Treatment Options for Ruxolitinib Intolerance or Resistance in Myelofibrosis

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TOTAL CME

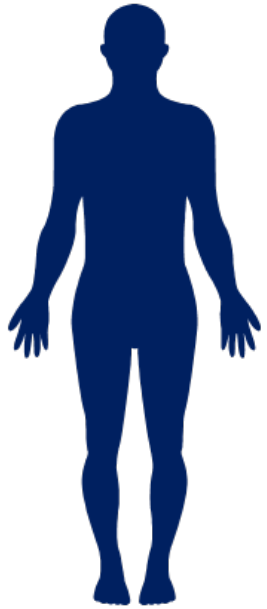
We Now Have 4 FDA-Approved JAKi

JAK Inhibitor	MF Relevant Targets	Major Clinical Trials in MF	Approval Date	Approved and Recommended Indications
Ruxolitinib	JAK1, JAK2	COMFORT-1/2 (phase 3)	2011	**FDA:** Frontline for intermediate- and high-risk MF
Fedratinib	JAK2	JAKARTA-1/2 (phase 3, 2) FREEDOM (phase 3b)	2019	**FDA:** Frontline or second-line for INT-2 and high-risk MF
Pacritinib	JAK2, ACVR1	PERSIST 1/2 (phase 3) PAC203 (phase 2)	2022	**FDA:** Frontline for intermediate- and high-risk MF with PLT < 50×10^9 **NCCN**: Second-line with any PLT count
Momelotinib	JAK1/2, ACVR1	SIMPLIFY-1/2 (phase 3) MOMENTUM (phase 3)	2023	**FDA**: Approved for patients with anemia

Fedratinib in Myelofibrosis: JAKARTA and JAKARTA-2 Trials

Phase 3 JAKARTA Trial

Fedratinib vs placebo in patients with Int-2/high-risk MF

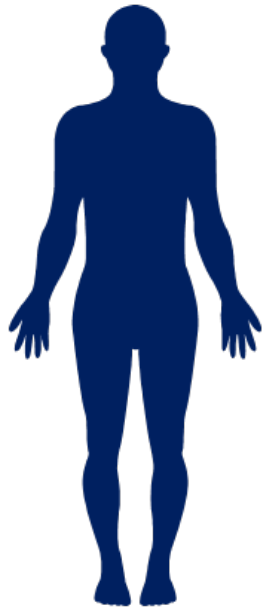


N = 289

	Fedratinib 400 mg	Fedratinib 500 mg
Spleen volume reduction ≥ 35%	37%	40%
Symptom burden reduction ≥ 50%	40%	34%
Discontinuation due to AEs	14%	25%

Phase 2 JAKARTA-2 Trial

Fedratinib vs placebo in patients with Int-2/high-risk MF resistant or intolerant to ruxolitinib



N = 97
*N = 79

	Primary analysis	Reanalysis (2019)*
Spleen volume reduction ≥ 35%	55%	30%
Symptom burden reduction ≥ 50%		27%
Discontinuation due to AEs	11.0%	

*More stringent criteria for relapse, refractory, and intolerance to ruxolitinib

15% of the patients in the fedratinib 400-mg group had a baseline platelet count <100 × 10^9/L

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651. Harrison CN, et al. *Lancet Haematol*. 2017;4(7):e317-e324. Harrison CN, et al. ASCO 2019. Abstract 7057.

Fedratinib Adverse Events

Adverse Event, %	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo (n = 95)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Nonhematologic						
Diarrhea	66	5	56	5	16	0
Vomiting	42	3	55	9	5	0
Nausea	64	0	51	6	15	0
Constipation	10	2	18	0	7	0
Asthenia	9	2	16	4	6	1
Abdominal pain	15	0	12	1	16	1
Fatigue	16	6	10	5	1	0
Hematologic						
Anemia	99	43	98	60	91	25
Thrombocytopenia	63	17	57	27	51	9
Lymphopenia	57	21	66	27	54	21
Leukopenia	47	6	53	16	19	3
Neutropenia	28	8	44	18	15	4

Black box warning

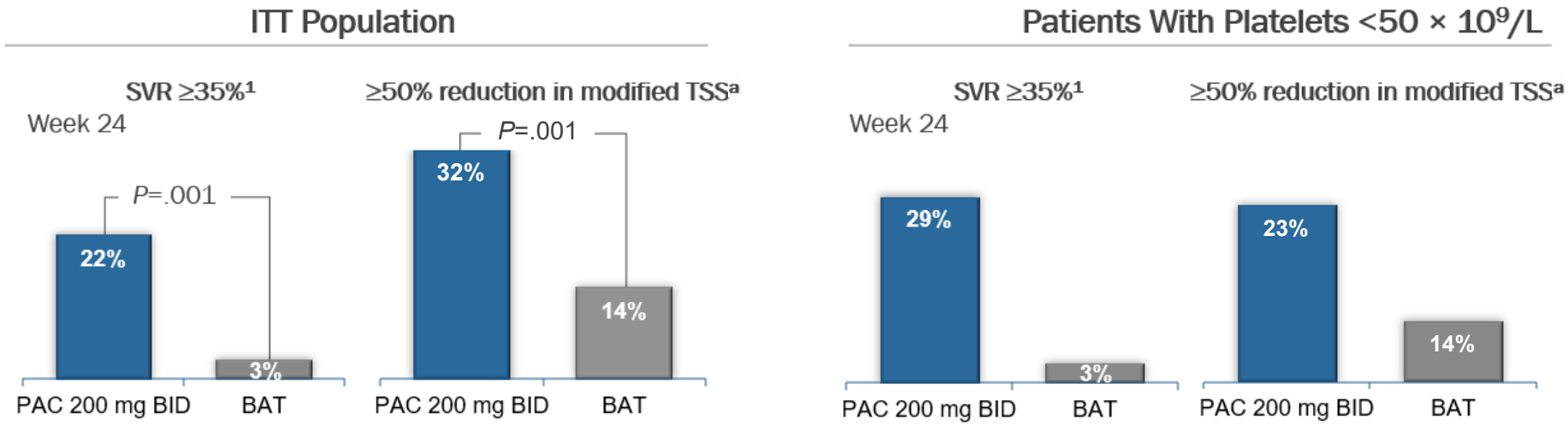
- Wernicke's encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

Considerations

- Measure and address thiamine levels prior to treatment initiation
- Do not start fedratinib in patients with thiamine deficiency

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.

Spleen Volume Reduction With Pacritinib (PERSIST-2)



- The proportions of patients with much improved or very much improved scores were 57% with pacritinib 200 mg BID vs 28% with BAT

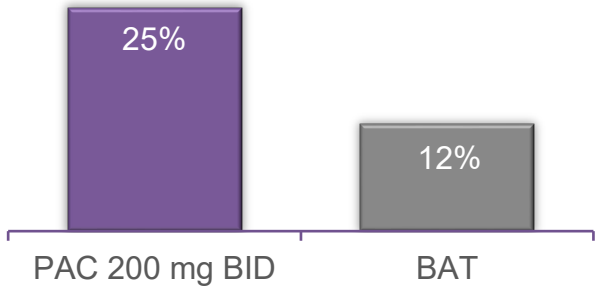
[a] Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

PERSIST-2: Hematologic Stability

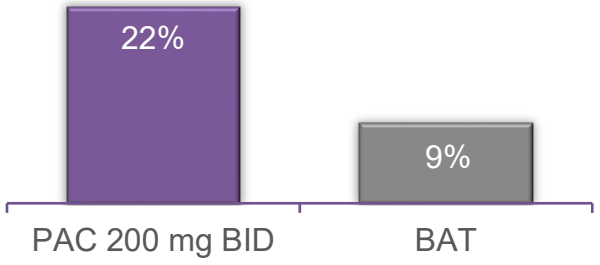
Clinical Improvement in Hemoglobin Levels in Patients With Baseline Anemia[a]

Baseline to week 24



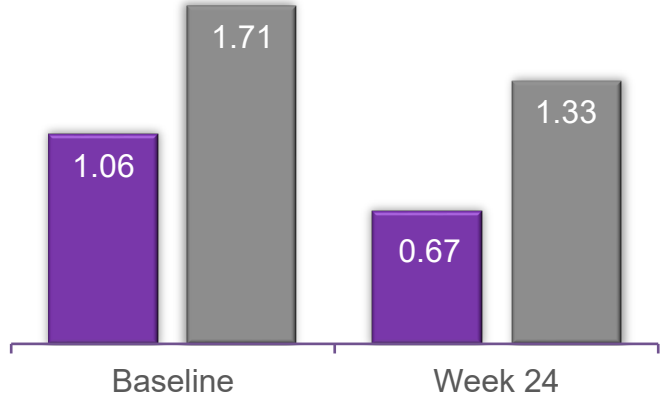
Pacritinib Reduced Transfusion Burden in Patients Not TI at Baseline

Baseline to week 24



Transfusion Burden in Patients Who Received ≥1 RBC Transfusion on Study

Units per month



TI defined according to Gale criteria (0 units over the course of 12 weeks).
[a] International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL.

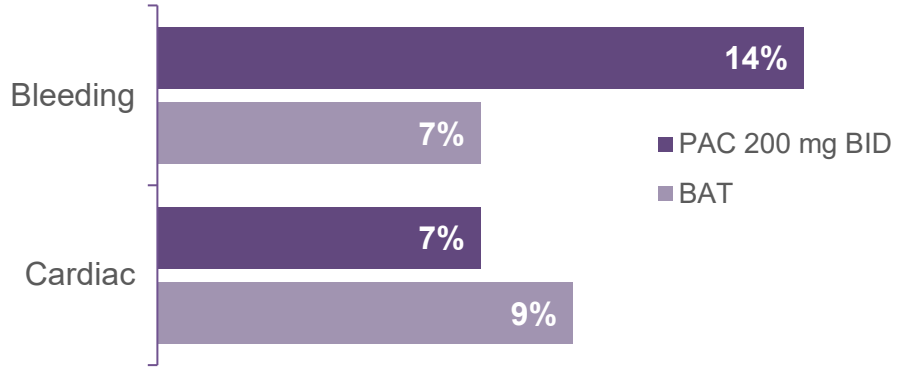
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; PAC, pacritinib; RBC, red blood cell; TI, transfusion independent..
Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

PERSIST-2: Adverse Event Profile

Adverse Reactions	PAC 200 mg BID (n = 106)	BAT (n = 98)
Any-grade AEs in >15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	24
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16
Grade ≥3 AEs in >5% of patients in either arm, %		
Thrombocytopenia	32	18
Anemia	22	14
Neutropenia	7	5
Pneumonia	7	3
Serious AEs in >3% of patients in either arm, %		
Anemia	8	3
Thrombocytopenia	6	2
Pneumonia	6	4
Congestive heart failure	4	2

- Diarrhea with pacritinib most often occurred during weeks 1-8, was manageable, and resolved within 1-2 weeks
- Neurologic AEs and opportunistic infections rarely reported with pacritinib

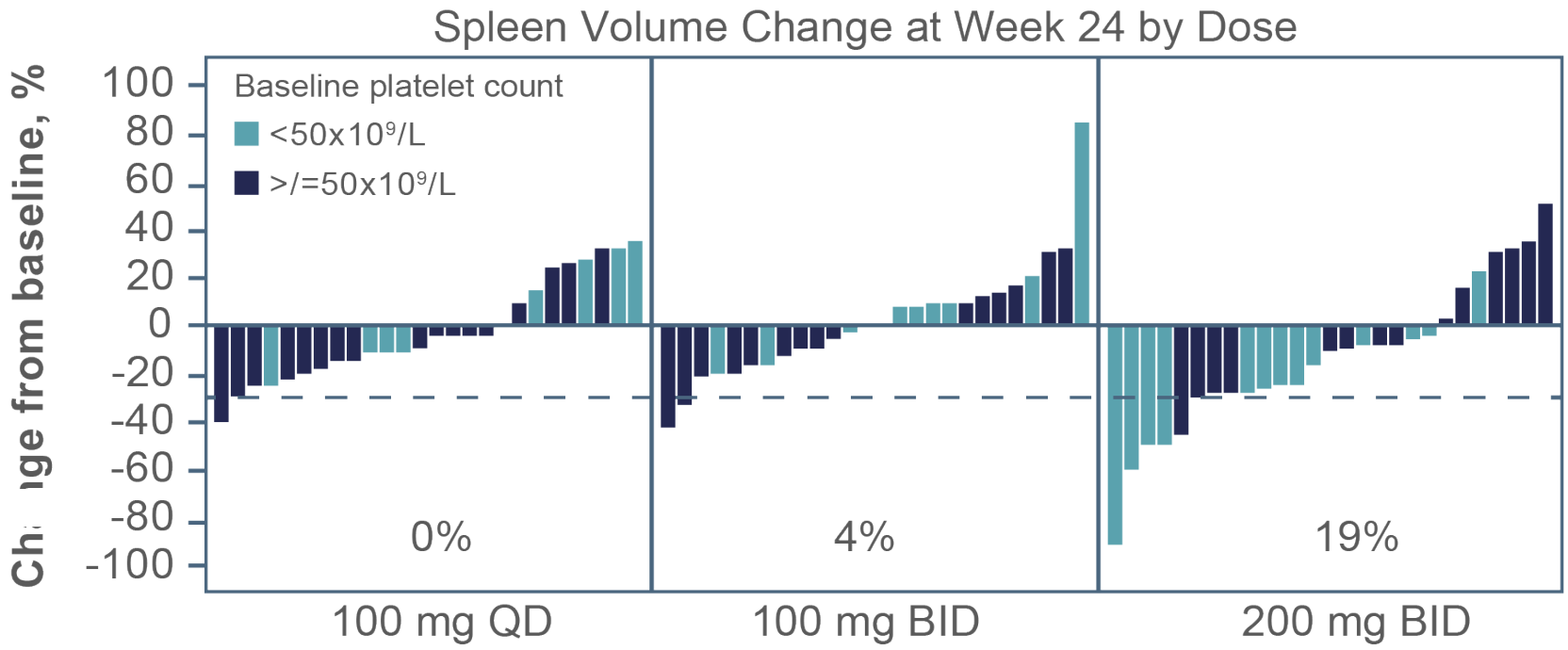
Grade ≥3 Events (Pooled[a])



- **Safety outcomes with pacritinib were similar for those with <50 × 10^9/L vs 50-100 × 10^9/L platelets at baseline**

[a] Pooled, per standardized MedDRA queries.
AE, adverse event; BAT, best available therapy; BID, twice daily; PAC, pacritinib.
Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

PAC203: Spleen Response Across Doses (Evaluable Population, Week 24)

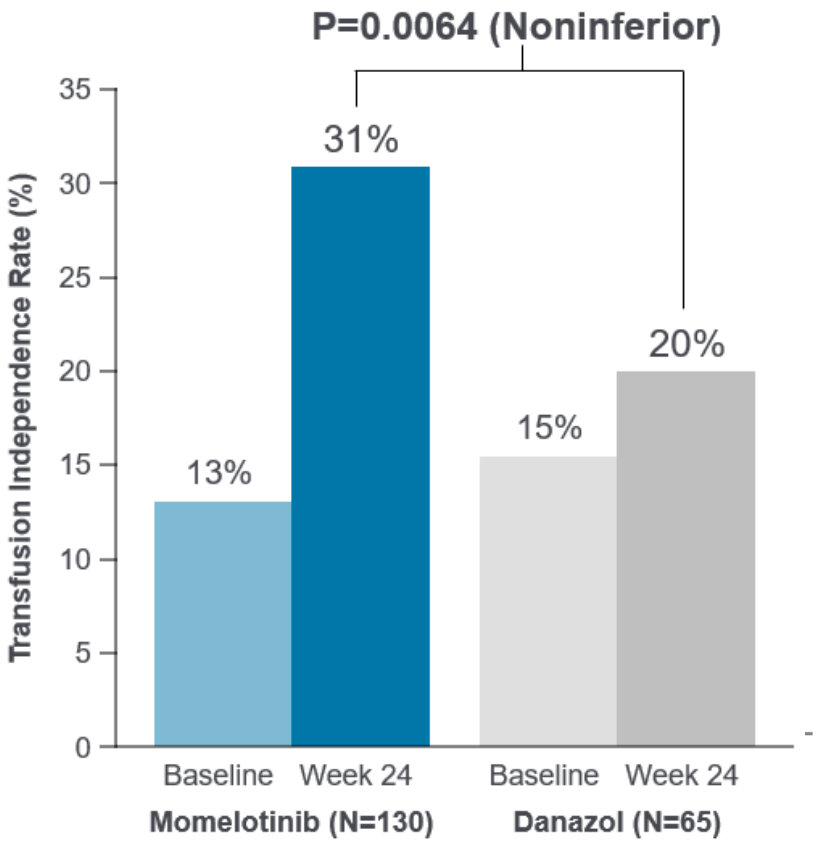


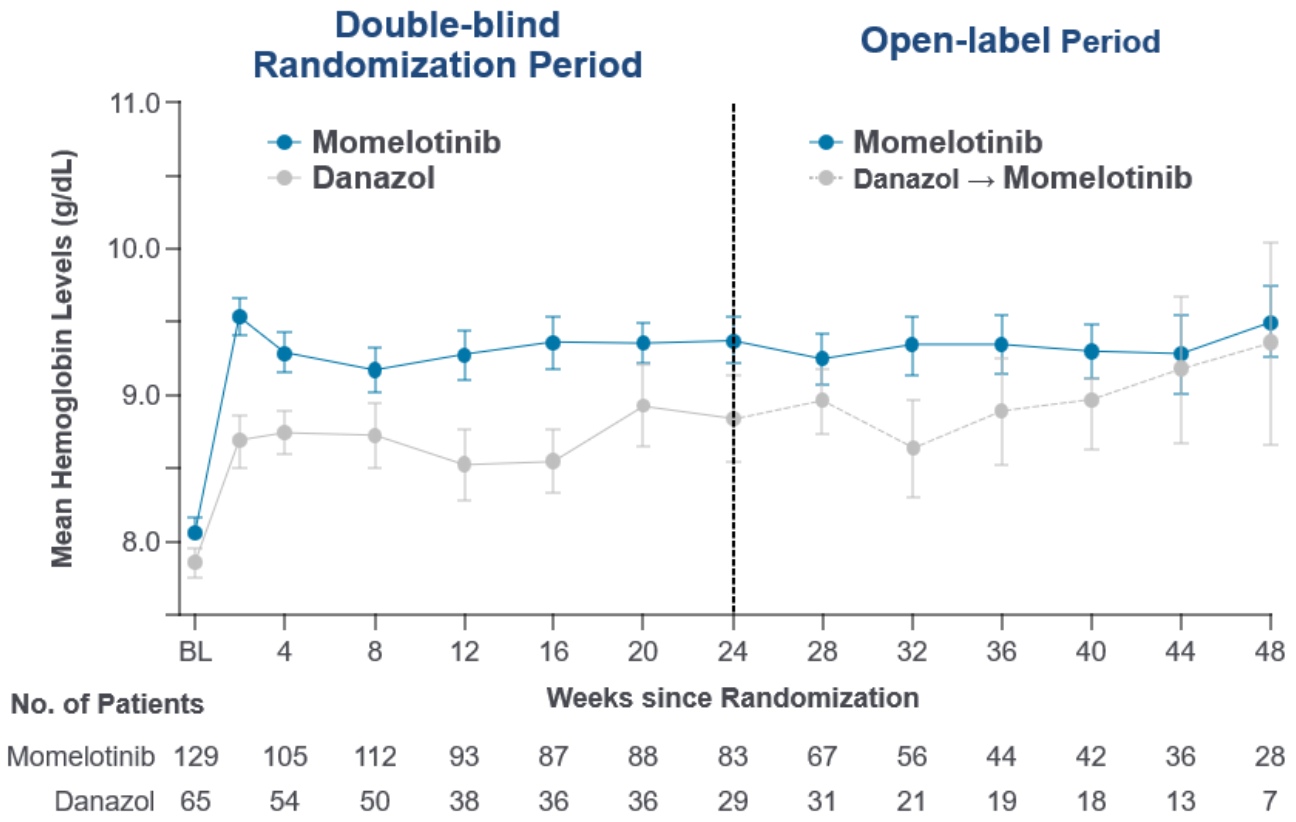
31% Evaluable SVR in patients with severe thrombocytopenia (<50 × 10^9/L) at baseline treated with 200 mg BID

BID, twice daily; QD, once daily; SVR, spleen volume reduction.

Gerds AT, et al. *Blood Adv*. 2020;4(22):5825-5835.

MOMENTUM: Transfusion Independence at Week 24





Verstovsek S, et al. *Lancet.* 2023;401(10373):269-280.

Momelotinib Treatment-Emergent Adverse Events

	Momelotinib group (n=130)		Danazol group (n=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological abnormalities (preferred term)				
Diarrhoea	29 (22%)	0	6 (9%)	1 (2%)
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Asthenia	17 (13%)	1 (1%)	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Weight decreased	14 (11%)	0	4 (6%)	0
Blood creatinine increased	10 (8%)	1 (1%)	10 (15%)	2 (3%)
Dyspnoea	10 (8%)	3 (2%)	9 (14%)	1 (2%)
Peripheral oedema	10 (8%)	2 (2%)	9 (14%)	0
Fatigue	8 (6%)	1 (1%)	7 (11%)	2 (3%)
Acute kidney injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)
Haematological abnormalities*				
Anaemia	129 (99%)	79 (61%)	65 (100%)	49 (75%)
Thrombocytopenia	99 (76%)	36 (28%)	40 (62%)	17 (26%)
Neutropenia	38 (29%)	16 (12%)	17 (26%)	6 (9%)

Data are n (%). *Haematological abnormalities are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase of the study, regardless of whether this grade was a change from baseline.

Verstovsek S, et al. *Lancet.* 2023;401(10373):269-280.

Summary

- Fedratinib has shown efficacy in improving SVR and TSS in first-line and second-line treatment
- Pacritinib is FDA-approved in first line for patients with platelets of <50 and has shown efficacy in improving TSS and SVR in a very thrombocytopenic group of patients
  - Least myelosuppressive of the JAKis and can be used at full dose regardless of cytopenias

Summary

- Momelotinib is FDA-approved for patients with MF with anemia
  - Approval is line agnostic
- It is important to recognize most JAK inhibitors have GI toxicity that occurs frequently at initiation of therapy