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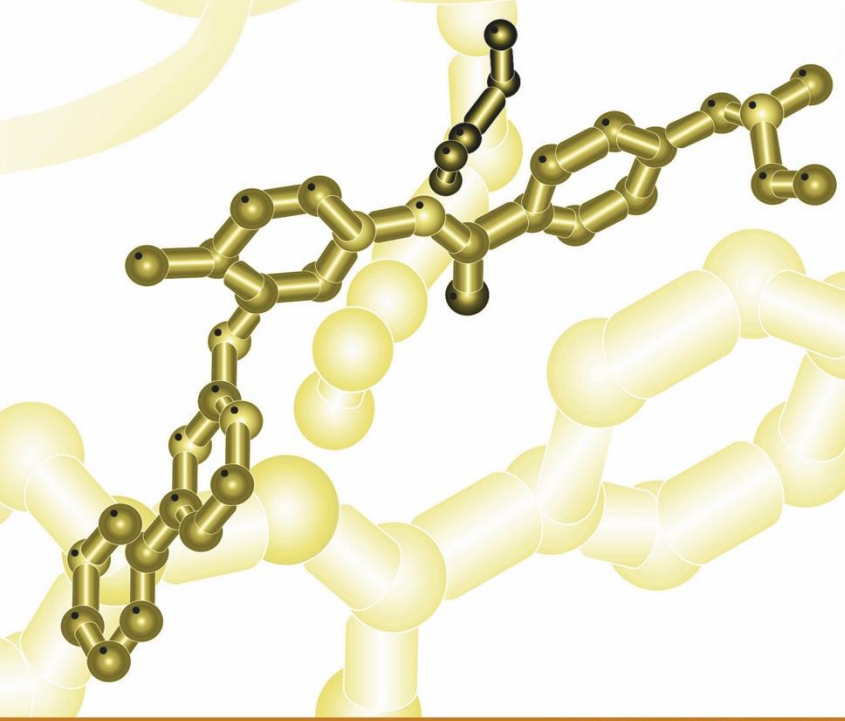

New Drugs in Hematology

President: Pier Luigi Zinzani
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BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

The Future of 1st Line Therapy in Myelofibrosis

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Disclosures of Andrew Kuykendall

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MorphoSys	X		X			X	
BMS	X					X	
GSK	X		X			X	
Incyte			X			X	
Abbvie			X				
Sobi						X	
Karyopharm			X			X	
Geron	X		X				X

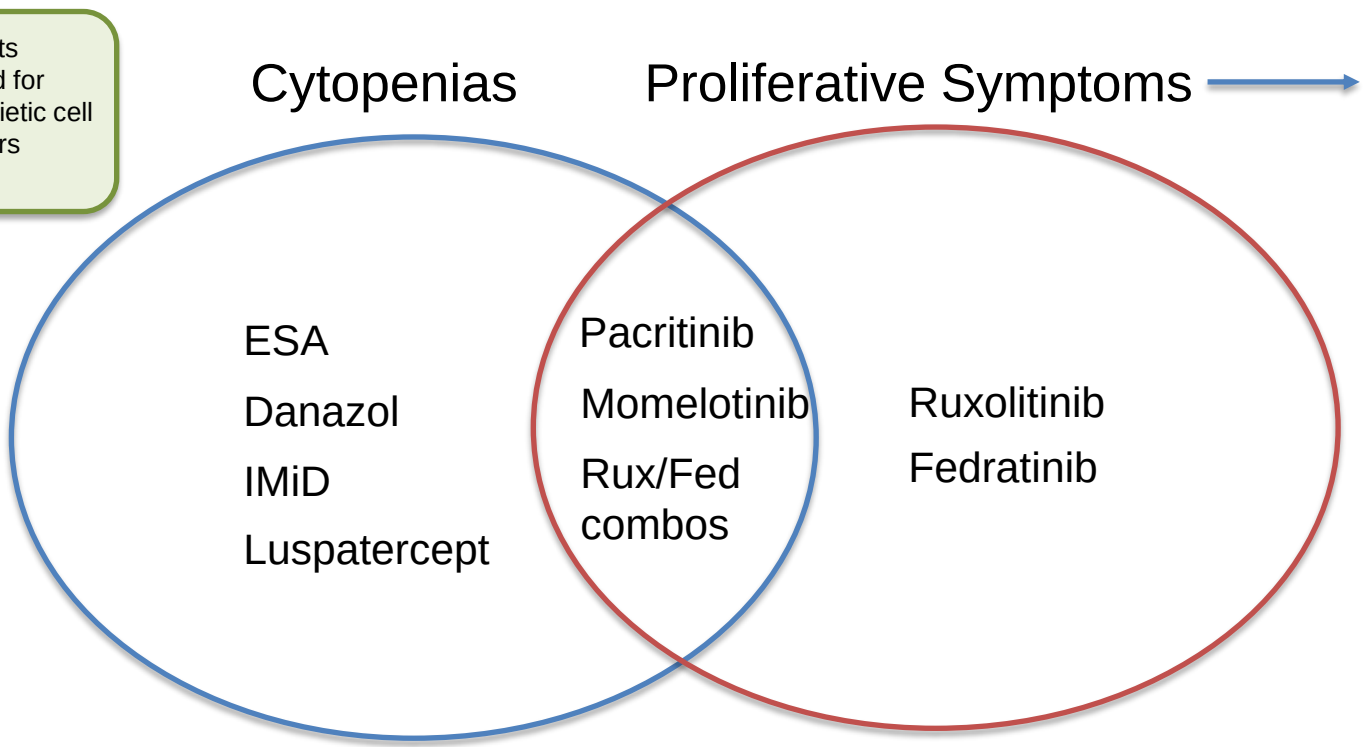
What is the current approach to "1st-Line" Treatment in Myelofibrosis

DISCLAIMER(s)

- 1st-line implies a "best option"
- We are unable to achieve histo-morphologic responses in patients with myelofibrosis.
- We are unable to induce molecular remissions in patients with myelofibrosis
- We can achieve **clinical benefit** which can "modify the disease" for individual patients and improve quality (and in some cases, quantity) of life.

1ST-line therapy is individualized based upon patient phenotype

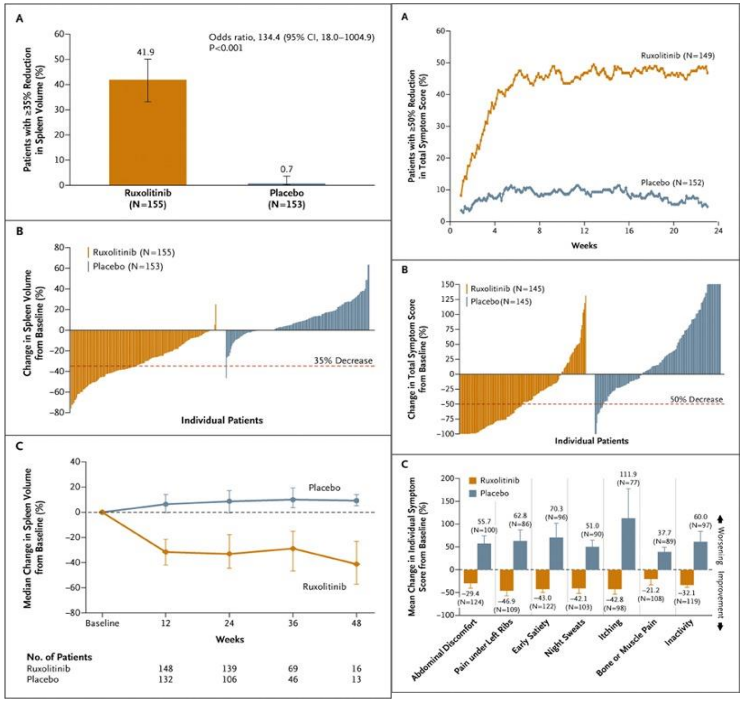
Higher-risk, fit patients should be considered for allogeneic hematopoietic cell transplant which offers curative potential

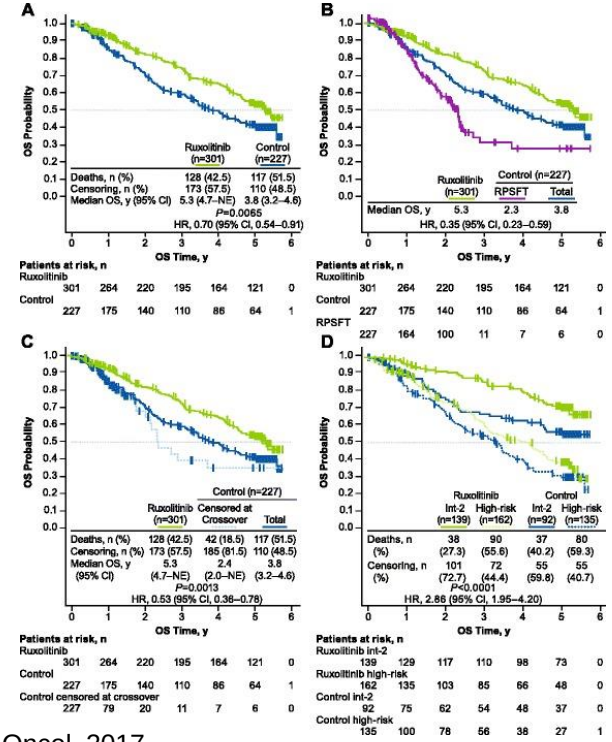


- Splenomegaly
- Fever
- Chills
- Night sweats
- Pruritus
- Weight loss
- Bone pain

ESA: Erythropoiesis-stimulating agents; IMiD: immunomodulatory imide agent (lenalidomide, thalidomide, pomalidomide)

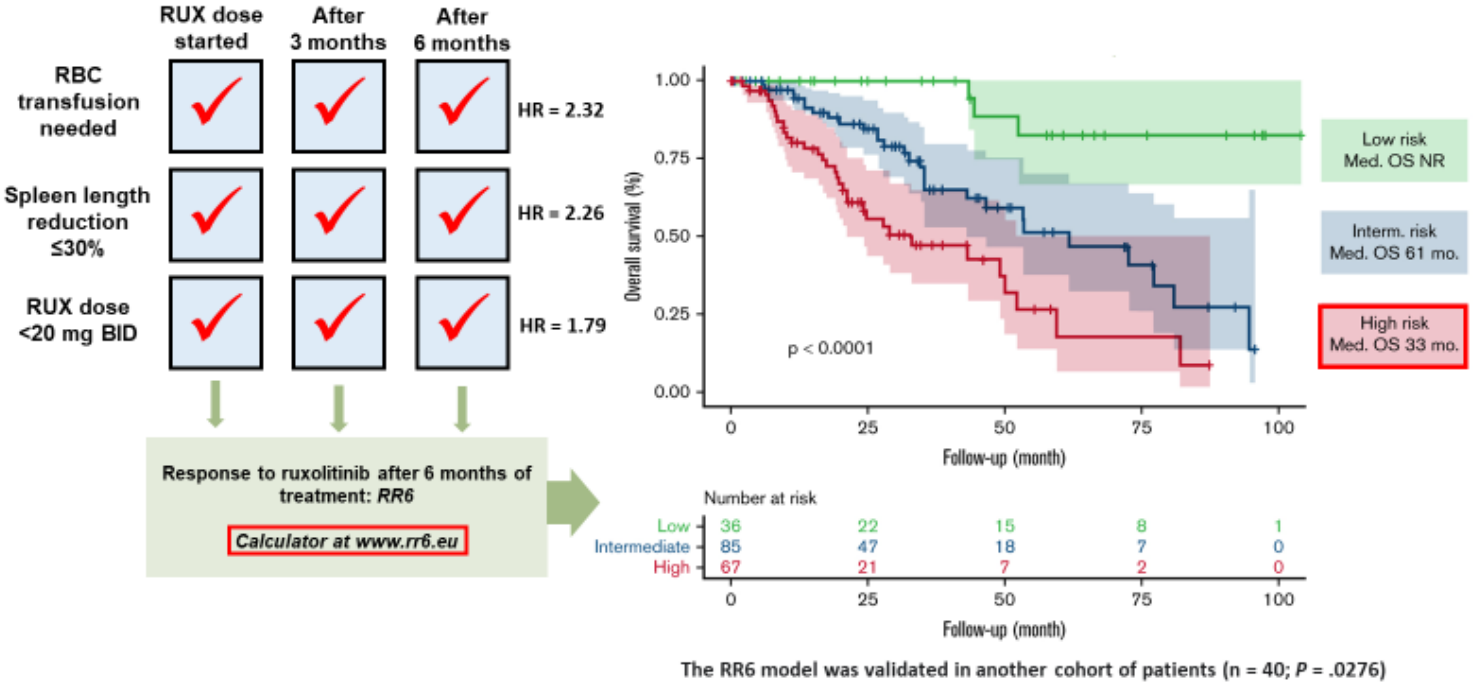
Ruxolitinib improves splenomegaly, disease-related symptoms and is associated with survival benefit





Verstovsek et al., NEJM, 2012; Harrison et al.., NEJM, 2012. Verstovsek et al., J Hematol Oncol, 2017

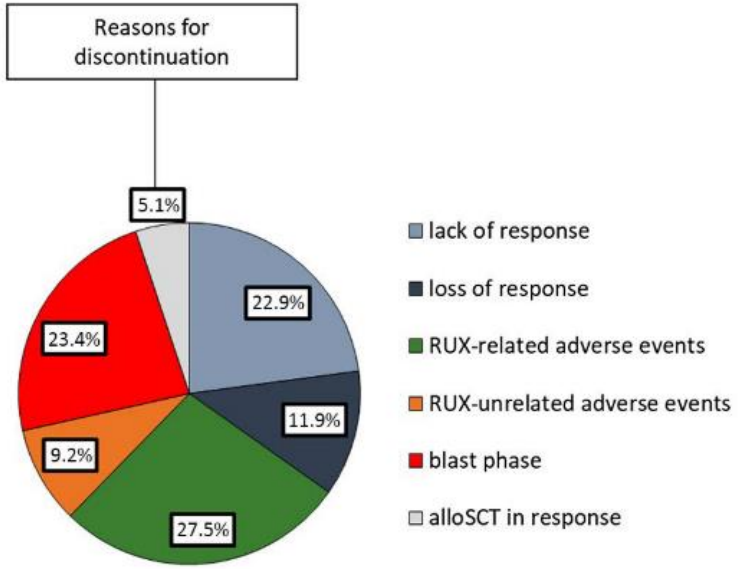
The RR6 model identifies transfusion requirements, lack of spleen response, and suboptimal dosing as risk factors for worse outcomes in patients treated with ruxolitinib

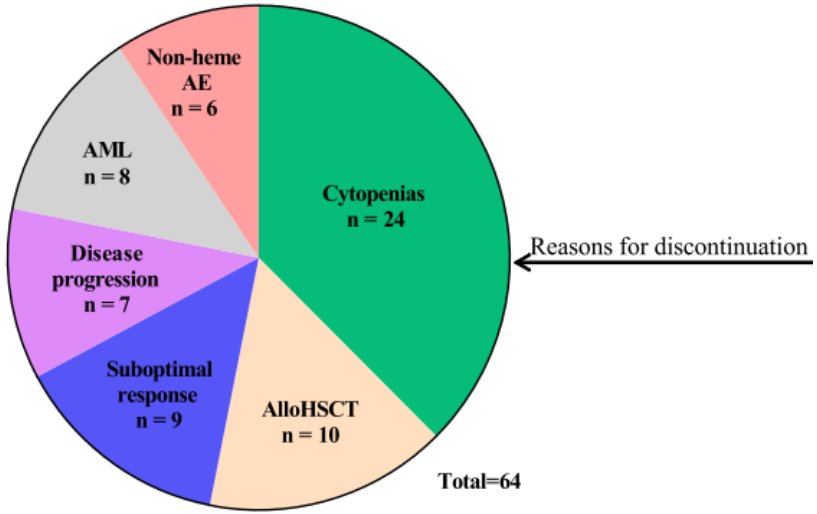


The RR6 model was validated in another cohort of patients (n = 40; *P* = .0276)

Maffioli et al., Blood Adv. 2022;6:1855-1864

However, ruxolitinib dosing is limited by cytopenias which leads to lower responses rates and treatment discontinuation



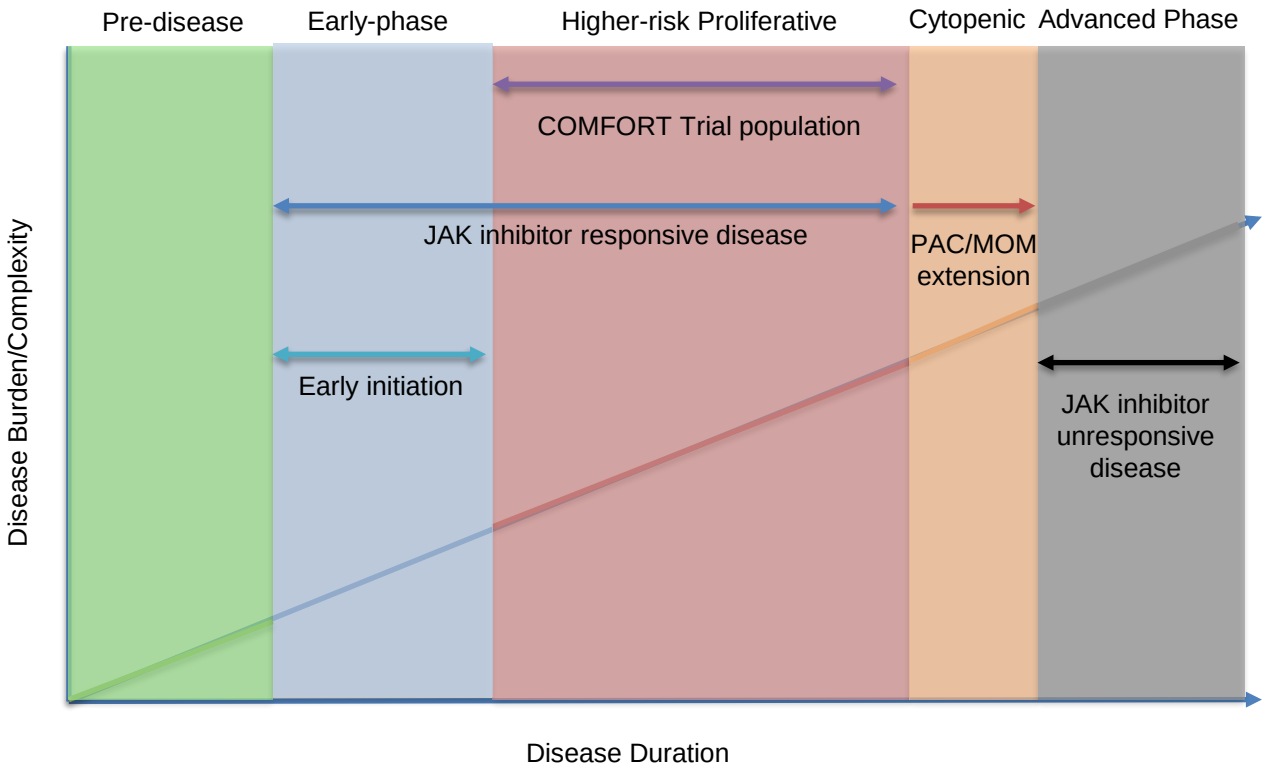


Palandri et al. Cancer. 2020; Kuykendall et al., Ann Hematol 2017

Early initiation of ruxolitinib may result more treatment success

		Week 24 Spleen Response	Grade ≥ 3 Anemia	Grade ≥ 3 Thrombocytopenia
Int-2 and high risk	COMFORT-I (n = 155)	41.9%	45.2%	12.9%
	COMFORT-II (n = 146)	32%	42%	8%
Int-1 risk patients	JUMP (n = 163)	63.8%	24.5%	11%
	ROBUST (n = 14)	57.1%	N/A	N/A
	Palandri (n = 17)	54.7%	21.7%	2.9%

Verstovsek. NEJM. 2012;366:799; Harrison. NEJM. 2012;366:787; Al-Ali. Haematologica. 2016;101:1065; Mead. Br J Haematol. 2015;170:29; Palandri. Hematol Oncol. 2018;36:285.


Pre-disease
Early-phase
Higher-risk Proliferative
Cytopenic
Advanced Phase
COMFORT Trial population
JAK inhibitor responsive disease
PAC/MOM extension
Early initiation
JAK inhibitor unresponsive disease
Disease Burden/Complexity
Disease Duration

The approval of less myelosuppressive JAK inhibitors offers additional 1st-line options

	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Approved in USA	2011	2019	2021	2023
Targets	JAK1/JAK2	JAK1/JAK2/FLT3/BRD4	JAK2/FLT3/IRAK1/ ACVR1	JAK1/JAK2/ACVR1
Frontline spleen response	28-42%	36%	19% (400 mg QD)	27%
Frontline symptom response	46%	36%	19% (400 mg QD)	28%
None-heme toxicity	Weight gain, non-melanoma skin cancers, shingles reactivation	Nausea, vomiting, diarrhea, amylase, lipase, encephalopathy*	Nausea, vomiting, diarrhea, bleeding, prolonged QTc	Mild GI
Heme toxicity	Anemia, thrombocytopenia	Anemia, thrombocytopenia		
Differentiators	OS benefit, JAK1/2, long-term experience, 1st to market	Robust benefit in 50-100K, 2nd line data	Active with marked thrombocytopenia, may help anemia	Robust data on anemia benefit, JAK1/2, safe in low platelets

So, while ruxolitinib is the most common 1st-line treatment for patients with MF, there is lack of consensus for certain phenotypes of patients with MF

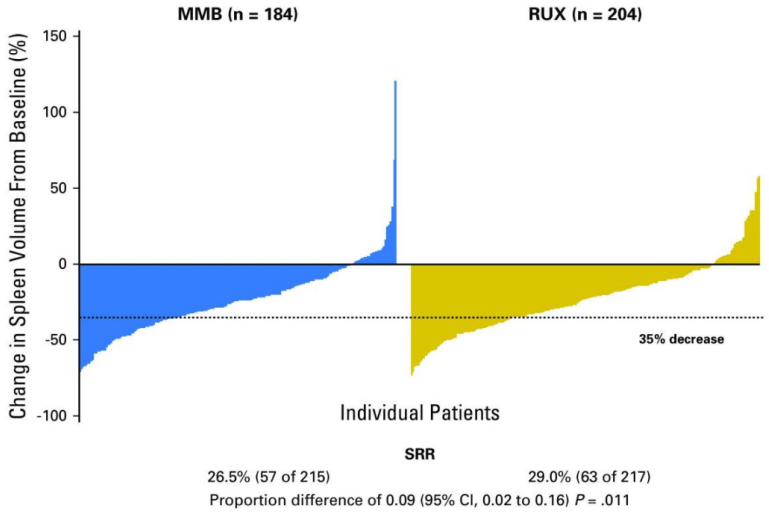
- Markedly thrombocytopenic (< 50 x 10^9/L)
- Moderately thrombocytopenic (50 x 10^9/L - 100 x 10^9/L)
- Anemic
- History of non-melanoma skin cancer
- High-molecular risk / Molecularly complex
- Low/intermediate-risk

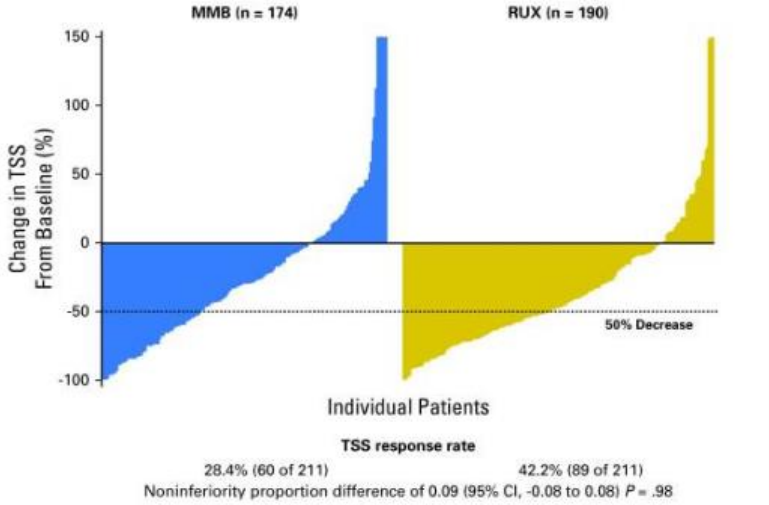
?

Pacritinib		
Fedratinib	Momelotinib	Pacritinib
Momelotinib	Pacritinib	
Non-Rux		
?		
Interferon		

Head-to-head comparisons of JAK inhibitors in the front-line setting are lacking

SIMPLIFY-1 assessed the non-inferiority of momelotinib vs. ruxolitinib in the JAK-inhibitor naïve setting





Momelotinib was non-inferior to ruxolitinib for spleen volume response but did not demonstrate non-inferiority in terms of symptom improvement

Mesa et al., JCO, 2017

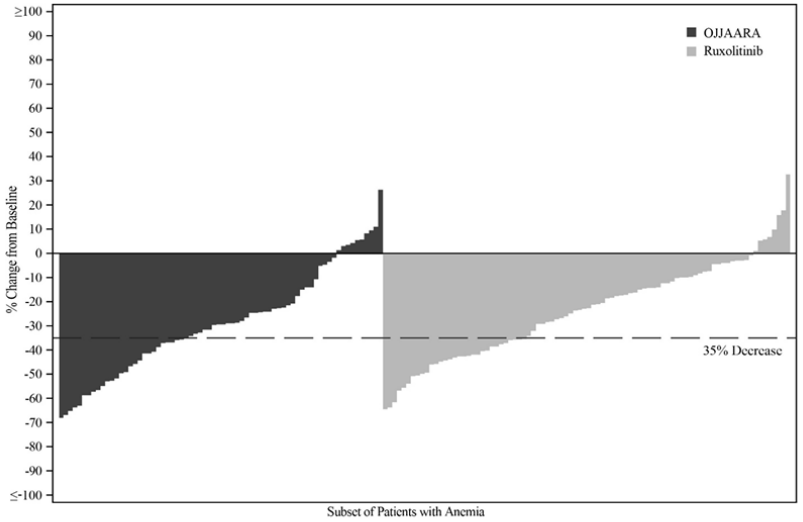
In the anemic subgroup of SIMPLIFY-1, spleen volume response rates were nearly identical

Table 5: Percent of Patients[a] Achieving 35% or Greater Reduction from Baseline in Spleen Volume at Week 24 in SIMPLIFY-1

	momelotinib n = 86	Ruxolitinib n = 95
Patients with Spleen Volume Reduction by 35% or More, n (%) (95% CI)	27 (31.4%) (21.8, 42.3)	31 (32.6%) (23.4, 43.0)

[a] Subset of patients with anemia (Hb <10 g/dL) at baseline.

Figure 2: Percent Change from Baseline in Spleen Volume for Each Patient at Week 24 in SIMPLIFY-1[a, b]

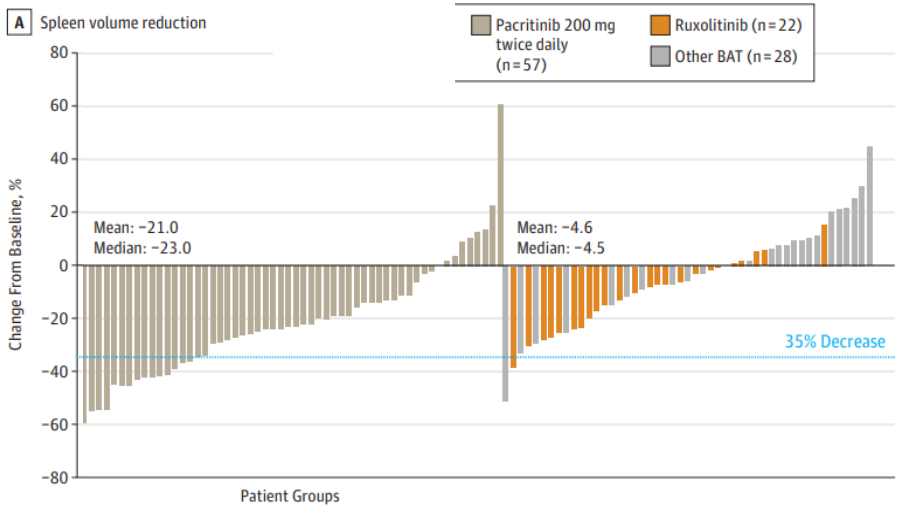


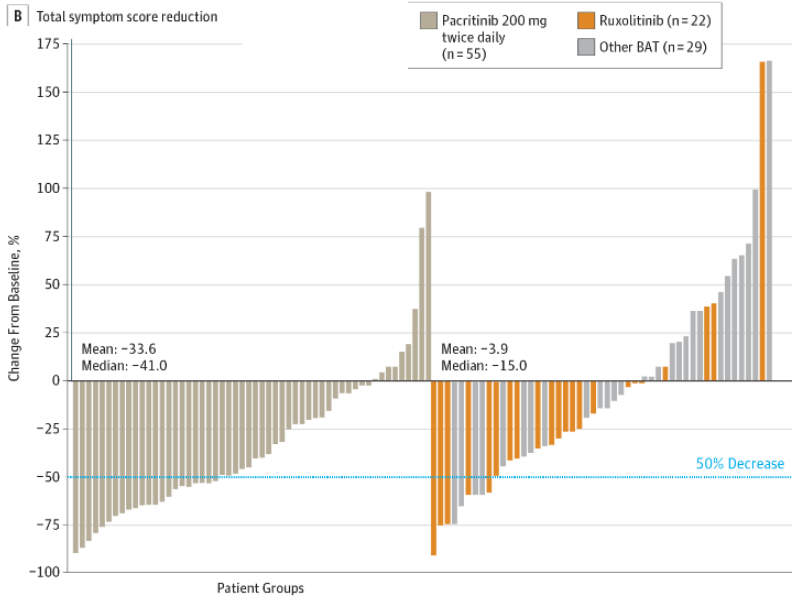
[a] Subset of patients with anemia (Hb <10 g/dL) at baseline.
[b] Missing data rates for OJJAARA and ruxolitinib were 19% and 8%.

SIMPLIFY-1 showed momelotinib was non-inferior to ruxolitinib for spleen volume response but did not demonstrate non-inferiority in terms of symptom improvement

www.accessdata.fda.gov

Pacritinib (200 mg BID) outperformed best available therapy in thrombocytopenic patients in mixed population





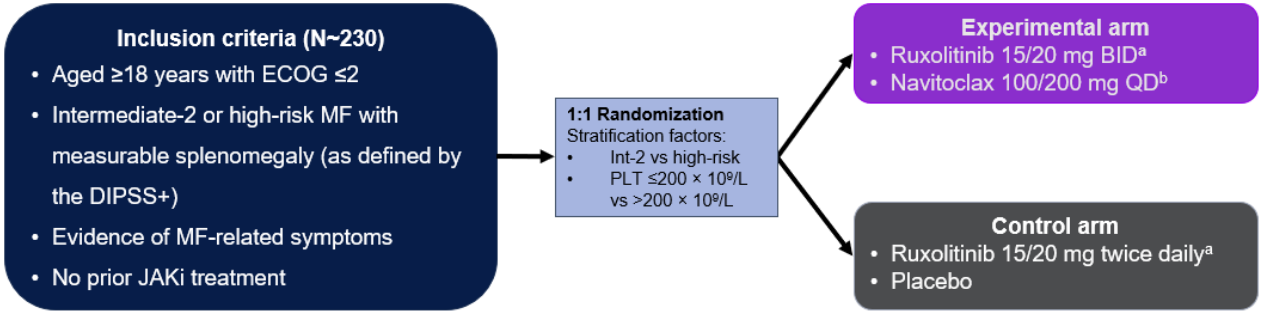
PERSIST-2 showed pacritinib was better than best available therapy in thrombocytopenic patients. **[Some pre-treated w rux, some BAT = rux]

Mascarenhas et al., JAMA Oncol, 2018

Are we entering the era of combination therapy?

- Is there an approval path forward?
- Is combination therapy for all or for some?
- Is the JAK inhibitor backbone interchangeable?
- Can genomic information help guide treatment decisions?
- What is the best way to improve anemia?

Navitoclax, a Bcl-2/Bcl-xL inhibitor, was evaluated in a double-blind phase 3 study in combination with ruxolitinib versus ruxolitinib + placebo (TRANSFORM-1)

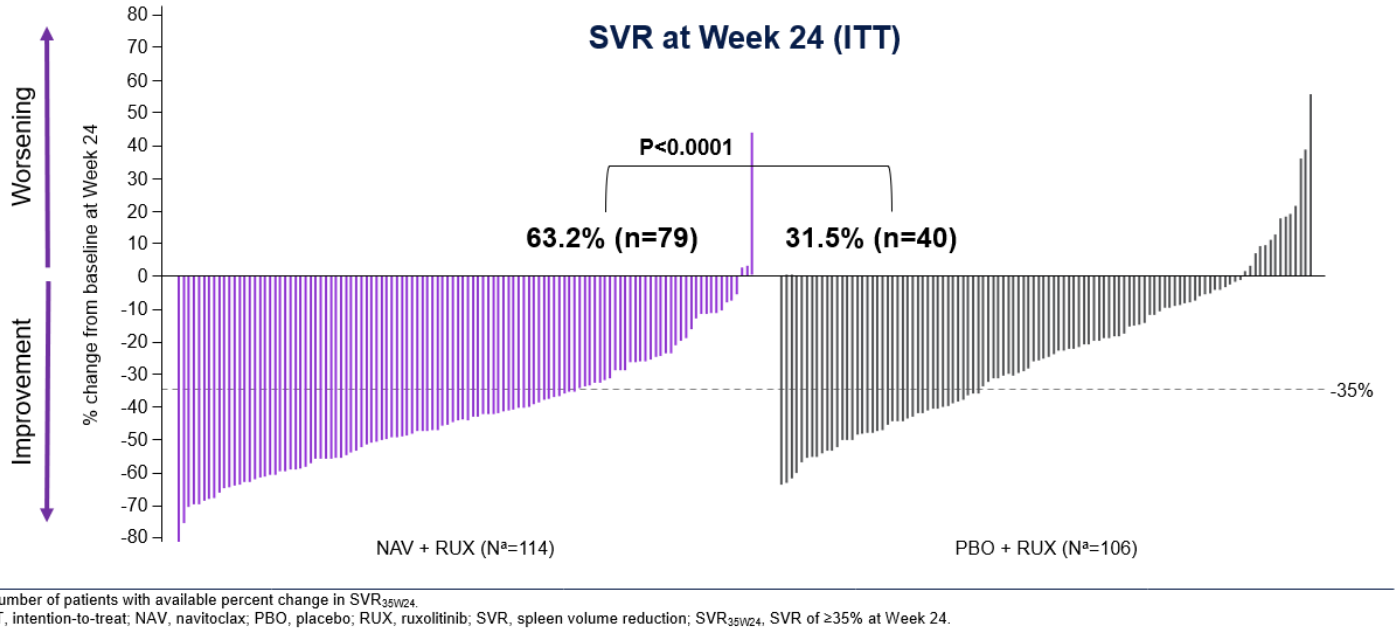


Endpoints

- Primary endpoint: SVR_{35W24} (assessed for superiority) as measured by MRI or CT scan, per IWG criteria
- Secondary endpoints:
  - Change in TSS[c] from baseline at Week 24 as measured by MFSAF v4.0
  - SVR_{35} at any time
  - Duration of SVR_{35}
  - Anemia response per IWG criteria
- Safety endpoints: AEs

Pemmaraju et al. ASH 2023. San Diego, CA.

The addition of navitoclax to ruxolitinib in the first-line setting led to a doubling of the spleen response rate (SVR) compared to ruxolitinib alone

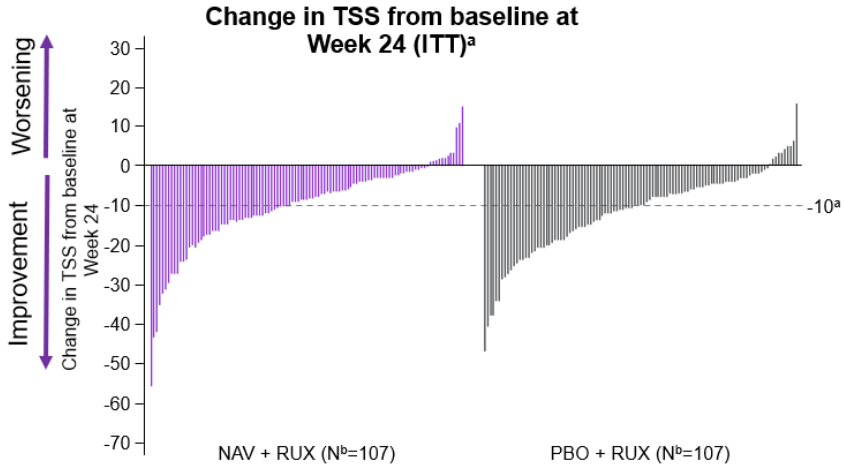


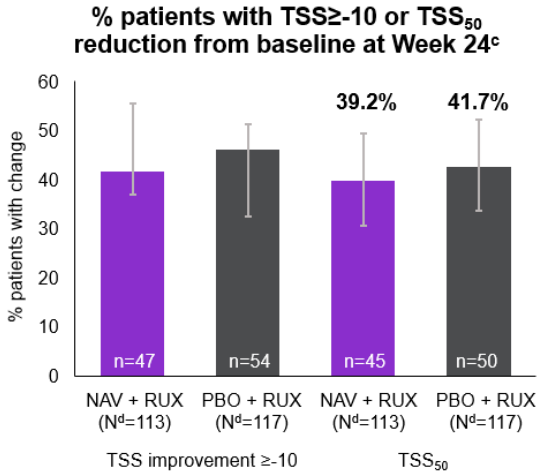
[a]Number of patients with available percent change in SVR_{35W24}.
ITT, intention-to-treat; NAV, navitoclax; PBO, placebo; RUX, ruxolitinib; SVR, spleen volume reduction; SVR_{35W24}, SVR of ≥35% at Week 24.

Pemmaraju et al. ASH 2023. San Diego, CA.

The addition of navitoclax to ruxolitinib in the first-line setting demonstrated similar symptom reduction compared to ruxolitinib alone

- At Week 24, the mean change in TSS from baseline was -9.7 (95% CI: -11.8, -7.6) with NAV + RUX compared with -11.1 (95% CI: -13.2, -9.1) with PBO + RUX arm in ITT population (P=0.2852)





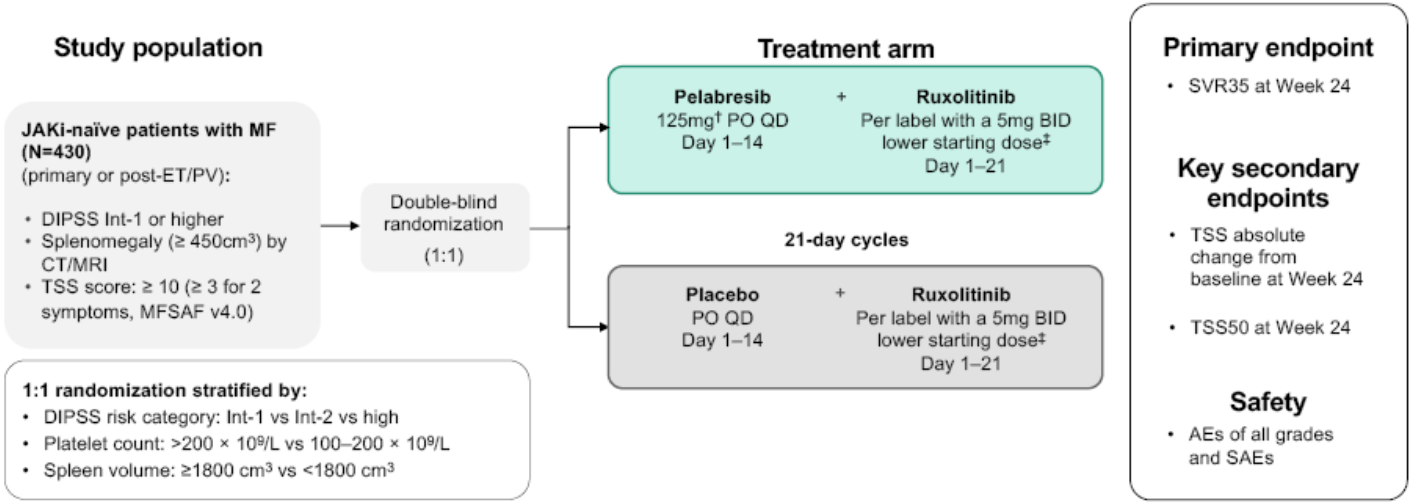
Pemmaraju et al. ASH 2023. San Diego, CA.

Adverse events were common with navitoclax + ruxolitinib, frequently leading to dose interruption/reduction, but this could be managed with close monitoring

	NAV + RUX (N=124)[a] N (%)		PBO + RUX (N=125)[a] N (%)	
Any AE	124 (100)		121 (97)	
Any AE grade ≥3	105 (85)		87 (70)	
Most common AEs (>30% patients receiving NAV)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Thrombocytopenia	112 (90)	63 (51)	62 (50)	19 (15)
Anemia	74 (60)	57 (46)	61 (49)	49 (39)
Neutropenia	56 (45)	47 (38)	7 (6)	5 (4)
Diarrhea	42 (34)	6 (5)	17 (14)	0
Bleeding/hemorrhagic events	30 (24)	2 (2)	27 (22)	7 (6)
COVID-19	26 (21)	1 (1)	23 (18)	7 (6)
Contusion	13 (10)	0	7 (6)	0
Abdominal pain	11 (9)	1 (1)	8 (6)	1 (1)
Abdominal pain upper	9 (7)	1 (1)	10 (8)	1 (1)
Bone pain	9 (7)	0	6 (5)	0
Any serious AE	32 (26)		40 (32)	
AEs leading to dose reduction				
Navitoclax/placebo	101 (81)		39 (31)	
Ruxolitinib	112 (90)		76 (61)	
AE leading to dose interruption				
Navitoclax/placebo	87 (70)		44 (35)	
Ruxolitinib	78 (63)		41 (33)	
All deaths	13 (10)		13 (10)	
Deaths ≤30 days following last dose of study drug	6 (5)		5 (4)	

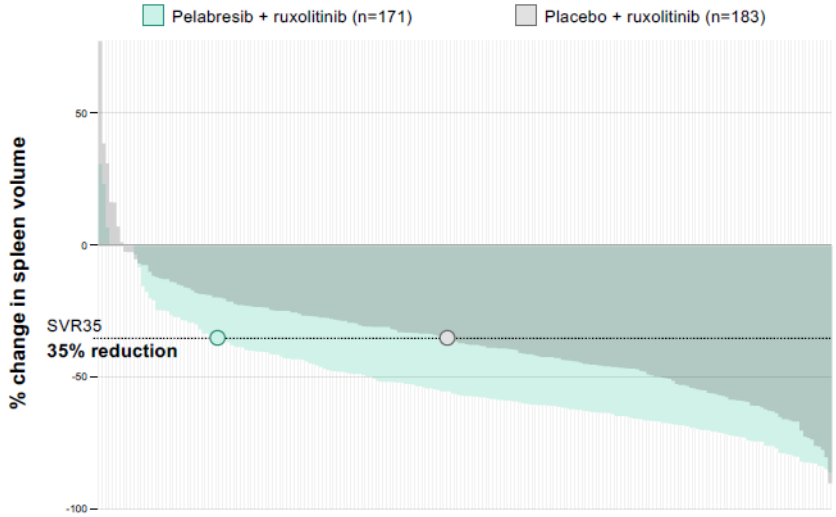
Pemmaraju et al. ASH 2023. San Diego, CA.

Pelabresib, a BET inhibitor, was evaluated in a double-blind phase 3 study in combination with ruxolitinib versus ruxolitinib + placebo (MANIFEST-2)



Rampal et al. ASH 2023. Oral Abstract 628.

The addition of pelabresib to ruxolitinib in the first-line setting led to a near doubling of the spleen response rate (SVR) compared to ruxolitinib alone

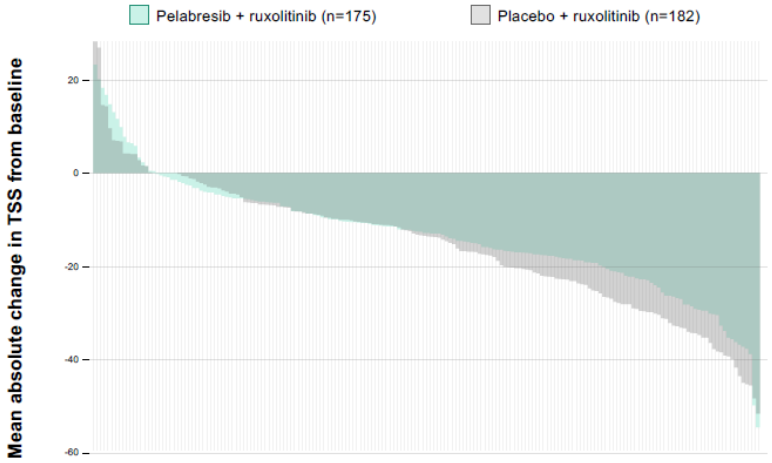


ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	P value
SVR35 at Week 24	65.9%	35.2%	
Difference‡ (95% CI)	30.4 (21.6, 39.3)		<0.001
Mean % change in spleen volume at Week 24*	–50.6 (n=171),	–30.6 (n=183),	
95% CI	-81.0, -38.2	-81.2, -106.8	

Rampal et al. ASH 2023. Oral Abstract 628.

The addition of pelabresib to ruxolitinib in the first-line setting was associated with a non-significant improvement on absolute symptoms core from baseline to week 24



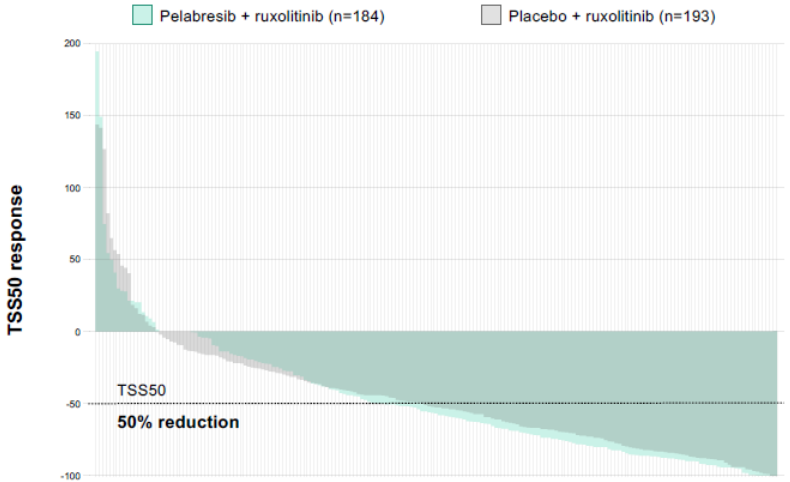
ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	P value
TSS change* from baseline at Week 24	–15.99	–14.05	
Mean difference* (95% CI)	–1.94 (–3.92, 0.04)		0.0545

- **Absolute change in TSS is a continuous endpoint** that estimates magnitude of symptom burden reduction with enhanced precision
  - This endpoint was added to the MANIFEST-2 clinical trial protocol following a Type C meeting with the U.S. Food and Drug Administration (FDA) in September 2023.

Rampal et al. ASH 2023. Oral Abstract 628.

The addition of pelabresib to ruxolitinib in the first-line setting was associated with a non-significant improvement in TSS response from baseline to week 24

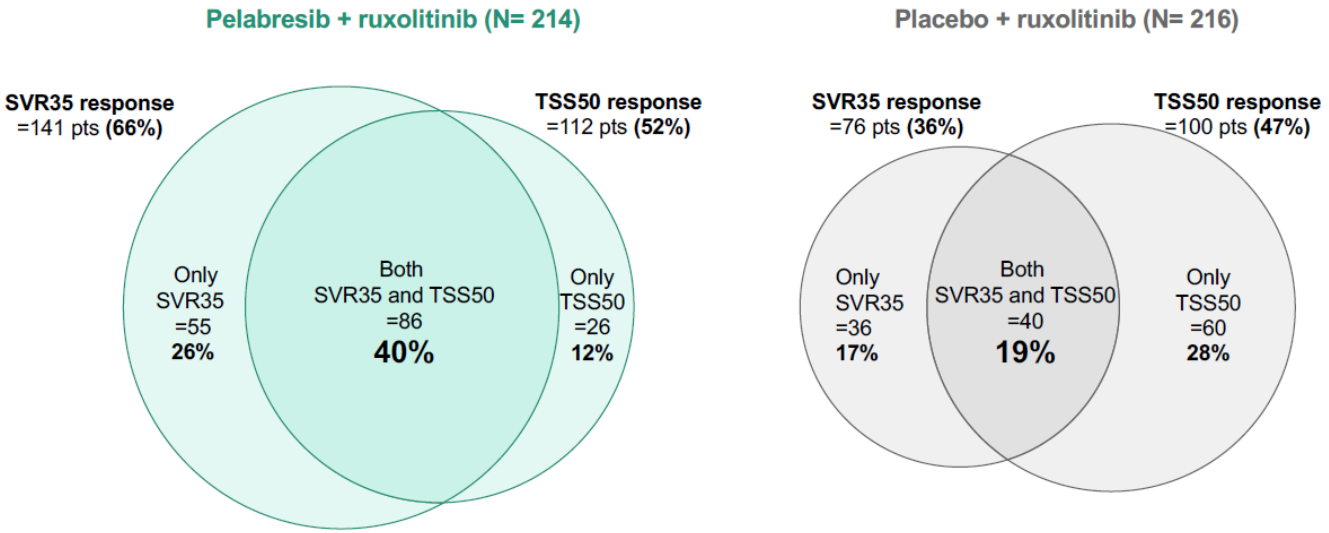


ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	P value
TSS50 at Week 24	52.3%	46.3%	
Difference (95% CI)	6.0 (-3.5, 15.5)		0.216

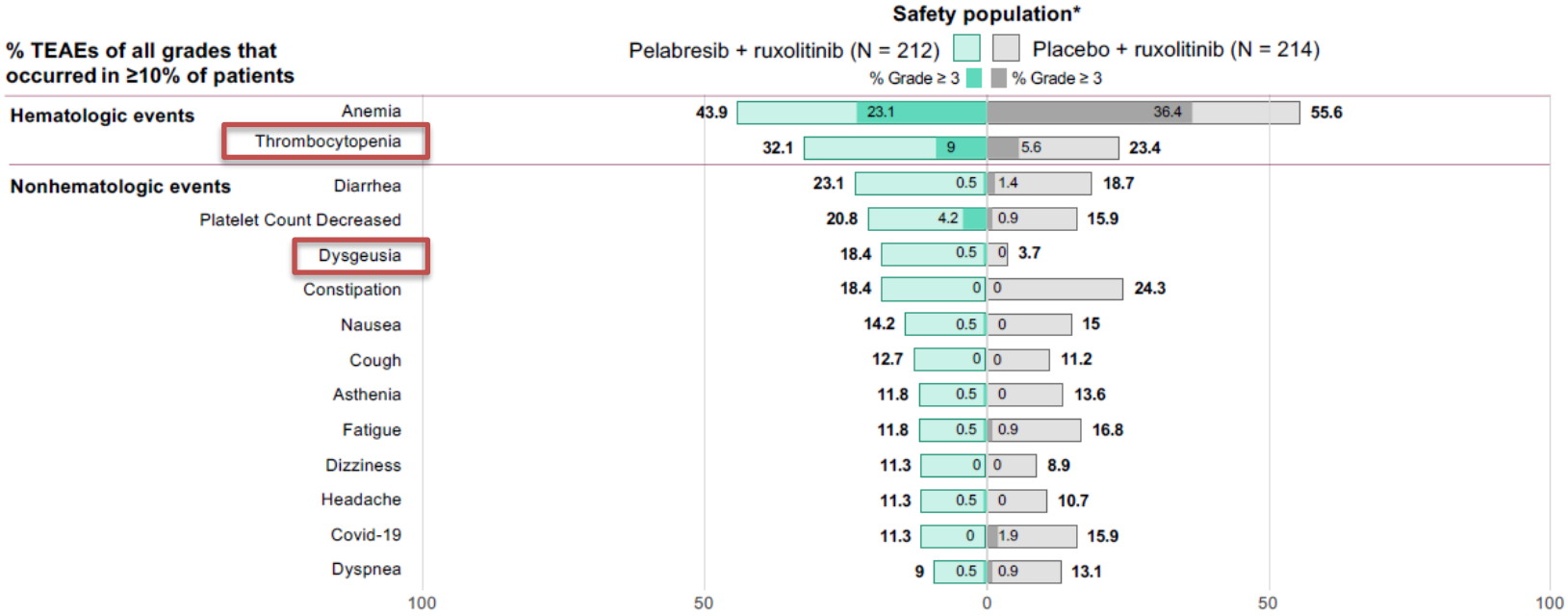
Rampal et al. ASH 2023. Oral Abstract 628.

The addition of pelabresib to ruxolitinib in the first-line setting was associated with a higher rate of double-responders who achieved both spleen and symptom responses



Rampal et al. ASH 2023. Oral Abstract 628.

The combination of ruxolitinib/pelabresib with lower rates of anemia, higher rates of thrombocytopenia and similar non-heme AE profile compared to ruxolitinib alone



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Future Combination Partners to Consider

- Luspatercept (Activin ligand trap)
- Selinexor (XPO1 inhibitor)
- Imetelstat (Telomerase inhibitor)
- Navtemadlin (MDM2 inhibitor)
- Zilurgisertib (ALK2 inhibitor)
- Bomedemstat (LSD1 inhibitor)
- BMS-986158 (BET inhibitor)
- INCB057643 (BET inhibitor)
- ABBV-744 (BET inhibitor)

Conclusions

- Ruxolitinib remains the mainstay of treatment for patients with MF with adequate blood counts.
- The approval of less myelosuppressive JAK inhibitors is particularly helpful in patients who develop cytopenias on ruxolitinib; however, these could be considered in the frontline setting in patients presenting with cytopenias.
- Overall, we have succeeded in being able to extend the benefits of JAK inhibitors to most patients.
- However, the treatment of myelofibrosis remains largely palliative.
- Future investigations should hinge on deepening responses (spleen, marrow, molecular).
- Combination therapies offer promise; however, given mixed results in registrational trials, their future is uncertain.