Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

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Houston, Texas

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Optimal Treatment of Myelofibrosis: Advances and Challenges

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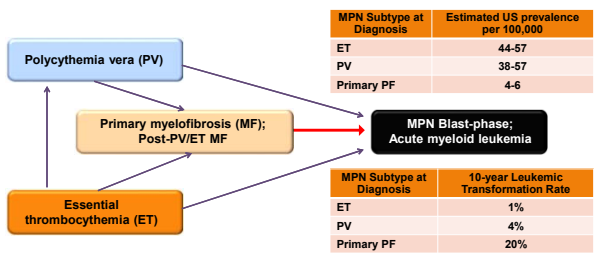
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

MPN Disease Continuum: Shared Biology and Clinical Features



MPN Subtype at Diagnosis	Estimated US prevalence per 100,000
ET	44-57
PV	38-57
Primary PF	4-6

MPN Subtype at Diagnosis	10-year Leukemic Transformation Rate
ET	1%
PV	4%
Primary PF	20%

Tefferi A. *Am J Hematol.* 2008;83:491-497.; Mehta J, et al. *Leuk Lymphoma.* 2014;55:595-600.; Rampal R, Mascarenhas J. *Curr Opin Hematol.* 2014;21:65-71.

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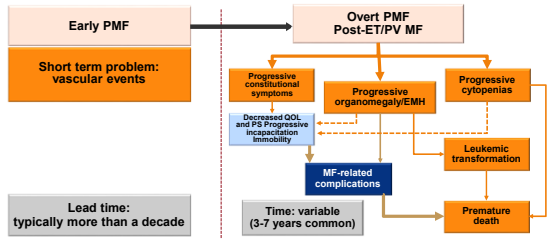
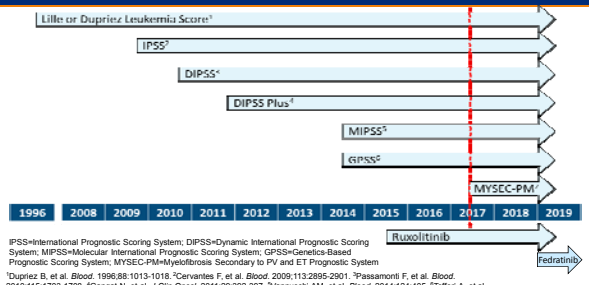
Myelofibrosis: Disease Course and Complications



EMH=extramedullary hematopoiesis; ET=essential thrombocythemia; PMF=primary myelofibrosis; PS=performance status; PV=polycythemia vera; QOL=quality of life.
Mughal TI, et al. *Int J Gen Med*. 2014;7:89-101.

Assessment of Prognosis in MF



IPSS=International Prognostic Scoring System; DIPSS=Dynamic International Prognostic Scoring System; MIPSS=Molecular International Prognostic Scoring System; GPSS=Genetics-Based Prognostic Scoring System; MYSEC-PM=Myelofibrosis Secondary to PV and ET Prognostic System

[1]Dupriez B, et al. *Blood*. 1996;88:1013-1018. [2]Cervantes F, et al. *Blood*. 2009;113:2895-2901. [3]Passamonti F, et al. *Blood*. 2010;115:1703-1708. [4]Gangat N, et al. *J Clin Oncol*. 2011;29:392-397. [5]Vannucchi AM, et al. *Blood*. 2014;124:405. [6]Tefferi A, et al. *Blood*. 2014;124:406. [7]Passamonti F, et al. *Leukemia*. 2017 May 31; doi:10.1038/leu.2017.169 [Epub ahead of print.]

Prognostic Models of Myelofibrosis

Parameter	Included in IPSS[2]	Included in DIPSS[3]	Included in DIPSS-Plus[4]
Age > 65 y	Yes (1 point)	Yes (1 point)	Yes[a]
Hgb < 10 g/dL	Yes (1 point)	Yes (2 points)	Yes[a]
WBC > 25×10^9/L	Yes (1 point)	Yes (1 point)	Yes[a]
PB blood blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes[a]
Constitutional symptoms	Yes (1 point)	Yes (1 point)	Yes[a]
Unfavorable karyotype[b]	No	No	Yes (1 point)
RBC transfusion dependence[c]	No	No	Yes (1 point)
Platelet count < 100×10^9/L	No	No	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

	Median Survival, Years		
Risk Group	IPSS[2]	DIPSS[3]	DIPSS-Plus[4]
Low	11.3	Not reached	15.4
Intermediate-1	7.9	14.2	6.5
Intermediate-2	4.0	4.0	2.9
High	2.3	1.5	1.3

Abbreviations: DIPSS, dynamic International Prognostic Scoring System; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell count.
[a]Zero, 1, 2, and 3 points are assigned to DIPSS categories of low, intermediate-1, intermediate-2, and high risk, respectively; features are not weighted individually.
[b]Complex karyotype or a single or 2 abnormalities including + 8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 rearrangement.
[c]Presentation with symptomatic anemia necessitating RBC transfusion at time of referral, or a history of RBC transfusions for myelofibrosis-associated anemia, without regard to the number of RBC transfusions.

[1]Bose P, Verstovsek S. *Cancer*. 2016;122:681-692. [2]Cervantes F, et al. *Blood*. 2009;113:2895-2901. [3]Passamonti F, et al. *Blood*. 2010;115:1703-1708; [4]Gangat N, et al. *J Clin Oncol*. 2011;29:392-397

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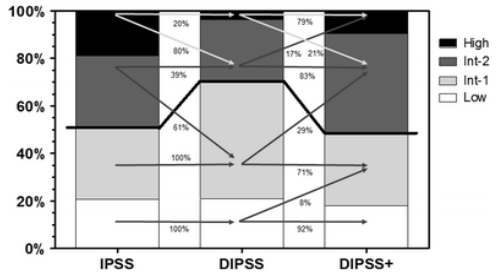
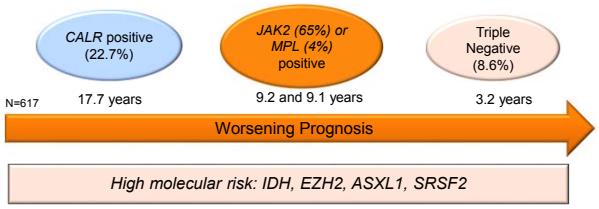
Distribution of Myelofibrosis Patients by the Different Prognostic Models



Hernandez-Boluda JC, et al. *Ann Hematol*. 2018;97(5):813-820.

Prognosis: Impact of Driver and "High Molecular Risk" Non-Driver Mutations in PMF



- Two or more HMR mutations also worsens survival

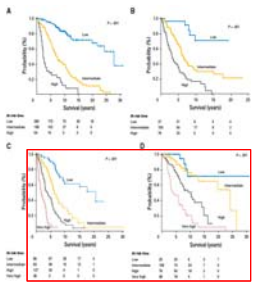
Rumi E, et al. *Blood*. 2014;124:1062-1069.; Vannucchi AM, et al. *Leukemia*. 2013;27:1861-1869.; Tefferi A, et al. *Leukemia*. 2014;28:1472-1477.; Guglielmelli P, et al. *Leukemia*. 2014;28:1804-1810.

MIPSS70 and MIPSS70-plus*

Key Elements:

- Hb <10 g/dL*
- WBC >25 x 109/L
- PLT <100 x 109/L
- Blasts ≥2%*
- Fibrosis > grade 1
- Constitutional symptoms*
- Absence of type 1/-like CALR mutation*
- HMR mutations*
  - *ASXL1*
  - *EZH2*
  - *SRSF2*
  - *IDH1/2*
- Two or more HMR*

Unfavorable karyotype*



Guglielmelli P, et al. *J Clin Oncol*. 2018;36(4):310-318; http://mipss70score.it.

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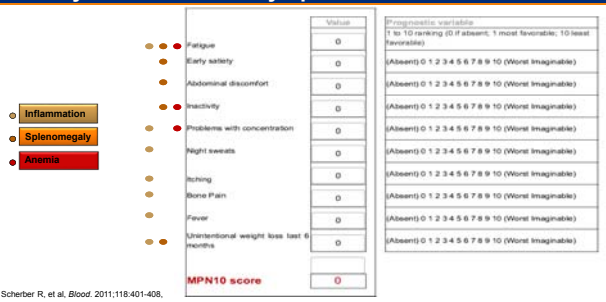
Once We Are Done with Prognostication: "Clinical Needs" Oriented Current Therapy for MF

Clinical need	Drugs/Intervention	
Anemia	• Corticosteroids • Danazol • Erythropoietin	• Thalidomide • Lenalidomide
Symptomatic splenomegaly	• Ruxolitinib, fedratinib • Hydroxyurea	• Cladribine, IMIDs • Splenectomy
Extramedullary hematopoiesis	• Radiation therapy	
Hyperproliferative (early) disease	• Interferon	
Risk of thrombosis	• Low-dose ASA	
Constitutional symptoms/ QoL	• Ruxolitinib, fedratinib • Corticosteroids	
Accelerated/blastic Phase	• Hypomethylating agents	
Improved survival	• Allo SCT • Ruxolitinib	

Barbui T, et al. *J Clin Oncol*. 2011;29:761-770.

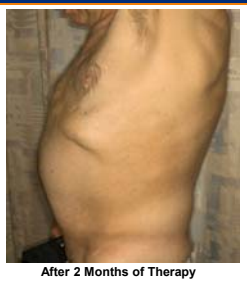
MPN10 (Total Symptom Score) An Easy Tool to Assess Symptoms in MPNs



Scherber R, et al, *Blood*. 2011;118:401-408.

What Does Ruxolitinib Do?

Patient Pre-Ruxolitinib Therapy



After 2 Months of Therapy

It is good for spleen and symptoms

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Ruxolitinib in IPSS-1 Patients

Higher Response Rate and Lower Toxicities

	Clinical Trial	Spleen Response at Week 24	Incidence of Anemia G3/G4	Incidence of Thrombocytopenia G3/G4	Incidence of Infections	Discontinuation rate
Intermediate-2– and high-risk patients	COMFORT-I (n = 155)[1]	41.9%	45%	13%	≈ 50%	21%[6]
	COMFORT-II (n = 146)[2]	32%	42%	8%	≈ 50%	38%
Intermediate-1– risk patients	JUMP INTM-1 (n = 163)[3]	56.9%	24.5%	11%	40%	19.6%
	ROBUST trial (n = 14)[4]	50%	NA	NA	NA	NA
	Italian study (n = 70)[5]	54.7%	21.7%	2.9%	17.1%	17.1%

IPSS intermediate-1 patients may possibly achieve higher reponse rates and experience lower toxicities than patients with higher-risk disease

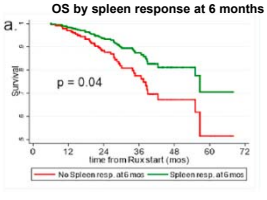
[1]Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807. [2]Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798. [3]Al-Ali HK, et al. *Haematologica*. 2016;101(9):1065-1073. [4]Mead AJ, et al. *Br J Haematol*. 2015;170(1):29-39. [5]Palandri F, et al. *Hematol Oncol*. 2017 [Epub ahead of print]. [6]Verstovsek S, et al. *Haematologica*. 2015;100(4):479-488.

Let's Talk About Something Else…

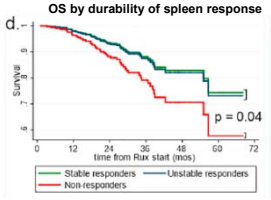
Spleen Response Affects Outcomes of Ruxolitinib-Treated Patients With MF

Multicenter study (N = 284)[1]

OS by spleen response at 6 months



OS by durability of spleen response



Baseline factors associated with lower spleen response to RUX include High/Int-2 disease severity, spleen size >20 cm; high WBC; delay in RUX start after diagnosis, and titrated doses <10 mg BID.[2,3]

[1]Palandri F, et al. *Leuk Res*. 2018;74:86-88. [2]Palandri F, et al. *Oncotarget*. 2017;8:79073-79086. [3]Menghrajani K, et al. *Leuk Lymphoma*. 2018; Sep 20:1-7 [E-pub ahead of print].

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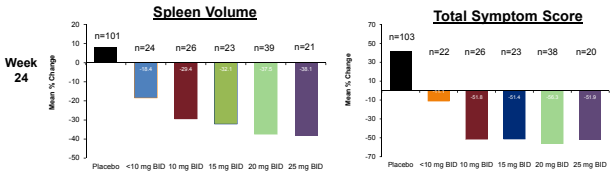
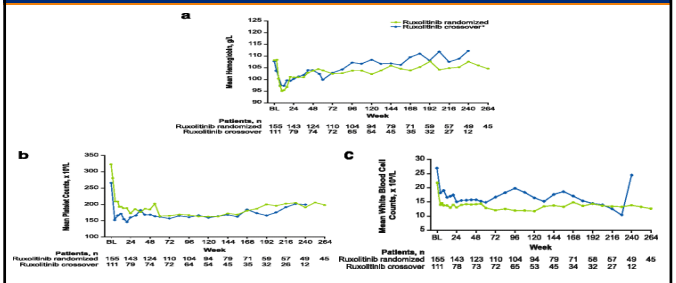
Ruxolitinib Efficacy by Titrated Dose: COMFORT-I



- Avoid starting with low dose!
- If starting low, then ESCALATE quickly to maximum safe dose
- Doses less than 10 mg BID are not effective long term

Verstovsek S, et al. *Onco Targets Ther*. 2013;7:13-21.

Key Safety Issue: Myelosuppression of Ruxolitinib in COMFORT-I



Verstovsek S, at al. *J Hematol Oncol*. 2017;10(1):55.

Tips on Using Ruxolitinib

- Indicated for splenomegaly or MF-related symptoms (regardless of a risk of dying)
- Anemia is NOT contraindication
- Avoid 'prophylactic underdosing' - maintain **maximum tolerated dose** to achieve larger reductions in splenomegaly **early** during treatment
- Development of anemia DOES NOT affect benefits of JAK2 inhibitor
  - Manage anemia as alternative to early dose reductions
- Avoid abrupt interruption of ruxolitinib in patients responding well
- Be aware of rare possibility of opportunistic infections
- Monitor for skin cancer

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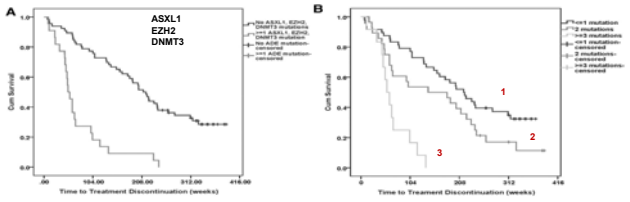
Type and Number of Mutations Predict Response to Ruxolitinib in MF



Patel KP, et al. *Blood*. 2015;126(6):790-797.

Bridging to Transplantation

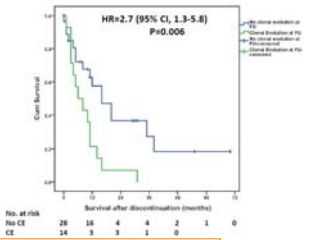
ELN-EBMT Consensus

- Available evidence is not sufficient to recommend splenectomy as a standard pre-transplant procedure that should be decided on a case-by-case basis, preferrably in controlled setting of registries or clinical trials
- **Pre-transplant JAK inhibitor therapy with ruxolitinib** is indicated in patients with a symptomatic spleen and/or constitutional symptoms at least 2 months prior to allo-SCT; titrate to maximum tolerated dose then tapered in 5-7 days prior to and stopped day before conditioning
- No recommendations on ruxolitinib post allo-SCT

Kroger N, et al., *Leukemia*. 2015;29:2126-2133.; Patriarca F, et al. *Exp Opin Biol Ther*. 2017;17(7):821-836.

Outcomes in MF After Ruxolitinib Discontinuation

- Survival after ruxolitinib d/c poor, median 14 months
- Shorter survival associated with **low platelets** at start (Plt <260 x 10^9/L; HR=2.7, *P*=.006) and end of therapy (Plt <100 x 10^9/L; HR=4.1, *P*=.001)
- 35% patients acquired a new mutation while receiving ruxolitinib; 61% *ASXL1*
- Patients showing clonal evolution had significantly shorter survival after d/c (6 vs 16 months, *P*=.006)



- **Salvage therapy or re-challenge** with ruxolitinib can provide responses after d/c
- This continues to be an area of unmet clinical need in MF

Newberry KJ, et al. *Blood*. 2017;130(9):1125-1131.; Kuykendall AT, et al. *Ann Hematol*. 2018;97(3):435-441.;Gerds A, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(11):e463-e468.

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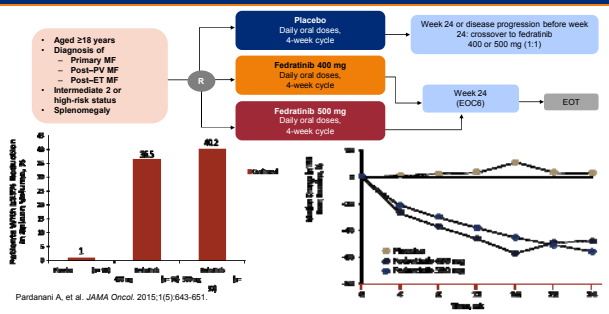
JAKARTA: Phase 3 Study in the first line



Pardanani A, et al. *JAMA Oncol.* 2015;1(5):643-651.

JAKARTA: Hematologic and Nonhematologic Events

Adverse Events, No. (%)	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Nonhematologic						
Diarrhea	63 (66)	5 (5)	54 (56)	5 (5)	15 (16)	0
Vomiting	40 (42)	3 (3)	53 (55)	9 (9)	5 (5)	0
Nausea	61 (64)	0	49 (51)	6 (6)	14 (15)	0
Constipation	10 (10)	2 (2)	17 (18)	0	7 (7)	0
Asthenia	9 (9)	2 (2)	15 (16)	4 (4)	6 (6)	1 (1)
Abdominal pain	14 (15)	0	12 (12)	1 (1)	15 (16)	1 (1)
Fatigue	15 (16)	6 (6)	10 (10)	5 (5)	9 (10)	0
Dyspnea	8 (8)	0	10 (10)	1 (1)	6 (6)	2 (2)
Weight decrease	4 (4)	0	10 (10)	0	5 (5)	0
Hematologic						
Anemia	95 (99)	41 (43)	94 (98)	58 (60)	86 (91)	24 (25)
Thrombocytopenia	60 (63)	16 (17)	55 (57)	26 (27)	48 (51)	9 (9)
Lymphopenia	54 (57)	20 (21)	63 (66)	26 (27)	50 (54)	19 (21)
Leukopenia	45 (47)	6 (6)	51 (53)	15 (16)	18 (19)	3 (3)
Neutropenia	27 (28)	8 (8)	42 (44)	17 (18)	14 (15)	4 (4)

Pardanani A, et al. *JAMA Oncol.* 2015;1(5):643-651.

JAKARTA-2: Open-Label Study in Patients with MF After Ruxolitinib Reanalysis at ASCO 2019

- Aged ≥18 years
- Intermediate-2 or high-risk status
  - Primary MF
  - Post–PV MF
  - Post–ET MF
- Platelet count ≥50 x 10^9/L
- Received RUX for ≥14 days
- Discontinued RUX ≥14 days prior to starting fedratinib

RUX resistant | **RUX intolerant**

Classification made by treating physician

Fedratinib

Once daily, starting dose 400 mg
Consecutive 4-week cycles

Reanalysis employed a more stringent definition of RUX failure

- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%)

Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria

- SVRR = 30%
- Symptoms RR = 27%
- Safety consistent with prior reports

Harrison CN, et al. Lancet Haematol. 2017;4:e317-e324.; Harrison CN, et al. ASCO 2019. Abstract 7057.

Thank You

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"Toward Improved Treatment Options" JAK Therapy and Beyond in Clinical Trials

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Professor of Medicine and Oncologic Sciences
University of South Florida College of Medicine
Vice, Chair, Malignant Hematology Department
Moffitt Cancer Center
Tampa, Florida

Optimizing Upfront Therapy

- Ruxolitinib is the standard of care for treatment of intermediate- and high-risk MF patients with splenomegaly and constitutional symptoms:
  - **Where do other JAK inhibitors fit as first-line therapy and for who?**
  - **Can we make ruxolitinib better?**

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JAK-2 Inhibitors

Drug	Other Target	Phase	Status
Ruxolitinib	JAK-1	III	Approved
Fedratinib	FLT-3, RET	III	Approved
Pacritinib	FLT-3	III	Ongoing
Momelotinib	JAK1, JNK1, TYK2, CDK2, RICJ2	III	Ongoing
NS-018	SRC, FLT3, ABL	I/II	Ongoing

Cervantes F. *Blood.* 2014;124(17):2635-2642.

Fedratinib in the Frontline

Trial	Study Design	Population	Response	Safety
JAKARTA-1 N = 289	Phase 3, randomized, placebo-controlled, 3-arm study (placebo, fedratinib 400 mg QD, fedratinib 500 mg QD)	Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥50×10^9/L, and splenomegaly	**Spleen** Fedratinib 400 mg **36%** Fedratinib 500 mg **40%** **TSS reduction >50%** Fedratinib 400 mg **36%** Fedratinib 500 mg **34%**	Gr 3/4 with placebo, fedratinib 400 mg, and fedratinib 500 mg: • Anemia **25%/43%/60%** • Thrombocytopenia **9%/17%/27%** • Diarrhea **0/5%/5%**

Trial	Study Design	Population	Response	Safety
Comfort-I N=309	Phase III, randomized, placebo-controlled	Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥100×10^9/L, and splenomegaly	**Spleen** **42%** **TSS reduction >50%** **46%**	Gr 3/4 with ruxoltinib: • Anemia **45%** • Thrombocytopenia **13%**
Comfort-II N=219	Phase III, randomized, Ruxolitinib vs BAT	Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥100×10^9/L, and splenomegaly	**Spleen** **32%**	Gr 3/4 with ruxoltinib: • Anemia **42%** • Thrombocytopenia **8%**

Pardanani A, et al *JAMA Oncol* 2015;1(5):643-651.; Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807.; Harrison C, et al. *N Engl J Med.* 2012;366:787-798.

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Pacritinib in the Frontline

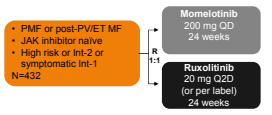
Trial	Study Design	Population	Response	Safety
PERSIST-1	Phase 3 randomized, open-label • PAC 400 mg QD (n=220) • BAT (n=107)	Eligible patients had intermediate of high-risk MF, PPV-MF, or PET-MF, **no platelets cutoff**, and splenomegaly	**Spleen 25%** Spleen with plat <100×10⁹/L **24%** Spleen with plat <50 ×10⁹/L **33%** **TSS reduction >50% 19%** **with plat <100×10⁹/L 25%** **plat <50 ×10⁹/L 27%**	Gr 3/4 with pacritinib: • Anemia **17%** • Thrombocytopenia **21%** • Diarrhea **6%**
PERSIST-2	Phase 3 randomized, open-label • PAC 400 mg QD (n=104) • PAC 200 mg BID (n=107) • BAT (n=100)	• Eligible patients had primary MF, PPV-MF, or PET-MF; **≤1 prior JAK2 inhibitors**; and **platelet counts ≤100K/µL**	**Spleen** Pacritinib 400qd **16%** Pacritinib 200 BID **22%** with plat <50 ×10⁹/L Pacritinib 400qd **18%** Pacritinib 200 BID **29%** **TSS reduction >50%** **17, 32%** plat <50 ×10⁹/L **16, 23%**	Gr 3/4 with pacritinib: • Anemia **27, 22%** • Thrombocytopenia **31, 32%** • Diarrhea **5%, 4%**

Trial	Study design	Population	Response	Safety
Comfort-I N=309	Phase III, randomized, placebo-controlled	Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥100×10⁹/L, and splenomegaly	**Spleen 42%** **TSS reduction >50% 46%**	Gr 3/4 with ruxolitinib: • Anemia **45%** • Thrombocytopenia **13%**
Comfort-II N=219	Phase III, randomized, Ruxolitinib vs BAT	Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥100×10⁹/L, and splenomegaly	**Spleen 32%**	Gr 3/4 with ruxolitinib: • Anemia **42%** • Thrombocytopenia **8%**

Mesa RA, et al. *Lancet Haematol*. 2017;4(5):e225-e236.; Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.; Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.; Harrison C, et al. *N Engl J Med*. 2012;366:787-798

Momelotinib in the Frontline

Phase 3 trial in JAK inhibitor-naïve patients



Efficacy Overview

Outcome Measure	Momelotinib n=215	Ruxolitinib n=217
≥35% reduction in spleen volume at week 24, %	26.5%	29%
	Noninferior; *P*=.011	
≥50% reduction in total symptom score, %	28.4%	42.2%
	Noninferiority not met; *P*=.98	

- **Transfusion rate, transfusion independence, and transfusion dependence were improved with momelotinib (all with nominal *P*≤019)**

Safety Overview

- The most common grade ≥3 hematologic abnormalities in either group were thrombocytopenia and anemia
- Grade ≥3 infections occurred in 7% of patients who received momelotinib and 3% of patients who received ruxolitinib
- Peripheral neuropathy 10%

Mesa RA, et al. *J Clin Oncol*. 2017;35:3844-3850.

My Take on JAK Inhibitors in the Frontline

- Ruxolitinib remains the standard of care for intermediate and high-risk MF patients with platelets >100 x 109/L
- Fedratinib has similar reported outcomes in terms of spleen response, less TSS score reduction, GI toxicity
- Pacritinib could become frontline choice for patients with thrombocytopenia
- Momelotinib could become a choice for patients with anemia

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Can We Make it Better: Ruxolitinib-based Therapy

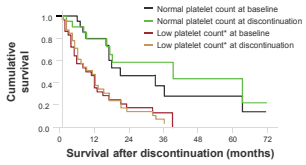
	Partner	Mechanism of Action	Phase
Accelerated phase	Azacitidine	HMA	II
Treatment related cytopenia	Decitabine	HMA	I/II
	Luspatercept/sotatercept	TGFB trap ligand	II
	Danazol	Androgen	II
	Thalidomide	IMiD	II
	Lenalidomide	IMiD	II
	Pomalidomide	IMiD	I/II
Disease modification/higher responses	PegIFN α-2a		I/II
	HDAC inhibitors	HDAC -	I/II
	Itacitinib	JAKi	II
	Navitoclax	BCL	II
	Parsaclisib	PI3Kδi	II
	PIM447	CDK4/6	Ib
	CPI-0610	BET -	I/II

Life Beyond Ruxolitinib

- Outcome after ruxolitinib failure is poor and MF treatment remains an unmet need:
  - **What is ruxolitinib failure?**
  - **What is the role of other JAK inhibitors after ruxolitinib failure?**
  - **Are there any new drugs on the horizon?**

Survival After Ruxolitinib Discontinuation Is Poor

Poor survival in patients after discontinuing ruxolitinib treatment:



Among 86 patients with MPN-MF who discontinued ruxolitinib in a phase 1/2 study:

35%	14 months	Low platelet count*
died while taking ruxolitinib	median survival after discontinuation (n=56)	associated with shorter survival

Newberry KJ, et al. *Blood*. 2017;130:1125-1131.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Defining Ruxolitinib Failure: IWG

Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia
Anemia response	Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level
	Transfusion-dependent patients: becoming transfusion-independent
Spleen response	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable or
	A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%
	A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response
	A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS
Progressive disease	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
	A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
	A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or
	Leukemic transformation confirmed by a bone marrow blast count of ≥20% or
	A peripheral blood blast content ≥20% associated with absolute blast count of ≥1 × 10(9)/L that lasts at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
	Loss of anemia response persisting for at least 1 month or
	Loss of spleen response persisting for at least 1 month

Tefferi A, et al. *Blood*. 2013;122(8):1395-1398.

Defining Ruxolitinib Failure: Recent Clinical Trials

- **Refractory:** RUX Tx ≥3 mo with <10% SVR or < 30% decrease in spleen size from BL[1]
- **Relapsed:** RUX Tx ≥3 mo with regrowth, defined as <10% SVR or <30% decrease in spleen size from BL, following an initial response[1]
- **Intolerant:** RUX Tx ≥28 d complicated by development of RBC transfusion requirement (≥2 units/mo for 2 mo); or grade ≥3 thrombocytopenia, anemia, hematoma/hemorrhage while on RUX[1]
- **Suboptimal response:** ruxolitinib for ≥6 months with stable dose for ≥8 weeks. Palpable spleen >10 cm below left subcostal margin on physical examination or palpable spleen 5–10 cm below left subcostal margin on physical examination AND active symptoms of MF defined as 1 symptom score ≥5 or 2 symptom scores ≥3 each[2]

1.Harrison CN, et al. ASCO 2019. Abstract 7057 2.Daver N, et al ASCO 2018 Abstract 353

Fedratinib as Second-line

Trial	Study Design	Population	Primary Outcome	Safety
JAKARTA-2 (NCT01523171) N = 97	Single-arm, open-label, nonrandomized, phase 2, multicenter study	Ruxolitinib-resistant/ intolerant intermediate/ high-risk primary MF, post-ET/PV MF	**Spleen response** **55% (95% CI, 44-66)**	Gr 3/4 AEs: anemia (38%) thrombocytopenia (22%) Discontinued due to AEs 19%

Harrison CN, et al. *Lancet Hematol*. 2017;4:e317-324.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

JAKARTA-2 at ASCO 2019

- In the original JAKARTA-2 analysis,[1] fedratinib demonstrated a 55% rate of ≥35% SVR in patients resistant or intolerant to RUX (≥14 days) per investigator assessment
- Reanalysis employed a more stringent definition of RUX failure

Main findings

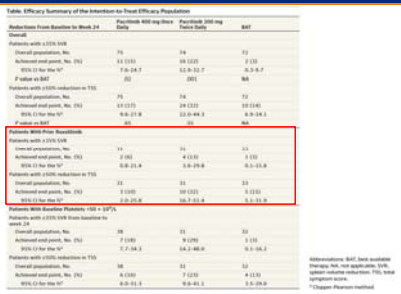
- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%)

Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria

- SVRR = 30%
- Symptoms RR = 27%

[1]Harrison CN, et al. *Lancet Hematol*. 2017;4:e317-324. [2]Harrison CN, et al. ASCO 2019. Abstract 7057.

Pacritinib as Second-line



Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

Momelotinib in Myelofibrosis: Simplify 2

Phase 3 trial in patients previously treated with ruxolitinib

- PMF or post-PV/ET MF
- Previous ruxolitinib treatment for ≥28 days
- Suboptimal responses or hematological toxic effects with ruxolitinib

N=156

R 2:1

- Momelotinib 200 mg once a day 24 weeks
- BAT * 24 weeks

*BAT could include ruxolitinib, chemotherapy, steroids, no treatment, or other standard interventions

Momelotinib in Myelofibrosis: Simplify 2

Efficacy Measure	Momelotinib n=104	BAT n=52
≥35% reduction in spleen volume at week 24, n (%)	7 (7%)	3 (6%)
Proportion difference (95% confidence interval)	0.01 (0.09-0.10) *P* = 0.90	

Safety Overview

- The most common grade ≥3 AEs were anemia (14% in the momelotinib group vs 14% in the BAT group), thrombocytopenia (7% vs 6%), and abdominal pain (1% vs 6%)
- Serious events were reported for 35% of patients in the momelotinib group and 23% of patients in the BAT group
- Deaths due to AEs were reported for 6% of patients receiving momelotinib and 8% of patients receiving BAT

Harrison CN, et al. *Lancet Haematol*. 2018;5(2):e73-e81.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Moving Beyond JAK Inhibitors

	Target	Agent
Promotion of Apoptosis	SMAC mimetic/IAP BCL-xL inhibitors LSD1 inhibitors XPO1 inhibitor	LCL-161 Navitoclax IMG-728 Selinexor
Targeting Hematopoietic Stem Cell/Micro-environment	CD123 Hsp90	Tagraxofusp PU-H71
Modulation of TP53 Pathway	MDM2 antagonists	Idasanutlin KRT-232
Targeting Fibrosis and Associated Cytokine	Pentraxin-2	PRM-151
Aurora Kinase Inhibition		Alisertib
Telomerase Inhibition		Imetelstat
Bromodomain and Extraterminal Protein Inhibition	BET -	CPI-0610

Modified from Economides MP, et al. *Curr Hematol Malig Rep*. 2019 Aug 1.

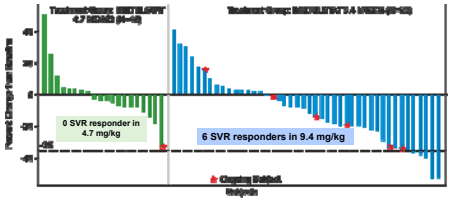
IMBARK Study: IMETELSTAT

- Study population
  - Int2/high-risk MF per DIPSS criteria
  - Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
    - Subjects must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy **and** EITHER:
      - No reduction in spleen volume or size after 12 weeks of JAKi therapy, **or**
      - Worsening splenomegaly* at any time after the start of JAKi therapy documented by:
        - Increase in spleen volume from nadir by 25% measured by MRI or CT, **or**
        - Increase in spleen size by palpation, CT, or ultrasound
  - Active symptoms of MF
  - Baseline measurable splenomegaly (palpable spleen ≥5 cm below LCM or ≥450 cm^3 by MRI)
- Study design: phase II 2 doses 4.7 mg/kg q 3 weeks (n=48) and 9.4 mg/kg q 3 weeks (n= 59)
  - 4.7 mg/kg arm closes and escalation allowed
  - Standard response criteria at week 24

*Adapted from IWG-MRT response criteria definition of progressive disease

SVR Per IRC at Week 24

- 6 (10.2%) subjects in the 9.4 mg/kg arm had ≥35% SVR at week 24
- 23 (37%) subjects in the 9.4 mg/kg arm had ≥10% SVR at week 24

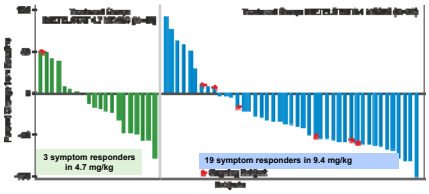


At time of cut-off, 20 subjects in the 4.7 mg/kg and 44 subjects in the 9.4 mg/kg had week 24 MRI, however ITT is used as denominator for percentages.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Symptom Response Based on TSS at Week 24

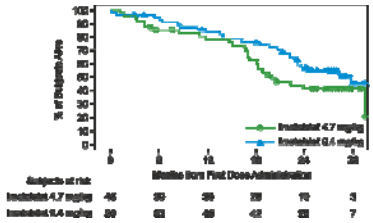
- 19 (32.2%) subjects in 9.4 mg/kg arm had ≥50% symptom response at week 24



At time of cut-off, 20 subjects in the 4.7 mg/kg and 43 subjects in the 9.4 mg/kg had week 24 TSS e-diary entries, however ITT is used as denominator for percentages.

Output: GEFTSS01, TEFSUM01

Overall Survival (ITT) for Imetelstat at Different Dose Levels



- **Median follow up: 27.4 months**
- **Median survival:**
  - **19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg**
  - **29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg**

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAK inhibitor or stem cell transplant and excluding subjects who were dose escalated or randomized after closure of the 4.7 arm), all generating similar results

Eligibility Criteria

IMbark Criteria

- Int-2/high-risk MF per DIPSS criteria
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Subjects must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy, or
    - Worsening splenomegaly* at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT, or
      - Increase in spleen size by palpation, CT, or ultrasound
- Active symptoms of MF
- Baseline measurable splenomegaly (palpable spleen ≥5 cm below LCM or ≥450 cm^3 by MRI)

Real World Data (RWD) Criteria

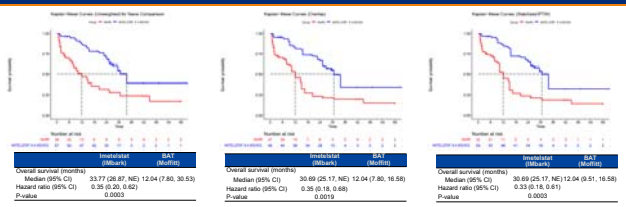
- Collected from a single-center study at the Moffitt Cancer Center, patients who had discontinued ruxolitinib
  - A closely matched cohort was identified using the guidelines for inclusion and exclusion criteria as defined in IMbark protocol
  - Cohort consisted of patients with MF who had discontinued JAKi due to lack or loss of response and were subsequently treated with BAT at the Moffitt Cancer Center from January 1998 to August 2018

*Adapted from IWG-MRT response criteria definition of progressive disease

Kuykendall A, et al. EHA 2019.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Statistically Significant Reductions in Risk of Death with Imetelstat Treatment Across Analyses



	Imetelstat (IMbark)	BAT (Moffitt)
Overall survival (months)		
Median (95% CI)	33.77 (26.87, NE)	12.04 (7.80, 30.53)
Hazard ratio (95% CI)	0.35 (0.20, 0.62)	
P-value	0.0003	

	Imetelstat (IMbark)	BAT (Moffitt)
Overall survival (months)		
Median (95% CI)	30.69 (25.17, NE)	12.04 (7.80, 16.58)
Hazard ratio (95% CI)	0.35 (0.18, 0.68)	
P-value	0.0019	

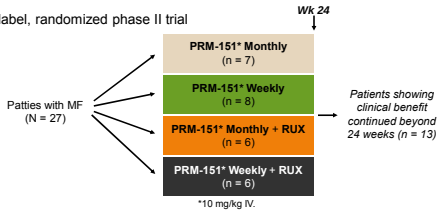
	Imetelstat (IMbark)	BAT (Moffitt)
Overall survival (months)		
Median (95% CI)	30.69 (25.17, NE)	12.04 (9.51, 16.58)
Hazard ratio (95% CI)	0.33 (0.18, 0.61)	
P-value	0.0003	

- Imetelstat conferred 65-67% lower risk of death compared to BAT in the unweighted analysis and per ATO and sIPTW weighting methods
- Results suggest favorable overall survival with imetelstat treatment when compared to closely matched RWD from patients treated with BAT

Kuykendall A, et al. EHA 2019.

PRM-151 in MF: Study Design

- Open-label, randomized phase II trial



*10 mg/kg IV.

- Primary endpoint: ORR by IWG consensus criteria for response to treatment in MF with myeloid metaplasia
- Secondary endpoints: Safety, change in BM fibrosis, change in MPN-SAF score, PK

Verstovsek S, et al. ASH 2015. Abstract 56.

PRM-151 in MF

- Thirteen patients completed 72 weeks of treatment with PRM-151
  - PRM-151 well tolerated with few AEs (1 grade 3 and no grade 4 AEs)
  - Reductions in bone marrow fibrosis were observed at week 12 and sustained through week 72 (54%)
  - Median Hb level increased in pts with baseline Hb <10 g/L with decreased need for RBC transfusions; 5 patients had Hgb increase by 24% (3 out 5 became RBC TI)
  - Median platelet counts increased in patients with baseline plat <100 x 109/L with a decreased need for platelet transfusions. Among 9 patients with plat <100 x 109/L platelets increased by 37%
  - 62% experienced a symptom score reduction of >50% and 2 patients experienced >50% reduction in splenomegaly
- Stage 2 of study currently enrolling patients not eligible for ruxolitinib to receive single-agent PRM-151 q4w x 36 weeks with blind randomization to 3 different dosages with open-label extension option beyond 36 weeks

Verstovsek S, et al. ASH 2015. Abstract 56.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

My ASH 2019 Watch List

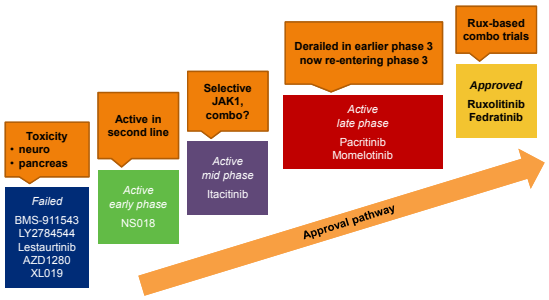
- Pacritinib
- BET inhibitors
- Navitoclax
- Luspatercept

Interactive Case Studies: Treatment Decisions After JAK Inhibitor "Failure"

Prithviraj Bose, MD
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

JAK Inhibitors and Status of Development in Myelofibrosis as Lead Indication



Current Status: Ruxolitinib in MF

- A highly effective drug benefiting many patients
- Overall survival benefit with long-term follow up[1]
- Anemia/thrombocytopenia may limit effective dosing; median duration of spleen response ≈3 years[2,3]
- Spleen response dose-dependent; correlates with survival[4,5]
- Resistance not due to mutations; ? due to "persistence";[6] re-challenge may help[7]
- Anemia due to rux not prognostically adverse;[8] rux overcomes adverse prognosis of disease-related anemia[9]
- Prognosis after discontinuation is poor[10,11]
- Definition of failure variable in clinical trials, unclear in clinical practice

[1]Verstovsek S, et al. *J Hematol Oncol*. 2017;10:156. [2]Verstovsek S, et al. *J Hematol Oncol*. 2017;10:55. [3]Harrison CN, et al. *Leukemia*. 2016;30:1701-1707. [4]Vannucchi AM, et al. *Haematologica*. 2015;100:1139-1145. [5]Miller CB, et al. *Clin Lymphoma Myeloma Leuk*. 2017;17:479-487. [6]Koppikar P, et al. *Nature*. 2012;489:155-159. [7]Gerds A, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:e463-468. [8]Gupta V, et al. *Haematologica*. 2016;101:e482-484. [9]Al-Ali HK et al. *Leuk Lymphoma*. 2016;57:2464-2467. [10]Newberry KJ, et al. *Blood*. 2017;130:1125-1131. [11]Kuykendall AT, et al. *Ann Hematol*. 2018;97:435-441.

Identification/Management of Progression/Resistance on Ruxolitinib

Feature	Treatment Options
Spleen	▪ Threshold: beyond baseline, ↑ by 5 cm, more symptomatic ▪ Optimize dose of ruxolitinib ▪ Switch to alternative JAK inhibitor (fedratinib now approved) ▪ Consider splenectomy
Symptoms	▪ Review cause (eg, mood disturbance, other medications) ▪ Optimize dose of ruxolitinib ▪ Consider alternative treatments (eg, steroid, antihistamine) ▪ Switch to alternative JAK inhibitor (fedratinib now approved)
More anemia or thrombocytopenia	▪ Exclude other causes (eg, drug–drug interaction) ▪ Determine if it needs treating ▪ Add EPO, danazol, low-dose thalidomide (50 mg/day)
Leukocytosis	▪ Determine the threshold for treatment ▪ Add hydroxycarbamide
Blasts	▪ Threshold depends on rate of rise </≥ 10%/15%/20% ▪ Expectant, consider adding HMA or rarely AML induction

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Ellen, an Older Patient Receiving Treatment for MF

Ellen is 75 years old, fit and active, with confirmed MF	She starts treatment with ruxolitinib	After at least 3 months
▪ PS of 1 ▪ Constitutional symptoms, splenomegaly, normal platelets at baseline	▪ 20 mg dose twice-daily ▪ She initially tolerates treatment well	▪ Rising splenomegaly ▪ Return of constitutional symptoms

Case 1: Newer JAK Inhibitors an Option for Ellen

Ellen exhibits lack of response to ruxolitinib

- *Emerging JAK inhibitors/clinical trials are likely treatment options in this setting*

Use of fedratinib is an appropriate next step

- *Supported by JAKARTA-2[1] findings*
- *Other emerging JAK inhibitors with potential applications in this case include pacritinib (PERSIST-2)[2] or momelotinib (SIMPLIFY-2)[3]*
- *Clinical trials (novel single agents or ruxolitinib-based combinations) also an option*

[1]Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-324. [2]Mascarenhas J, et al. *JAMA Oncol.* 2018;4:652-659. [3]Harrison CN, et al. *Lancet Haematol.* 2018;5:e73-81.

Towards a Consensus Definition of Ruxolitinib Failure: JAKARTA-2 Re-analysis at ASCO 2019

- In the original JAKARTA-2 analysis,[1] fedratinib demonstrated a 55% rate of ≥35% SVR in patients resistant or intolerant to RUX (≥14 days) per investigator assessment
- Reanalysis[2] employed a more stringent definition of RUX failure
- Relapsed: Ruxolitinib treatment for ≥3 months with regrowth, defined as <10% SVR or <30% decrease in spleen size from baseline, following an initial response
- Refractory: Ruxolitinib treatment for ≥3 months with <10% SVR or <30% decrease in spleen size from baseline
- Intolerant: Ruxolitinib treatment for ≥28 days complicated by development of RBC transfusion requirement (≥2 units per month for 2 months); or grade ≥3 thrombocytopenia, anemia, hematoma and/or hemorrhage while receiving ruxolitinib

Main Findings

- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%)

Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria

- SVRR = 30%
- Symptoms RR = 27%
- Safety consistent with prior reports

[1]Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-324. [2]Harrison CN, et al. ASCO 2019. Abstract 7057.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Robert, a Patient on Long-Term Therapy With Ruxolitinib

Robert is a 70-year-old man diagnosed with MF 5 years earlier	Within the past 6 months	At the most recent clinic visit
▪ 4.5-year treatment history of ruxolitinib ▪ Successful management of constitutional symptoms and splenomegaly	▪ Intermittent return of several constitutional symptoms (fatigue and joint/bone pain)	▪ Increasing spleen size (now 8 cm below costal margin) ▪ Falling counts (platelets now at 55 x 10^9/L)

Case 2: Clinical Trial-Based Therapy

Robert is a candidate for second-line therapy, eager to pursue another option

- *Many novel targeted strategies are being developed in clinical trials*

Clinical trial-based therapy recommended

- *Options currently being assessed include bromodomain inhibitors (CPI-0610), MDM2 inhibitors (KRT-232), LSD1 inhibitors (IMG-7289), therapies targeting CD123 (tagraxofusp), etc.*
- *The telomerase inhibitor imetelstat,[1] the anti-fibrotic agent PRM-151[2] and the AURKA inhibitor alisertib[3] have been studied in the post-ruxolitinib setting*

[1]Mascarenhas J, et al. ASH 2018. Abstract 685. [2]Verstovsek S, et al. EHA 2019. Abstract S828. [3]Gangat N, et al. *Clin Cancer Res*. 2019;25:4898-4906.

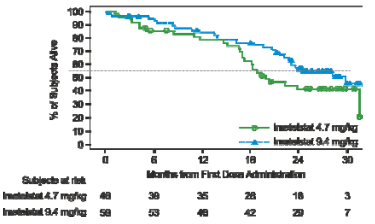
IMBARK™ Trial: Major Inclusion Criteria

- Int-2/high-risk MF per DIPSS criteria
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy **and** EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy, **OR**
    - Worsening splenomegaly* at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT, **or**
      - Increase in spleen size by palpation
- Active symptoms of MF
- Baseline measurable splenomegaly (palpable spleen ≥5 cm below LCM or ≥450 cm^3 by MRI)

*Adapted from IWG-MRT response criteria definition of progressive disease.
Mascarenhas J, et al. ASH 2018. Abstract 685.

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Overall Survival (ITT) for Imetelstat at Different Dose Levels



- Median follow-up: 27.4 months
- Median survival:
  - 19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg
  - 29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAKi or stem cell transplant and excluding patients who were dose escalated or randomized after closure of the 4.7 mg/kg arm), all generating similar results

Mascarenhas J, et al. ASH 2018. Abstract 685.

JAK2 Inhibitor "Persistence" and Ruxolitinib Re-challenge

- Unlike CML, mutations impairing TKI binding have not been described
- Type 1 JAK2 inhibitors are ATP-competitive and bind the kinase in its active conformation
- Signaling may continue unabated (ie, "persist") via heterodimerization of activated JAK2 with another member of the JAK family (JAK1 or TYK2) despite the presence of a type 1 JAK2 inhibitor
- May be reversed by temporary withdrawal of the drug and by type 2 JAK2 inhibitors, eg, CHZ868
- Anecdotal reports of restoration of responsiveness to ruxolitinib by temporary withdrawal followed by re-challenge

Koppikar P, et al. *Nature*. 2012;489(7414):155-159.; Meyer SC, et al. *Cancer Cell*. 2015;28(1):15-28.; Gerds A, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(11):e463-468.

Susan, a Patient with Suboptimal Response to Ruxolitinib

Susan, a 55-year-old woman presents with	Further Testing Shows	Susan Starts on Ruxolitinib
▪ 15% weight loss ▪ Splenomegaly 12 cm below costal margin ▪ No sibling donor	▪ WBC: 32 x 10^9/L ▪ Blasts: 1% ▪ Hb: 14.5 g/dL ▪ Platelets: 367 x 10^9/L ▪ LDH: 675 units	▪ 20 mg dose twice-daily ▪ After 6 months, spleen has improved but remains 3 cm below costal margin ▪ Intermittent constitutional symptoms

Additionally, biopsy results and mutational analyses confirm a diagnosis of PMF

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Case 3: Combination Therapy via a Clinical Trial

Susan is a classic case of "suboptimal response"

- *Some benefit from JAK inhibitor therapy, but lack of complete success suggests a need for more potent therapy*

Combination-based clinical trials an option

- *Many trials are testing JAK inhibitor-based combination in MF—Susan is likely a good candidate for such options: ruxolitinib + PI3Kδi (Parsaclisib,[1] umbralisib[2]); ruxolitinib + BETi (CPI-0610)[3]; ruxolitinib + HSP90i (PU-H71); ruxolitinib + Bcl-2/Bcl-xLi (navitoclax)*

Definitions of sub-optimal response to ruxolitinib vary across trials

[1]Daver N, et al. ASH 2018. Abstract 353. [2]Moyo TK, et al. EHA 2018. Abstract S133. [3]Hoffman R, et al. EHA 2019. Abstract S831.

Suboptimal Response to Ruxolitinib (Parsaclisib Trial)

- Treated with ruxolitinib for ≥6 months with stable dose for ≥8 weeks immediately prior to enrollment
- Palpable spleen >10 cm below left subcostal margin on physical examination at screening

OR

- Palpable spleen 5–10 cm below left subcostal margin on physical examination **AND** active symptoms of MF at the screening visit defined as one symptom score ≥5 or two symptom scores ≥3 each, using the Screening Symptom Form*

MF=myelofibrosis
Screening Symptom Form: 10-point scale for each of the 7 symptoms. Symptoms include: night sweats, pruritus, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, and inactivity.
Daver N, et al. ASH 2018. Abstract 353

Challenging Scenarios: Evidence-based Solutions

Anemia

- Ruxolitinib + ESA ± danazol ± IMiD
- Consider pacritinib* or momelotinib* or adding luspatercept* or sotatercept* or CPI- 0610* to ruxolitinib

Thrombocytopenia

<50 x10^9/L:
Consider low dose ruxolitinib ± danazol ± IMiD or pacritinib*

<50 x10^9/L refractory to ruxolitinib: consider pacritinib*

*Investigational

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Challenging Scenarios: Evidence-based Solutions (Cont'd)

Progression of spleen and/or symptoms on ruxolitinib	▪ Dose escalation or switch to alternative JAK inhibitor (eg, fedratinib as per JAKARTA-2) ▪ Clinical trial of combination therapy ▪ Allo SCT if applicable (best before progression)
Progression to accelerated or blast phase	▪ Perhaps continue ruxolitinib; retrospective evidence of benefit (Masarova ASH 2017) ▪ Combination of ruxolitinib with an HMA ▪ Intensive chemo and allo SCT if appropriate