2026

DEBATES AND DIDACTICS in Hematology and Oncology

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Moving the Bar in Myeloproliferative Neoplasms

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Disclosures

Consulting/Honoraria: GSK, PharmaEssentia, Blueprint Medicines, Sobi, Incyte, Novartis, Cycle Therapeutics, Geron, BMS, Merck, Disc Medicine, Cogent Biosciences

DSMB: Karyopharm

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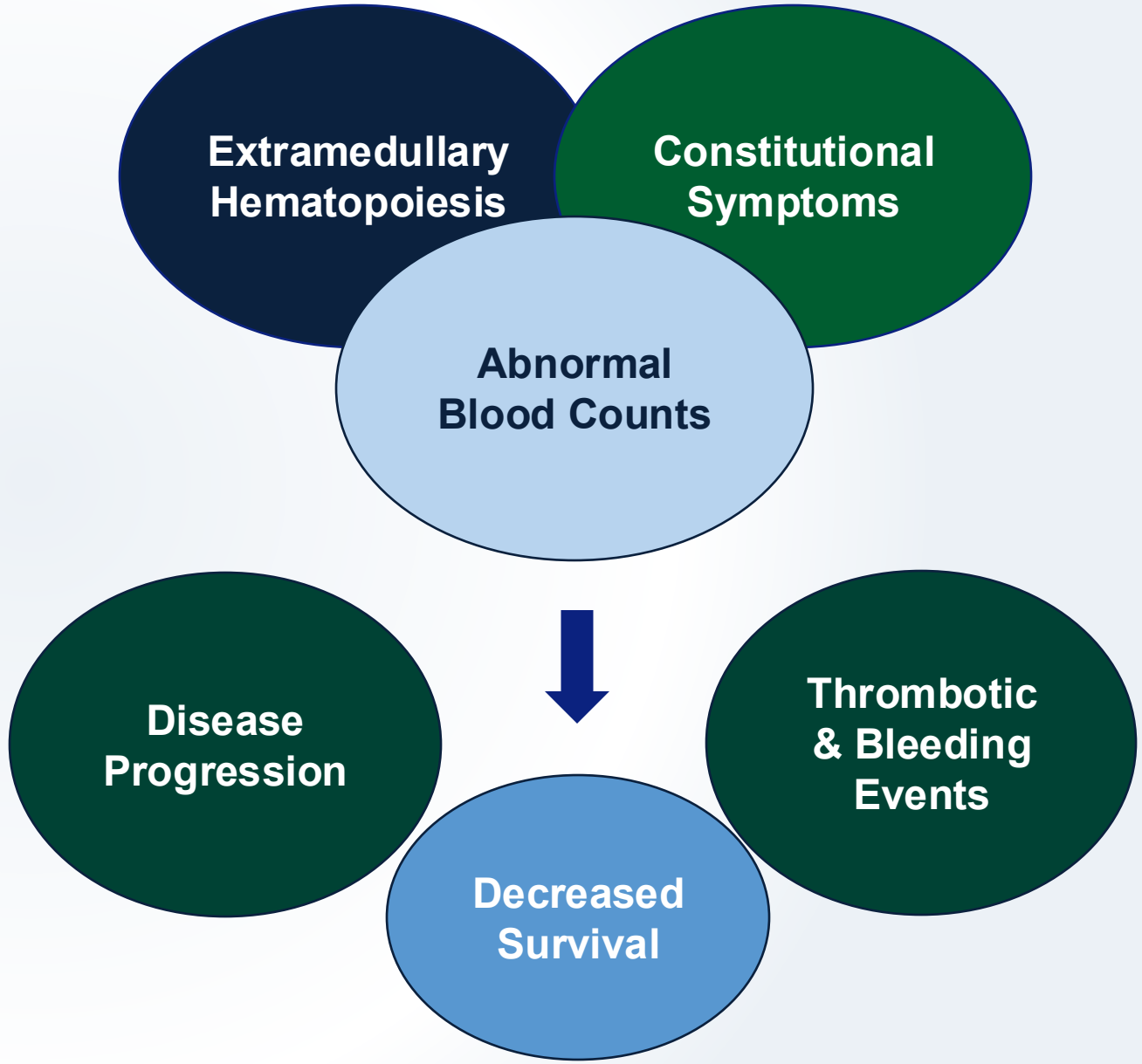
Myeloproliferative Neoplasms (MPNs): Background

Clonal hematopoietic stem cell disorders characterized by myeloproliferation and aberrant inflammatory cytokine signaling

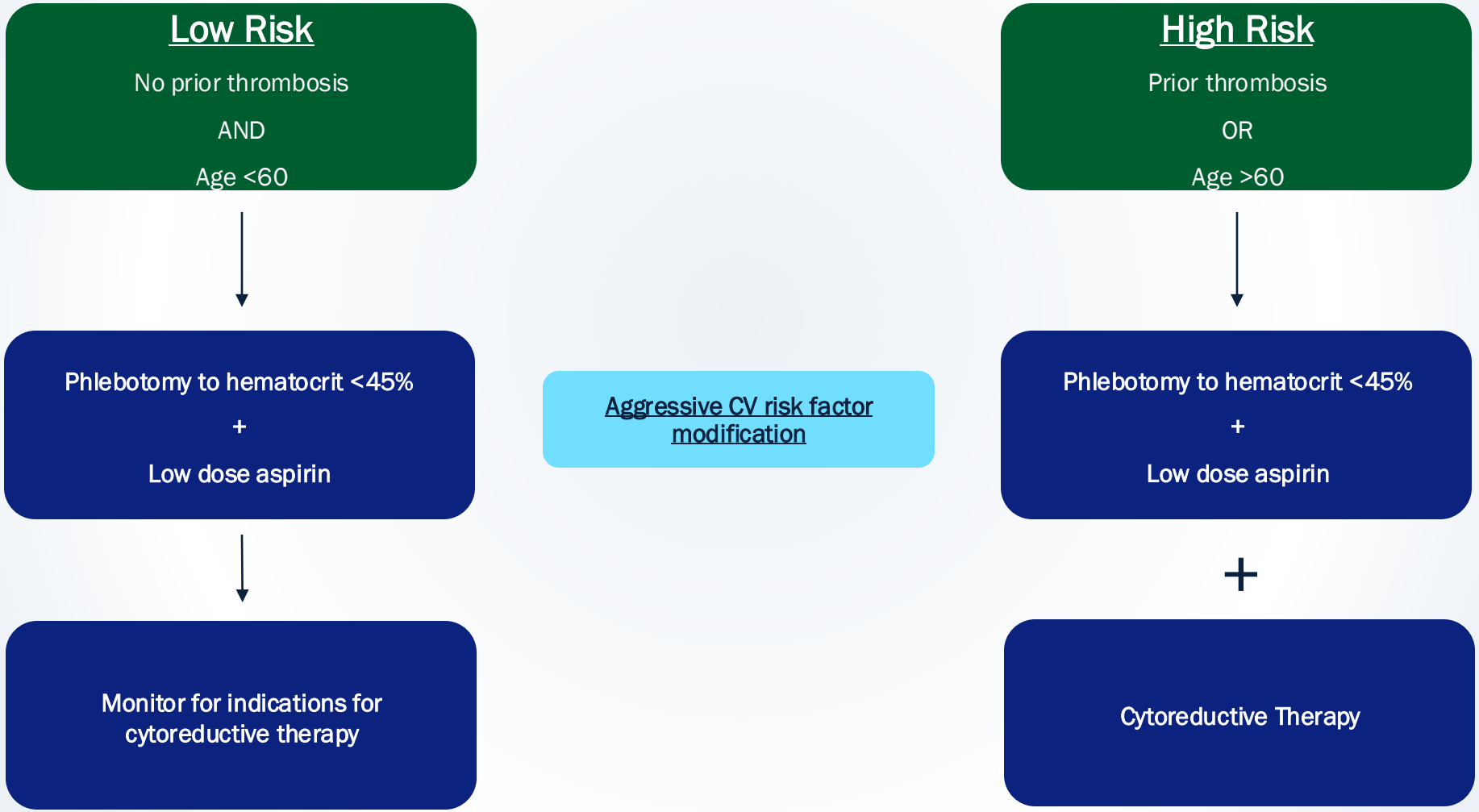
Table 1. Myeloproliferative neoplasms.

Chronic myeloid leukaemia	
Polycythaemia vera	Ph Negative, Classical MPNs
Essential thrombocythaemia	Ph Negative, Classical MPNs
Primary myelofibrosis	Ph Negative, Classical MPNs
Chronic neutrophilic leukaemia	
Chronic eosinophilic leukaemia	
Juvenile myelomonocytic leukaemia	
Myeloproliferative neoplasm, not otherwise specified	



Khoury JD, et al. *Leukemia* 2022; 36:1703-1719

Risk Stratification and Management of PV



Tefferi A, et al. *Am J Hematol* 2020; 95: 1599-1613

Additional Considerations in Risk Stratification

Low Risk

No prior thrombosis

AND

Age <60

Other thrombosis risk factors:

Leukocytosis, *JAK2* allele frequency, CV risk factors

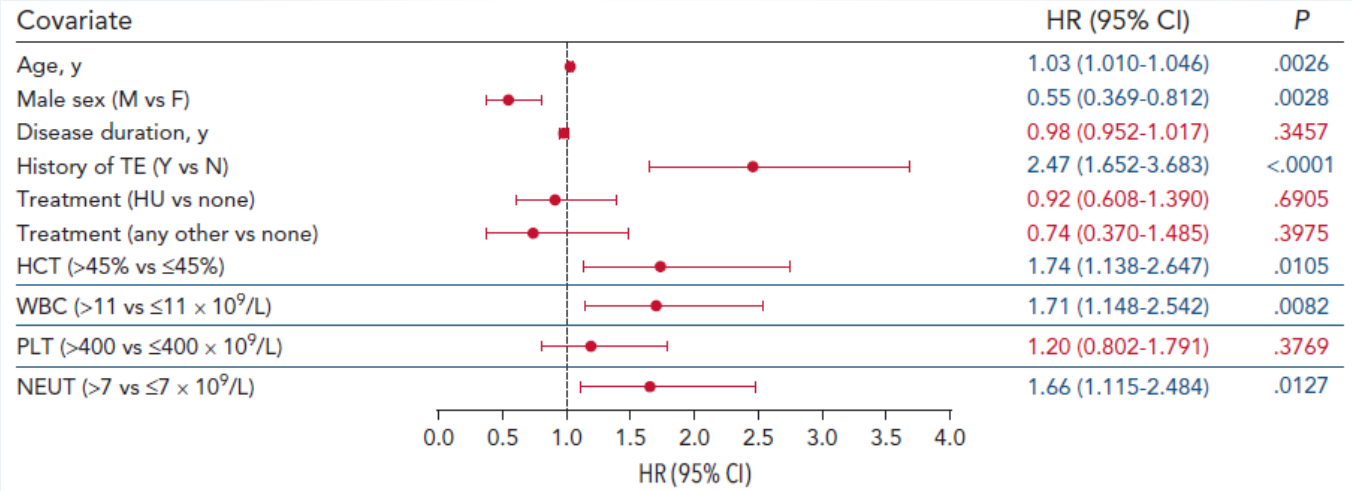
→

High Risk

Prior thrombosis

OR

Age >60



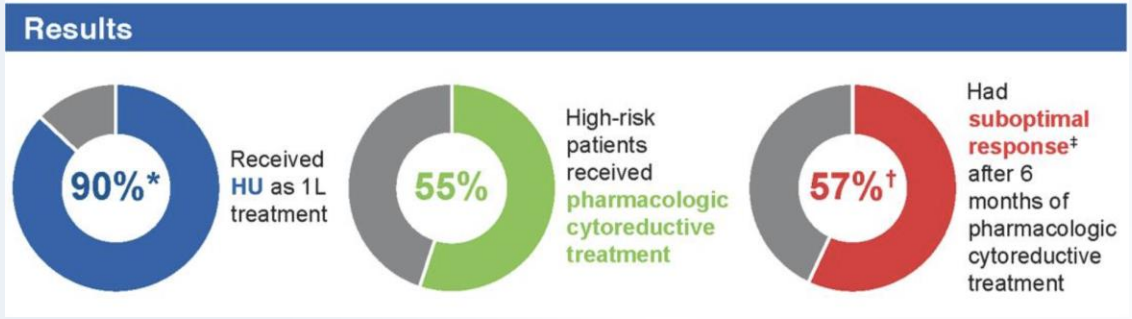
	PV JAK2^{V617F} VAF	
	<50%	>50%
Quantitative		
WBC, ×10⁹/L	9.3[35]	12.4[35]
Hg, g/dL	14.6[35]	15.9[35]
Platelets, ×10⁹/L	571[35]	490[35]
Qualitative		
Venous thrombosis risk ratio	1.0[35,*]	2.97[35,*]
CRP, mg/L	27% > 3[36]	63% > 3[36]
LDH, U/L	304[12]	480[12]
PRV-1 (CD177) expression, fold upregulation	20[12]	576[12]
Clonal expansion		
Splenomegaly prevalence	12%[12]	91%[12]
Red cell mass (% of normal)	150%[37]‡	180%[37]‡
CD34 circulation, ×10⁶/L	3[12]	6[12]
15-year myelofibrosis free survival	100%[11]	40%[11]

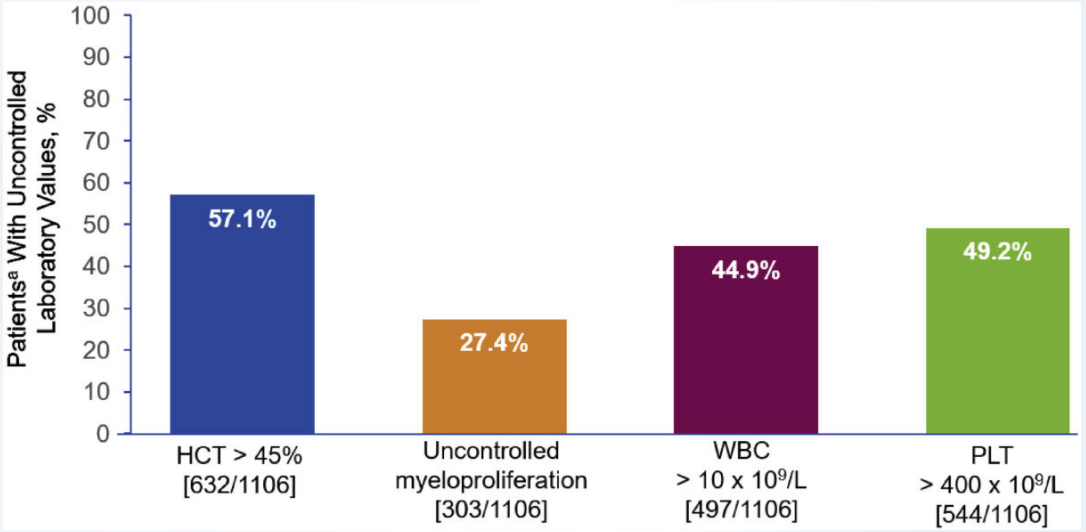
Gerds AT, et al. *Blood* 2024;18:143(16):1646-1655. Moliterno AR, et al *Blood* 2023; 141(16):1934-1942

Real-World Data Demonstrates Inadequate Management of PV in US Clinical Practice

Table 2. Treatment patterns.

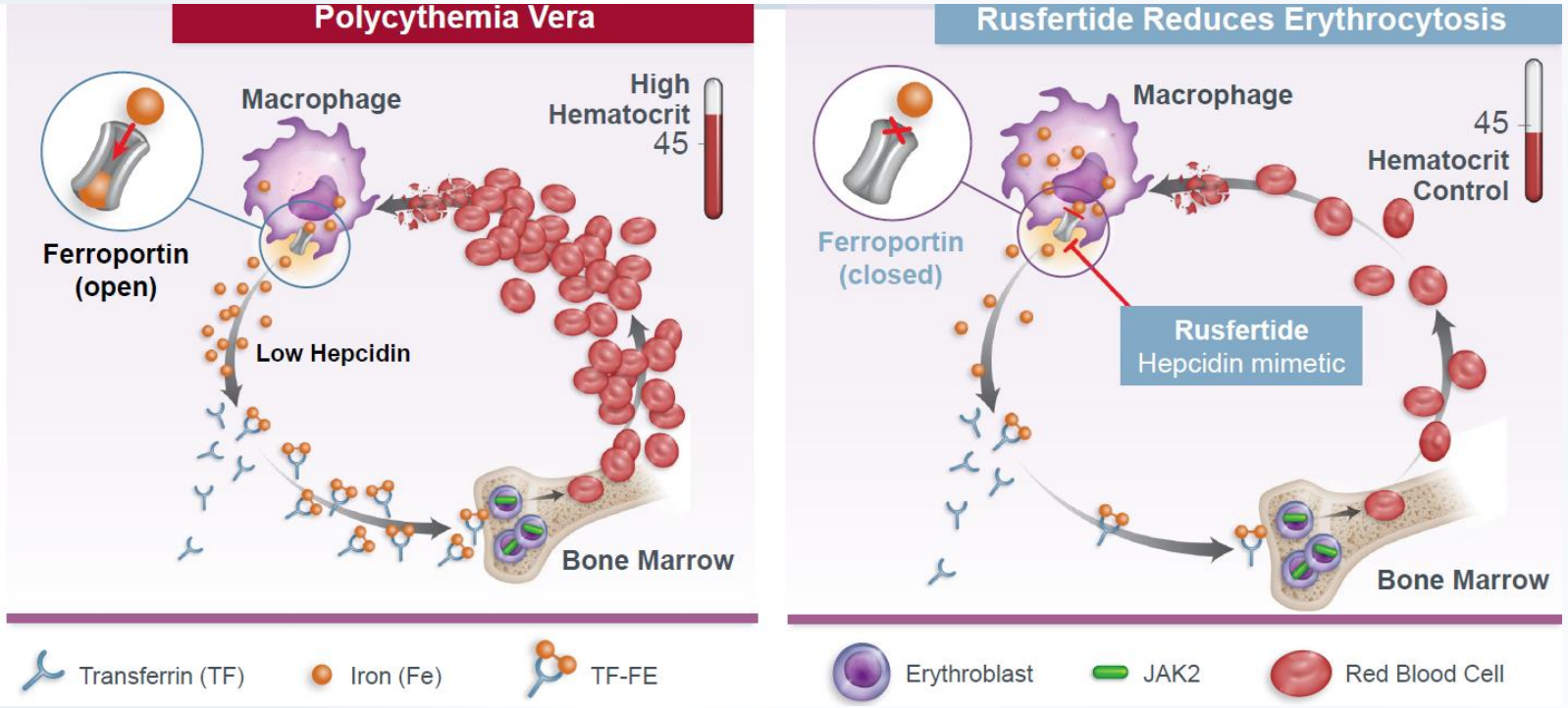
	Overall ($N = 5871$)
High risk at diagnosis	$n = 4185$
First-line cytoreductive treatment,* *n* (%)	
Hydroxyurea	2068 (49.4)
Ruxolitinib	182 (4.3)
Anagrelide	47 (1.1)
Interferon/PEGylated interferon	2 (0.0)
Busulfan	3 (0.1)
Radiophosphorus	1 (0.0)
No pharmacologic cytoreductive treatment	1882 (45.0)
Low risk at diagnosis	$n = 1686$
First-line cytoreductive treatment, *n* (%)	
Hydroxyurea	480 (28.5)
Ruxolitinib	45 (2.7)
Anagrelide	12 (0.7)
Interferon/PEGylated interferon	3 (0.2)
No pharmacologic cytoreductive treatment	1146 (68.0)

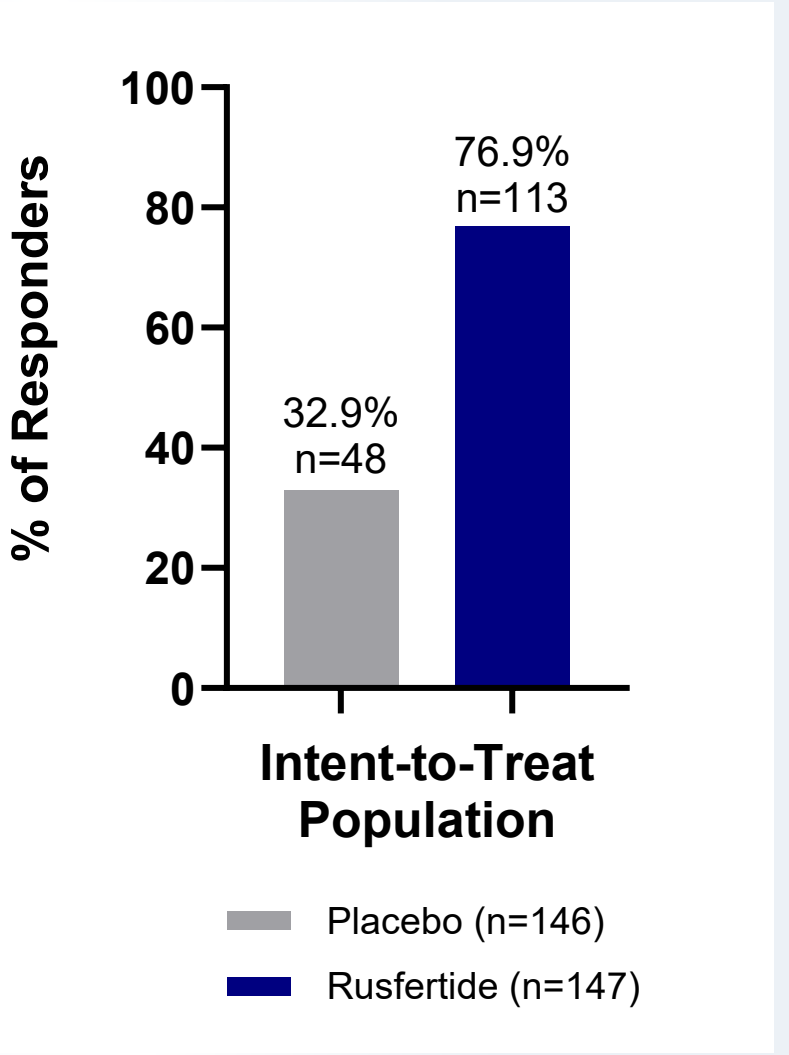




Lyons RM, et al. *Curr Med Res Opin*. 2025 Jan;41(1):43-51. Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk*. 2020; 20(4):219-225. Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(12):788-795

Rusfertide Provides Effective Hematocrit Control in PV

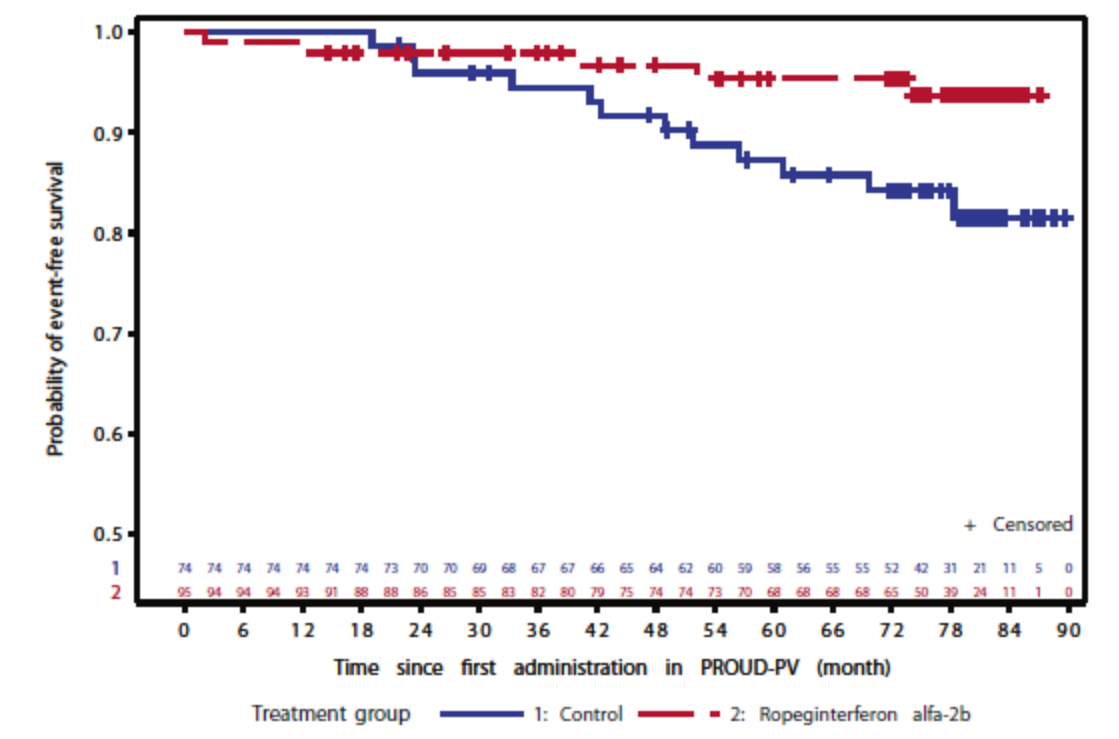




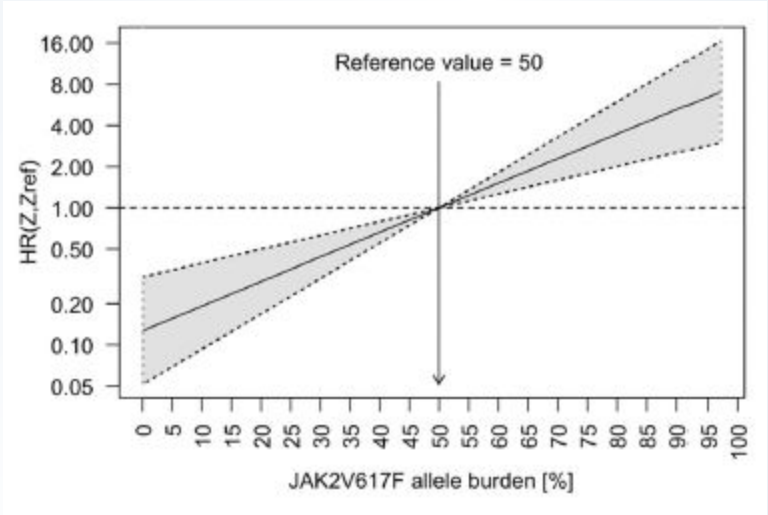
Responder = absence of phlebotomy eligibility (confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%), no phlebotomies, and completion of Part 1a.

Ritchie EK, et al. *Blood*. 2023; 142 (Supplement 1): 745
Kuykendal A, et al. *J Clin Oncol* 43, LBA3 (2025)

Moving Beyond Hematocrit Control: Ropeginterferon Provides Disease Modification in PV

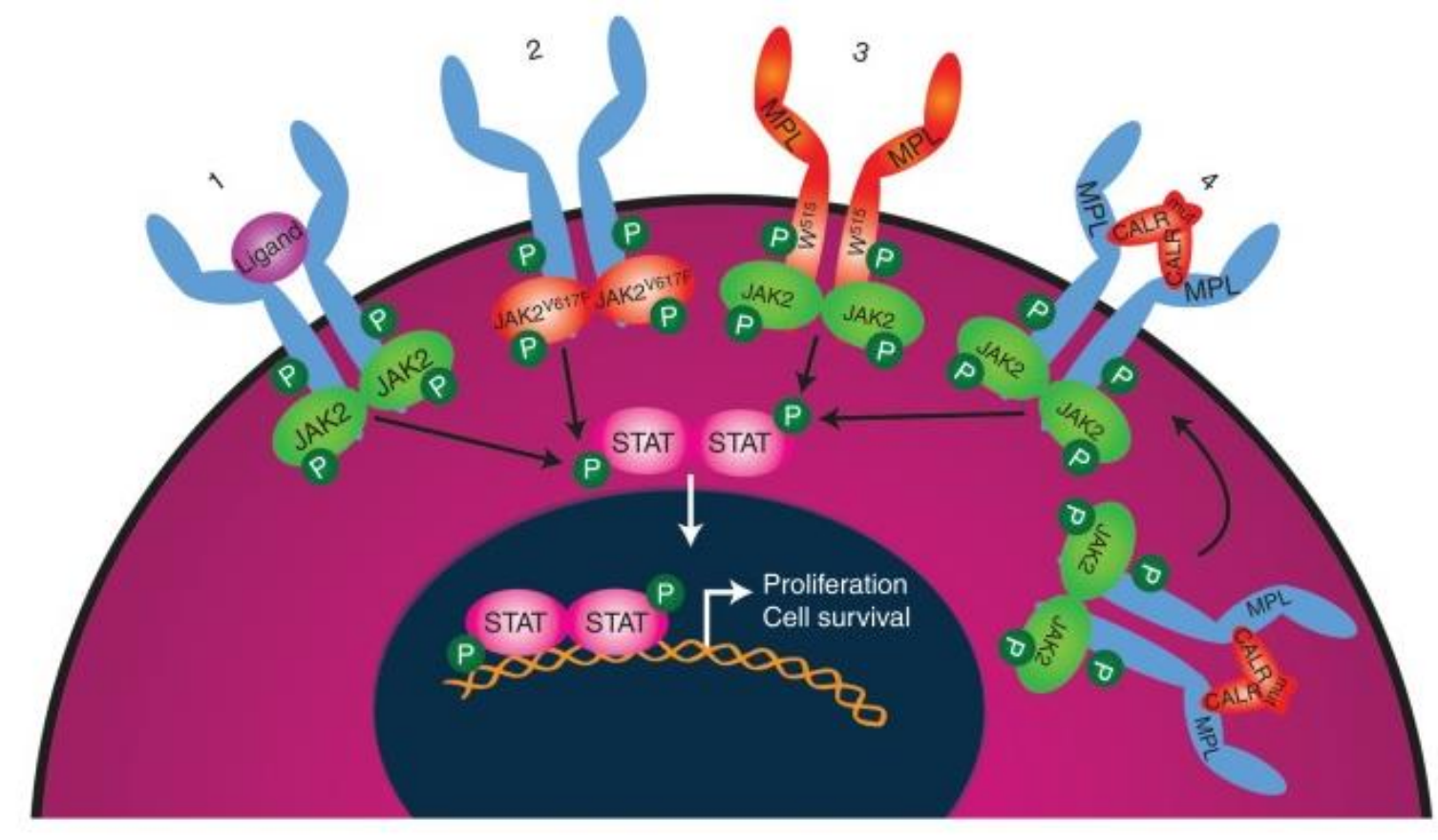


At 6 years	Hydroxyurea	Ropeginterferon
Molecular Response	19.4%	66.0%
Median JAK2 V617F allele burden	50.4% (baseline 39.4%)	8.5% (baseline 37.3%)



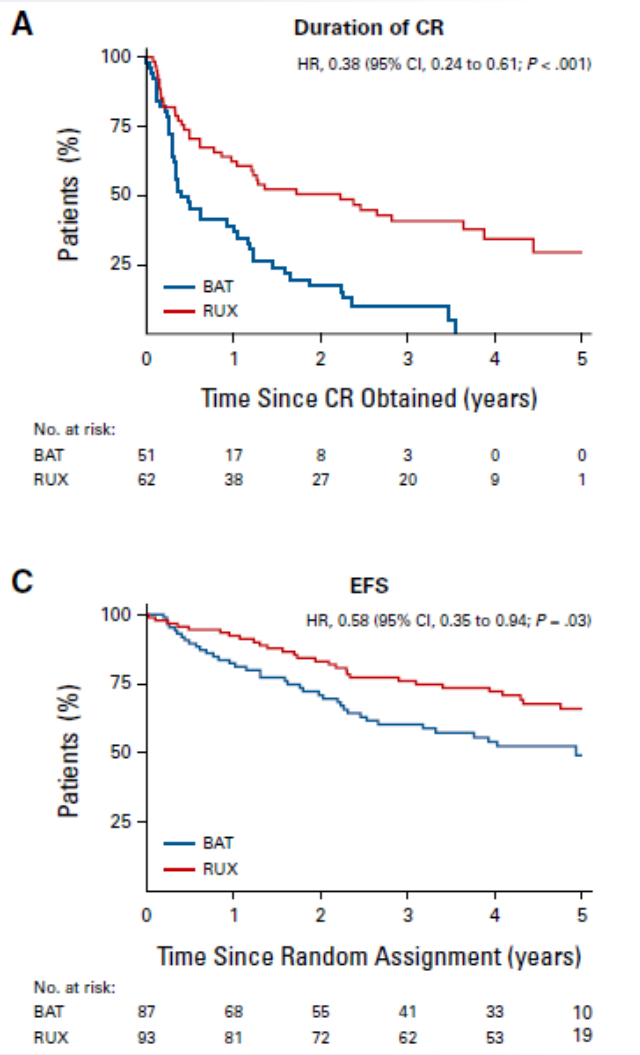
Gisslinger H, et al. L*ancet Haematol*. 2020; 7:e196-208. Gisslinger H, et al. *Leukemia.* 2023; 37:2129-2132. Kiladjian J, et al. HemaSphere. 2025;9:e70137

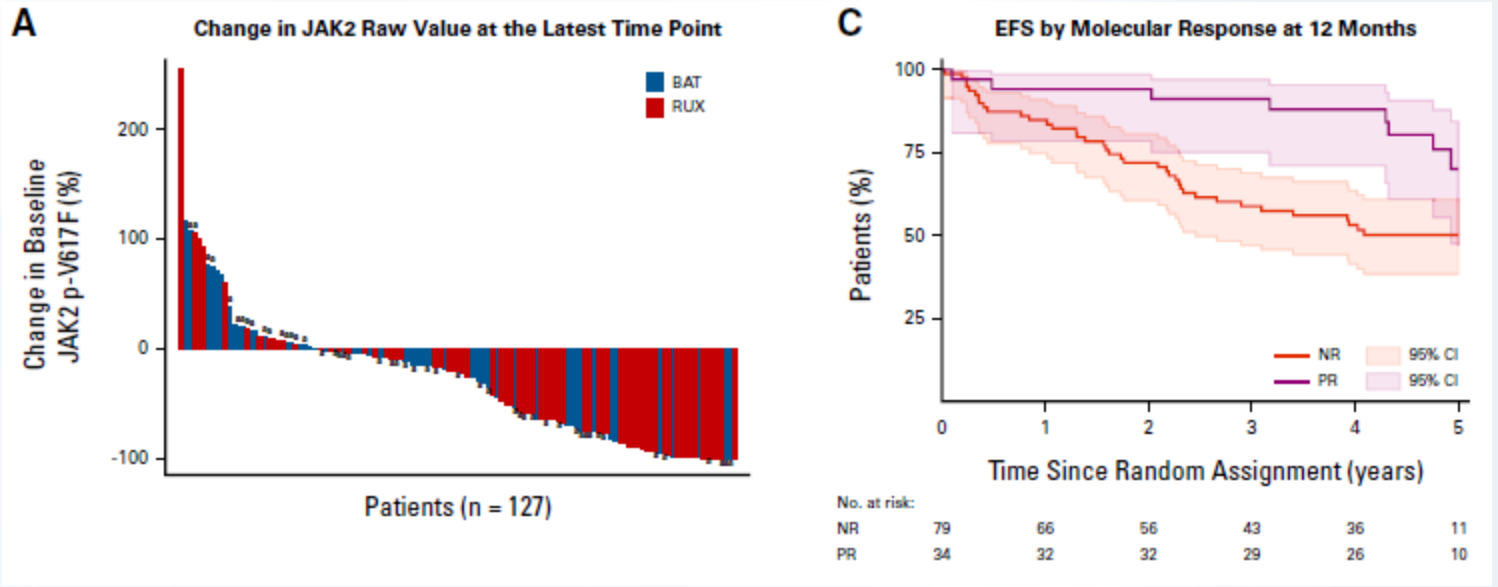
Central Role of JAK-STAT Signaling in MPN Biology Provides Key Therapeutic Target



Marneth AE, Mullally A. *Cold Spring Harb Perspect Med*. 2020 Feb 3;10(2):a034876

Beyond Hydroxyurea: Ruxolitinib Provides Benefit Beyond Hematologic Control in PV





- **CR rate:** 46% vs. 23% with BAT (ORR 97% vs. 93%)
- **Molecular response (>50% JAK2 V617F VAF reduction):** 56% vs. 25%
- **PFS, EFS, and OS** all correlated with molecular response at last timepoint in total cohort and ruxolitinib-treated patients (not in BAT)

Harrison CN, et al. *J Clin Oncol.* 2023 Jul 1;41(19):3534-3544.

Individualizing JAK Inhibitor Therapy in MF

Not all patients require a JAKi at diagnosis

Frontline, Proliferative

- **Ruxolitinib**
- Fedratinib
- *Novel combinations

Frontline, Cytopenic

Plts <50

- **Pacritinib**
- Consider Momelotinib

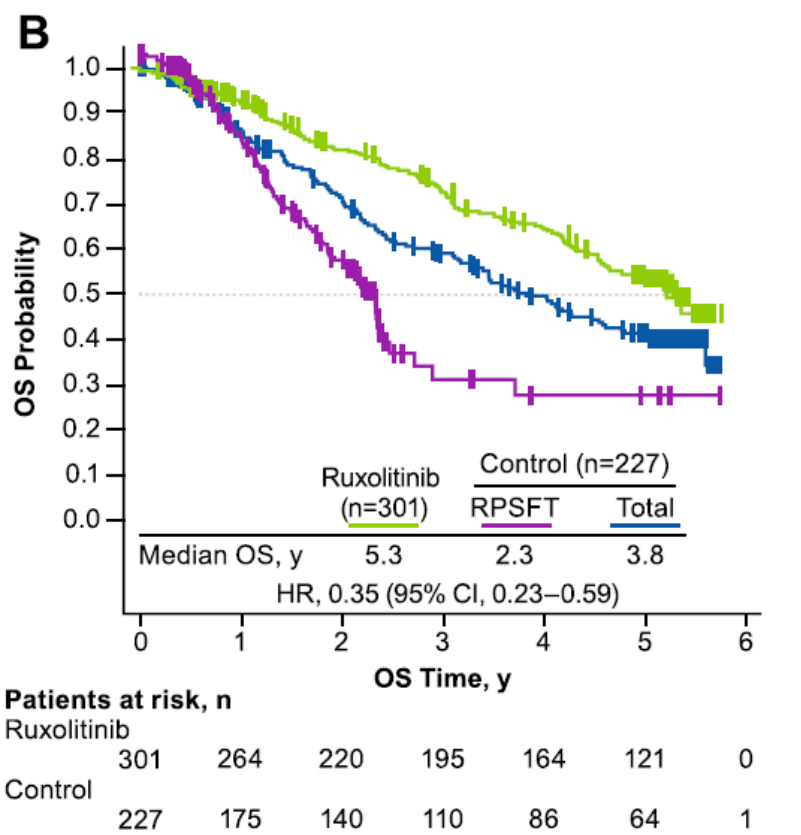
Anemia

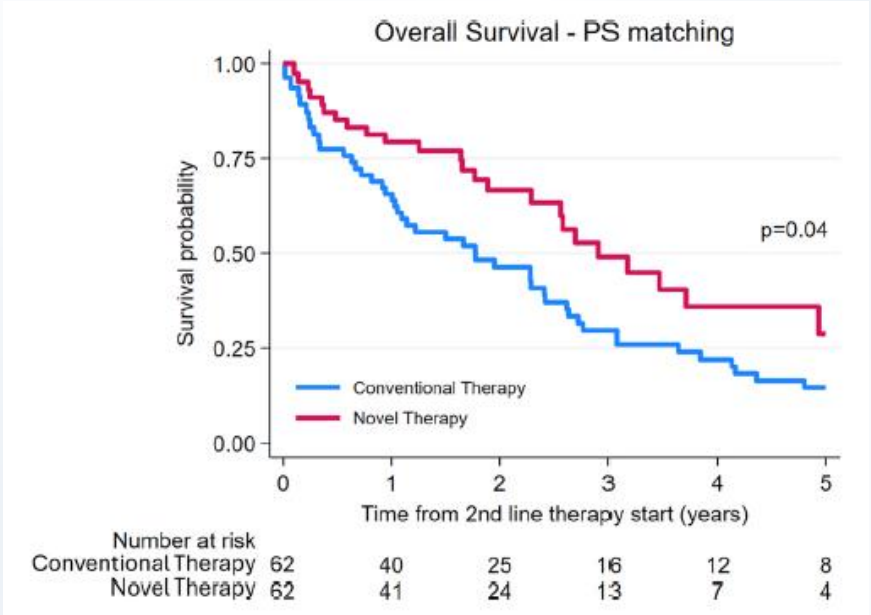
- **Momelotinib**
- Ruxolitinib (dose optimized +/- anemia-directed therapies)
- Pacritinib

Second Line (Ruxolitinib failure)

- Fedratinib
- Momelotinib
- Pacritinib
- *Novel agents

Ruxolitinib Provides Symptomatic Benefit and Improves Survival in MF, but Has Limitations



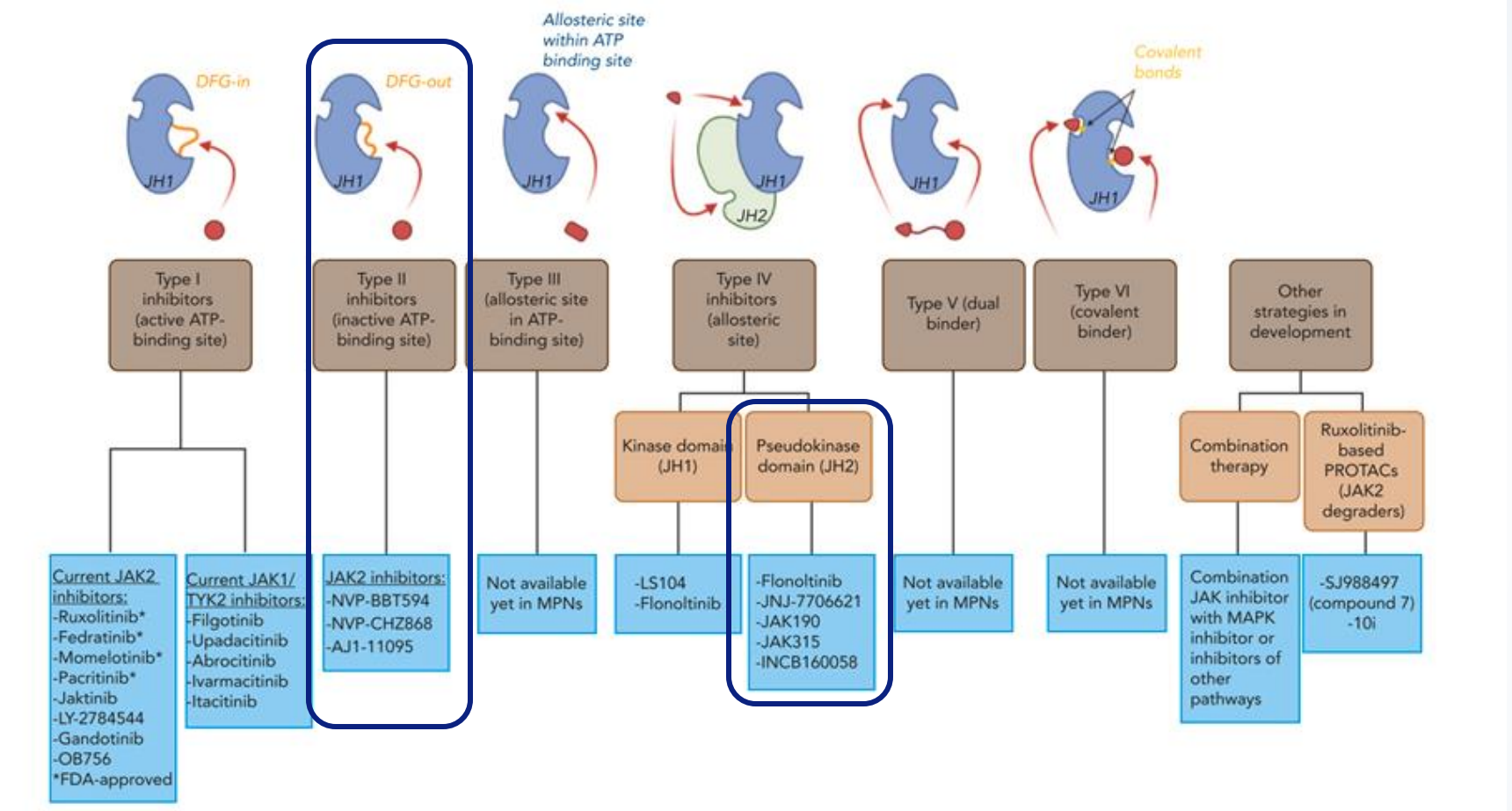


Limitations:

- Does not impact disease progression
- Cytopenias
- Loss of response over time
- Treatment discontinuation is common
- Poor outcomes after discontinuation

Verstovsek S, et al. *N Engl J Med* 2012; 366(9):799-807. Verstovsek S, et al. *Journal of Hematology & Oncology* 2017; 10:156
Palandri F, et al. *Leuk Res* 2025; 154:107719

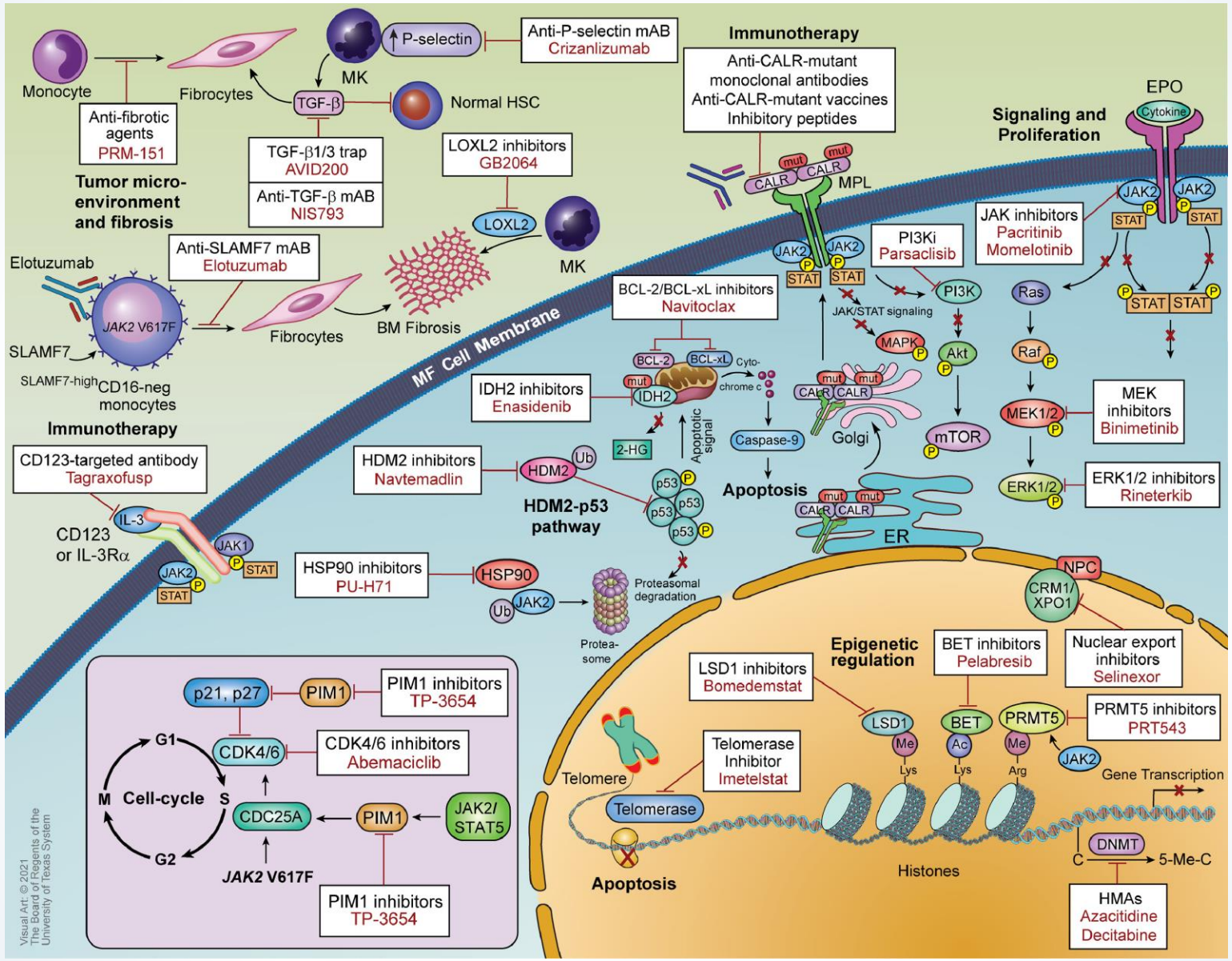
The Next Generation of JAK Inhibitors



- Mutation-specific JAKi (e.g. INCB160058) highly selective for JAK2V617F
- “Type 2” JAKi’s may overcome JAKi persistence.

Constantinescu SN, et al. *Blood* 2026;147(12):1255-1266. Koppikar P, et al. *Nature* 2012;489(7417):155-159
Rai S, et al. *Blood* 2022; 140(supplement 1): 6722-6723. Meyer SC, et al. *Cancer Cell* 2015;28(1):15-28.
Stubbs MC, et al. *Blood* (2023) 142 (Supplement 1): 860

Moving Beyond JAK Inhibition in MPNs



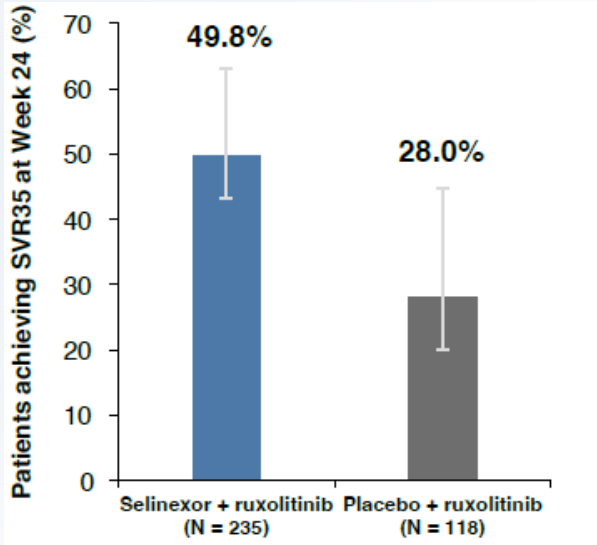
Chiftoides HT, et al. *Clin Lymph, Myeloma, Leuk.* 2022;22(4):210-223

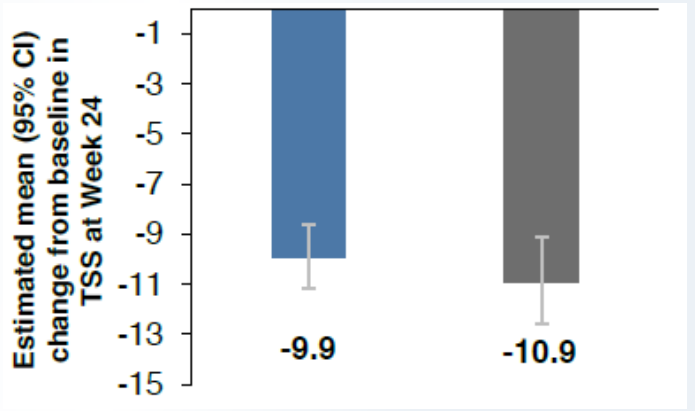
JAKi Combinations Hold Promise, but Haven't Broken Through (yet)

Pelabresib in combination with ruxolitinib in JAKi naïve patients

Endpoint	Pelabresib + Rux (n=214)	Placebo + Rux (n=35.2%)	P value
SVR35 wk 24	65.9%	35.2%	<0.001
SVR35 wk 96 (Pts on treatment)	45.3% (91%)	30.1% (57.5%)	
TSS Change wk 24	-15.99	-14.05	0.0545
TSS Change wk 96	-15.07	-12.48	
RBC Transfusion requirement wk 96	33.1%	39.9%	
Leukemia transformation	5.1%	3.7%	
Overall Survival			HR 0.986

Selinexor in combination with ruxolitinib in JAKi naïve patients



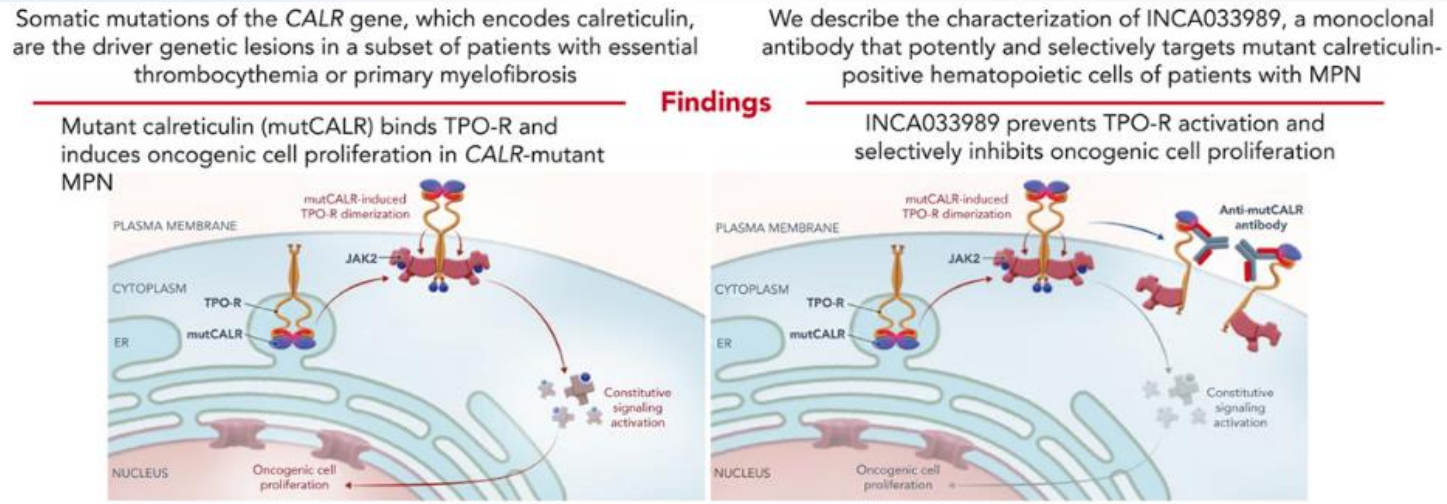


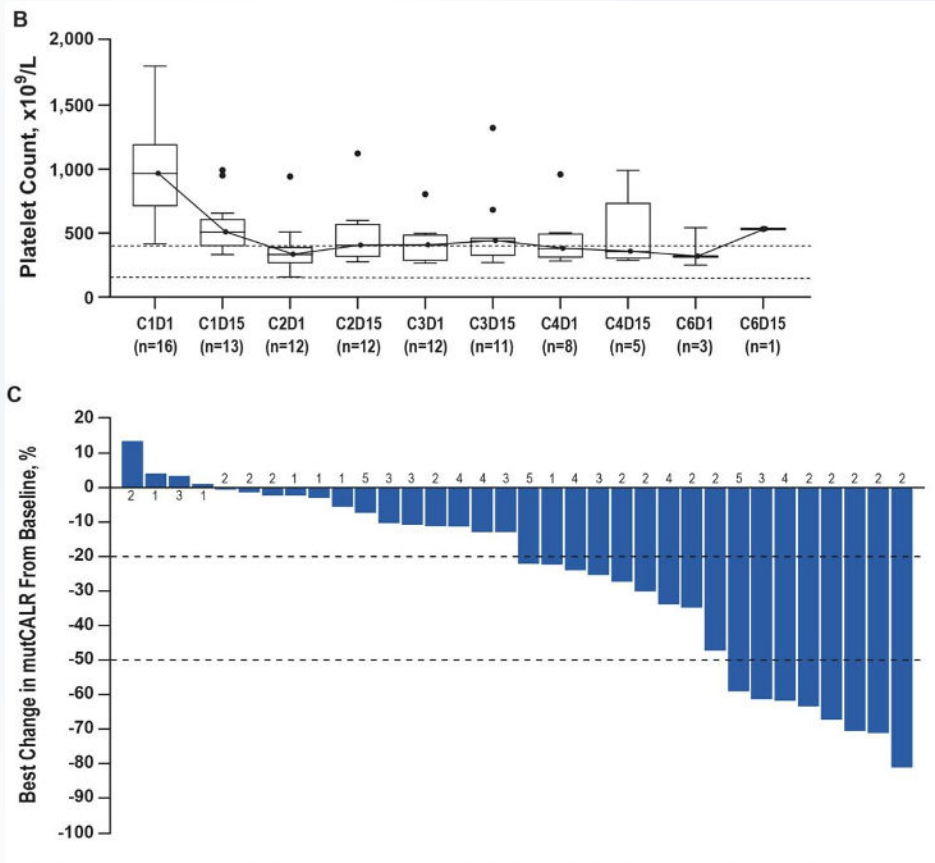
At week 48, improved OS (HR 0.48, p=0.02).

SVR35 was associated with OS

Rampal R, et al. *Blood* (2025) 146 (Supplement 1): 910. Rampal RK, et al. *Nat* Med 2025;31(5):1531-1538.
Bose P, et al. *J Clin Oncol* 2026.

Targeting Mutant *CALR* is a Promising Strategy in ET and MF





- Monoclonal antibodies
- Bispecific antibodies
- CAR T-cells
- ADCs
- Vaccines

Reis ES, et al. Blood. 2024 Nov 28;144(22):2336-2348. Mascarenhas J, et al. *EHA* (2025). Mascarenhas J, et al. *Blood* (2025) 146 (Supplement 1): 484. Gupta V, et al. *Blood* (2025) 146 (Supplement 1): 1024

Summary

- Significant advances have been made in our understanding of MPN biology, which has improved therapeutic options (namely JAK inhibitors).
- Real-world data demonstrates inferiority compared to prospective trials and poor adherence to treatment guidelines.
- Evolution in risk stratification (PV and ET), treatment goals, and trial endpoints are necessary.
- With numerous drugs in development, clinical trial enrollment should be prioritized to advance the field.

Q&A