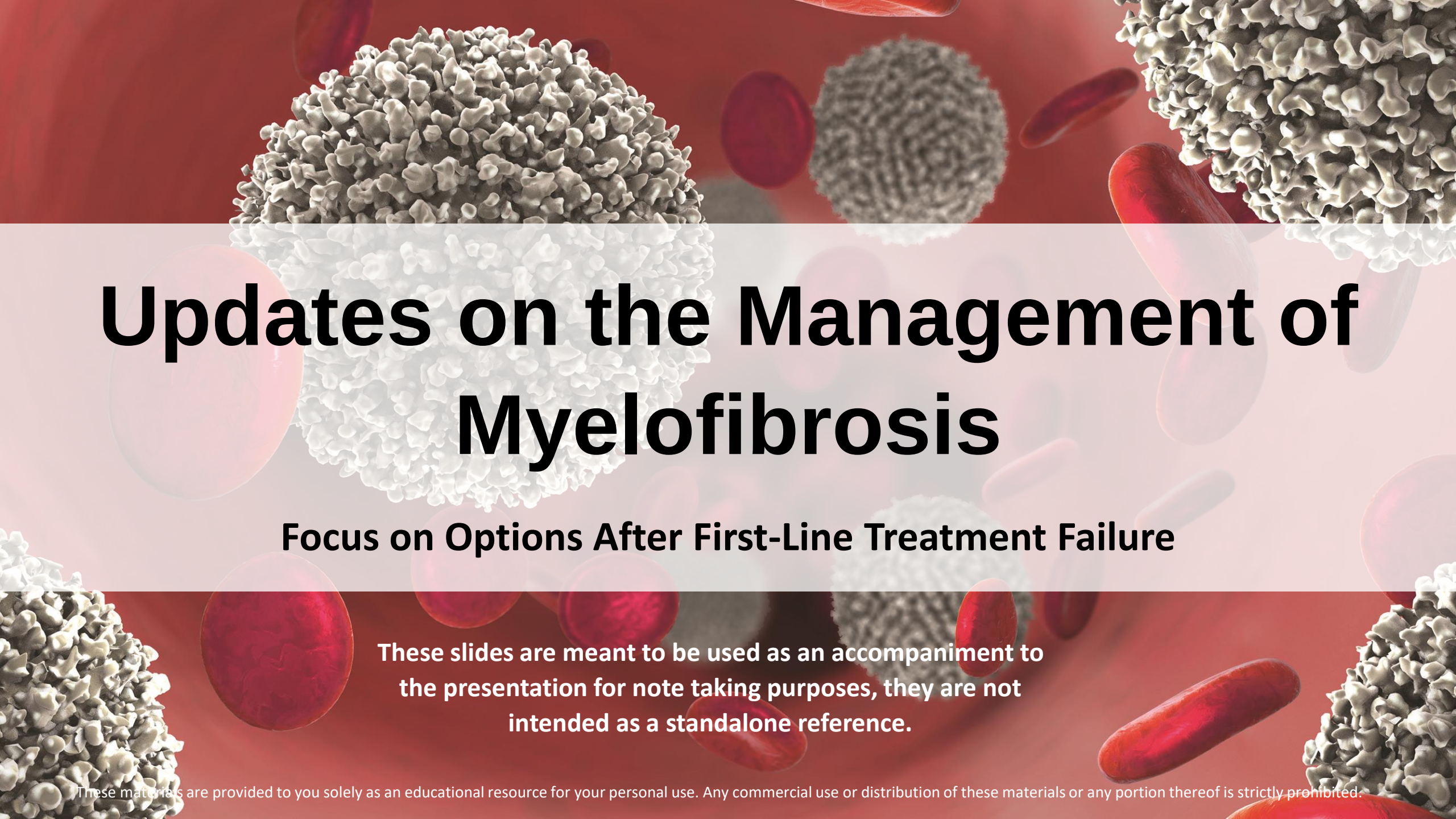
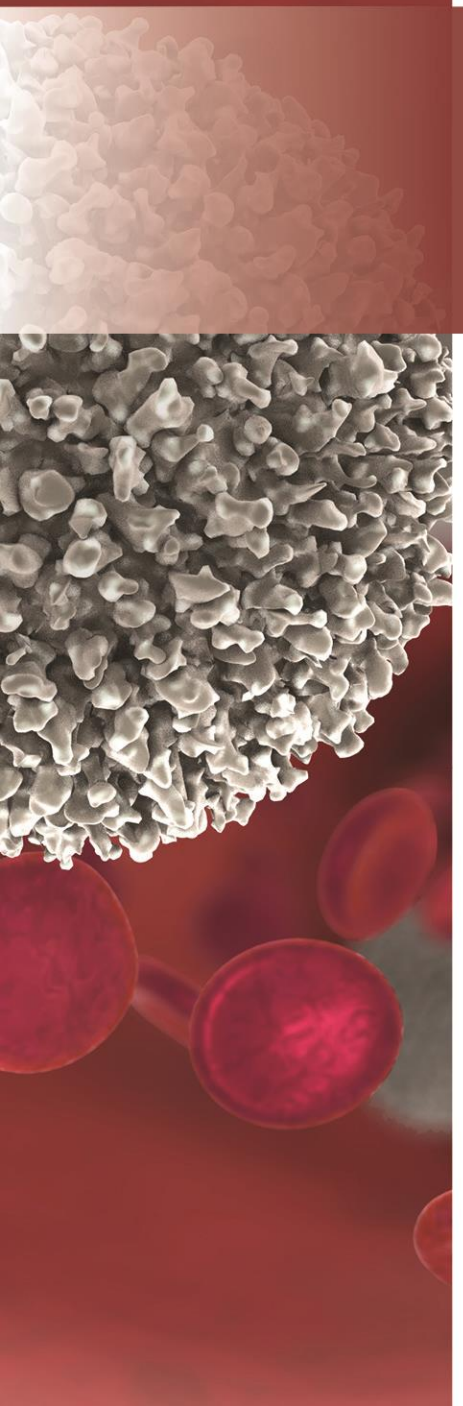


Updates on the Management of Myelofibrosis

Focus on Options After First-Line Treatment Failure

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



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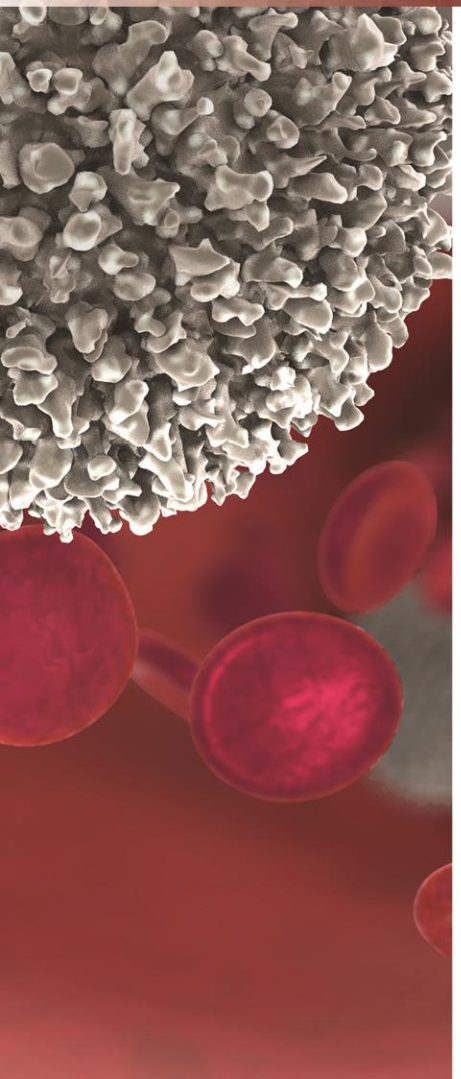
Faculty



Craig W. Freyer, PharmD, BCOP
Clinical Pharmacy Specialist, Hematology/Oncology
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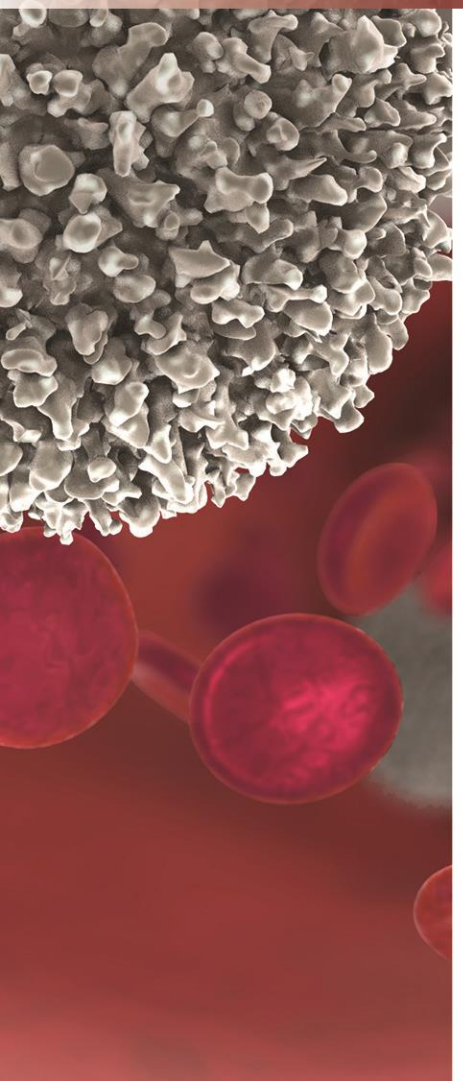
Philadelphia, PA

Dr. Freyer is a board-certified clinical pharmacy specialist in hematology/oncology, stem cell transplant, and cellular therapy at the Hospital of the University of Pennsylvania in Philadelphia. His clinical and research interests include clinical optimization and supportive care for patients with myeloid and lymphoid malignancies as well as for patients undergoing chimeric antigen receptor T-cell therapy and stem cell transplant. Dr. Freyer completed his hematology/oncology pharmacy residency training at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL, and is a graduate of the University of Connecticut School of Pharmacy.

Disclosures



Dr. Freyer has disclosed that he has received consulting fees from EUSA Pharma and Servier Pharmaceuticals, and non-CE fees from Astellas Pharma.

The clinical reviewer, **Lisa Holle, PharmD, BCOP, FHOPA**, has disclosed that she has no actual or potential conflicts of interest related to this program.

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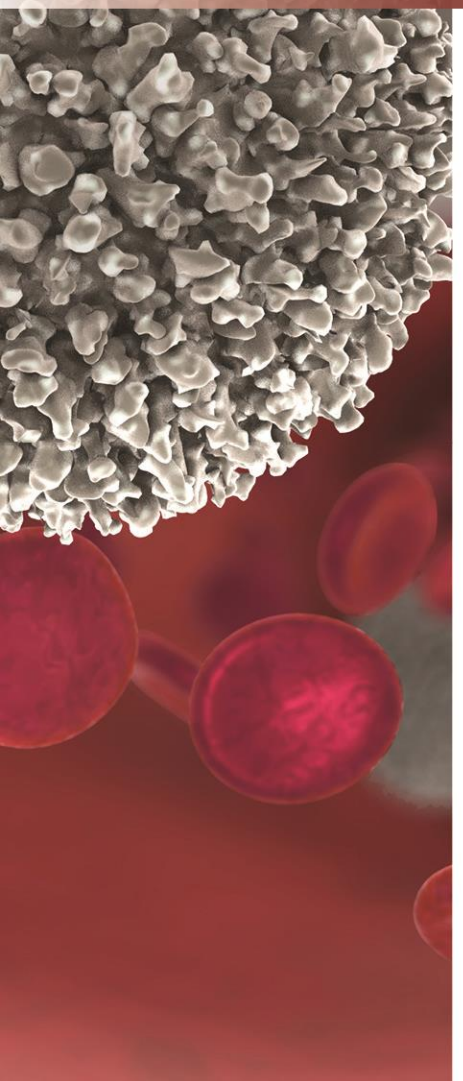

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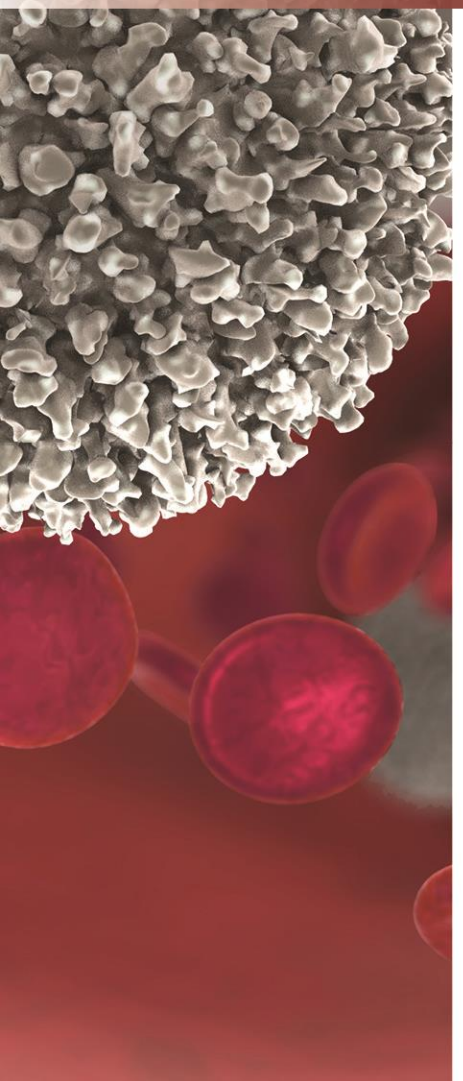
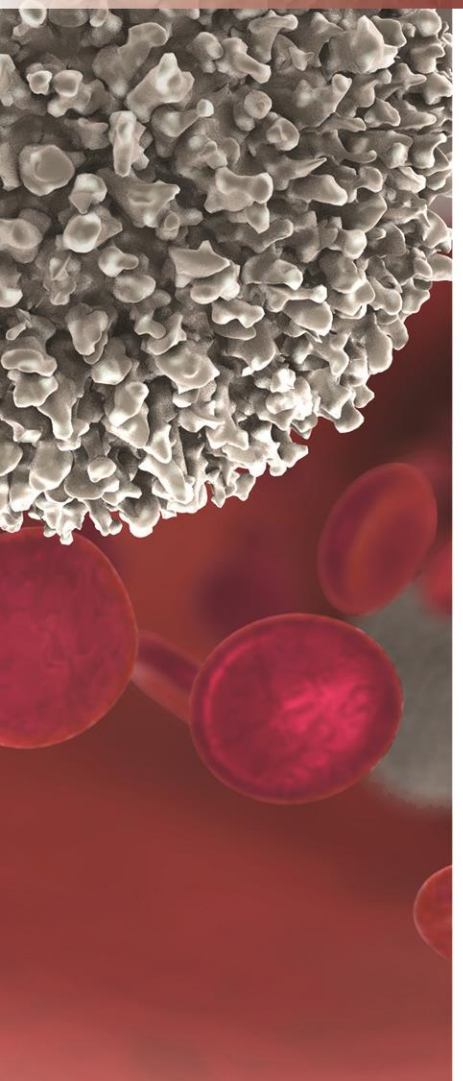


Learning Objectives

- **Describe** the efficacy and safety of JAK2 inhibitors in myelofibrosis
- **Identify** patients with myelofibrosis who may be failing initial ruxolitinib therapy
- **Discuss** clinical data supporting the use of fedratinib and/or other therapies in patients with myelofibrosis experiencing ruxolitinib failure
- **Develop** a treatment plan for a patient with myelofibrosis who has failed initial ruxolitinib therapy

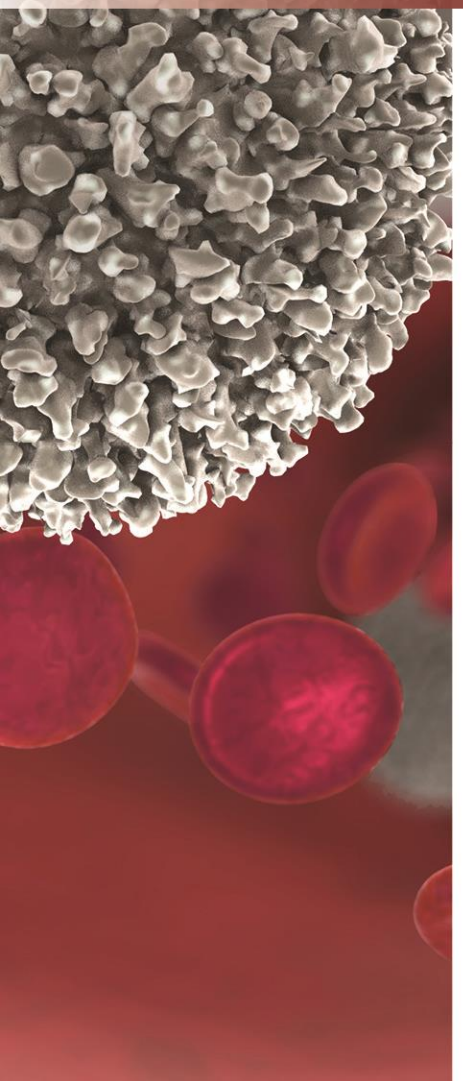
Introduction to Myelofibrosis (MF)



- Myeloproliferative neoplasm (MPN)
- Epidemiology
  - Rare, prevalence 1.76-4.05/100,000 people
  - Male > Female, median age 70 years
- Biological features
  - Clonal megakaryocytic and myeloid proliferation
  - Reticulin and collagen fibrosis → marrow destruction
  - Extramedullary hematopoiesis, neoangiogenesis
  - Osteosclerosis
  - Cytokine pathway activation, **chronic inflammation**

Garmezy B, et al. *Blood Rev*. 2021;45:100691.

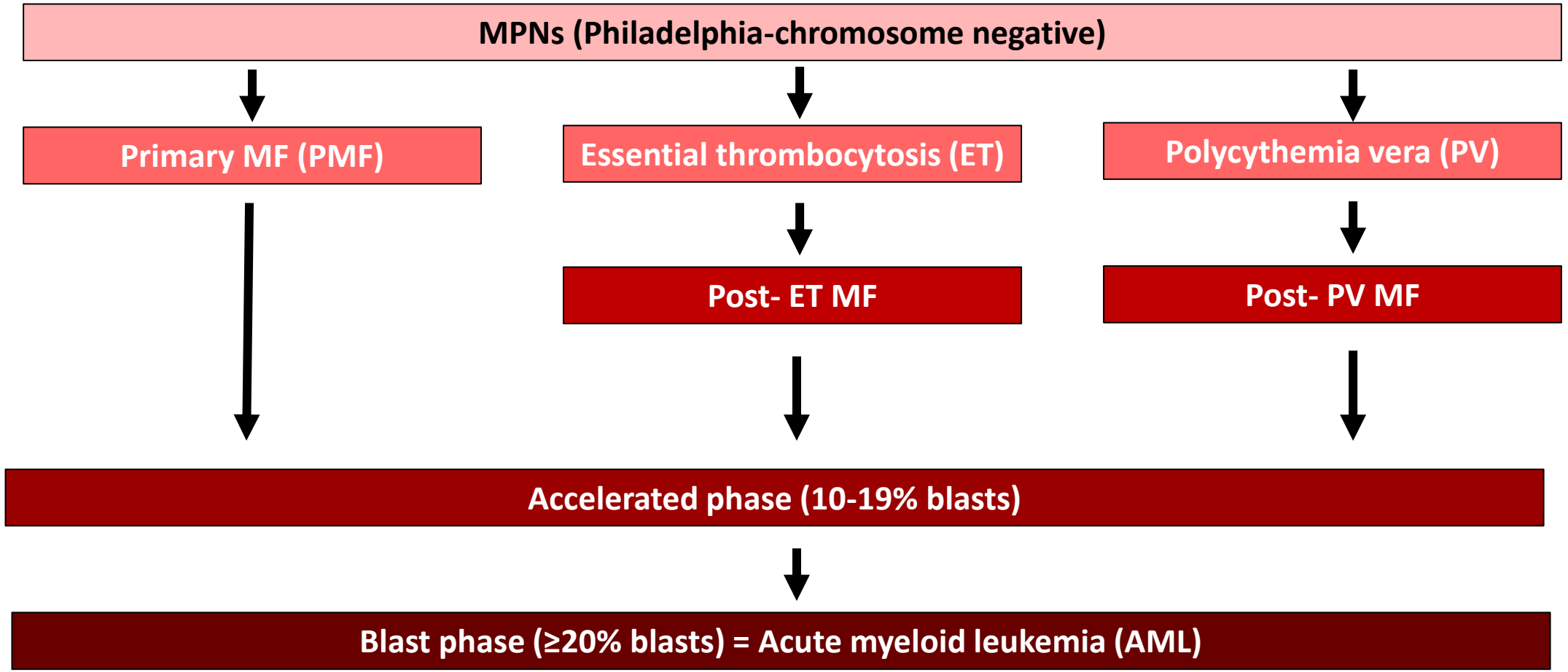
Introduction to MF



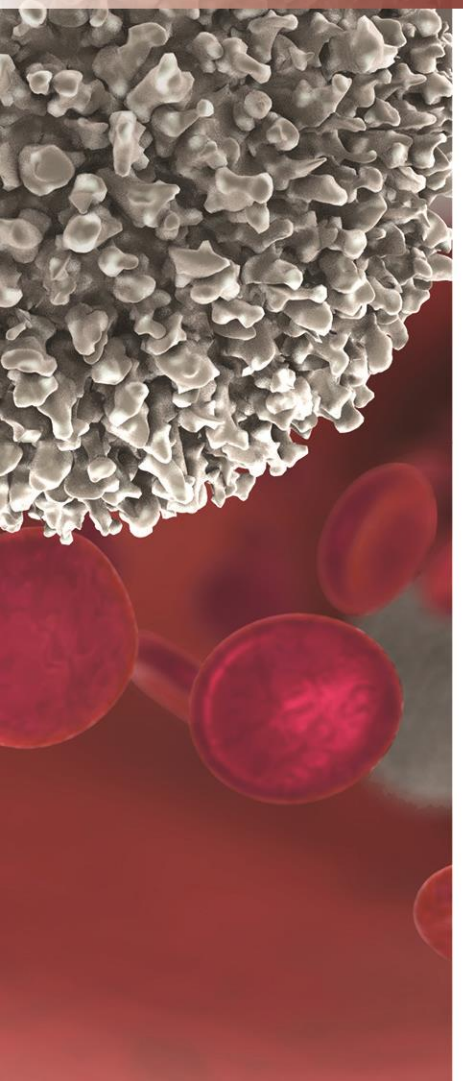
- Clinical manifestations
  - Inflammation → constitutional symptoms, thromboembolism
  - Marrow destruction → cytopenias → infections, bleeding, anemia
  - Extramedullary hematopoiesis → splenomegaly → portal hypertension
  - Leukocytosis
- Activating genetic mutations (mt)
  - *JAK2 V617F*, *MPL*, *CALR*: ~90% of patients (~10% “triple negative”)
  - Other mutations: *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*—poor prognosis
- Cytogenetic abnormalities (del 20q, del 13q, +8, others)

Garmezy B, et al. *Blood Rev*. 2021;45:100691.

Myeloproliferative Neoplasm (MPN) Classification



Garmezy B, et al. *Blood Rev*. 2021;45:100691.

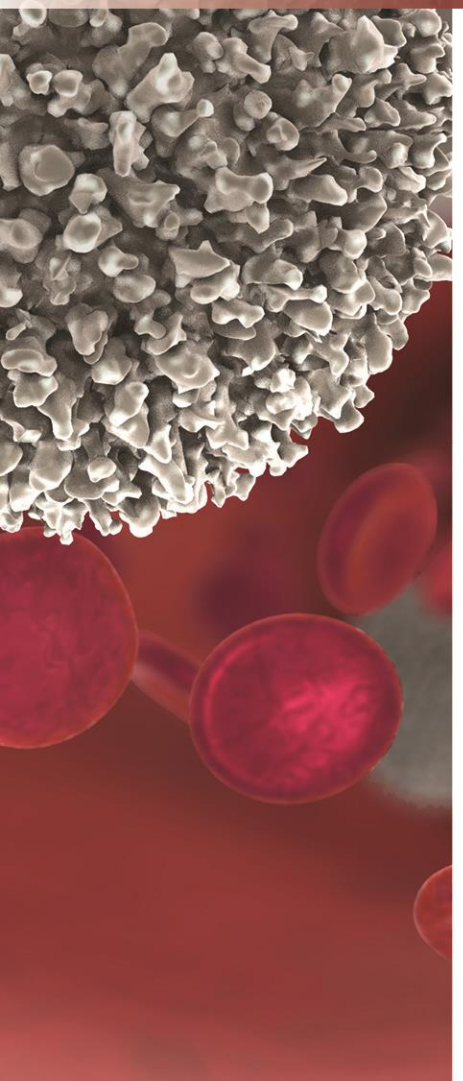


WHO PMF Diagnostic Criteria

- Requires 3 major and ≥1 minor criteria
  - Major
    - Megakaryocytic proliferation and atypia with reticulin and/or collagen fibrosis grades 2-3
    - Not meeting WHO criteria for another MPN or myeloid neoplasm
    - Presence of *JAK2*, *CALR*, or *MPL* mutation or another clonal marker or absence of minor reactive marrow fibrosis seen with infection or inflammation
  - Minor
    - Presence of ≥1 on 2 consecutive occasions: anemia not related to another cause, leukocytosis (≥11K/mm^3), palpable splenomegaly, elevated LDH, immature granulocytes + nucleated RBCs

LDH, lactose dehydrogenase; PMF, primary myelofibrosis; RBCs, red blood cells; WHO: Word Health Organization.

NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative Neoplasms, v1.2022.



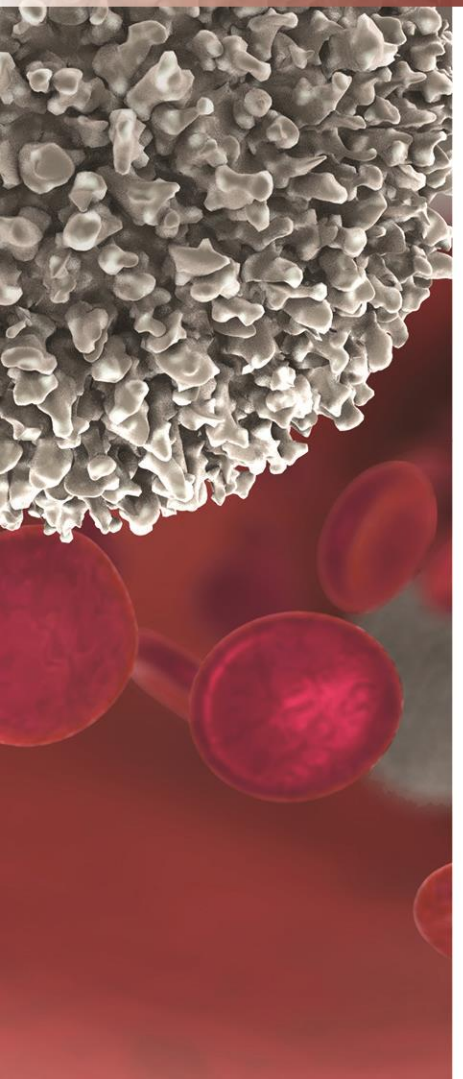
WHO Post-PV, Post-ET MF Diagnostic Criteria

- Prior PV or ET
- Grade 2-3 marrow fibrosis
- ≥2 of the following:
  - PV: anemia or sustained loss of phlebotomy requirement
  - ET: anemia + ≥2g/dL Hgb reduction
  - Leukoerythroblastic PB
  - New/worsening splenomegaly
  - ≥1 constitutional symptoms:
    - >10% weight loss in 6 mo, night sweats, unexplained fever >37.5°C

ET, essential thrombocytosis; Hgb, hemoglobin; mo, months;
PB, peripheral blood; PV, polycythemia vera.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

MF Clinical Presentation



- Fatigue
- Fevers
- Night sweats
- Unintentional weight loss
- Pruritus
- Abdominal pain
- Early satiety
- Bone pain
- Headaches

- Lead to reduced functional status, QOL, and ability to conduct ADLs

ADLs, activities of daily living; QOL, quality of life.

Harrison CN, et al. *Ann Hematol*. 2017;96(10):1653.
NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

Prognostics: DIPSS-Plus

Dynamic International Prognostic Scoring System (DIPSS)

Variable	0 point	1 point	2 points
Age (y)	≤65	>65	
WBC (K/mm^3)	≤25	>25	
Hemoglobin (g/dL)	≥10		<10
PB blasts (%)	<1	≥1	
Constitutional symptoms	No	Yes	

DIPSS score: Low (0), INT-1 (1-2), INT-2 (3-4), High (5-6).

Other scoring systems: MIPPS, MIPSS-70+, MYSEC-PM.

INT, intermediate; OS: overall survival; PB, peripheral blood; PLT, platelets; WBC, white blood cells.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.
Gangat N, et al. *J Clin Oncol*. 2011;29(4):392.

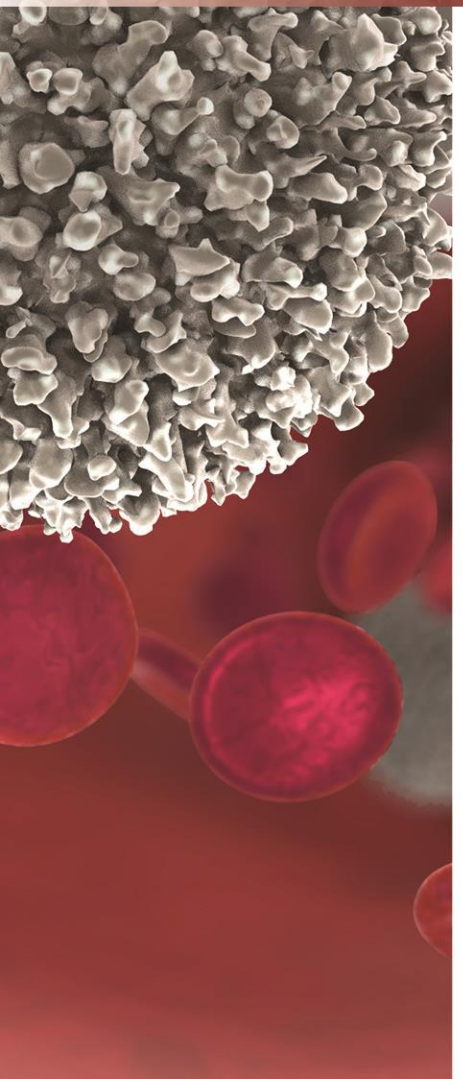
DIPSS-Plus

Variable	Points
DIPSS score • Low • INT-1 • INT-2 • High	 0 1 2 3
PLT <100K/mm^3	1
Transfusion dependent	1
Unfavorable karyotype*	1

Score	Low (0)	Int-1 (1)	Int-2 (2-3)	High (4-6)
OS (mo)	185	78	35	16

*Unfavorable: complex, sole or 2 abnormalities containing +8, -7/7q, q(17q), -5/5q, -12p, inv(3), 11q23 rearrangement.

Symptom Assessment: MPN-SAF TSS

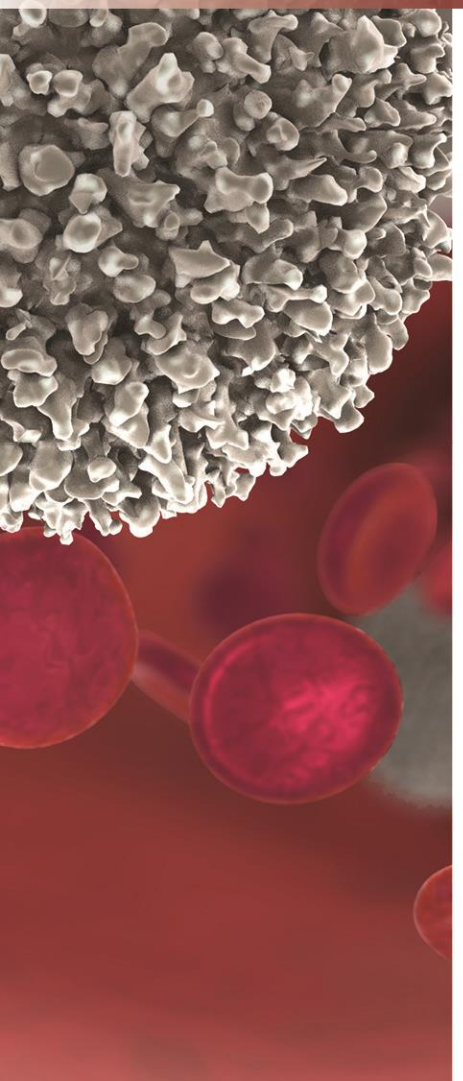


- **MPN-SAF TSS** = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
- Patient self-assessment
- Baseline and during treatment
- **Symptom response = ≥50% reduction in MPN-SAF**
- Score 0-10 (0 = symptom absent, 1 = favorable, 10 = unfavorable)
- Questions assess:

Early satiety	Abdominal discomfort
Inactivity	Problems w/concentration
Night sweats	Pruritus
Bone pain	Fever
Unintentional weight loss	Fatigue (via the brief fatigue inventory)

Scherber R, et al. *Blood.* 2011;118(2):401. Emanuel R, et al. *J Clin Oncol*. 2012;30(33):4098.
NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

Principles of MF Treatment



- Primarily palliative symptom management
- Low risk
  - Asymptomatic: active observation
- Supportive care
  - Pruritus: moisturizers, antihistamines, topical steroids
  - Bone pain: NSAIDs, antihistamines
  - Headache: aspirin, triptans
  - ESAs: anemia with EPO <500 mU/mL
  - G-CSF: neutropenia, recurrent infections; use cautiously
  - Antibiotic prophylaxis: recurrent infections, neutropenia, post splenectomy

EPO, erythropoietin; ESAs, erythropoiesis-stimulating agents; G-CSF, granulocyte-colony stimulating factor; NSAIDs, nonsteroidal anti-inflammatory drugs.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

Treatment Response Criteria

Response	Required Criteria
CR	**BM:** normocellular, <5% blasts, grade ≤1 fibrosis AND **PB:** Hgb ≥10 g/dL, neutrophils ≥1K/mm^3, PLT ≥100K/mm^3, <2% immature myeloid cells AND **Clinical:** asymptomatic, spleen/liver not palpable
PR	**BM:** as above OR **PB:** (as above) AND **Clinical:** asymptomatic, spleen/liver not palpable
Progression	New or worsening palpable splenomegaly OR leukemic transformation (BM blasts >20% or PB blasts >20% w/absolute blasts >1K/mm^3 for ≥2 wk
Stable	Belonging to none of the above

Not generally used (or helpful) for describing response to JAKi!

Response	Required Criteria
Clinical improvement	Anemia, spleen, or symptoms response without progression or worsening cytopenias
Anemia response	Transfusion independent: ≥2g/dL increase in Hgb Transfusion dependent: becoming transfusion independent
Spleen response	Reduction in spleen volume (see reference for detail)
Symptoms response	**≥50% reduction in MPN-SAF TSS**

Sometimes used for describing response to JAKi…

BM, bone marrow; CR, complete response; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PB, peripheral blood; PLT, platelets; PR, partial response.

Tefferi A, et al. *Blood*. 2013;122(8):1395.

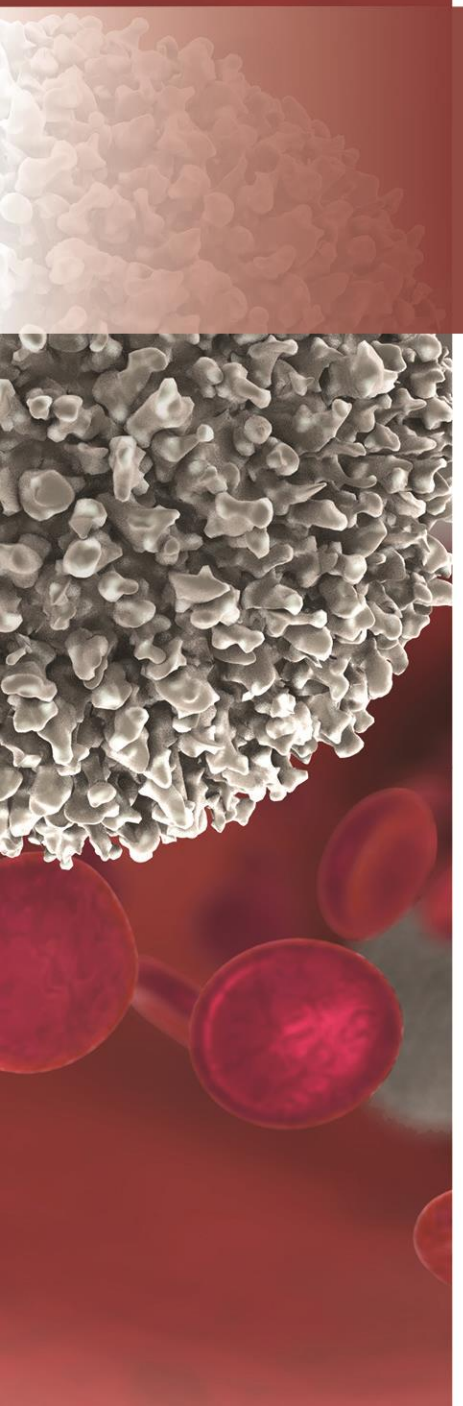
Cytogenetic and Molecular Response Criteria

Response	Required Criteria
Cytogenetic remission	CR: eradication of preexisting abnormality PR: ≥50% reduction in abnormal metaphases
Molecular remission	CR: eradication of preexisting abnormality PR: ≥50% reduction in allele burden
Cytogenetic/molecular relapse	Reemergence of preexisting cytogenetic or molecular abnormality

Not generally helpful for describing response to JAKi!

CR: complete response; JAK, Janus kinase; PR, partial response.

Tefferi A, et al. *Blood*. 2013;122(8):1395.



Treatment Response Criteria to JAK Inhibitors

- Clinical trials
  - Splenic volume reduction (SVR)
    - Assessed by CT or MRI in studies typically after 6-12 cycles (24-48 weeks)
    - General response threshold is SVR of ≥35%
    - SVR correlates with OS in some studies
  - Symptom response
    - ≥50% reduction in MF-SAF score after 6 cycles (24 weeks)
- Real world modifications
  - Often depends on the primary symptom that led to treatment
  - Spleen assessment more common with ultrasound/physical than CT/MRI
  - Significant clinical benefit can be observed w/o meeting formal response criteria
  - Molecular remissions are very rare

CT, computed tomography; MF-SAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; OS, overall survival; w/o, without.

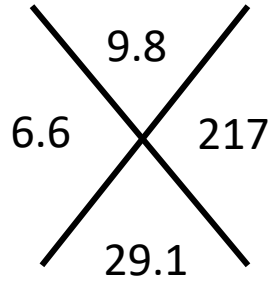
Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799.
Palandri F, et al. *Leuk Res*. 2018;74:86.
Gupta V, et al. *JCO Oncol Pract*. 2020;16(7):351.

Patient Case

AR is a 60-year-old patient who presents to clinic with a recent diagnosis of MF. They were found to be anemic on routine bloodwork. No nutritional etiology for anemia was identified. They were referred to a hematologist who completed a bone marrow biopsy:

- Grade 2 reticulin fibrosis, decreased red cell precursors, megakaryocytic proliferation, 2% blasts
- Nucleated red cells are noted on the smear but there are no blasts

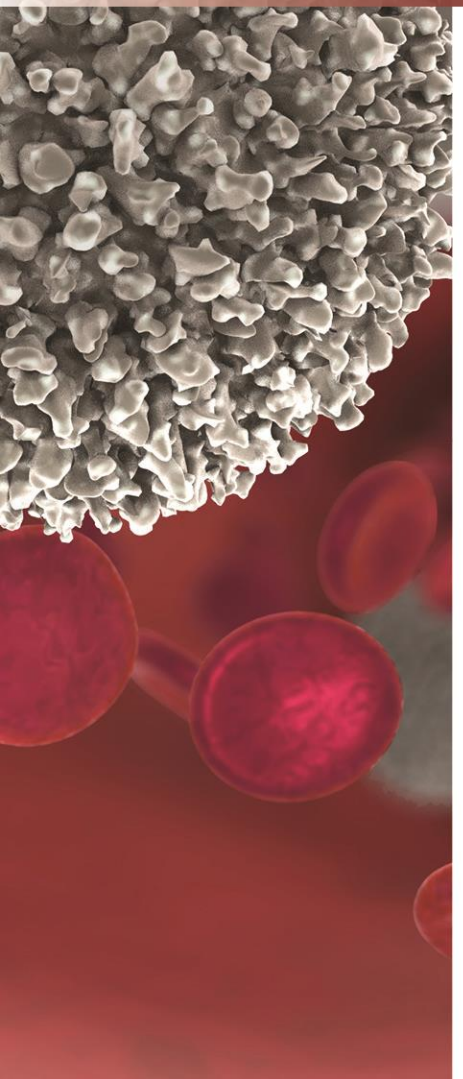
Labs today:



- Genetic sequencing identified a *JAK2 V617F* mutation
- The patient was found to have a normal male karyotype
- The patient had mild palpable splenomegaly on exam; 4 cm below the left coastal margin (LCM)
- The patient had no constitutional symptoms

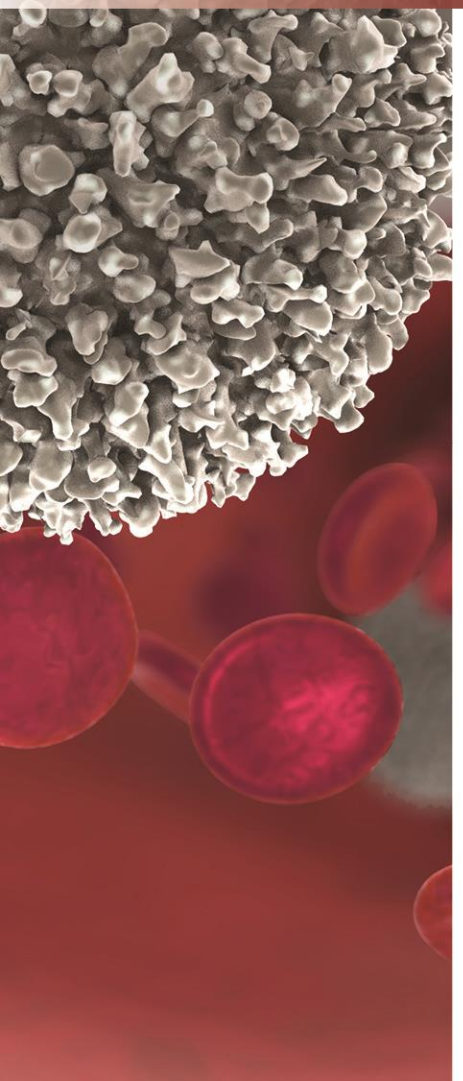
How should AR be treated at the current time?

MF Management: Lower Risk



- Asymptomatic: observation (or clinical trial)
- Symptomatic
  - Hydroxyurea
  - Peginterferon alfa-2a
  - Ruxolitinib (RUX, off-label)

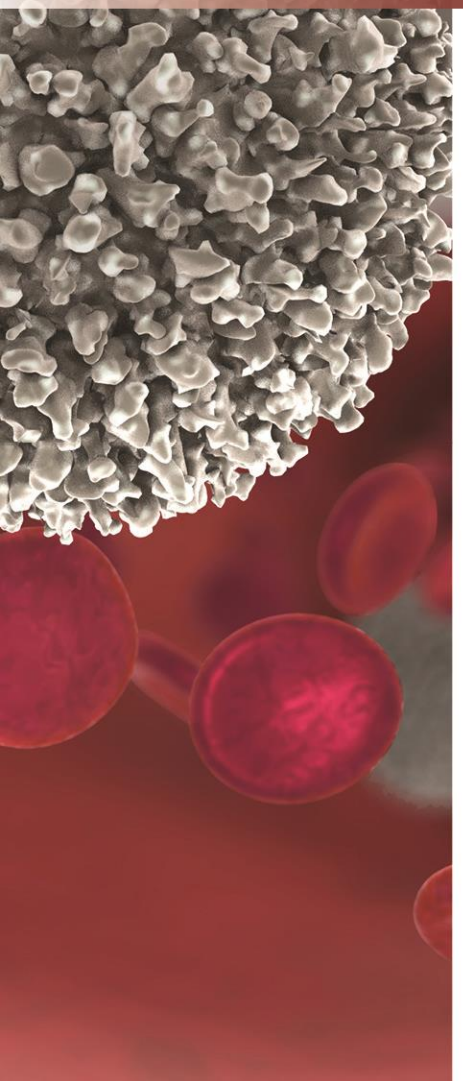
Hydroxyurea



- Ribonucleotide reductase inhibitor
- 500 mg PO daily, titrated to response/tolerability
- Observed improvement in bone pain (100%), constitutional symptoms (82%), pruritus (50%), splenomegaly (40%), anemia (12.5%)
- May also control leuko/thrombocytosis, reduce marrow fibrosis
- Tolerability concerns
  - Anemia worsened in 45%
  - Oral/leg ulcers in 12.5%
- Current role limited to cytoreduction, symptom palliation

Martinez-Trillos A, et al. *Ann Hematol*. 2010;89(12):1233.

Peginterferon Alfa-2a

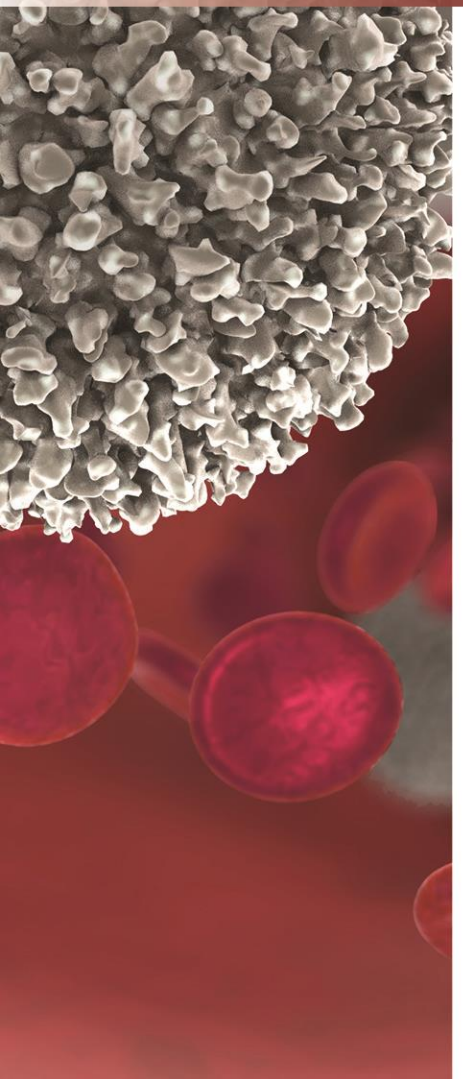


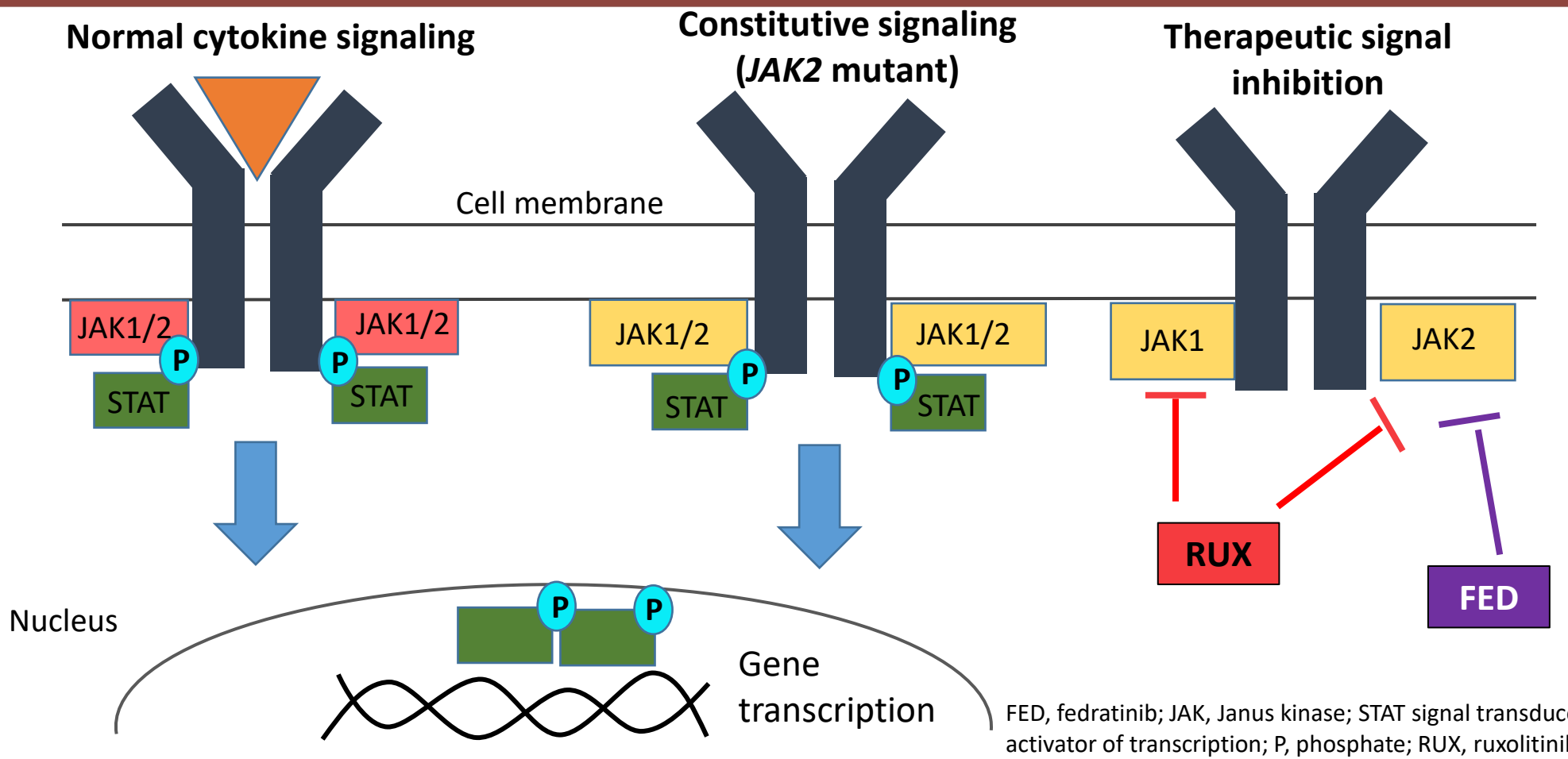
- Pro-apoptotic, antiproliferative, anti-angiogenic
- Mean starting dose: 107 mcg/week SC
- Improvement in:
  - Anemia (72% ORR, 64% CR), leukocytosis (69% ORR), thrombocytosis (83% ORR)
  - Splenomegaly (47% ORR), constitutional symptoms (82% ORR)
- Slow onset (4-9 months)
- May reduce marrow fibrosis and reduce *JAK2* allele burden
- Significant adverse effects
  - Neuropsychiatric (depression)
  - Flu-like symptoms, musculoskeletal pain

CR, complete response; ORR, overall response rate; SC, subcutaneous.

Ianotto JC, et al. *Br J Haematol*. 2013;162(6):783.

How JAK Inhibitors Work





FED, fedratinib; JAK, Janus kinase; STAT signal transducer and activator of transcription; P, phosphate; RUX, ruxolitinib.

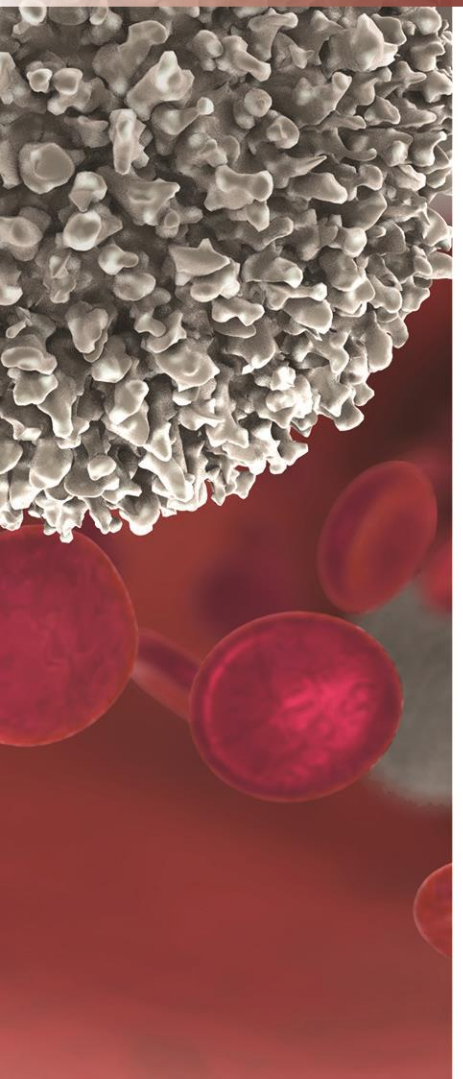
Ruxolitinib in Lower-Risk MF

	Low risk (n = 25)		INT-1 risk (n = 83)	
Parameter	**Pretreatment**	**Best Response**	**Pretreatment**	**Best Response**
Mod/sev splenomegaly, %	64	16	53	10
No/mild splenomegaly, %	8	60	44	85
Mod/sev fatigue, %	90	37	76	42
Toxicities				
Grade ≥3 PLT↓, %	12		6	
Grade ≥3 anemia, %	20		23	
Dose reduction, %	12		19	

Mod/sev, moderate/severe; INT-1, intermediate-1; PLT: platelets.

Davis KL, et al. *Adv Hematol*. 2015;2015:848473.

Ruxolitinib in Lower-Risk MF

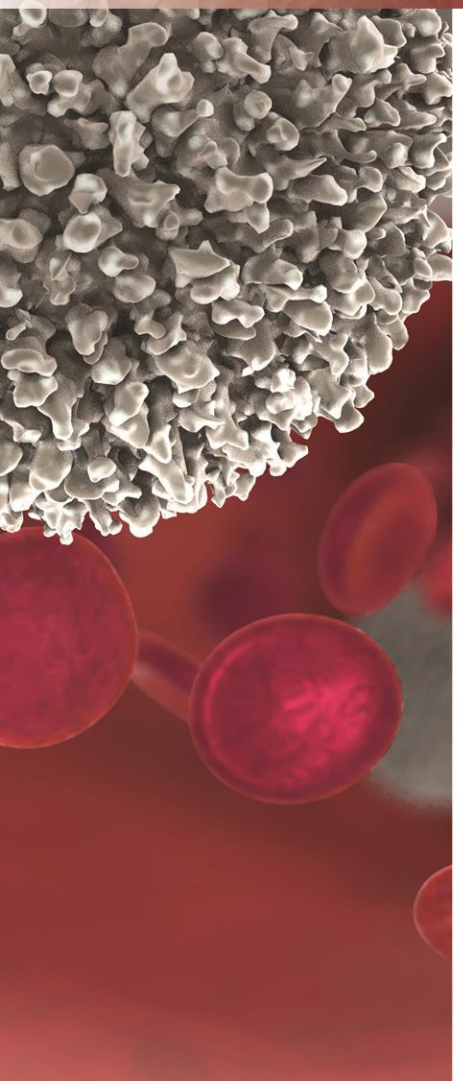


- INT-1, n = 70, RUX ≥10 mg PO BID for all patients (~70% 20 mg BID)
- Efficacy
  - Spleen response: 54.7%
  - Symptoms response: 80%
  - 2-year OS 80.1%, median OS 56.7 mo
- Toxicity
  - Grade ≥3 anemia 21.7%, thrombocytopenia 2.9%
  - Grade ≥2 infection: 15.9%
  - 17.1% discontinuation
  - 80.6% maintained dose of ≥15 mg BID, only 7.5% reduced to <10 mg BID

INT-1, intermediate-1; RUX, ruxolitinib.

Palandri F, et al. *Hematol Oncol*. 2018;36(1):285.

Anemia Management



- Transfusions
- Check, replete iron, B12, folate
- Check serum erythropoietin level
  - <500 mU/mL: ESA
  - ≥500 mU/mL:
    - Danazol
    - IMiD +/- prednisone
    - Luspatercept
    - Clinical trial
- Momelotinib? (investigational)

ESA, erythropoiesis-stimulating agent; IMiD, immunomodulatory agent.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

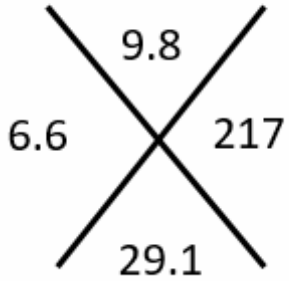
Patient Case

AR: mild splenomegaly, no constitutional symptoms. Has anemia, *JAK2 V617F* mutation (+), 2% blasts, normal karyotype.

How should AR be treated at the current time?

A. Ruxolitinib 20 mg PO BID
B. Peginterferon alfa-2a SC
C. Epoetin-alfa IV if EPO <500 IU/mL
D. Fedratinib 400 mg PO daily

Labs today:



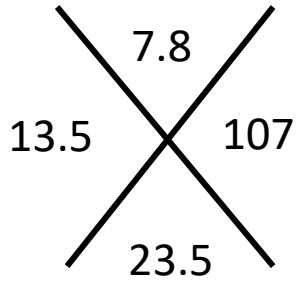
IV, intravenous; SC, subcutaneous.

Patient Case

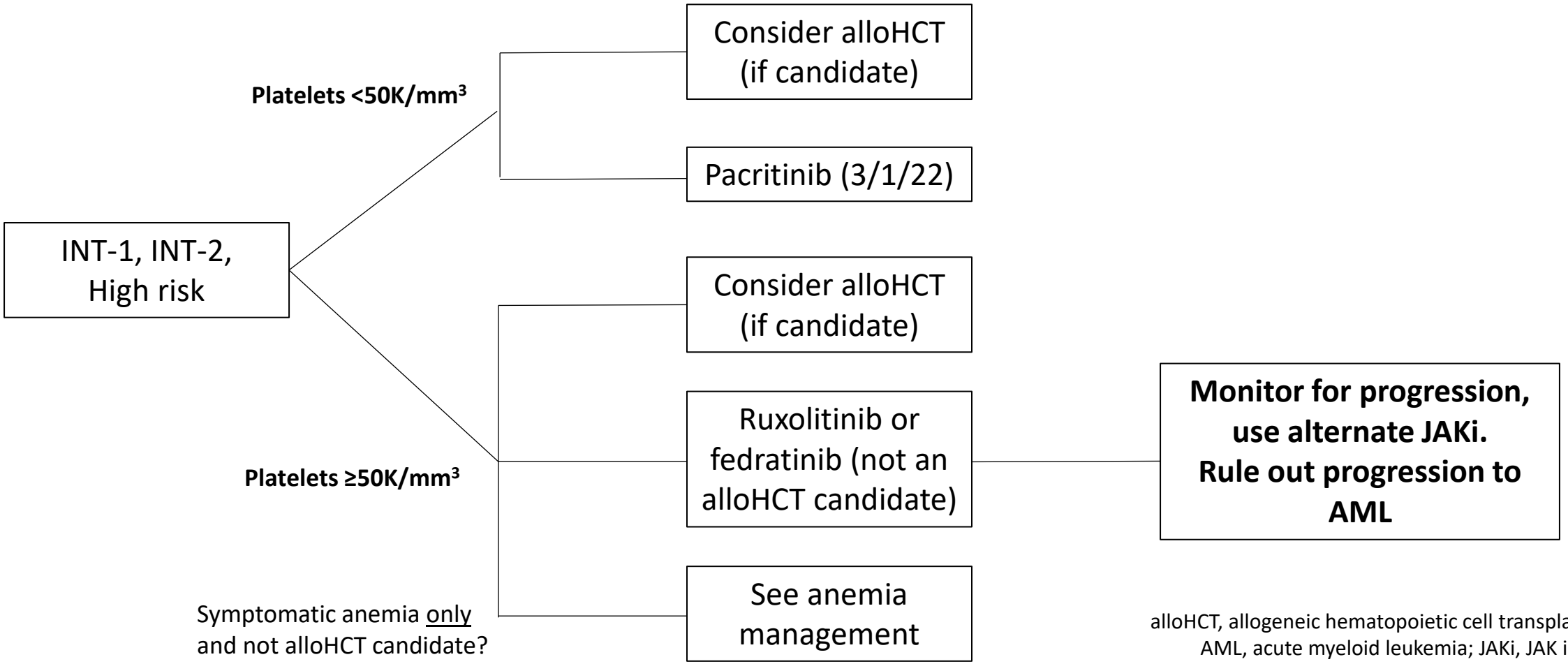
AR is started on the therapy you recommended. They return to clinic years later, now at 66 years old, describing weight loss, poor appetite, persistent pruritus, and progressive fatigue.

- A repeat bone marrow biopsy shows grade 3 reticulin fibrosis and 3% blasts
- They have new splenomegaly on physical exam, palpable >5 cm below left costal margin

Labs today:



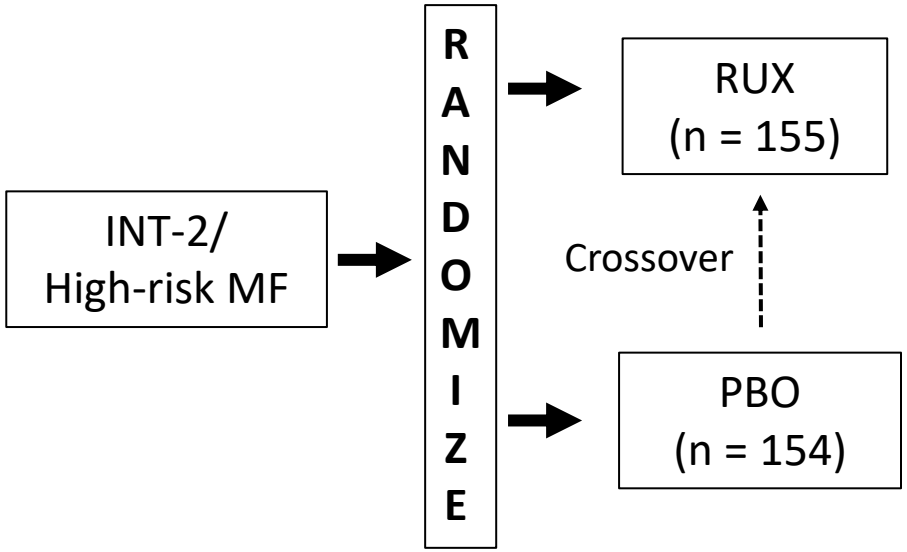
MF Management: Higher Risk



alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; JAKi, JAK inhibitor.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

RUX in INT-2/High-Risk MF: COMFORT-1



Key inclusion criteria/baseline characteristics:

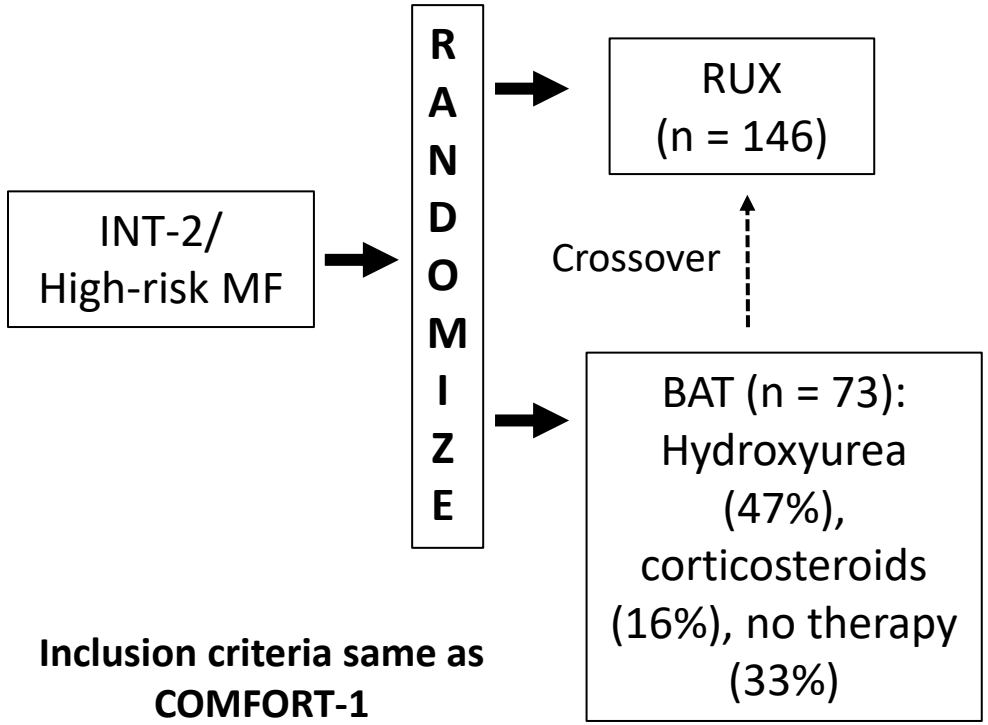
- PLT >100K/mm^3
- IPPS-INT-2 (38%)/High (61%)

Outcome	RUX	PBO
≥35% SVR at 24 wk, %	42	0.7
	OR 134.4, *P* < .001	
≥50% MF-SAF TSS ↓ at 24 wk, %	46	5
	OR 15.3, *P* < .001	
TSS change, median %	-56	+42
Treatment discontinuation due to AE, %	11	10.6
Grade ≥3, %:		
• Anemia	45.2	19.2
• Thrombocytopenia	12.9	1.3

AE, adverse event; ↓: decrease; IPPS-INT-2, International Prognostic Scoring System intermediate-2; MF-SAF TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score; OR, odds ratio; PBO, placebo; PLT, platelets; RUX, ruxolitinib; SVR, splenic volume reduction.

Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799.

RUX vs BAT in INT-2/High-Risk MF: COMFORT-2



Inclusion criteria same as COMFORT-1

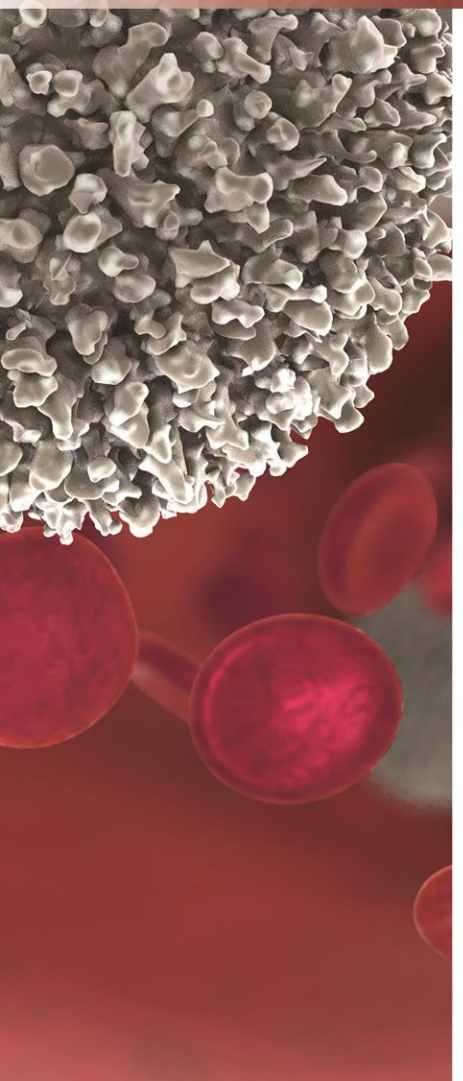
Outcome	RUX*	BAT
≥35% SVR, % • At 24 wk (*P* < .001) • At 48 wk (*P* < .001)	 32 28	 0 0
Change in spleen length at 48 wk, %	-56	+4
Treatment discontinuation due to AE, %	8	5

*QOL improved due to symptom improvement on several scales in the RUX group.

AE, adverse event; BAT, best available therapy; INT-2, intermediate-2; QOL, quality of life; RUX, ruxolitinib; SVR, splenic volume reduction.

Harrison C, et al. *N Engl J Med*. 2012;366(9):787-98.

Modified RUX Dosing to Limit Cytopenias

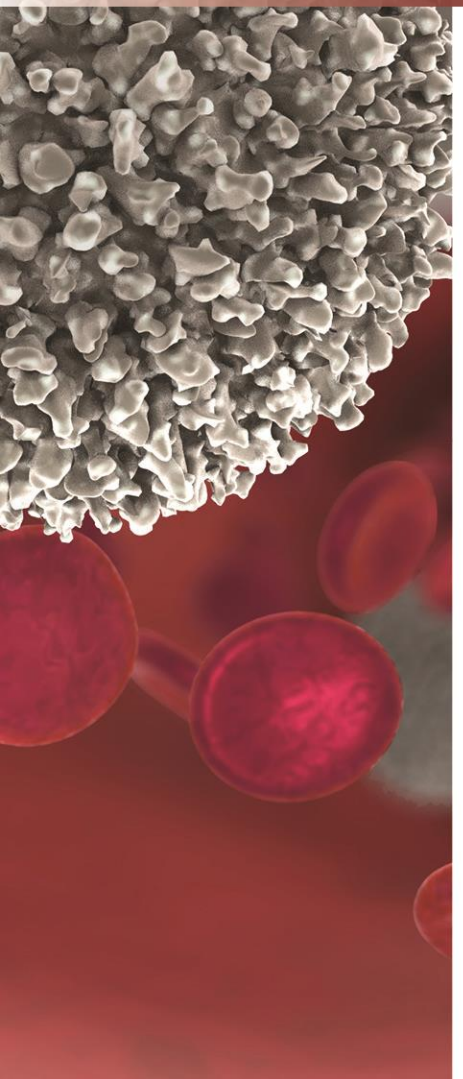


- Aim: preserve clinical benefit but reduce early cytopenias
- 10 mg BID, increase by 5 mg BID at weeks 12-18 (if lack of efficacy), max 20 mg BID
- Inclusion criteria: Hgb >6.5 g/dL, PLT >100K/mm^3
- Results: N = 45, 69% INT-1
  - SVR at 24 wk, median: -17.3%; ≥35% SVR at 24 wk: 15.6%
  - Week 24 TSS change, median: -45.6 %
  - Efficacy outcomes showed dose-response
  - Grade ≥3 anemia: 20%

TSS, total symptom score.

Talpaz, M et al. *J Hematol Oncol*. 2018;11(1):101.

How to Use Ruxolitinib



- FDA approval: INT/high-risk MF
- Taper dose cautiously to avoid withdrawal symptoms/MF flare
- Starting dose based on PLT
  - **PLT <50K/mm^3: not indicated;** 50-99K/mm^3: 5 mg BID
  - 100-200K/mm^3: 15 mg BID; >200K/mm^3: 20 mg BID
  - Renal dose adjustment if PLT <150K/mm^3 AND CrCl <60 mL/min
- Increase Q4W in 5-mg increments if insufficient response (max 10 mg BID if PLT <100K/mm^3, 25 mg BID if >100K/mm^3). Discontinue if no improvement/response at 6 months
- Toxicities
  - Myelosuppression, hyperlipidemia, diarrhea,
  - Major adverse cardiac events, TB (screen if high risk)
  - Hepatitis B reactivation, PML, zoster infections, nonmelanoma skin cancers, other secondary malignancies

CrCl, creatinine clearance; PML, progressive multifocal leukoencephalopathy; Q4W, every 4 weeks; TB, tuberculosis.

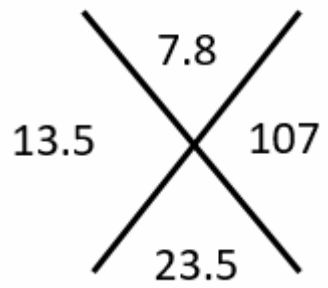
NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.
Jakafi (ruxolitinib) package insert. Incyte Corp; 2021.

Patient Case

AR is not deemed to be a suitable candidate for alloHCT at this time due to lack of a suitable donor.

DIPSS = 4; INT-2

Labs today:



How should AR be treated at the current time?

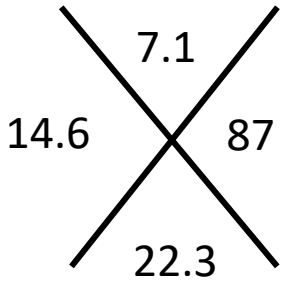
A. Active surveillance
B. Pacritinib 400 mg PO BID
C. Hydroxyurea 500 mg PO BID
D. Ruxolitinib 15 mg PO BID

Patient Case

AR is started on therapy and continues it for 2 years with improved splenomegaly (at best: 25% SVR on imaging). AR gains back 20 pounds and pruritus resolves.

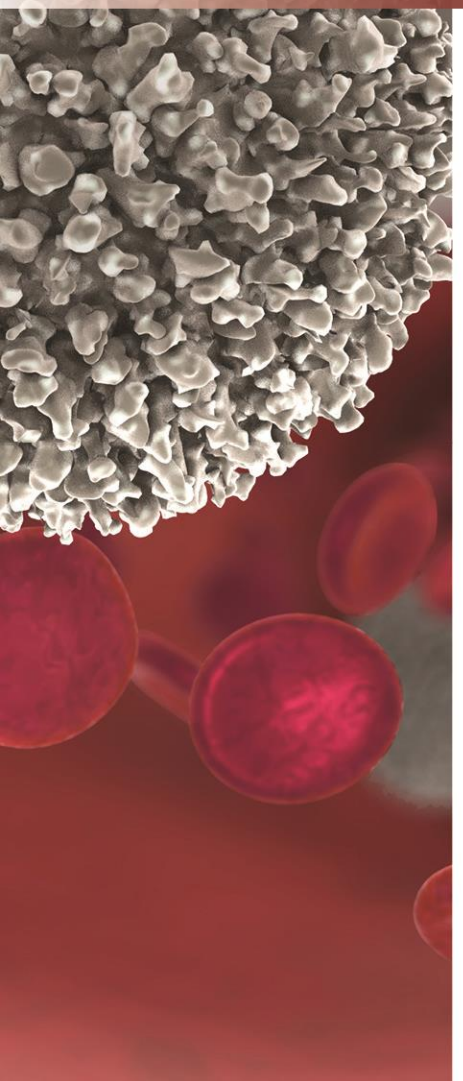
At age 68, AR is referred back to the hematology clinic with increased abdominal fullness and pain, fatigue, lower extremity swelling, weight loss, and worsened splenomegaly (now palpable >8 cm below LCM, 60% increased in size on imaging). Patient does not report missing any doses of MF medication.

Labs today:



A repeat bone marrow biopsy shows grade 3 reticulin fibrosis and 5% blasts and still has a *JAK2 V617F* mutation. AR now has a -5q karyotype.

Limitations With Ruxolitinib



- Efficacy:
  - Most patients do NOT meet COMFORT-1/2 endpoints
  - Limited disease-modifying effect
  - Median duration of spleen response ~3 years
  - At 5 years, only ~25% remain on treatment
  - Not curative, symptoms rapidly recur upon discontinuation, risk of withdrawal
- Toxicity:
  - Less efficacious when PLT <100K/mm^3 due to need for dose reduction
  - Not indicated when PLT <50K/mm^3
  - Clinically significant cytopenias, gradual onset of effect
  - High discontinuation rates long term

Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799.
Harrison C, et al. *N Engl J Med*. 2012;366(9):787.
Cervantes F, et al. *Blood*. 2017;129(7):832.
Talpaz M, et al. *J Hematol Oncol*. 2013;6(1)81.
Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55.

Life After RUX (1)

- Median RUX exposure 17.5 mo, median OS 13.2 mo
- 41% discontinuation at 3 years, due to:
  - Lack of/loss of spleen response (23%, 12%)
  - BP progression (23%), alloHCT (5%)
  - Anemia (10.5%), thrombocytopenia (7%)
- Characteristics associated with discontinuation
  - INT-2/High DIPSS
  - Transfusion dependent
  - PLT <100K/mm^3
  - Unfavorable karyotype
  - Peripheral blasts
    - 1-5%: 43% discontinuation at 2 years; 6-9%: 62%

OS by reason for RUX discontinuation:

- Loss of spleen response: 32.4 mo
- Lack of spleen response: 27.9 mo
- RUX AE: 13.2 mo
- BP progression: 3.9 mo
- Non-RUX AE: 3.6 mo

alloHCT, allogeneic hematopoietic cell transplantation; BP, blast phase; DIPSS, Dynamic International Prognostic Scoring System; OS, overall survival.

Palandri F, et al. *Cancer*. 2020;126(6):1243.

Life After RUX (2)

- 38% discontinued due to cytopenias (anemia 33%), median 3.8 mo
  - alloHCT: 16%, lack of response: 14%, AML: 13%, progressive symptoms: 11%
    - Progressive symptoms: median discontinuation 21 mo
    - Primary refractory: 5 mo
  - Hgb <10 g/dL and PLT <100K/mm^3 at initiation predicted discontinuation due to cytopenias
    - ~50% for anemia, ~60% for thrombocytopenia, discontinued at ~3 mo
- Salvage therapy ORR: 26%, mostly with IMiDs
- mOS post RUX discontinuation: 13 mo

alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; IMiDs, immunomodulatory agents; mOS, median overall survival; ORR, overall response rate.

Kuykendall AT, et al. *Ann Hematol*. 2018;97(3):435.

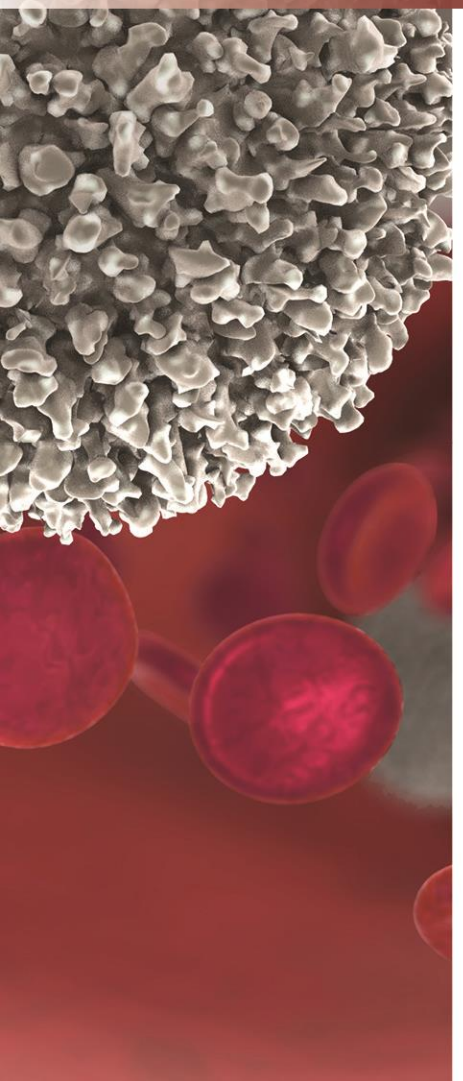
Proposed Definitions of RUX Failure

Pattern of Failure	Definition
Suboptimal spleen response	<25% ↓ in palpable spleen length after ≥3 mo optimally dosed JAKi
Loss of spleen response	≥50% ↑ in spleen length from best response
Transfusion-dependent anemia	≥4 units of RBC in 8 wk occurring ≥6 mo from RUX initiation
Severe thrombocytopenia	Unable to maintain unsupported PLT >25K/mm^3 (>35-50K/mm^3 if on anticoagulation)
Suboptimal symptom response	<50% ↓ in MF-SAF TSS after 3 mo of optimally dosed JAKi
Loss of symptom response	≥50% ↑ in MF-SAF TSS from best response
AP/BP transformation	
Second cancers	
Infections	

AP/BP, accelerated/blast phase; ↑/↓, increase/decrease; JAKi, JAK inhibitor; MF-SAF, Myelofibrosis Symptom Assessment Form Total Symptom Score; RBC, red blood cell.

Gupta V, et al. *JCO Oncol Pract*. 2020;16(7):351.
Mesa RA. *JCO Oncol Pract*. 2020;16(7):361.

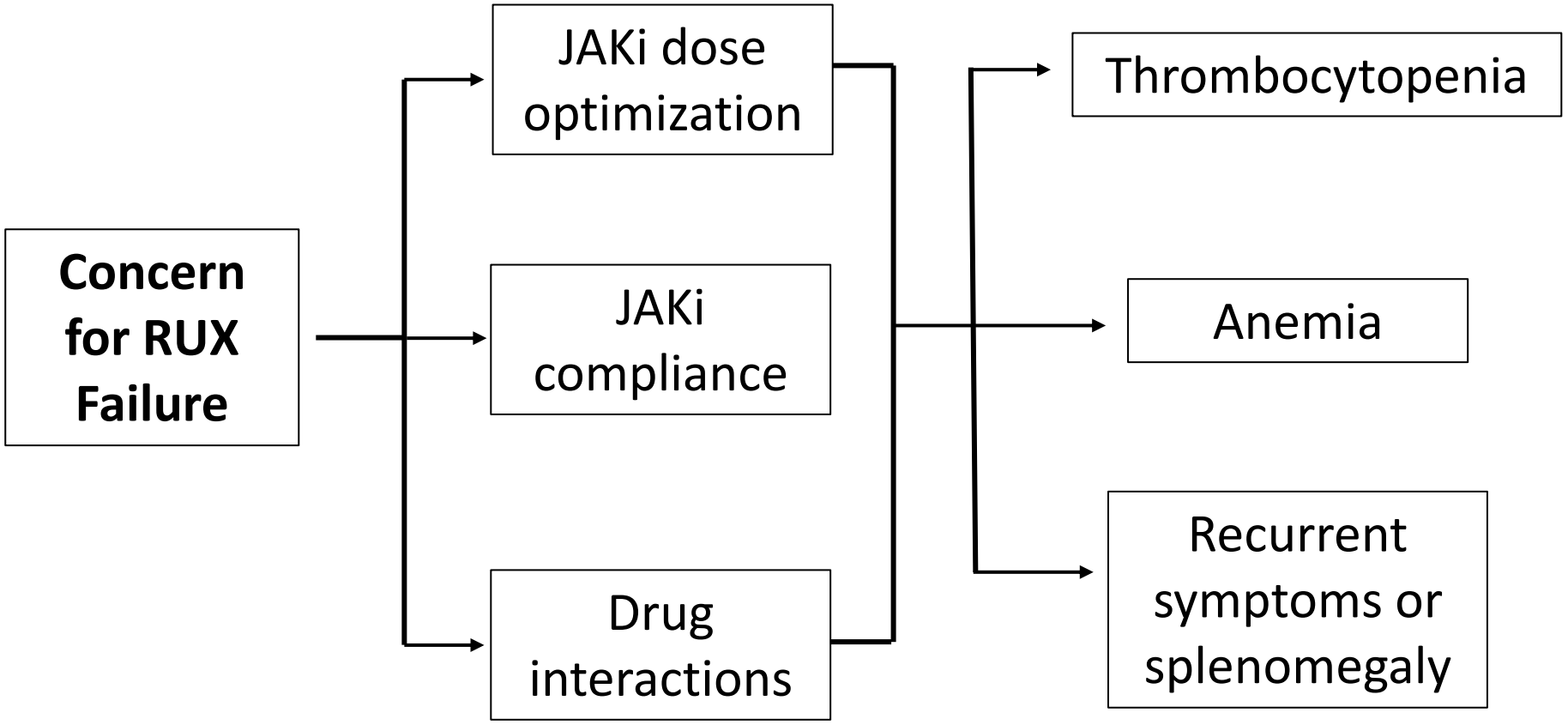
Proposed Definitions of JAKi Failure (IMBARK)



- Worsening splenomegaly-related abdominal pain at anytime following JAKi start AND either:
  - No reduction in spleen volume/size after 12 wk of JAKi (refractory) OR
  - Worsening splenomegaly at any time after the start of JAKi after an initial response, as documented by:
    - Increased spleen volume from nadir by 25% (by MRI or CT) OR
    - Increase in spleen size by palpation
- Patients with only JAKi intolerance were not included

Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881.

Investigating RUX Failure



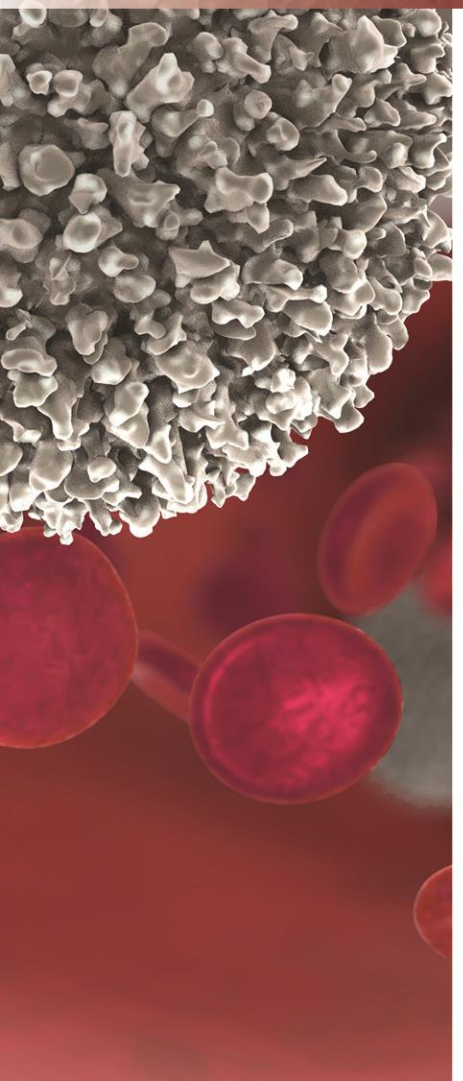
<u>Cytopenias</u>:

Early: JAKi dose reduction

Late: Concern for MF progression

Gupta V, et al. *JCO Oncol Pract*. 2020;16(7):351.
Pardanani A, Tefferi A. *Blood*. 2018;132(5):492.

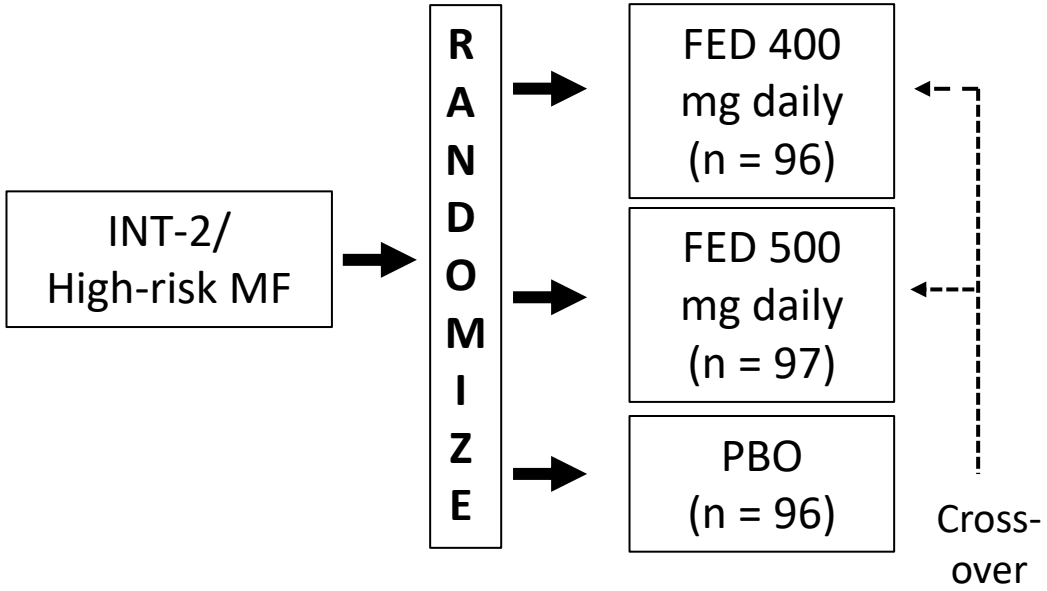
Options for RUX Failure



- RUX rechallenge
- Fedratinib (FED)
- Pacritinib (PAC; if PLT <50K/mm^3)
- Investigational: Momelotinib (MOM; if significant anemia?)
- alloHCT
- Splenectomy
- Splenic radiation
- Clinical trial

Gupta V, et al. *JCO Oncol Pract*. 2020;16:351.

FED in INT-2/High-Risk MF: JAKARTA



Outcome	FED 400	FED 500	PBO
≥35% SVR at 24 wk, %	36*	40*	1
≥50% MF-SAF TSS ↓ at 24 wk, %	36*	34*	7
Treatment discontinuation due to AEs, %	14	25	8
Grade ≥3, %:			
• Anemia	43	60	25
• Thrombocytopenia	17	27	9

*P < .001 vs PBO.

Key inclusion criteria/baseline characteristics:

- IPPS INT-2 (52%)/High (48%)
- **PLT >50K/mm³**
- **No prior JAKi therapy**

Other key AEs included:

- GI toxicities
- Increased transaminases, amylase, lipase
- **Wernicke encephalopathy (WE; n = 4), led to study termination**

FED, fedratinib; GI, gastrointestinal; PBO, placebo.

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643.
Pardanani A, et al. *Br J Haematol*. 2021;195(2):244.

FED in MF Previously Treated With RUX: JAKARTA-2

- Single-arm, open-label, phase 2 trial
- Key inclusion criteria: PLT >50K/mm^3
- INT-1 (16%), INT-2 (48%), or High-risk (35%)
- RUX-resistant (66%)
  - Progression/loss of response = 44%
- RUX-intolerant (33%)
  - Hematologic toxicity = 24%
- Median prior RUX: 10 mo, 79% had ≥2 prior therapies
- Per protocol[1]: no formal definition of RUX resistant/intolerant/refractory

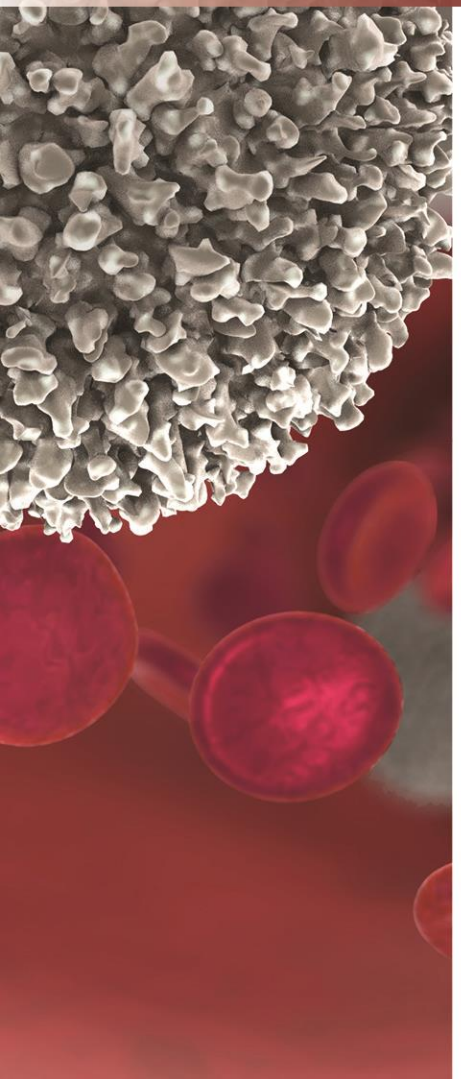
Outcome	FED 400 (N = 83)
≥35% SVR at 24 wk, % (per protocol)[1]	55
≥35% SVR at 24 wk, % (stringent criteria)[2]	30
≥50% MF-SAF TSS ↓ at 24 wk, % (per protocol)[1]	26
Treatment discontinuation due to AEs, % (per protocol)[1]	19
Grade ≥3, % (per protocol)[1]: • Anemia • Thrombocytopenia	 38 22

Study terminated early. Primary endpoint had last observation carried forward if 24-wk assessment missing.[1]
N = 81 received thiamine supplementation, no cases of WE observed.

WE, Wernicke encephalopathy.

1. Harrison CN, et al. *Lancet Haematol*. 2017;4(7):e314.
2. Harrison CN, et al. *Am J Hematol*. 2020;95(6):594.

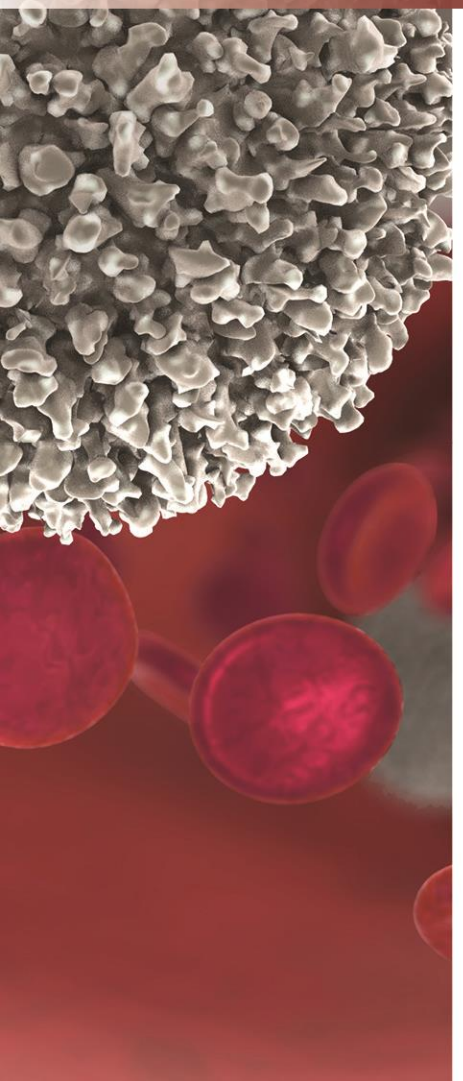
Stringent Criteria Cohort of JAKARTA-2



- **Relapsed**: RUX ≥3 mo with spleen regrowth (<10% SVR or <30% decrease in spleen size from baseline following an initial response) *(19% of study cohort)*
- **Refractory**: RUX ≥3 mo with <10% SVR or <30% decrease in spleen size from baseline *(48% of study cohort)*
- **Intolerant**: RUX ≥28 days complicated by RBC transfusion requirement (≥2 units/mo x 2 mo), grade ≥3 thrombocytopenia, anemia, hematoma, and/or hemorrhage while on RUX *(14% of study cohort)*

Harrison CN, et al. *Am J Hematol*. 2020;95(6):594.

How to Use Fedratinib

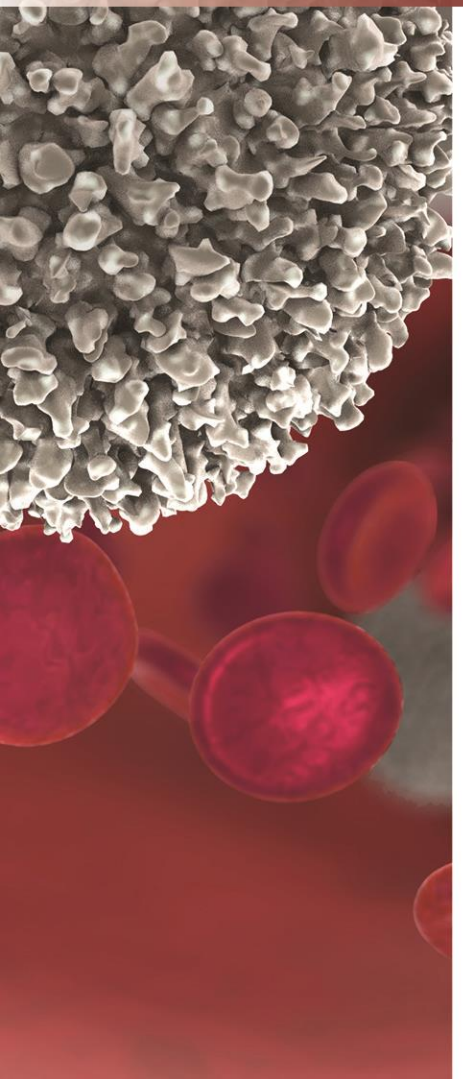


- FDA approval: INT-2/High-risk MF
- WE: thiamine level, replete if low prior to starting
  - 8/670 developed *potential* WE (2 *likely*, 1 *confirmed*)
- 400 mg PO daily if PLT ≥50K/mm^3
- Reduce to 200 mg daily if strong CYP3A4 inhibitors
- Reduce to 200 mg daily if CrCl <30 mL/min
- Toxicities
  - Myelosuppression, hepatotoxicity, nausea/vomiting, elevated pancreatic enzymes
  - Major cardiac adverse events, secondary malignancies

WE, Wernicke encephalopathy.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.
Harrison CN, et al. *Blood*. 2017;130(supp l1):4197.

Fedratinib: Future Directions



- FREEDOM (NCT03755518)
  - FED in INT/High-risk MF previously treated with RUX (with concomitant luspatercept for subjects with anemia)
- FREEDOM-2 (NCT03952039)
  - FED vs BAT in INT/High-risk MF previously treated with RUX

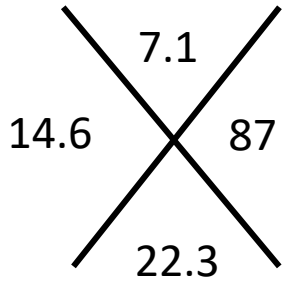
BAT, best available treatment.

NCT03755518, NCT03952039. www.clinicaltrials.gov.

Patient Case

AR is determined to have suffered from loss of splenic and symptom responses from prior therapy. They are slowly tapered off over 2 weeks. The patient is interested in pursing additional treatment but is not a candidate for alloHCT.

Labs today:



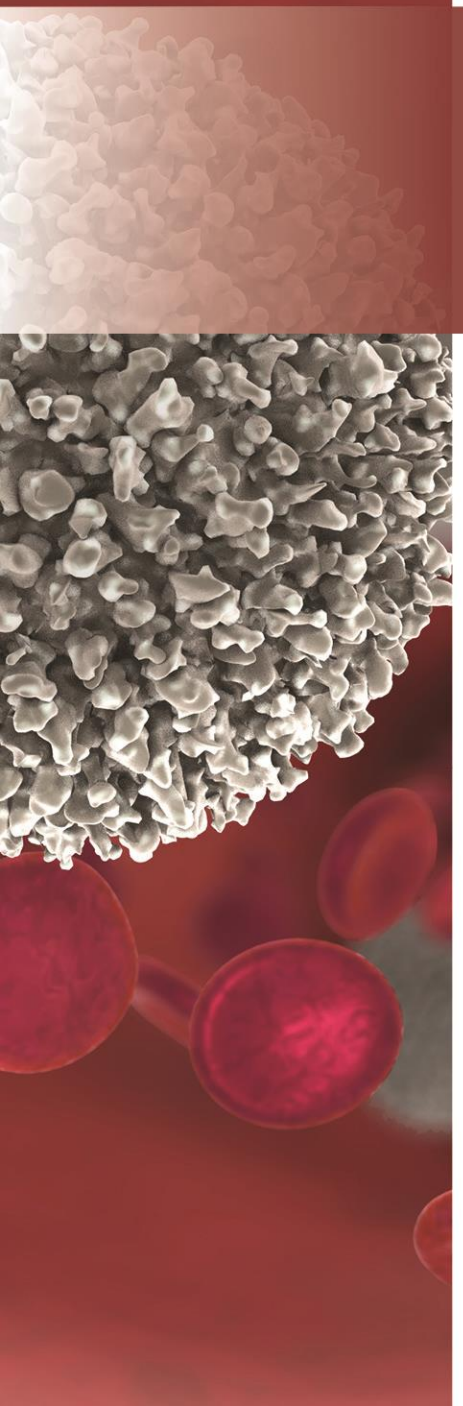
Which of the following would be the <u>most appropriate</u> treatment for AR at this time?

A. Danazol 600 mg PO daily

B. Pacritinib 200 mg PO BID

C. Hydroxyurea 500 mg PO daily

D. Fedratinib 400 mg PO daily



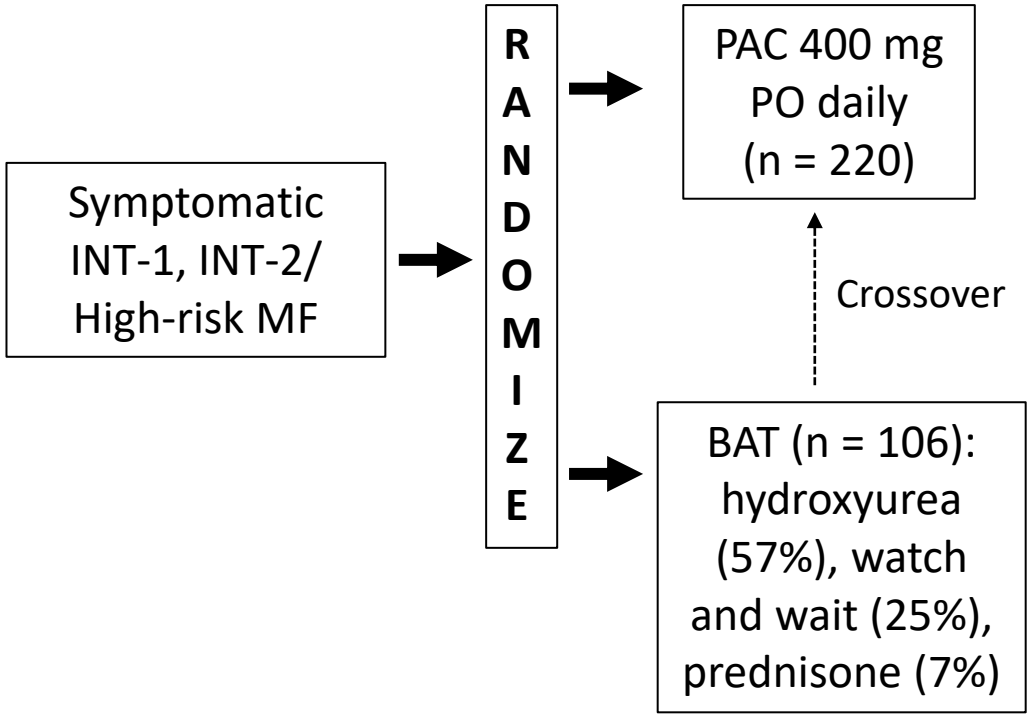
New JAK Inhibitors: Pacritinib and Momelotinib

- Pacritinib (PAC): JAK2 and FLT3 inhibitor
  - Also inhibits IRAK1
- Momelotinib (MOM): JAK1/2 inhibitor
  - Increases plasma iron bioavailability for erythropoiesis via inhibition of ACVR1-mediated hepatic expression of hepcidin

ACVR1, activin A receptor type 1; FLT3, fms-like tyrosine kinase 3; IRAK1, Iinterleukin-1 receptor-associated kinase 1.

Mesa RA, et al. *Lancet Haematol*. 2017;4(5):e225.
Mesa RA, et al. *J Clin Oncol*. 2017;35(34):3844.

PAC vs BAT Irrespective of Cytopenias: PERSIST-1



Outcome	PAC	BAT	p
≥35% SVR at 24 wk, %	19	5	0.0003
≥50% MF-SAF TSS ↓ at 24 wk, %*	19	10	0.24
≥50% MF-SAF TSS ↓ at 48 wk, %*	15	0	0.0027
Transfusion dependent → independent, %	25	0	0.043
Grade ≥3, %: • Anemia • Thrombocytopenia	 17 12	 15 11	NR

*Evaluable population: PAC = 53, BAT = 36.

NR: not reported.

Key inclusion criteria/baseline characteristics:

- **No prior JAKi therapy**
- ***No exclusions for anemia/thrombocytopenia***
- **BAT excluded RUX**
- DIPPS-INT-1 (53%), INT-2 (32%), High (14%)

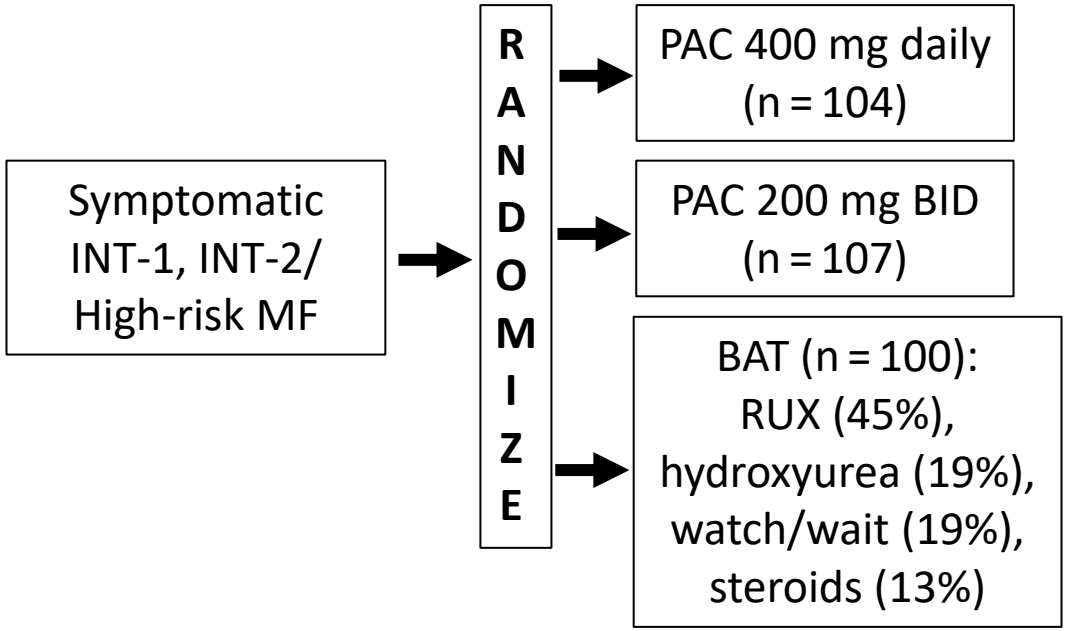
Baseline PLT count:

- PAC: 16% <50K/mm^3, 17% 50K-≤100K/mm^3
- BAT: 15% <50K/mm^3, 17% 50K-≤100K/mm^3

BAT, best available treatment; PAC, pacritinib.

Mesa RA, et al. *Lancet Haematol*. 2017;4(5):e225.

PAC vs BAT (Including RUX) in MF With Thrombocytopenia: PERSIST-2



Outcome	PAC QD (n = 75)	PAC BID (n = 74)	BAT (n = 72)
≥35% SVR at 24 wk, %*	15, *P* = .02	22, *P* = .01	3
≥50% MF-SAF TSS ↓ at 24 wk, %*	17, *P* = .65	32, *P* = .01	14
Symptom score change, median %	-27	-41	-15
Baseline PLT <50K/mm^3, %	51	42	44

*Each *P*-value compared to BAT.

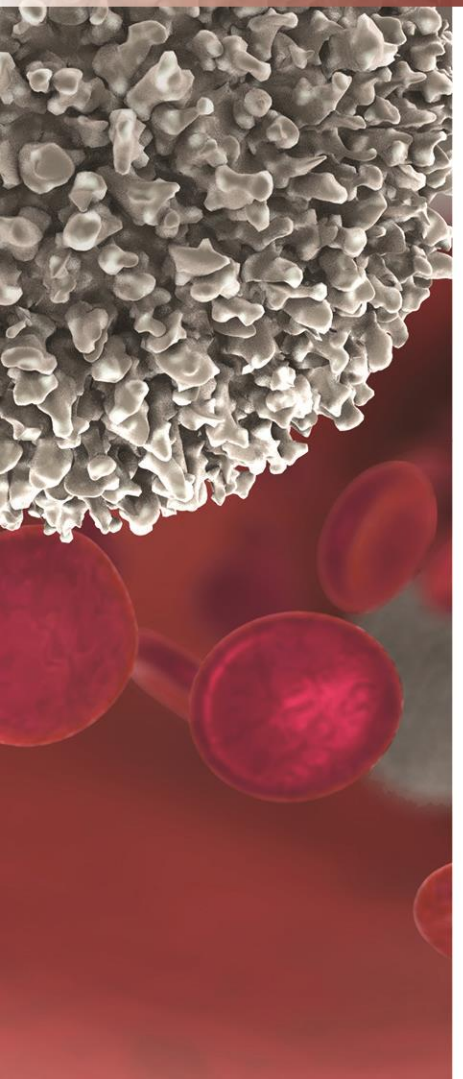
Key inclusion criteria/baseline characteristics:

- **Allowed 1-2 prior JAKi (prior RUX = 48%)**
- **PLT ≤100K/mm^3 was required**
- DIPPS-INT-1 (18%), INT-2 (52%), High (30%)

BAT, best available treatment; PAC, pacritinib.

Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652.

How to Use Pacritinib

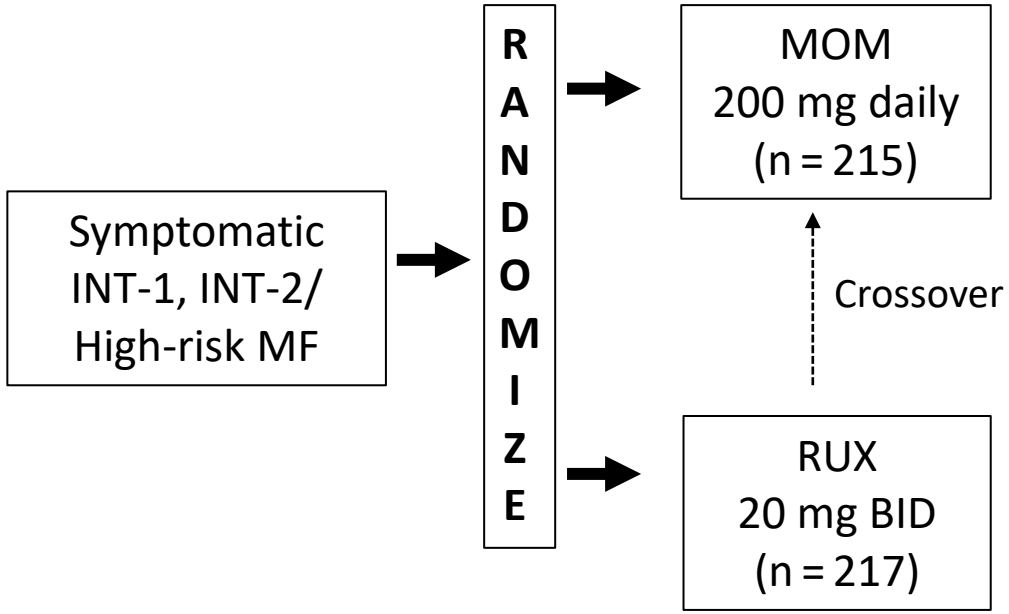


- Approved for MF **with PLT <50K/mm^3**, dosed 200 mg PO BID
- Diarrhea is common
  - Reduced w/BID vs daily dosing, use loperamide, hydration
  - Hold if grade ≥3
- Early trials placed on hold due to concern for cardiac, thrombotic events
  - PERSIST-1/2 showed no significant difference in these events between arms
- QTc prolongation, avoid if baseline >480 msec, hold if >500 msec
  - Correct hypokalemia
- Hold 7 days prior to procedures
- Avoid moderate CYP3A4 inducers/inhibitors, caution w/P-gp substrates
- Major cardiac adverse events, infection, secondary malignancies

P-gp, P-glycoprotein.

Vonjo (pacritinib) package insert. CTI BioPharma Corp; 2022.

MOM in JAKi-naïve Patients: SIMPLIFY-1



Key inclusion criteria/baseline characteristics:

- **PLT >50K/mm³** (≥100K/mm³ if hepatic dysfunction)
- **No prior JAKi therapy**
- IPPS INT-1 (21%), INT-2 (33%), High (46%)

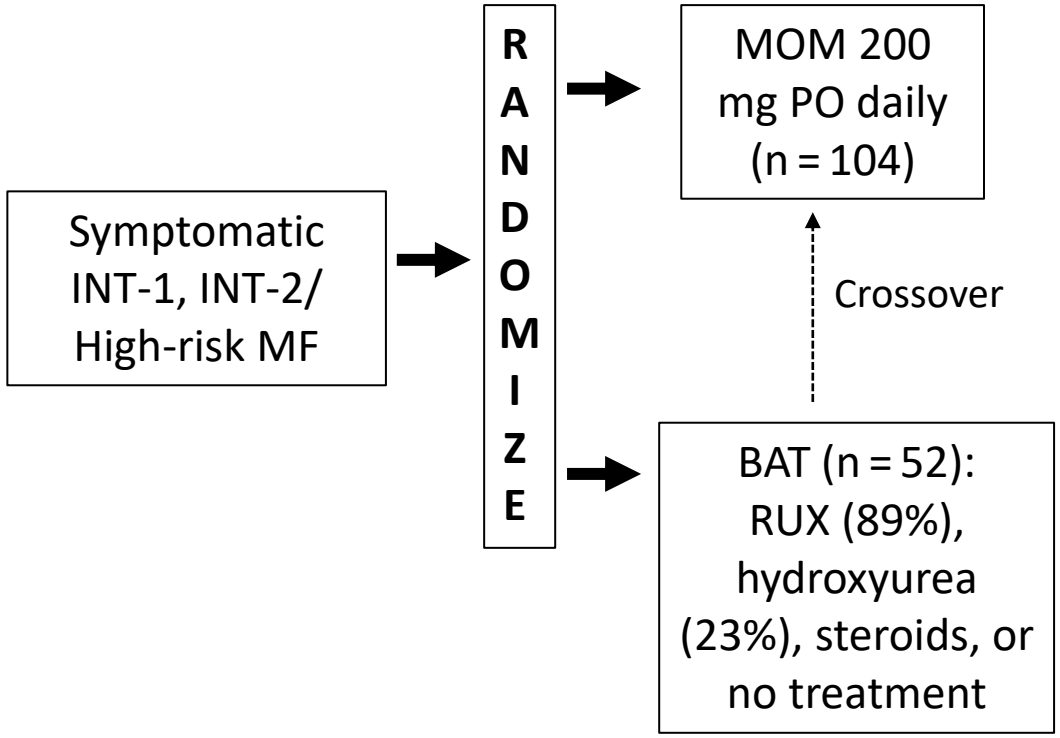
Outcome	MOM	RUX	*P**
≥35% SVR at 24 wk, %	26.5	29	0.011
≥50% MF-SAF TSS ↓ at 24 wk, %	28.4	42.2	0.98
RBC transfusion independent at wk 24, %	66.5	49.3	< .001
RBC transfusion dependent at wk 24, %	30.2	40.1	0.19
Treatment discontinuation due to AEs, %	13.1	5.6	NR

**P*-value for non-inferiority analysis.
Notable AE: peripheral neuropathy: 10% (MOM), 5% (RUX).

MOM, momelotinib; NR, not reported.

Mesa RA, et al. *J Clin Oncol*. 2017;35(34):3844.

MOM vs BAT in Previously RUX-treated MF: SIMPLIFY-2



Outcome	MOM	BAT	*P*
≥35% SVR at 24 wk, %	7	6	0.90
≥50% MF-SAF TSS ↓ at 24 wk, %	26	6	0.0006
RBC transfusion independent at wk 24, %	43	21	0.0012
RBC transfusion dependent at wk 24, %	50	64	0.10

Peripheral neuropathy: MOM (11%), BAT (0%).
"First-dose effect": MOM (4%), BAT (0%).

Prior hematologic toxicity to RUX:
Prior RUX ≥28d and required RBC transfusion OR required dose reduction to ≤20 mg BID AND had anemia, grade ≥3 thrombocytopenia, or grade ≥3 bleeding

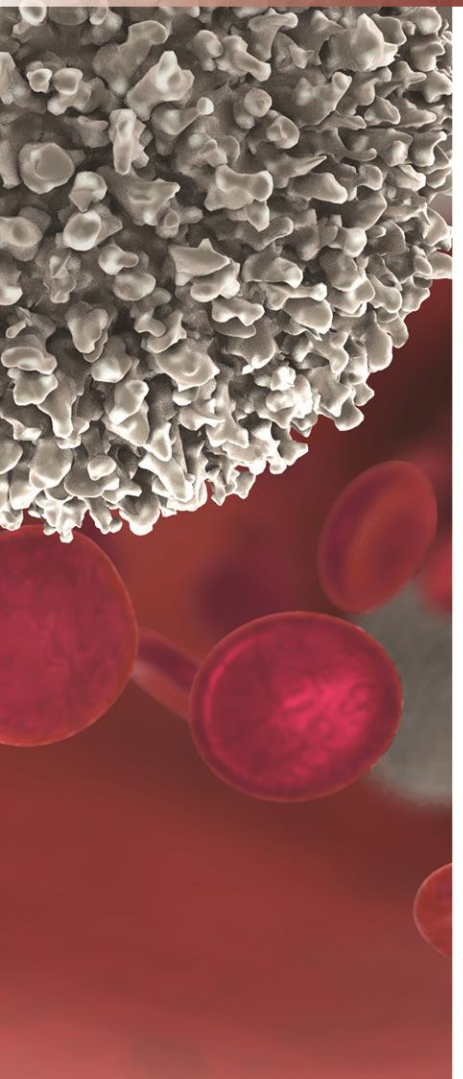
Key inclusion criteria/baseline characteristics:

- Prior RUX treatment
- ***No PLT threshold for inclusion***
- No preexisting peripheral neuropathy grade ≥2
- DIPPS INT-1 (25%), INT-2 (58%), High (17%)

MOM, momelotinib; NR, not reported.

Harrison CN, et al. *Lancet Haematol*. 2018;5(2):e73.

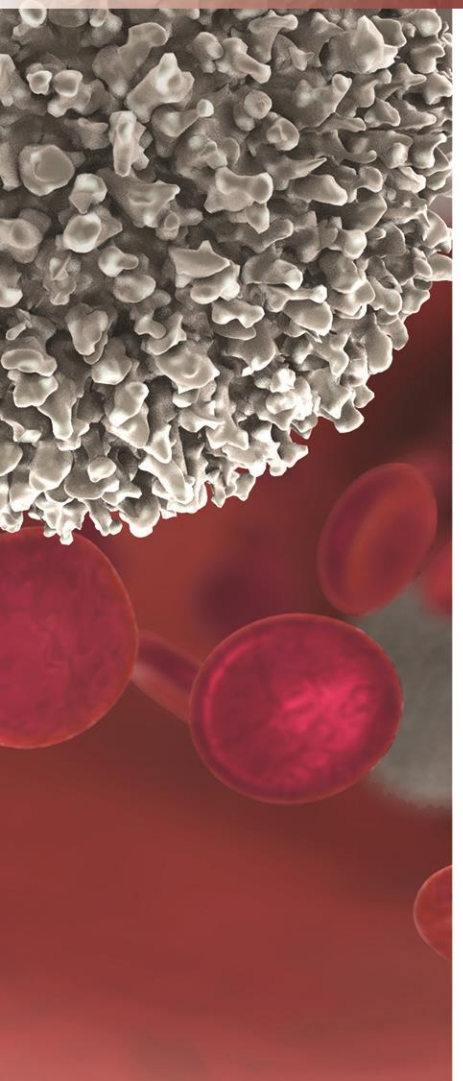
Future Directions for PAC and MOM



- PAC vs physician's choice in MF with severe thrombocytopenia (<50K/mm^3)
  - PACIFICA (NCT03165734)
- MOM vs danazol in symptomatic and anemic MF patients
  - MOMENTUM (NCT04173494)

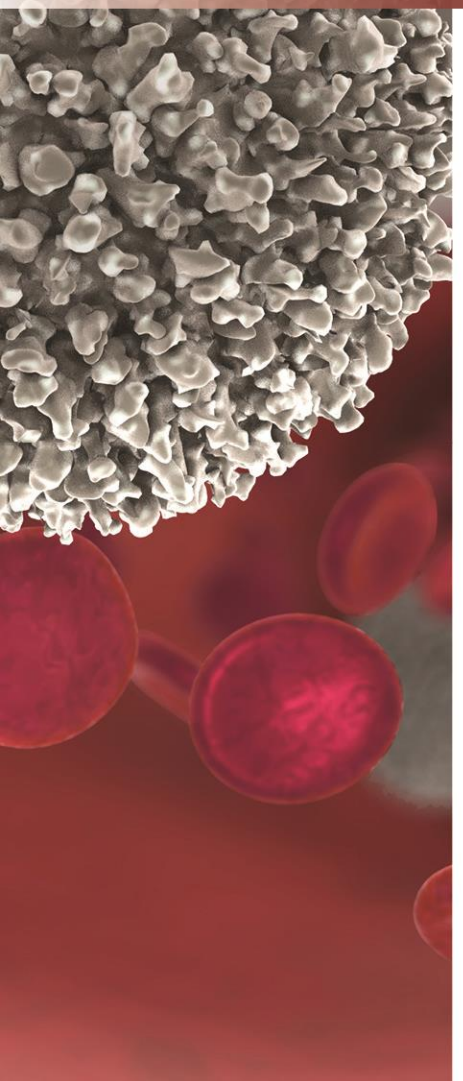
NCT03165734, NCT04173494. www.clinicaltrials.gov..

JAKi in MF: Room for Improvement



- Majority of patients (still) do NOT meet primary efficacy endpoints in trials
- Tolerability may limit dose optimization
- Are SVR ≥35% and ≥50% TSS ↓ reasonable endpoints for second-line JAKi trials?
- JAKi resistance?
- Type 1 vs type 2 JAKi
- Patients with AP/BP still do poorly

New Treatment Approaches

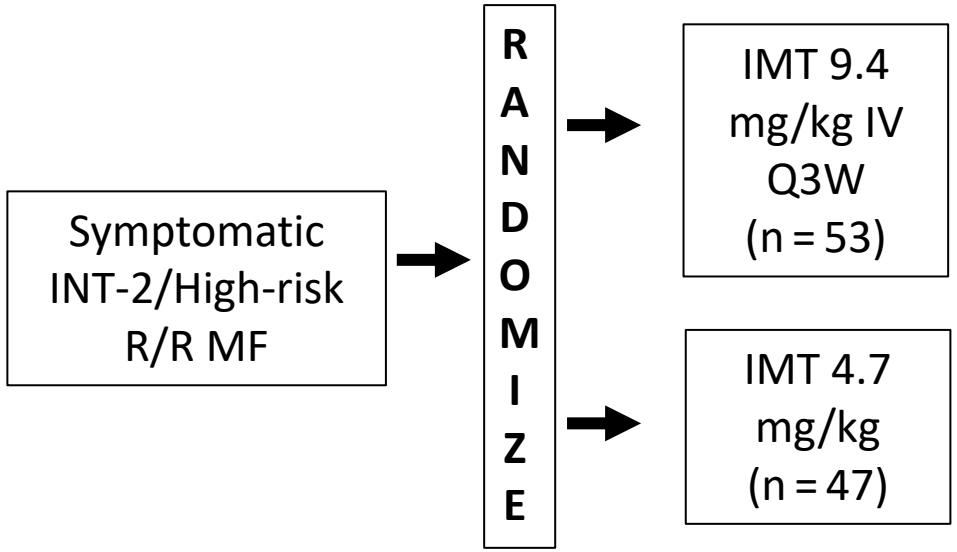


- JAKi “add on” approaches: RUX + …
  - PI3Kδ inhibitors (parsaclisib, umbralisib)
  - BET protein inhibitors (CPI-0610)
  - BCL-2/BCL-XL antagonists (navitoclax)
- Imetelstat (IMT)
  - Telomerase inhibitor
    - Oligonucleotide targeting telomerase RNA template
  - IV Q3W

BCL, B-cell lymphoma; BET, bromodomain and extra-terminal; PI3Kδ, phosphoinositide 3-kinase delta.

Bose P, et al. *Leuk Lymphoma*. 2020;61(8):1797.
Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881.

Imetelstat in R/R MF (MYF2001)



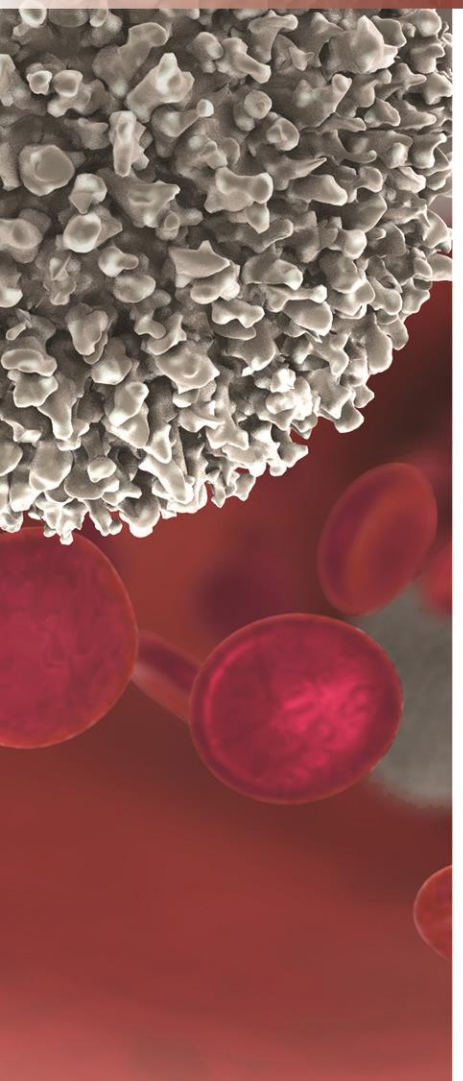
Key inclusion criteria/baseline characteristics:

- R/R MF with prior JAKi therapy with documented progression
- 2/3 had ≥2 prior regimens

Outcome	9.4 mg/kg	4.7 mg/kg
≥35% SVR at 24 wk, %	10.2	0
≥20% SVR at 24 wk, %	22	2.1
≥10% SVR at 24 wk, %	37.3	8.3
≥50% MF-SAF TSS ↓ at 24 wk, %	32.2	6.3
Clinical improvement by IMWG, %	25.4	16.7
Transfusion dependent → independent, %	25	14.3
Reduction in marrow fibrosis ≥1 grade, %	40.5	20
VAF ↓≥25%, %	42.1	5.6
OS, median (mo)	29.9	19.9

IMT, imetelstat; IMWG, International Myelofibrosis Working Group; R/R, relapsed or refractory; VAF, variant allele frequency.

Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881.



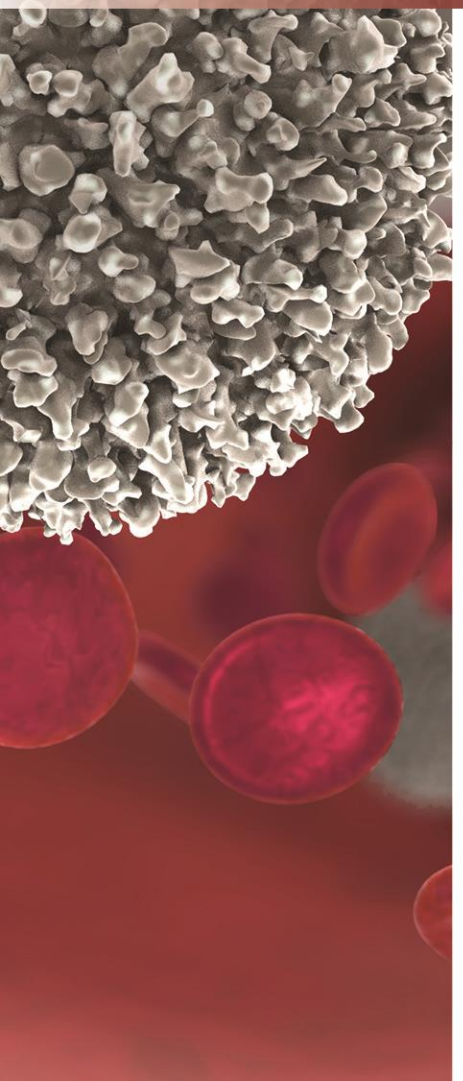
Accelerated or Blast Phase MF

- Accelerated: 10-19% blasts
- Blast phase: ≥20% blasts

- AML-type induction or hypomethylating agent +/- JAKi
- Low intensity options preferred if not alloHCT candidate

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.

Allogeneic Hematopoietic Cell Transplantation (alloHCT)

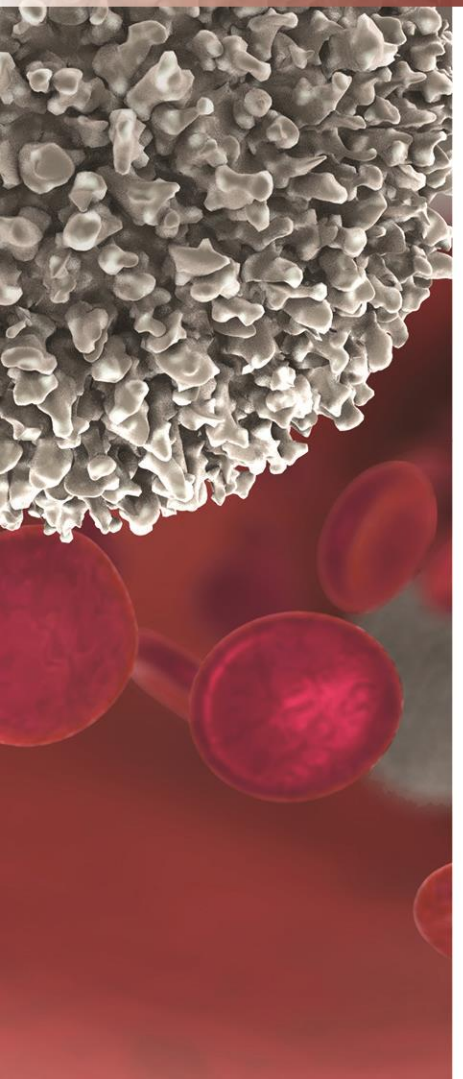


- The only curative option, early referral is critical
- Bridging therapy for blast reduction
- Most patients will receive RIC (≥45 y)
- No prospective comparisons to determine optimal regimen
- Graft failure, poor graft function, and veno-occlusive disease are more common than in other populations
- Taper off JAKi gradually, stopping near start of conditioning
- Pre-alloHCT RUX appears to improve alloHCT outcomes

RIC, reduced-intensity conditioning.

NCCN Guidelines. Myeloproliferative Neoplasms, v1.2022.
Kroger NM, et al. *Leukemia*. 2015;29(11):2126.

When to consider alloHCT



INT-1 risk only if:

Age <65 y, therapy-refractory, transfusion-dependent anemia, adverse cytogenetics, >2% peripheral blasts

INT-2 risk

High risk

alloHCT

Kroger NM, et al. *Leukemia*. 2015;29(11):2126.

Retrospective Study of alloHCT

- N = 2224, 2000-2014
- MAC: Flu/Bu (47%), Bu/Cy (17%), TBI-based (14%)
- RIC: Flu/Bu (57%), Flu/Mel (20%)

In multivariable analysis, worse NRM and OS associated with:

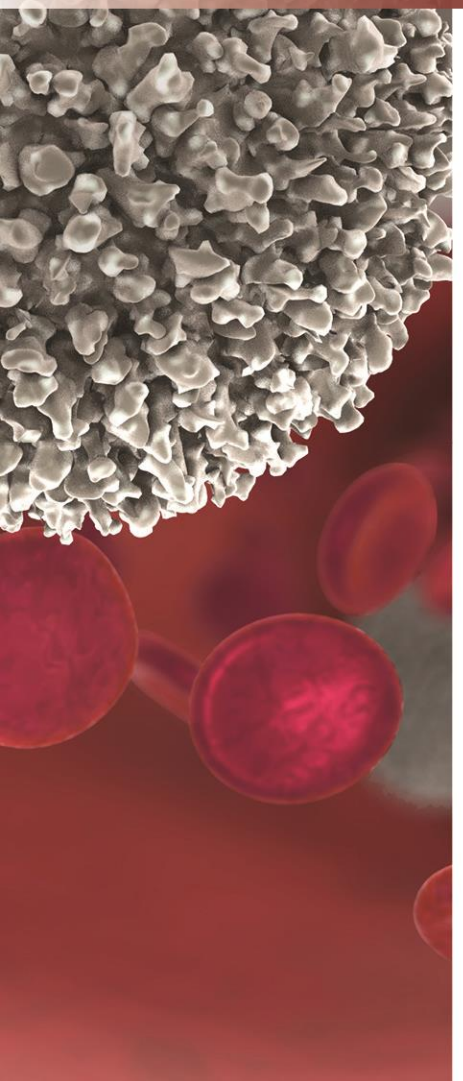
- MAC: >50 years, MUD, KPS ≤80
- RIC: 60-70 years, MMUD, KPS ≤80
- No variables had a significant impact on relapse
- Individual regimen had no significant impact on OS

Outcomes	MAC (n = 781)	RIC (n = 1443)	*P*
5-year GRFS, %	32.4	26.1	0.001
Relapse at 1 year, % • 3 years	10.9 17.2	14 19.7	0.08
5-year OS, %	53	51	0.78
1-year NRM, % • 3 years	25.5 32.2	26.3 32.8	NR
Grade 2-4 aGVHD, %	28	31	NR
Grade 3-4 aGVHD, %	12	16	NR
Extensive cGVHD, %	27	31	NR
Graft failure, %	9.5	13.6	0.005

a/cGVHD, acute/chronic graft-versus-host disease; GRFS, GVHD-free, relapse free survival; KPS, Karnofsky Performance Status; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; NRM: nonrelapse mortality. **Regimens:** Bu/Cy, busulfan/cyclophosphamide; Flu/Bu, fludarabine/busulfan; Flu/Mel, fludarabine/melphalan; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation.

McLornan D, et al. *Biol Blood Marrow Transplant*. 2019;25(11):2167.

Pharmacist Considerations



- Assure appropriate dosing
  - PLT count, drug interactions
- Counsel on therapeutic expectations
  - Delayed onset, minimum expected duration of therapy
  - Expectations must be realistic
- Counsel on risks of abrupt RUX withdrawal, adverse effects
- Screen for drug interactions
- Adverse effect identification and treatment
- MF symptomatic treatment
- Assist in securing financial assistance for drug acquisition

Questions & Answers

Thank You!