Managing Treatment-Related Toxicities With JAK Inhibitor Therapy in Myelofibrosis

John Mascarenhas, MD
Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY

TOTAL CME

Ruxolitinib: Practical Considerations

Recommended dosage

- Based on platelet counts

Management considerations

- Cytopenias are initially more pronounced
- May cause lipid elevation and weight gain
- Increased infection risk (VZV/HSV)
- Increase skin cancer risk
- Withdrawal syndrome with abrupt discontinuation

Fedratinib in MF: Practical Considerations

Recommended dosage

- 400 mg orally once daily with or without food

Safety considerations

- Frequency and severity of GI AEs can be reduced via early implementation of GI prophylaxis (eg, antiemetics)
- Monitoring thiamine levels before fedratinib initiation and periodically during therapy is recommended (thiamine supplements can be useful)

Momelotinib in MF: Practical Considerations

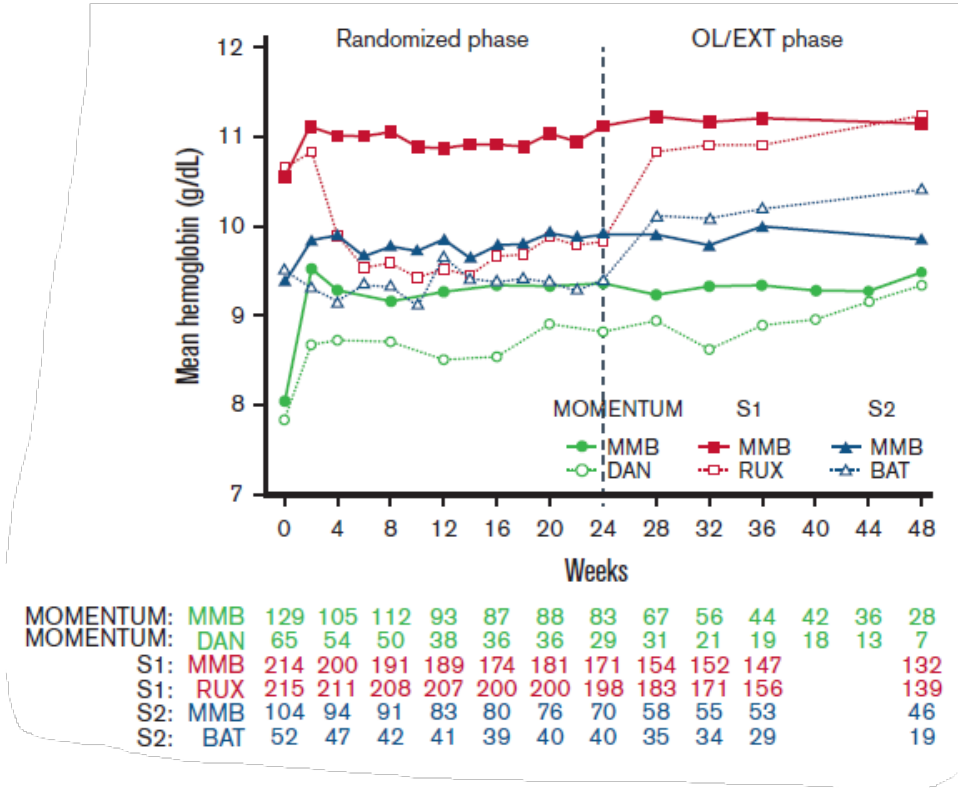
Dosing

- 200 mg orally once daily with or without food

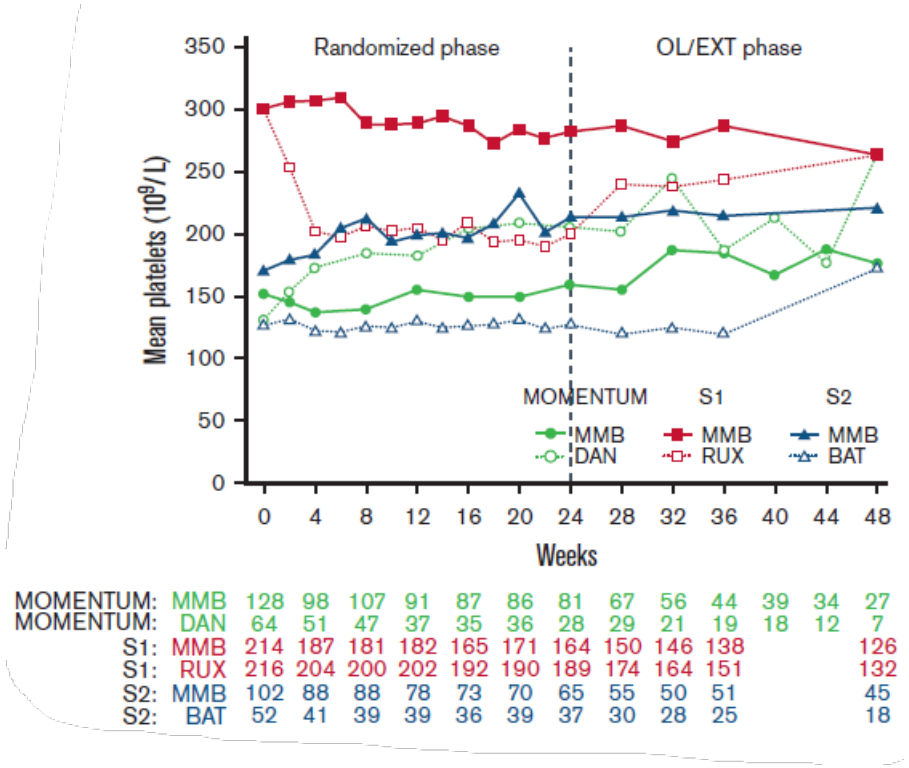
Safety considerations

- The most common AEs reported in studies to date are thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea
- Monitor for signs and symptoms of infection
- Thrombocytopenia and neutropenia: Manage by dose reduction or interruption
- Hepatotoxicity: Obtain liver tests before therapy initiation and periodically throughout treatment

Integrated Safety Analysis of Momelotinib Phase 3 Trials



MOMENTUM:	MMB	129	105	112	93	87	88	83	67	56	44	42	36	28
MOMENTUM:	DAN	65	54	50	38	36	36	29	31	21	19	18	13	7
S1:	MMB	214	200	191	189	174	181	171	154	152	147			132
S1:	RUX	215	211	208	207	200	200	198	183	171	156			139
S2:	MMB	104	94	91	83	80	76	70	58	55	53			46
S2:	BAT	52	47	42	41	39	40	40	35	34	29			19



MOMENTUM:	MMB	128	98	107	91	87	86	81	67	56	44	39	34	27
MOMENTUM:	DAN	64	51	47	37	35	36	28	29	21	19	18	12	7
S1:	MMB	214	187	181	182	165	171	164	150	146	138			126
S1:	RUX	216	204	200	202	192	190	189	174	164	151			132
S2:	MMB	102	88	88	78	73	70	65	55	50	51			45
S2:	BAT	52	41	39	39	36	39	37	30	28	25			18

- **Adverse events with MMB were mostly grade 1/2, noncumulative, and associated with low rates of discontinuation**
- **In this large heterogeneous MF dataset evaluating a JAKi, 12% of patients received MMB ≥ 5 years**

Verstovsek S, et al. *Blood Adv*. 2023;7(14):3582-3591.

Pacritinib in MF: Practical Considerations

Recommended dosage

- 200 mg orally twice daily

Safety considerations

- Avoid in patients with active bleeding; hold prior to surgical procedures
- For significant diarrhea: Antidiarrheals, dose reduction, or dose interruption
- Thrombocytopenia: Manage by dose reduction or interruption
- Avoid use in patients with baseline QTc >480 ms
- Interrupt and reduce dosage in patients who have a QTcF >500 ms

Safety Profile of Pacritinib Similar to or Better Than Best Available Therapy

Patients With Events Per 100 Patient-Years at Risk (Number of Patients / Total Patient-Years)	PAC203 PAC	PERSIST-2			Pooled PAC
		PAC	BAT	BAT=RUX	
Cancers					
Malignancy – excluding leukemic transformation[a]	**0** (0/29.6)	**8** (5/63.7)	**7** (3/40.8)	**11** (2/17.8)	**5** (5/93.3)
Non-melanoma skin cancer[b]	**0** (0/29.6)	**5** (3/64.2)	**7** (3/40.8)	**11** (2/17.8)	**3** (3/93.8)
Viral Infections					
Viral infection[c]	**7** (2/29.2)	**5** (3/65.1)	**12** (5/41.1)	**11** (2/18.3)	**5** (5/94.3)
Zoster[d]	**0** (0/29.6)	**0** (0/65.7)	**2** (1/41.5)	**6** (1/18.3)	**0** (0/95.3)
Fungal infection	**10** (3/29.1)	**5** (3/64.1)	**12** (5/40.8)	**6** (1/18.3)	**6** (6/93.1)

[a] Includes all events within the Systems Order Class (SOC) "Neoplasms benign, malignant, and unspecified," excluding acute leukemia, myelofibrosis, and benign tumors.
[b] Includes basal cell and squamous cell carcinoma of the skin, as determined by medical review.
[c] Includes any infection event attributed to a specific virus (eg, cytomegalovirus reactivation, herpes keratitis), or described as being "viral" (eg, viral gastroenteritis, viral upper respiratory tract infection), as determined by medical review
[d] Includes any infection event relating to "zoster" or "shingles," as determined by medical review

Risk-adjusted incidence rate calculated based on exposure-adjusted incidence per 100 patient-years:
100 X (number of patients with an event / Total patient-years at risk of the event)
Total patient-years at risk of the event calculated as:

- For patients with no event: [(date last dose – date first dose)] + 1/365.25
- For patients with an event: [(date event – date first dose)] + 1/365.25

Pemmaraju N, et al. 2022 ASCO Annual Meeting. Poster 7058.

Summary

- Cytopenias are common with ruxolitinib so follow blood counts
- Manage GI AEs on fedratinib and pacritinib with antiemetics and antidiarrheal agents
- Monitor and replete vitamin B1 as necessary on fedratinib
- Monitor blood counts and liver enzymes with momelotinib
- Baseline EKG for all JAK inhibitors and monitor; hold for QTc >500 msec