Mass General Brigham
Mass General Cancer Center

Novel Advances in Myelofibrosis: Diagnosis, risk stratification and therapy

Gabriela Hobbs, MD
Clinical Director, Leukemia Service, Massachusetts General Hospital
Assistant Professor, Harvard Medical School

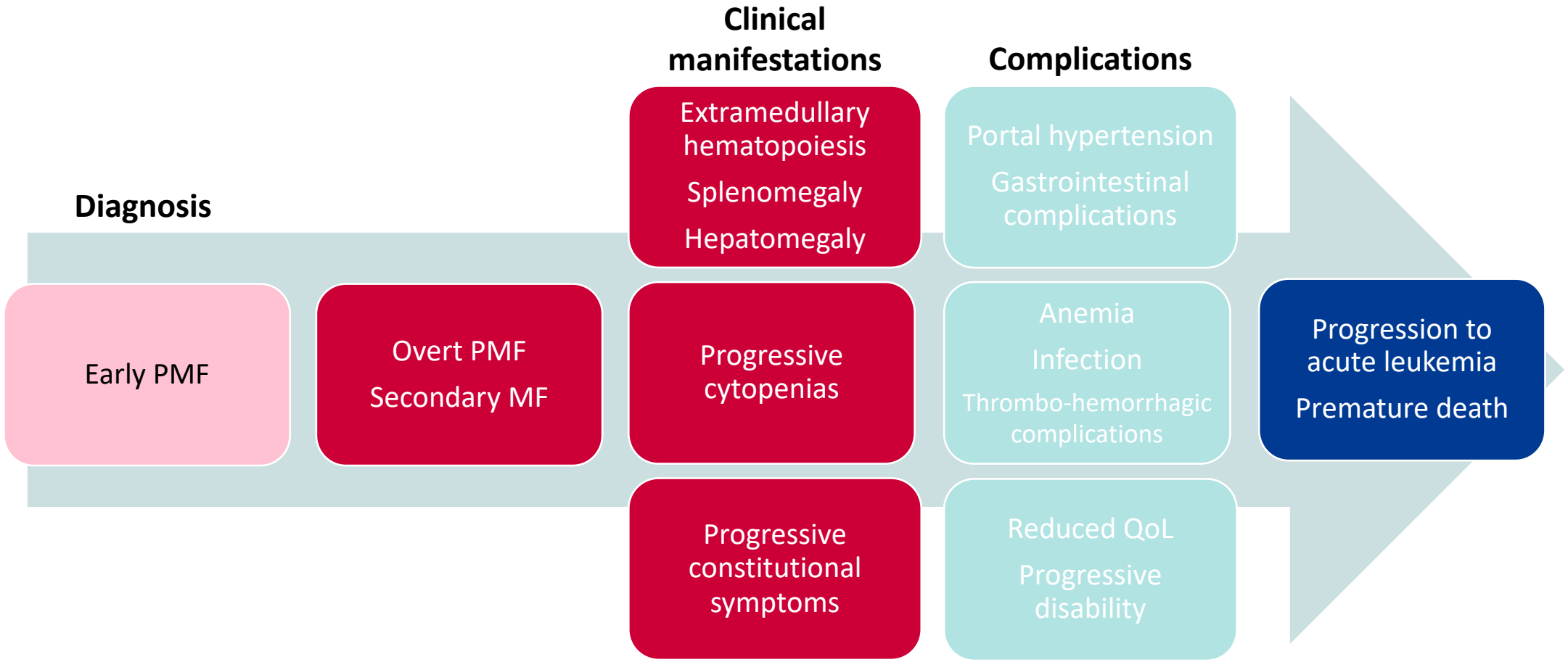
July 19-21 2024
New Orleans Summer Conference

Case

Mr. PT is a 70 yo M with myelofibrosis with a CALR and ASXL1 mutation, WBC is 9 x 10^9, hemoglobin is 10.5 g/dL and platelets are 143 x 10^9, he has 2% circulating blasts. He endorses night sweats, unintentional weight loss and itching, on exam spleen is palpated 10 cm below the costal margin. Bone marrow biopsy shows 2+ fibrosis. He is started on ruxolitinib 15 mg BID. He was not considered for transplant based on renal insufficiency and advanced COPD.

After 9 months of therapy, spleen is palpable 6 cm below costal margin, he is now anemic with a hemoglobin of 8.5 g/dL and thrombocytopenic with a platelet count of 40. Repeat bone marrow rules out disease progression to acute leukemia.

MF Is a Progressive Condition



PMF = primary myelofibrosis; QoL = quality of life

Mughal TI, Vaddi K, Sarlis NJ, Verstovsek S. *Int J Gen Med*. 2014;7:89-101.

Risk Stratification in MF

"Before I begin, one of the acronyms I'm going to use is completely made up. See if you can figure out which one."

4

MIPPS70: Mutation-Enhanced International Prognostic Scoring System

MIPSS70 Parameter	Points		
	0	1	2
Anemia	≥ 10 g/dL	< 10 g/dL	
Leukocytosis	< 25 x 10^9/L		≥ 25 10^9/L
Platelet Count	≥ 100 x 10^9/L		< 100 x 10^9/L
Circulating Blasts	< 2%	≥ 2%	
Bone Marrow Fibrosis Grade	< MF-2	≥ MF-2	
Constitutional Symptoms	Absent	Present	
Absence of *CALR* type 1/like mutation	No	Yes	
High-molecular risk (HMR) mutations*	No	Yes	
≥2 HMR mutations	No		Yes

MYSEC-PM: Myelofibrosis Secondary to PV and ET-Prognostic Mode

MYSEC-PM Parameter	Points			
		0	1	2
Age	0.15 x Age (years)			
Constitutional Symptoms		Absent	Present	
Anemia		≥ 11 g/dL		< 11 g/dL
Thrombocytopenia		≥ 150 x 10^9/L	< 150 x 10^9/L	
Circulating Blasts		< 3%		≥ 3%
CALR Status		Mutated		Unmutated

MYSEC-PM Risk Group	Points	Med Survival (yr)
Low	0-11	NR
Intermediate-1	>11-14	9.3 (95% CI: 8.0-NR)
Intermediate-2	>14-16	4.5 (95% CI: 3.2–7.9)
High	>16	2 (95% CI: 1.7–3.9)

Survival Varies by Risk

DIPSS+

	Median Survival, Years		
Risk Group	IPSS [2]	DIPSS [3]	DIPSS-Plus [4]
Low	11.3	Not reached	15.4
Intermediate-1	7.9	14.2	6.5
Intermediate-2	4.0	4.0	2.9
High	2.3	1.5	1.3

MIPSS70

Risk category	Score	OS (yr)	HR
Low	0–1	27.7	1
Intermediate	2–4	7.1	5.5 (3.8-8.0)
High	≥5	2.3	16.0 (10.2-25.1)

MYSEC-PM:

	Median OS (yr)
Low	NR
Int-1	9.3
Int-2	4.4
High	2

DIPSS, dynamic International Prognostic Scoring System; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell count

Case continued:

70M, MF with CALR/ASXL1 treated with rux, not a transplant candidate, after 9 mo of therapy, spleen is palpable and is now anemic hgb 8.5, thrombocytopenic plts of 40.

- How would you risk stratify Mr. PT?
- Which score?
- What risk factors are present?

How to Approach Treatment

Assess risk

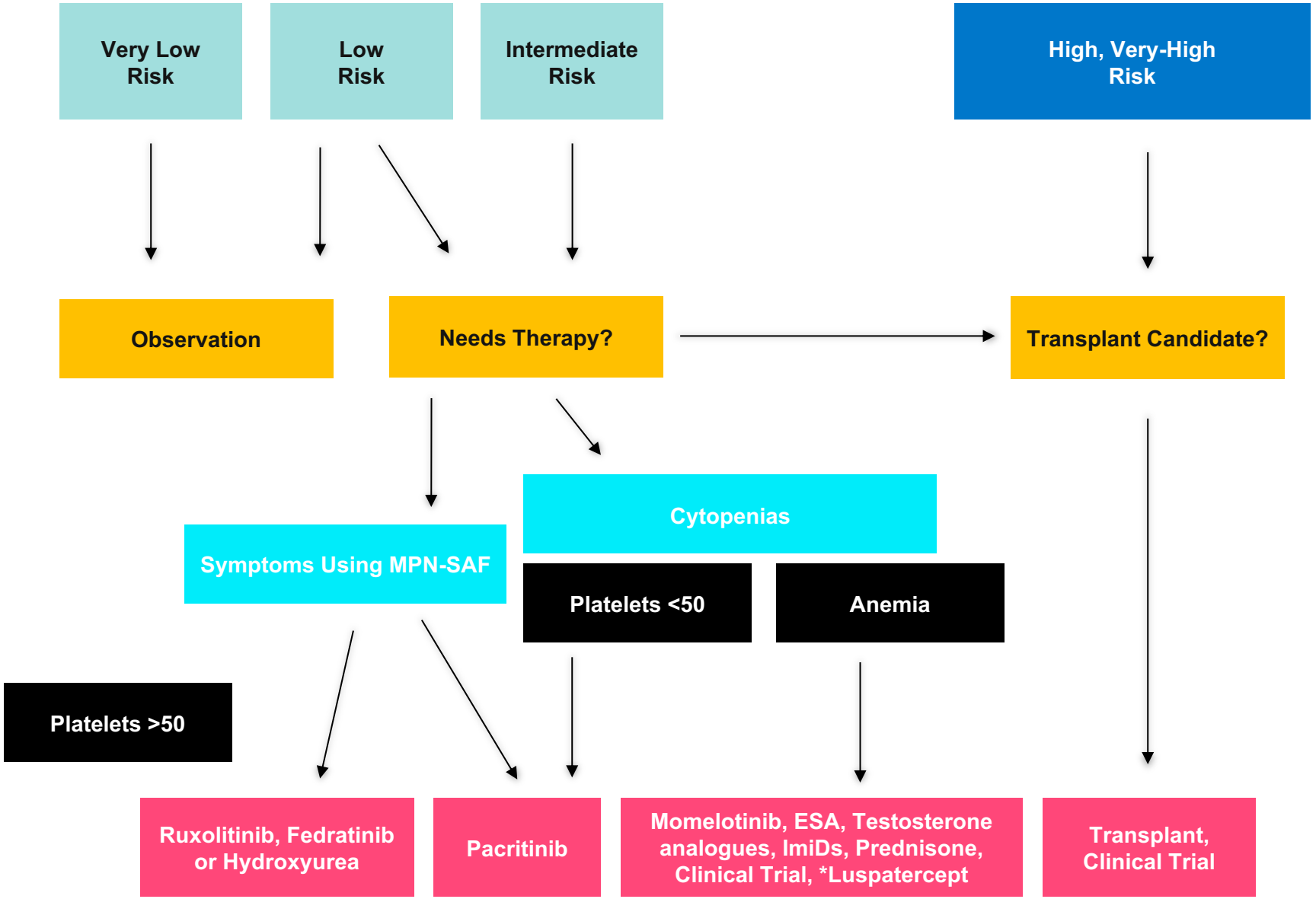
- Is the patient a transplant candidate?
- Do they desire a transplant?
- What is their risk?

Assess symptoms

- Do they have spleen related symptoms (early satiety, abdominal discomfort)?
- Do they have constitutional symptoms (fatigue, night sweats, weight loss)?

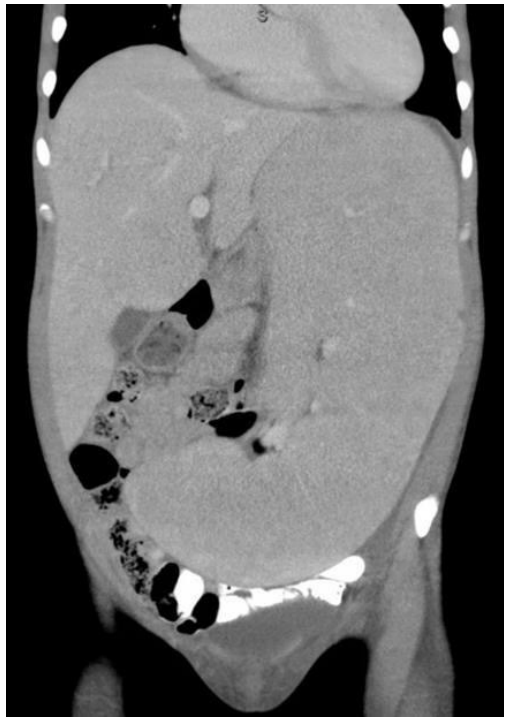
Do they have cytopenias?

Myelofibrosis treatment approach- 2024



*off label

Indications for JAK inhibitor therapy



- JAKi are not mutation specific
- JAKi do not prevent disease progression

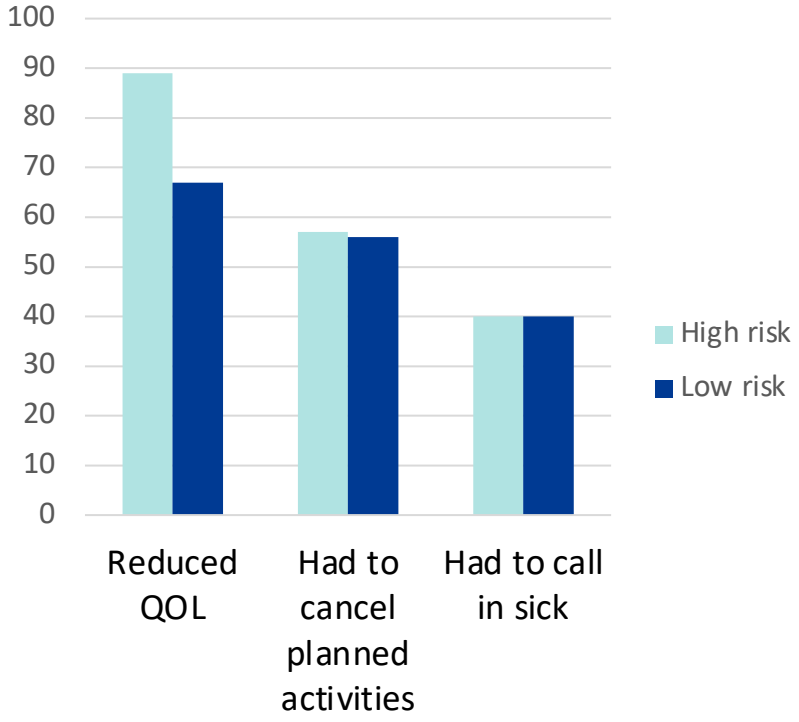
Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Symptom	1 to 10 (0 if absent) ranking (1 is most favorable and 10 least favorable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past **24 hours**	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the PAST 24 HOURS how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

MF Impact on Quality of Life and Employment

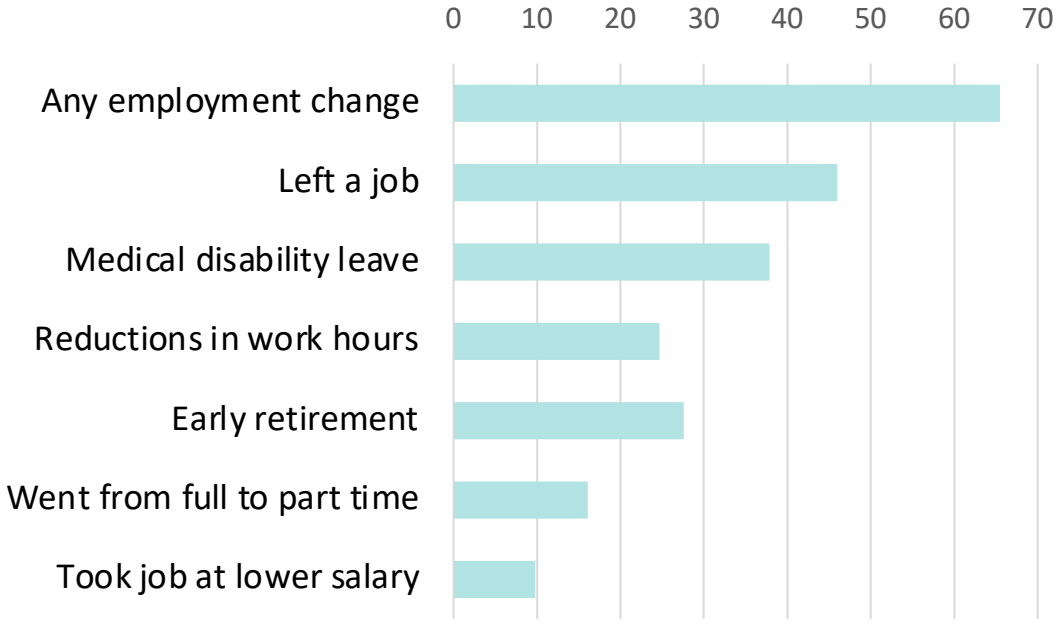
MPN Landmark Survey (US)[1]

Even low risk disease has an impact on QoL and activities of daily living



Living with MPNs Survey (US)[2]

MF has a high impact on employment status and work productivity



% of MF patients who were employed at diagnosis (n = 174)

MPN = myeloproliferative neoplasms; QoL = quality of life

1. Mesa R, et al. *BMC Cancer*. 2016;16:167.
2. Yu J, et al. *BMC Cancer*. 2018;18(1):420.

JAK Inhibitors for Treatment of MF

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

NDA, new drug application; PLT = platelets

Passamonti F, et al. *Blood*. 2023;141(16):1954-1970.
Tefferi A. *Am J Hematol*. 2023;98(5):801-821.

Ruxolitinib

Ruxolitinib administration and dosing:

Baseline Platelet counts	Ruxolitinib Dose
>200 x 10^9/L	20 mg BID
100-200 x 10^9/L	10 mg BID
50-99 x 10^9/L	5 mg BID

Dose Adjustments:

- Dose is not generally adjusted in the first 4 weeks.
- Subsequent doses can be adjusted every 2 weeks**.**
- Adjust dose for CYP3A4 inhibitors
- If no response/intolerance- Taper ruxolitinib to discontinue

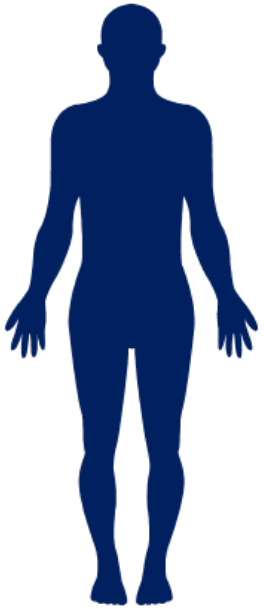
Side effects and considerations:

- VZV reactivation (acyclovir prophpylaxis vs vaccine)
- Check lipids before use
- Advise patients about weight gain

Fedratinib in Myelofibrosis: JAKARTA and JAKARTA-2 Trials

Phase 3 JAKARTA Trial

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

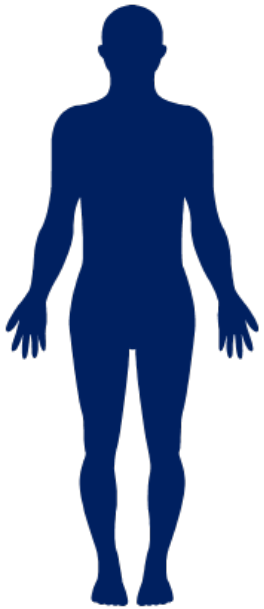


N = 289

	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):317–324; Harrison CN et al. ASCO 2019. Abstract 7057.

Pacritinib

PERSIST-2[1]

Phase 3 randomized trial comparing pacritinib with best available therapy (BAT)

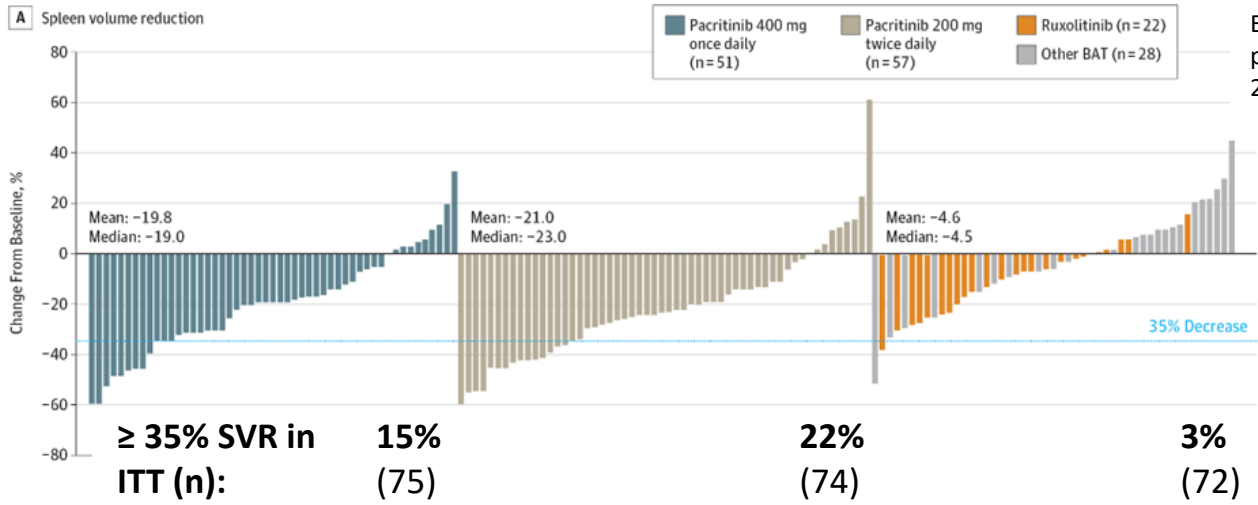
- Pacritinib: 400 mg once daily versus 200 mg twice daily

Enrollment criteria:

- ≥ Intermediate-1 risk MF
- Thrombocytopenia: platelets < 100 × 10^9/L
- Previously treated or JAK inhibitor-naïve

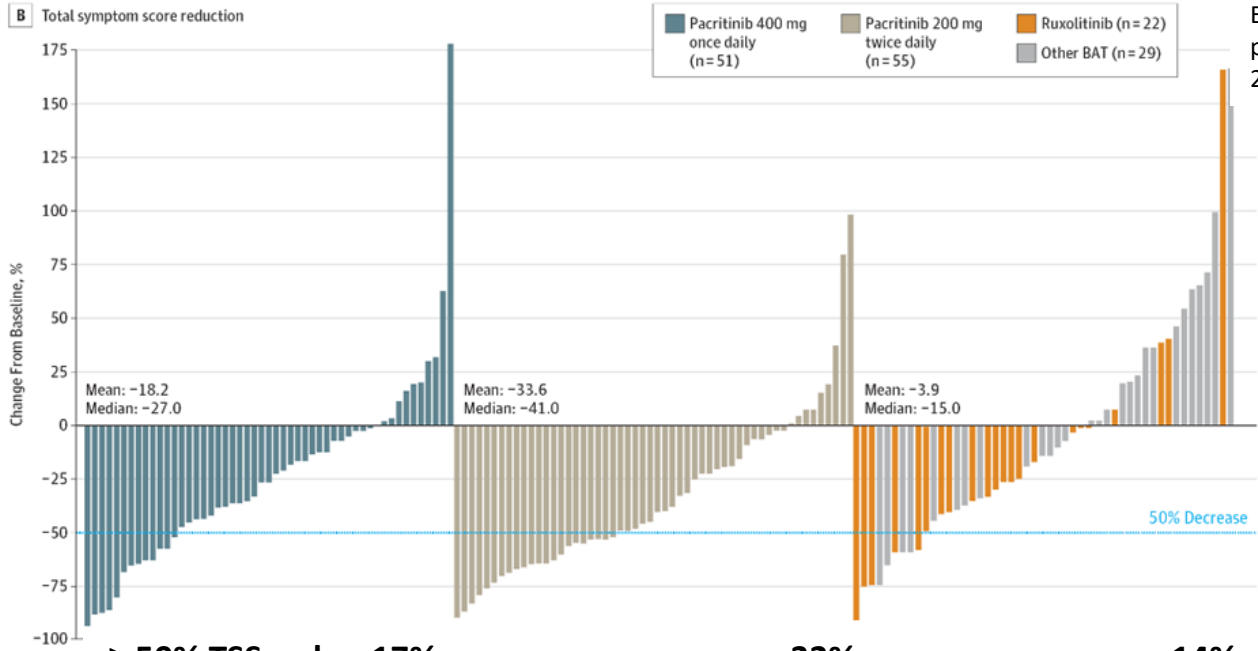
Control arm treatments:

- Ruxolitinib (n = 44)
- Hydroxyurea (n = 19)
- Prednisone and/or prednisolone (n = 13)
- Watchful waiting (n = 19)



Evaluable patients at 24 weeks

≥ 35% SVR in ITT (n):	**15%** (75)	**22%** (74)	**3%** (72)



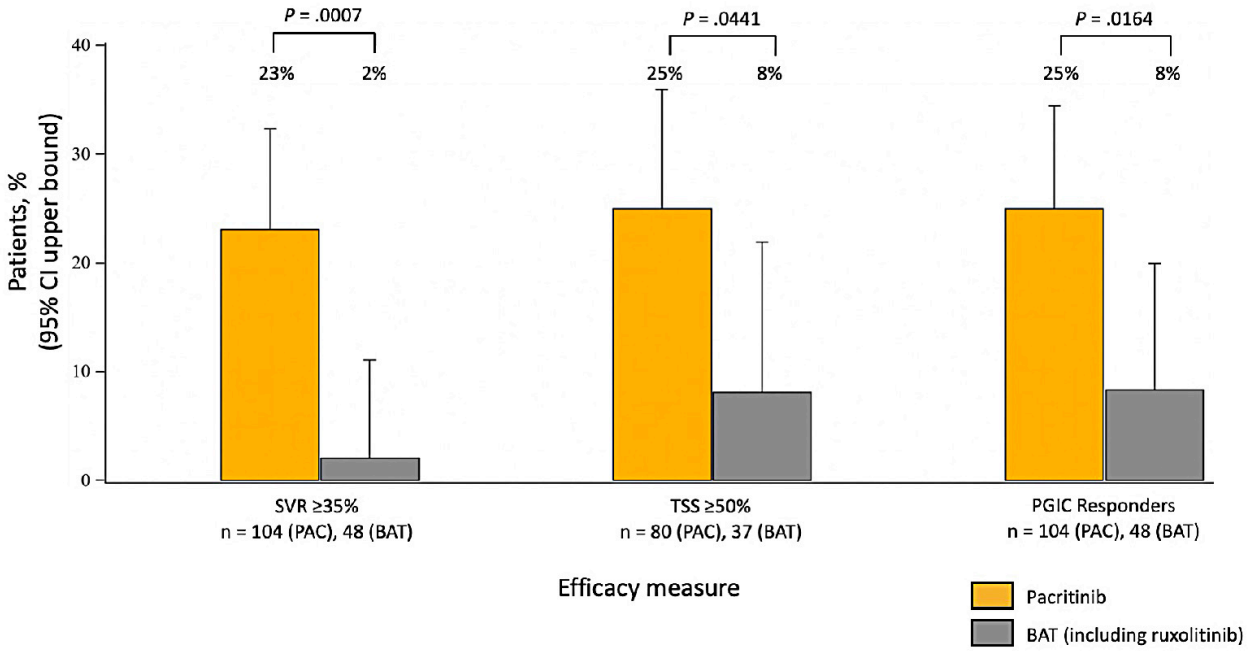
Evaluable patients at 24 weeks

≥ 50% TSS red. in ITT (n):	**17%** (75)	**32%** (74)	**14%** (72)

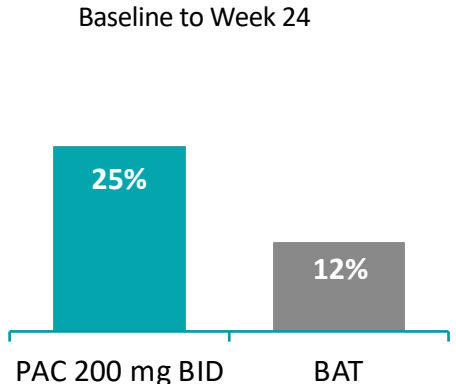
ITT = intent to treat population; SVR = spleen volume reduction; TSS red. = total symptom score reduction

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

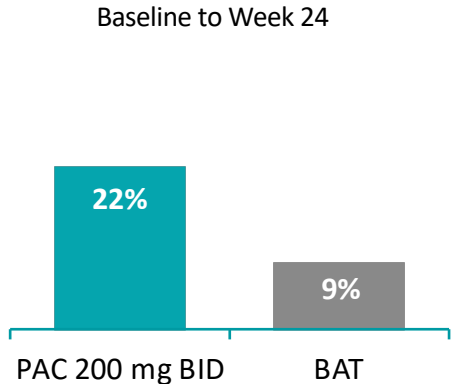
Pacritinib for severe thrombocytopenia and anemia



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

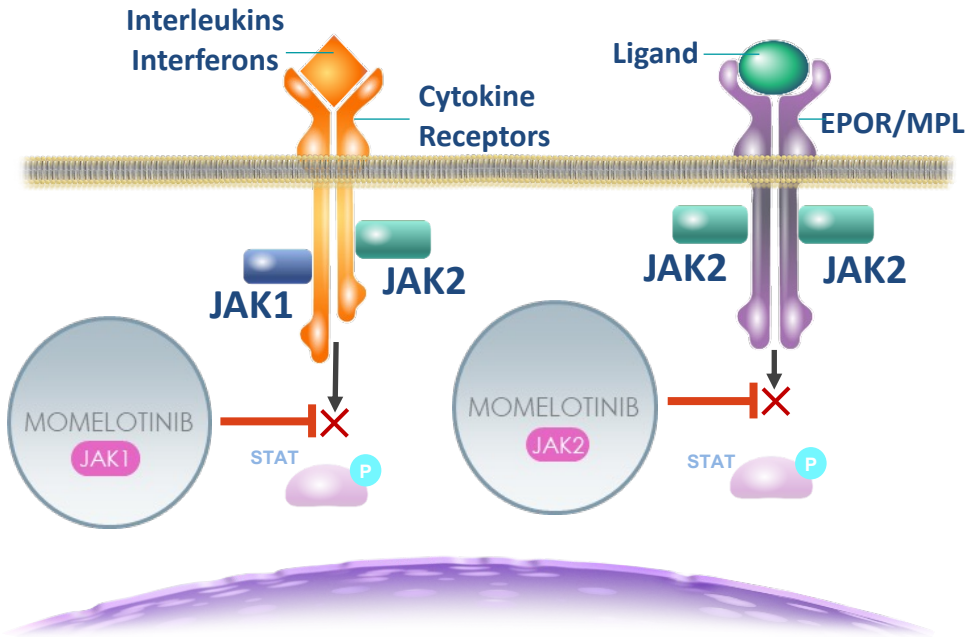


Reduced Transfusion Burden[b] in Patients not Transfusion Independent at Baseline

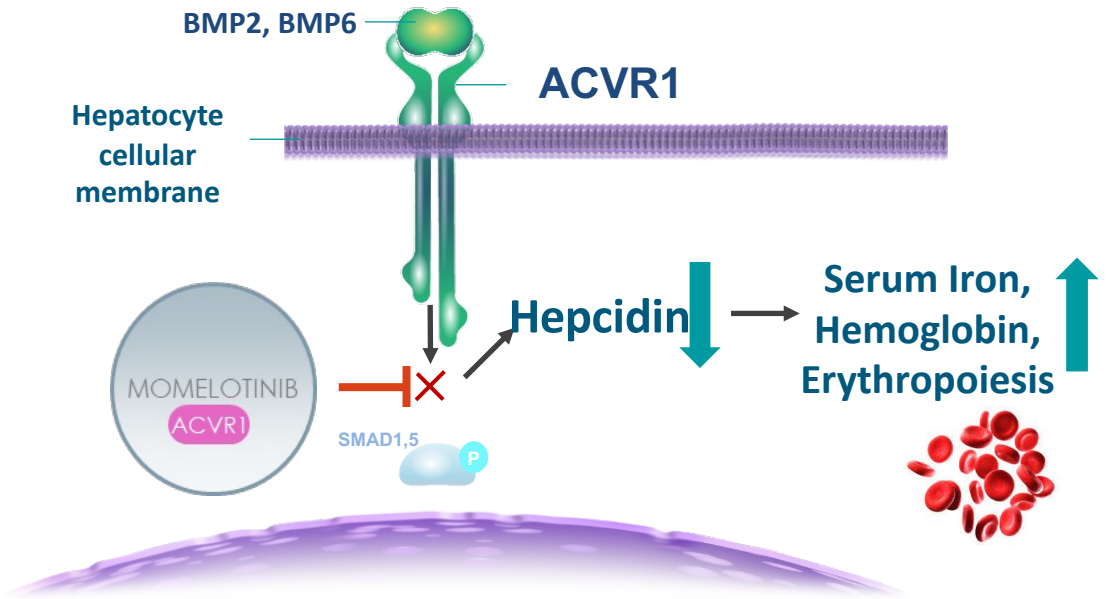


Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

Momelotinib Mechanism of Action



Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**[1,2]



Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF[3,4]

MPL = myeloproliferative leukemia protein

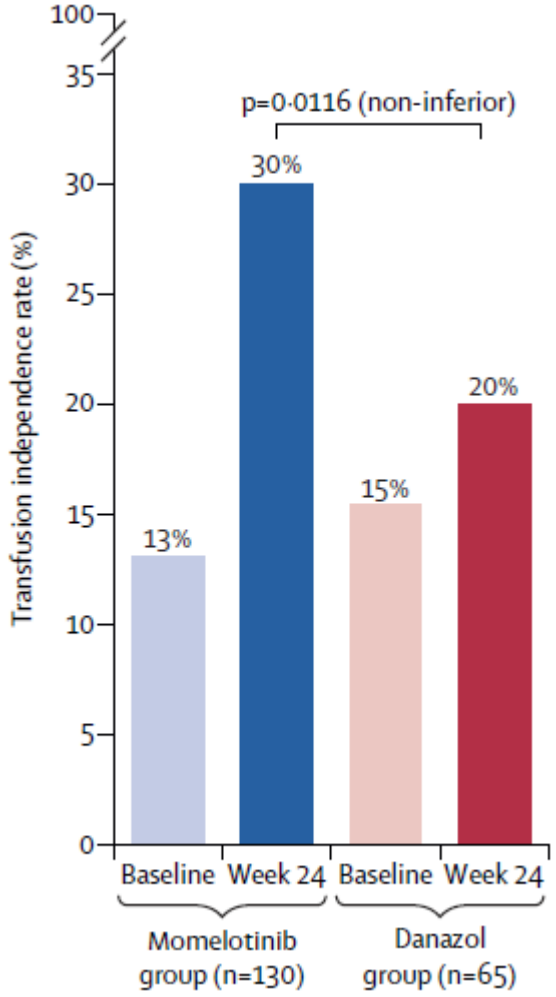
1. Chifotides HT, et al. *J Hematol Oncol*. 2022;15(1):7.
2. Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458.
3. Asshoff M, et al. *Blood*. 2017;129(13):1823-1830.
4. Oh S, et al. *Blood Adv*. 2020;4(18):4282-4291.

Momelotinib

MOMENTUM

- Phase 3 double-blind, randomized, controlled trial comparing momelotinib with danazol in patients previously treated with ruxolitinib
- Enrollment criteria:
  - ≥ Intermediate-1 risk MF previously treated with a JAK inhibitor
  - Anemic (Hb < 10 g/dL), symptomatic (TSS > 10)

At 24 weeks	Momelotinib (n = 130)	Danazol (n = 65)	P value
TSS response rate, % (≥ 50% reduction in TSS score)	25	9	0.0095
Spleen response rate, % (≥ 35% spleen volume reduction)	22	3	0.0011
Rate of zero transfusions to week 24	35	17	0.0012



Hb = hemoglobin; TSS = total symptom score

Verstovsek S, et al. *Lancet*. 2023;401(10373):269-280. [published correction appears in *Lancet*. 2023 Apr 29;401(10386):1426].

Case continued: How would you manage Mr. PT?

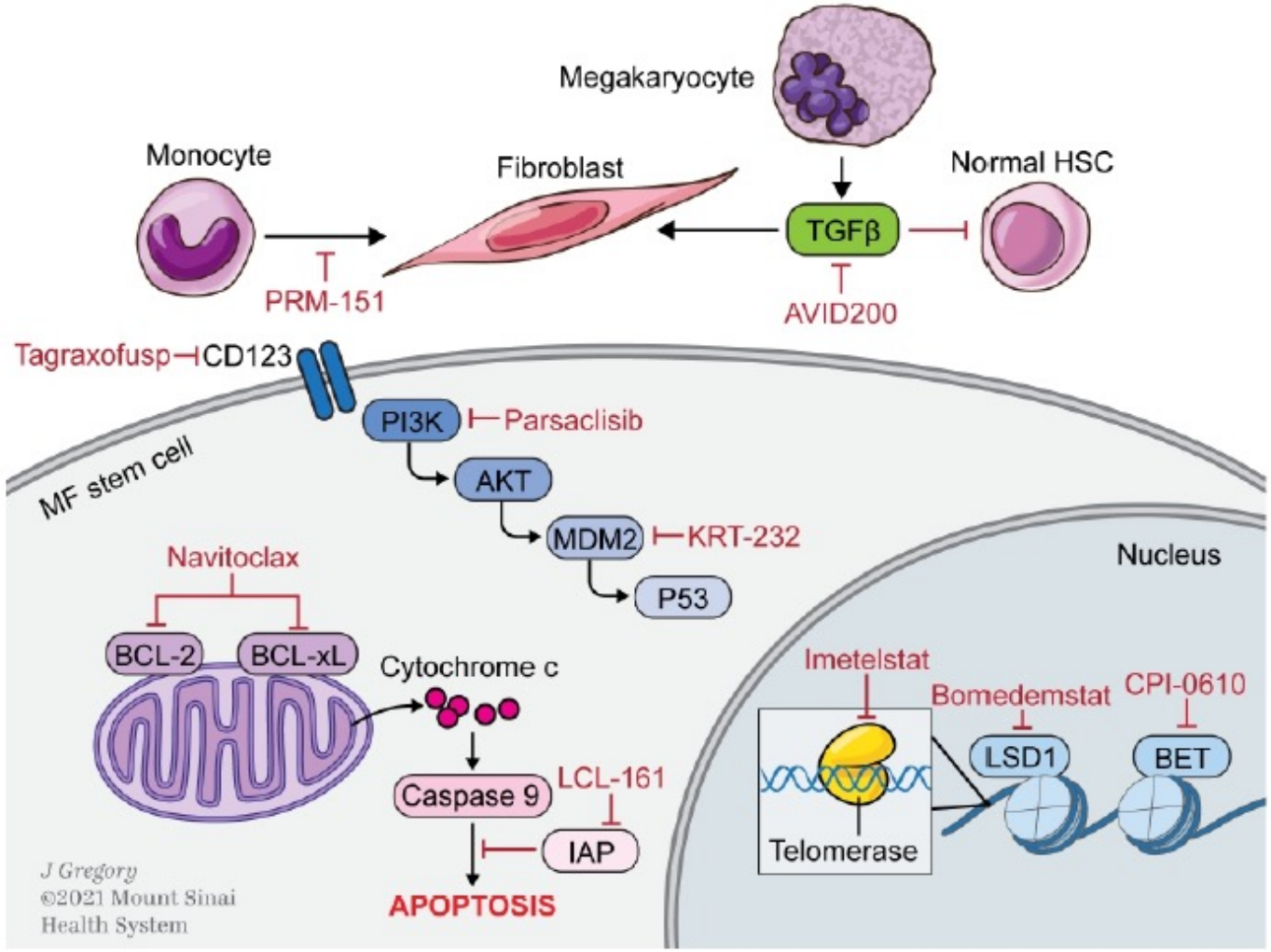
70M, MF with CALR/ASXL1 treated with rux, not a transplant candidate, after 9 mo of therapy, spleen is palpable and is now anemic hgb 8.5, thrombocytopenic plts of 40.

1. Increase ruxolitinib to 20 mg BID
2. Decrease ruxolitinib to 10 mg BID
3. Switch to Fedratinib 400 mg daily
4. Switch to Pacritinib 200 mg BID

New Treatment Targets in MF

- Luspatercept
- Combination studies:
  - BET inhibition (pelabresib)
  - Bcl-2/Bcl-xL (Navitoclax- development ended)
  - MDM2 inhibition (Navtmedalin)

- Monotherapy with promise- PIM-1 Kinase inhibition, lysyl oxidase inhibitor

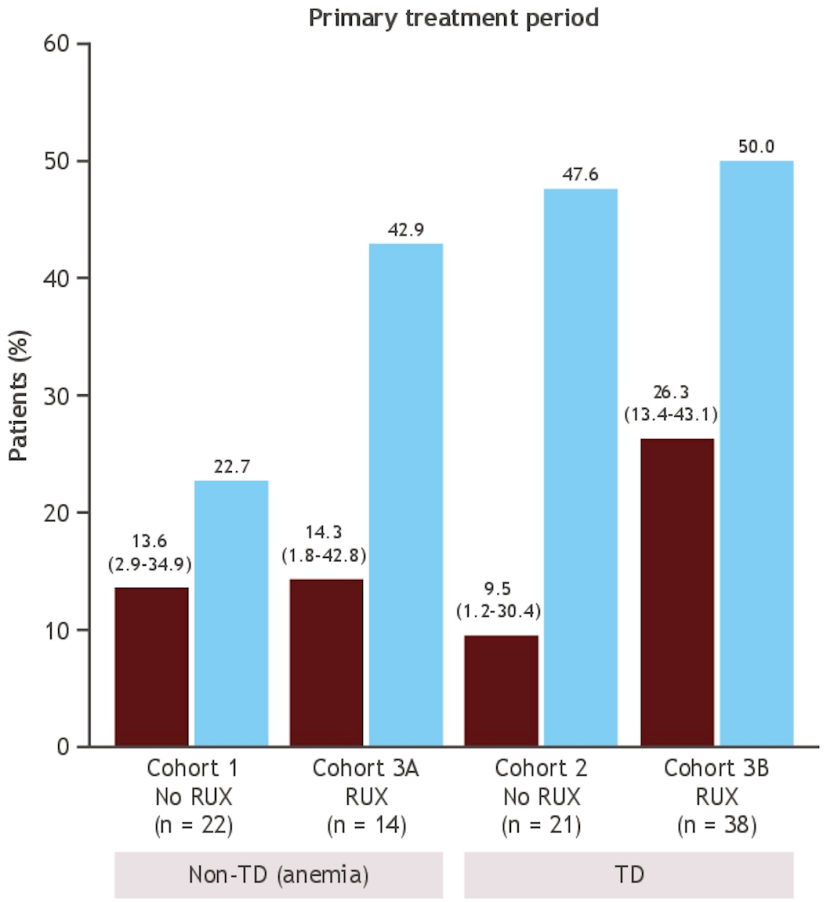


Tremblay D, Hoffman R. *Expert Opin Emerg Drugs*. 2021;26(4):351-362.

Luspatercept Shows Efficacy In the Setting of MF-induced Anemia

- Phase 2 trial assessing erythroid maturation agent luspatercept in patients with MF associated anemia ±TD[1]
- Safety profile of luspatercept consistent with previous studies
- Treatment with luspatercept induced improvements in anemia and transfusion burden in all cohorts

Use of luspatercept for MF-induced anemia in TD patients with TD on JAK2i therapy is being assessed in the phase 3 INDEPENDENCE study[2]

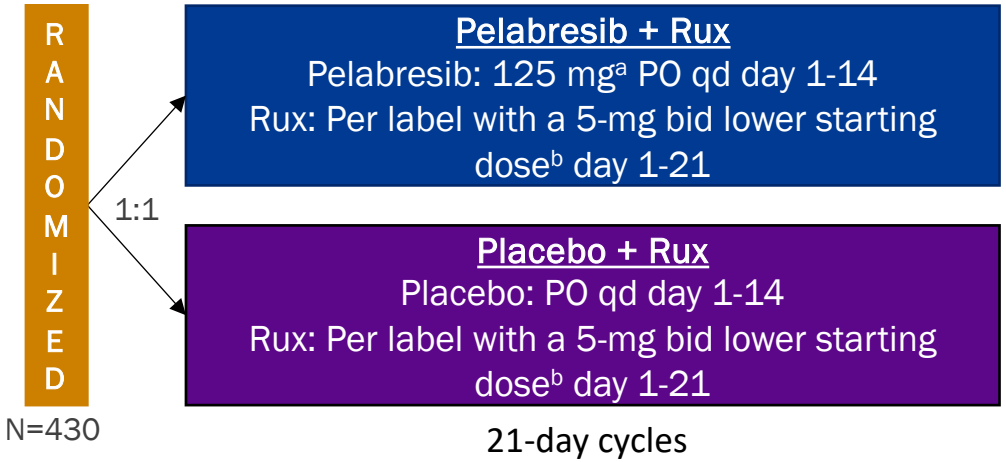


1. Gerds A et al. ASCO 2023. Abstract 7016. 2. https://clinicaltrials.gov/ct2/show/NCT04717414.

Phase 3 MANIFEST-2 Study of Pelabresib and Rux for JAKi Treatment-Naive MF: Study Design and Patients

Key Eligibility Criteria

- JAKi-naive patients with 1L MF (primary or post-ET/PV)
- DIPSS intermediate-1 or higher
- Splenomegaly (≥450 cm^3) by CT/MRI
- TSS ≥10 (≥3 for two symptoms, MFSAF v4.0)



Primary endpoint: SVR_{35} at week 24
Secondary endpoints: TSS absolute change from baseline at week 24, TSS50 at week 24, safety

Patient Characteristics		Pelabresib + Rux (n=214)	Placebo + Rux (n=216)
Median age, years (min, max)		66 (19, 84)	66 (26, 88)
MF subtype, n (%)	Primary	107 (50.0)	110 (50.9)
	Post-PV	45 (21.0)	53 (24.5)
	Post-ET	62 (29.0)	53 (24.5)
DIPSS, n (%)	Intermediate-1	128 (59.8)	127 (58.8)
	Intermediate-2	75 (35.0)	74 (34.3)
	High risk	11 (5.1)	15 (6.9)
Mutations, n (%)	*JAK2 V617F*	125 (67.2)	122 (64.6)
	CALR	45 (24.2)	50 (26.5)
	High-risk mutations	72 (38.7)	88 (46.6)
ECOG PS, n (%)	0	107 (50.0)	109 (50.5)
	1	97 (45.3)	95 (44.0)
Hb ≤10 g/dL, n (%)		70 (32.7)	76 (35.2)
Platelets >200×10^9/L, n (%)		154 (72.0)	157 (72.7)
TSS, median (range)		26.6 (7.3-66.4)	24.7 (9.0-68.4)
RBC transfusion at baseline, n (%)		35 (16)	25 (12)

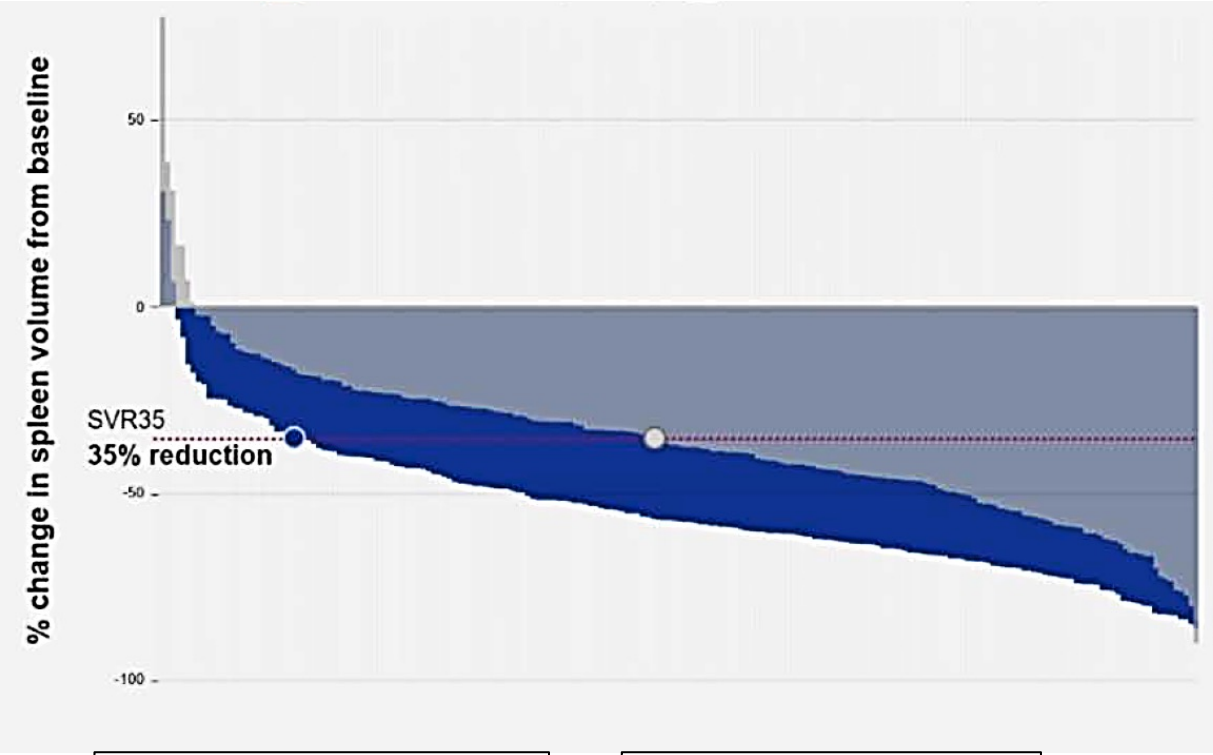
[a] The starting dose for pelabresib was 125 mg qd and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg qd. [b] Ruxolitinib was started at 10 mg bid (baseline platelet count 100-200×10^9/L) or 15 mg bid (baseline platelet count >200×10^9/L) with a mandatory dose increase by 5 mg bid after 1 cycle and a maximum dose of 25 mg bid per label.

Rampal R, et al. ASH 2023. Abstract 628.

23

Results From the Phase 3 MANIFEST-2 Study of Pelabresib and Rux for JAKi Treatment-Naive MF: SVR_{35} at Week 24

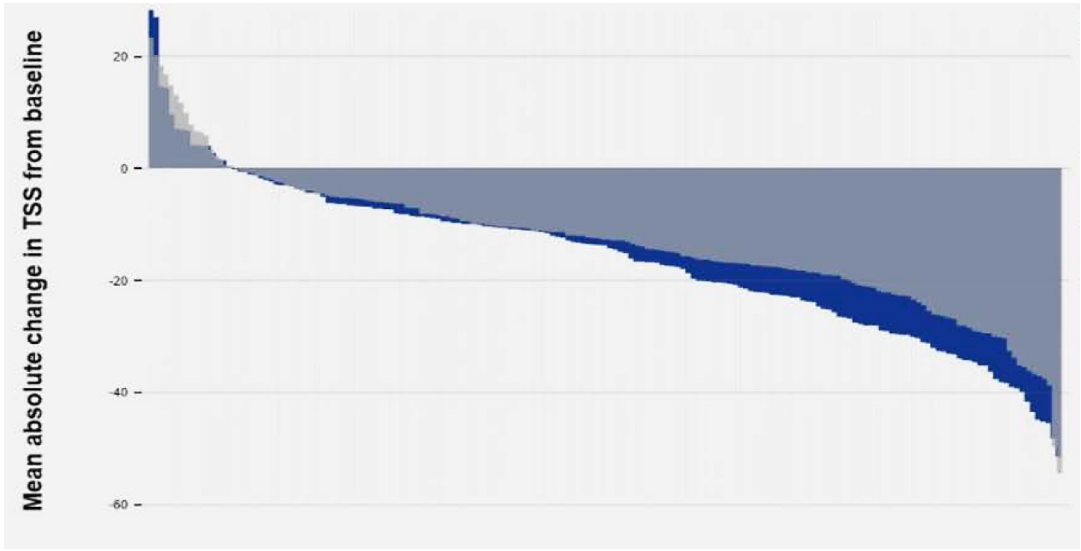
SVR at Week 24



Pelabresib + Rux (n=171[a])

Placebo + Rux (n=183[a])

Absolute TSS at Week 24



ITT Population	Pelabresib + Rux (n=214)	Placebo + Rux (n=216)
TSS change[b] from baseline at week 24	-15.99	-14.05
Mean difference[c] (95% CI)	-1.94 (-3.92 to 0.04)	
P value	0.0545	

[a] Waterfall plots represent patients who have baseline and week 24 data. [b] Calculated by stratified Cochran-Mantel-Haenszel test. [c] Patients without week 24 assessment are considered nonresponders.

Rampal R, et al. ASH 2023. Abstract 628.

24

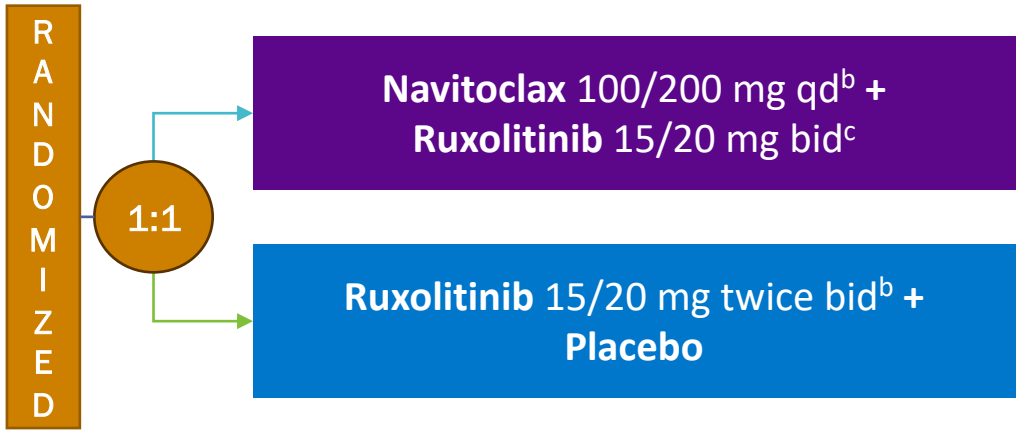
Phase 3 TRANSFORM-1 Trial of Navitoclax + Rux Versus Rux + Placebo in Untreated MF: Study Design and Patients

Key Eligibility Criteria

- Intermediate-2 or high-risk MF with measurable splenomegaly[a]
- Evidence of MF-related symptoms
- No prior JAKi treatment

Stratification

- Intermediate-2 vs high-risk
- Platelets ≤200×10^9/L vs >200×10^9/L



Primary endpoint: SVR_{35} from baseline to week 24 (superiority)

Secondary endpoints: MPN-SAF TSS response rate from baseline to week 24, SVR_{35} at any time, duration of SVR_{35}, anemia response, safety

Patient Characteristics		Nav + Rux (n=125)	Rux + Pbo (n=127)
Median age (range), years		70 (42-87)	69 (37-85)
Median time from last MF diagnosis to study entry (range), months		8 (0.3-181.6)	6 (0.3-198.8)
Type of MF	Primary	63 (50)	72 (57)
	Post-PV/ET	62 (50)	55 (43)
DIPSS risk category, n (%)	Intermediate-1	8 (6)	5 (4)
	Intermediate-2	104 (83)	110 (87)
	High risk	13 (10)	12 (9)
Median prior LOT (range)		1 (1-3)	1 (1-4)
Median spleen volume (range), cm^3		1441 (419-8020)	1639 (219-5664)
Median TSS (range)		21 (0.1-60.6)	24 (6.7-61.6)
Transfusion dependent at baseline		5 (4)	4 (3)
Driver mutations	*JAK2 V617F*	81 (65)	79 (62)
	CALR	22 (18)	26 (20)
	MPL W515	14 (11)	10 (8)
HMR mutations, n/N (%)		57/120 (48)	50/117 (43)

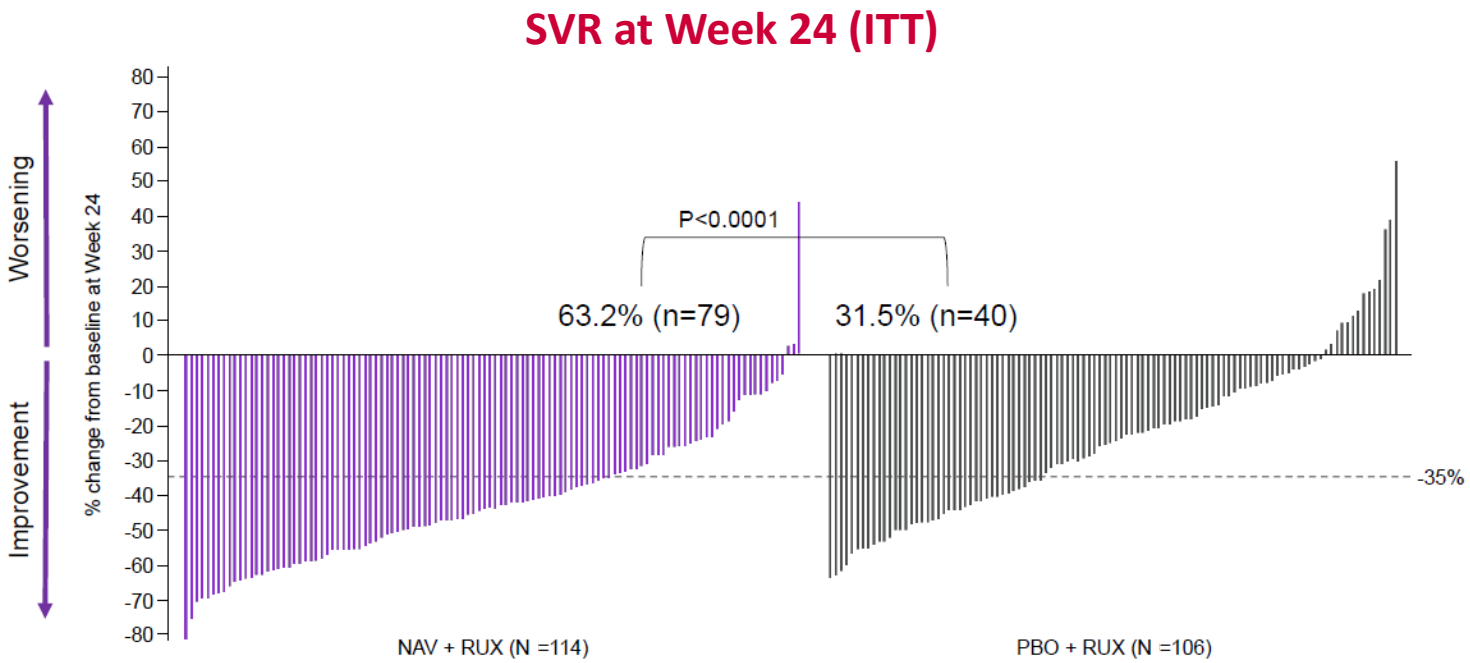
Median follow-up was 14.9 months (range, 0.0-29.5).

[a] As defined by the DIPSS+. [b] Platelets >200×10^9/L: 20 mg bid, platelets 100-200×10^9/L: 15 mg bid. [c] Platelets >150×10^9/L: 200 mg qd, platelets ≤150×10^9/L: 100 mg qd and escalate to 200 mg after ≥7 days, if tolerable (platelets ≥75×10^9/L).

Pemmaraju N, et al. ASH 2023. Abstract 620.

25

Results From the Phase 3 TRANSFORM-1 Trial of Navitoclax + Rux Versus Rux + Placebo in Untreated MF: SVR_{35}



SVR_{35} Rates	Nav + Rux (n=125)	Rux + Pbo (n=127)
SVR_{35} at week 24, n (%)	79 (63.2)	40 (31.5)
95% CI, *P* value	31.0 (19.5-42.5), *P*<0.0001	
Median duration of study follow-up (range), months	14.8 (1.0-29.5)	14.9 (0.0-28.8)
SVR_{35} at any time on-study, n (%)	96 (76.8)	53 (41.7)
95% CI, *P*-value	34.6 (23.6, 45.6), *P*<0.0001[a]	
Median time to first SVR_{35} response (range), weeks	12.3 (10.1-48.3)	12.4 (11.3-72.3)
Subjects who lost SVR_{35} response, n/N (%)	18/96 (18.8)	14/53 (26.4)
12-month duration of SVR_{35} rate, % (95% CI)	76.7 (64.7-85.0)	76.9 (59.8-84.4)

- A significantly higher number of patients achieved SVR_{35W24} in the Nav + Rux arm compared with the Rux + Pbo arm (79 [63.2%] vs 40 [31.5%]; *P*<0.0001)
- Time to first SVR_{35} response was similar in the Nav + Rux arm compared with the Rux + Pbo arm (median [range]: 12.3 [10.1-48.3] vs 12.4 [11.3–72.3] weeks)

[a] Nominal *P* value.

Pemmaraju N, et al. ASH 2023. Abstract 620.

26

Ruxolitinib pre-, during-, and post-transplantation in MF patients (NCT03427866)

Patient with Myelofibrosis
Transplant candidate
Available donor

Objectives:
1 year GRFS
Seondary- PFS, OS, NRM
GVHD, engraftment, time on rux

Pre-Transplant

Day -14
Initiate/continue Ruxolitinib 5mg BID

Transplant

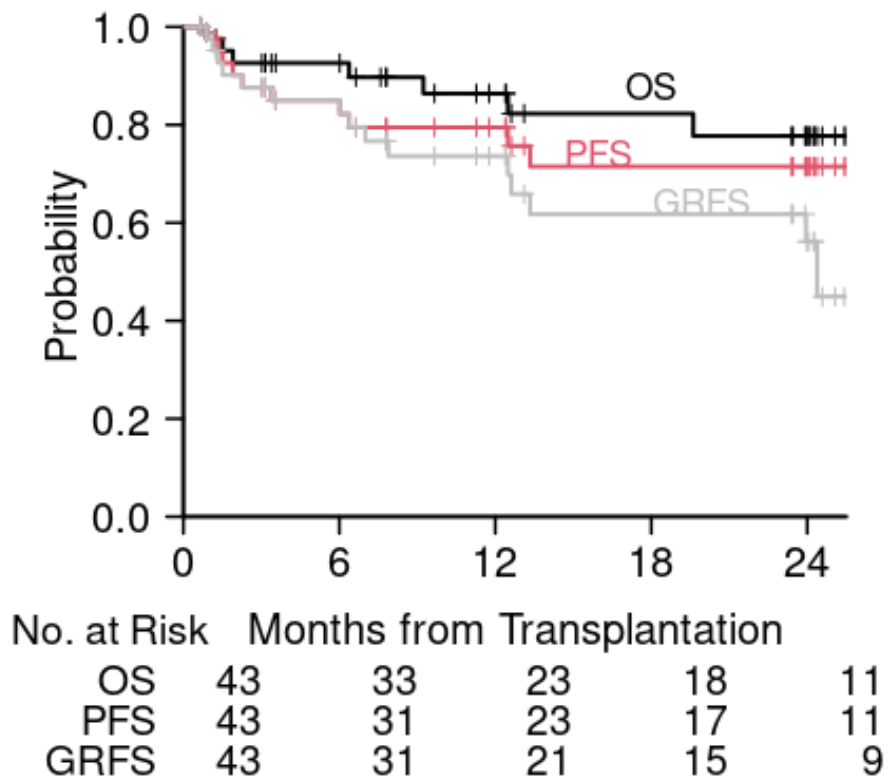
Continue Ruxolitinib through conditioning and transplant

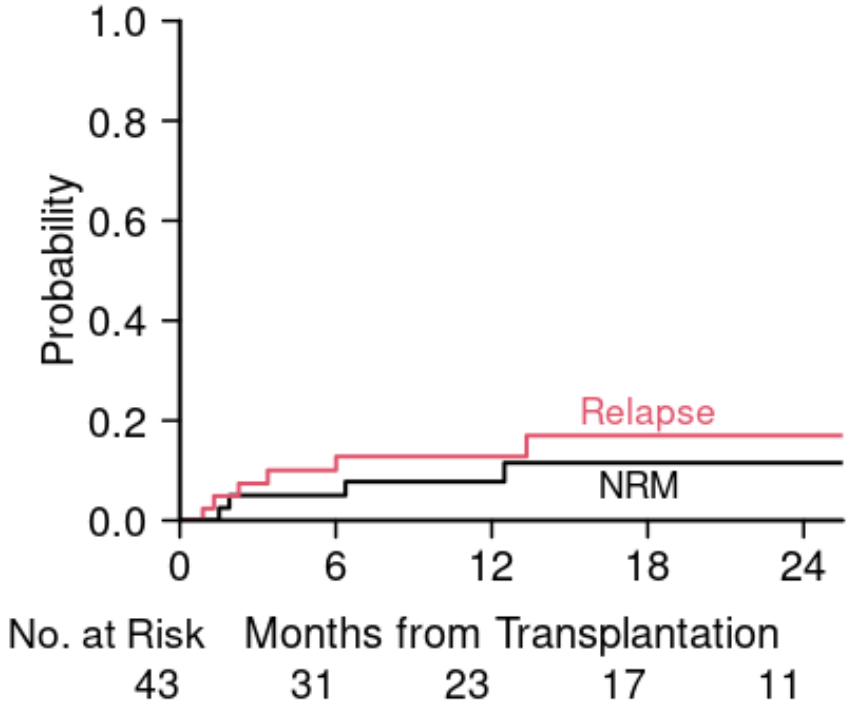
Day 30-1 year

Day 30 and count recovery: Increase Ruxolitinib to 10 mg BID

27

Outcomes

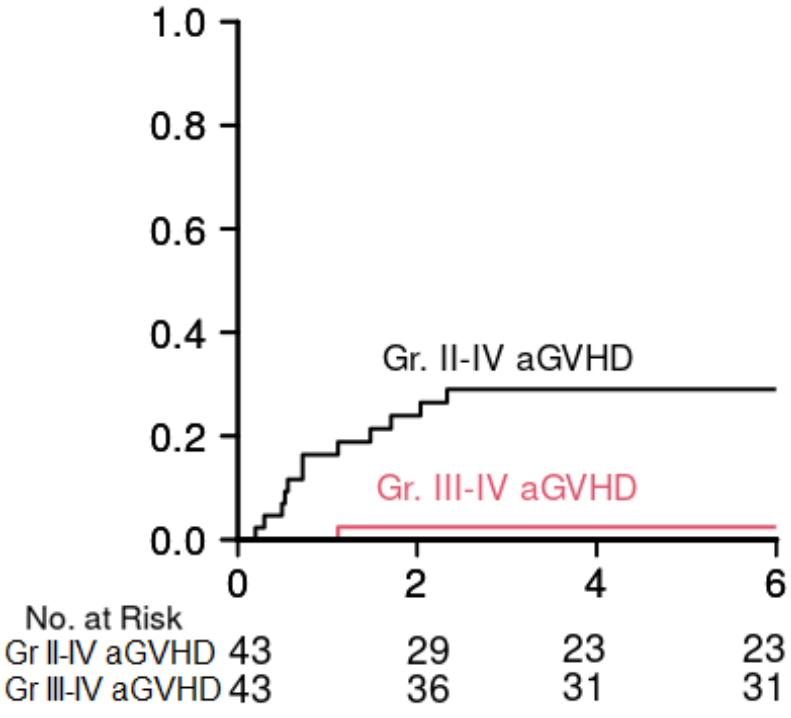


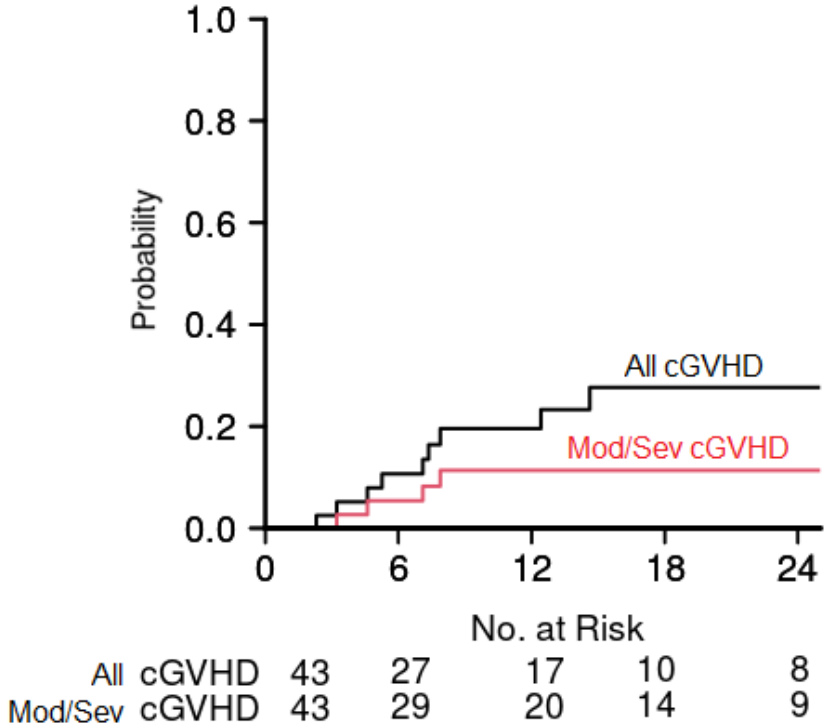


	% (95% CI)
1y OS	86 (70, 94)
1y PFS	79 (63, 89)
1y GRFS	74 (56, 85)
1y Cum Inc NRM	10 (3, 22)
1y Cum Inc Relapse	10 (3, 22)

28

GVHD





6m gr 2-4 aGVHD	**29 (16, 43)**
6m gr 3-4 aGVHD	2.4 (0.2, 11)
1y cGVHD	20 (8.4, 34)
1y moderate/severe cGVHD	11 (3.5, 24)

29

Thank you

HARVARD MEDICAL SCHOOL