2025 DEBATES AND DIDACTICS in Hematology and Oncology

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Emerging Targets in Myeloproliferative Neoplasms

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Disclosures

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

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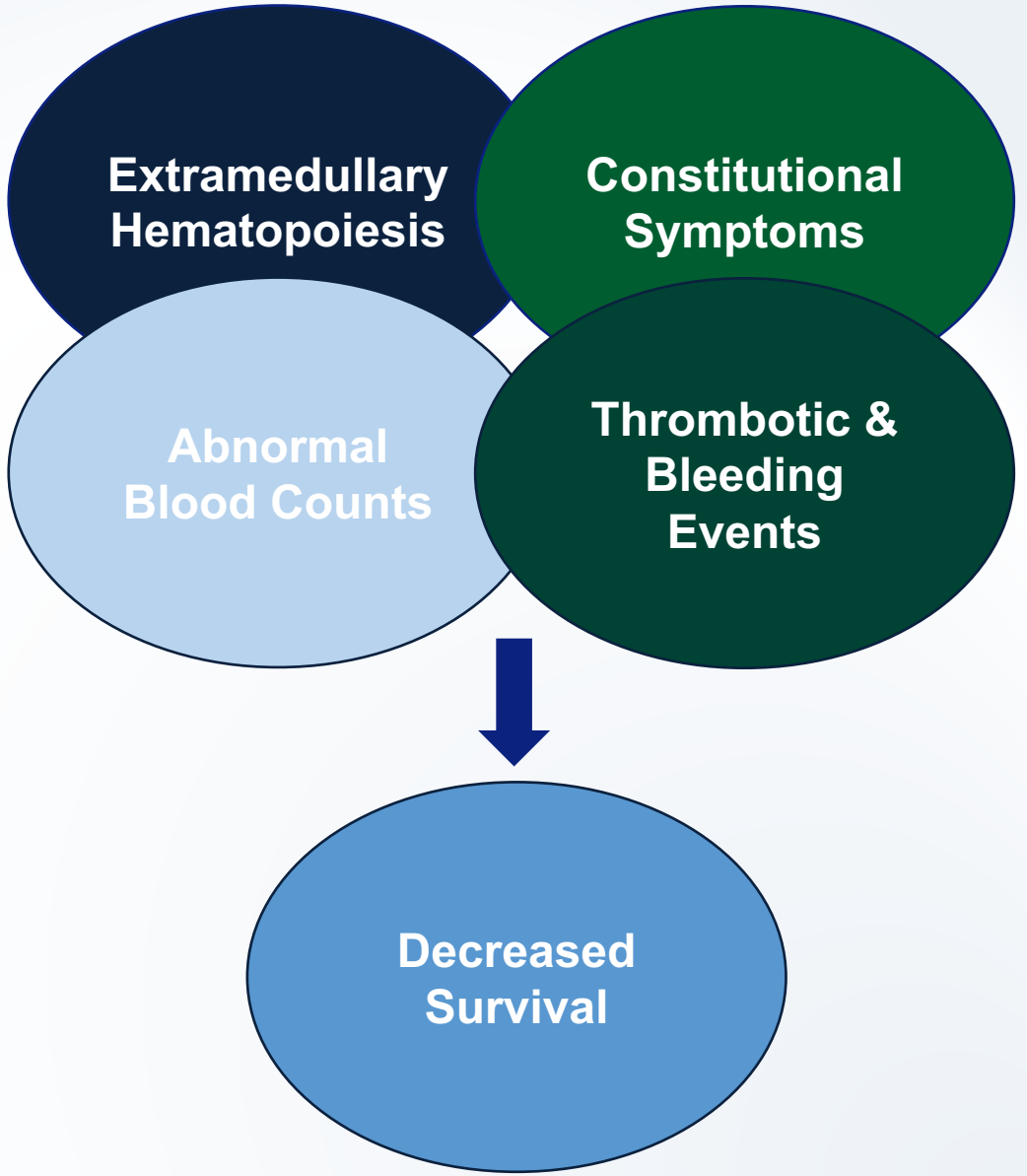
Myeloproliferative Neoplasms (MPNs)

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

Propensity for fibrotic and/or leukemic transformation

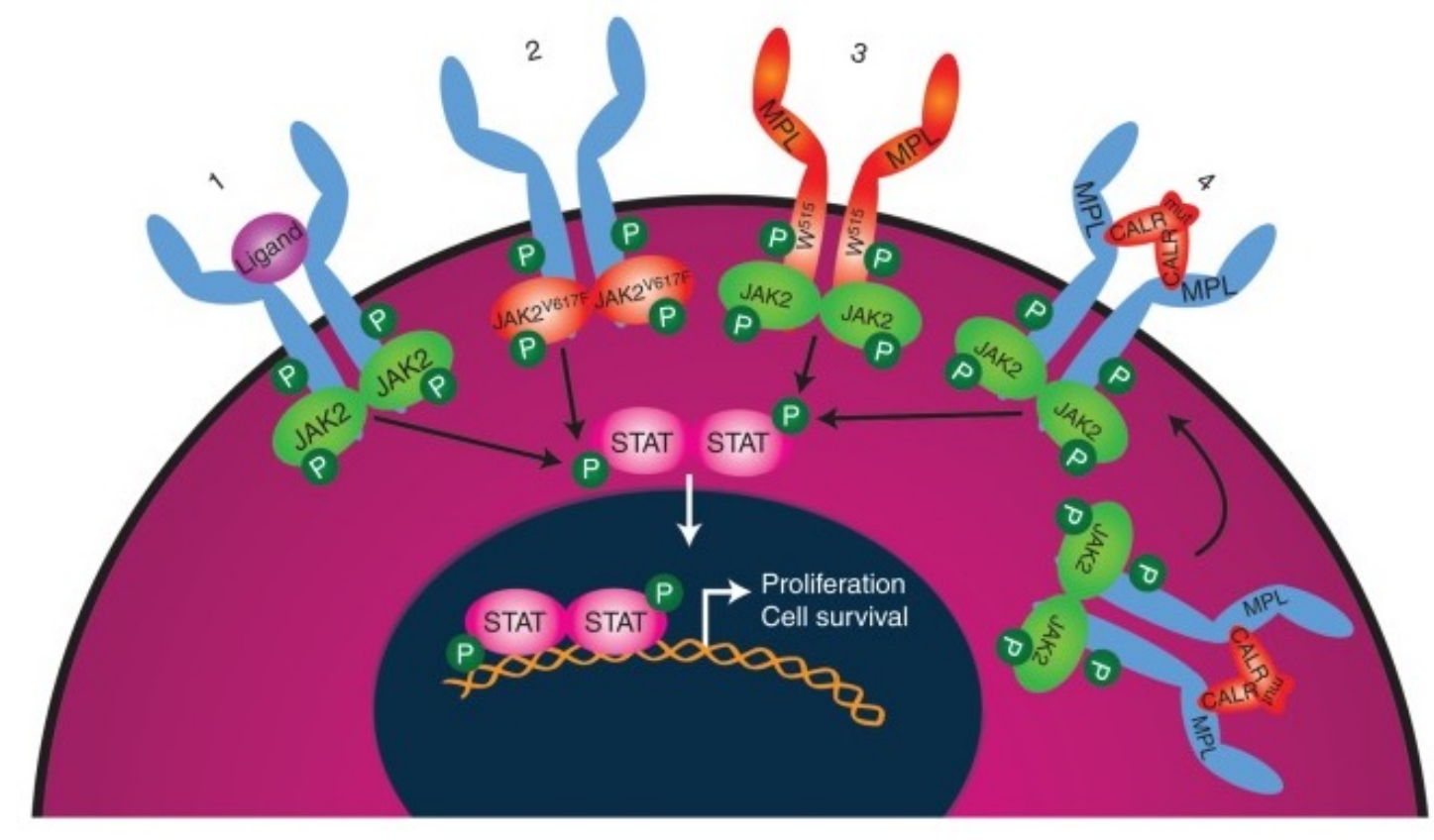
Table 1. Myeloproliferative neoplasms.

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



We Have Options Now: Approach to JAKi Therapy in Symptomatic Myelofibrosis

Not all patients require a JAKi at diagnosis

Frontline, Proliferative

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

Frontline, Cytopenic

Platelets <50

- **Pacritinib**

Anemia

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

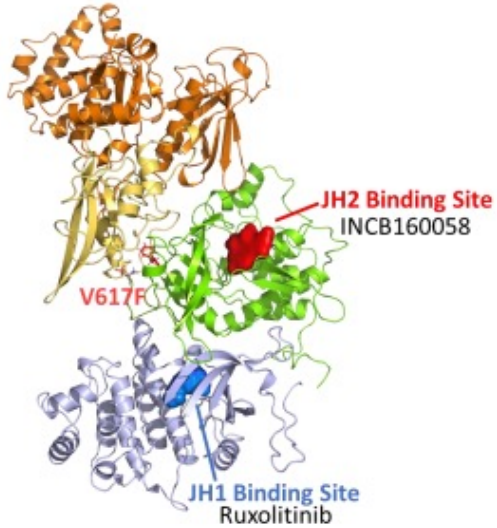
Second Line (Rux failure)

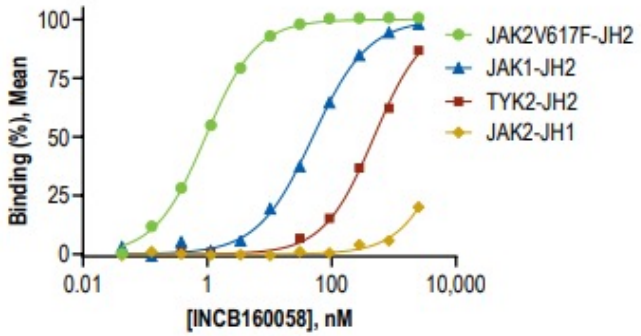
- Fedratinib
- Momelotinib
- Pacritinib
- *Novel agents

*Patients should be considered for clinical trials and allo-HCT whenever possible

Novel JAKi's in Development

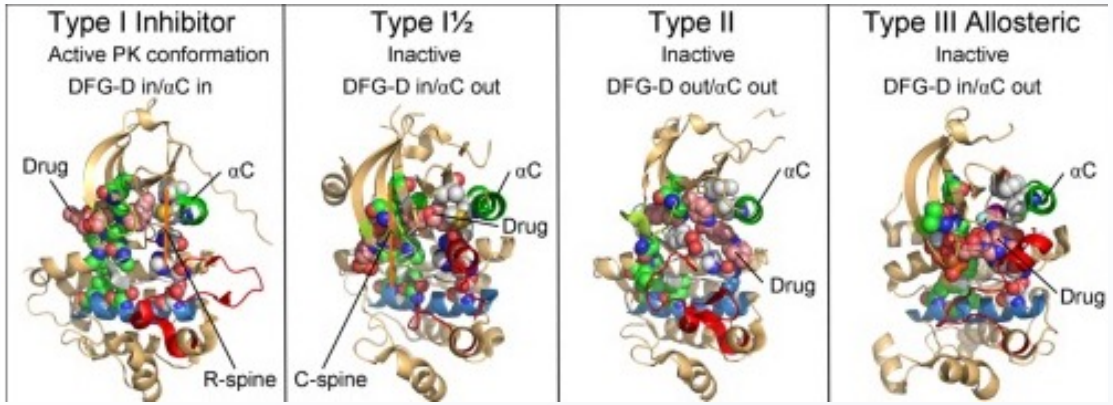
V617F mutation-specific JAK inhibitor





	Selectivity for JAK2V617F-JH2
JAK2-JH1	>2500×
JAK1-JH2	50×
TYK2-JH2	500×

"Type 2" JAK inhibitors

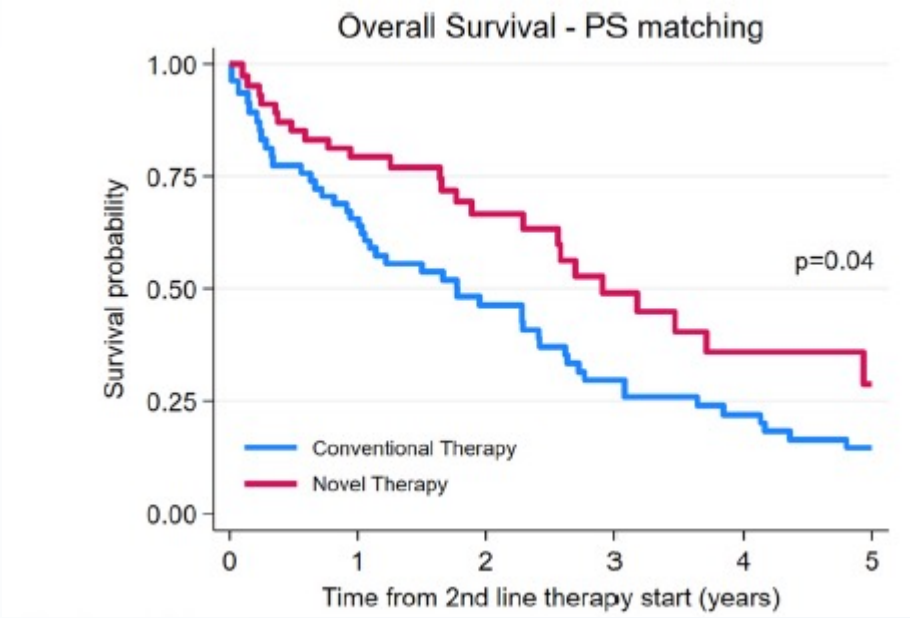


- Existing JAKi are "type 1".
- Type 1 inhibitors develop a form of acquired resistance termed "persistence"
  - This can be overcome with Type 2 inhibitors

Stubbs MC, et al. *Blood* (2023) 142 (Supplement 1): 860
Roskoski R, et al. *Pharmacological Research* 2016 103:26-48

JAK inhibitors: Are They Enough?

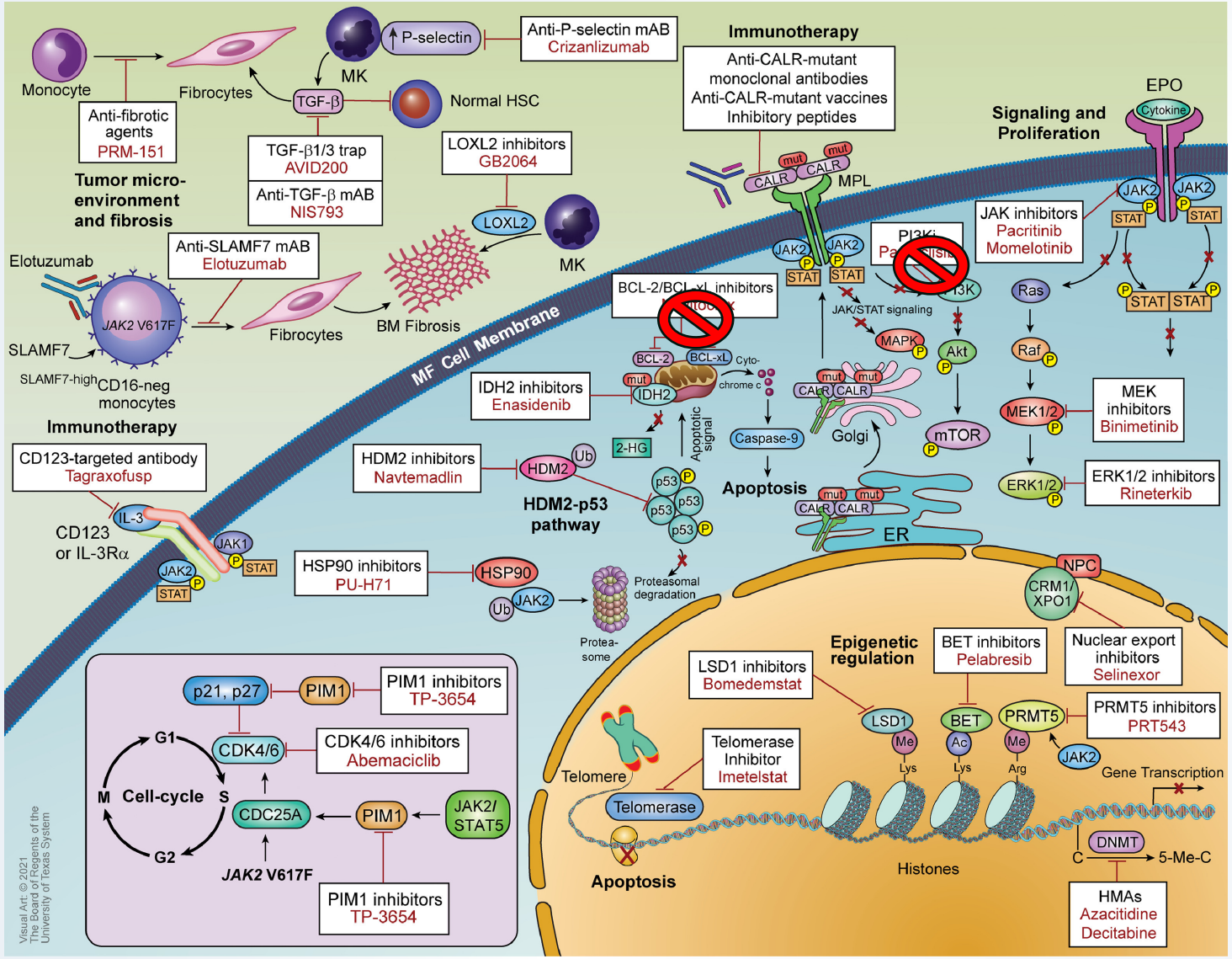
- In myelofibrosis, JAKi are not curative and generally do not demonstrate disease-modifying activity
  - Do not decrease rate of leukemic transformation
  - Bone marrow responses, molecular responses are rare
    - In PV, substantial reduction in JAK2 allele burden has been demonstrated (MAJIC-PV study)
- Real-world OS benefit observed in myelofibrosis (higher-risk, symptomatic patients)
  - Likely a result of improvements in splenomegaly, nutrition, and symptomatology
- In myelofibrosis, median time to discontinuation in the real-world setting is 12-18 months, with poor OS following discontinuation



Harrison CN, et al. *J Clin Oncol*. 2023;41(19):3534-3544
Palandri F, et al. *Leukemia Research* 2025 154: 107719

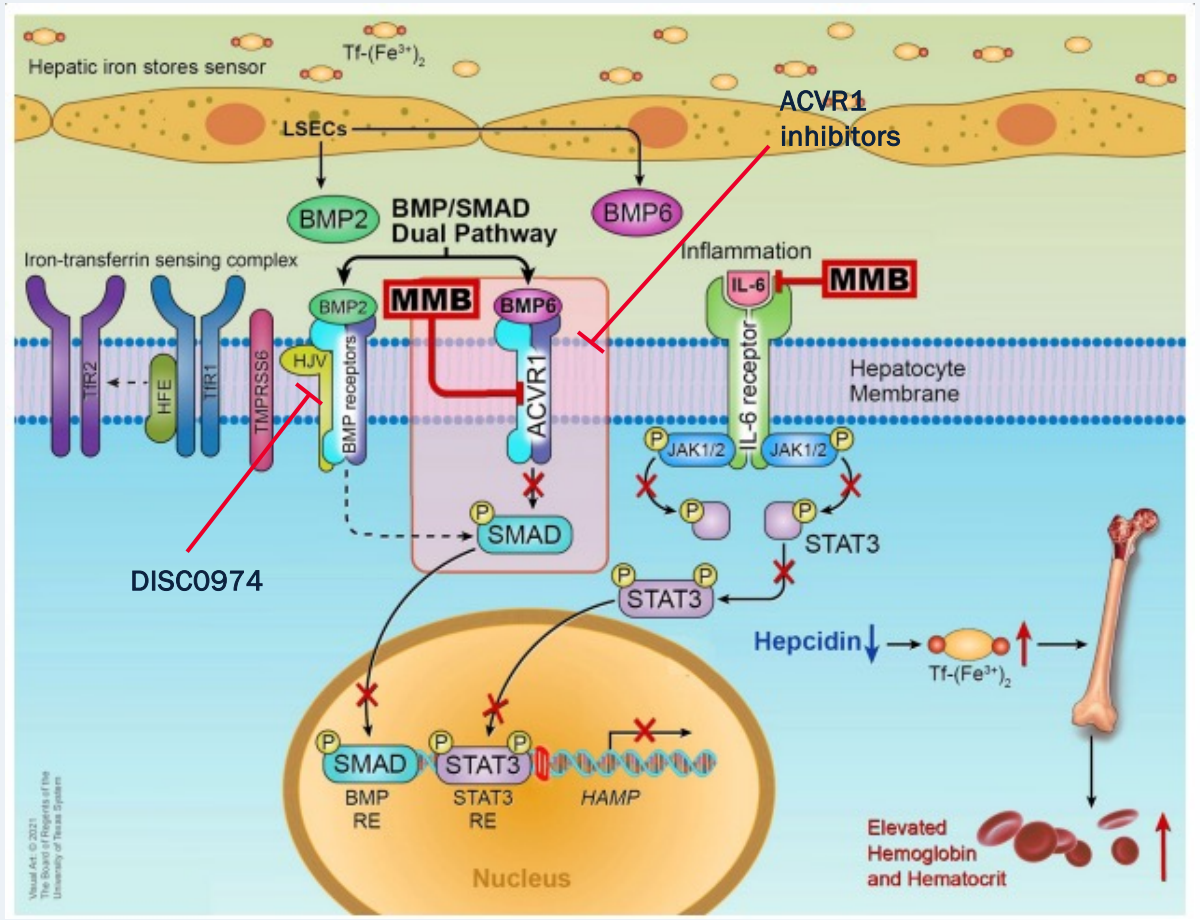
Therapeutic Targets in MPNs

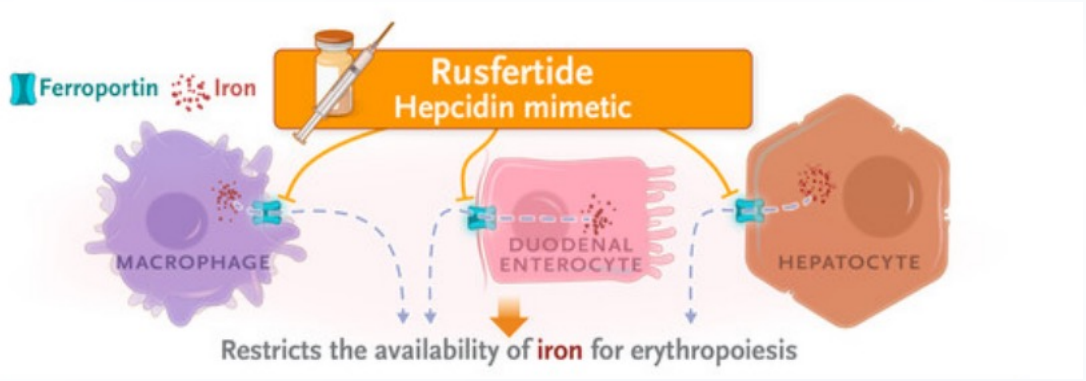
- Monotherapy activity demonstrated with numerous agents; however, the field is largely exploring combination approaches with a JAKi



Chifotides, Helen T. et al. *Clin Lymph, Myeloma Leuk.* 2022;22(4):210 - 223

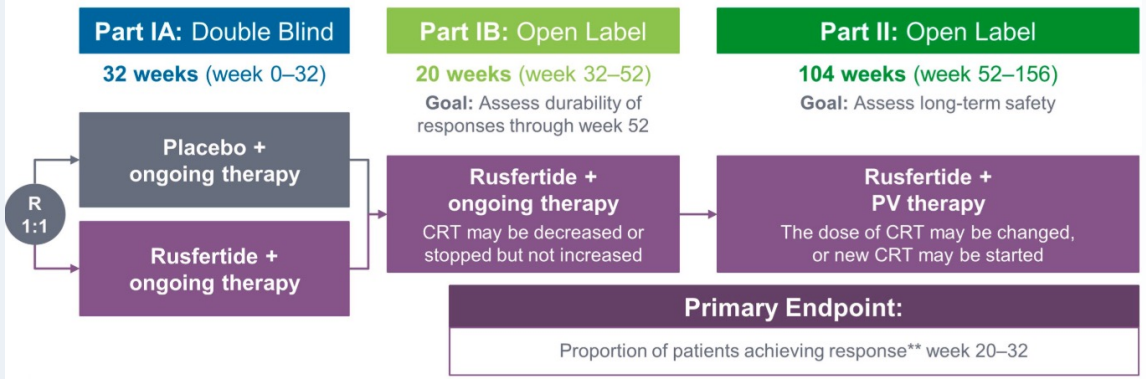
Modulation of Hepcidin Pathway Holds Promise in PV and Myelofibrosis



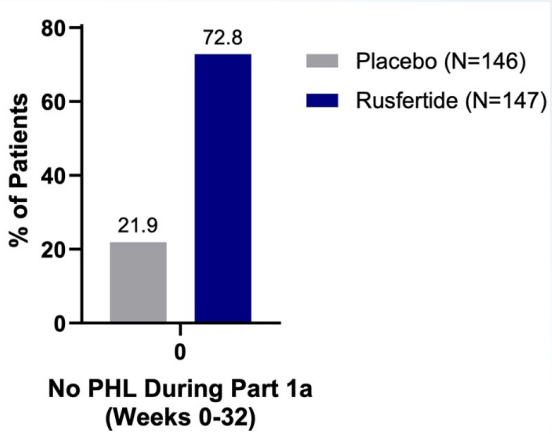


Chifotides et al. Journal of Hematology & Oncology 2021, 15(1):7
Kremyanskaya M, et al. *N Engl J Med.* 2024;390:723-735
Ritchie EK, et al. *Blood*. 2023; 142 (Supplement 1): 745

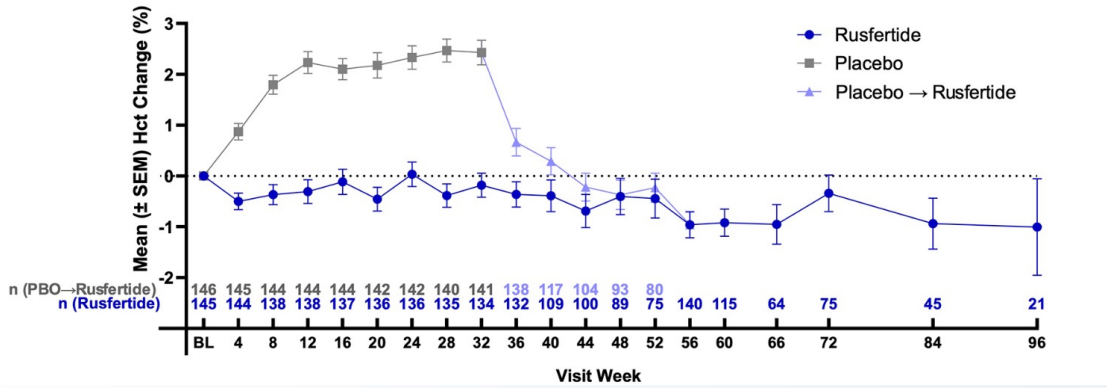
Rusfertide Demonstrates Efficacy in Phase 3 VERIFY Study



Number of Phlebotomies	Placebo (n=146)	Rusfertide (n=147)
Mean (SD)	1.8 (1.5)	0.5 (1.2)
p-value*	<0.0001	

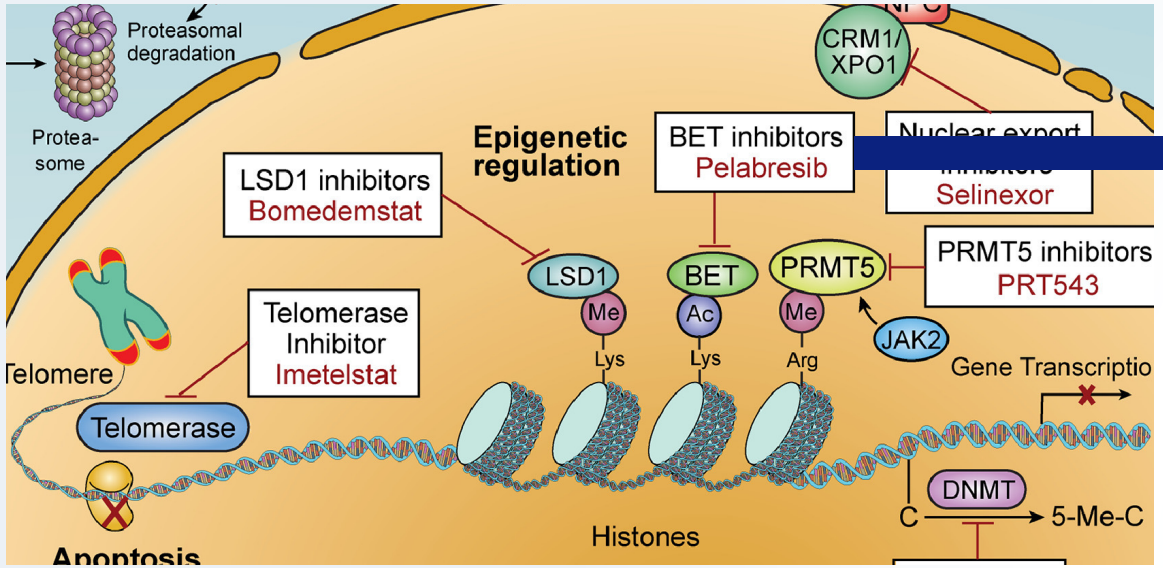


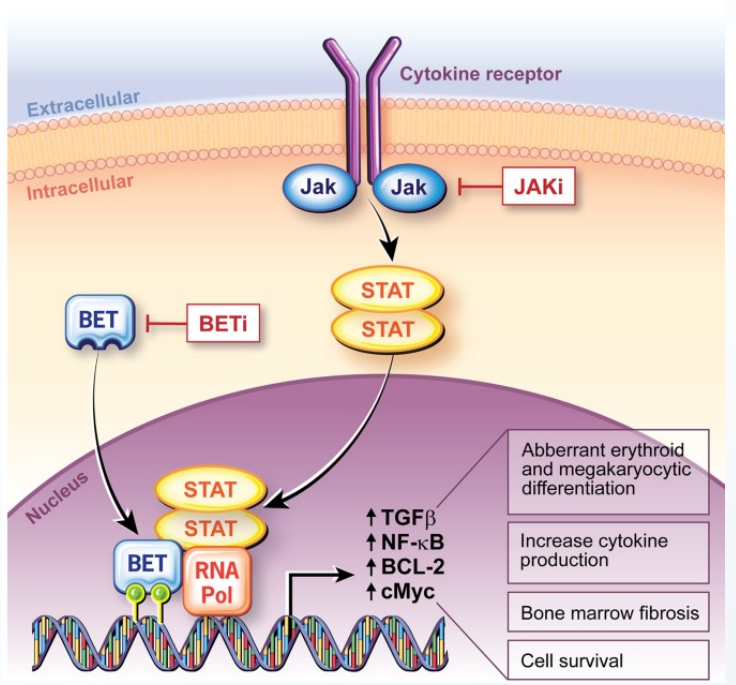
	Placebo (n = 146)	Rusfertide (n = 147)
Hct <45% (Baseline through Week 32), n (%)[a]	21 (14.4)	92 (62.6)
p-value*		<0.0001



Verstovsek S, et al. *Blood.* 2022; 140(supplement 1):3929-3931
Kuykendall A, et al. *J Clin Oncol* 43, 2025 (suppl 17; abstr LBA3)

Epigenetic Regulation is a Key Target in MPNs with Several Emerging Therapies

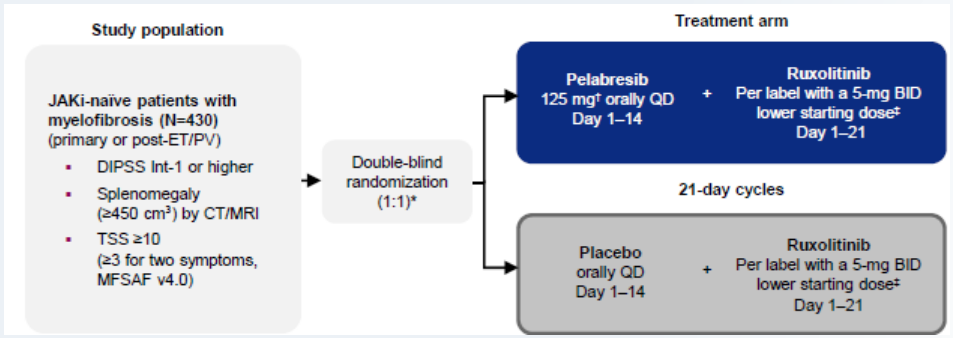


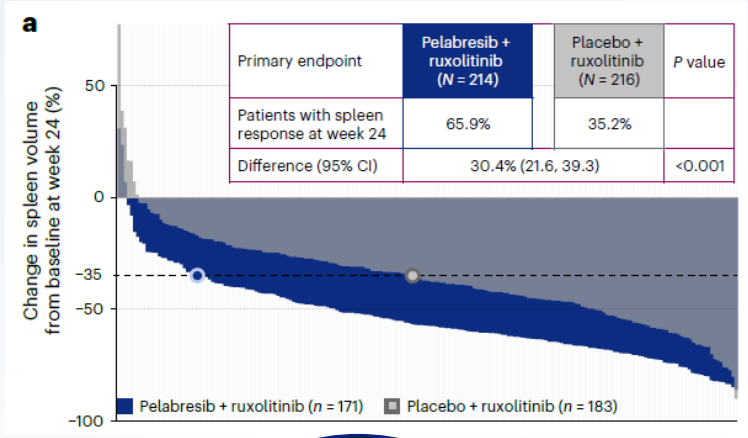


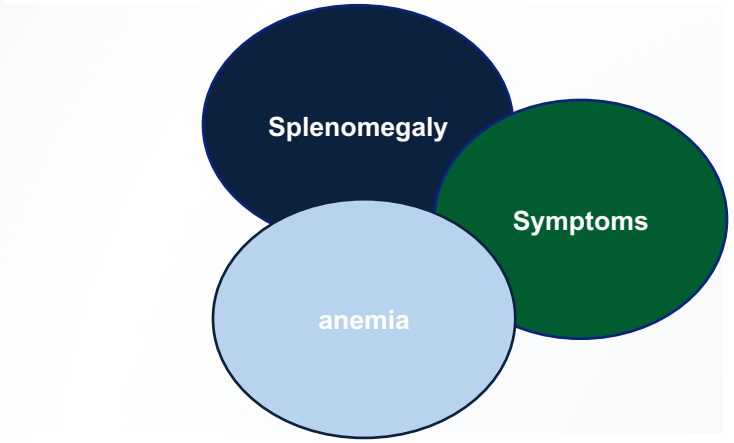
*multiple BET inhibitors are in development

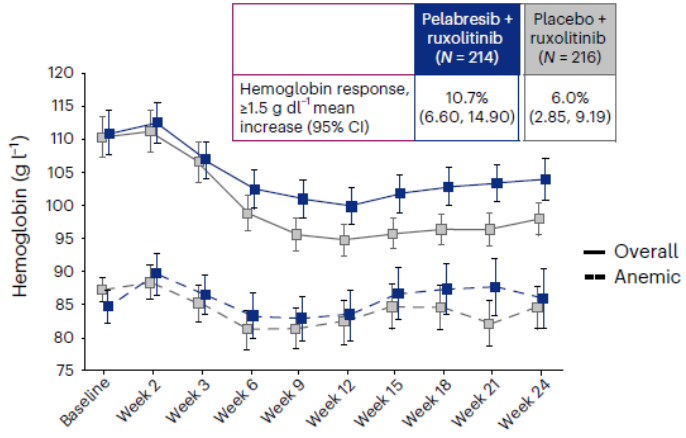
Chifotides, Helen T. et al. *Clin Lymph, Myeloma Leuk.* 2022;22(4):210 – 223
Mascarenhas J, et al. *Leukemia* 2021; 35: 3361-3363.

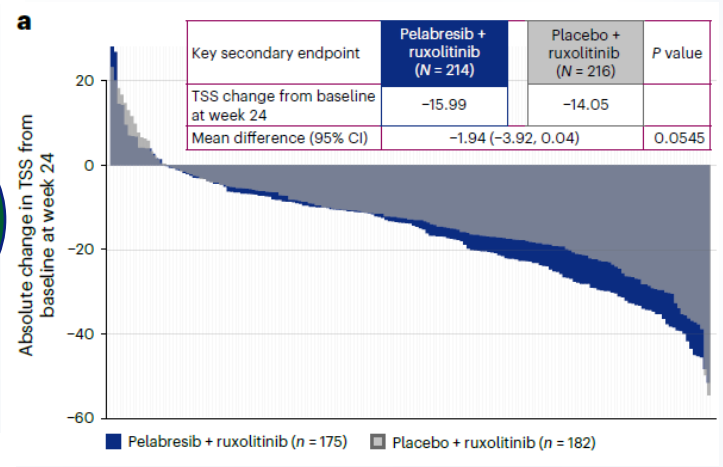
Pelabresib Demonstrates Efficacy in the Phase 3 Manifest-2 Study





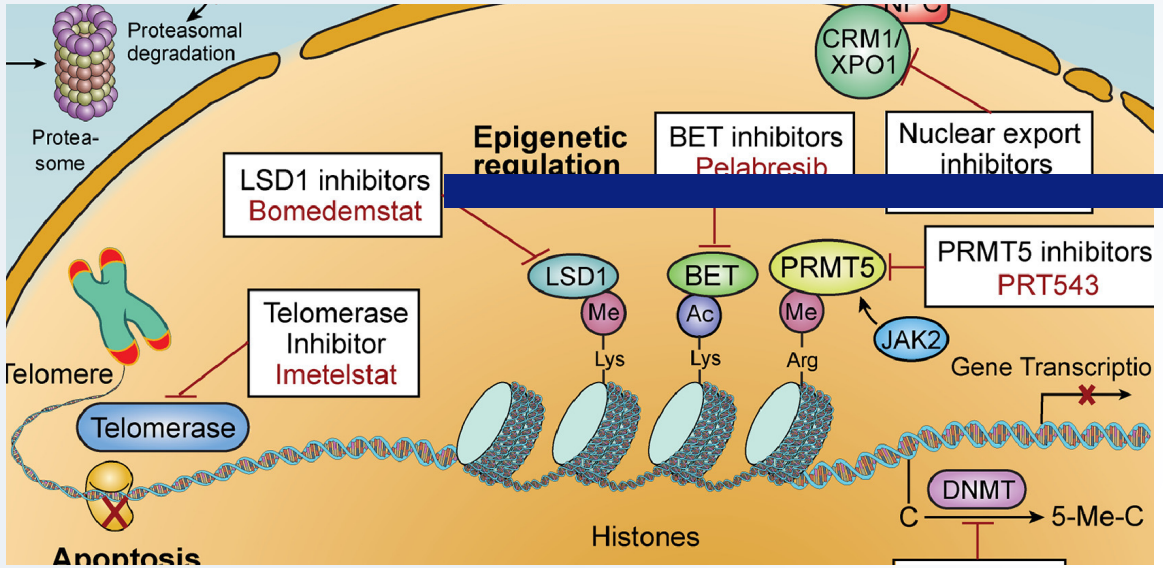


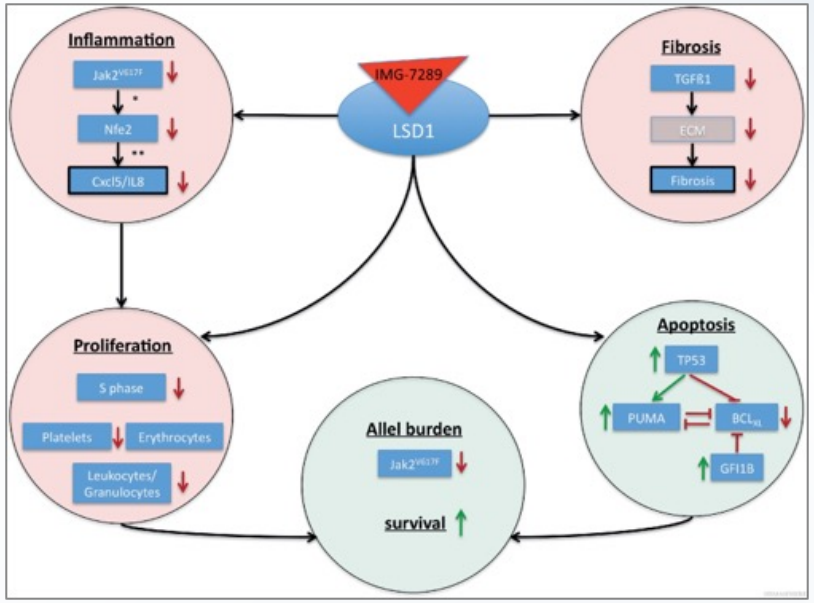




Rampal, R.K. , et al. *Nat Med* **31**, 1531–1538 (2025).

The LSD1 Inhibitor Bomedemstat is Active Across MPN Subtypes

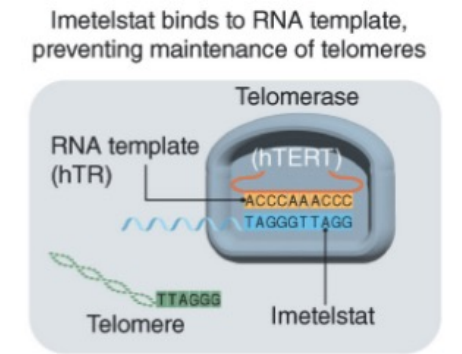


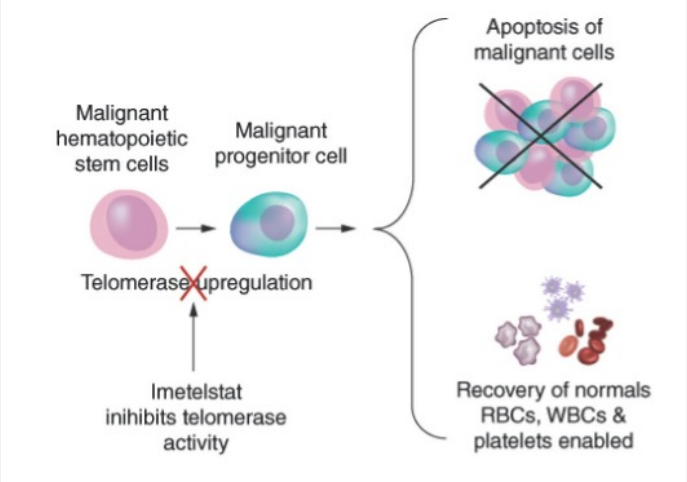


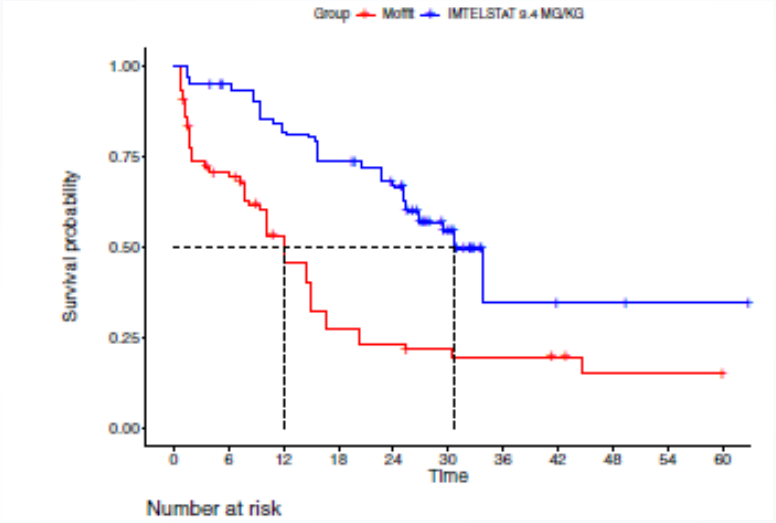
- LSD1: histone demethylase involved in epigenetic regulation
  - Plays a role in proliferation, self-renewal, and differentiation
  - Regulates megakaryocyte and erythrocyte maturation
- Activity has been demonstrated in ET, PV and Myelofibrosis
  - Interest in blast phase MPNs as well as other myeloid malignancies (MDS, AML)

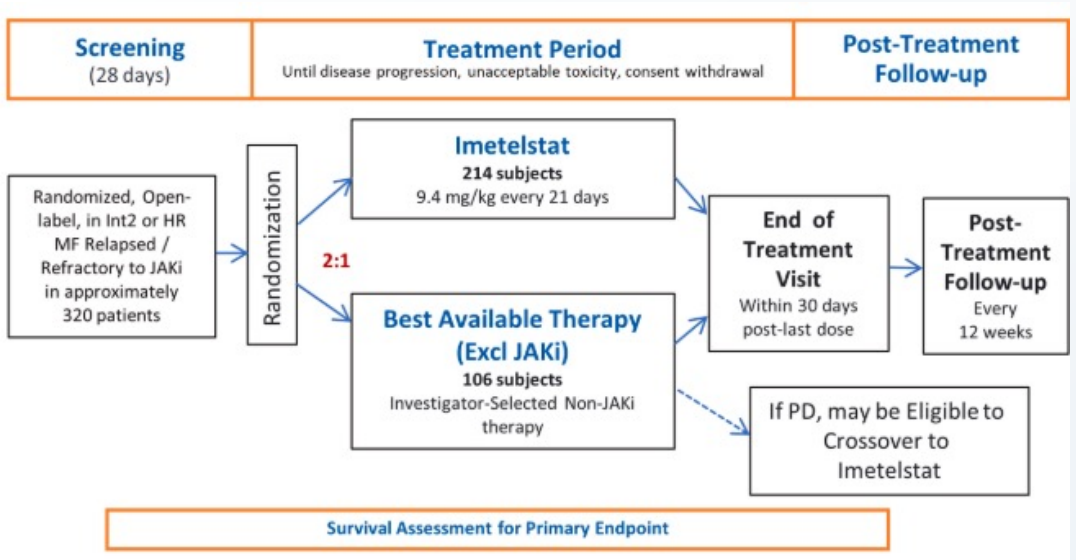
Jutzi JS, et al. *Hemasphere* 2018; 2(3):e54.
Gill H, et al. *Blood* 2022; 140 (Supplement 1):1784-87
Gill H, et al. *Blood* 2023; 142(supplement1):621.
Palandri F, et al. *Blood* 2021; 138(Supplement 1):386.
Rinaldi C, et al. *ASCO* 024, abstract TPS6595.

The First-in-Class Telomerase Inhibitor Imetelstat Demonstrates Activity in Myelofibrosis; Now in Phase 3 Testing







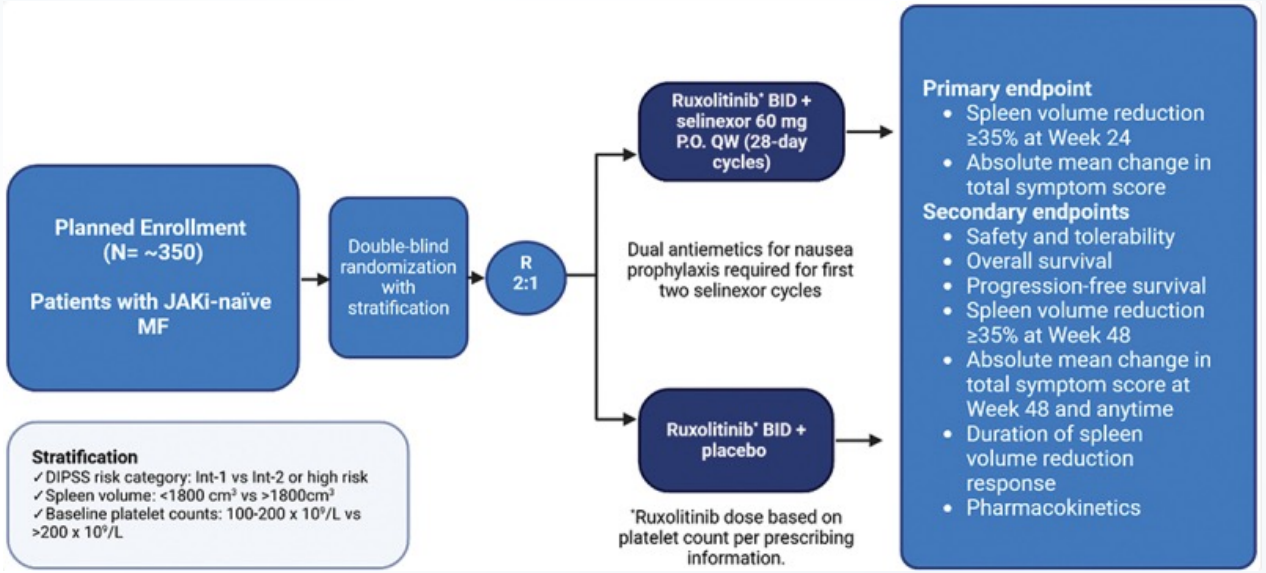


Mascarenhas J, et al. Future Oncol. 2022; 18(22): 2392-2402.
Mascarenhas J, et al. EHA Library 2020; EP1107. Mascarenhas J, et al. Blood 2020; 136(Supplement 1):39-40
Mascarenhas J, et al. *Blood* (2022) 140(supplement 1): 6826-6829
Kuykendall A, et al. Ann Hematol. 2022; 101(1):139-146

Selinexor Demonstrates Promising Early Efficacy in Combination with Myelofibrosis in the SENTRY study

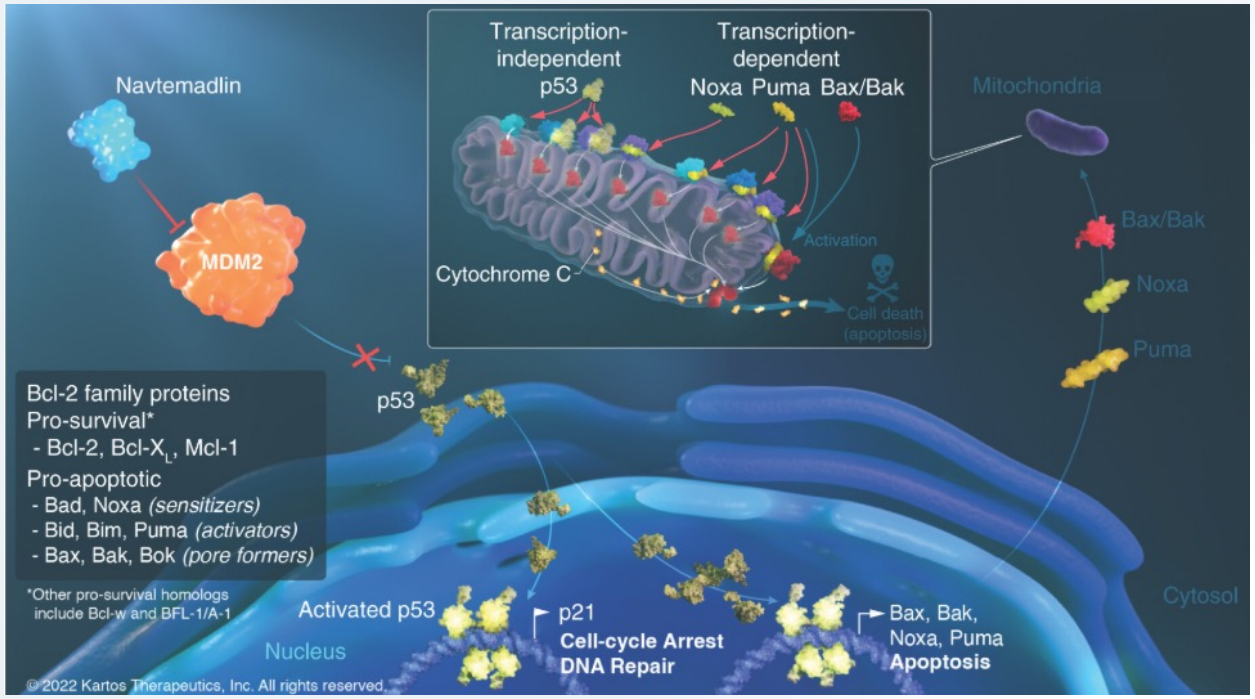
	Selinexor 40mg weekly (n=10)	Selinexor 60mg weekly (n=14)
SVR35	40%	79%
TSS50	10%	58%

- Most common AEs:
  - Nausea (75%)
  - Fatigue (58%)
  - Anemia (54%)
  - Thrombocytopenia (54%)



Tantravahi S, et al. *Blood* (2023) 142(Supplement 1): 622
Mascarenhas J, et al. *Future Oncol* 2025; 21(7):807-813

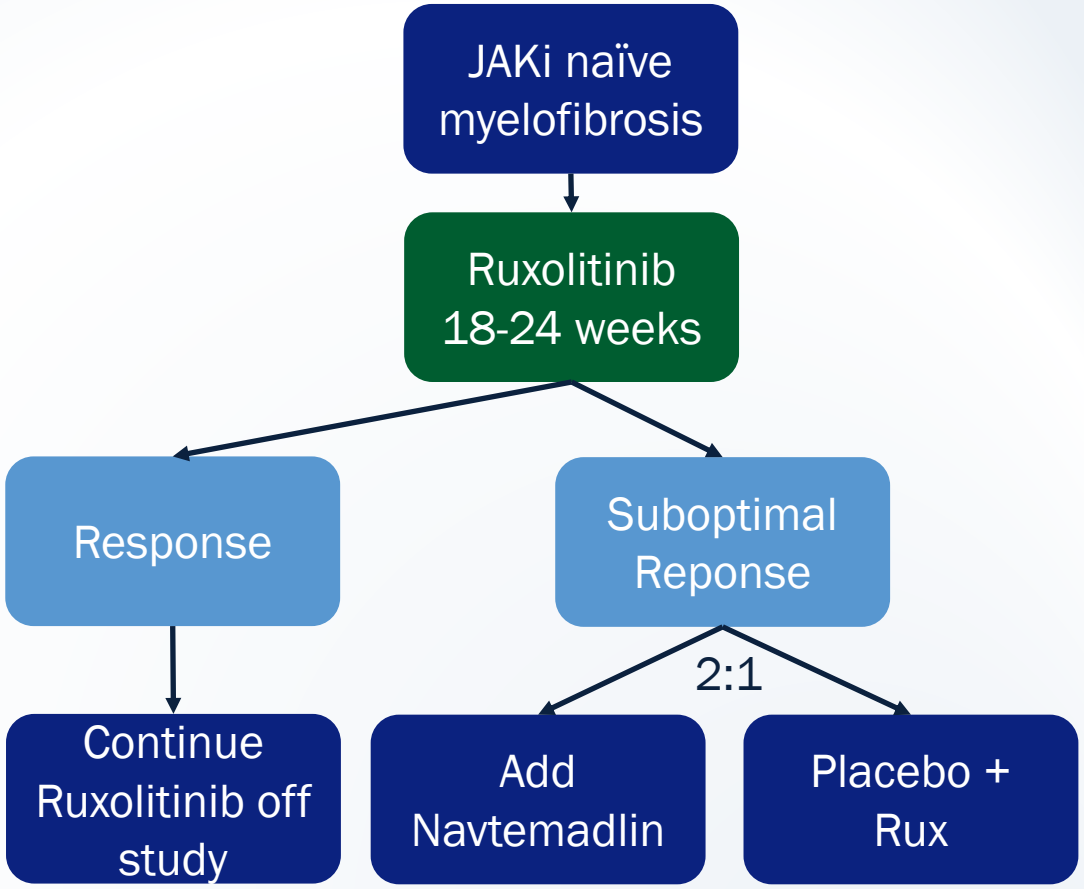
Navtemadlin, an Inhibitor of MDM2, in Development as an "Add-on" to Ruxolitinib



	Navtemadlin (n=123)	Best Available Therapy (n=60)
SVR35	15%	5%
TSS50	24%	12%

- BOREAS was a phase 3 study in myelofibrosis R/R to jAKi

Phase 3 POIESIS study



Mascarenhas J, et al. *Blood* (2024) 144 (supplement 1): 1000
Verstovsek S, et al. *Future Oncology* 2022, 18(37):4059-4069

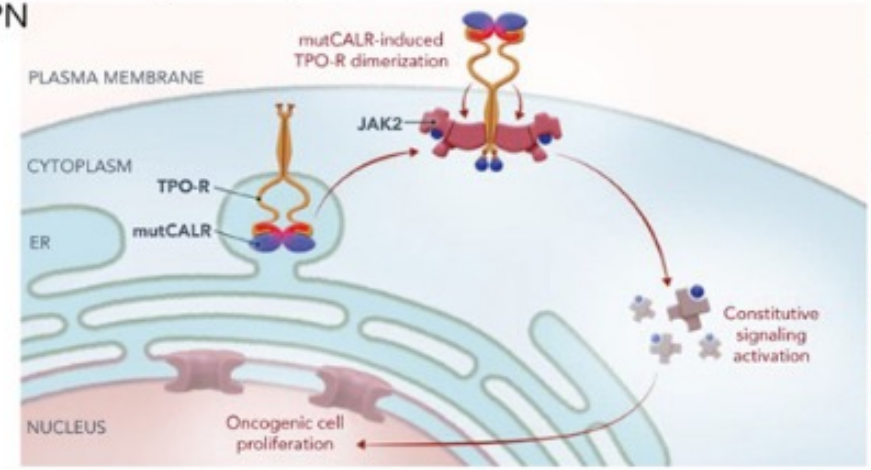
Targeting Mutant CALR is an Exciting Novel Strategy in MPNs

Somatic mutations of the *CALR* gene, which encodes calreticulin, are the driver genetic lesions in a subset of patients with essential thrombocythemia or primary myelofibrosis

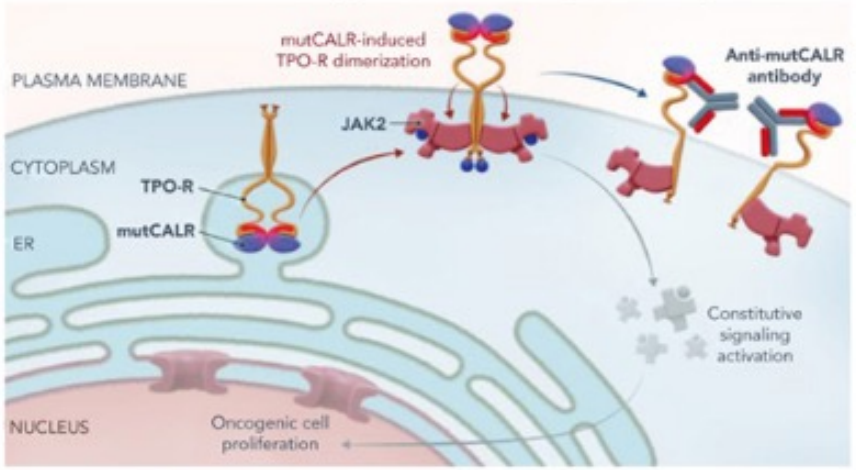
We describe the characterization of INCA033989, a monoclonal antibody that potently and selectively targets mutant calreticulin-positive hematopoietic cells of patients with MPN

Findings

Mutant calreticulin (mutCALR) binds TPO-R and induces oncogenic cell proliferation in *CALR*-mutant MPN



INCA033989 prevents TPO-R activation and selectively inhibits oncogenic cell proliferation



In development:

- mABs
- Bispecifics
- CAR T-cells
- Vaccines

Reis ES, et al. Blood. 2024 Nov 28;144(22):2336-2348

Conclusions

- JAK inhibitors have revolutionized the therapy of MPNs, yet there is considerable room for improvement
  - MPN biology is complex and not solely reliant on JAK-STAT signaling
  - Therapies that alter the natural history of the disease are needed
- Numerous non-JAKi therapies are in development that appear promising
  - Combination approaches with JAKi appear to hold the most promise
- Critical evaluation of endpoints utilized in MPN trials is needed to move the field forward

Q&A