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CHALLENGING CASES

Hematologic Disorders

Challenging Cases conducted: April 1, June 16, June 25, June 26, and August 21

Challenging Cases in…

Myelofibrosis

Program conducted:
April – August 2025

Note: Aggregated results and high-level summary based on 5 practices (≤28 HCPs total responses) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

Participating Practices

• New Mexico Cancer Center (n=6)	April 1, 2025
• HealthPartners (n=7)	June 16, 2025
• Toldeo Clinic Cancer Centers (n=5)	June 25, 2025
• Cancer Center of Kansas (n=5)	June 26, 2025
• Ironwood Cancer & Research Centers (n=5)	August 21, 2025

High-level Summary

Challenging Cases in… Myelofibrosis

- In general, ruxolitinib is the preferred first-line treatment option for a patient with higher-risk myelofibrosis that is not a transplant candidate; comfort, experience, time on market, and long-term data including five-year outcomes are key decision factors
  - Pactrinib is "*the drug of choice*" for patients with low platelets
  - Some preference for momelotinib for patients with anemia upfront with mixed responses; noted it does not have a category 1 NCCN Guideline status
- Most have used all three JAK inhibitors (pacritinib, ruxolitinib and momelotinib); at least one prescriber indicated that MOA is not an important differentiator, just the endpoint
- Mixed views on the importance of regimens with Category 1 status in the NCCN Guidelines
  - Some clinicians closely follow NCCN guidelines, noting "*category one is always preferred, if possible*" and find that payers follow them too.
  - Others acknowledged the guidelines but relied more on patient-specific factors and insurance formulary
- Dose reduction and temporary regimen holiday of ruxolitinib often occurs to manage platelet counts and or anemia; can impact efficacy and many emphasized it was important not to go below 10 mg BID
  - Some reported maintaining symptom and spleen control even on reduced doses (5–10 mg), though results were inconsistent
  - Some described adjustments as a "*moving target*", constantly trying to find the right dose.

High-level Summary

Challenging Cases in… Myelofibrosis

- Switching from ruxolitinib to pacritinib or momelotinib is done if symptomatic
  - Some add luspatercept or ESA to ruxolitinib to improve hemoglobin if other symptom control is good
  - Pacritinib was favored for thrombocytopenia, noted having compelling post-ruxolitinib data
  - Momelotinib showed benefit for anemia, some patients experiencing sustained hemoglobin improvement, others reported neurological side effects or limited benefit
  - Fedratinib use was less common, with mixed experiences and ongoing anemia issues
- Several noted that insurance can influence prescribing behaviors
  - Experience of insurance challenges with switching varied: some clinicians reported no issues, others experienced pushback and brand preference
- Most will change their prescribing behavior based on the Challenging Case presentation
  - Exposure to new and compelling data for pacritinib and momelotinib, with some more likely to incorporate these agents in the future
  - More open to early use of pacritinib in patients with low platelets or patients with anemia based on the presented data
  - Less likely to persist with suboptimal responses to ruxolitinib
    - Awareness and use of RR6 prognostic tool (response to ruxolitinib after 6 months of treatment) was limited at the time of presentation with some acknowledging it would be useful and plan to apply in practice
  - For others, prescribing behavior was reinforced during the presentation

Challenging Cases in… Myeloproliferative Neoplasms

Myelofibrosis

Patient case: Cytopenic Myelofibrosis (MF)

- Myelofibrosis (MF) is characterized by activated JAK-STAT signaling and inflammation
- Symptoms of MF may go unrecognized in early disease, but with progression and associated disease complications they can lead to reduced QoL, functional status, and activities of daily living as well as impact prognosis of myelofibrosis patients
- Proliferative and cytopenic MF are clinically and biologically different and present across a spectrum
- Patients with MF with severe cytopenia have significantly shorter overall survival

- ***What is the optimal treatment for high-risk patients?***

Patient History

71-year-old male

Presents with bruising, fatigue, night sweats, weight loss and abdominal pain

Diagnosis

Ultrasound revealed splenomegaly (14 cm)

WBC: 22 x 10^9/L

Hemoglobin: 9.5 g/dL

Platelets: 140 x 10^9 /L

Blasts: 1%

Mutation: low *JAK2* V617F allele burden

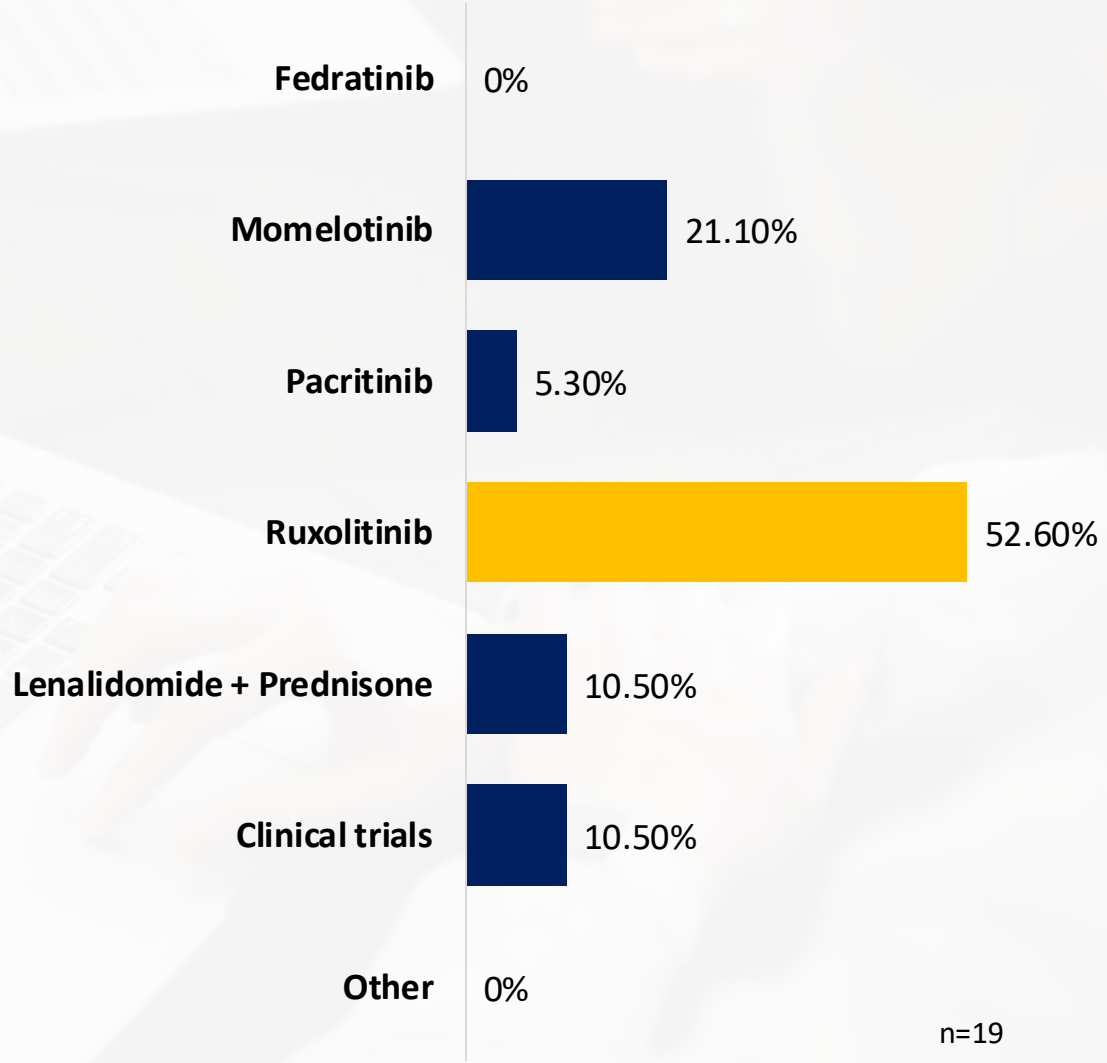
Cytopenic MF

Not a candidate for transplant

What first line systemic treatment do you recommend?

ARS Results from HCP Participants

What first-line treatment do you recommend for a patient with higher-risk myelofibrosis that is not a transplant candidate?



NCCN Guidelines: Myelofibrosis – Higher risk

Version 1.2025 — February 21, 2025

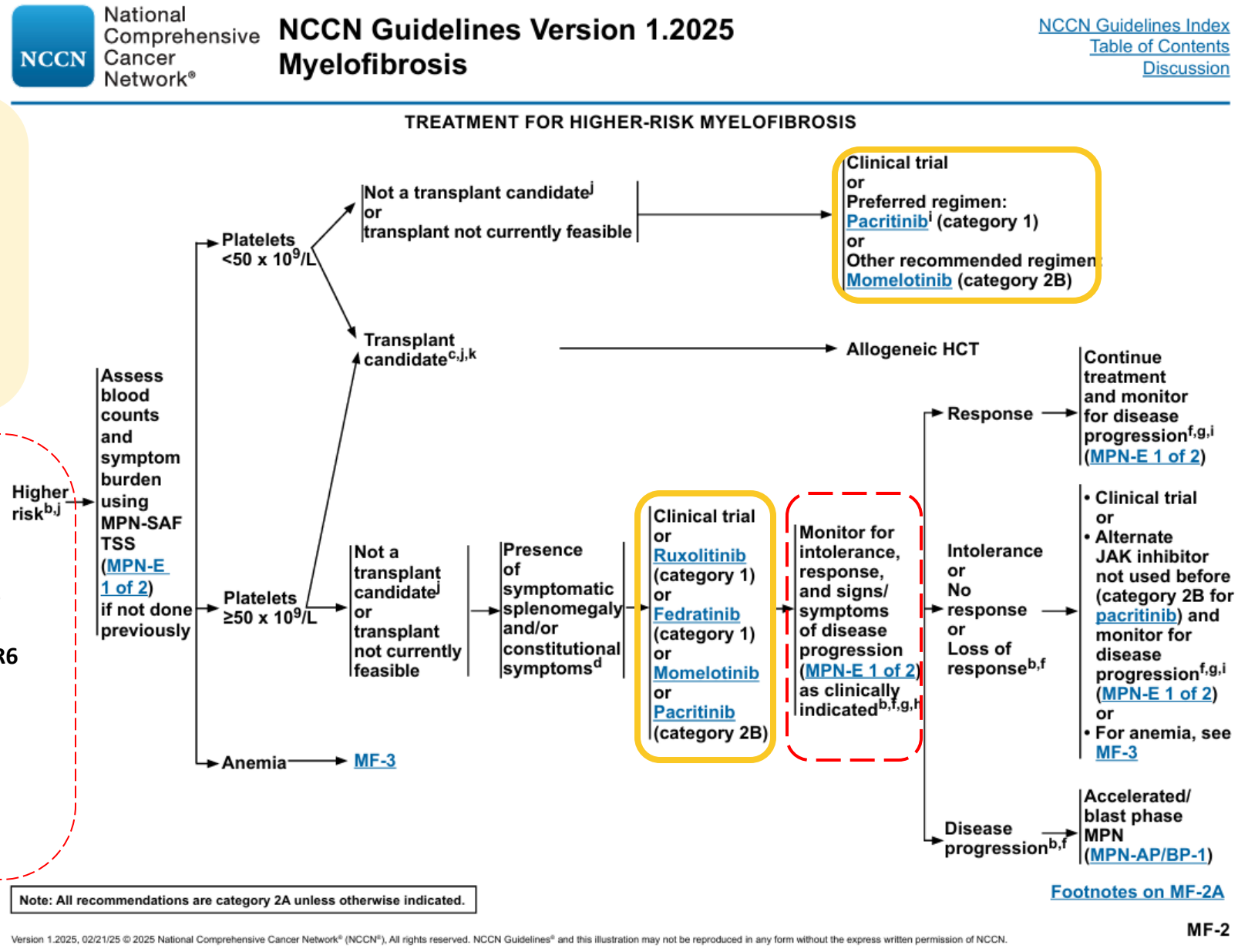
How do you view category 1 regimens versus other regimens?

How do you monitor for intolerance / response?

Updates in Version 1.2025 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 2.2024 include:

- g Response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician. **RR6 may also be used to gauge response**. Continuation of JAK inhibitors is recommended based on the discretion of the clinician.

- h **For ruxolitinib, use RR6 model to assess. Maffioli M, et al. Blood Adv 2022;6:1855-1864.**



Comparison of current JAK inhibitors

	Indication
JAKAFI (ruxolitinib)	***Approved November 2011 :*** A kinase inhibitor indicated for treatment of **intermediate or high-risk myelofibrosis**, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults.
INREBIC (fedratinib)	***Approved August 2019:*** A kinase inhibitor indicated for the treatment of adult patients with **intermediate-2 or high-risk primary or secondary** (post-polycythemia vera or post-essential thrombocythemia) **myelofibrosis (MF)**
VONJO (pacritinib)	***Approved February 2022:*** A kinase inhibitor indicated for the treatment of adults with **intermediate or high-risk primary or secondary** (post-polycythemia vera or post-essential thrombocythemia) **myelofibrosis with a platelet count below 50 × 10^9/L**
OJJAARA (momelotinib)	***Approved September 2023:*** A kinase inhibitor indicated for the treatment of **intermediate or high-risk myelofibrosis (MF)**, including primary MF or secondary MF [post polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults **with anemia**.

But not all JAK inhibitors are created equally…

How aware are you of the MOA differences in the currently available JAK inhibitors?

Comparison of current JAK inhibitors

	Indication	JAK1 Inhibition exacerbates thrombocytopenia and immunosuppression	JAK2 Inhibition mediates cytokine signaling and key GFs for hematopoiesis and immune function	ACVR1 Inhibition downregulates hepcidin production	IRAK1 Inhibition suppresses downstream NFκB activation; reduces inflammation
JAKAFI (ruxolitinib)	***Approved November 2011 :*** A kinase inhibitor indicated for treatment of **intermediate or high-risk myelofibrosis**, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults.	✓	✓	---	---
INREBIC (fedratinib)	***Approved August 2019:*** A kinase inhibitor indicated for the treatment of adult patients with **intermediate-2 or high-risk primary or secondary** (post-polycythemia vera or post-essential thrombocythemia) **myelofibrosis (MF)**	✓	✓	---	---
VONJO (pacritinib)	***Approved February 2022:*** A kinase inhibitor indicated for the treatment of adults with **intermediate or high-risk primary or secondary** (post-polycythemia vera or post-essential thrombocythemia) **myelofibrosis with a platelet count below 50 × 10^9/L**	---	✓	✓	✓
OJJAARA (momelotinib)	***Approved September 2023:*** A kinase inhibitor indicated for the treatment of **intermediate or high-risk myelofibrosis (MF)**, including primary MF or secondary MF [post polycythemia vera (PV) and post-essential thrombocythemia (ET)], **in adults with anemia.**	✓	✓	✓	---

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Comparison of current JAK inhibitors	Trial	Study Design	≥35% spleen volume reduction at Week 24 (unless otherwise stated)	Rate of TSS Reduction of ≥50% From Baseline at Week 24
JAKAFI (ruxolitinib)	**COMFORT-I**	Ruxolitinib vs placebo	42% vs 0.7% placebo (P<0.0001)	45.9 % vs 5.3%
	COMFORT-II	Ruxolitinib vs best available treatment*	29% vs 0% at week 48 (P<0.0001)	---
INREBIC (fedratinib)	**JAKARTA**	Fedratini vs placebo	37% vs 1%	40% vs 9%
			BOX WARNING: serious and fatal encephalopathy, including Wernicke's encephalopathy	
VONJO (pacritinib)	**PERSIST-2**	Pacritinib vs best available treatment** Baseline Platelets <50 × 10^9/L	29% vs 3%	23% vs 13%
OJJAARA (momelotinib)	**MOMENTUM**	Momelotinib vs danazol	22% vs 3%	25% vs 9%

*BAT in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.
**PERSIST-II: The most commonly used active single agents in the BAT arm were ruxolitinib (n = 44 [45%]), hydroxyurea (n = 19 [19%]), and prednisone and/or prednisolone (n = 13 [13%]); 19 patients (19%) received watchful-waiting only

Patient History

71-year-old men

Presents with bruising, fatigue, night sweats, weight loss and abdominal pain

Ultrasound revealed splenomegaly (14 cm)

WBC: 22 x 10^9/L

Hemoglobin: 9.5 g/dL

Platelets: 140 x 10^9 /L

Blasts: 1%

Mutation: low *JAK2* V617F allele burden

Cytopenic MF

Not a candidate for transplant

Treatment

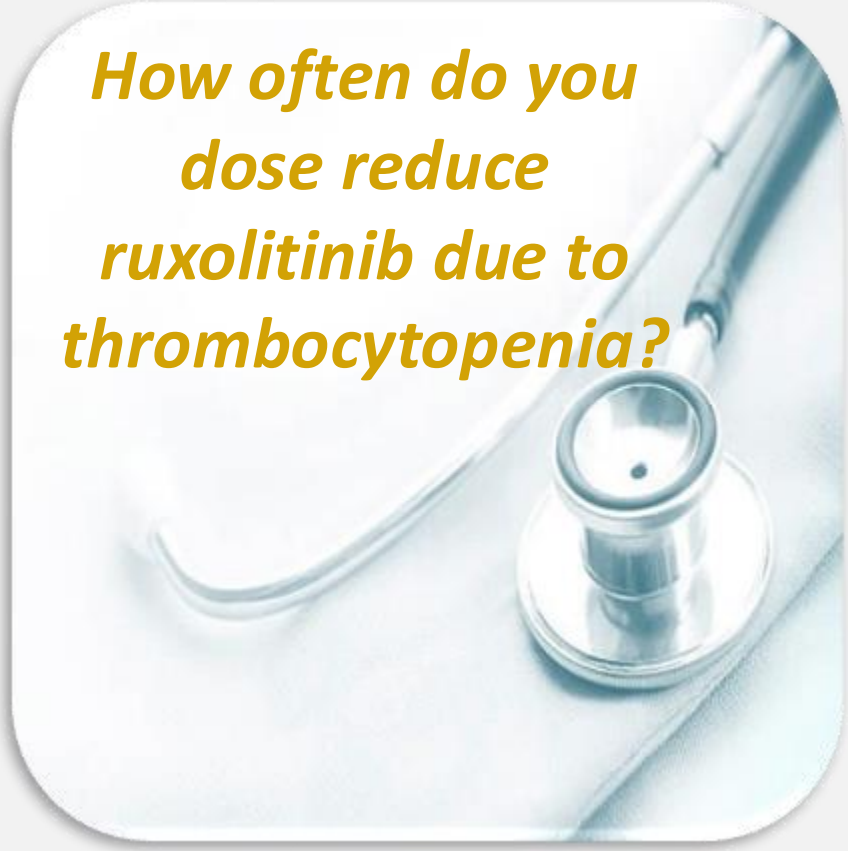
Received ruxolitinib

15 mg orally twice daily

Monitor complete blood counts every 2 to 4 weeks

Worsening treatment related side effects

How often do you dose reduce ruxolitinib due to thrombocytopenia?



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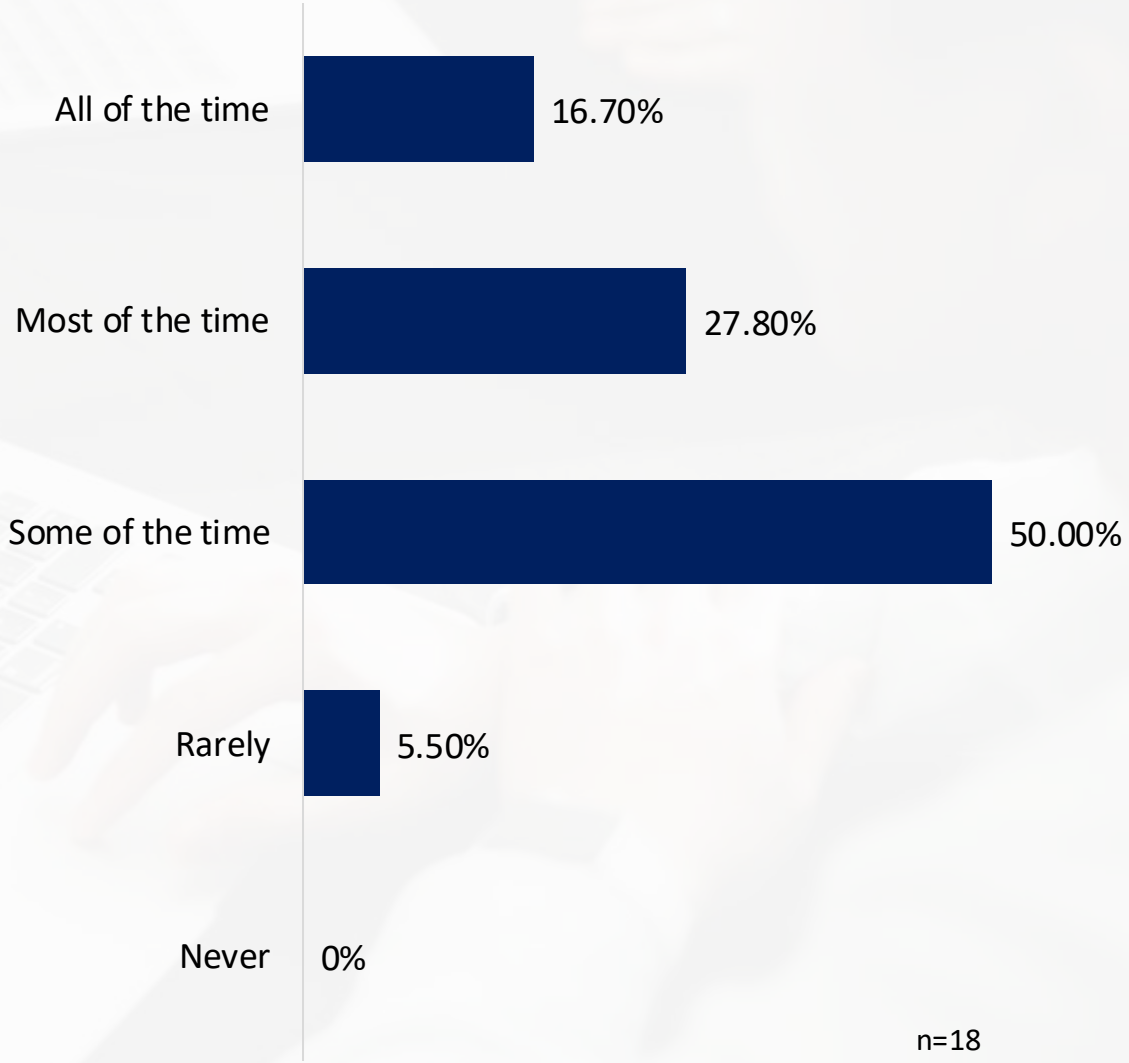
ARS Results from HCP Participants

How often do you have to dose reduce ruxolitinib due to thrombocytopenia?



How often do you switch JAK inhibitors?

Do you experience any challenges with approval?

Preferred regimens versus other recommended regimens?

Symptomatic vs controlled symptoms?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Myeloproliferative Neoplasms

July 8, 2025

MANAGEMENT OF MF-ASSOCIATED ANEMIA[d]

Assess for and treat alternative causes of anemia (ie, bleeding, nutritional deficiencies, hemolysis)

Ongoing symptomatic splenomegaly and/or constitutional symptoms →

Preferred regimens
- Clinical trial
- Momelotinib

Other recommended regimens
- Pacritinib
- Ruxolitinib combination
  - Luspatercept-aamt
  - ESAs[l] (if serum EPO <500 mU/mL) (category 2B)
  - Danazol[m] (category 2B)

No splenomegaly or constitutional symptoms →

Preferred regimen
- Clinical trial

Other recommended regimens
- ESAs[l] (if serum EPO <500 mU/mL)
- Luspatercept-aamt
- Danazol[m]
- Pacritinib (category 2B)
- Momelotinib (category 2B)

Useful in certain circumstances
- Lenalidomide + prednisone[n] for del(5q) (category 2B)

Splenomegaly and constitutional symptoms well controlled on current JAK inhibitor →

Preferred regimen
- Clinical trial

Other recommended regimens
- JAK inhibitor combination[o]
  - Add ESAs[l] (if serum EPO <500 mU/mL)
  - Add luspatercept-aamt
  - Add danazol[m] (category 2B)

Useful in certain circumstances
- Change to pacritinib
- Change to momelotinib

[d] Supportive Care for Patients with MPN (MPN-F).
[l] ESAs include epoetin alfa and darbepoetin alfa. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[m] Prostate cancer screening and monitoring of LFTs as well as the use of concomitant medications such as statins are recommended over concerns for increased risk of rhabdomyolysis.
[n] Start as a combination followed by tapering of prednisone over 3 months.
[o] JAK inhibitors may be continued for the improvement of splenomegaly and other disease-related symptoms.

Note: All recommendations are category 2A unless otherwise indicated.

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Patient History

71-year-old male

Presents with bruising, fatigue, night sweats, weight loss and abdominal pain

Received ruxolitinib

15 mg orally twice daily

Insufficient response, no symptom improvement or spleen size reduction

Diagnosis

Ultrasound revealed splenomegaly (14 cm)

WBC: 22 x 10^9/L

Hemoglobin: 8.2 g/dL

Platelets: 62 x 10^9 /L

Blasts: 1%

Mutation: low *JAK2* V617F allele burden

Cytopenic MF

Not a candidate for transplant

What systemic treatment do you recommend next?

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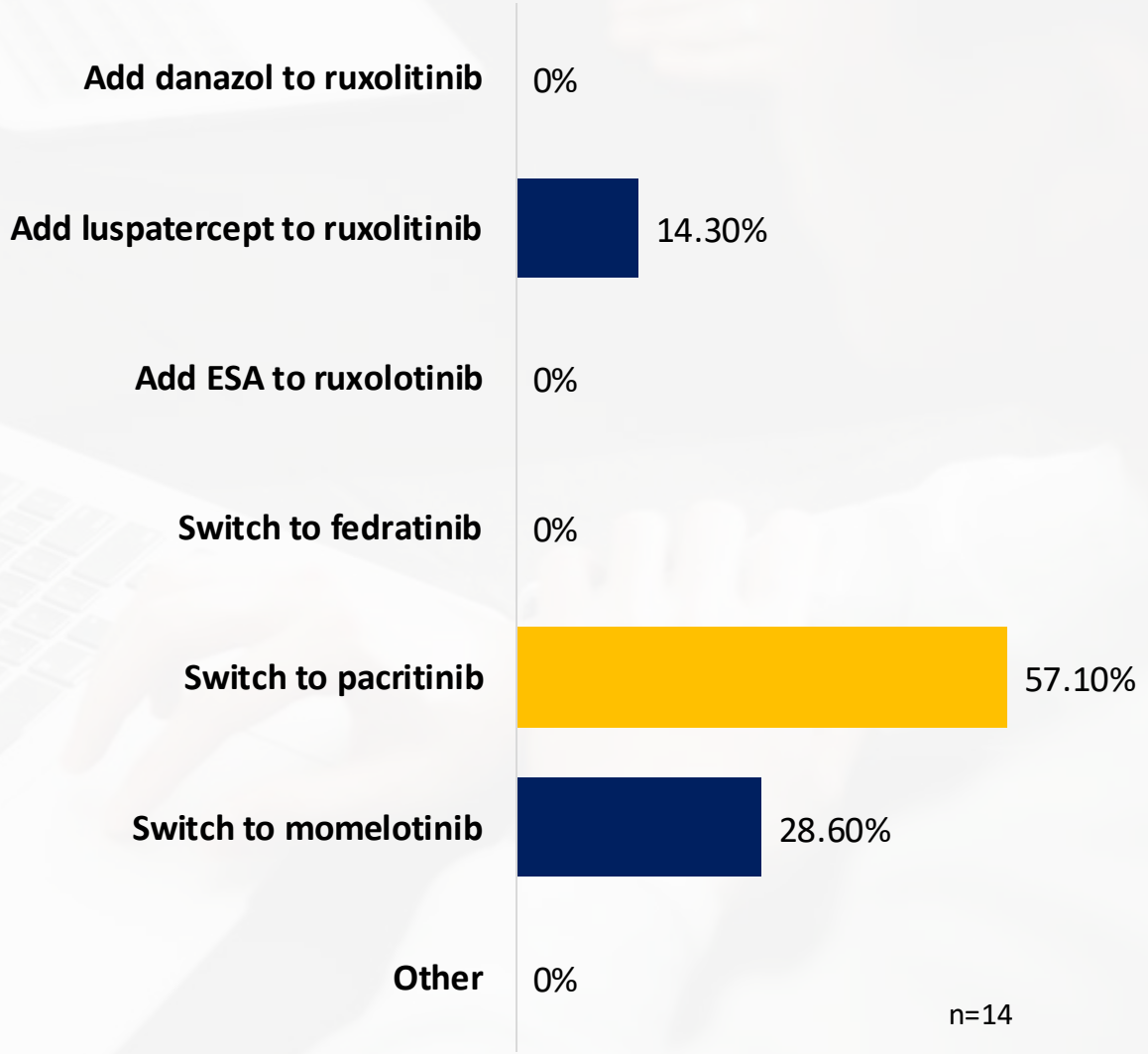
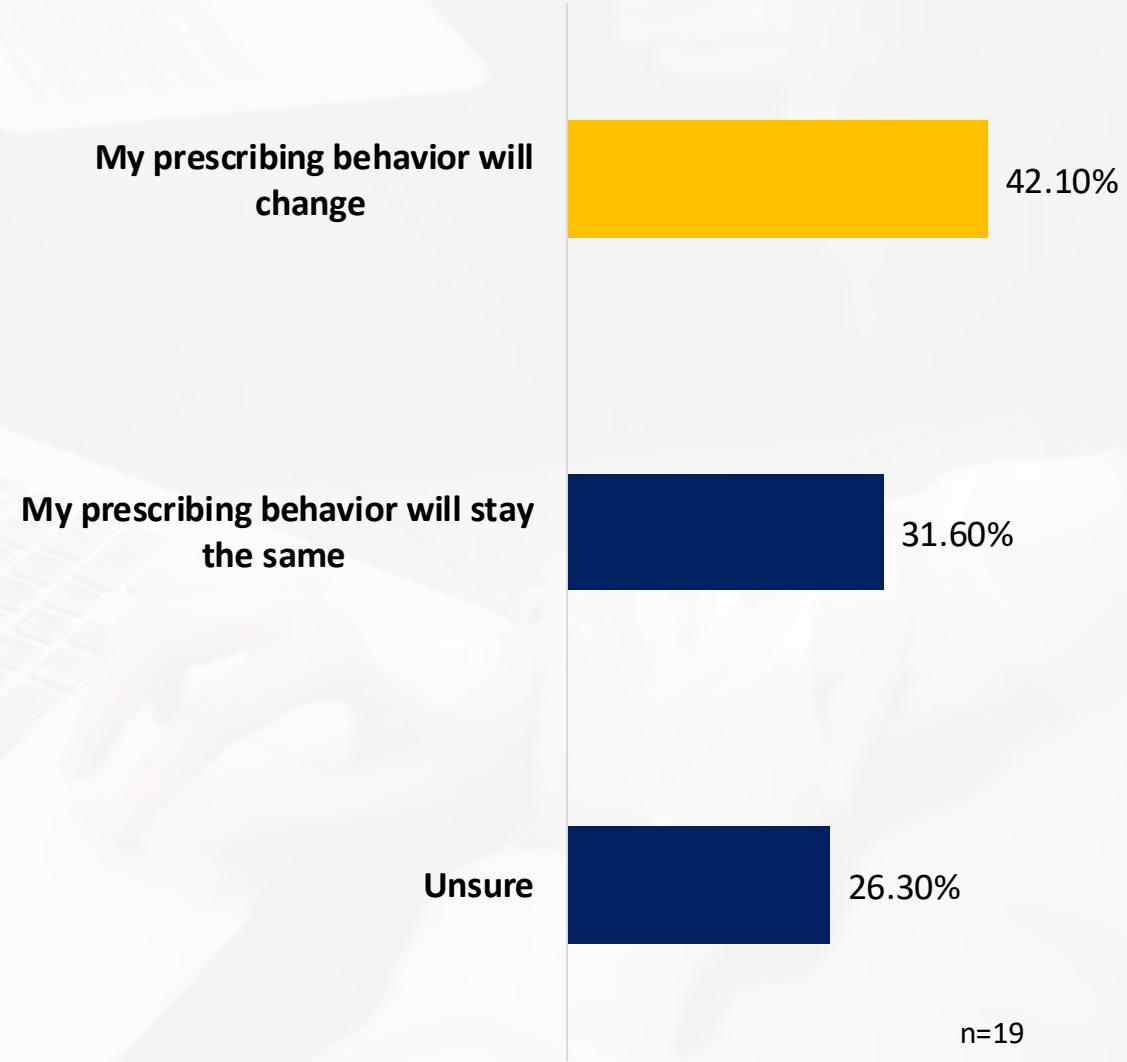
ARS Results from HCP Participants

If insufficient response on Ruxolitinib, what would be your next therapeutic choice for this higher-risk patient?



ARS Results from HCP Participants

How will the Challenging Case impact your prescribing behavior for higher-risk myelofibrosis?



Key Takeaways

Myelofibrosis

Patient case: untreated metastatic disease

- *Control of spleen and anemia symptoms, with an ultimate goal of overall survival*
- *Awareness of the difference between the currently available JAK inhibitors*
- *No head-to-head trials, but retrospective analysis can provide insights*
- *Clinical trial data, NCCN Guidelines, and FDA approvals guide treatment decisions*

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