Novel Therapies in Myeloproliferative Neoplasms, Ruxolitinib Combinations and Beyond

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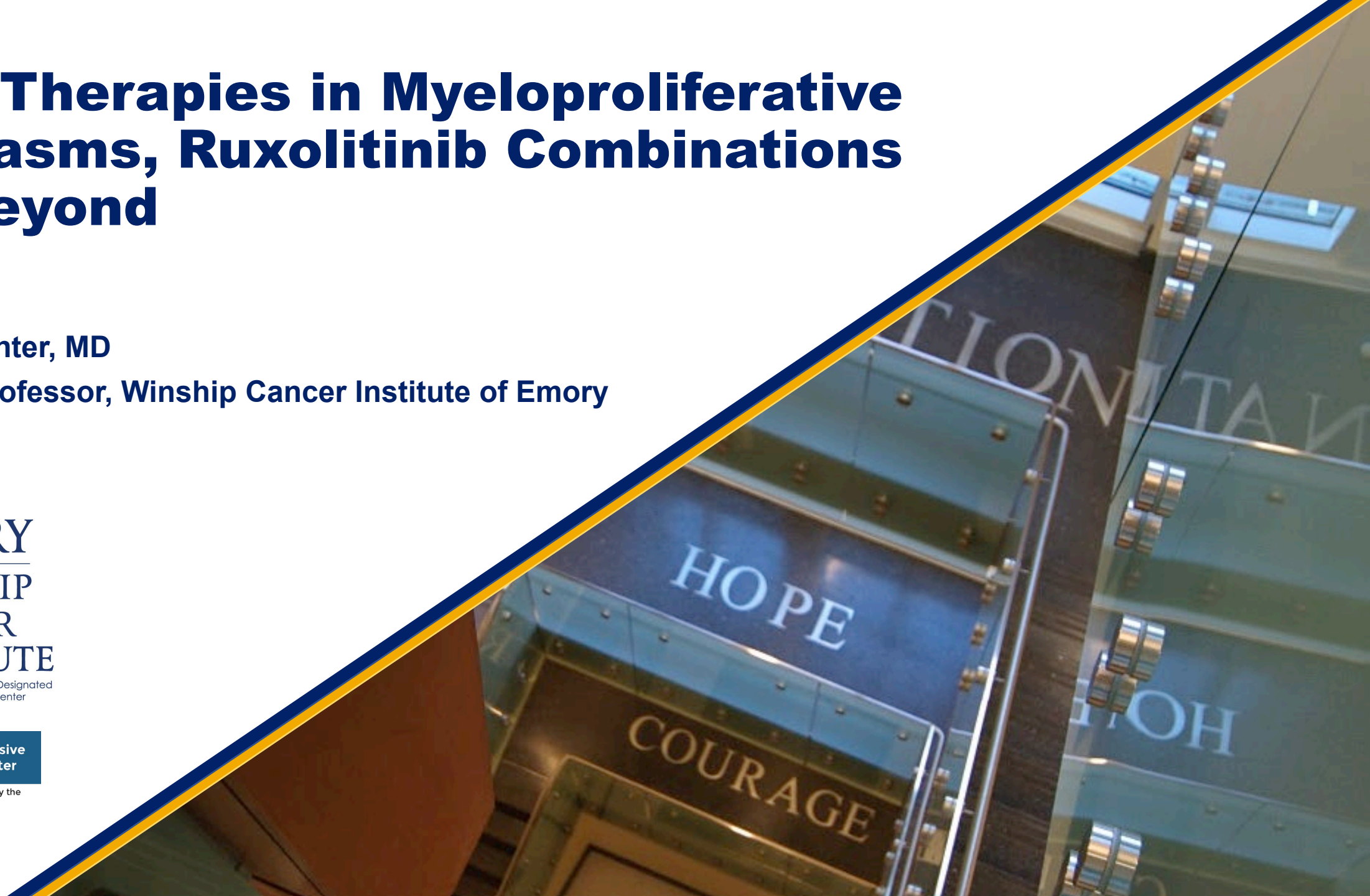


Disclosures

- I have no relevant conflicts of interest to disclose

Objectives

- Review current treatment options in myeloproliferative neoplasms
- Discuss agents that have recently been approved
- Highlight emerging therapies with a focus on agents in late-stage development
  - JAK inhibitors and combination approaches
  - Novel targeted therapies

Case

- A 68-year-old male presents with early satiety and weight loss. Physical exam reveals splenomegaly extending ~12cm below the costal margin and CBC demonstrates WBC of 15 with 3% blasts, Hgb of 9.0 and plts of 176. Bone marrow biopsy confirms myelofibrosis, with no increase in bone marrow blasts. Cytogenetics 46,XY. NGS panel identifies mutations in *JAK2* and *ASXL1*. What would you recommend for treatment?

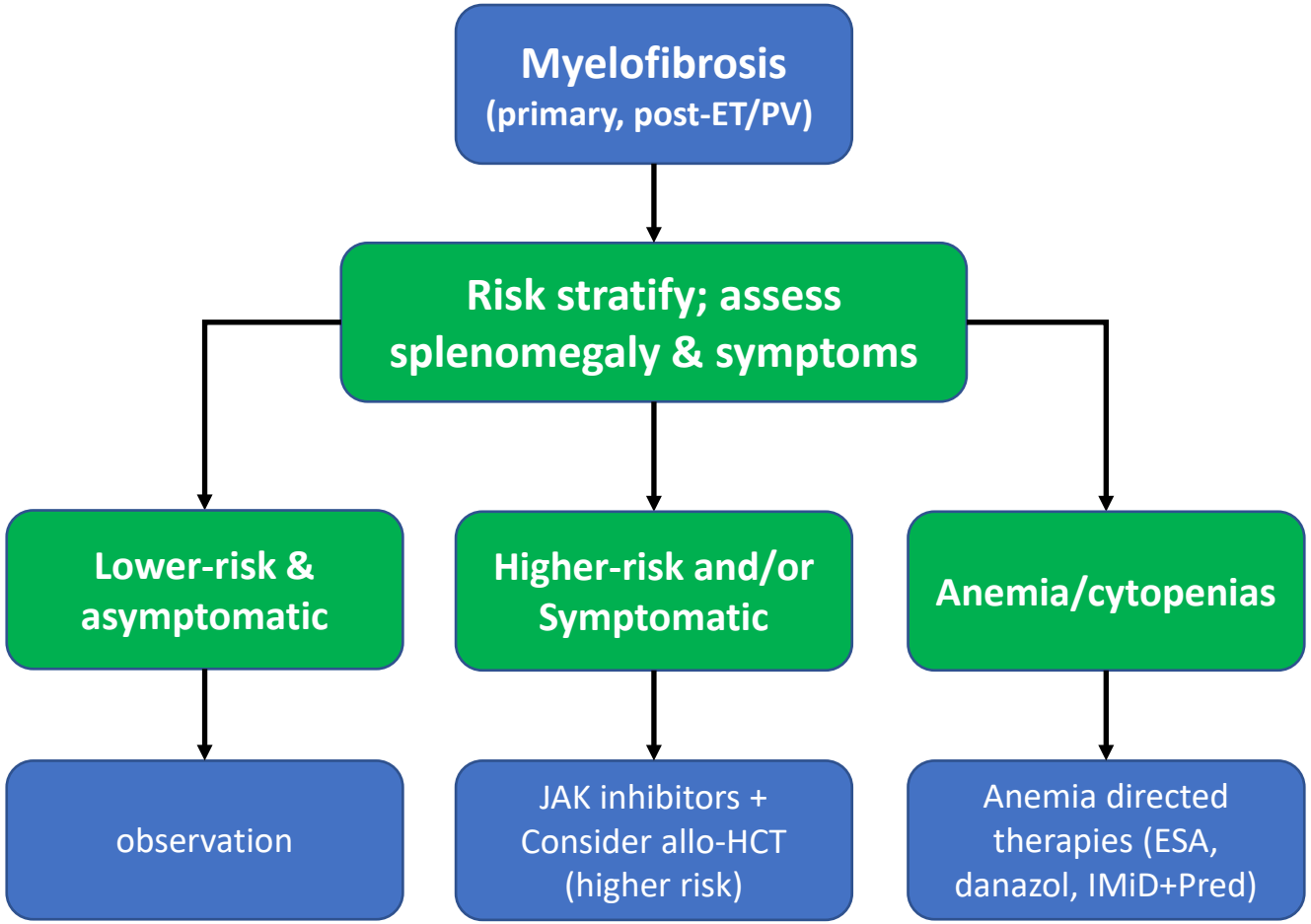
a. referral for allo-HCT

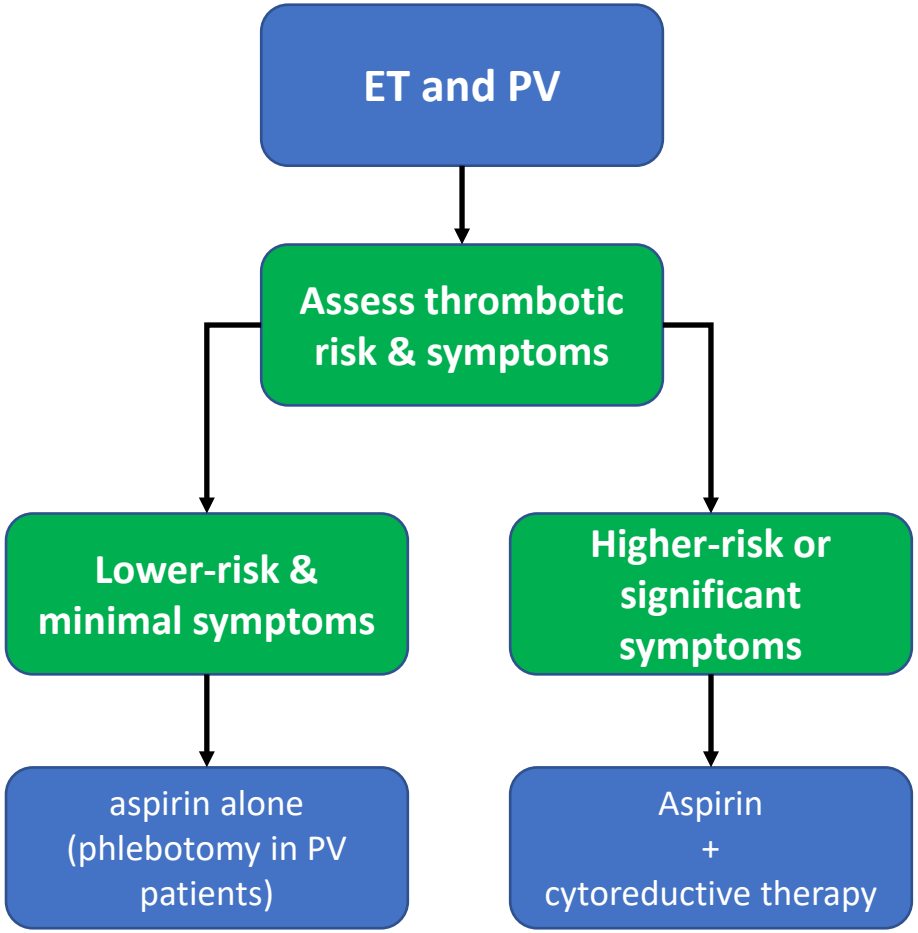
b. ruxolitinib 15mg twice daily

c. fedratinib 400mg daily

d. clinical trial

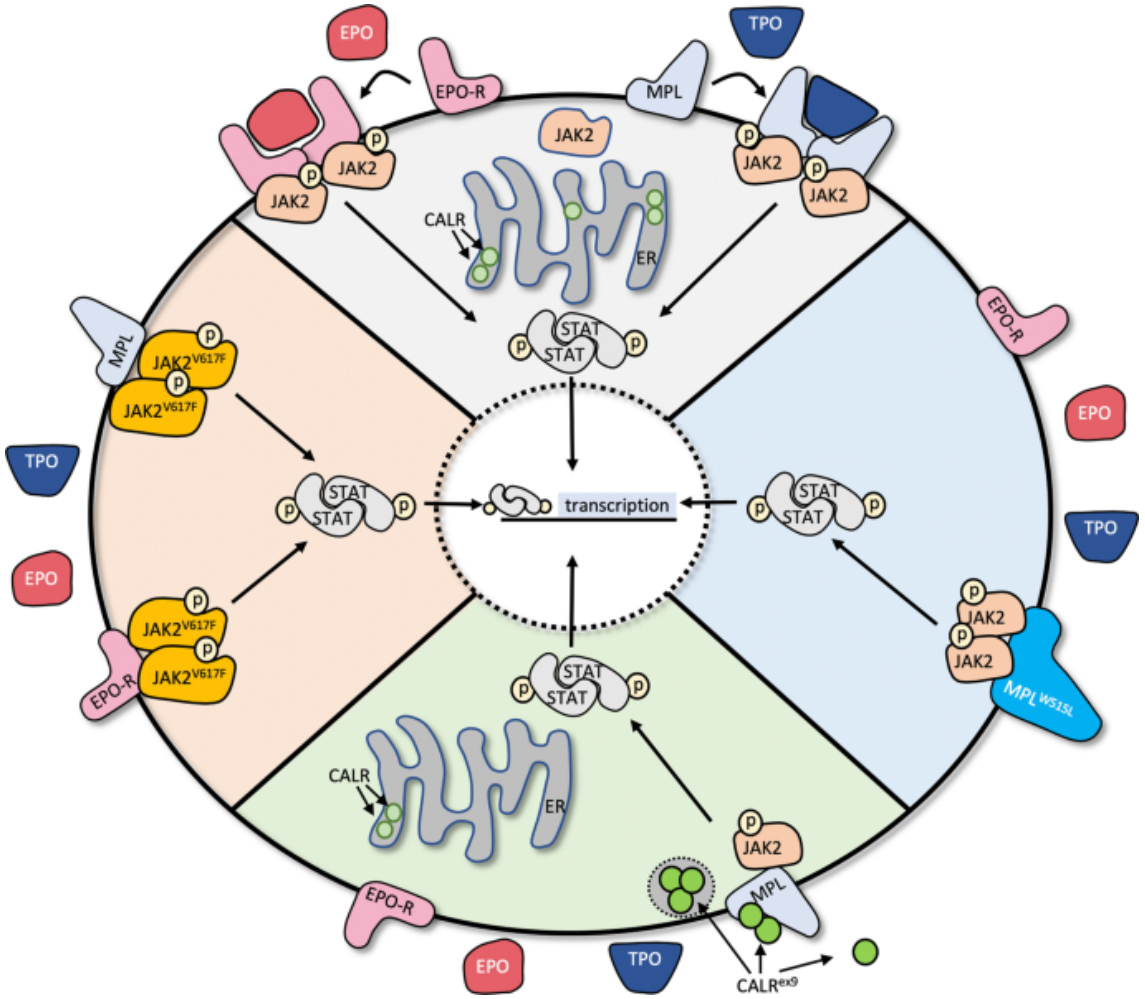
Treatment paradigms in MPNs





*Clinical trials should be considered in all settings, when available

JAK-STAT signaling is a hallmark of MPNs

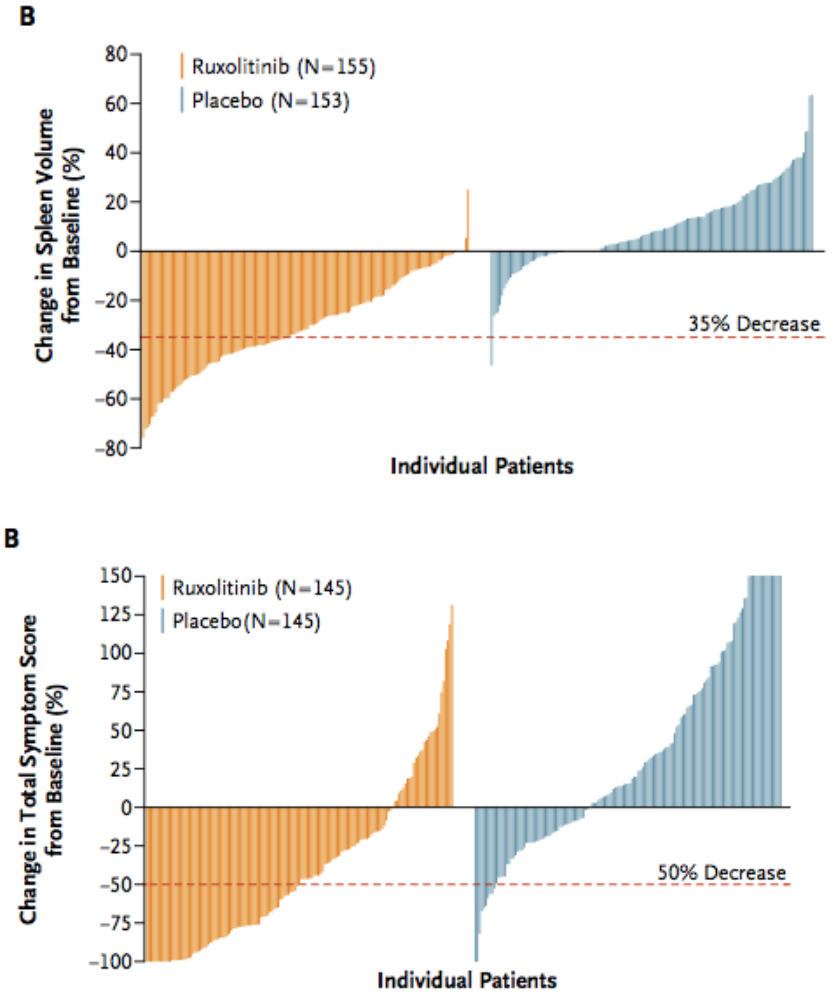


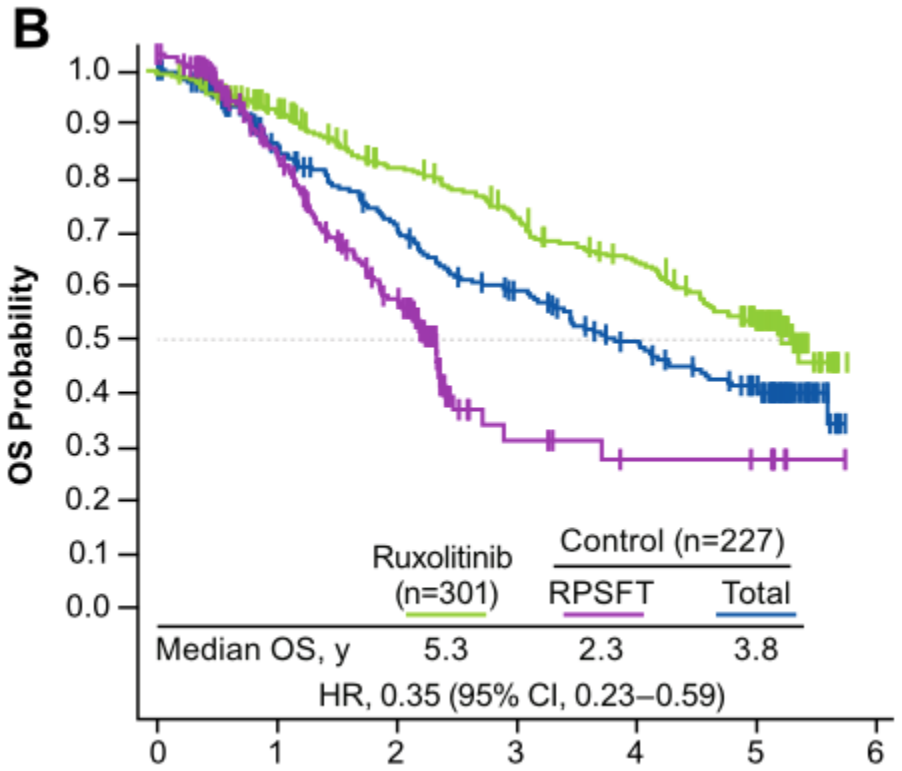
Schieber M, et al. *Blood Cancer Journal* 2019; 9(9):74

Ruxolitinib: the standard of care in symptomatic, higher-risk MF patients

Spleen Volume Reduction of ≥ 35% (SVR35) : 41.9%

Total Symptom score improvement of ≥ 50% (TSS50): 45.9%





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

RESPONSE Trial: Ruxolitinib is an effective 2nd line agent in PV

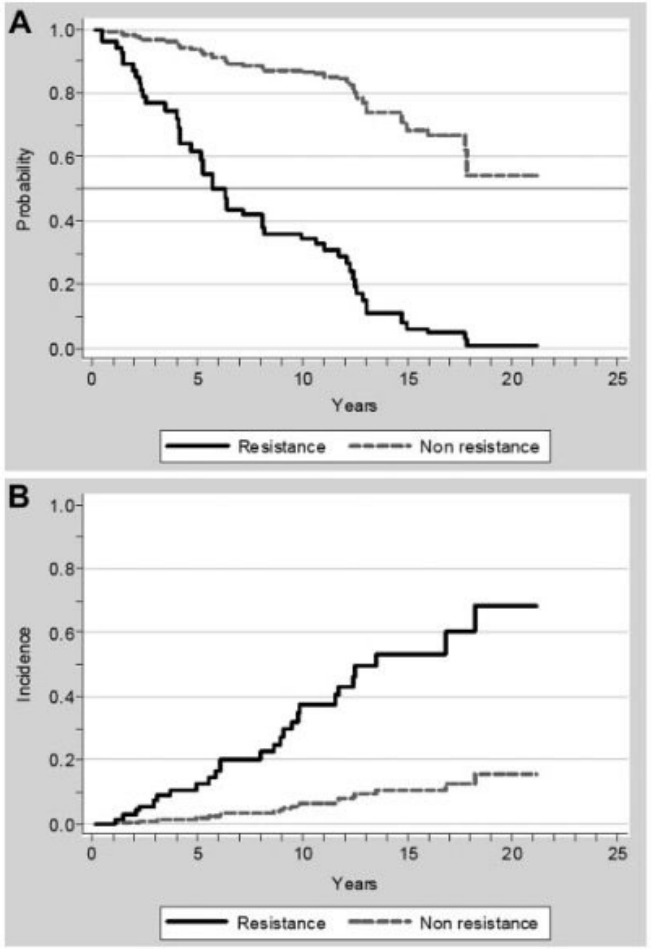
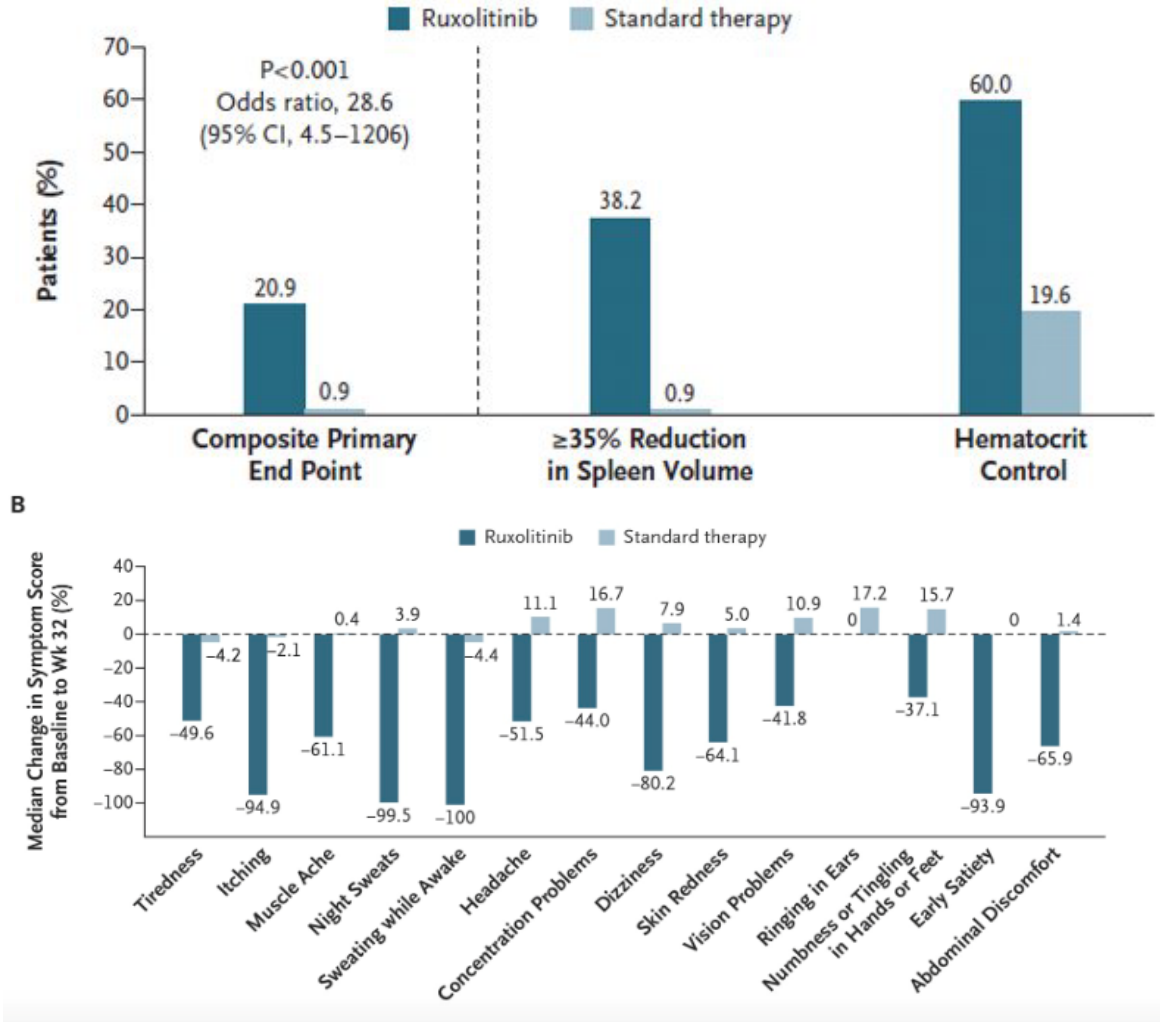
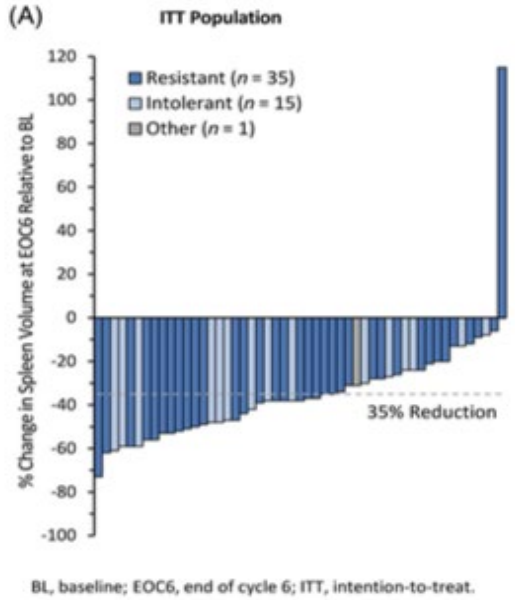


Figure 3. Effect of resistance to HU on survival and on risk of transformation

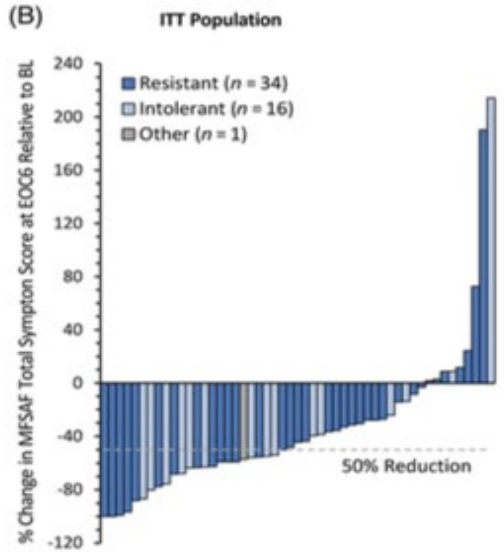


Barosi G, et al. (ELN) *Br J Haemotol* 2010;148:961-963. Alvarez-Larran A et al, *Blood* 2012; 119:1363-1369
Vannucchi A et al, NEJM, 2015, 372: 428-435. Passamonti F, et al. *Lancet Oncol* 2017; 18:88-99

Fedratinib: a selective JAK2 inhibitor with activity in 2nd line setting



BL, baseline; EOC6, end of cycle 6; ITT, intention-to-treat.



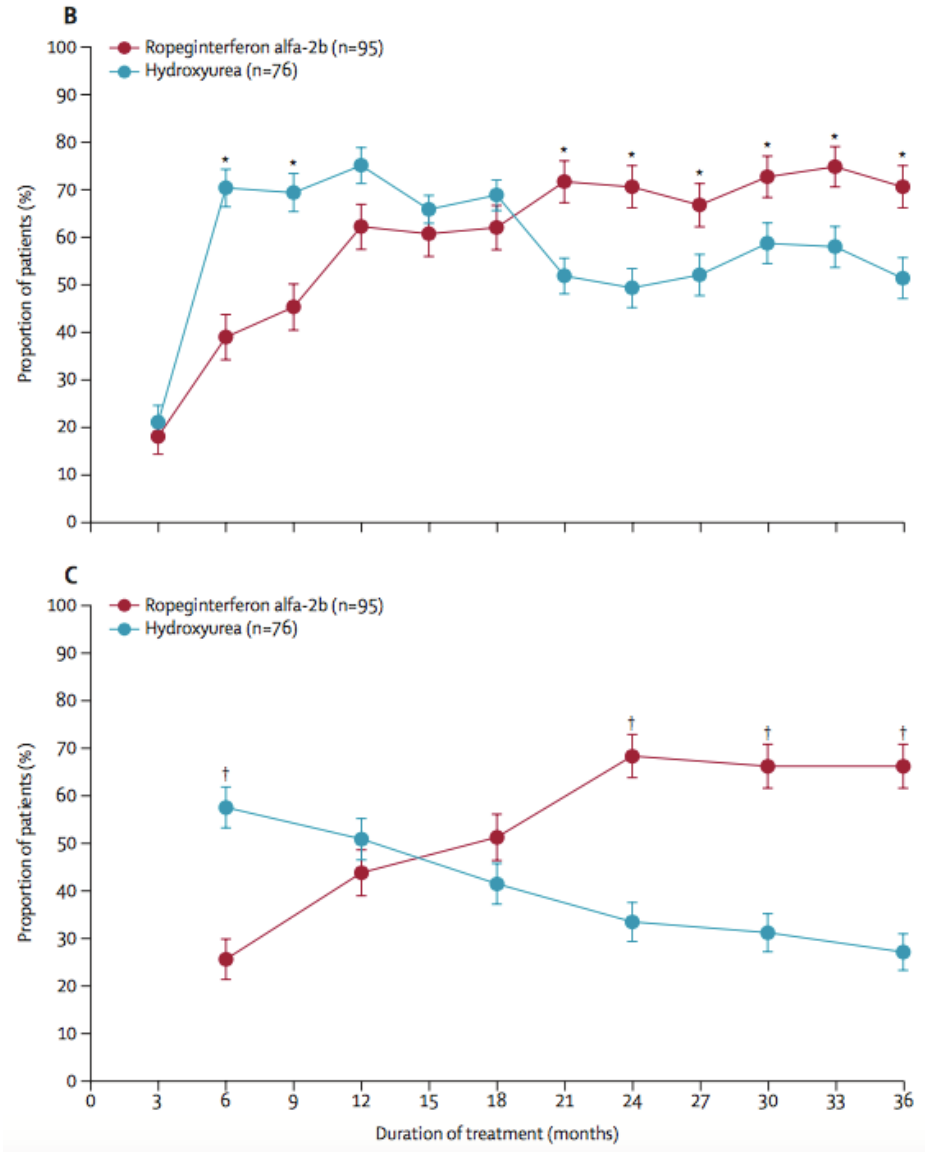
	ITT population (N = 97)		Stringent criteria cohort (n = 79)	
SVRR at EOC6 (overall), n (%)	30 (31%)		24 (30%)	
[95% CI]	[22, 41]		[21, 42]	
Prior ruxolitinib outcome	Resistant[a] n = 64	Intolerant[a] n = 32	Relapsed/refractory[b] n = 65	Intolerant[b] n = 14
SVRR, n (%)	21 (33%)	9 (28%)	20 (31%)	4 (29%)
[95% CI]	[22, 46]	[14, 47]	[20, 43]	[8, 58]

- TSS50: 27% in ITT population and stringent criteria cohort
- AE's were similar to prior studies: Diarrhea in 62% of patients' Grade 3-4 anemia in 38%, thrombocytopenia in 22%
- 20% of patients discontinued treatment due to AE's
- Black box warning for encephalopathy

Harrison C, et al. *Lancet Haematol* 2017; 4(7):e317-e324. Harrison C, et al. *Am J Hematol* 2020; 95(6):594-603

Recently Approved Agents for the treatment of MPNs

Ropeginterferon alfa-2b is a new therapeutic option in patients with PV

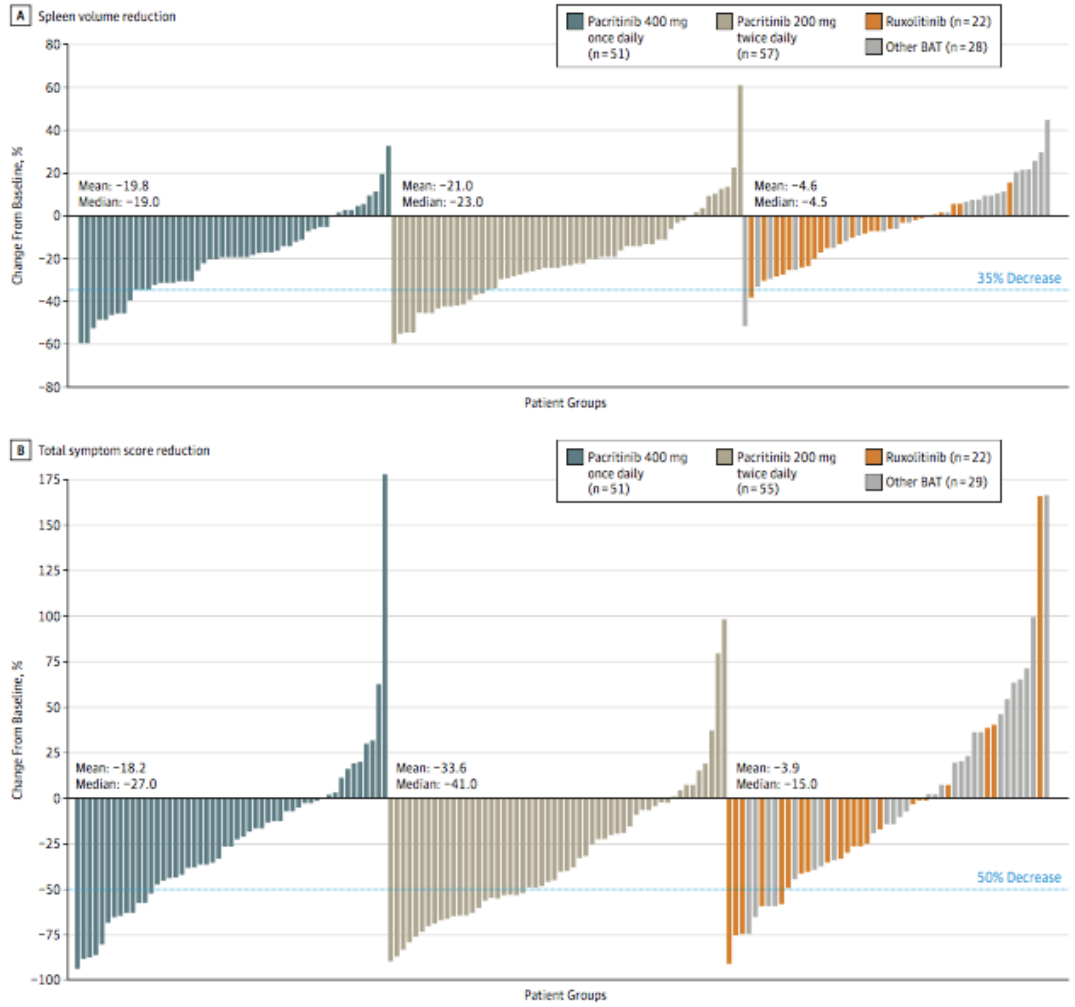


Gisslinger H, et al. *Lancet Haematol* 2020; 7:e196-e208. Gisslinger H, et al. *Blood* 2015; 126(15): 1762-1769

Pacritinib: Extending benefit of JAKi to thrombocytopenic patients

- JAK2 > JAK1, and activity against FLT3, IRAK1, CSF1R

	Pacritinib	BAT
SVR35	42/220 (19%)	5/107 (5%)
plts <100k	12/72 (17%)	0/34
plts <50k	8/35 (23%)	0/16
TSS50	19/100 (19%)	5/48(10%)
plts <100k	7/28 (25%)	1/13 (8%)
plts <50k	3/11 (27%)	0/5

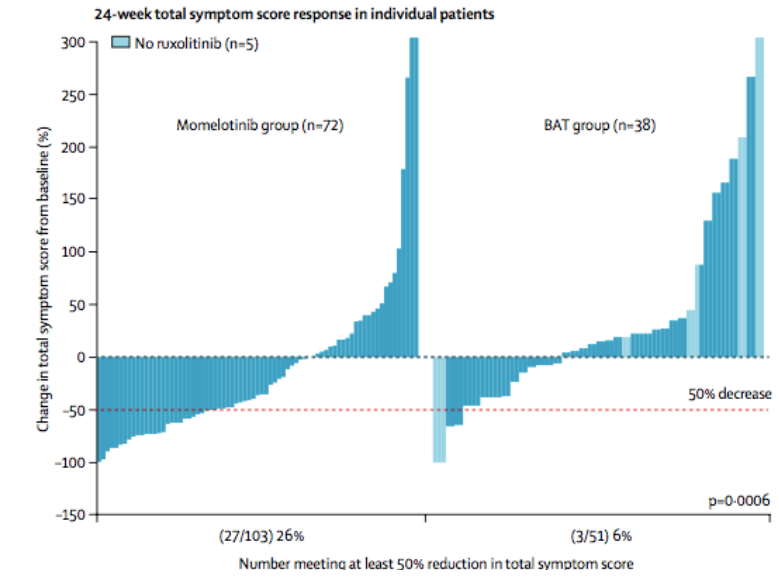


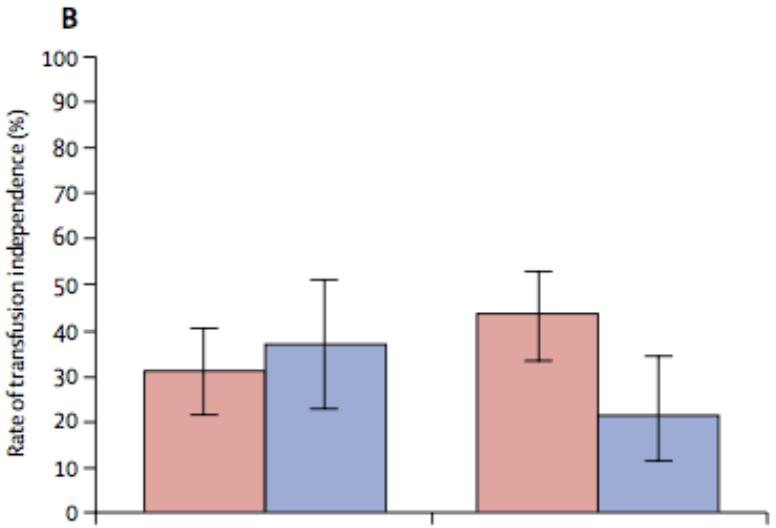
Mesa RA, et al. *Lancet Haematol* 2017; 4(5):e225-e236.
Mascarenhas et al. *JAMA Oncol* 2018; 4(5):652-659
Gerds AT, et al. *Blood Adv.* 2020; 4(22):5825-5835

Agents Under Investigation

Focus on agents in later stages of development

Momelotinib: JAKi in development for patients with anemia



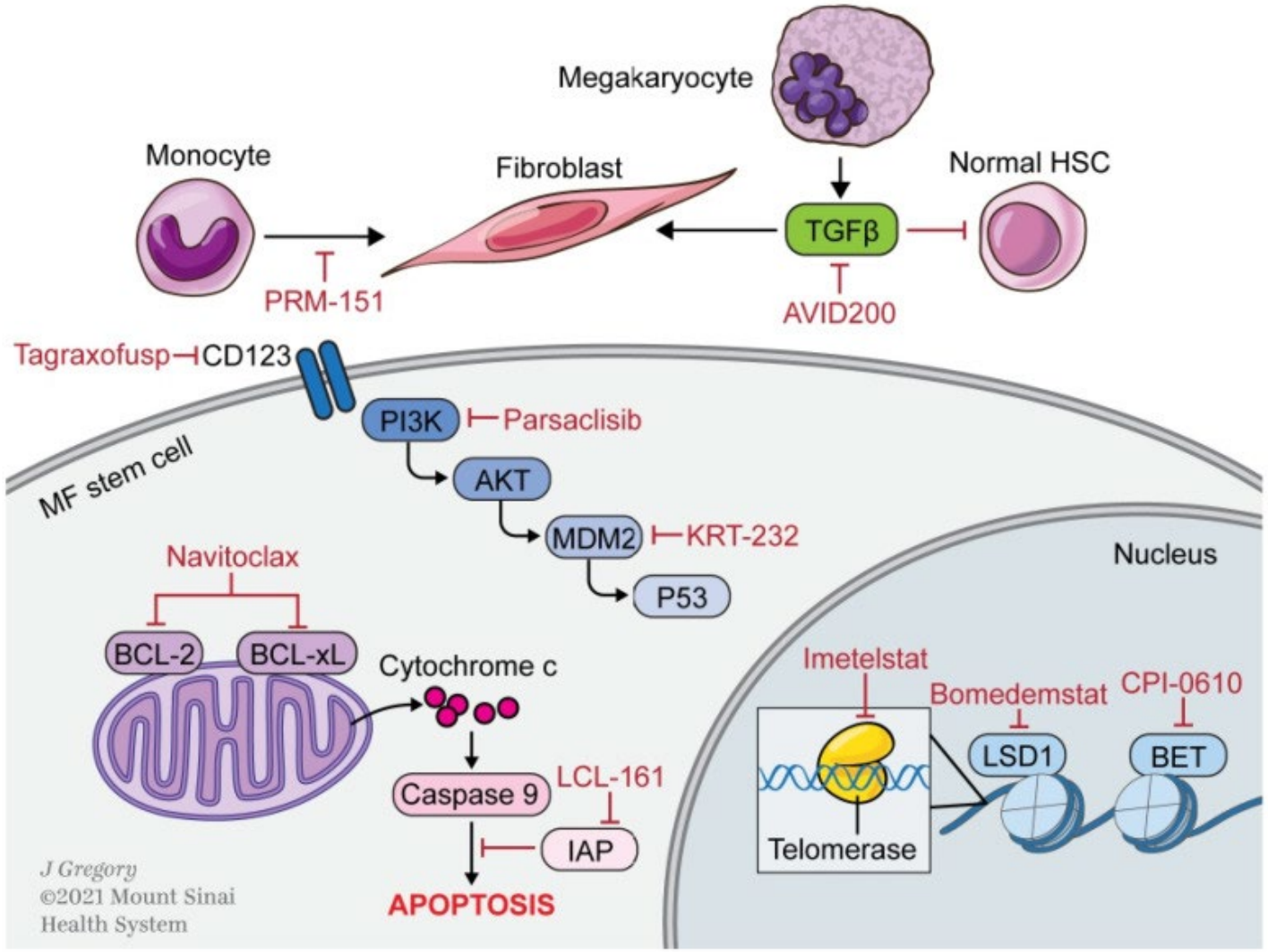


- Activity against activin A receptor type-1 (ACVR1)/ALK-2 in addition to JAK1/2

Endpoint (24 wks)	Momelotinib (n=130)	Danazol (n=65)	p-value
TSS50 (primary)	24.6%	9.2%	0.0095
Transfusion independence (at baseline)	30.8% (13%)	20.0% (15%)	0.0064
SVR35	23.1%	3.1%	0.0006

Mesa R, et al. ASCO 2022 abstract 7002.Mesa RA, et al. *J Clin Oncol* 2017; 35(34):3844-3850. Harrison CN, et al. *Lancet Haematol* 2018; 5(20):e73-e81. Mesa R, et al. *EHA Library* 2021; 324610;S202. Asshoff M, et al. *Blood* 2017; 129(13):1823-1830

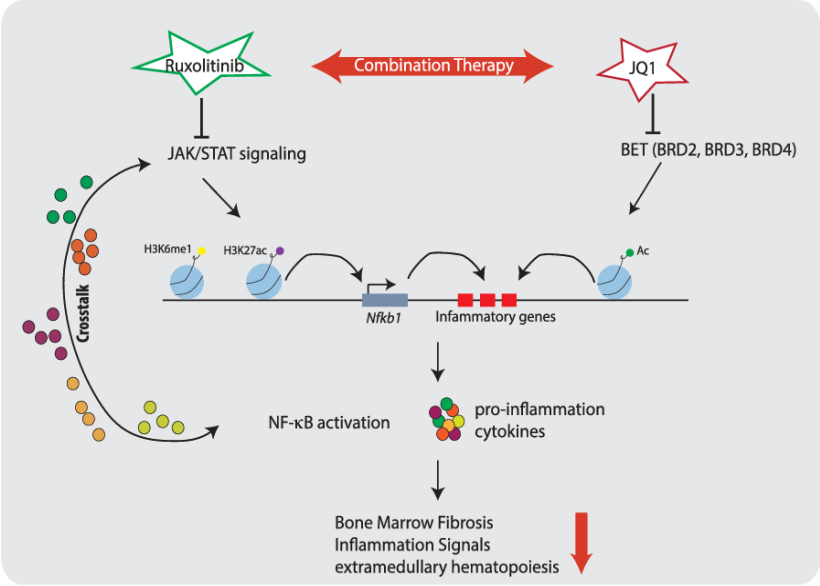
Many novel targets have been identified in Myelofibrosis



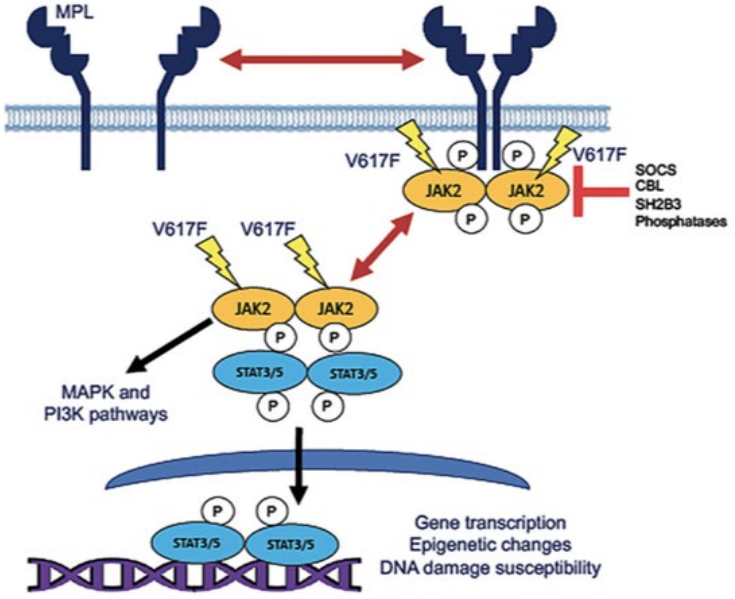
Tremblay D, et al. *Cells* 2021; 10(5):1034

Novel pathways that display synergy with JAKi

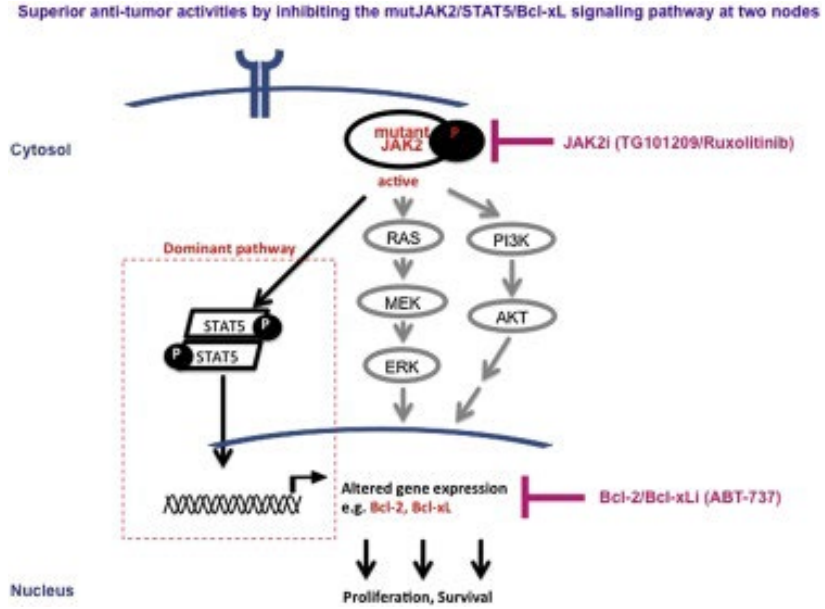
Bromodomain (BET) inhibitors



PI3K inhibitors



Apoptosis: Bcl-2, Bcl-xL inhibitors



Jiang Q, et al. *Cancer Cell* 2018; 33(1):3-5. Kleppe M, et al. *Cancer Cell* 2018; 33(1):29-43. Waibel M, et al. *Cell Rep* 2013; 5(4):1047-1059. Petiti J, et al. *J Cell Mol Med* 2020; 24(18):10978-10986. Guo J, et al. *PloS one* 2015; 10(3):e0114363. Fisher DAC, et al. *Front Immunol* 2021; 12:683401. Akada H, et al. *Blood* 2010; 115(17):3589-97. Grimwade LF, et al. *Br J Haematol* 2009; 147(4):495-506. Khan I, et al. *Leukemia* 2013; 27(9):1882-1890. Bartalucci N, et al. *Clin Lymphoma Myeloma Leuk* 2013; 13(2):S307-9.

Pelabresib (CPI-0610): MANIFEST phase 2 study

	Arm 1: monotherapy	Arm 2: "add on" to ruxolitinib	Arm 3: combination in JAKi naive
Patients treated	Non-TD: n = 27 TD: n = 19	n = 86	n = 84
SVR35 at 24 weeks	Non-TD: 30%	20%	68%
TSS50 at 24 weeks	Non-TD: 48%	37%	56%
Erythroid response	TD: 21% achieved TI non-TD: 59.1%	TD: 16% (TI) Non-TD: 17.4%	24% (1.5g/dL from baseline)
Bone marrow	Decreased fibrosis (31%, at least 1 grade), increased erythroid progenitors (50%), decreased megakaryopoiesis (57%)		
AEs	Anemia, thrombocytopenia, GI (nausea and diarrhea) and respiratory tract infections		

*eligibility: DIPPS ≥ int-2, symptomatic (MF-SAF), splenomegaly (non-TD cohorts) or transfusion dependent (TD cohorts)

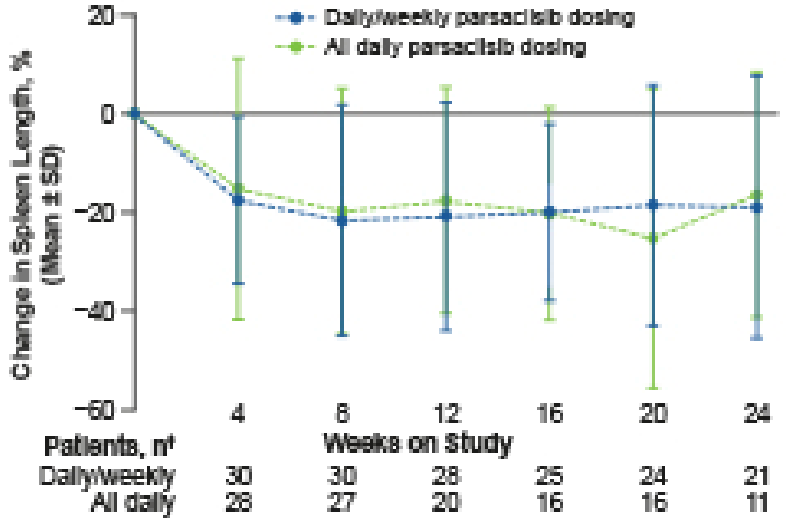
Kremyanskaya M, et al. ASH annual meeting 2021. Vertovsek S, et al. ASH annual meeting 2021. Verstovsek S, et al. EHA 2021. Kremyanskaya M, et al. EHA 2021. Mascarenhas J, et al. EHA 2022.

Parsaclisib: a highly selective PI3Kδ inhibitor active in patients with suboptimal response

A

Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n = 29	n = 27
≥10% to <25% reduction	8 (28)	11 (41)
≥25% to <35% reduction	1 (3)	3 (11)
≥35% reduction	0	1 (4)
Week 24	n = 29	n = 23
≥10% to <25% reduction	2 (7)	6 (26)
≥25% to <35% reduction	3 (10)	5 (21)
≥35% reduction	1 (3)	2 (9)

B



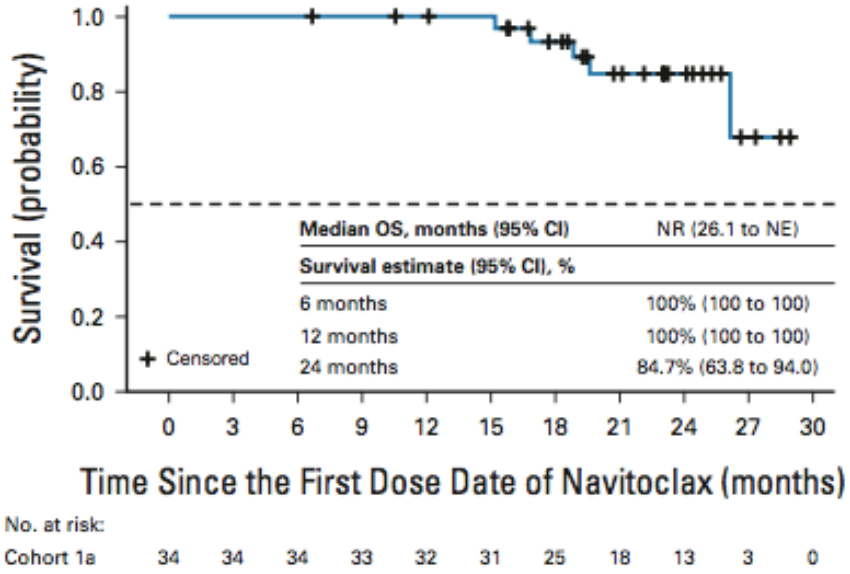
- Median %change in TSS at week 12: -14.0% (daily/weekly), -37.4% (daily)
- Spleen responses maintained in patients with platelets <100 (but 43% required dose interruptions)
- Most common Gr 3/4 AE was thrombocytopenia in ~1/3 of patients; no colitis was seen

Yacoub A, et al. *EHA Library* 2021; EP1075
Yacoub A, et al. *EHA Library* 2022; P1063

Navitoclax in patients with suboptimal response to ruxolitinib

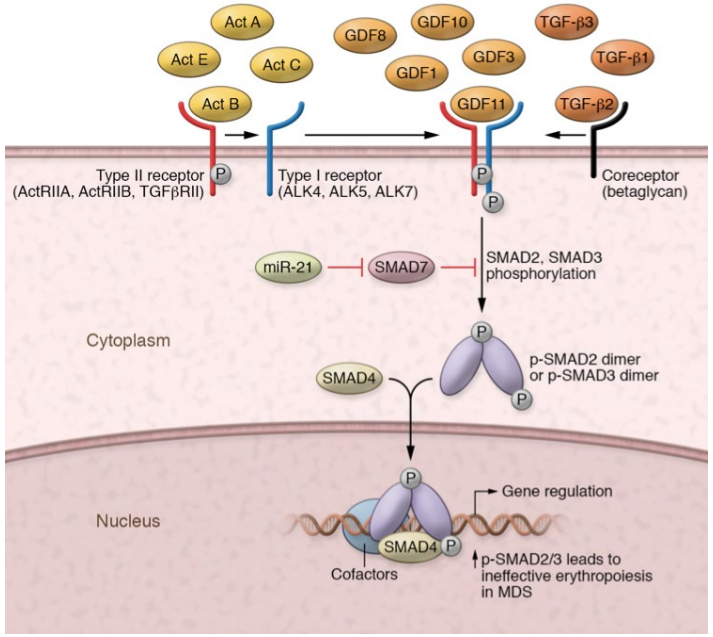
Assessment	N = 34
SVR_{35}, No. (%)	
Week 12	6 (18)
Week 24	9 (26.5)
Week 48	8 (24)
Week 72	7 (21)
Any time	14 (41)
Median duration of SVR_{35}, months (95% CI)	
All patients	13.8 (8.2 to NE)
Patients with HMR	13.8 (8.2 to NE)
Patients without HMR	19.6 (5.6 to NE)
≥ 50% spleen length palpation reduction, No. (%)	
Week 24	17 (50)
Any time	20 (59)
TSS_{50}, n/N (%)	
Week 24	6/20[b] (30)
Any time	12/29[c] (41)
BMF improvement by ≥ 1 grade[d], n/N (%)	
Week 24	7/33 (21)
Any time	11/33 (33)
By 1 grade	7/33 (21)
By 2 grades	4/33 (12)
Anemia response, n/N (%)	
Intention-to-treat population	7/34 (21)
Improvement in Hb of ≥ 2 g/dL	6/9[e] (67)
Transfusion independence	1/2[f] (50)

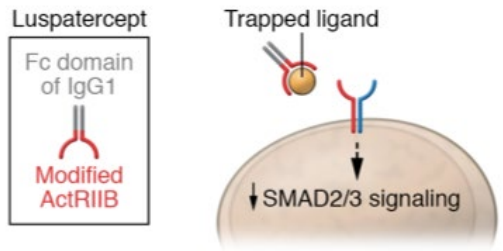
- High molecular risk (HMR) mutations had no impact on response or survival
- OS improvement seen in patients with reduction in fibrosis and driver mutation allele frequency
- Thrombocytopenia is common (grade ≥3 in 56%)
- 65% required dose interruptions, 15% discontinued navitoclax due to AEs



Harrison CN, et al. *J Clin Oncol* 2022; 40(15):1671-1680.
Pemmaraju N, et al. *Lancet Haematol* 2022; S2352-3026(22)00116-8

Luspatercept for the treatment of MF-associated anemia



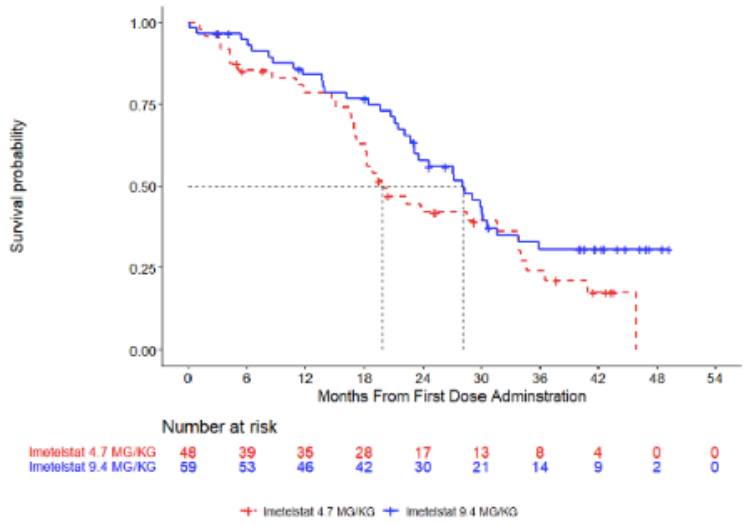


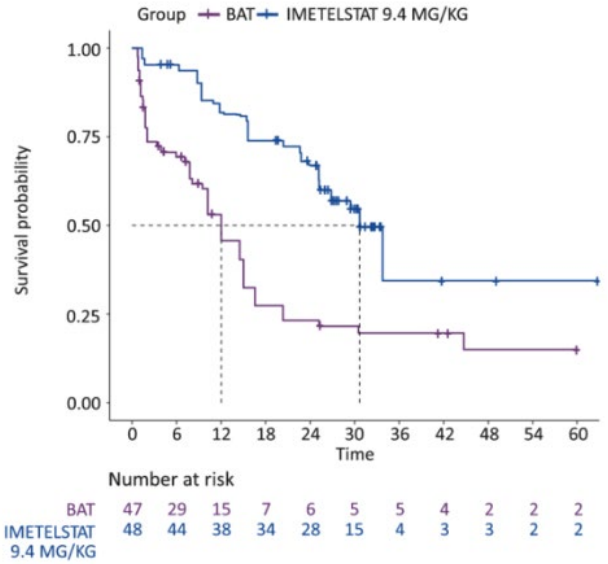
	Cohort 1: non-TD, off Rux	Cohort 3A: non-TD, on Rux	Cohort 2: TD, off rux	Cohort 3B: TD, on rux
# of patients	n=20	n=14	n=21	n=22
Mean hgb increase ≥1.5 g/dL	3 (15%)	8 (57%)		
RBC-TI ≥12 weeks			4 (19%)	8 (36%)
≥50% reduction in RBC transfusions			8 (38%)	10 (45.5%)

Gerds AT, et al. *Blood* 2019; 134(Supplement 1):557
Gerds AT, et al. *Blood* 2020; 136(Supplement 1):47-48
Verma A, et al. *J Clin Invest* 2020; 130(2):582-589

Imetelstat: a first in class telomerase inhibitor

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%)



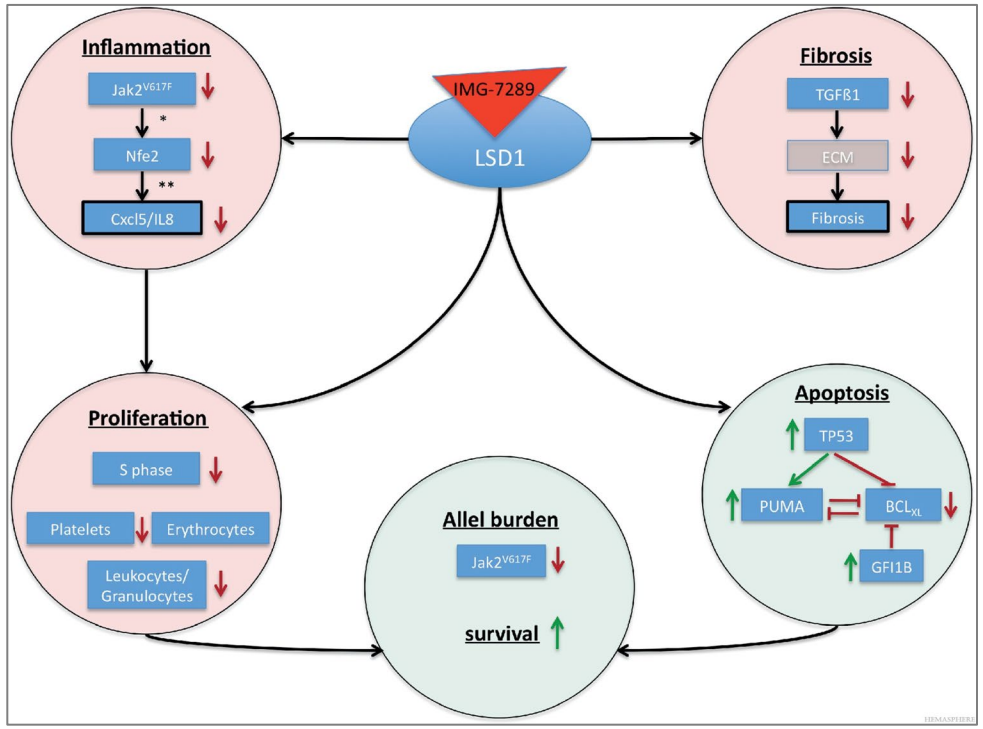


Mascarenhas J, et al. *EHA Library* 2020; EP1107

Kuykendall A, et al. *EHA Library* 2019; PS1456

Mascarenhas J, et al. *Blood* 2020; 136(Supplement 1):39-40

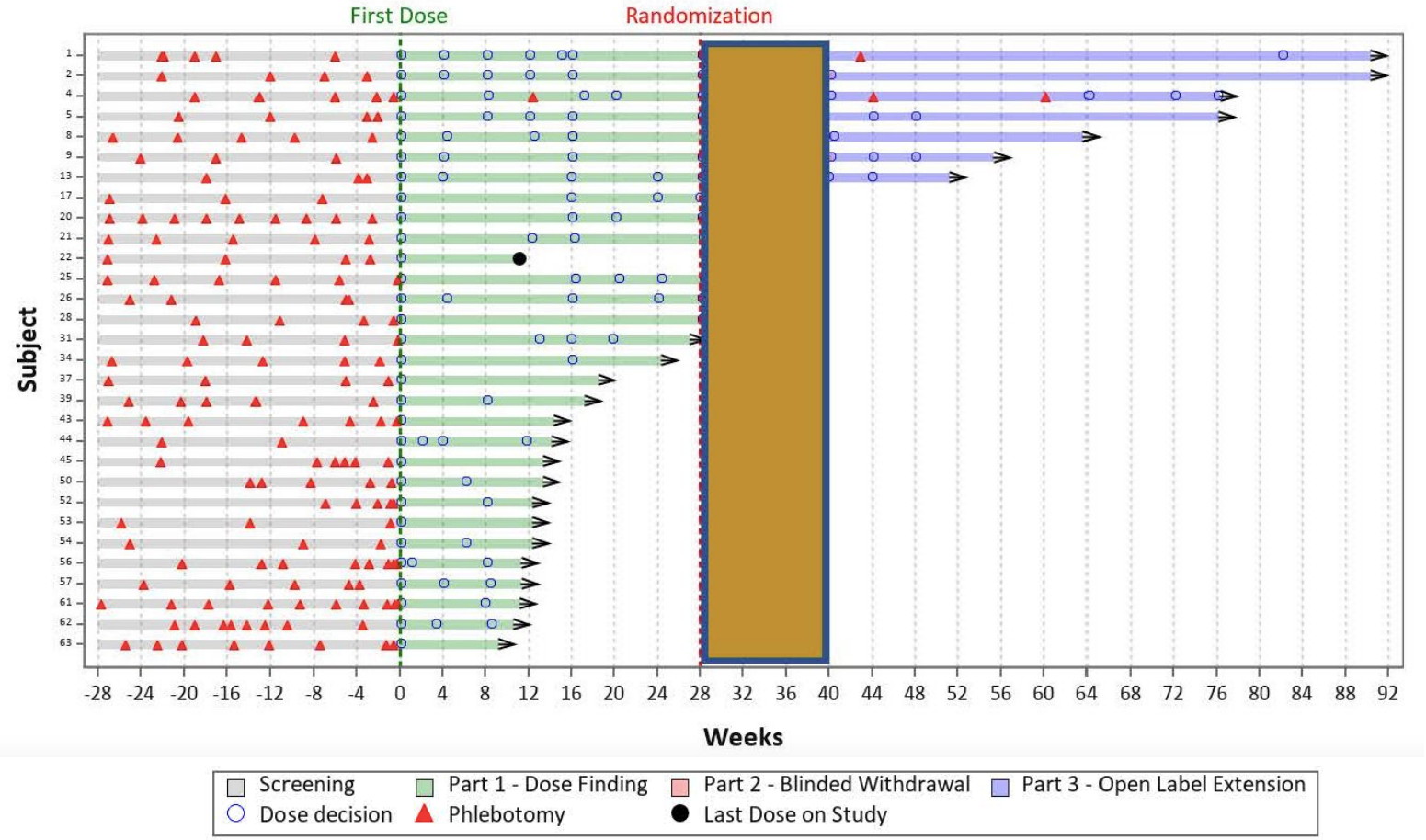
LSD1: a novel therapeutic target in MPNs



- Bomedemstat is a lysine-specific demthylase-1 (LDS1) inhibitor
  - LSD1: histone demethylase involved in proliferation, self-renewal and differentiation
- Phase 2 study in previously treated ET
  - normalization of platelets (81%), WBCs (89%)
  - symptom improvements
- Phase 2 study in previously treated MF
  - 89% with symptom improvement (TSS50 of 39%)
  - 78% with improvement in splenomegaly (SVR35 of 37%)
  - reductions in mutation frequencies observed

Jutzi JS, et al. *Hemasphere* 2018; 2(3):e54. Gill H, et al. *Blood* 2021; 138(supplement1):139. Palandri F, et al. *Blood* 2021; 138(Supplement 1):386

Rusfertide (PTG-300) eliminates phlebotomy requirements in PV patients



- Hepcidin mimetic: impairs iron absorption and mobilization, reducing erythropoiesis
- Phase 2 study of 63 PV patients requiring phlebotomy (+/- cytoreductive therapy)

Ginzburg Y, et al. *Blood* 2021; 138(Supplement 1):390. Hoffman R, et al. *ASH 2021 Annual Meeting,* abstract 388.

Conclusions

- Inhibiting constitutive JAK-STAT activation has revolutionized treatment of MPNs, but limitations persist
- New JAK inhibitors have the potential to extend the benefit of JAK inhibition to additional patient populations, with several recently approved or in late-stage development
- Combination approaches are actively being investigated to improve efficacy and overcome resistance to JAKi
- A variety of novel therapeutics targeting pathways beyond JAK-STAT hold significant promise

Thank You

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