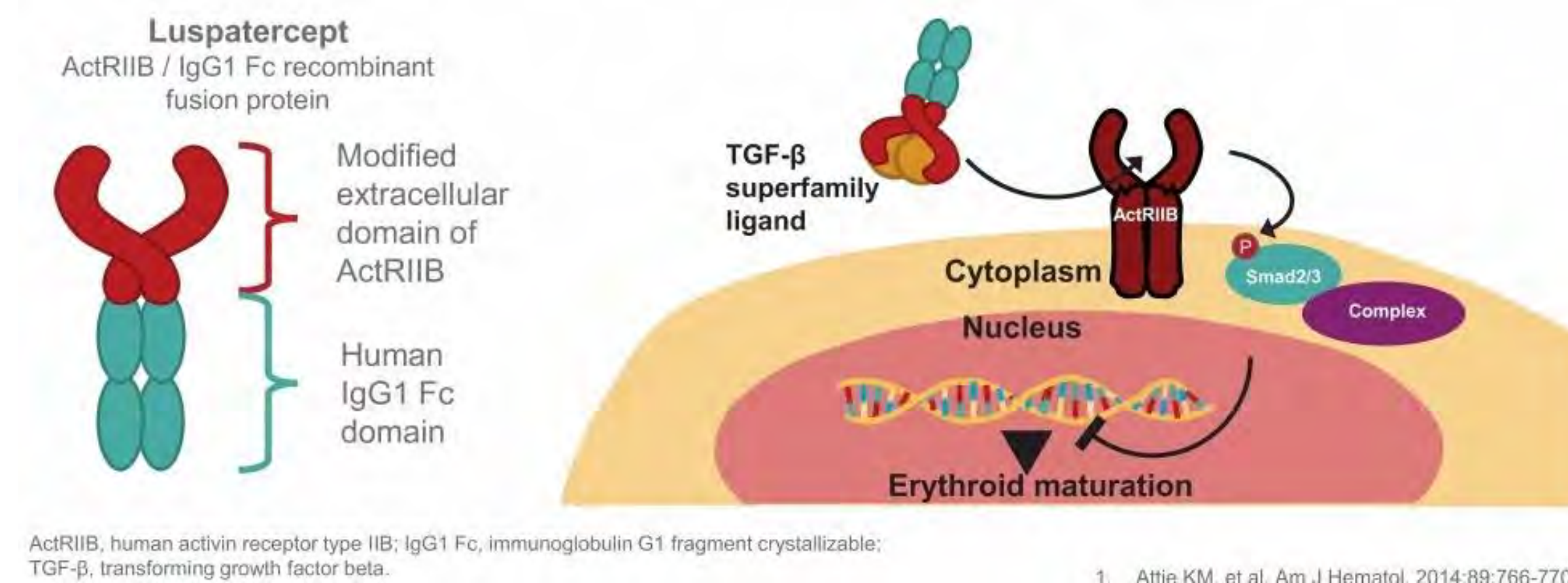
Pathophysiology of Anemia in Myelofibrosis Is Multifactorial and Only Partially Understood¹⁻³

Anemia in myelofibrosis results from multiple factors, which are incompletely understood¹



1. Naymagon L, Mascarenhas J. Hemasphere. 2017;1(1):e1. 2. Ganz T. N Engl J Med. 2019;381(12):1148-1157.
3. Oh ST, et al. Blood Adv. 2020;4(18):4282-4291. 4. Tefferi A, et al. Leukemia. 2018;32(10):2274-2278.

Luspatercept



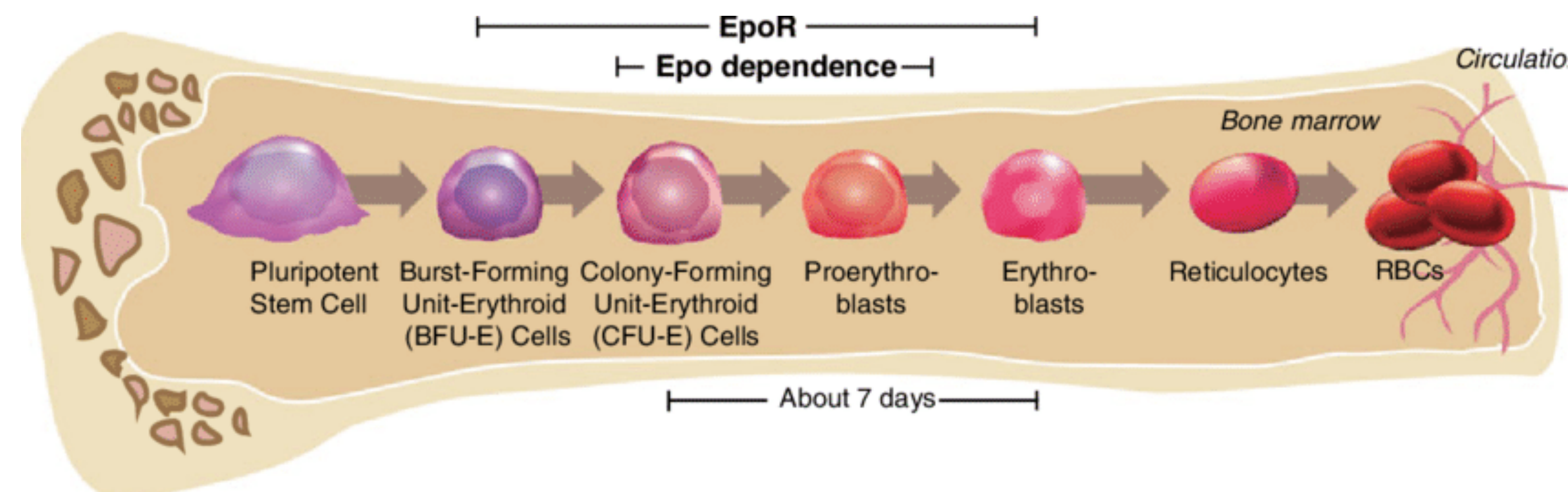
Selective inhibitor of TGF- β superfamily ligands



Aberrant Smad 2/3 signaling inhibition



Late Erythroid Maturation (non EPO-dependent)



Elritercept (KER-050) is designed to target disorders of ineffective hematopoiesis including myelofibrosis

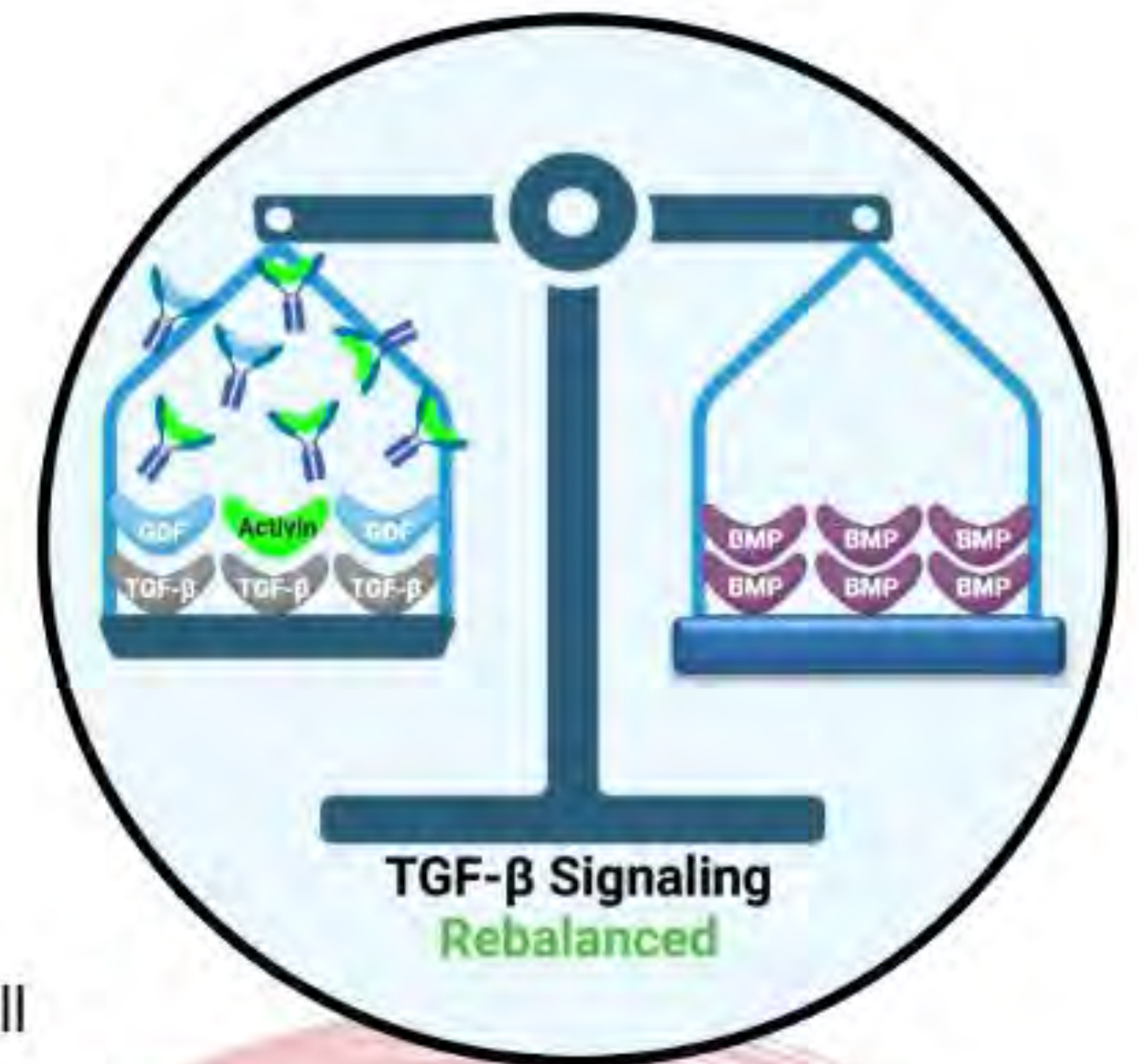


Elritercept

- Designed to inhibit select TGF-beta superfamily ligands, including **Activin A**, which has been associated with **ineffective hematopoiesis, inflammation, disease pathogenesis and progression**^{1,2,3}

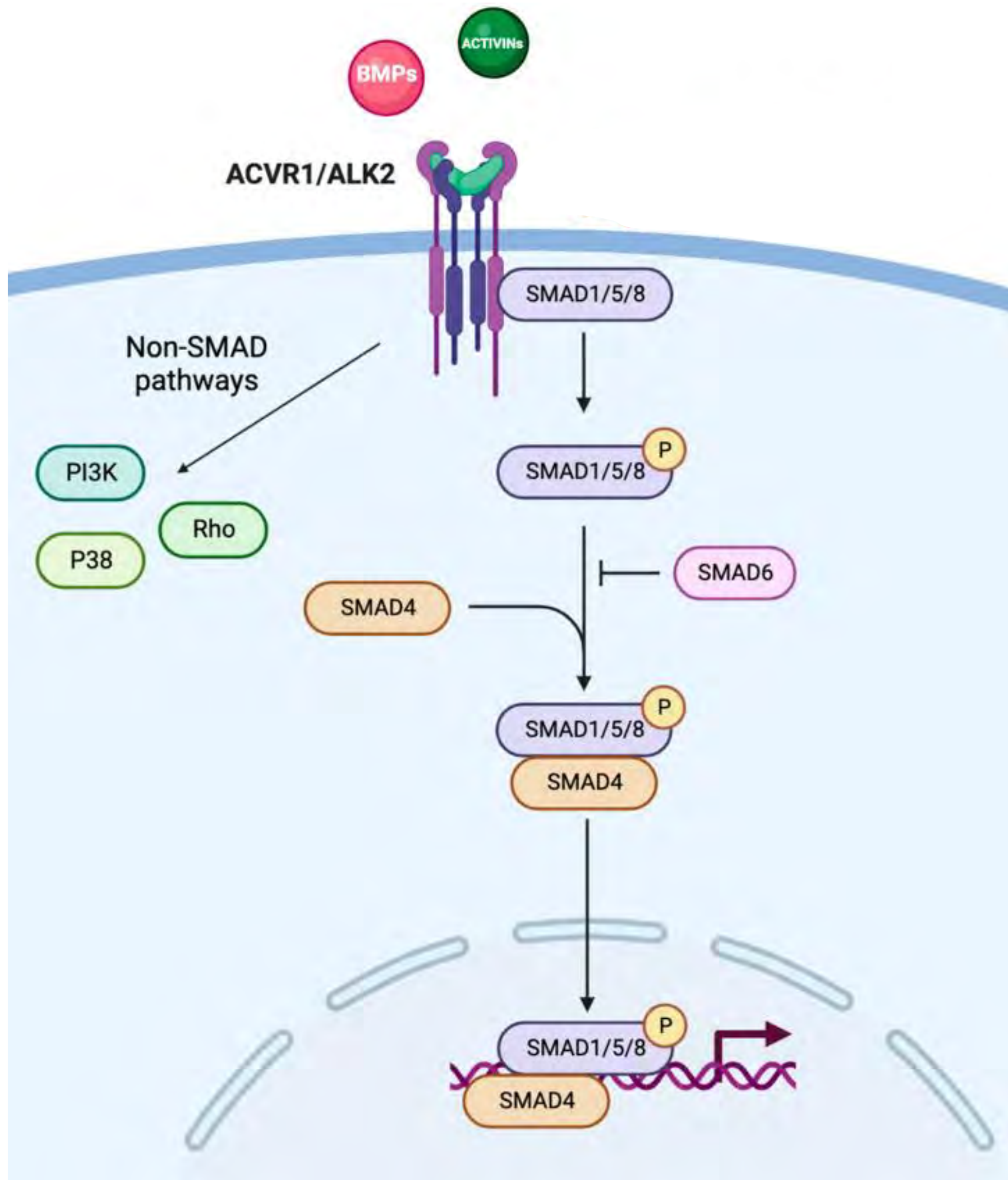
Preclinical data showed that the research form of **elritercept** (RKER-050):

- induced erythropoiesis in mouse model of myelofibrosis⁴
- reversed ruxolitinib-associated reductions in hemoglobin, hematocrit, and red blood cell (RBC) count⁵
- increased platelet counts⁶



1. Verma A et al., J Clin Invest 2020. Portale F et al., Haematologica 2019. 3, Phillips D et al., Cytokine Growth Factor Rev 2009. 4 Moses et al., EHA 2023. 5. Nathan et al., ASH 2021. 6. Moses et al. Gordon Research Conference: Cell Biology of Megakaryocyte and Platelets, 2023. Modified from Harrison C et al., EHA 2024. TGF-b = Transforming Growth Factor beta.

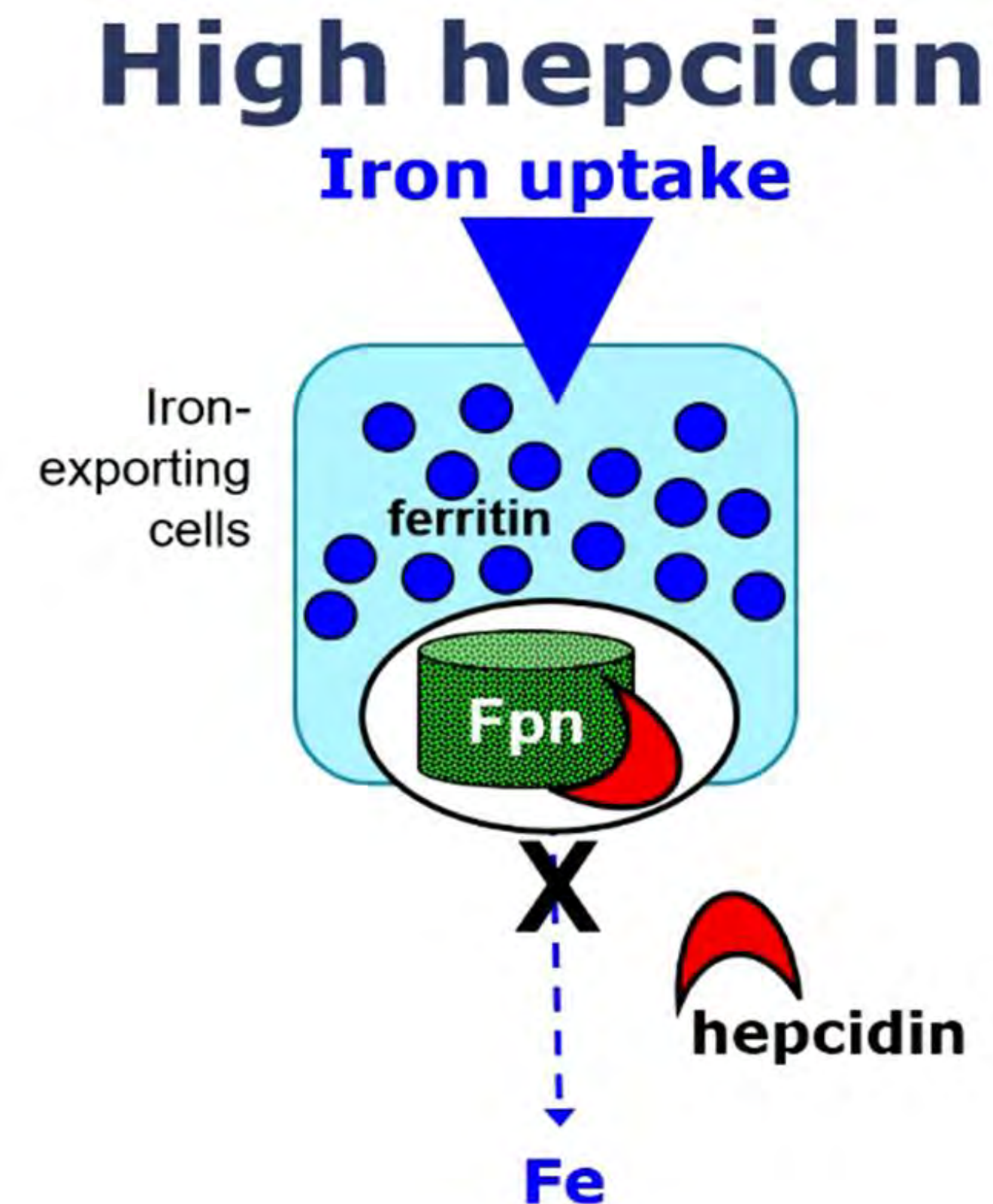
ACVR1



The **ACVR1** receptor functions in the **development and regulation** of the bone, heart, cartilage, nervous, and reproductive systems

In other diseases, dysregulated ACVR1 signaling has been linked to **cardiac malformations**, alterations in the **reproductive system**, and certain **cancers**

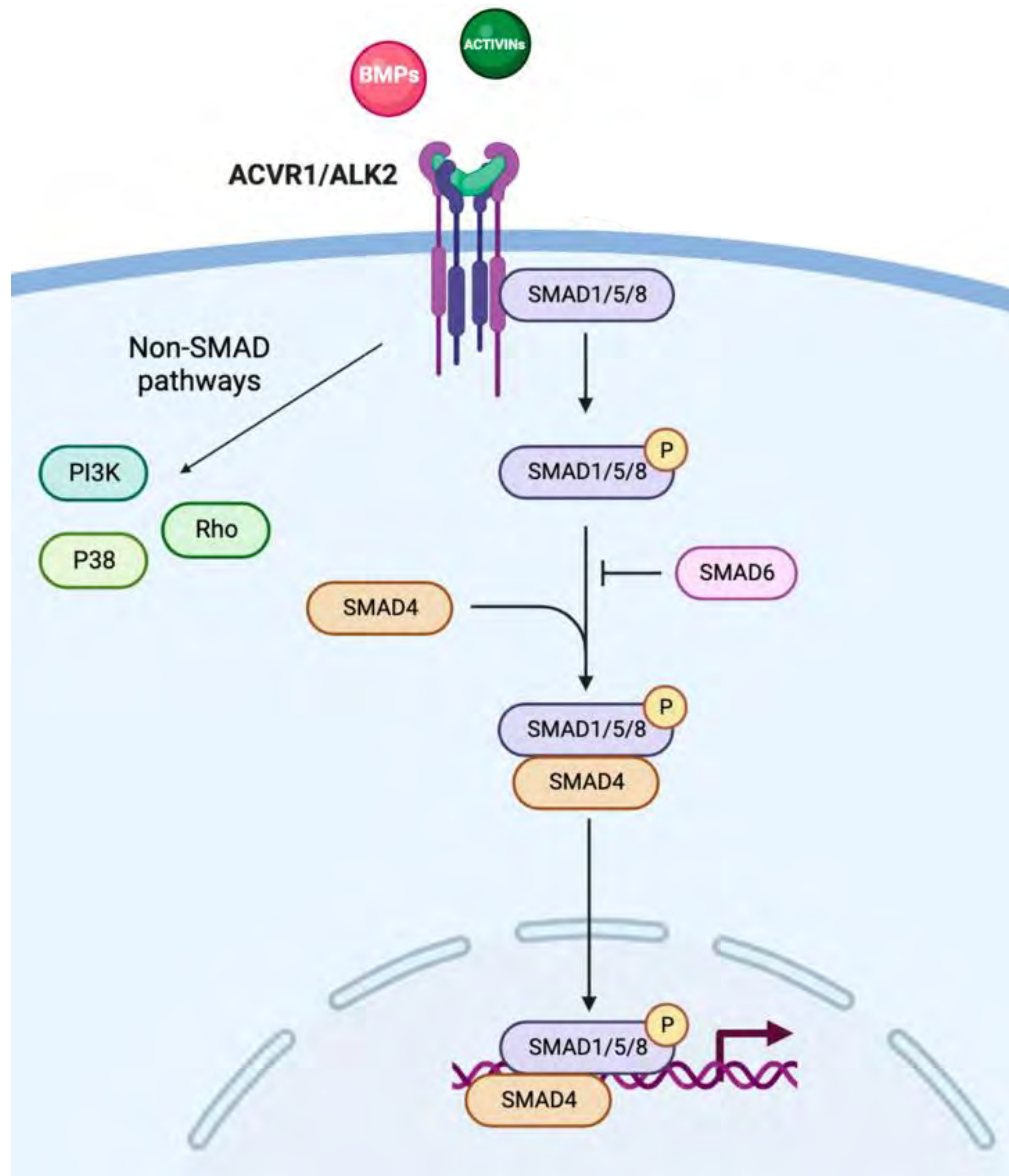
ACVR1 is a key regulator of **hepcidin** production and is expressed on the surface of hepatocytes; **hepcidin** is a peptide hormone secreted in the liver that serves as a **master iron regulator**



Nemeth E et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004 Dec 17;306(5704):2090-3.

Duminuco A et al. ACVR1: A Novel Therapeutic Target to Treat Anemia in Myelofibrosis. *Cancers (Basel)*. 2023 Dec 28;16(1):154.

ACVR1

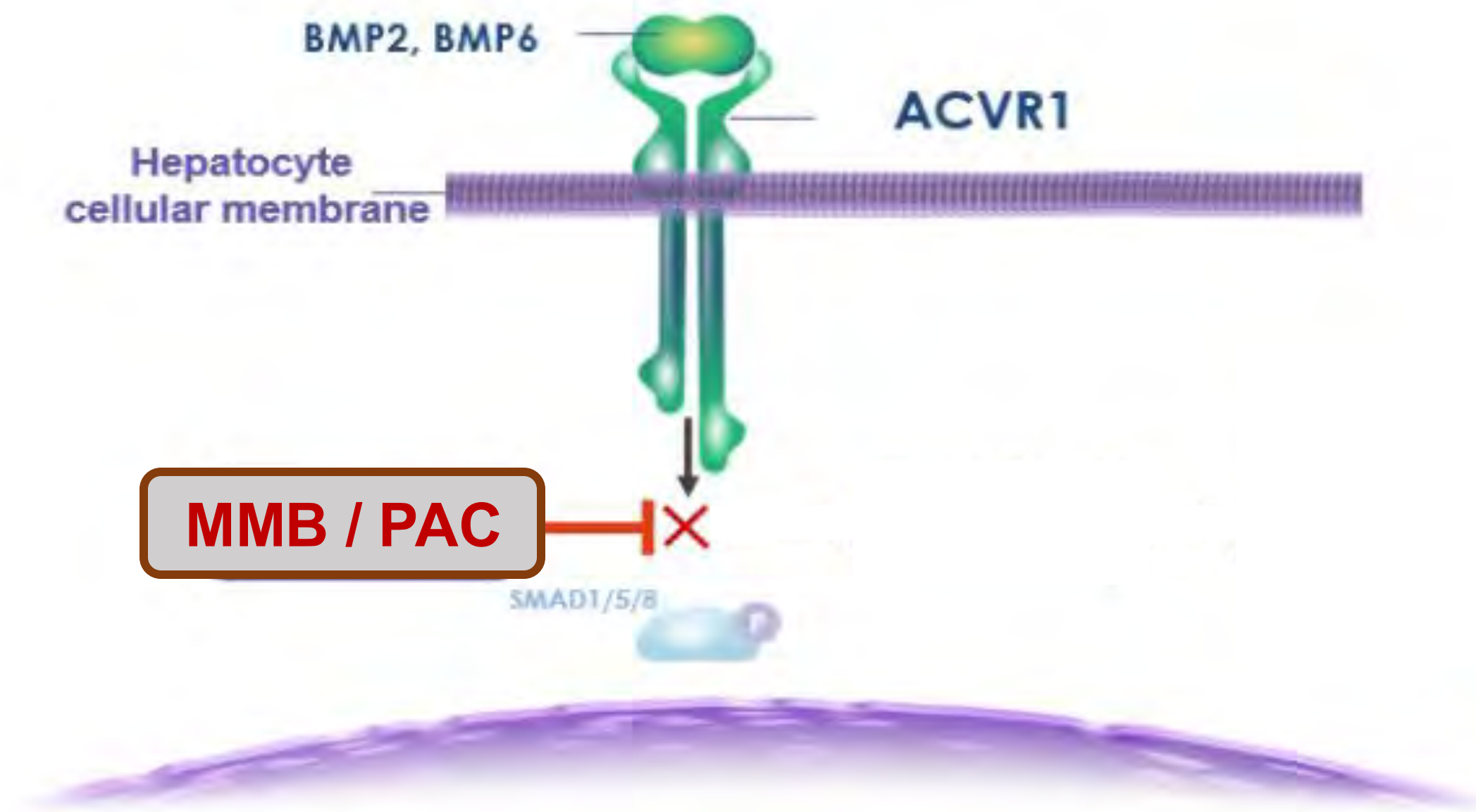


In MF, chronically **activated ACVR1 signaling** leads to markedly **elevated hepcidin levels**

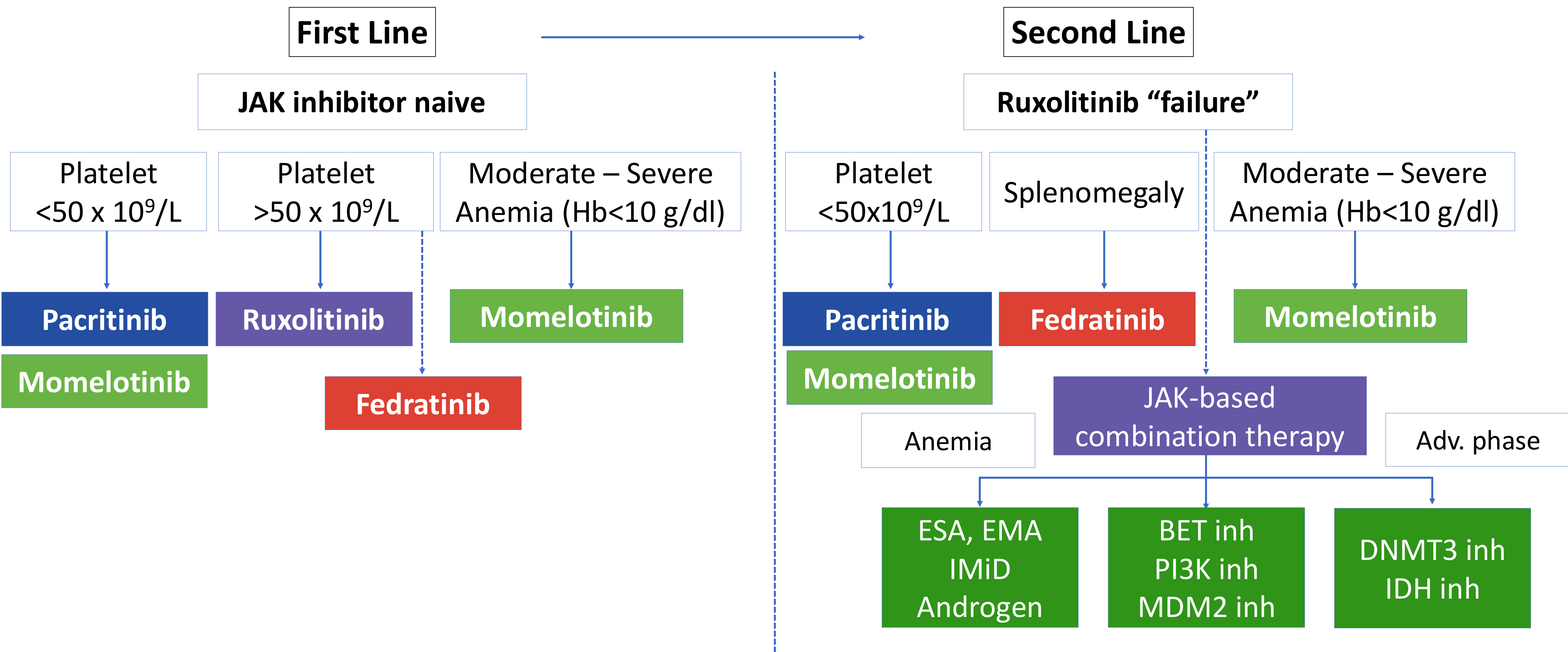
Elevated hepcidin levels inhibit iron transport and iron homeostasis, driving iron-restricted anemia and anemia of MF

Upregulation of **inflammatory cytokines** in the bone marrow disrupts erythropoiesis and is associated with upregulation of circulating hepcidin; cytokines associated with anemia include **TGF- β , IL-2, IL-6, and TNF- α**

Inhibiting ACVR1 results in **decreased hepcidin** transcription and an increase in **iron availability**, thereby improving iron-restricted anemia



Proposed Positioning of JAK Inhibitors in Myelofibrosis



Modified from Venugopal. J Hematol Oncol. 2020;13:162.





Grazie!
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