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Beyond JAK Inhibition in Myeloproliferative Neoplasms

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Disclosures

- Consulting/Honoraria: GSK, Cogent Biosciences, PharmaEssentia, Blueprint Medicines, Sobi (formerly CTI biopharma)

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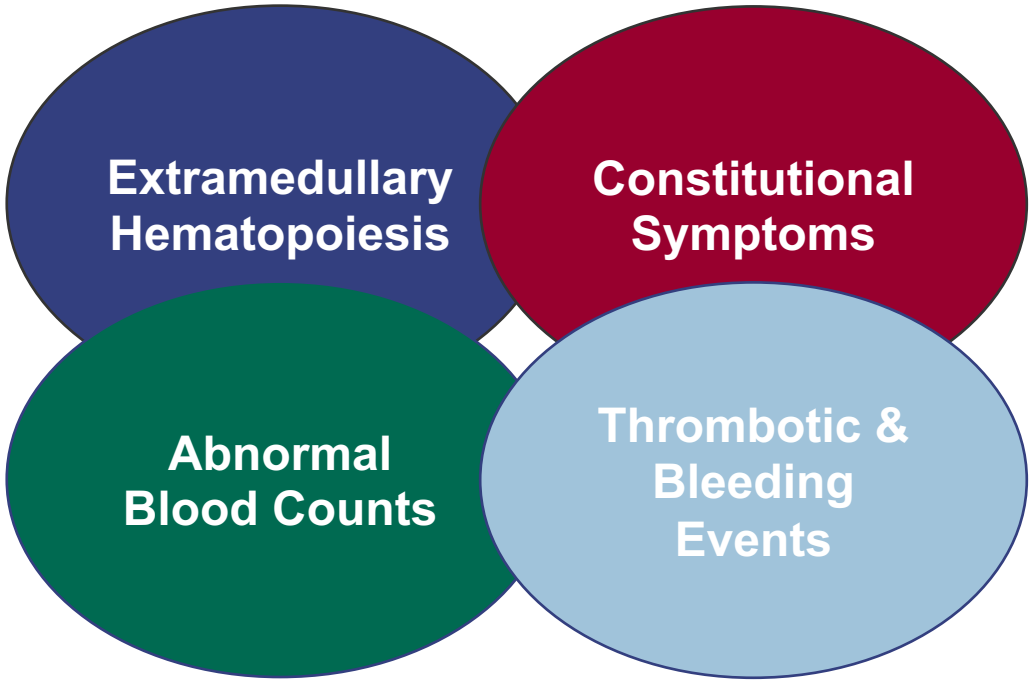
Myeloproliferative Neoplasms (MPNs)

- Clonal hematopoietic stem cell disorders characterized by myeloproliferation and aberrant inflammatory cytokine signaling
- Propensity for fibrotic and/or leukemic transformation

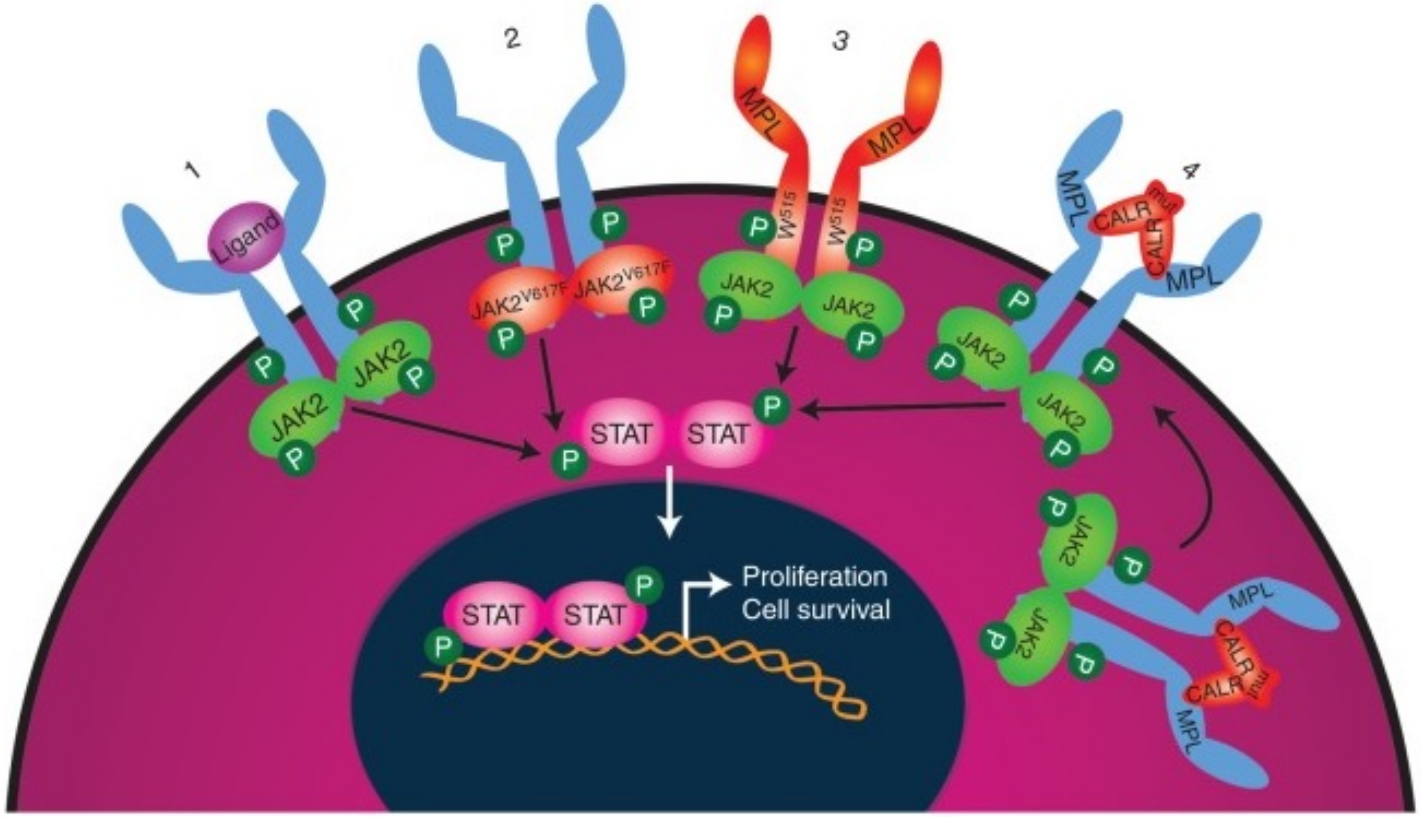
Table 1. Myeloproliferative neoplasms.

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



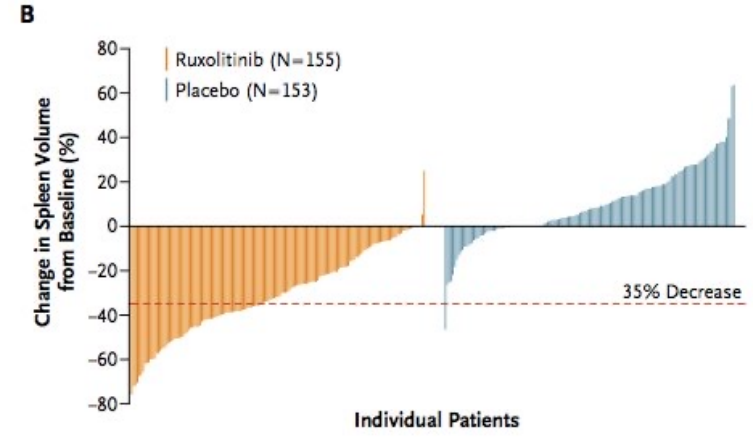
Khoury JD, et al. *Leukemia* 2022; 36:1703-1719

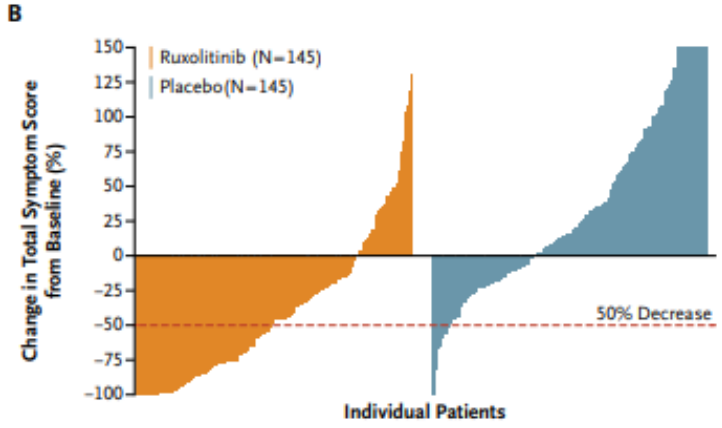
Activated JAK-STAT Signaling is Central to MPN Pathogenesis



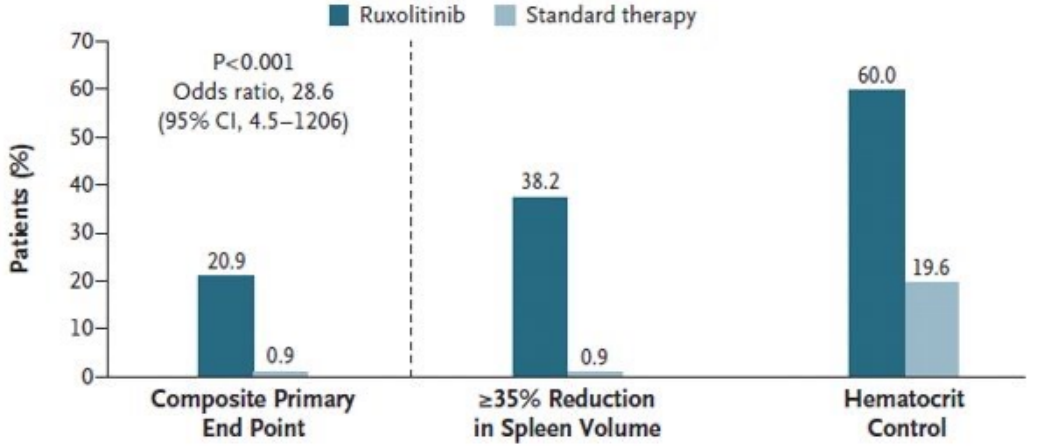
JAK Inhibitors Change the Treatment Paradigm in MPNs: Ruxolitinib

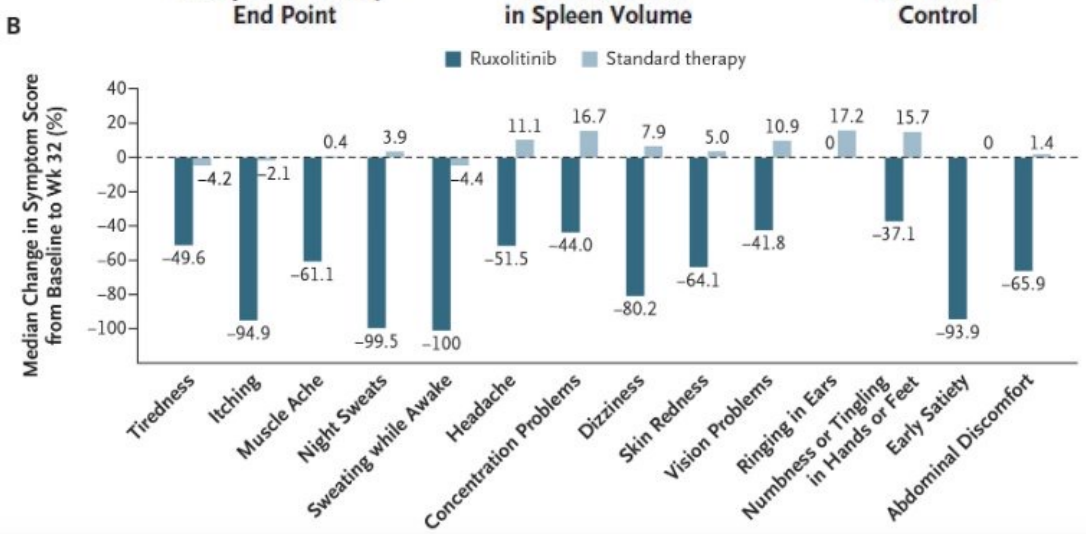
Myelofibrosis





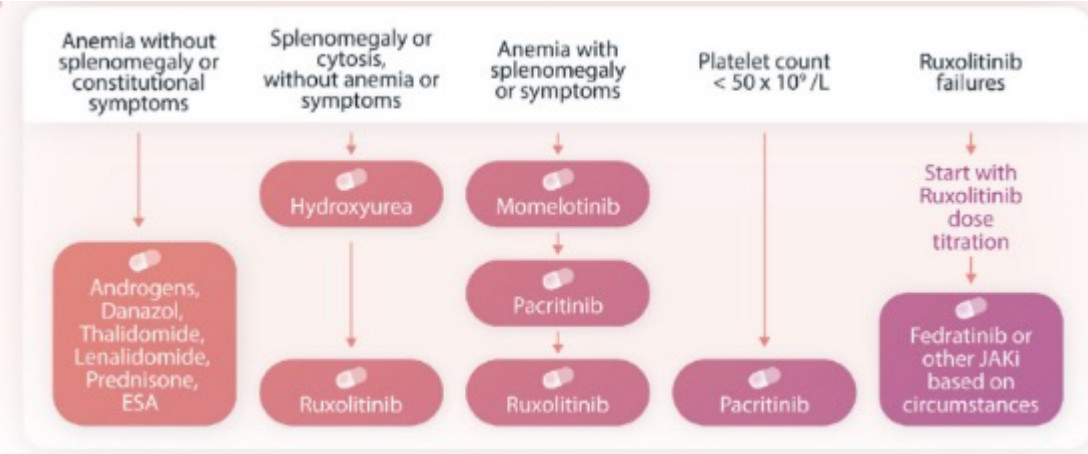
Polycythemia Vera





Verstovsek S, et al. *N Engl J Med* 2012; 366(9):799-807. Harrison C, et al. *N Engl J Med* 2012; 366(9): 787-98.
Verstovsek S, et al. *Journal of Hematology & Oncology* 2017; 10(1):156
Vannucchi A et al, *N Engl J Med*, 2015, 372: 428-435. Passamonti F, et al. *Lancet Oncol* 2017; 18:88-99

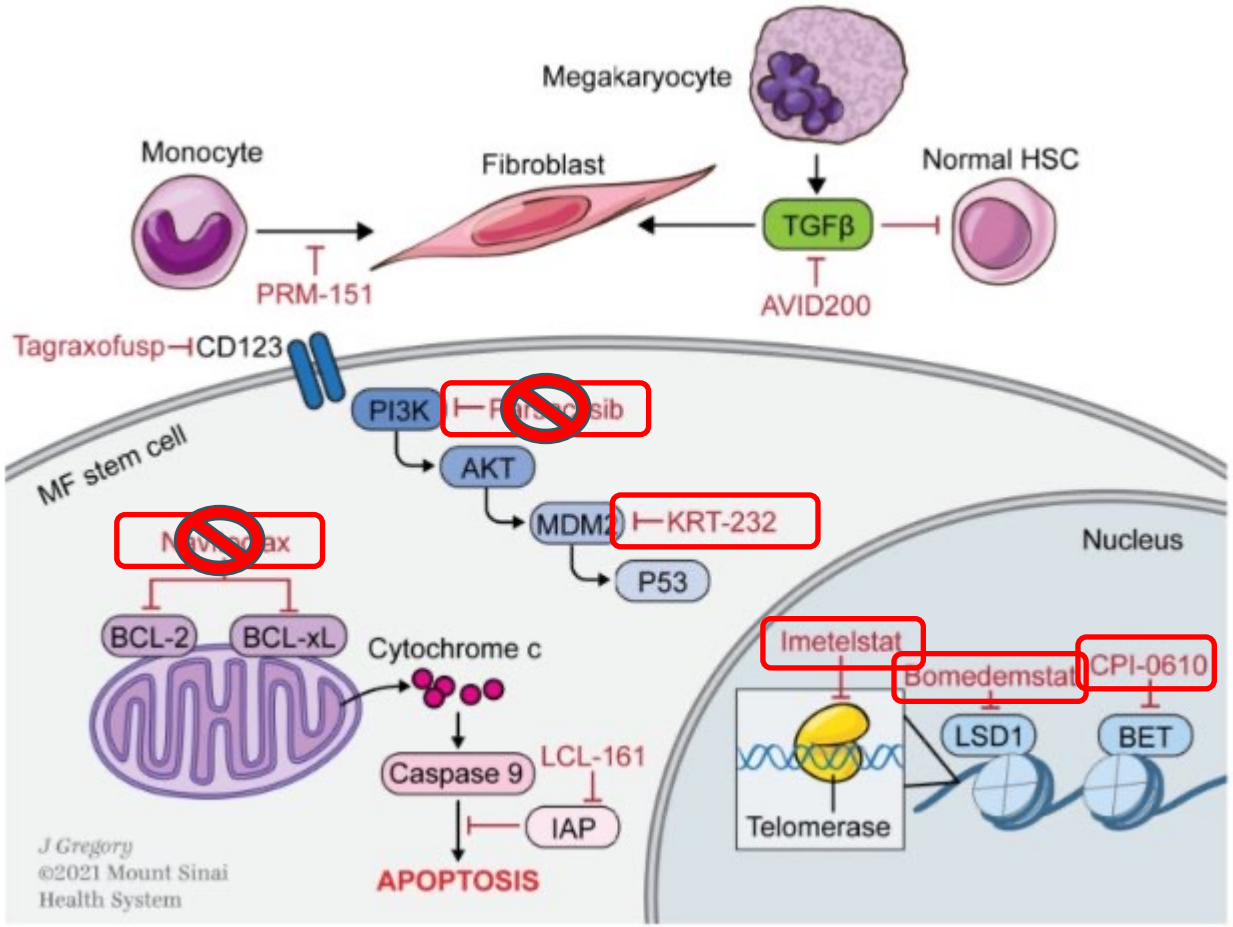
JAK Inhibitors in Myelofibrosis: Four Agents Now Approved



- While improvement in overall survival has been observed with ruxolitinib, JAK inhibitors are not curative
- Molecular and pathologic responses are uncommon
- Cytopenias and other toxicities can be challenging
- Median duration of treatment with ruxolitinib ~9-18 months
- Historical outcomes after ruxolitinib failure are poor (~11-14 months)

Tefferi A, et al. *Haematologica.* 2023;108:2919-2932. Al-Ali HK, et al. *Haematologica.* 2016; 101(9):1065-73. Palandri F, et al. *Cancer*. 2022; 6(6):1855-1864. Kuykendall AT, et al. *Ann Hematol*. 2018; 97(3):435-441. Passamonti F, et al. *Future Oncol.* 2022; 18(18):2217-2231. Mascarenhas J, et al. *J Med Econ.* 2022; 23(7):721-727. Koschmieder S, et al. *Ann Hematol.* 2023; 102(12):3383-3399.

Emerging Targets in MPNs



- TP-3543 (PIM Kinase inhibitor)
- Aurora Kinase inhibitors
- Selinexor
- PXS-5505 (LOX inhibitor)
- ALK2/ACVR1 (INCB00928)
- Rusfertide (Hepcidin Mimetic; PV)
- KER-050 (activin receptor type IIA ligand trap)
- Luspatercept

- JAK inhibitors:
  - Jaktinib
  - "Mutation-specific" JAK inhibitors (INCB160058)
  - Type 2 JAK inhibitors

Tremblay D, Mascarenhas J. Cells. 2021 Apr 27;10(5):1034

Navitoclax: a BCL-2/BCL-XL Inhibitor in Myelofibrosis

Inclusion criteria (N~230)

- Aged ≥18 years with ECOG ≤2
- Intermediate-2 or high-risk MF with measurable splenomegaly (as defined by the DIPSS+)
- Evidence of MF-related symptoms
- No prior JAKi treatment

1:1 Randomization

Stratification factors:

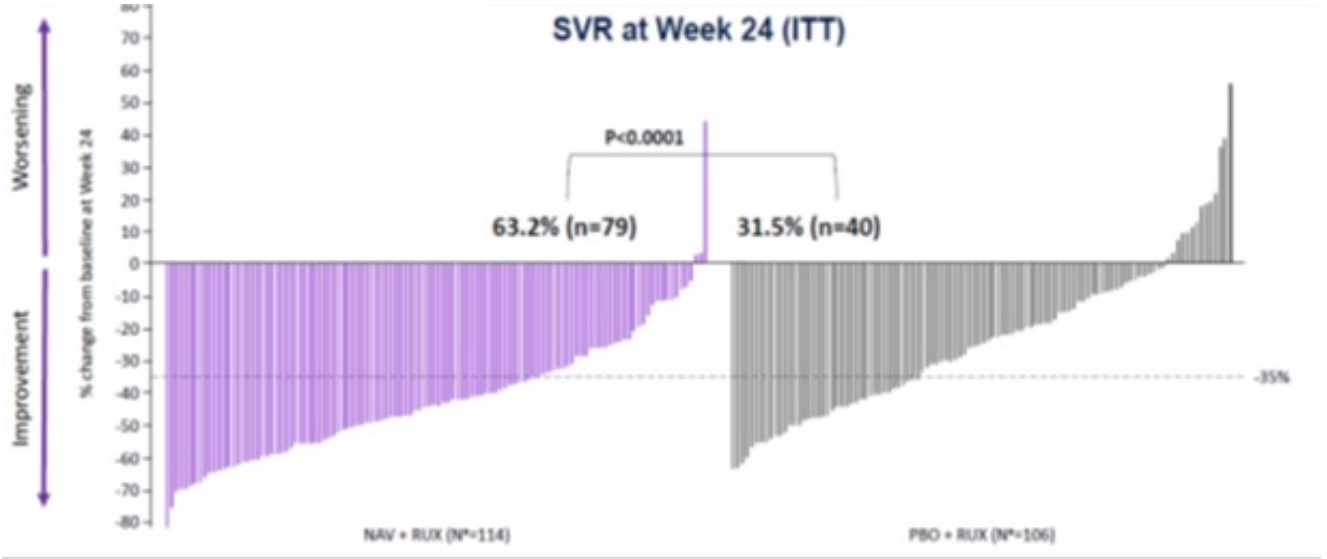
- Int-2 vs high-risk
- PLT ≤200 × 10^9/L vs >200 × 10^9/L

Experimental arm

- Ruxolitinib 15/20 mg BID[a]
- Navitoclax 100/200 mg QD[b]

Control arm

- Ruxolitinib 15/20 mg twice daily[a]
- Placebo



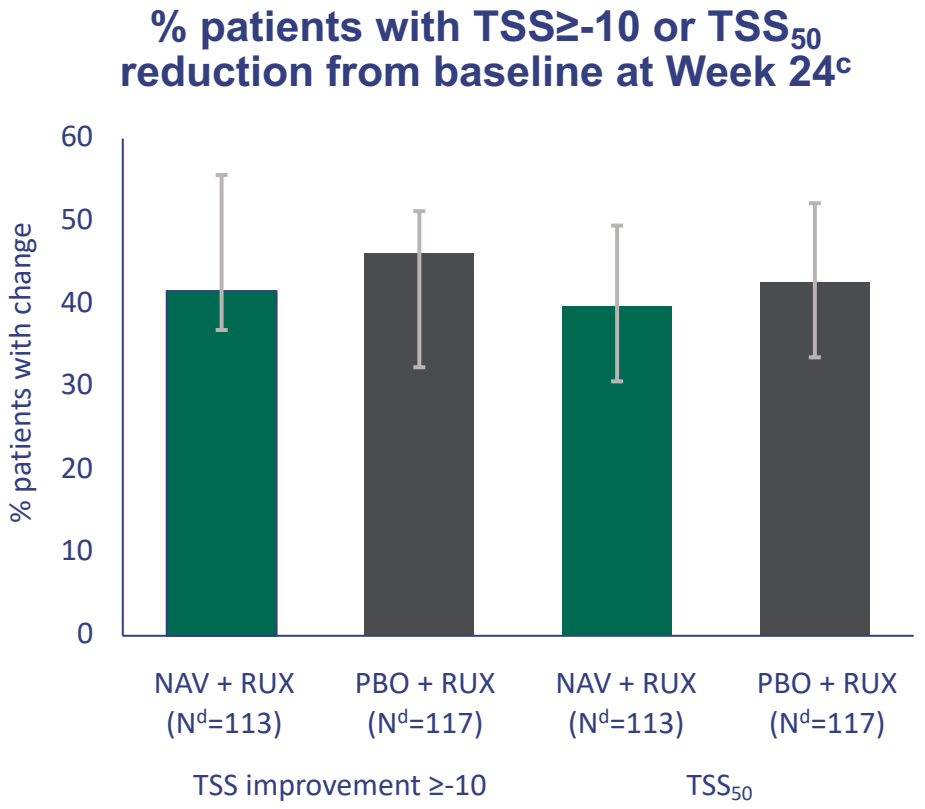
Pemmaraju N, et al. *Blood.* 2023; 142(Supplement 1): 620.
Pemmaraju N, et al *EHA* 2024, abstract S222

Navitoclax Fails to Improve Symptom Burden, Leads to Significant Myelosuppression: Development Halted

- At Week 24, the mean change in TSS from baseline:
  - -9.7 (95% CI: -11.8, -7.6) with NAV + RUX
  - -11.1 (95% CI: -13.2, -9.1) with PBO + RUX

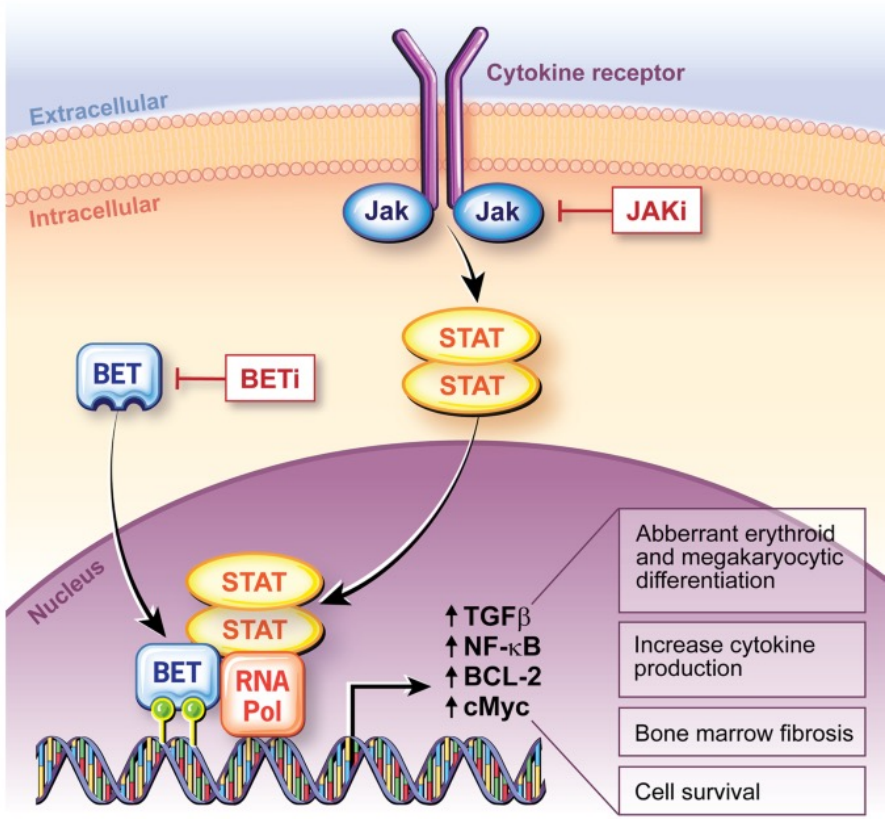
Table 2. Safety data

	NAV + RUX (N=124)	PBO + RUX (N=125)
Any AE	124 (100)	121 (97)
Any AE grade ≥3	105 (85)	87 (70)
Most common AEs (>30% patients receiving NAV)		
Thrombocytopenia, any grade [grade ≥3]	112 (90) [63 (51)]	62 (50) [19 (15)]
Anemia, any grade [grade ≥3]	74 (60) [57 (46)]	61 (49) [49 (39)]
Diarrhea, any grade [grade ≥3]	42 (34) [6 (5)]	17 (14) [0]
Neutropenia, any grade [grade ≥3]	56 (45) [47 (38)]	7 (6) [5 (4)]
Any serious AE	32 (26)	40 (32)
All deaths	13 (10)	13 (10)
Deaths <30 days following last dose of study drug	6 (5)	5 (4)



Pemmaraju N, et al. *Blood.* 2023; 142(Supplement 1): 620. Pemmaraju N, et al *EHA* 2024, abstract S222

Pelabresib: a Bromodomain and Extra-Terminal (BET) Protein Inhibitor in Myelofibrosis



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)

Treatment arm

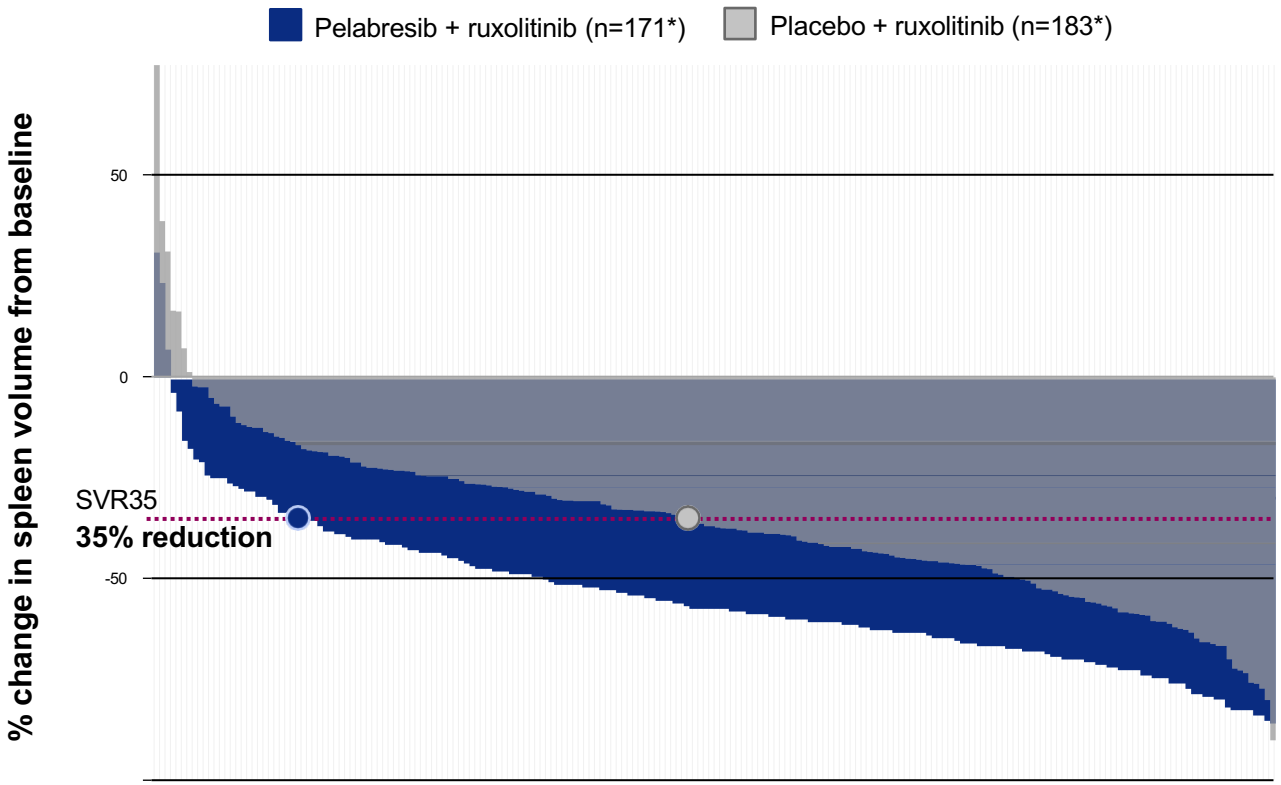
Pelabresib 125 mg* PO QD Day 1–14 + **Ruxolitinib** Per label with a 5-mg BID lower starting dose† Day 1–21

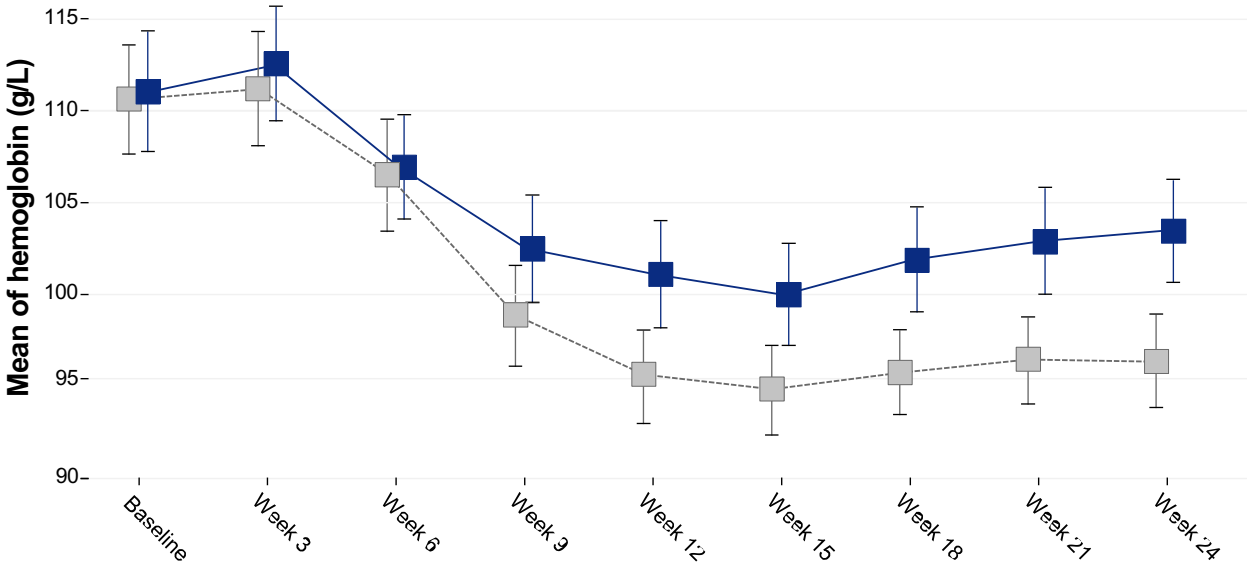
21-day cycles

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

Mascarenhas J, et al. *Leukemia* 2021; 35: 3361-3363. Rampal R, et al. *Blood* 2023; 142(Supplement 1): 628. Rampal R, et al. *EHA* 2024, abstract S221

Pelabresib Improves Splenomegaly and Anemia in Combination with Ruxolitinib in Myelofibrosis

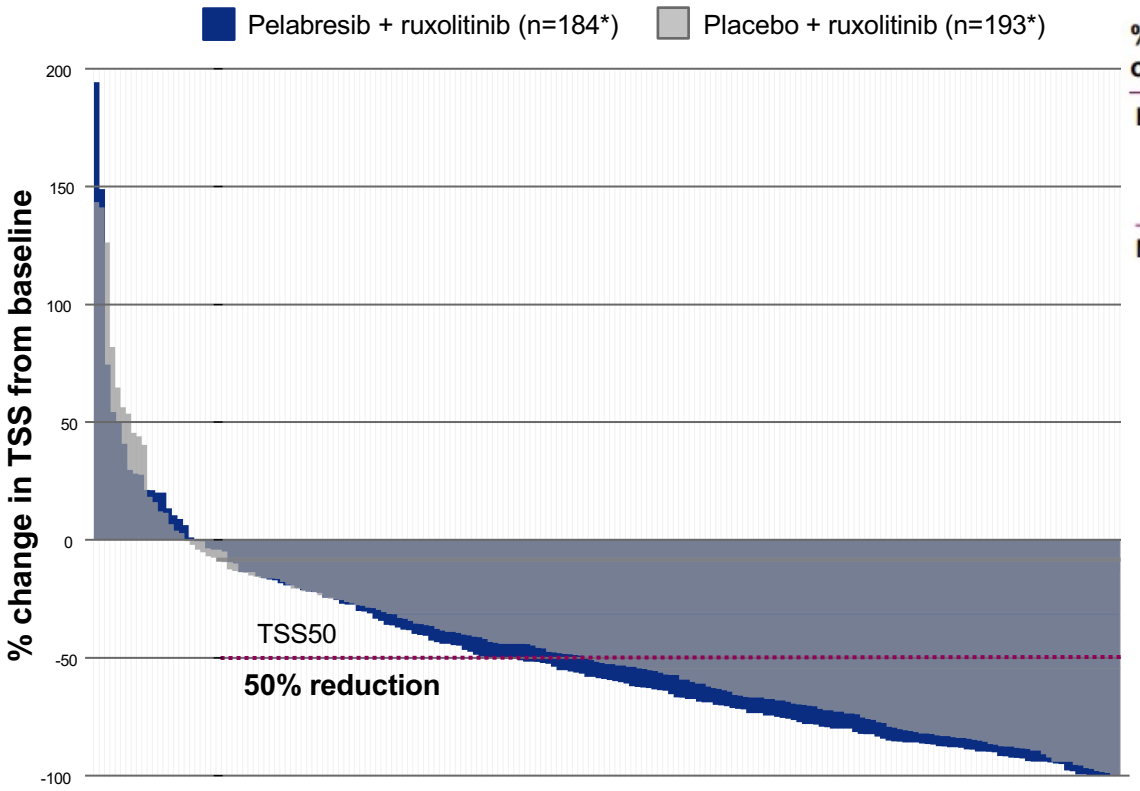


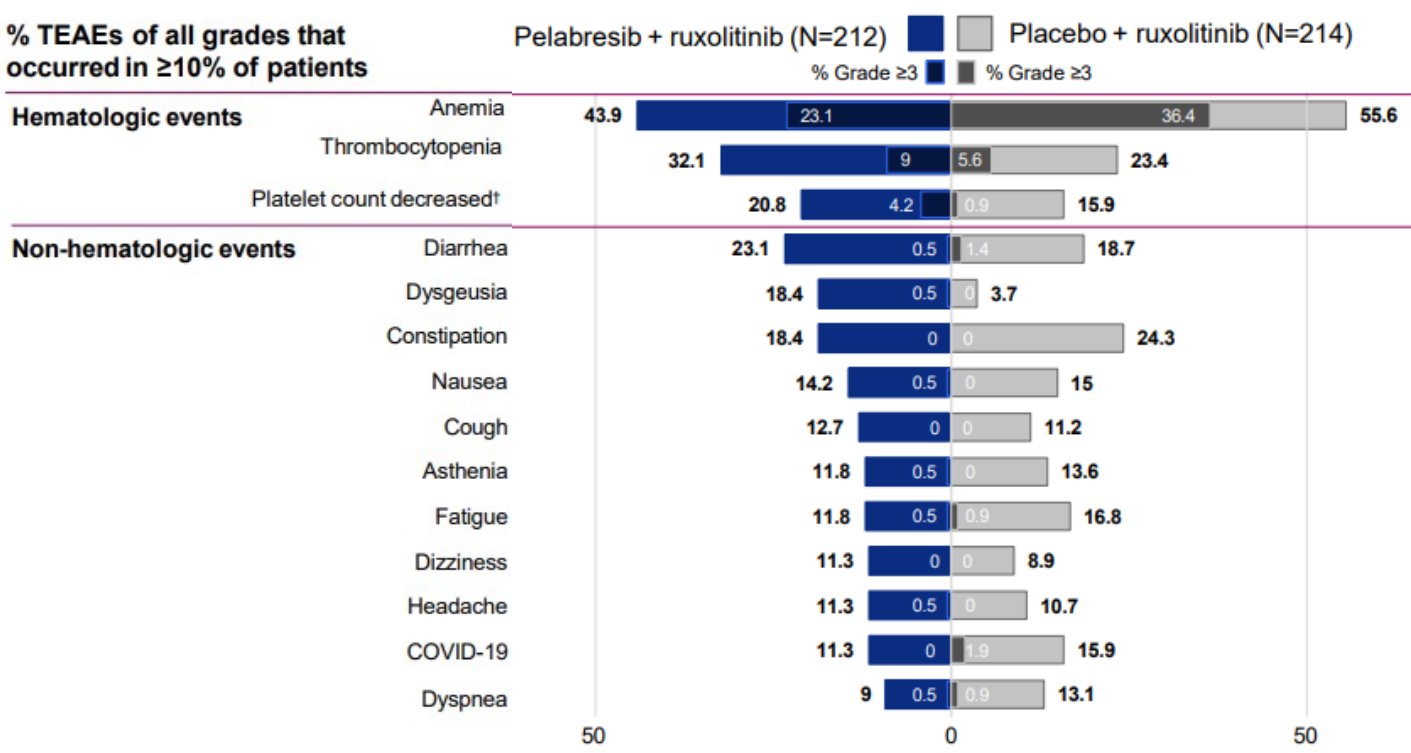


	Pelabresib + Rux	Placebo + Rux	P-value
SVR35 at Week 24	65.9%	35.2%	<0.001

Rampal R, et al. *Blood* 2023; 142(Supplement 1): 628. Rampal R, et al. *EHA* 2024, abstract S221

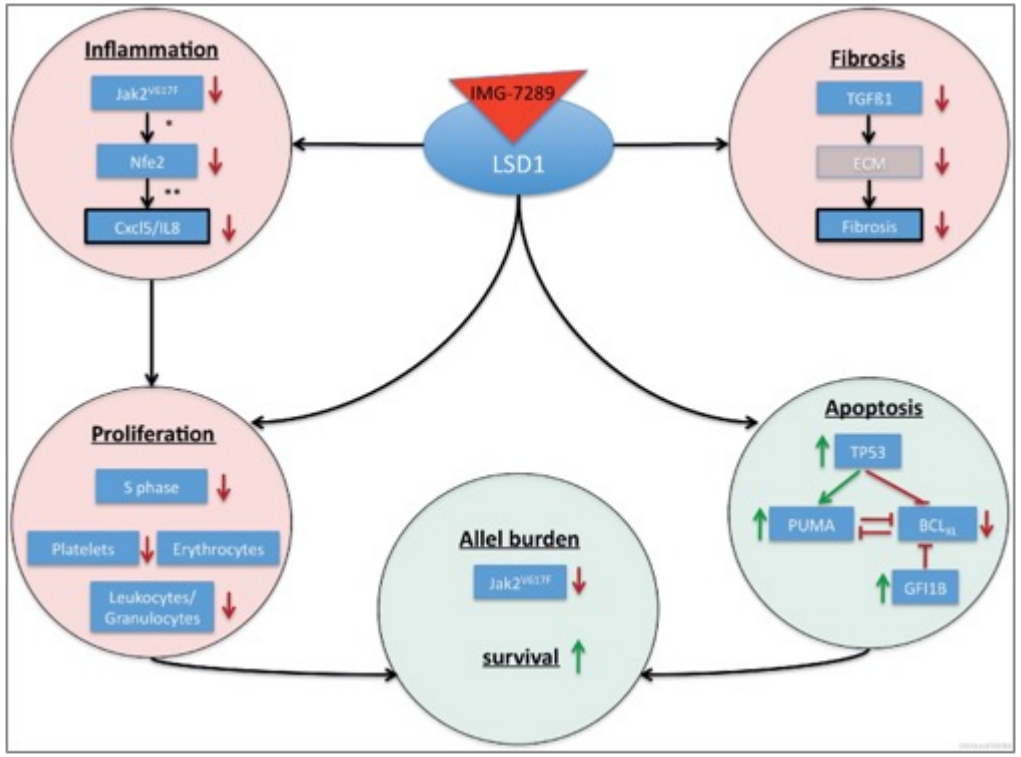
Pelabresib Fails to Improve Symptom Burden





	Pelabresib + Rux	Placebo + Rux	P-value
TSS50 at Week 24	52.3%	46.3%	0.216

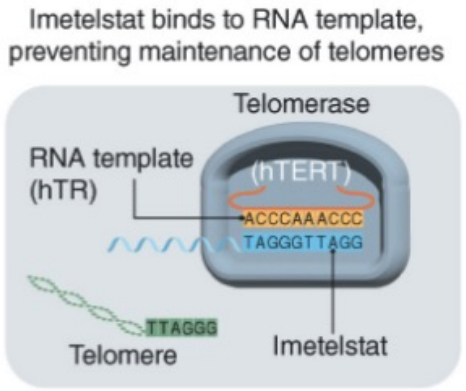
Bomedemstat: a Novel LSD1 Inhibitor with Clinical Activity in MPNs

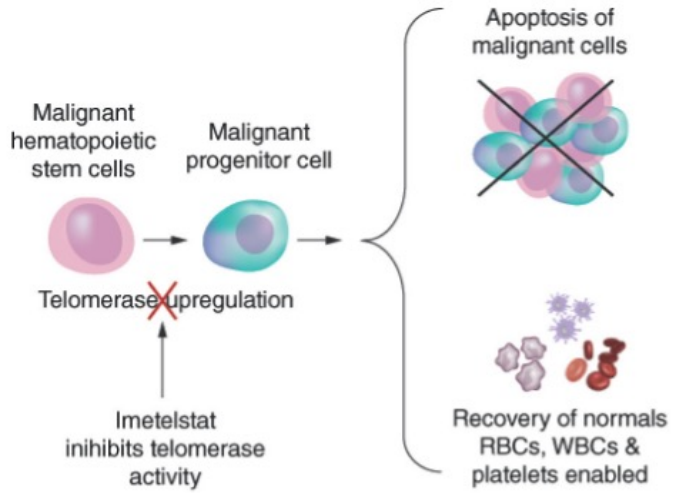


- LSD1: histone demethylase involved in epigenetic regulation
  - Plays a role in proliferation, self-renewal, and differentiation
  - Regulates megakaryocyte and erythrocyte maturation
- Early activity demonstrated in:
  - Essential Thrombocythemia
  - Polycythemia Vera
  - Myelofibrosis, in combination with ruxolitinib (treatment naïve and after JAK inhibitor failure)

Jutzi JS, et al. *Hemasphere* 2018; 2(3):e54. Gill H, et al. *Blood* 2022; 140 (Supplement 1):1784-87 Gill H, et al. *Blood* 2023; 142(supplement1):621. Palandri F, et al. *Blood* 2021; 138(Supplement 1):386. Rinaldi C, et al. *ASCO* 024, abstract TPS6595.

Imetelstat: Telomerase Inhibitor with Clinical Activity in Myelofibrosis





Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Symptoms Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)
Reduction in bone marrow fibrosis , n/N (%)	4/20 (20.0%)	16/37(43.2%)
≥ 25% Reduction in VAF of JAK2, CALR or MPL , n/N (%)	1/18 (5.6%)	8/19 (42.1%)

Mascarenhas J, et al. *Future Oncol.* 2022; 18(22): 2392-2402. Mascarenhas J, et al. *EHA Library 2020*; EP1107. Mascarenhas J, et al. *Blood* 2020; 136(Supplement 1):39-40

Imetelstat Impact on Overall Survival in JAK Inhibitor Refractory Myelofibrosis

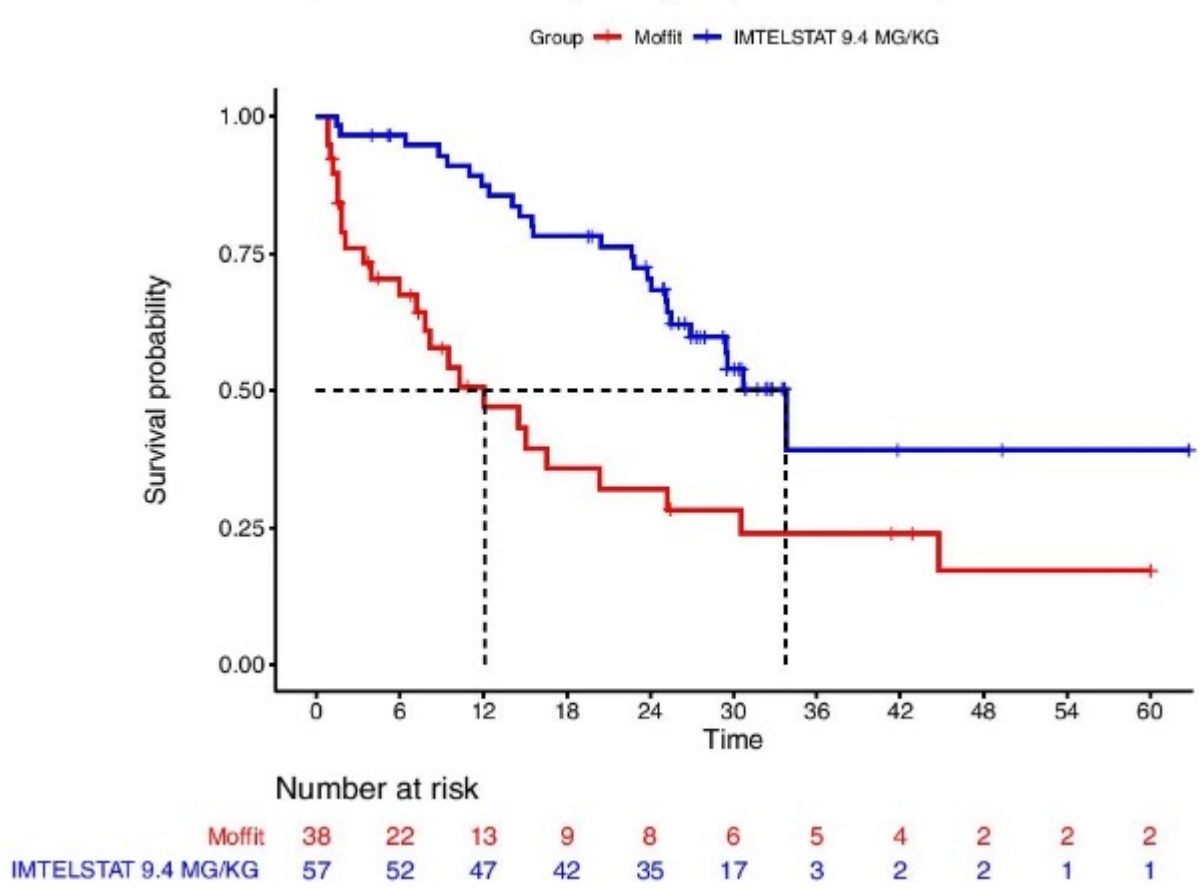
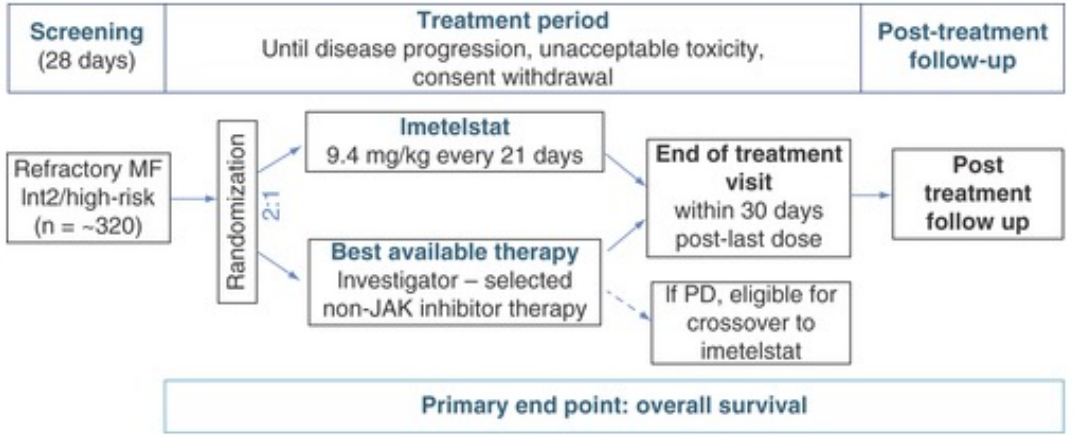


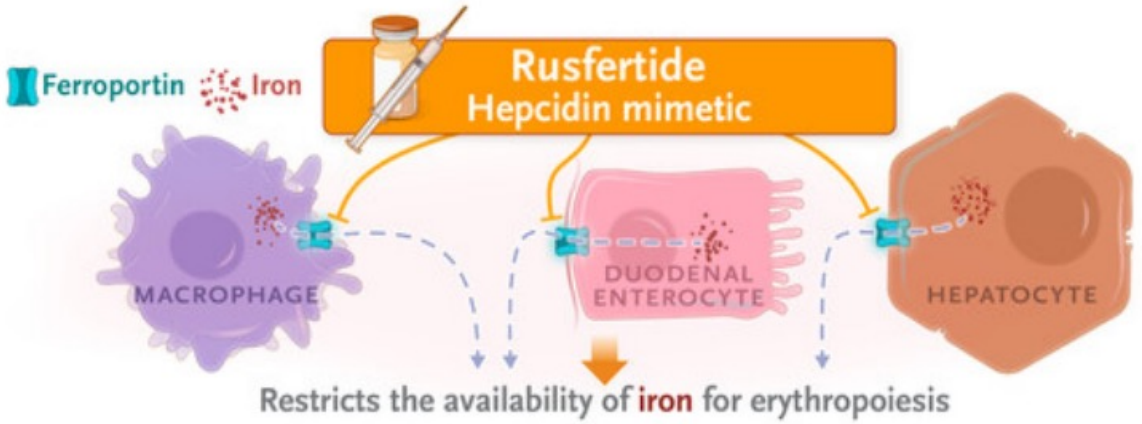
Figure 2. Phase III IMpactMF study design schema.

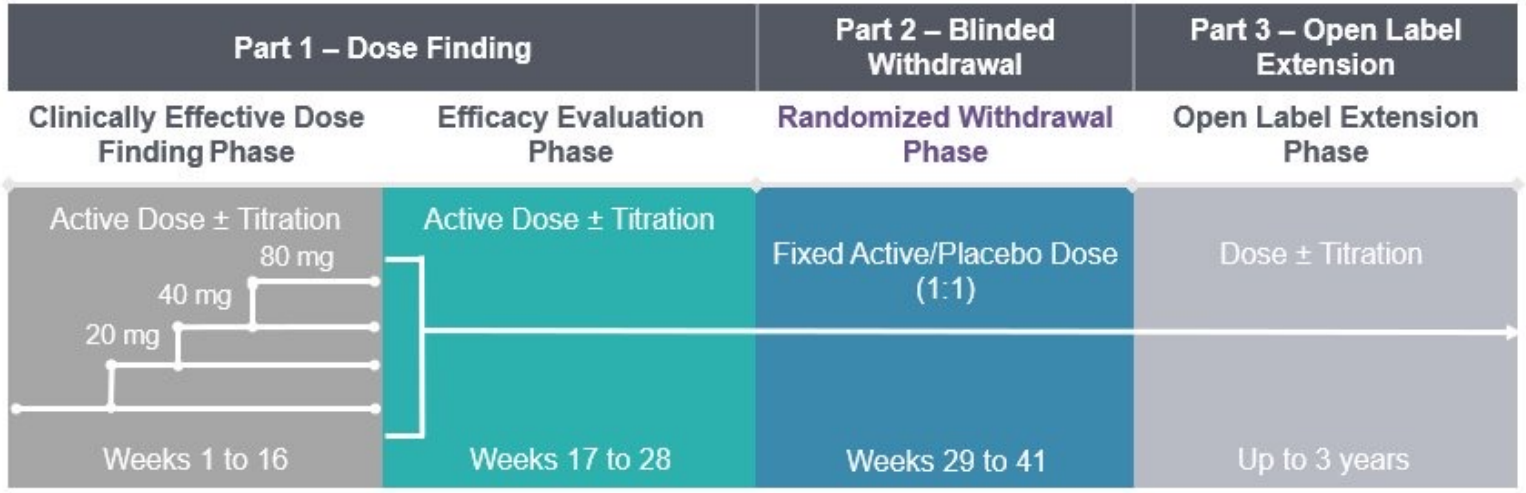
Int2: Intermediate-2; MF: Myelofibrosis; PD: Progressive disease.



Kuykendall AT, et al. *Annals of Hematology* 2021; 101: 139-146. Mascarenhas J, et al. *Future Oncol.* 2022; 18(22): 2392-2402.

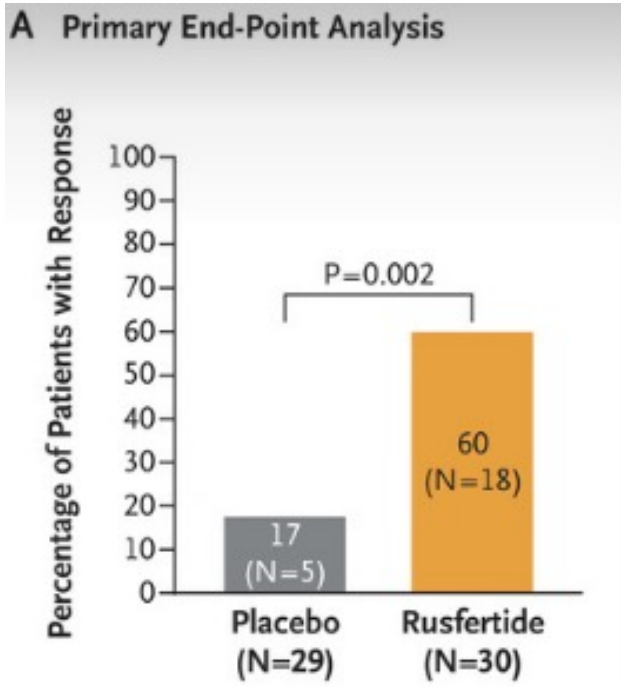
Rusfertide: a Novel Hepcidin Mimetic in PV

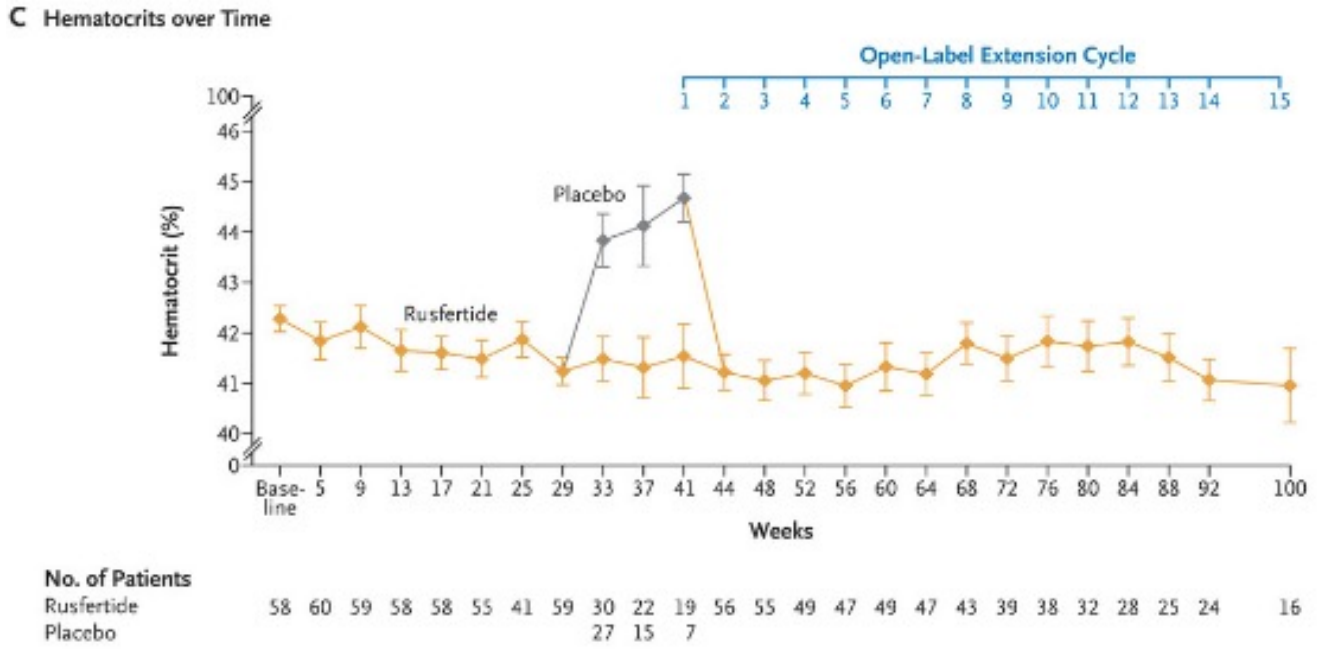




Kremyanskaya M, et al. *N Engl J Med.* 2024;390:723-735.
Ritchie EK, et al. *Blood*. 2023; 142 (Supplement 1): 745.

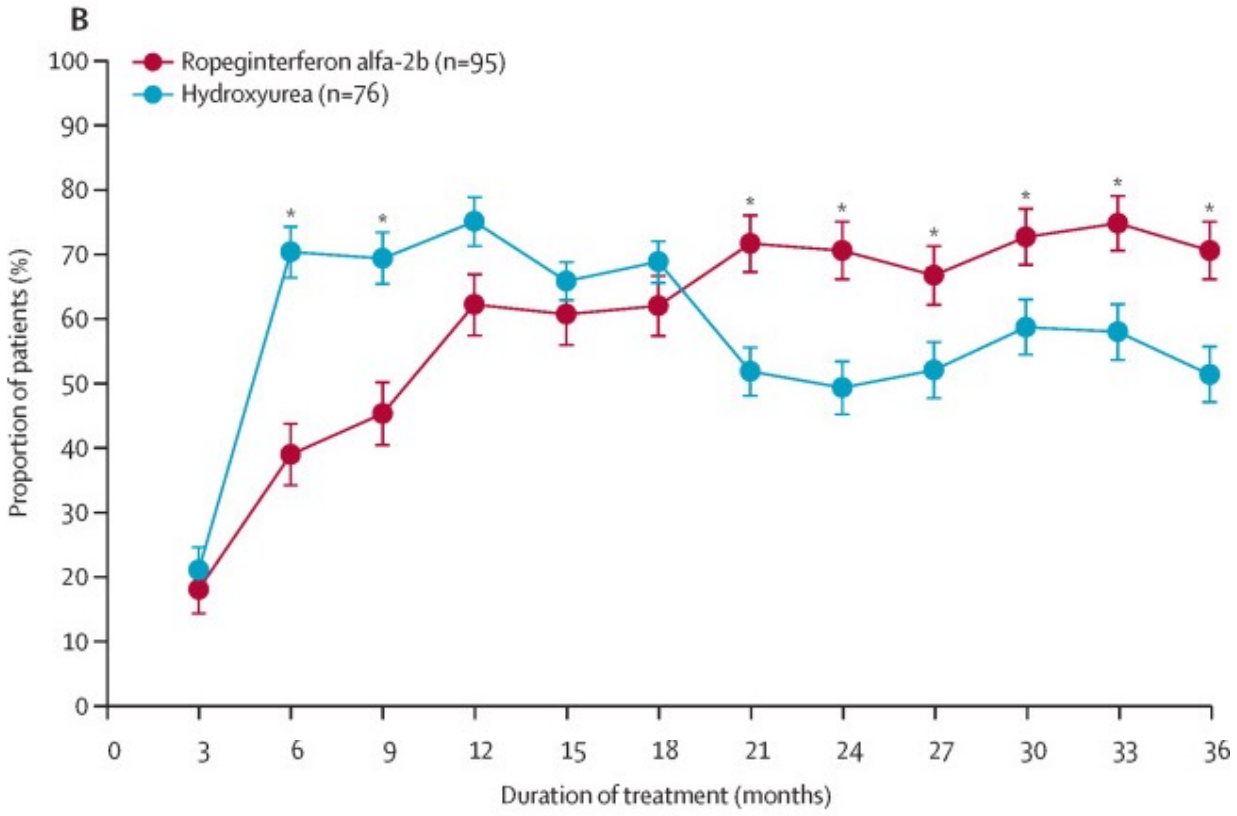
Rusfertide Effectively Controls Hematocrit in Phlebotomy-Dependent PV

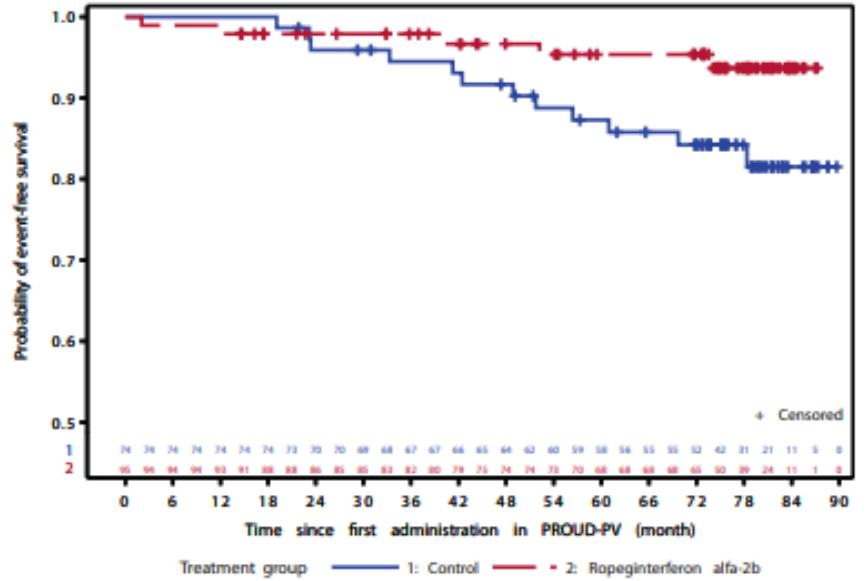




Interferon: An Oldie but a Goodie

*Ropeginterferon alfa-2b approved for the treatment of PV in November, 2021





At 6 years	Hydroxyurea	Ropeginterferon
Molecular Response	19.4%	66.0%
Median *JAK2* V617F allele burden	50.4%	8.5%

Gisslinger H, et al. L*ancet Haematol*. 2020; 7:e196-208.
Gisslinger H, et al. *Leukemia.* 2023; 37:2129-2132.

Conclusions

- JAK inhibitors have revolutionized the treatment of MPNs
  - Outcomes remain suboptimal, particularly in myelofibrosis
- Numerous agents are currently under investigation targeting a wide array of cellular pathways
- JAK inhibitor-based combination therapies appear the most likely path forward to improve outcomes in myelofibrosis
- Patients with myelofibrosis should be treated on a clinical trial whenever possible

Thank You

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