Optimizing outcomes of JAK inhibition in myelofibrosis: Practical considerations for the clinic

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What are the key considerations when selecting a JAK inhibitor for first-line therapy in myelofibrosis?

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Classification of myelofibrosis

Several prognostic models are used to categorize patients with MF based on multiple criteria[1,2]

Most commonly used

IPSS
At diagnosis only

DIPSS
Anytime*

DIPSS+
At treatment initiation†

MIPSS70/70+v2.0
Preferred for PMF

MYSEC-PM
For post-PV/post-ET MF

Each prognostic model uses a point system for different variables to identify the risk category[1,2]

Patient with MF

- Age >65 years
- Blast cells ≥1%, ≥2% or >3%
- Constitutional symptoms
- Driver mutations
- Haemoglobin <10 or <11 g/dL
- Platelet count <100 or <150 x 10^9/L
- WBC count >25 x 10^9/L

Prognostic scoring identifies intermediate/high-risk patients who may benefit from more intensive treatment[2]

*If recent karyotyping is unavailable;[1] †if molecular testing is unavailable.[1]
DIPSS, Dynamic IPSS; ET, essential thrombocythemia; IPSS, International Prognostic Scoring System; MF, myelofibrosis; WBC, white blood cell.
MIPSS70, Mutation-Enhanced International Prognostic Scoring System; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; PMF, primary MF; PV, polycythemia vera.
1. Gerds AT, et al. *J Natl Compr Canc Netw*. 2022;20:1033–62; 2. Duminuco A, et al. *J Clin Med*. 2023;12:2188.

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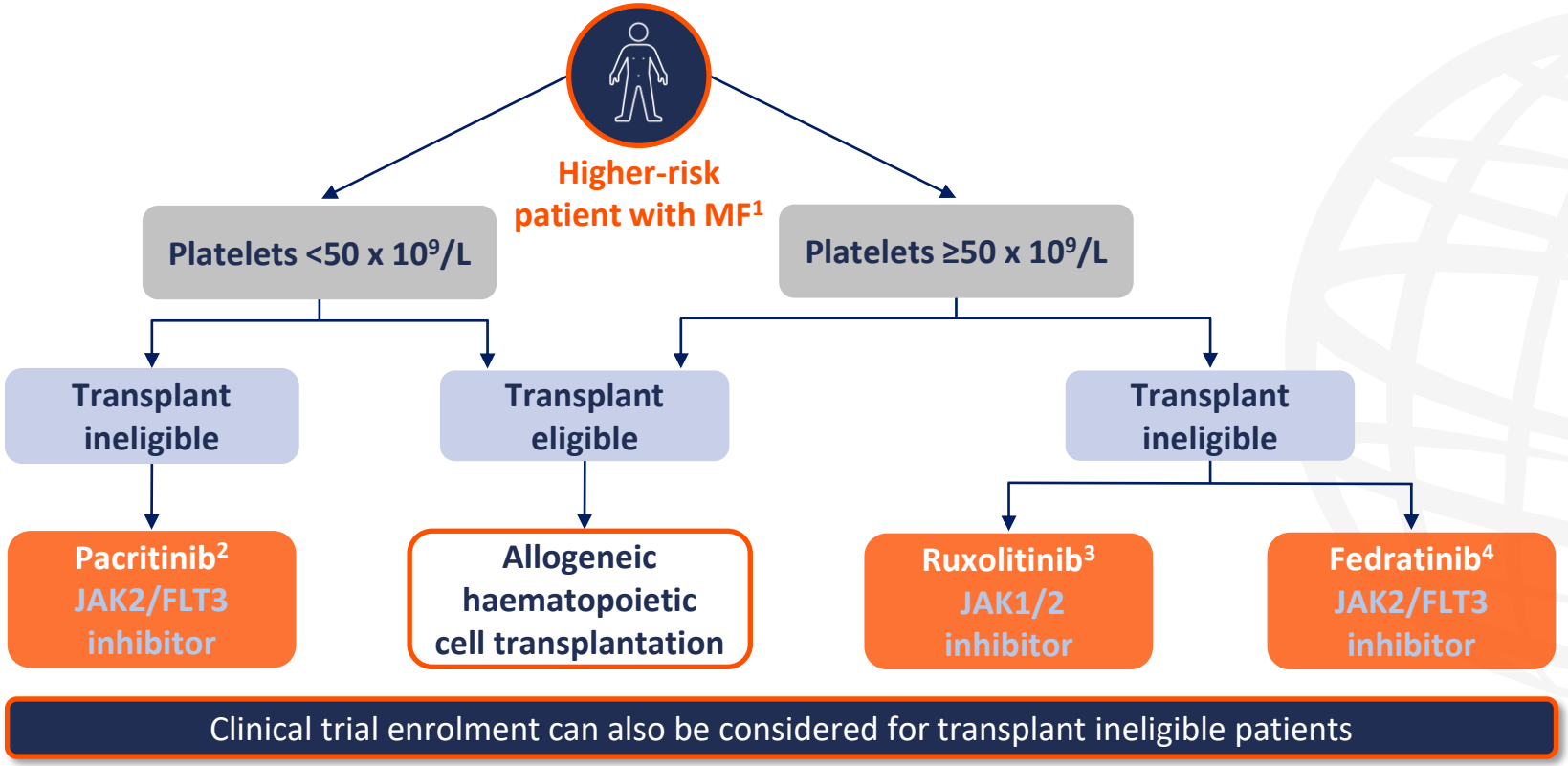
NCCN treatment algorithm for higher-risk myelofibrosis



FLT3, FMS-like tyrosine kinase 3; JAK, Janus kinase; MF, myelofibrosis; NCCN, National Comprehensive Cancer Network.

1. Gerds AT, et al. *J Natl Compr Canc Netw*. 2022;20:1033–62; 2. FDA. Pacritinib PI. Available at: https://bit.ly/3nRrr49 (accessed 4 May 2023);
3. FDA. Ruxolitinib PI. Available at: https://bit.ly/3VWFwtv (accessed 4 May 2023); 4. FDA. Fedratinib PI. Available at: https://bit.ly/3O27sKE (accessed 4 May 2023).

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Efficacy data for approved JAK inhibitors in MF

	COMFORT-I[1]	COMFORT-II[2]	JAKARTA[3]	JAKARTA-2[4]	PERSIST-1[5]	PERSIST-2[6]
Treatment and N number	**RUXOLITINIB** vs PBO (N=309)	**RUXOLITINIB** vs BAT (N=219)	**FEDRATINIB** vs PBO (N=289)	**FEDRATINIB** (rux intolerant/ resistant; n=83*)	**PACRITINIB** vs BAT excluding anti-JAK2i (N=327)	**PACRITINIB** vs BAT (n=221†)
Dose (BL platelet count)	Q2D 15 mg (100–200 × 10^9/L) OR 20 mg (>200 × 10^9/L)	Q2D 15 mg (≤200 X 10^9/L) OR 20 mg (>200 X 10^9/L)	QD 400 mg OR 500 mg (≥50 × 10^9/L)	QD 400 mg	QD 400 mg	QD 400 mg OR Q2D 200 mg (<100 × 10^9/L)
Primary endpoint at 24 weeks: **A. SVR ≥35%**	41.9% vs 0.7% (p<0.001)	32% vs 0% (p<0.001); 28% vs 0% at 48 weeks (p<0.001)	400 mg: 37% vs 1% (p<0.0001)[7] 500 mg: 40% vs 1% (p<0.001)	55%	19% vs 5% (p=0.0003)	18% vs 3% (p=0.001); Q2D vs BAT: 22% vs 3% (p=0.001)
B. ≥50% ↓ in TSS						25% vs 14% (p=0.08); Q2D vs BAT: 32% vs 14% (p=0.01)
Long-term outcomes	**2-yr follow-up:** Improved survival with rux vs PBO (p=0.03)[8]	**5-yr follow-up:** Rux benefits maintained[9]	Ongoing FREEDOM and FREEDOM2 trials[10]		**At week 60:** Durable response;[11] Durable ↓ in SVR in thrombocytopenic pts[12]	**Retrospective study pooled PERSIST-1 and -2:** Better outcomes in SVR, TSS and symptoms with pac vs BAT[13]

Direct comparisons between trials should not be made due to differences in trial design.

*N=97 enrolled; †N=311 enrolled. BAT, best available therapy; BL, baseline; JAK, Janus kinase; MF, myelofibrosis; pac, pacritinib; PBO, placebo; pts, patients; QD, once daily; Q2D, twice daily; rux, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score; yr, year.

1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799–807; 2. Harrison CN, et al. *N Engl J Med*. 2012;366:787–98; 3. Pardanani A, et al. *JAMA Oncol*. 2015;1:643–51; 4. Harrison CN, et al. *Lancet Haematol*. 2017;4:e317–24; 5. Mesa RA, et al. *Lancet Haematol*. 2017;4:e225–36; 6. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652–9; 7. Pardanani A, et al. *Br J Haematol*. 2021;195:244–8; 8. Verstovsek S, et al. *Haematologica*. 2013;98:1865–71; 9. Harrison CN, et al. *Blood*. 2015;126:59; 10. Harrison CN, et al. *Br J Haematol*. 2022;198:317-27; 11. Mesa RA, et al. *J Clin Oncol*. 2016;34(Suppl. 15):7065; 12. Harrison CN, et al. *J Clin Oncol*. 2016;34(Suppl. 15):7011; 13. Verstovsek S, et al. *Haematologica*. 2022;107:1599–1607.

What side effects are associated with JAK inhibitor use in myelofibrosis and how can they be managed?

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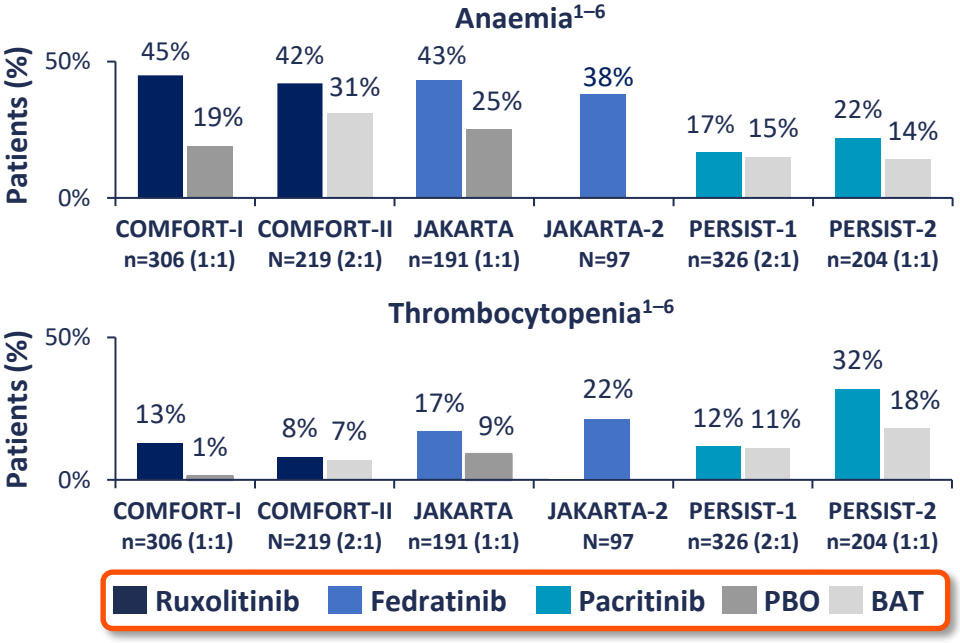
Anaemia and thrombocytopenia: Key AEs in JAK inhibitor trials

Most frequent grade 3 or 4 haematologic AEs*



Five most common non-haematologic AEs†

Ruxolitinib (COMFORT-I)[1]	**Incidence ≥10%** Fatigue, diarrhoea, ecchymosis, peripheral oedema, dyspnoea
Fedratinib (JAKARTA)[3]	**Incidence ≥10%** Diarrhoea, nausea, vomiting, fatigue, abdominal pain
Pacritinib (PERSIST-2)[6]	**Incidence ≥15%** Diarrhoea, nausea, peripheral oedema, vomiting, fatigue

Direct comparisons between trials should not be made due to differences in trial design.

*Where more than one dosing arm were included in trials, data are reported for the approved dose; †ordered from most to least common.

AE, adverse event; BAT, best available therapy; JAK, Janus kinase; PBO, placebo.

1. Verstovsek S, et al. *N Engl J Med.* 2012;366:799–807; 2. Harrison C, et al. *N Engl J Med*. 2012;366:787–98; 3. Pardanani A, et al. *JAMA Oncol*. 2015:1:643–51;
4. Harrison CN, et al. *Lancet Haematol*. 2017;4:e317–24; 5. Mesa RA, et al. *Lancet Haematol*. 2017;4:e225–36; 6. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652–9.

What are the options following treatment failure on a first-line JAK inhibitor in patients with myelofibrosis?

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When to discontinue JAK inhibitor treatment

No response

After ≥3 months on MTD

No spleen response (<20% ↓ in length/volume vs BL)

No symptom response (<20% ↓ in MPN-SAF score vs BL)

Loss of response

After ≥1 months on MTD

Loss of spleen response (return to BL; length ↑ vs BR; ≥25% ↑ in length/volume vs BL)

After ≥3 months on MTD

Loss of symptom response (return to BL; ≥30% ↑ in MPN-SAF score vs BL; ≥50% ↑ vs BR)

Progressive disease

After ≥3 months on MTD

New palpable splenomegaly

At any point

Progression to **accelerated/blast phase**

Leukaemic transformation

Intolerance

After ≥4 weeks of treatment

Unable to receive optimal dose to achieve clinical response

Unacceptable toxicity

BL, baseline; BR, best response; JAK, Janus kinase; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; MTD, maximum tolerated dose.

Mascarenhas J, et al. *Future Oncol*. 2023;19:763–73.