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

touch™ ONCOLOGY

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by USF Health and touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by USF Health and touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in USF Health and touchIME activities*
- *USF Health and touchIME accept no responsibility for errors or omissions*

A conversation between:

Dr Raajit Rampal
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Prof. John Mascarenhas
Icahn School of Medicine at Mount Sinai
New York, NY, USA

touch™ ONCOLOGY

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

Dr Raajit Rampal

Memorial Sloan Kettering Cancer Center
New York, NY, USA

touch™ ONCOLOGY

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

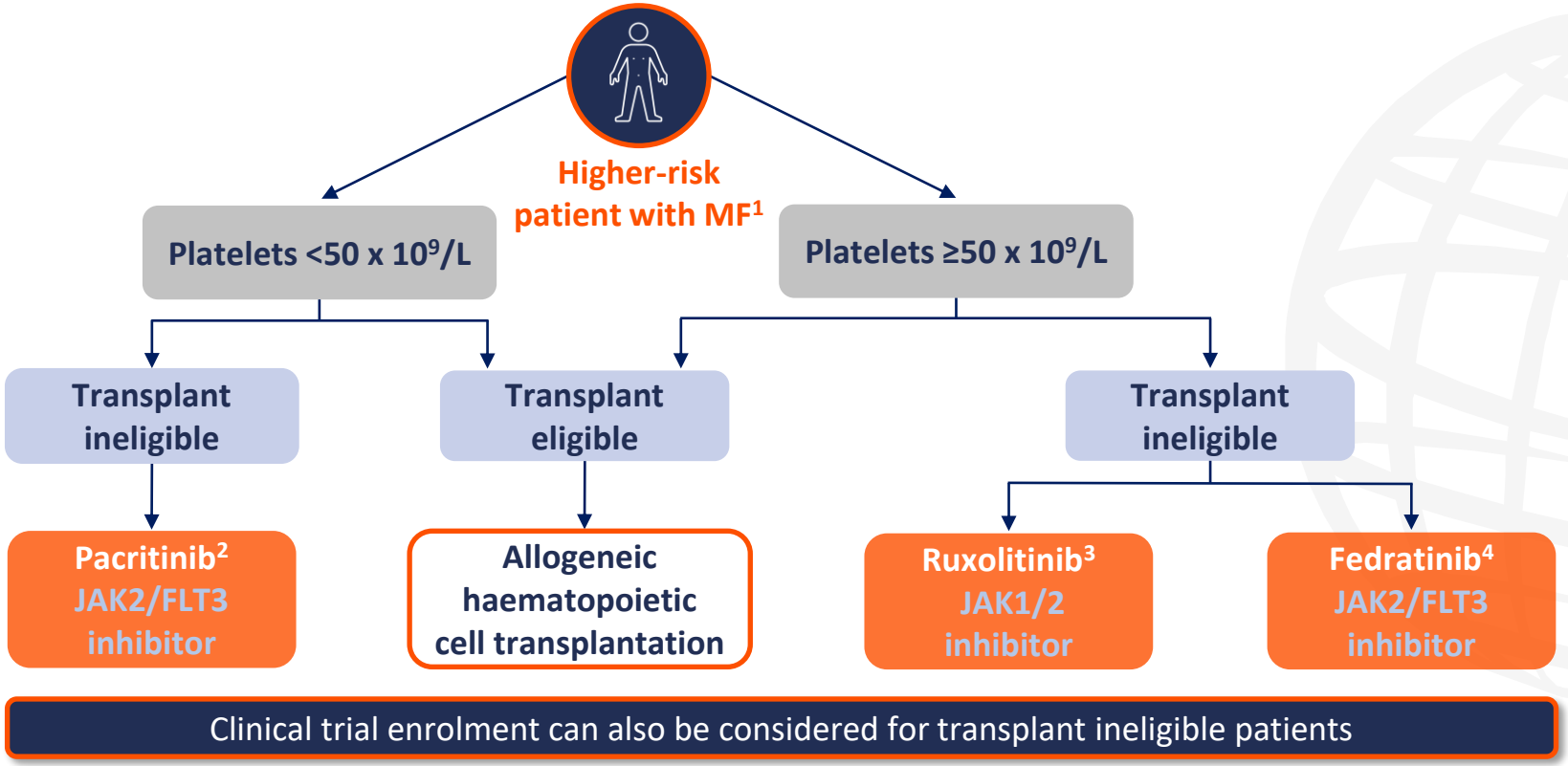
- Age >65 years
- Blast cells ≥1%, ≥2% or >3%
- Constitutional symptoms
- Driver mutations
- Haemoglobin <10 or <11 g/dL
- Platelet count <100 or <150 x 10^9/L
- WBC count >25 x 10^9/L

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.

touch™ ONCOLOGY

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).

touch™ ONCOLOGY

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.

touch™ ONCOLOGY

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

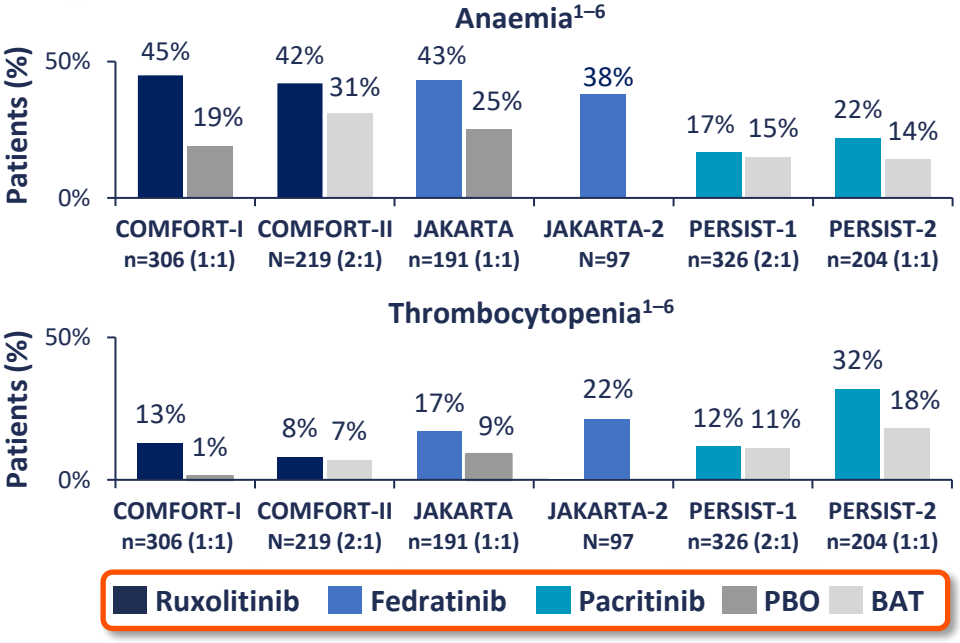
Dr Raajit Rampal

Memorial Sloan Kettering Cancer Center
New York, NY, USA

touch™ ONCOLOGY

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.

touch ONCOLOGY

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

Dr Raajit Rampal

Memorial Sloan Kettering Cancer Center
New York, NY, USA

touch™ ONCOLOGY

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.