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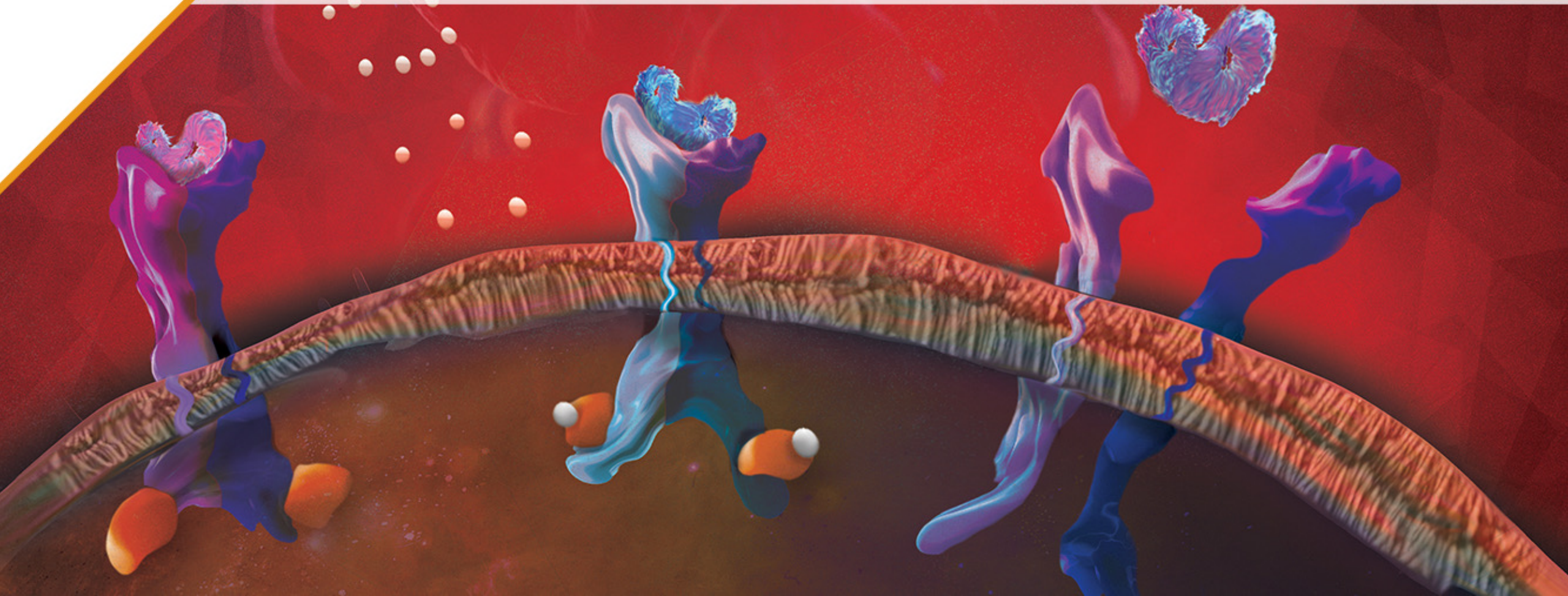
Incorporating Scientific Advances into Myelofibrosis Treatment Plans:

A Quality Improvement Initiative



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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Summarize myelofibrosis disease burden and impact on patients' quality of life
- Apply guideline-recommended, evidence-based prognostic and risk stratification approaches in clinical practice
- Evaluate clinical safety, efficacy data, and tolerability/durability data for approved and emerging therapeutic agents/combinations, including data pertaining to improving quality of life and reducing symptom burden (anemia and transfusion dependency)
- Develop personalized care and treatment plans that incorporate disease-specific and patient-specific factors

Chapter 1
MF Symptom Burden and QOL Impact

Topics for Discussion

- MF treatment planning
- Assessing symptom burden: evolution of tools
- Symptom burden throughout the disease continuum
- Tracking symptoms as part of treatment planning
- Impact of symptoms on QOL

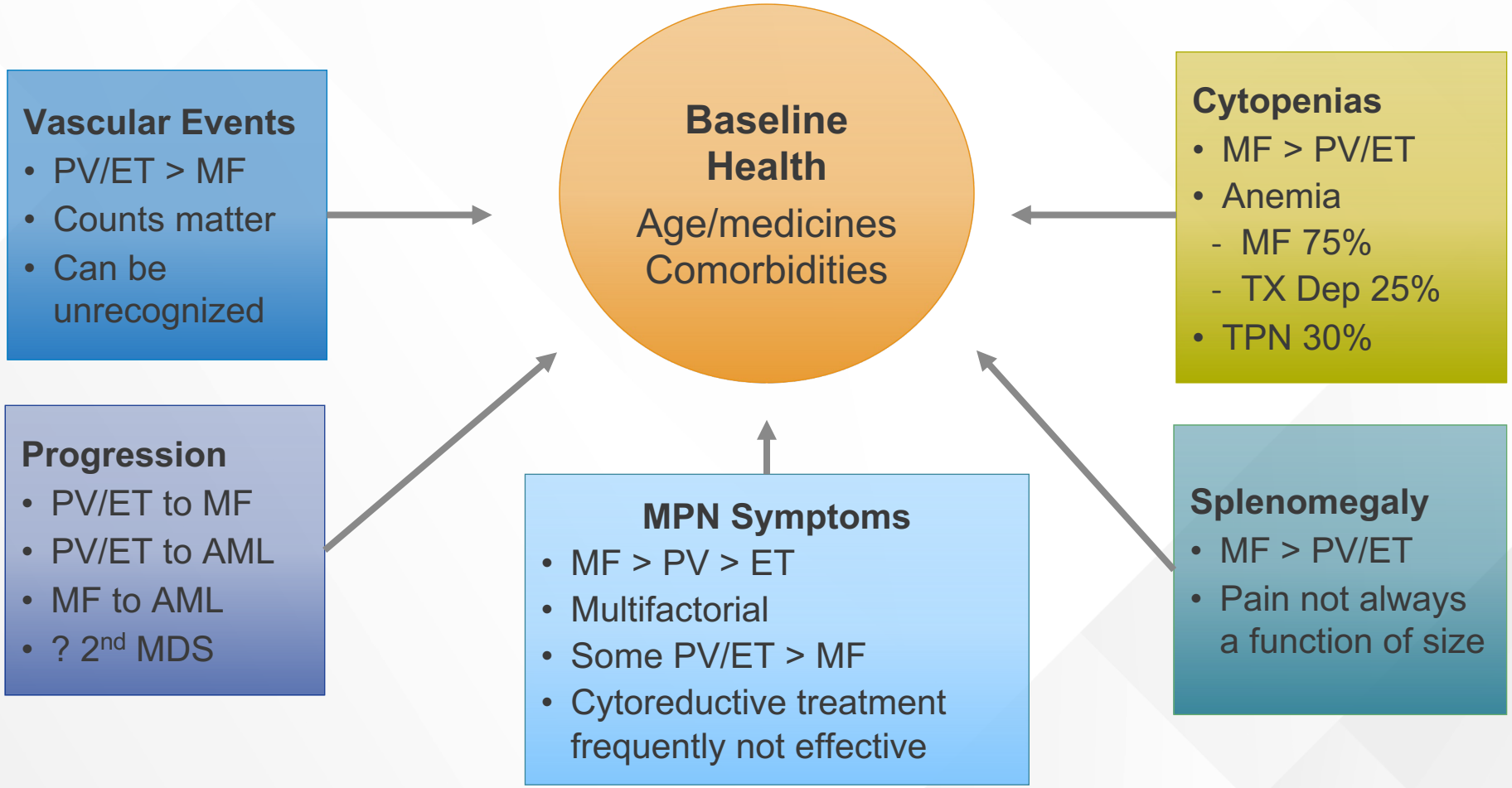
MF, myelofibrosis; QOL, quality of life.

Myelofibrosis Treatment Planning

- Staging myelofibrosis and treatment goals
  - MF symptoms
  - Molecular phenotype
  - Prognostic scores
  - Burden and disease phenotype
- Treatment of myelofibrosis
  - JAK inhibition and rationale
    - Ruxolitinib
    - Fedratinib
    - Pacritinib
    - Momelotinib
  - Success, failure and monitoring

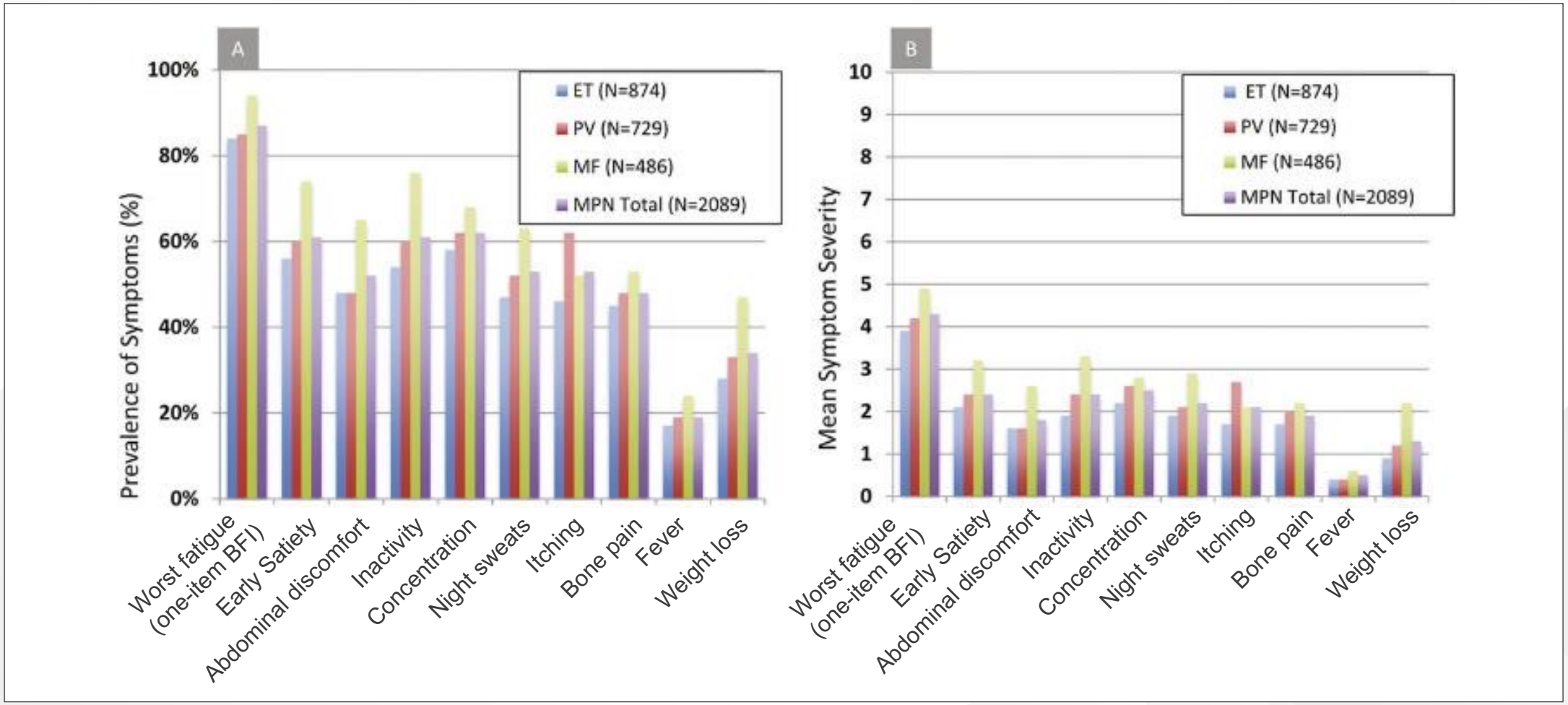
JAK, Janus kinase.

Assessing MPN Burden – WHO Diagnosis Does Not Tell Whole Story



AML, acute myeloid leukemia; ET, essential thrombocythemia; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; QOL, quality of life; TPN, thrombocytopenia; TX Dep, treatment dependent; WHO, World Health Organization.
Courtesy of Ruben A. Mesa, MD, FACP.

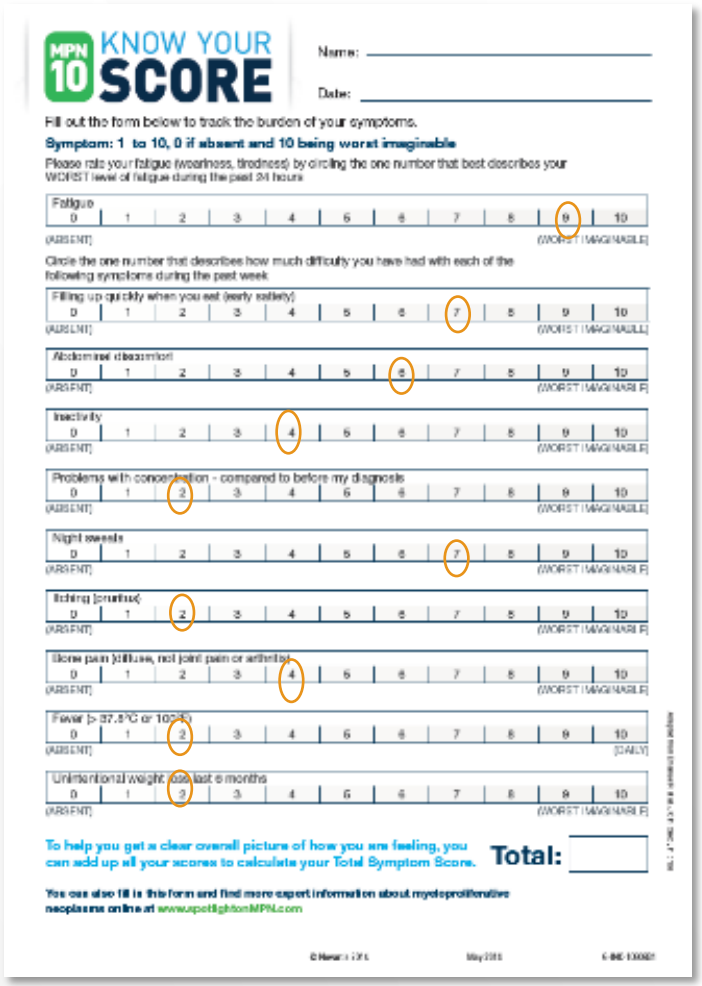
Classic Signs and Symptoms of MPNs

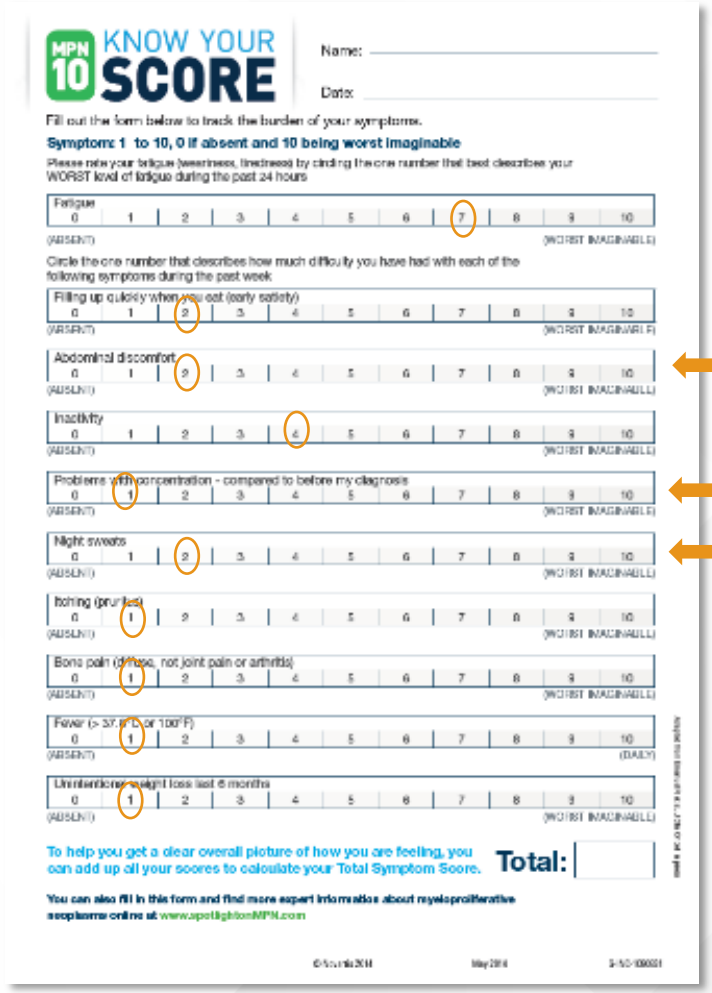


BFI, Brief Fatigue Inventory; ET, essential thrombocytopenia; MF, myelofibrosis; MPNs, myeloproliferative neoplasms; PV, polycythemia vera.

Geyer HL, Mesa RA. *Blood.* 2014;124(24):3529-3537.

MPN-10: Allows Visual Assessment





Emanuel RM, et al. *J Clin Oncol.* 2012;30(33):4098-4103.

Symptoms/Signs Assessed by Each Measure

Item	MPN-10[2]	MFSAF v2.0[3,4]	MFSAF-revised	MFSAF v4.0[5]
Fatigue	X		X	X
Night sweats	X	X	X	X
Itching	X	X	X	X
Abdominal discomfort	X	X	X	X
Pain under ribs on left side		X	X	X
Early satiety	X	X	X	X
Bone pain	X	X*	X	X
Inactivity	X	X**	X**	
Concentration problems	X			
Fever	X			
Weight loss	X			
Scale score range	0-100	0-60	0-70	0-70

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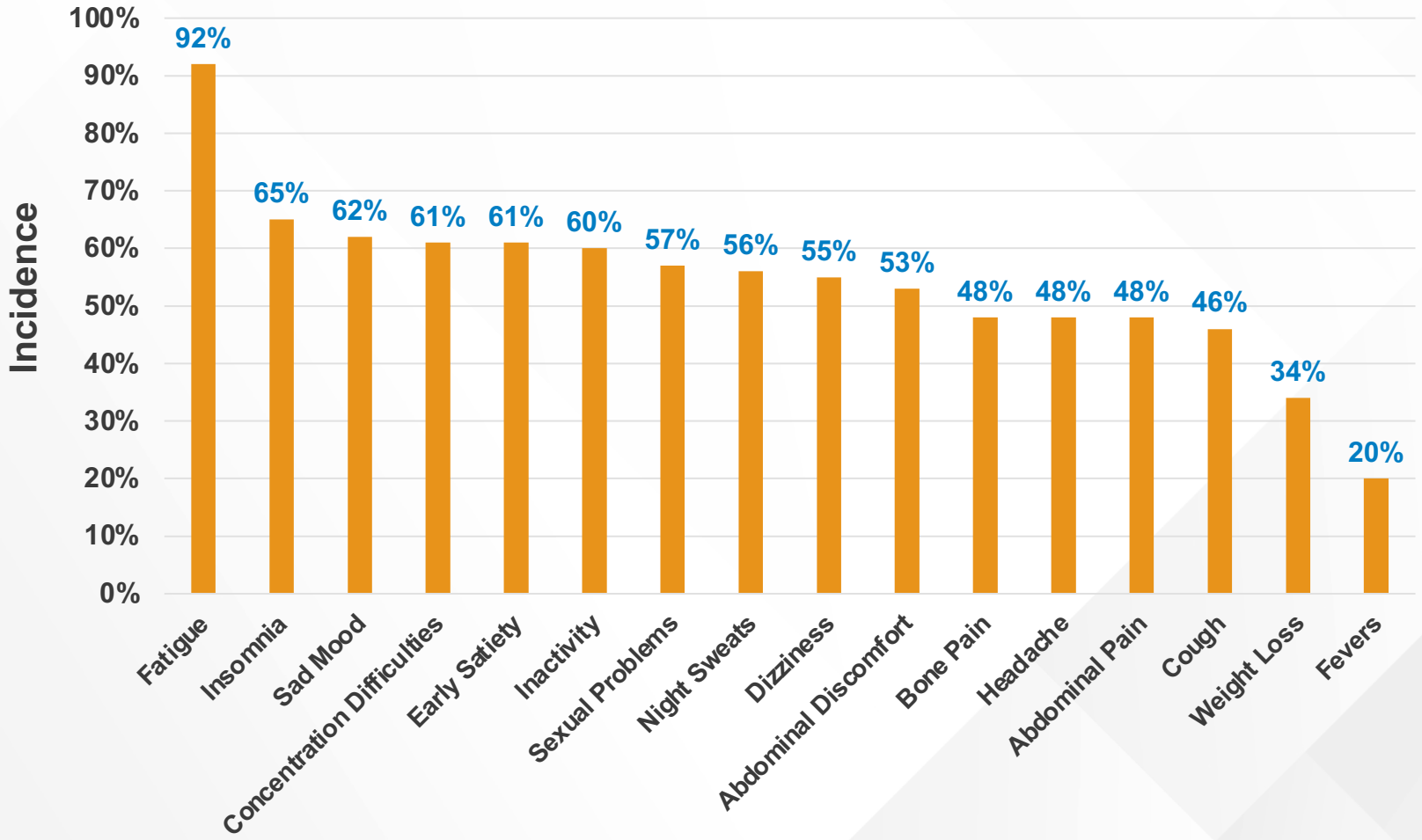
*This item was “bone or muscle pain” for the MFSAF v2.0. **This item was not used to compute the scale score.
MPN, myeloproliferative neoplasm; MFSAF, myelofibrosis symptom assessment form. Adapted from Dueck et al, 2017.

1. Dueck AC, et al. *Blood*. 2017;130(Supplement 1):2168. 2. Emanuel RM, et al. *J Clin Oncol*. 2012;30(33):4098-4103. 3. Mesa RA, et al. *Leuk Res*. 2009;33(9):1199-1203. 4. Mesa RA, et al. EHA 2011. Poster 0912. 5. Gwaltney C, et al. *Leuk Res*. 2017;59:26-31.

MPN Symptom Burden: A Diverse, Disabling Constellation of Symptoms



MPN, myeloproliferative neoplasm.
Courtesy of Ruben A. Mesa, MD, FACP.
Data adapted from Scherber R, et al. *Blood*. 2011;118(2):401-408.

MPN Recent Phase 3 Trials

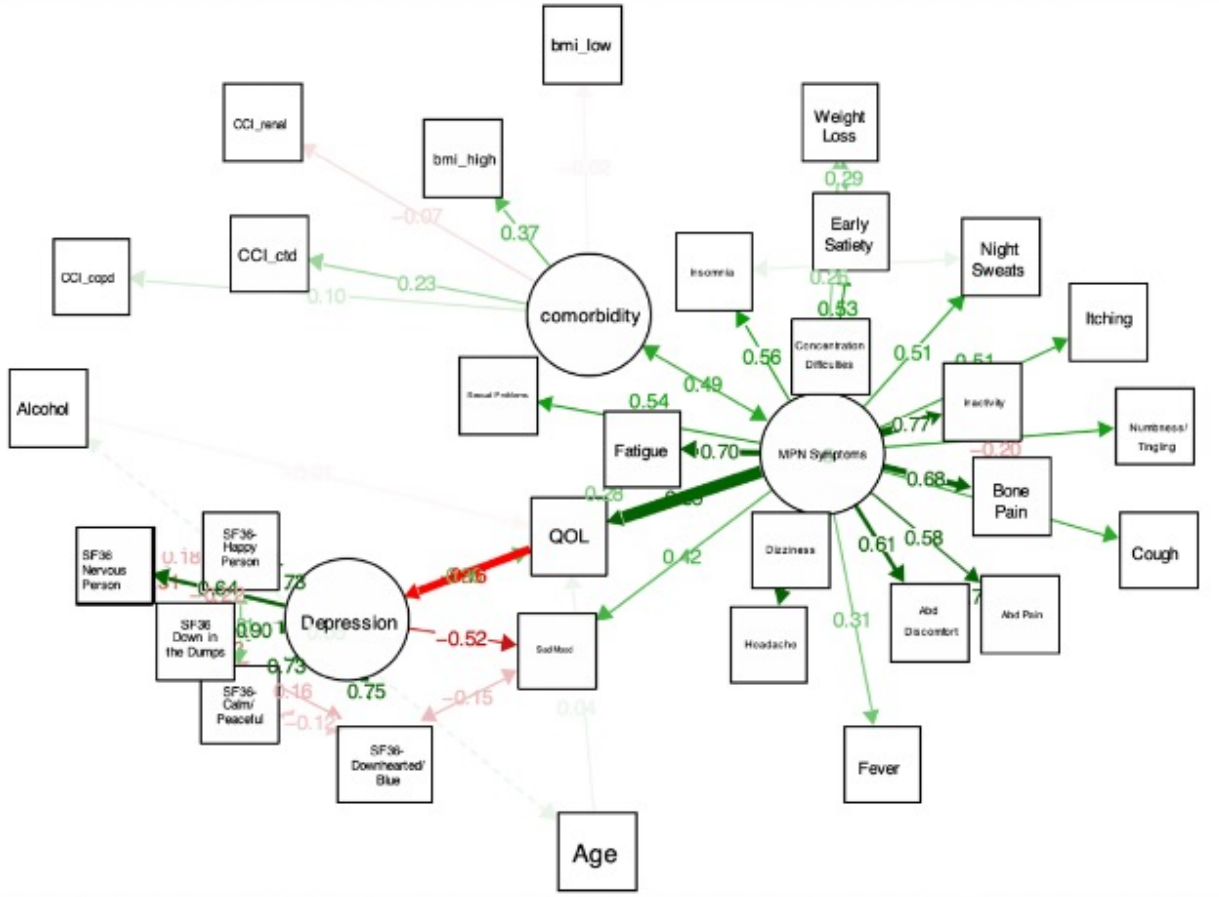
MPN Symptom Assessment

Disease	Drug (Trial)	MPN Symptom Tool
MF	Ruxolitinib (COMFORT 1)	MF-SAF 2.0
	Ruxolitinib (COMFORT 2)	FACT-Lym
	Fedratinib (JAKARTA)	MF-SAF
	Pacritinib (PERSIST 1&2)	MPN-SAF
	Momelotinib (SIMPLIFY 1&2)	MPN-SAF
	Pomalidomide (RESUME)	FACT-An
	Ruxolitinib (RETHINK)	MPN-10
PV	Ruxolitinib (RESPONSE)	MPN-SAF
	Ruxolitinib (RELIEF)	MPN-SAF
	PEG INFa2a (MPD-RC 112)	MPN-SAF
ET	Ruxolitinib (MAGIC)	MPN-SAF
	PEG INFa2a (MPD-RC 112)	MPN-SAF

ET, essential thrombocythemia; FACT-An, Functional Assessment of Cancer Therapy–Anemia; FACT-Lym, Functional Assessment of Cancer Therapy–Lymphoma; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PEG INFa2a, pegylated interferon alfa-2a; PV, polycythemia vera; SAF, symptom assessment tool.

A Structural Equation Model of QOL in Myeloproliferative Neoplasms

SEM was developed using covariance structural analysis modeling with QOL as a dependent variable



BMI, body mass index. CCI_copd, Charlson Comorbidity Index_chronic obstructive pulmonary disorder; CCI_ctd, Charlson Comorbidity Index_connective tissue disorder; QOL, quality of life; SEM, structural equation model; SF-36, Short Form 36 questionnaire.

Scherber RM, et al. *Blood.* 2019;134(suppl 1):2181.

MPN Symptom Burden – Take-Home Points

- MPNs cause a range of disease burden
- MPN symptoms are common and can be severe
- MPN symptoms can affect prognosis, treatment plans, and dosing
- Tracking MPN symptoms is recommended in NCCN Guidelines
- MPN symptoms impact QOL and are linked to MPN biology

MPN, myeloproliferative neoplasm; NCCN, National Comprehensive Cancer Network; QOL, quality of life.

Chapter 2
Molecular Markers & Prognosis

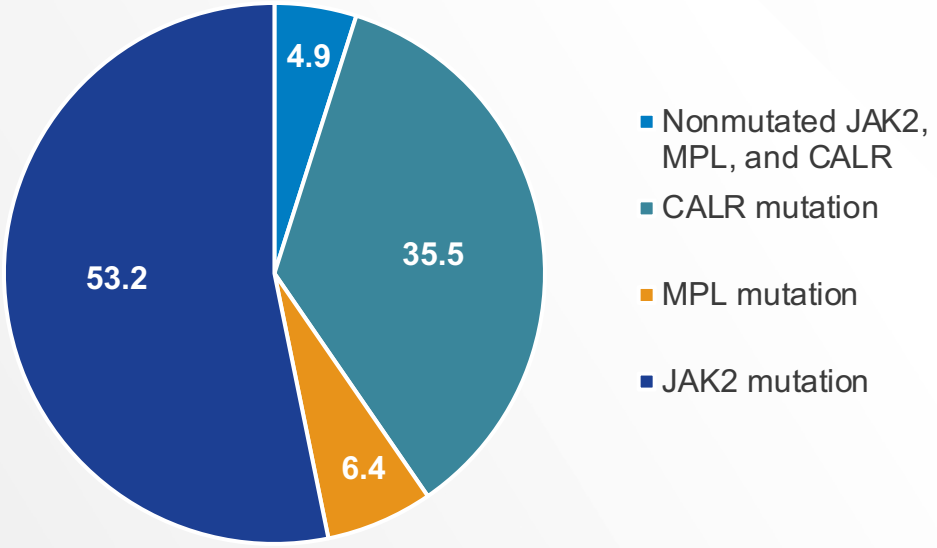
Topic for Discussion

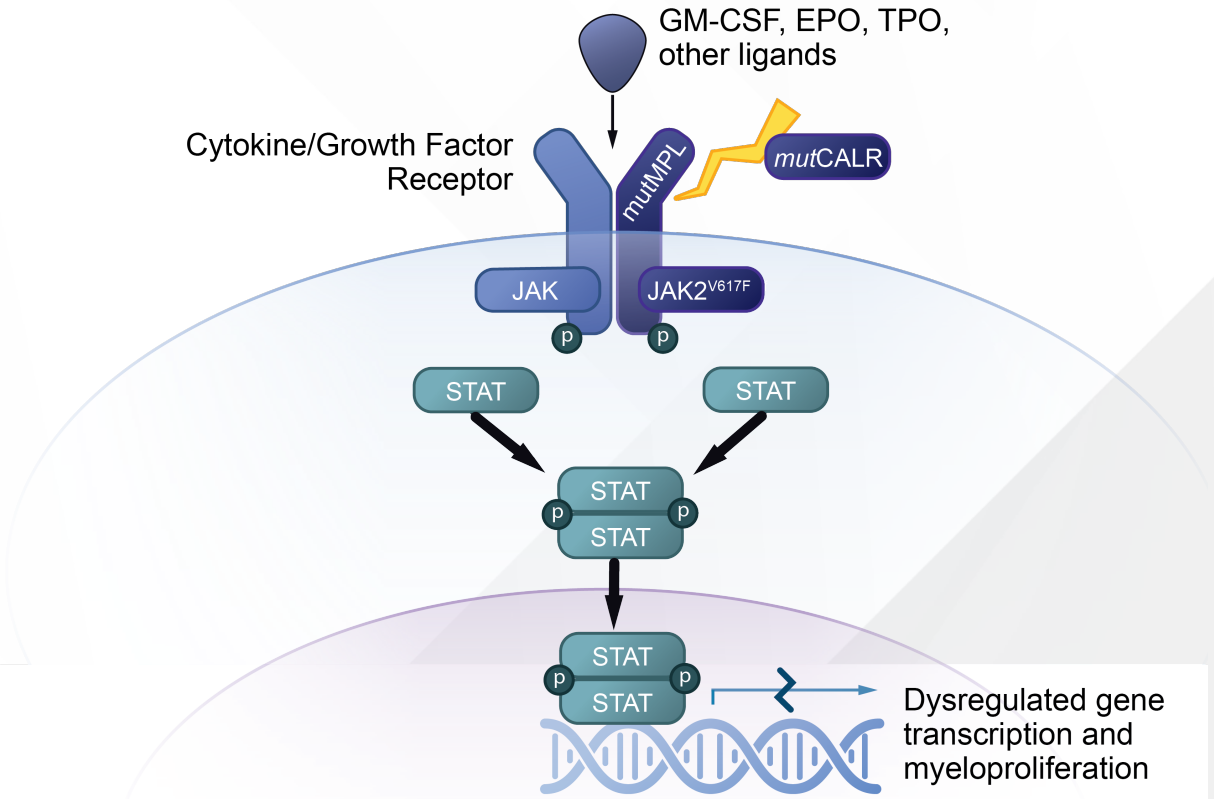
- The role of the JAK-STAT pathway in MF
- Evolution of prognostic models in MF
- Clinical prognostic models
- Mutation-enhanced prognostic scoring systems
- Guideline recommendations for risk stratification of MF
- Scoring systems for sMF and HSCT

HSCT, hematopoietic stem-cell transplantation; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MF, myelofibrosis; sMF, secondary myelofibrosis.

The Relevance of the JAK-STAT Pathway in MF

- JAK/STAT pathway plays a central role in cell proliferation, differentiation, and survival[1-3]
- JAK2 V617F mutation is present in about half of patients with primary MF.[4]

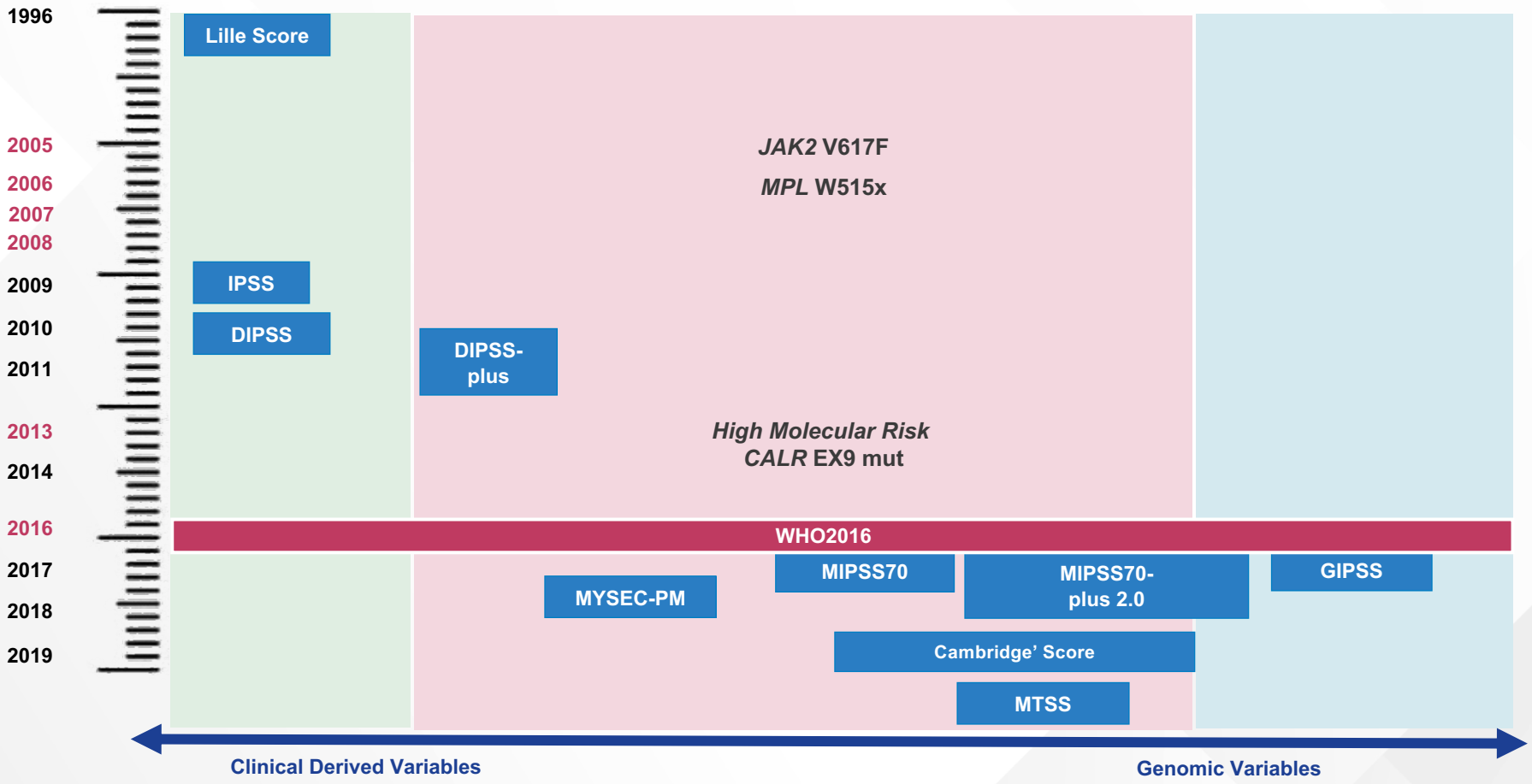




CALR, calreticulin; EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; JAK-STAT, Janus kinase-signal transducer and activator of transcription; TPO, thrombopoietin.

1. Schwartz DM, et al. *Nat Rev Drug Discov*. 2017;16:843-862; 2. O'Sullivan JM, Harrison CN. *Mol Cell Endocrinol*. 2017;451:71-79; 3. Tefferi A. *Am J Hematol.* 2021;96:145-162; 4. Klampfl T, et al. *N Engl J Med*. 2013;369(25):2379-90.

The Evolution of Prognostic Models in MF



DIPSS, Dynamic IPSS; GIPSS, genetically inspired prognostic scoring system; IPSS, International Prognostic Scoring System; MIPSS, Mutation-Enhanced International Prognostic Score System; MTSS, Myelofibrosis Transplant Scoring System; MYSEC-PM, MYelofibrosis SECondary to PV and ET prognostic model; WHO, World Health Organization.

Slide Courtesy of Dr. Andrew Kuykendall – Moffitt Cancer Center

"Clinical" Prognostic Models of Myelofibrosis[1]

Parameter	IPSS[2]	DIPSS[3]	DIPSS-Plus[4]
Age > 65 y	Yes (1 point)	Yes (1 point)	Yes[a]
Hgb < 10g/dL	Yes (1 point)	Yes (2 points)	Yes[a]
WBC > $25x10^9$/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 x 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

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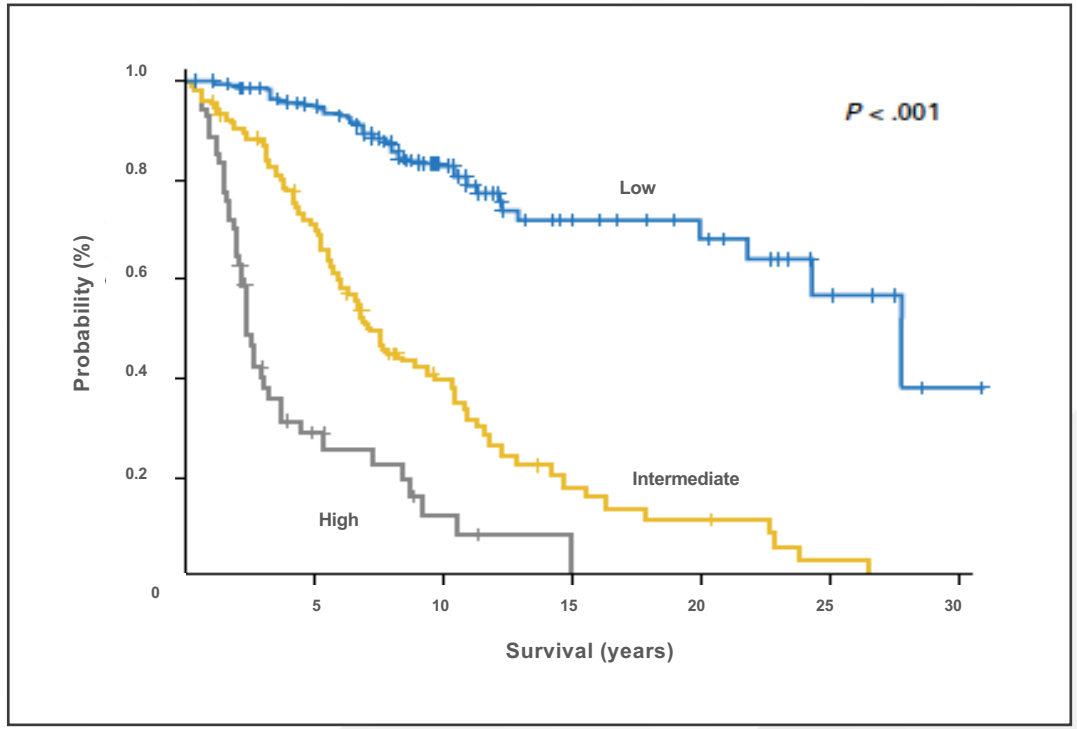
DIPSS, Dynamic IPSS; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; PB, peripheral blasts; RBC, red blood cell; WBC, white blood cell

1. Bose P, Verstovsek S. *Cancer*. 2016;122(5):681-692. 2. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.
3. Passamonti F, et al. *Blood*. 2010;116(15):2857-2858.
4. Gangat N, et al. *J Clin Oncol*. 2011;29(4):392-397.

MIPSS70-plus: Integrated Genetic and Clinical Score

Variables	Rank
Hb <100g/L	1
WBC >25x10^9/L	2
PLT <100x10^9/L	2
PB blasts ≥2%	1
Constitutional Symptoms	1
Grade ≥2 BM fibrosis	**1**
Absence CALR Type1	**1**
HMR category*	**1**
≥2 HMR mutations	**2**

Risk category	Score	OS (y)	HR
Low	0-1	27.7	1
Intermediate	2-4	7.1	5.5 (3.8-8.0)
High	**≥5**	**2.3**	**16.0 (10.2-25.1)**



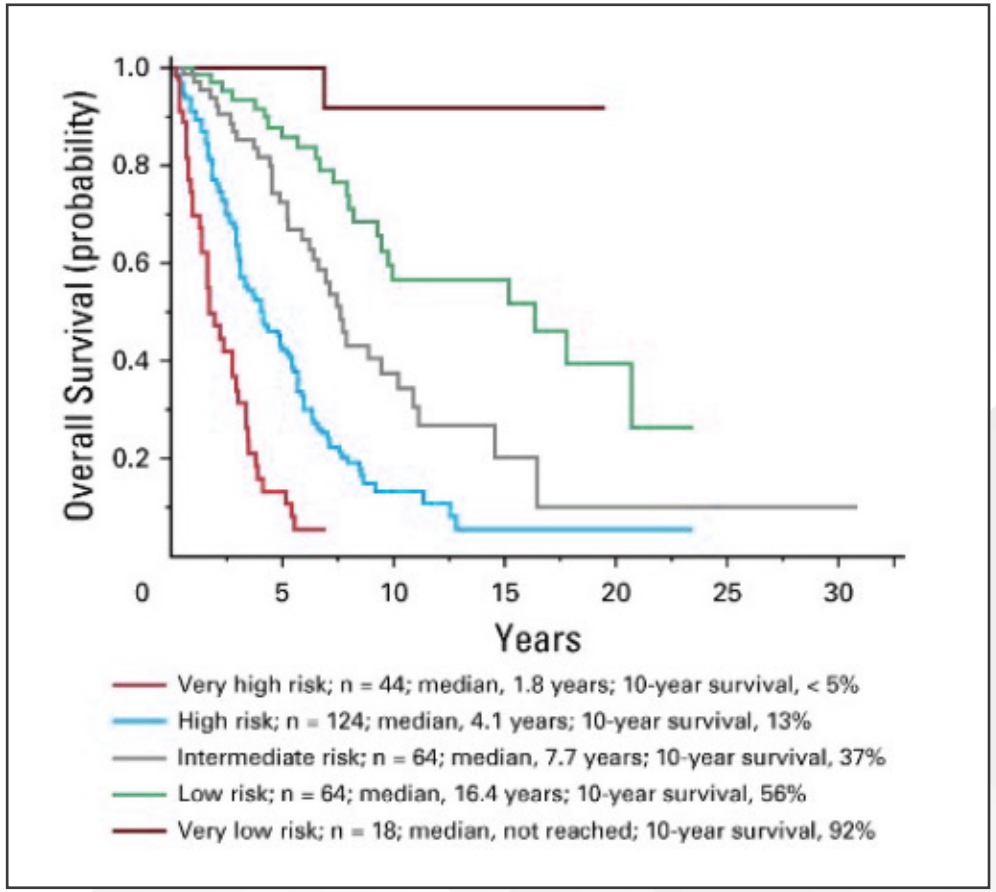
http://www.mipss70score.it/index.html

* HMR category = any mutation in: *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*
BM, bone marrow; CALR, calreticulin; Hb, hemoglobin; HMR, high molecular risk; MIPSS, Mutation-Enhanced International Prognostic Score System; OS, overall survival; PB, peripheral blasts; PLT, platelets; RBC, red blood cell; WBC, white blood cell.
Guglielmelli P et al. *J Clin Oncol*. 2018;36(4):310-318; Tefferi A et al. *J Clin Oncol*. 2018;36(17):1769-1770.

MIPSS70-plus v2.0: Mutation Enhanced Prognostic Score System

Variables	Weighted Value
Severe anemia: Hb <80 g/L (female); <90 g/L (male)	2
Moderate anemia: Hb 80 to 99 g/L (female); 90 to 100 g/L (male)	1
PB blasts ≥2%	1
Constitutional Symptoms	2
Absence CALR Type1	2
HMR*	2
≥2 HMR mutations	3
Unfavorable Karyotype*	**3**
Very High Risk Karyotype*	**4**

Risk category	Score	10-years OS (y)
Very Low	0	92%
Low	1-2	56%
Intermediate	3-4	37%
High	5-8	13%
Very High	≥9	<5%



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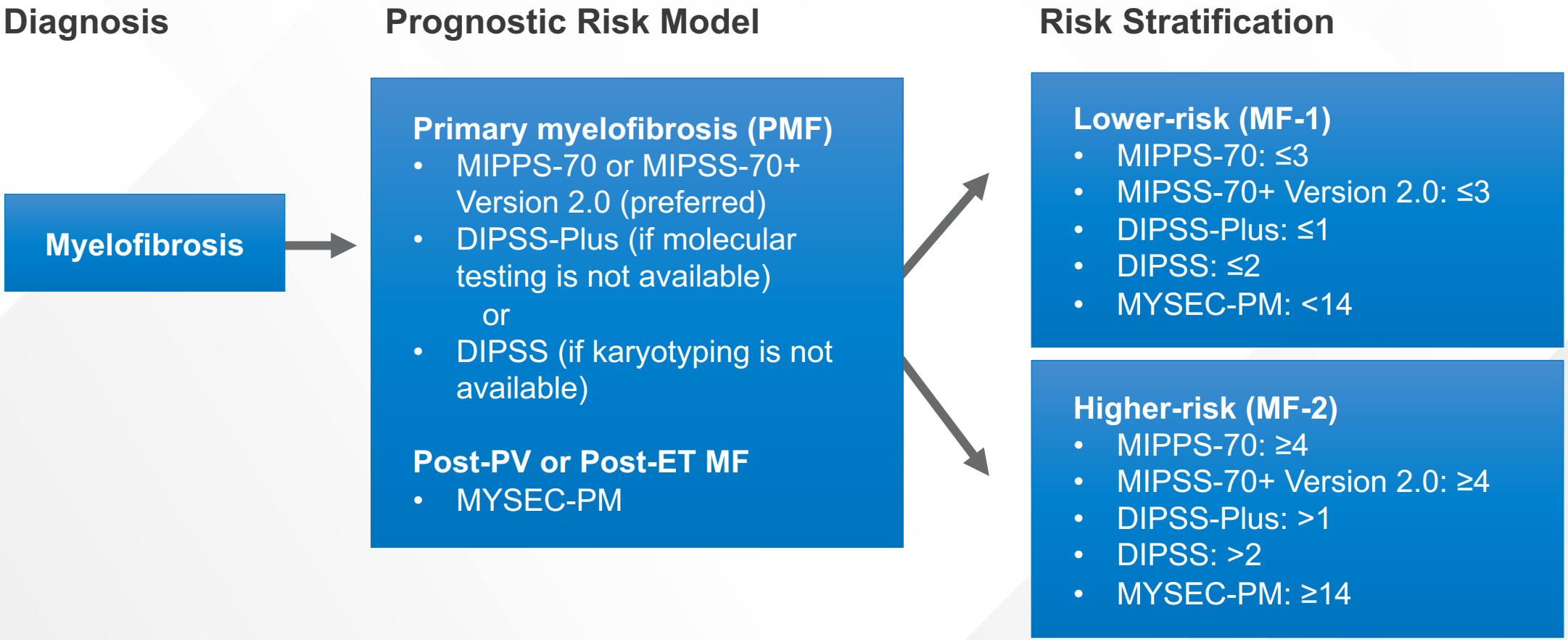
*More information available at: http://www.mipss70score.it/index.html
CALR, calreticulin; Hb, hemoglobin; HMR, high molecular risk; MIPSS, Mutation-Enhanced International Prognostic Score System; OS, overall survival; PB, peripheral blasts.
Tefferi A et al. *J Clin Oncol*. 2018;36(17):1769-1770.

NCCN Simplified Risk Stratification for MF



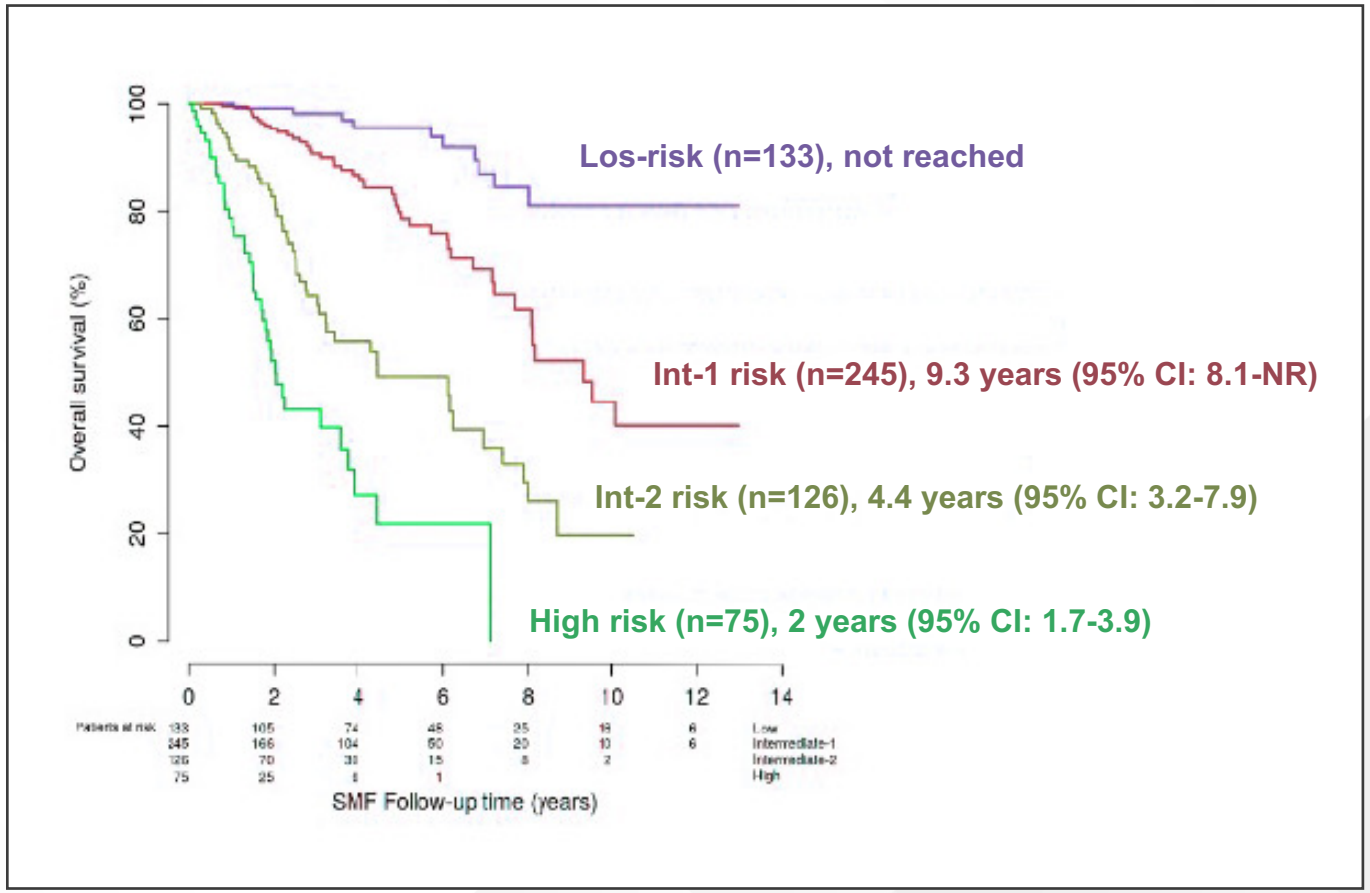
DIPSS, Dynamic International Prognostic Score System; MF, myelofibrosis; MIPSS, Mutation-Enhanced International Prognostic Score System; MYSEC-PM, MYelofibrosis SECondary to PV and ET prognostic model; NCCN, National Comprehensive Cancer Network.

NCCN Guidelines Myeloproliferative Neoplasms (Version 3.2022). NCCN.org.

The MYSEC-PM Score for Patients with sMF

Covariates	Points
Age, years	0.15
Hemoglobin <11 g/dL	2
Platelet < 150 x10^9/L	1
Circulating blast cells ≥ 3%	2
CALR-unmutated genotype	2
Constitutional symptoms	1

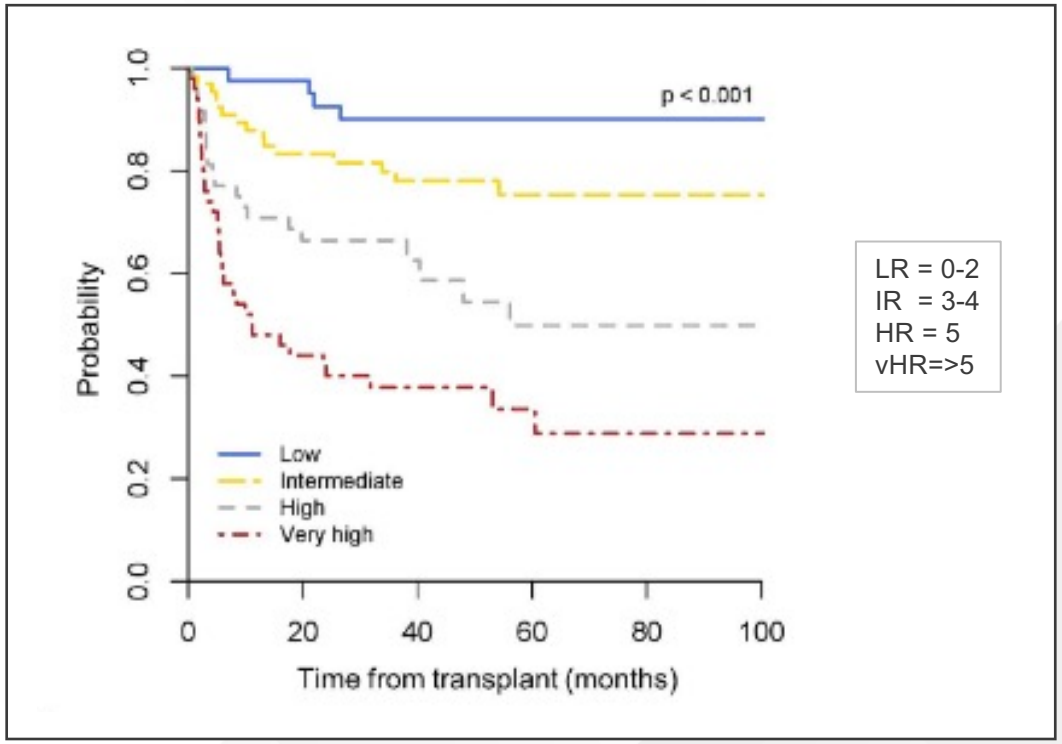
LR = <11 points
Int-1 = 11-<14
Int-2 = 14-<16
High = ≥16



CALR, calreticulin; MYSEC-PM, MYelofibrosis SECondary to PV and ET prognostic model; sMF, secondary myelofibrosis.
Passamonti F, et al. *Leukemia.* 2017; 31(12):2726-2731.

Comprehensive Clinical-Molecular Transplant Scoring System for MF Patients Undergoing HSCT (MTSS)

	Hazard ratio (95% CI)	*P*	Weighted score
Age ≥ 57 years	1.65 (1.15-2.36)	0.006	1
Karnofsky performance status <90%	1.50 (1.06-2.13)	0.021	1
non-CALR/MPL driver mutation genotype	2.40 (1.30-4.71)	0.012	2
ASXL1 mutation	1.42 (1.01-2.01)	0.041	1
HLA-mismatch unrelated donor	2.08 (1.45-2.97)	<0.001	2
WBC count >25x10^9/L	1.57 (1.16-2.41	0.007	1
Platelet count <150x10^9/L	1.67 (1.16-2.40)	0.006	1



The 5-year survival was 90% (low), 77% (intermediate), 50% (high), and 34% (very high) in the training cohort (n = 205) (*P* <0.001, respectively)

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CALR, calreticulin; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation. MTSS, Molecular Transplant Scoring System; vHR, very high risk;WBC, white blood cell

Gagelmann N, et al. *Blood*. 2019;133(20):2233-2242.

MF Molecular Markers & Prognosis Take Home Points

- Driver mutations (JAK2-V617F, CALR, MPL) in vast majority of patients with MF
- Some additional somatic mutations associated with adverse prognosis in MF
- Many prognostic models for MF that incorporate clinical features and molecular findings

CALR, calreticulin; MF, myelofibrosis; JAK, Janus kinase; MPL, thrombopoietin receptor gene.

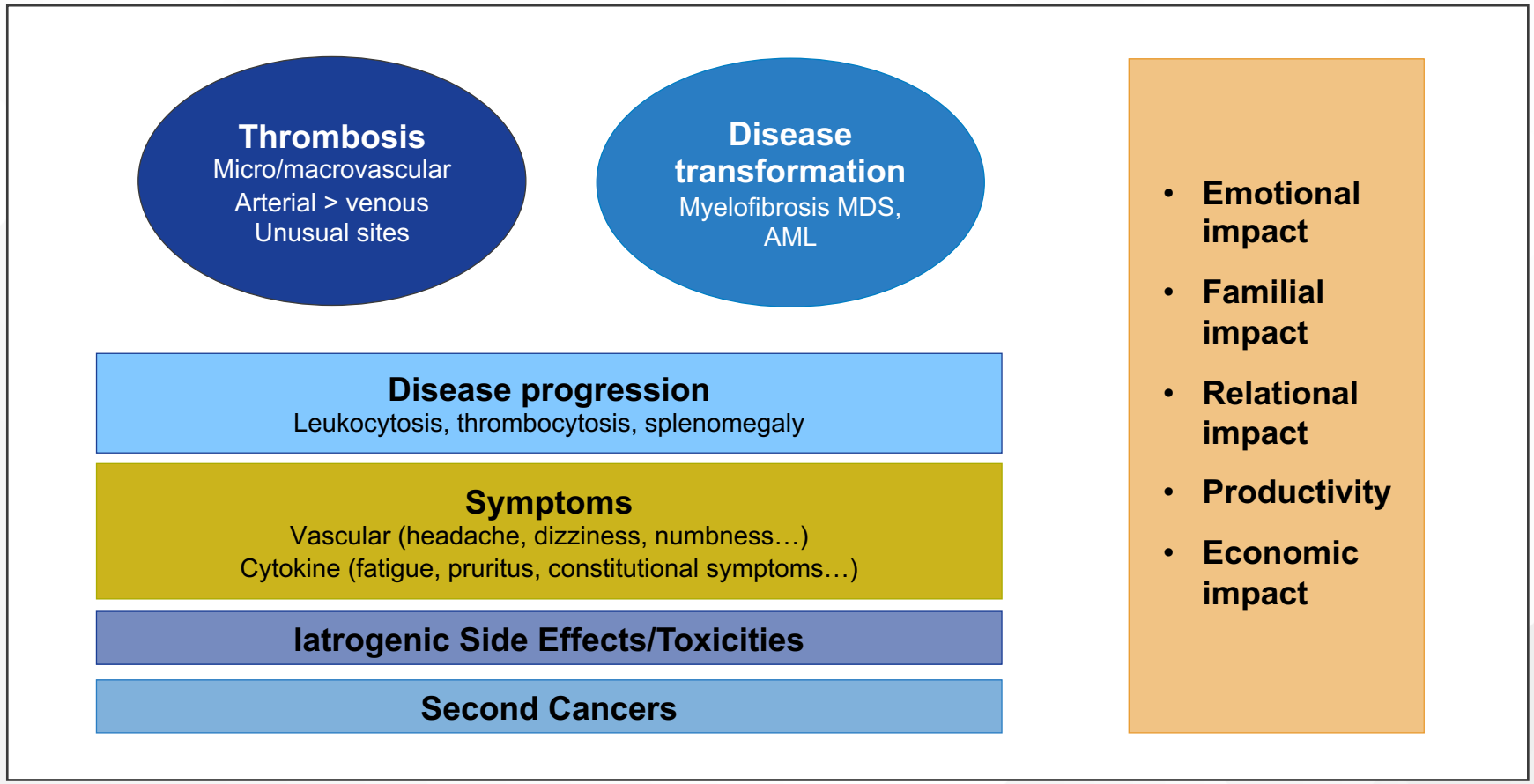
Chapter 3
Treatment and Management of MF

Topics for Discussion

- Goals of management
- Current NCCN guideline recommendations
- JAK inhibitor landscape
- First-line setting
  - Ruxolitinib
  - Fedratinib
- Second-line setting
  - Ruxolitinib
  - Pacritinib
  - Momelotinib

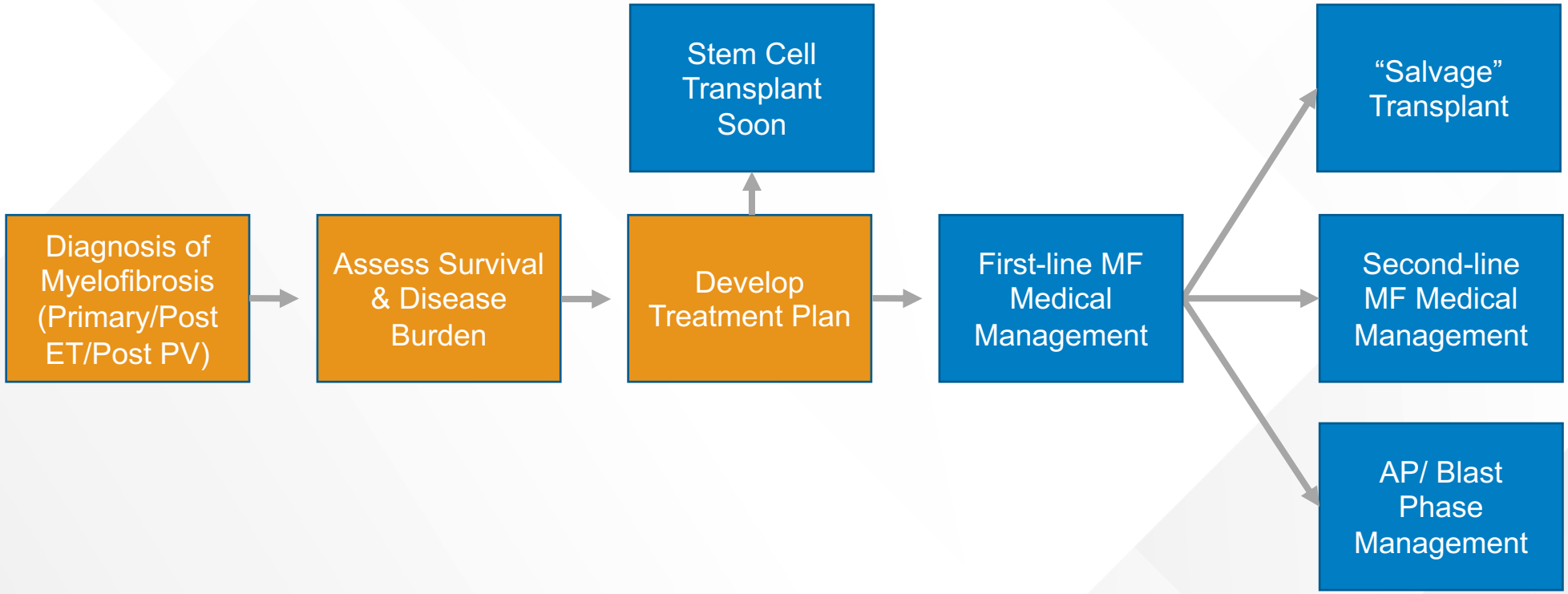
JAK, Janus kinase; NCCN, National Comprehensive Cancer Network

The Burden of Disease, Goals of Management



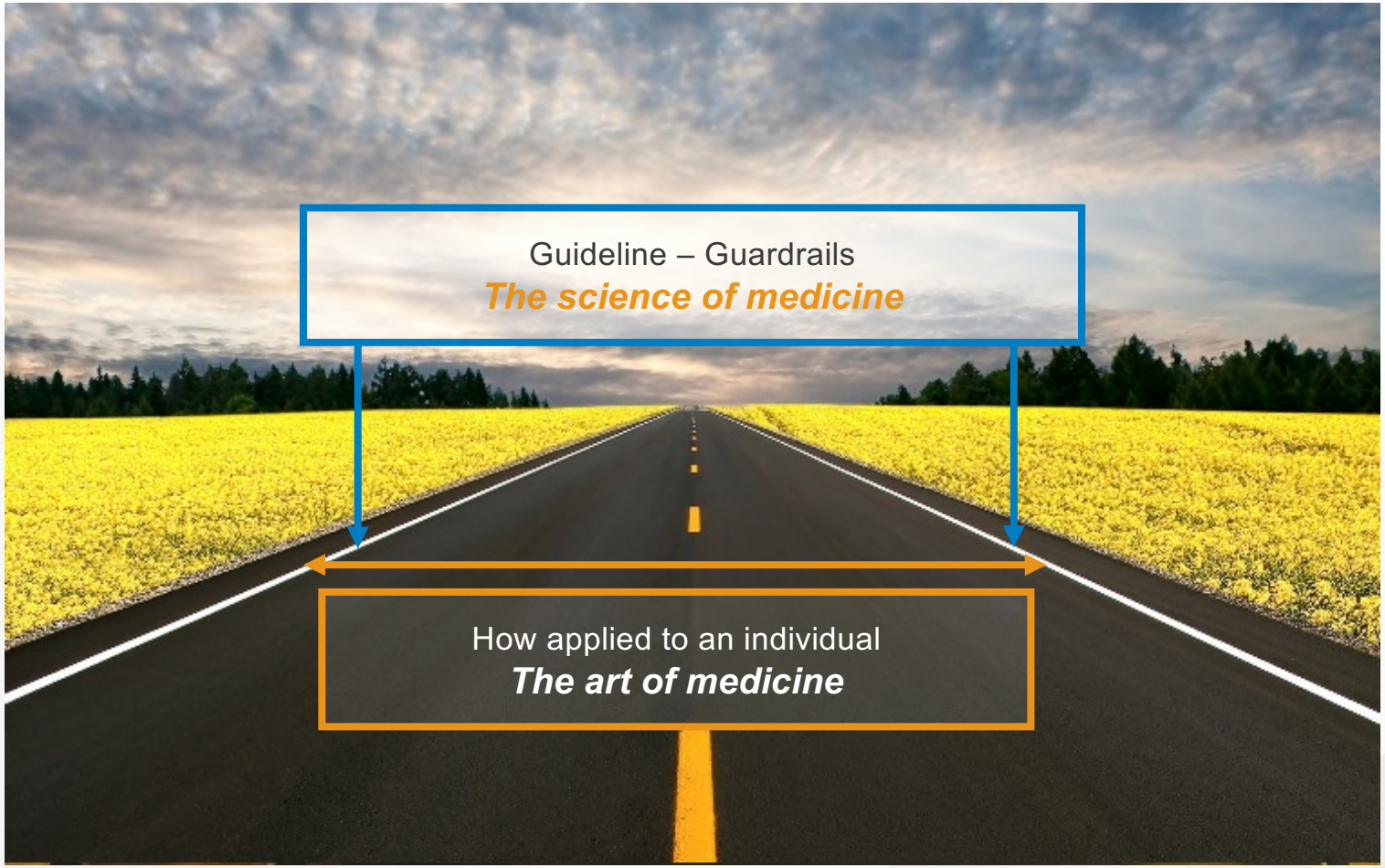
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Management of Myelofibrosis 2023



AP, accelerated phase; ET, essential thrombocytopenia; MF, myelofibrosis; PV, polycythemia vera.
Courtesy of Ruben A. Mesa, MD, FACP.

What Is a Treatment Guideline?



NCCN Guidelines® Summary: Treatment For Myelofibrosis

Risk	Risk Stratification	Treatment Options	

Lower-Risk	• MIPSS-70 ≤3
	• MIPSS-70+ Version 2.0: ≤3
	• DIPSS-Plus: ≤1
	• DIPSS: ≤2
	• MYSEC-PM: <14
		• Clinical trial
		• Observation
		• Useful in certain circumstances:
		  • Ruxolitinib
		  • Peginterferon alfa-2a
		  • Hydroxyurea, if cytoreduction would be symptomatically beneficial	

Higher-Risk	• MIPSS-70 ≥4 • MIPSS-70+ Version 2.0: ≥4 • DIPSS-Plus: >1 • DIPSS: >2 • MYSEC-PM: ≥14	**Transplant candidate**	• Allogeneic HCT
		Platelets <50 x 10^9/L	• Pacritinib or Trial
		Platelets ≥50 x 10^9/L	• Ruxolitinib • Fedratinib • Clinical trial No response or loss of response: • Fedratinib (for patients previously treated with ruxolitinib), Pacritinib PLT <50 x 10^9/L

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DIPSS, Dynamic International Prognostic Score System; HCT, hematopoietic stem cell transplantation; MIPSS, Mutation-Enhanced International Prognostic Score System; MYSEC-PM, MYelofibrosis SECondary to PV and ET prognostic model; NCCN, National Comprehensive Cancer; PLT, platelet.

NCCN Guidelines Myeloproliferative Neoplasms (Version 3.2022). NCCN.org.

NCCN Guidelines® Summary: Management of MF-Associated Anemia

- Rule out coexisting causes:
  - Bleeding
  - Iron
  - Vitamin B12 or folate deficiency
  - Hemolysis
- Treat coexisting causes:
  - Replace iron, folate, vitamin B12, if needed
  - Treat hemolysis if clinically indicated
  - RBC transfusions (leuko-reduced)
- Supportive care

Serum EPO	Management
<500 mU/mL	• ESAs — Darbepoetin alfa — Epoetin alfa • Clinical trial
≥500 mU/mL	Preferred regimens: • Clinical trial Useful in certain circumstances: • Danazol • Lenalidomide +/- prednisone • Thalidomide +/- prednisone

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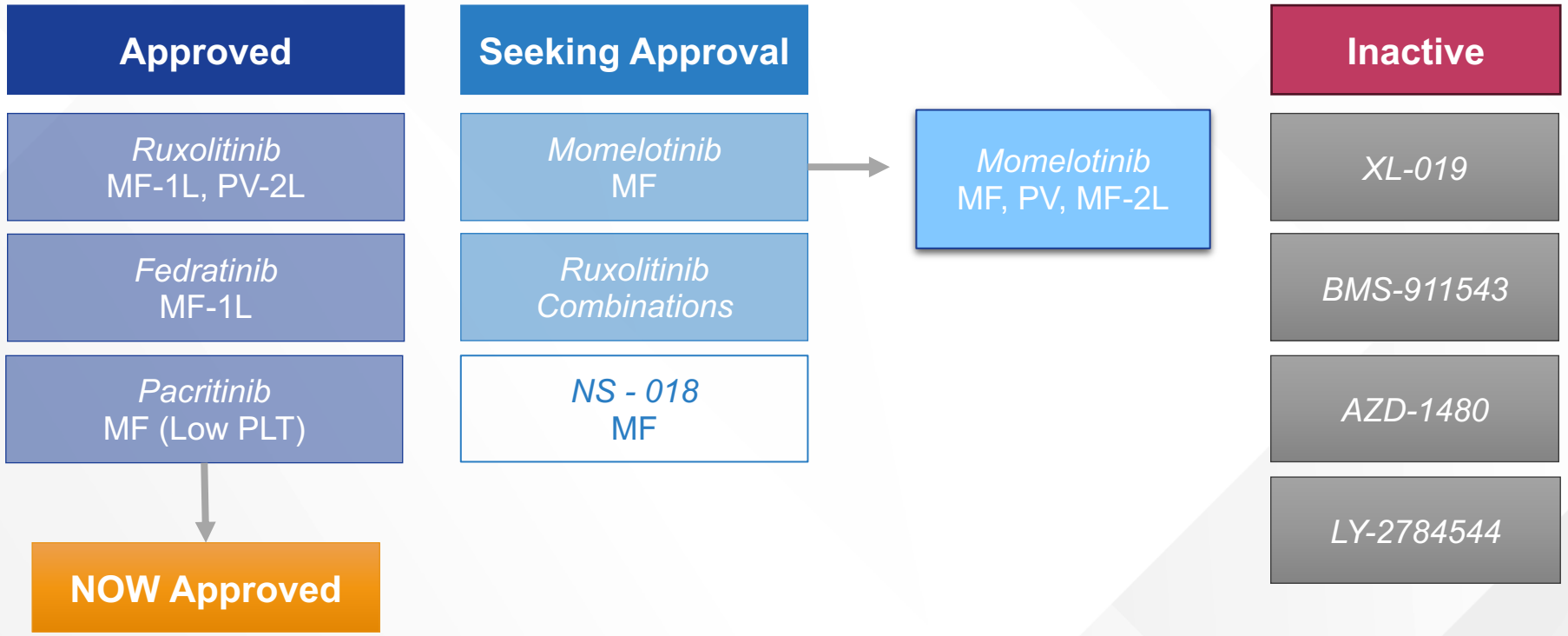
EPO, erythropoietin; ESAs, erythropoiesis-stimulating agents; HCT, hematopoietic stem cell transplantation; MF, myelofibrosis; NCCN, National Comprehensive Cancer Network.; RBC, red blood cell.

NCCN Guidelines Myeloproliferative Neoplasms (Version 3.2022). NCCN.org.

JAK Inhibitor Landscape 2023



JAK, Janus kinase; MF, myelofibrosis; PLT, platelets; PV, polycythemia vera.

COMFORT-I Study Design

Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial

- Patients (≥ 18 y) with int-2 or high-risk MF
- PMF, PPV-MF, or PET-MF
- PLT count ≥ 100,000
- Palpable spleen ≥ 5 cm
- PB < 10%
- ECOG PS ≤ 3
- Refractory or intolerant to or not candidates for available therapy

N = 309

R
1:1

RUX twice daily
- 15 mg twice daily for a PLT count of 100 × 10^9 to 200 × 10^9/L
- 20 mg twice daily for a count > 200 × 10^9 L

N = 155

Placebo

N = 154

Crossover for splenomegaly

N = 36

- Primary endpoint: Number of patients in whom ≥ 35% SVR was achieved from BL to week 24 as measured by MRI (or CT scan in applicable patients)
- Secondary endpoints: Proportion of patients with ≥ 50% reduction in TSS from BL to week 24 as measured by the MF-SAF 2.0, OS, duration of SVR

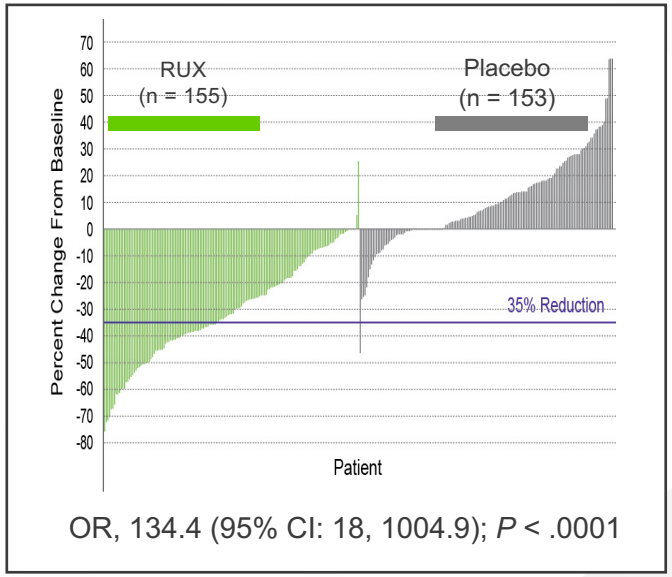
AXIS Medical Education

BL, baseline; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MF, myelofibrosis; MF-SAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; OS, overall survival; PB, peripheral blast; PLT, platelet; PMF, post myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; PET-MF, post-essential thrombocythemia myelofibrosis; R, randomized; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.
Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807.

COMFORT-I Results

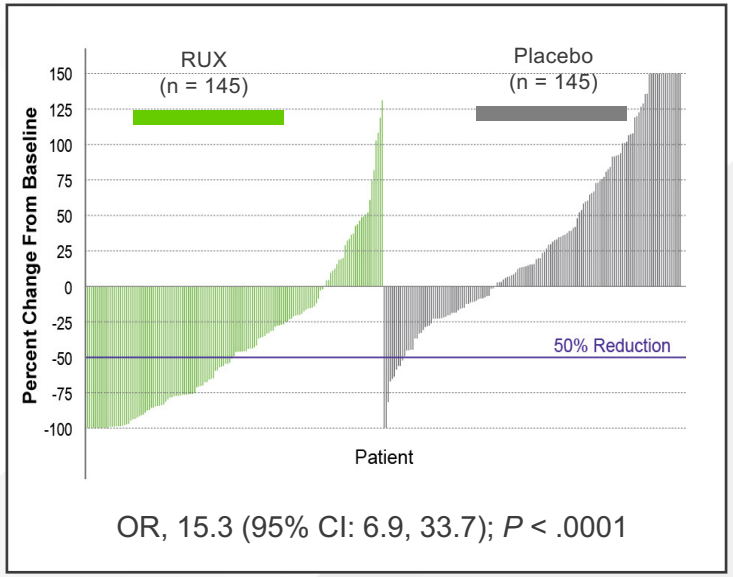
- Primary endpoint: the proportion of patients in whom ≥ 35% SVR was achieved from BL to week 24 (as measured by MRI or CT scan)
  - 41.9% in RUX group reached the primary endpoint vs 0.7% in the placebo group (P < .0001)
  - A similar proportion of patients in the RUX group had a ≥ 50% reduction in palpable spleen length
- SVR responses were seen with RUX in JAK2 V617F-positive patients and JAK2 V617F-negative patients, relative to placebo

SVR at 24 Weeks



OR, 134.4 (95% CI: 18, 1004.9); *P* < .0001

TSS at 24 Weeks



OR, 15.3 (95% CI: 6.9, 33.7); *P* < .0001

AXIS Medical Education

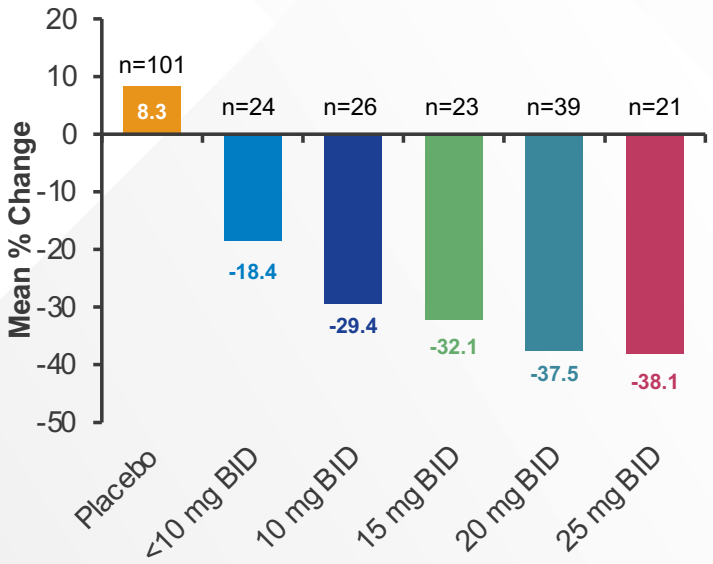
BL, baseline; CT, computed tomography; MRI, magnetic resonance imaging; OR, odds ratio; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.

Verstovsek S et al. *N Engl J Med*. 2012;366(9):799-807.

Ruxolitinib Efficacy by Titrated Dose: COMFORT-I

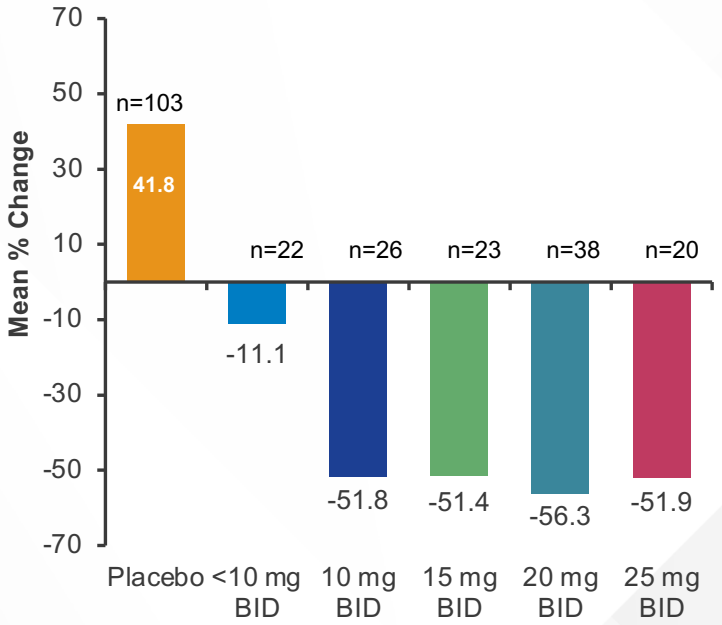
Spleen Volume

Week 24



Total Symptom Score

Week 24



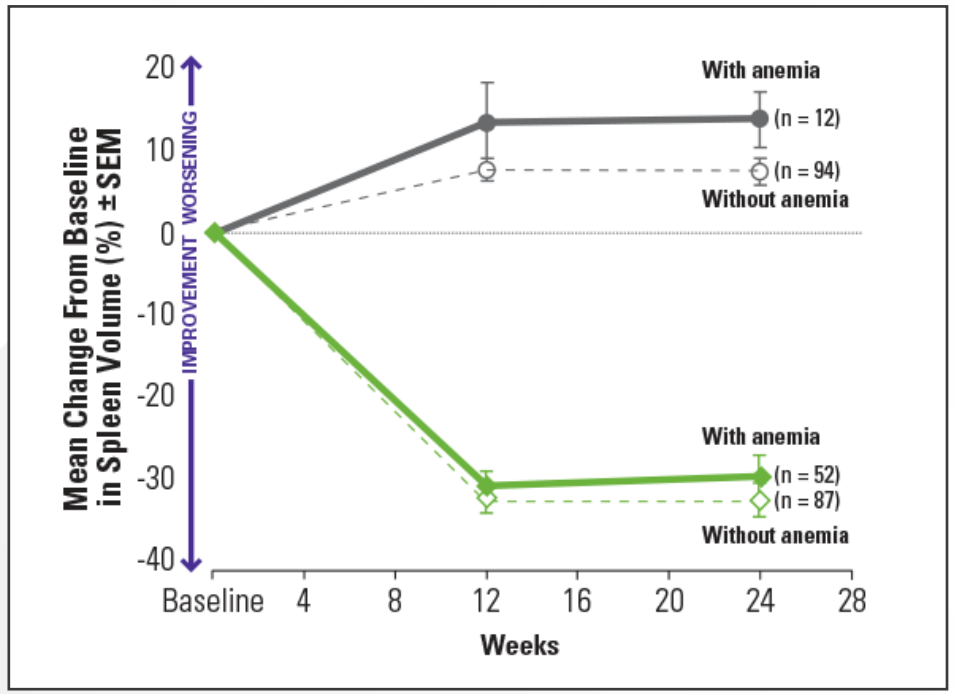
- Avoid starting with low dose!
- Start dosing per guidelines and modify based on platelets if needed
- Doses less than 10 mg BID are not effective long term

BID, twice daily

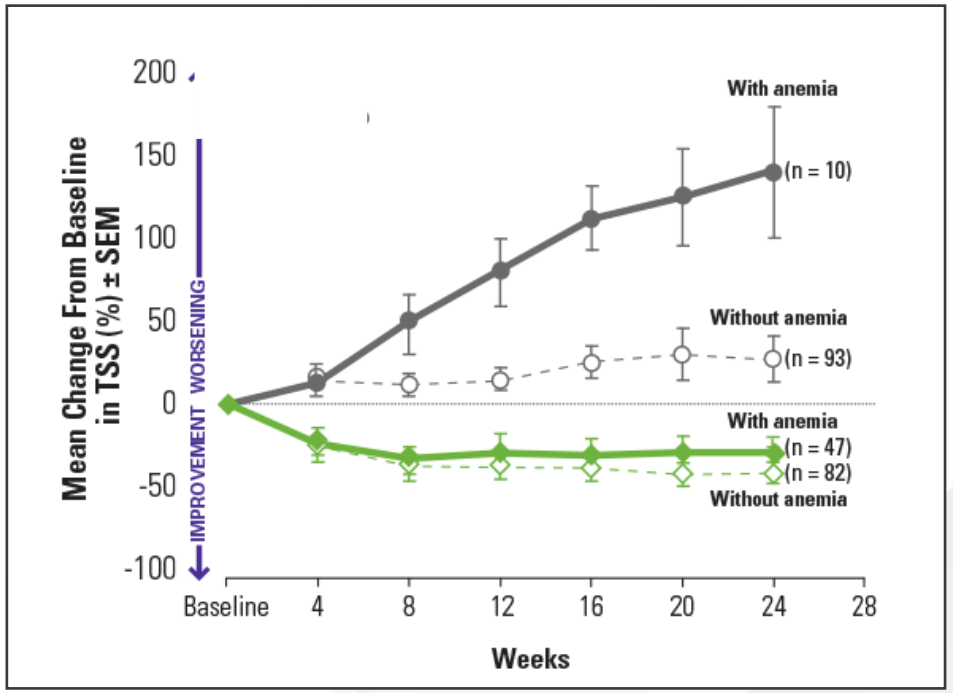
Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807.

Development of Anemia Does Not Affect Response to Ruxolitinib Treatment: COMFORT-I

Spleen Volume



Total Symptom Score



Placebo Ruxolitinib

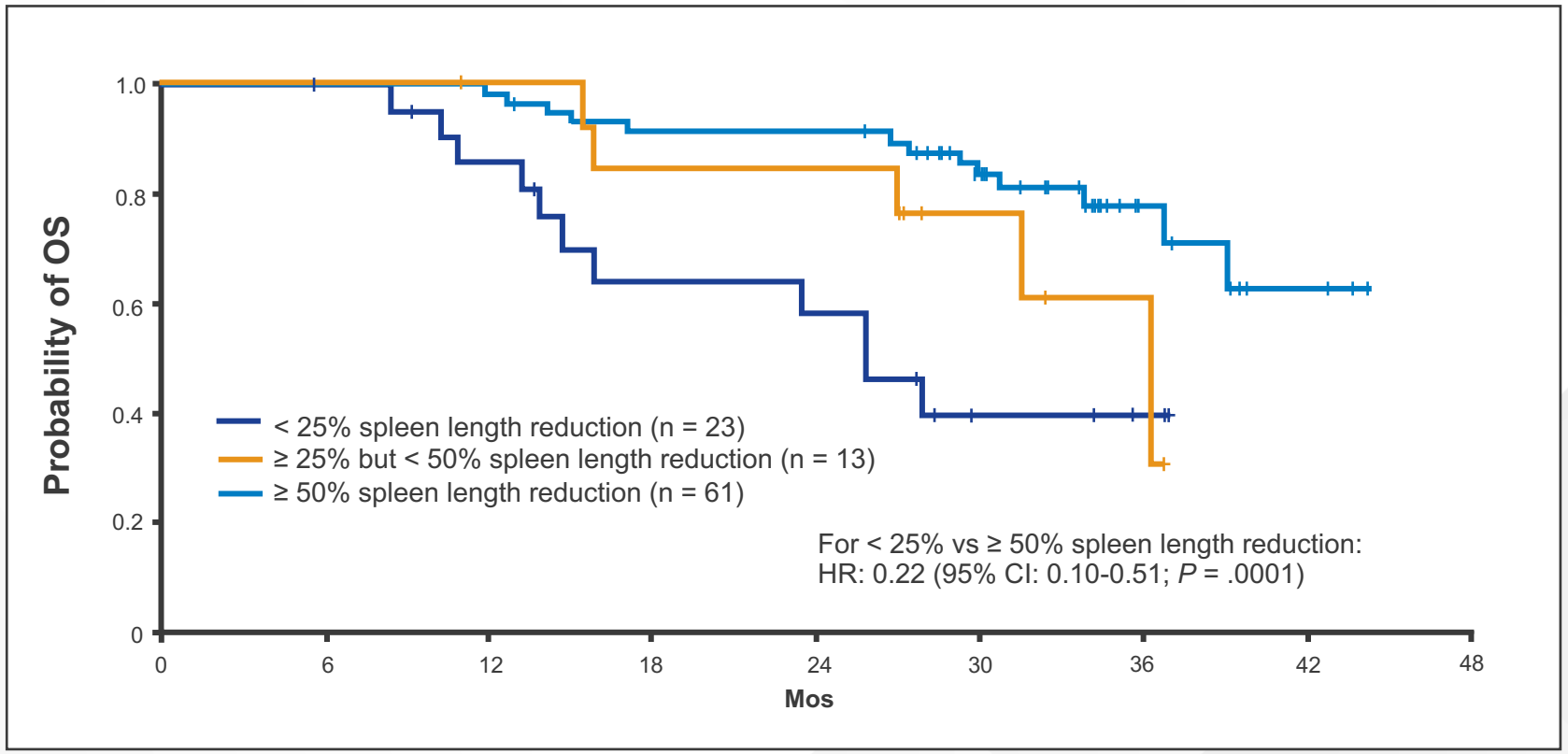
Baseline anemia is not a contraindication for ruxolitinib use

SEM, standard error mean; TSS, total symptom score.

Verstovsek S, et al. Oral presentation at 47th ASCO Annual Meeting; Chicago, IL; June 3-7, 2011. Abstract 6500.

Overall Survival Improves with Spleen Length Reduction in Patients Receiving Ruxolitinib

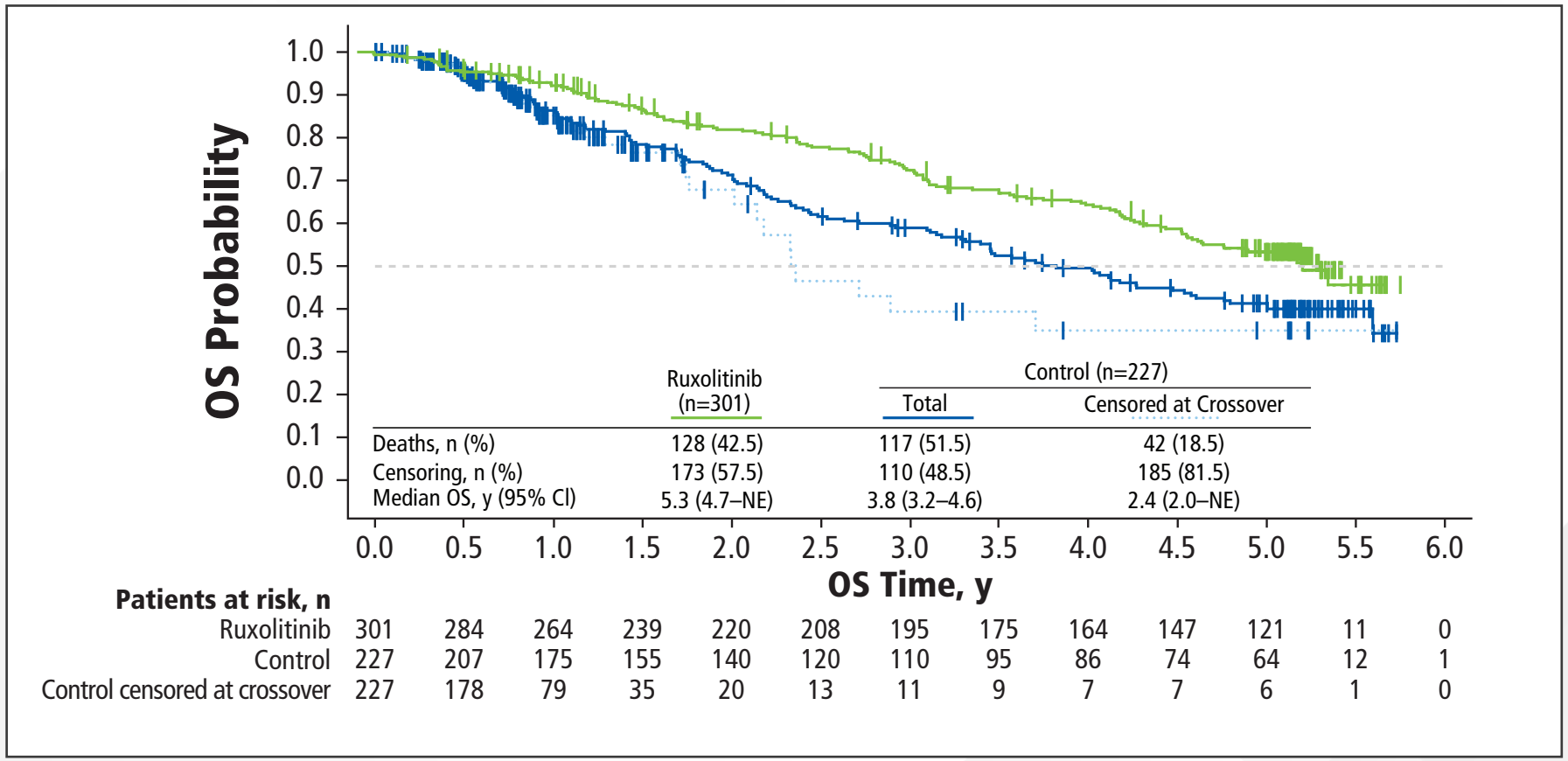
Open-label, single-arm phase 1/2 study (N = 107)



HR, hazard ratio; OS, overall survival.

Verstovsek S, et al. *Blood*. 2012;120(6):1202-1209.

Overall Survival Improves with Ruxolitinib: Pooled Analysis 5-Year Data COMFORT-I and COMFORT-II

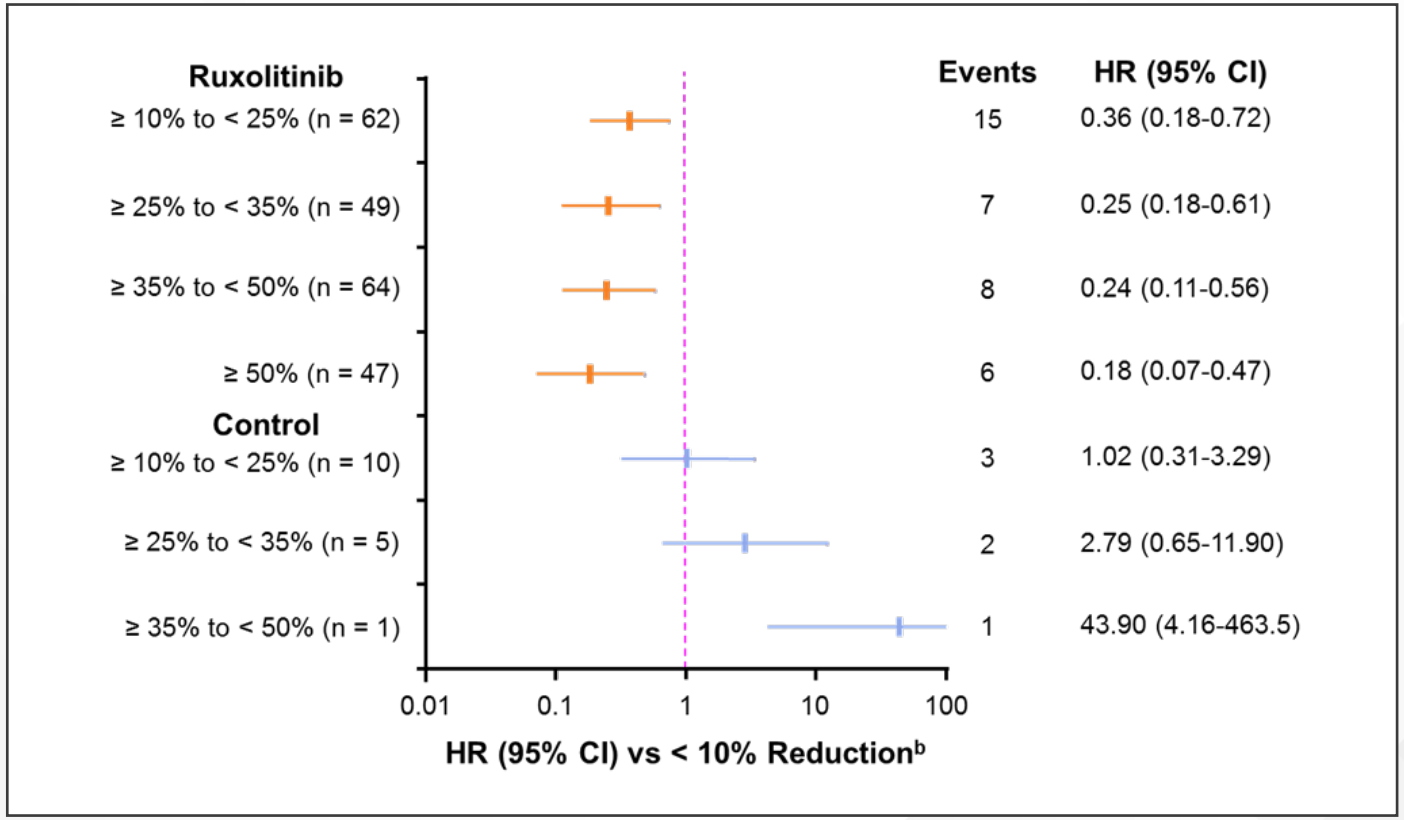


NE, not estimable; OS, overall survival.

Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):156.

Correlation of Spleen Volume Reduction at week 24 and OS

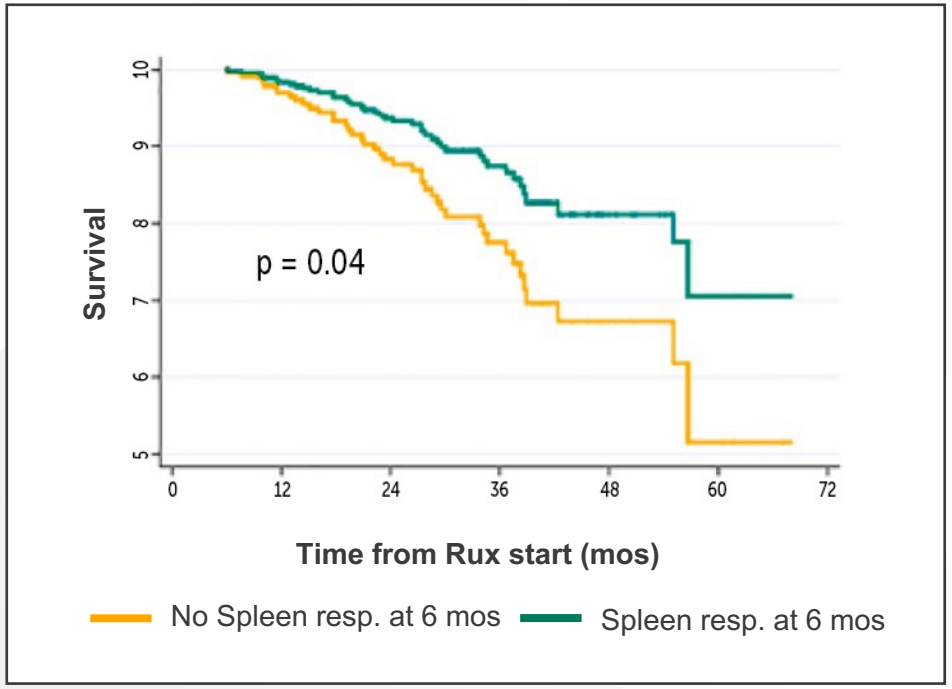
Pooled Analysis COMFORT-I and COMFORT-II



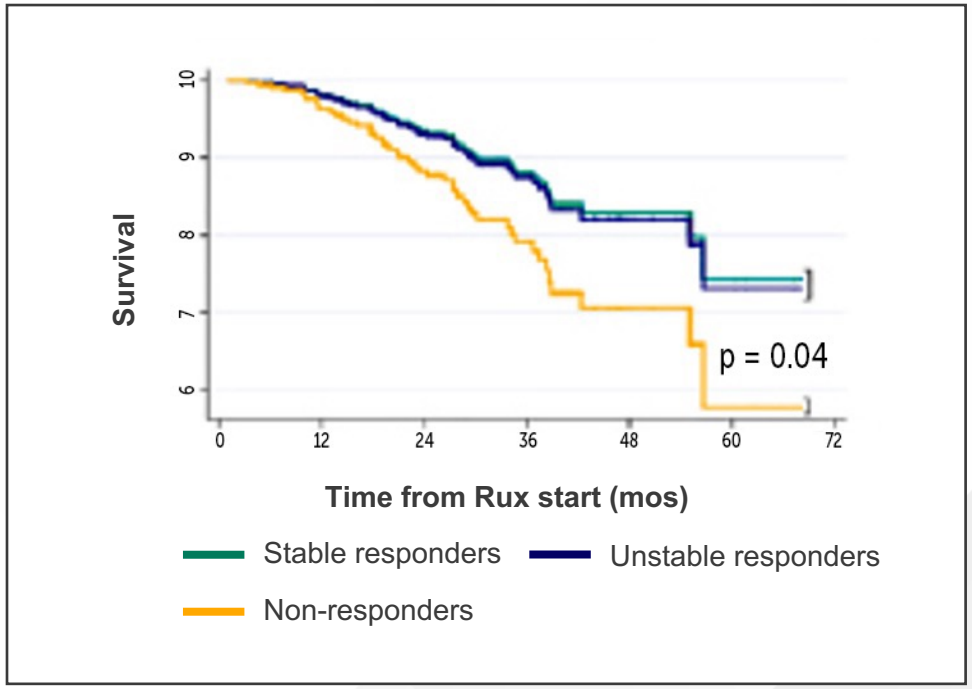
[a] Includes patients known to be alive at week 24. [b] Category includes patients with a < 10% reduction from baseline in spleen volume at week 24 or no assessment (ruzolitinib, n = 64; control, n = 189); among these patients, there were 26 deaths (events) in the pooled ruxolitinib group and 63 deaths in the control group.
HR, hazard ratio; OS, overall survival.
Vannucchi AM, et al. *Haematologica.* 2015;100(90:1139-1145.

Spleen Response Affects Outcomes of Ruxolitinib-Treated Patients With MF

OS by spleen response at 6 months[1]



OS by durability of spleen response[1]



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]

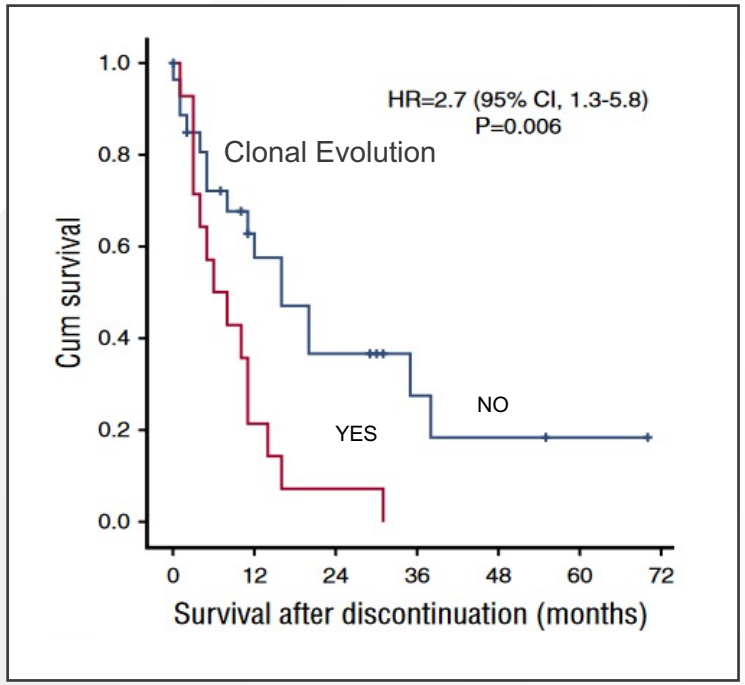
AXIS Medical Education

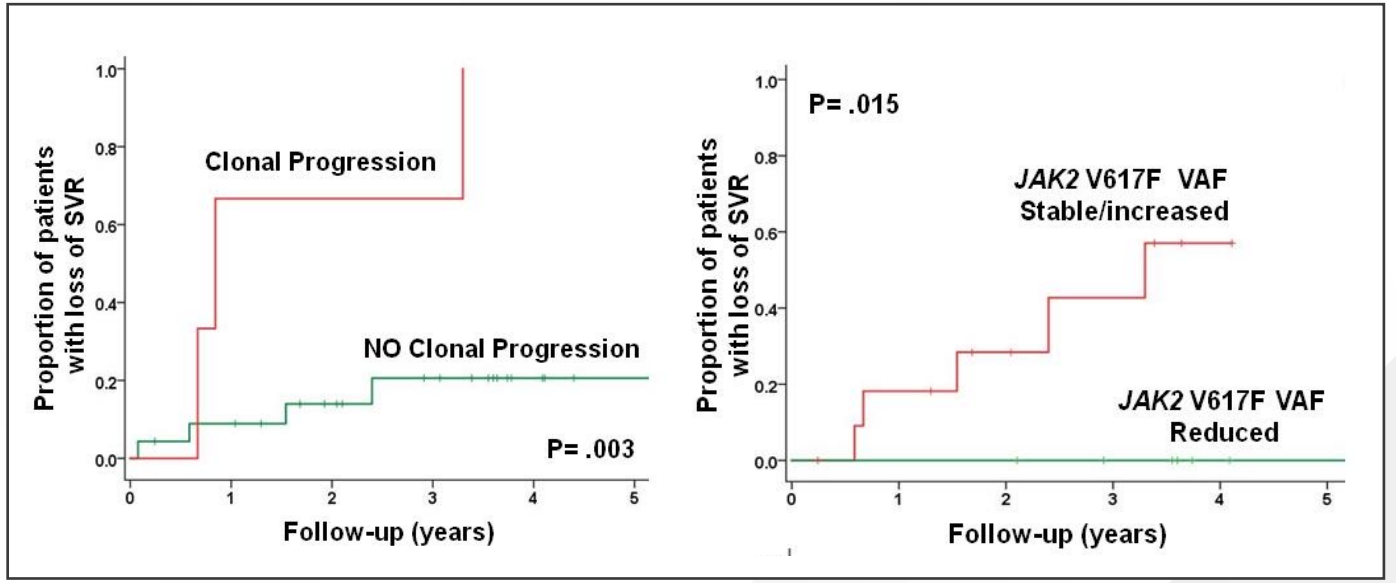
BID, twice daily; MF, myelofibrosis; OS, overall survival; Resp, responders; Rux, ruxolitinib; WBC, white blood cells.

1. Palandri F, et al. *Leuk Res.* 2018;74:86-88; 2. Palandri F, et al. *Oncotarget.* 2017;8(45):79073-79086; 3. Menghrajani K, et al. *Leuk Lymphoma*. 2019;60(4):1036-1042.

Clonal Evolution Contributes to/Indicates Ruxolitinib Failure

- About 50% of responder patients on Rux had lost response by 3 years in COMFORT-I and COMFORT-II study[1,2]



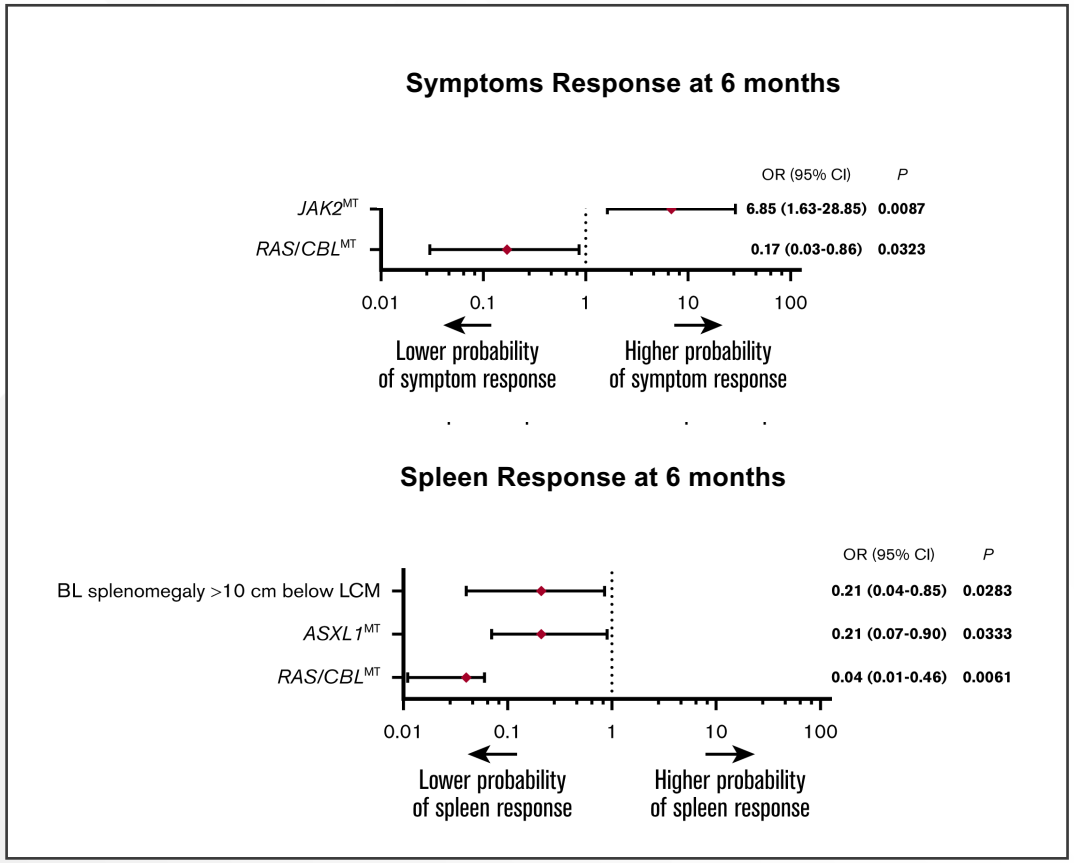


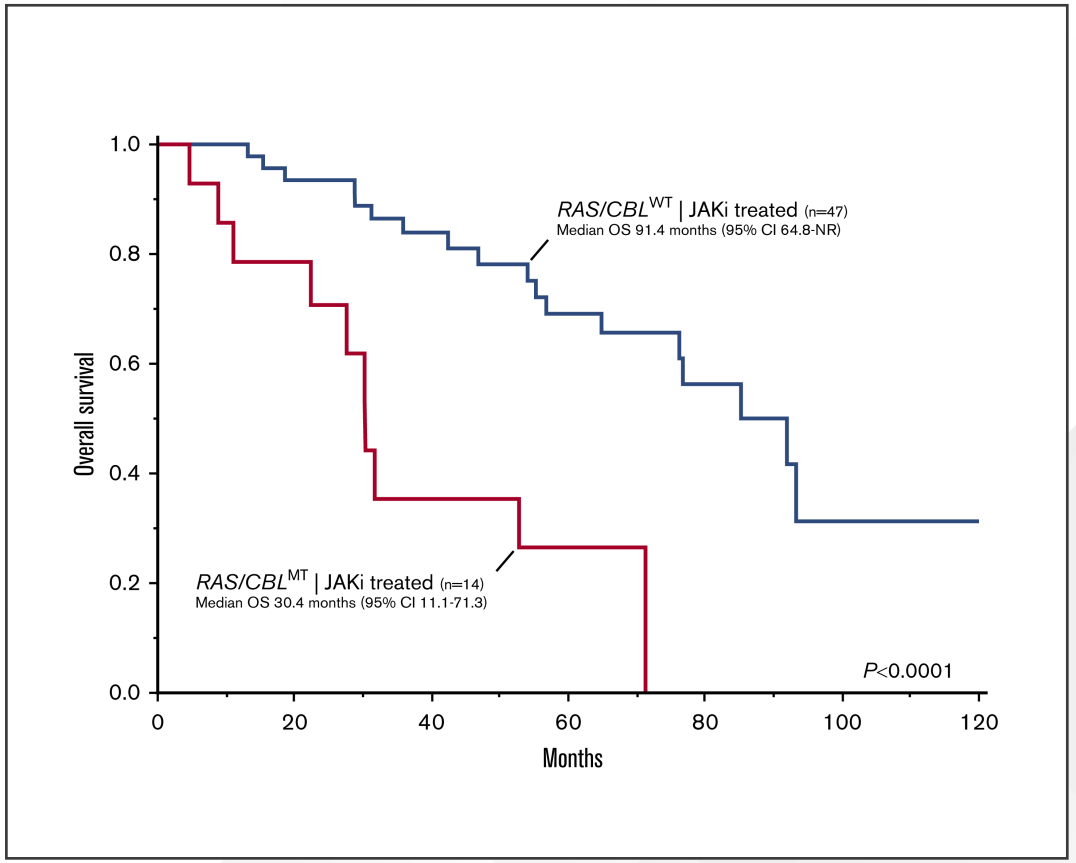
- Median duration of SVR of 10 mo vs not-reached in pts with or w/o clonal progression.[3]
- None of the 7 patients who showed decrease of ≥20% from baseline JAK2V617F VAF lost SVR compared to 6 out of 13 (46.1%) who showed stable or increased JAK2V617F VAF (HR=61.8,95% CI 1.01–870.2)[4]

Cum, cumulative; HR, hazard ratio; Rux, ruxolitinib; SVR, spleen volume reduction; VAF, variant allele frequency.

1. Verstovsek S et al. *J Hematol Oncol*. 2017;10(1):156. 2. Harrison CN et al. *Leukemia*. 2016;30(8):1701-1707. 3. Newberry KJ et al. *Blood*. 2017;130(9):1125-1131. 4. Pacilli A, et al. *Blood Cancer J*. 2018;8(12):122.

RAS/CBL Mutations Predict Resistance to JAKi in MF





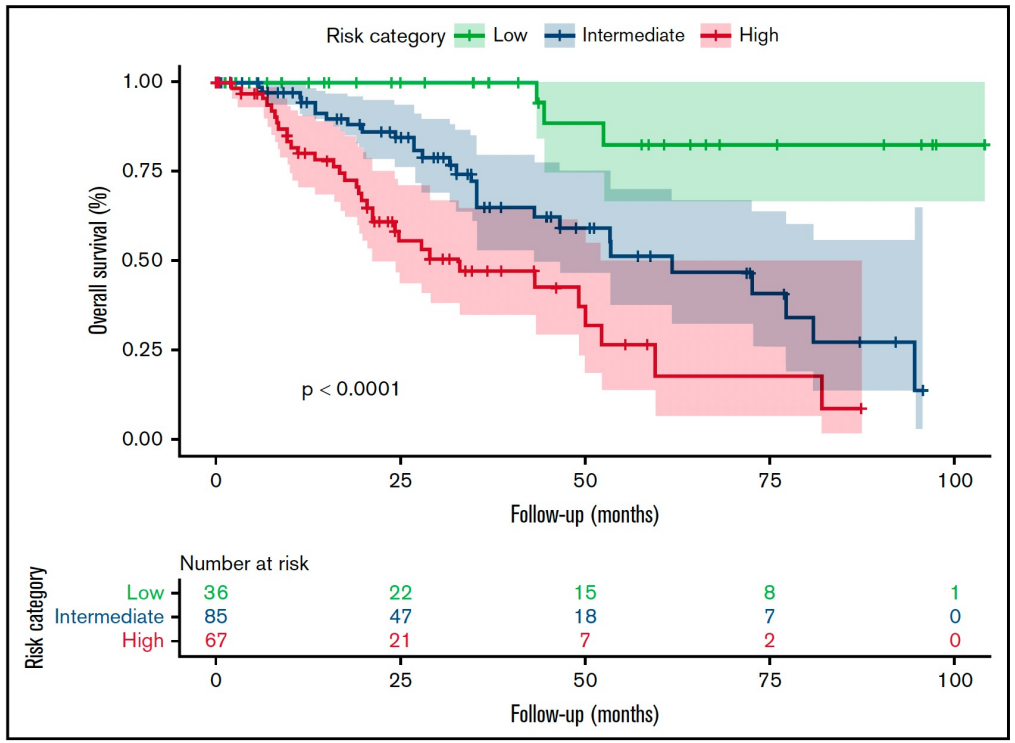
BL, baseline; JAKi, Janus kinase inhibitor; LCM, left costal margin; MF, myelofibrosis; OR, odds ratio; MF, myelofibrosis; MF-RUXO time interval, time interval between myelofibrosis diagnosis and initiation of JAKis.

Coltro G, et al. *Blood Adv*. 2020;4(15):3677-3687.

RR6, a Model to Predict Survival After 6 Months of Ruxolitinib in MF

Parameters	Points
RUX dose <20 mg BID at BL, 3 mos, 6 mos	1
≤30% spleen length reduction at 3 mos and 6 mos	1.5
RBC transfusions at 3 mos and/or 6 mos	1
RBC transfusions at BL, 3 mos, 6 mos	1.5

Risk category	% of pts	OS (months)	HR	Score
Low	19	NR		0
Intermediate	45	61	43-80	1-2
High	36	33	21-50	≥2.5



RR6 prognostic model[1]

BID, twice daily; BL, baseline; HR, hazard ratio; MF, myelofibrosis; OS, overall survival; RBC, red blood cell; RR6, Response to Ruxolitinib After 6 Months; RUX, ruxolitinib.

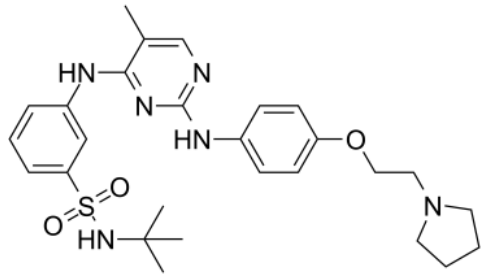
1. Maffioli M et al. *Blood Adv.* 2022;6(6):1855-1864.

Fedratinib FDA Approved for MF*
August 16, 2019

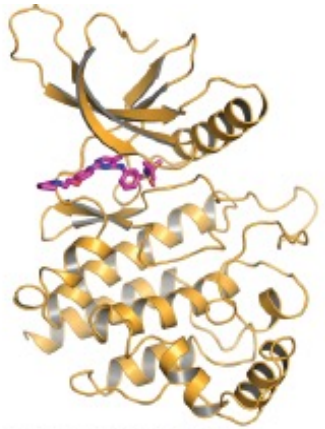
*With intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).
FDA, US Food and Drug Administration; MF, myelofibrosis.
FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fedratinib-myelofibrosis.

Fedratinib

- Oral, JAK2-selective inhibitor with once-daily dosing approved in the US for treatment of intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF with platelet counts ≥50 × 10^9/L[1]
- Fedratinib has higher inhibitory activity for JAK2 over JAK1, JAK3, and TYK2[2]
- Fedratinib was investigated for treatment of MF in JAK-inhibitor-naïve patients in the phase 3 JAKARTA trial, and in patients previously treated with RUX in the phase 2 JAKARTA2 trial[3,4]
- JAKARTA and JAKARTA2 allowed enrollment of patients with platelet counts of ≥50 × 10^9/L at study entry[3,4]



FEDRATINIB

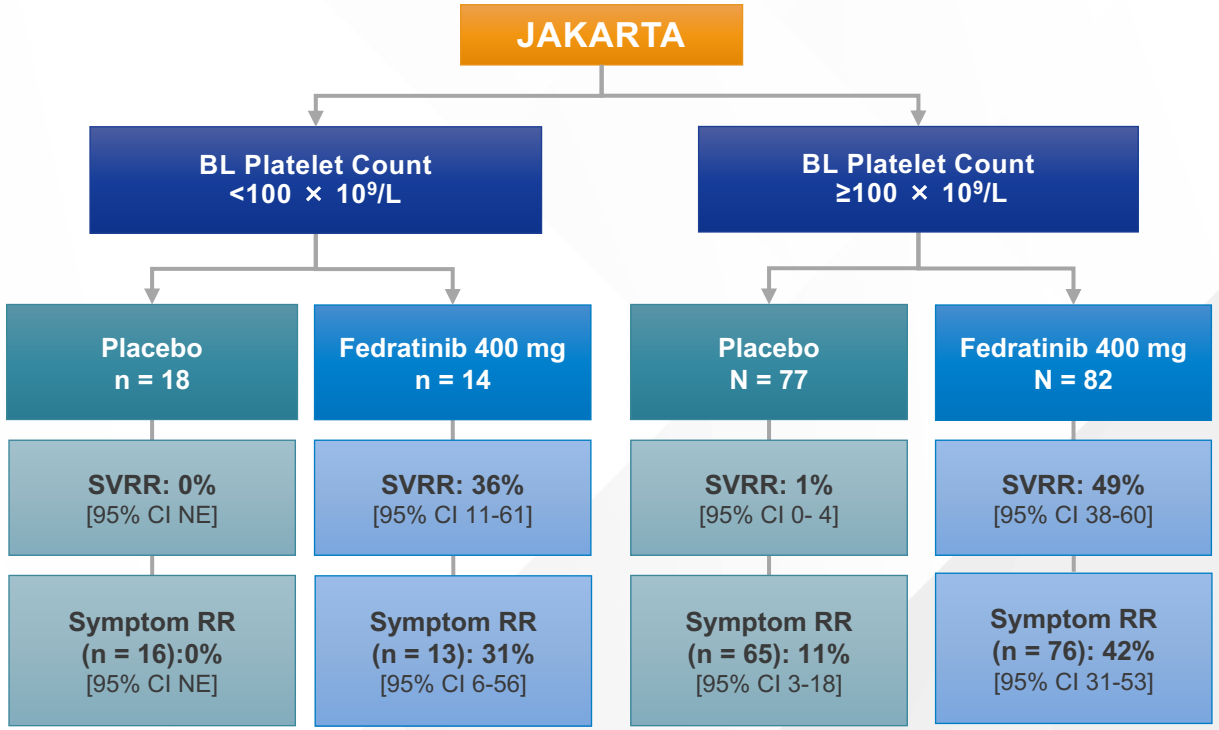


JAK2 KINASE DOMAIN – Fedratinib Complex[5]

1. INREBIC® (fedratinib) prescribing information. BMS; 10/2022. 2. Wernig G, et al. *Cancer Cell.* 2008;13:311-320.
3. Pardanani A, et al. *JAMA Oncol.* 2015;1(5):643-651. 4. Harrison CN, et al. *Lancet Haematol*. 2017;4:e317–324.
5. Hantschel O. *ACS Chem Biol.* 2015;10(1):234-245.
ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; RUX, ruxolitinib.

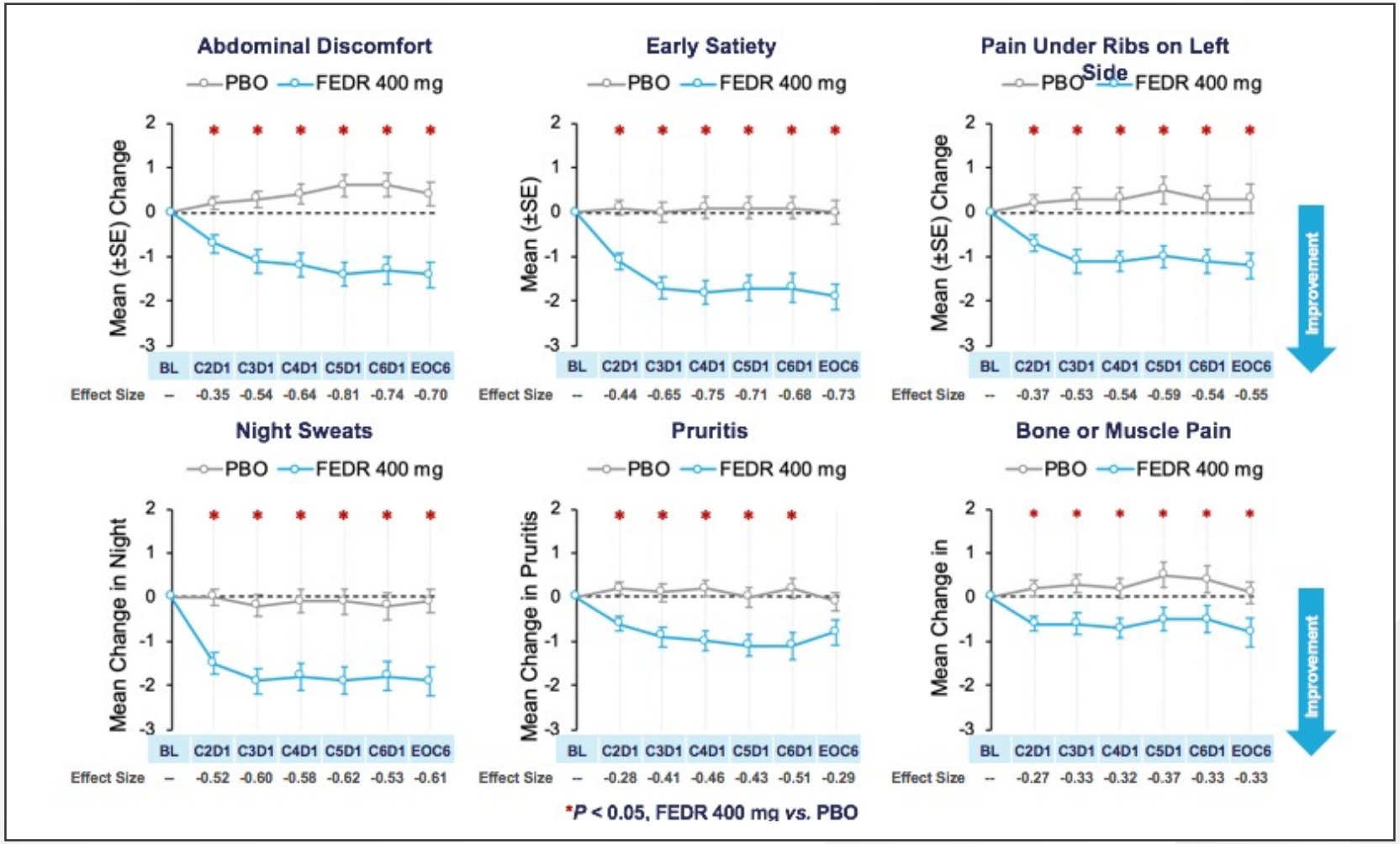
JAKARTA: Spleen Volume and Symptom Responses

- Among all patients, SVRR (≥35% spleen volume reduction) was significantly higher with fedratinib 400 mg/day versus placebo (47% vs 1%, respectively; *P* < .0001)
- Symptom RR was also significantly improved with fedratinib overall
- Within the fedratinib 400 mg treatment arm there was no statistically significant difference in SVRR or symptom RR between BL platelet count subgroups



Statistical comparisons between BL platelet count subgroups should be interpreted with caution due to small sample sizes.
BL, baseline; NE, not estimable; RR, response rate; SVRR, spleen volume response rate.
Harrison CN, et al. *Blood* 2019;134(suppl 1):668.

JAKARTA: Fedratinib Superior to Placebo for Individual Symptom Control

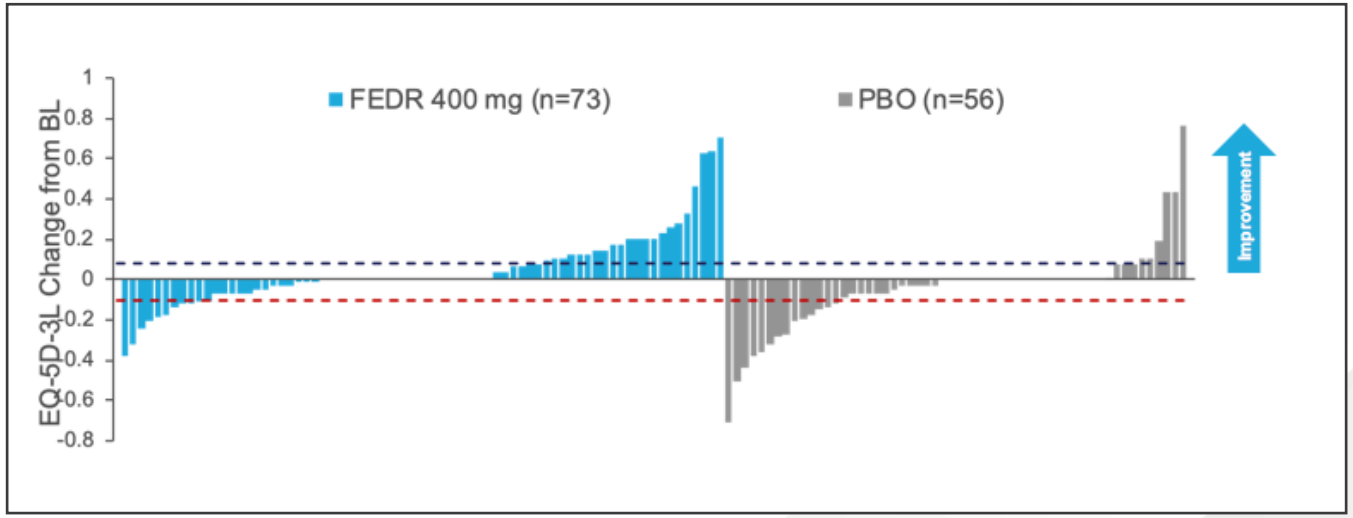


BL, baseline; C*x*D*x*, cycle *x* day *x;* EOC6, end of cycle 6; FEDR, fedratinib; PBO, placebo, SE, standard error.

Mesa RA, et al. *Blood* 2019;134(suppl 1):704.

JAKARTA: Fedratinib Improved Patient-reported Overall Health Status at EOC6 per EQ-5d-3L

Mean EQ-5D-3L health utility score was clinically meaningfully improved at EOC6 with FEDR 400 mg



	FEDR 400 mg	PBO
LS mean change	0.039	–0.040
P	.008	

Mean EQ-5D-3L health utility score at baseline was 0.70 in the FEDR 400 mg arm and 0.72 in the PBO arm
EOC6, end of cycle 6; EQ-5d-3L, EuroQol with 5 dimensions and 3 levels of severity; FEDR, fedratinib; HRQoL, health-related quality of life; LS, least squares; PBO, placebo.
Mesa RA, et al. *Blood.* 2019;134(suppl 1):704.

Second Line

JAKARTA2: Patient Cohorts

- Fedratinib 400 mg QD for consecutive 28-day cycles
- ITT population: all 97 patients enrolled in JAKARTA2
- Ruxolitinib failure cohort: 79 patients who met new, stringent definitions of ruxolitinib relapsed/refractory or intolerant
- Sensitivity cohort: the subset of 66 patients within the ruxolitinib failure cohort who received 6 cycles of fedratinib, or who discontinued fedratinib before cycle 6 for reasons other than "study terminated by sponsor"

ITT Population	Ruxolitinib Failure Cohort
• Ruxolitinib treatment for ≥14 days, and resistant or intolerant to ruxolitinib per investigator discretion: – Resistant: No response or stable disease, evidence of disease progression, or loss of response – Intolerant: Discontinuation due to unacceptable toxicity	Relapsed: Ruxolitinib treatment for ≥3 mo with regrowth, defined as <10% SVR or <30% decrease in spleen size from baseline, following an initial response Refractory: Ruxolitinib treatment for ≥3 mo 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 U/mo for 2 mo); or grade ≥3 thrombocytopenia, anemia, hematoma, and/or hemorrhage while receiving ruxolitinib

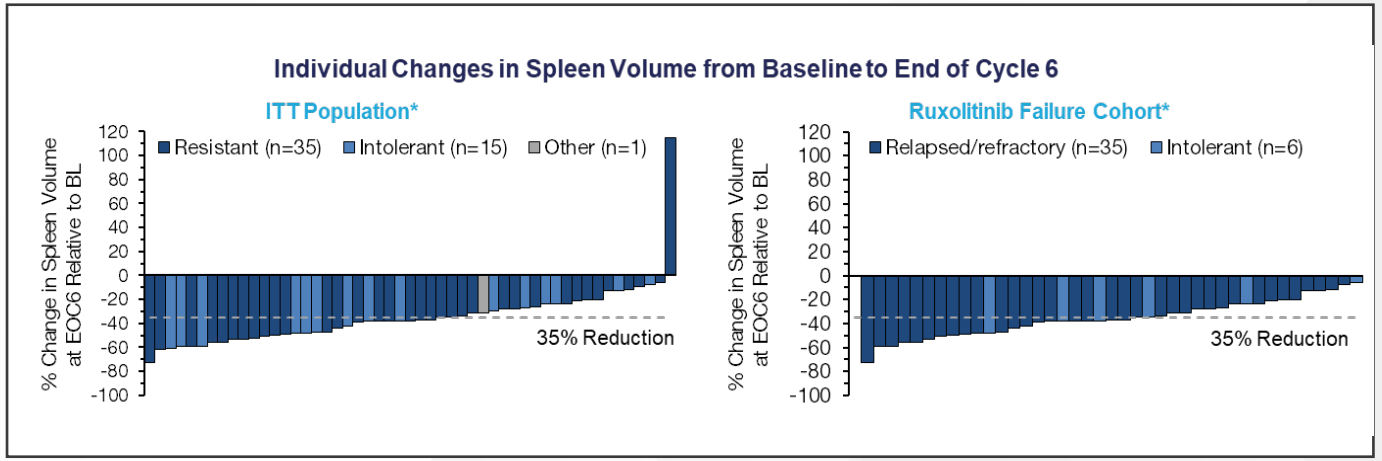
QD, once a day; ITT, intention-to-treat; RBC, red blood cell; SVR, spleen volume reduction.

Harrison CN, et al. European Hematology Association 2019 annual meeting. Abstract PS1459.

JAKARTA2: Spleen and Symptom Response Rates

- Clinically relevant prognostic baseline disease characteristics indicate a population of difficult-to-treat patients with advanced MF disease and high disease burden
- Spleen volume and symptom response rates were consistent among the 3 patient cohorts
- Median duration of spleen response (months) was not reached (95% CI 7.2-NR) in the ITT population, ruxolitinib failure cohort, or sensitivity cohort

Variable	ITT Population (N = 97)		Ruxolitinib Failure Cohort (N = 79)		Sensitivity Cohort (N = 66)	
	n	% of Patients (95% CI)	n	% of Patients (95% CI)	n	% of Patients (95% CI)
Spleen volume response rate	97	31% (22-41)	79	30% (21-42)	66	36% (25-49)
Symptom response rate*	90	27% (18-37)	74	27% (17-39)	62	32% (21-45)



*Includes patients with an evaluable baseline and ≥1 post-baseline MFSAF assessment.
BL, baseline, EOC6, end of cycle 6; ITT, intention-to-treat; MF, myelofibrosis; NR, not reached.
Harrison CN, et al. European Hematology Association 2019 annual meeting. Abstract PS1459.

FREEDOM: Fedratinib Safety Data – ASH 2022

Any grade AEs	Patients, %
At least one TEAE	89.5%
Serious AEs	7.9%
Anemia	60.5%
Thrombocytopenia	34.2%
GI-related	
Nausea	39.5%
Vomiting	18.4%
Diarrhea	39.5%

- Most GI AEs were grade 1/2 and decreased in subsequent cycles.
- No patients required treatment discontinuation due to low thiamine levels.
- There were no cases of WE reported.
- Few deaths occurred during treatment and follow-up; none were related to study medication.

In this first fedratinib study proactively assessing a GI mitigation strategy and thiamine monitoring, results showed GI AEs were easily mitigated and no WE was reported.

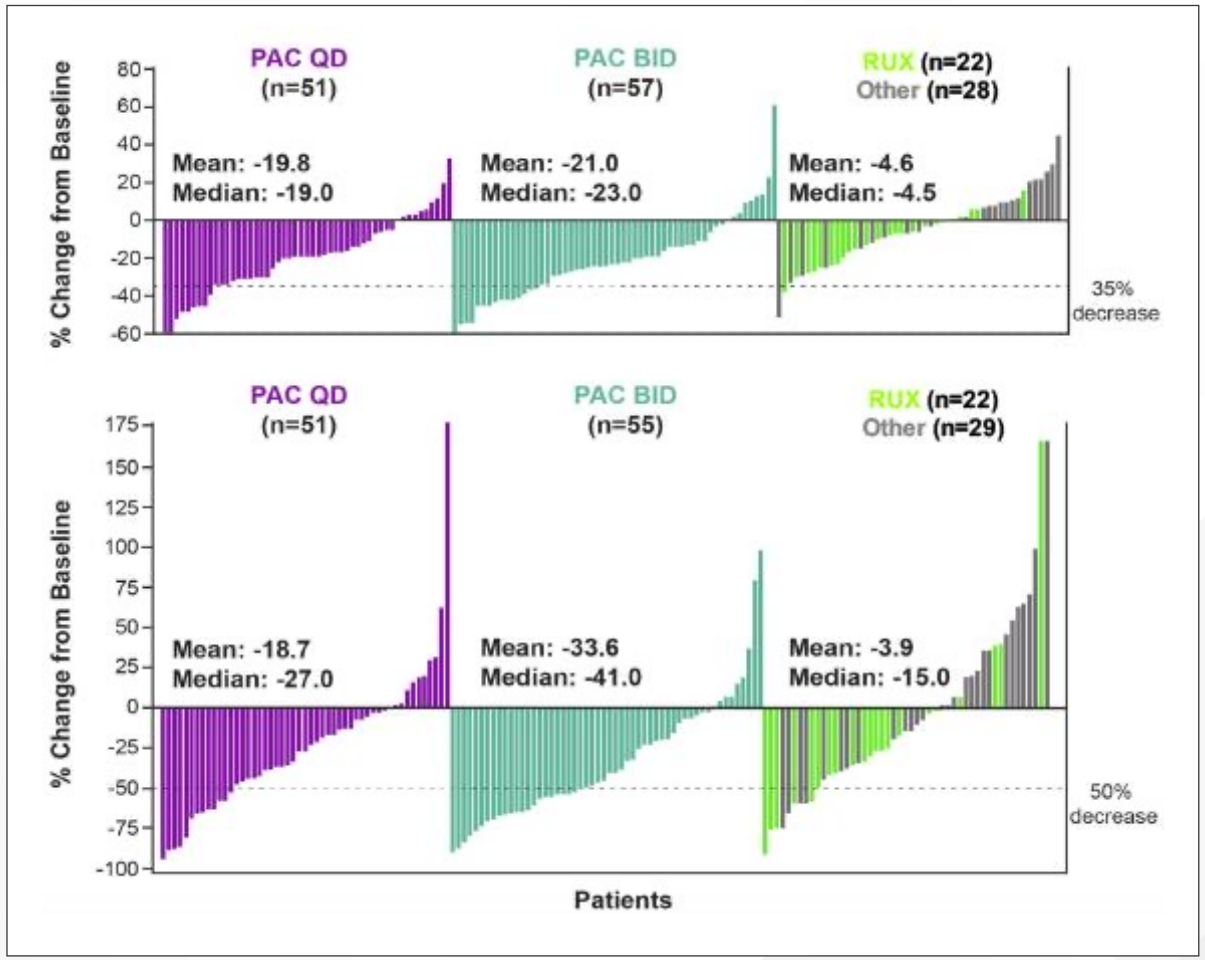
AXIS Medical Education

AEs, adverse events; ASH 2022, American Society of Hematology 2022 Annual Meeting; GI, gastrointestinal; TEAE, treatment-emergent adverse event; WE, Wernicke's encephalopathy.
Gupta V, et al. ASH 2022. Abstract 1711.

Pacritinib FDA Approved for MF*
February 28, 2022

*Intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 10^9/L
FDA, US Food and Drug Administration; MF, myelofibrosis.
FDA.gov. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-adults-rare-form-bone-marrow-disorder

PERSIST 1: Pacritinib Efficacy Analysis by Arm



BID, twice daily; PAC, pacritinib; QD, dialy; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.
Adapted from Mesa RA, et al. *Lancet Hematol*. 2017;4(5):E225-E236.

PERSIST 2: Pacritinib

- Phase 3 randomized international multicenter study
- 311 patients with myelofibrosis and platelet count 100×10^9/L or less
- Crossover from BAT was allowed after week 24 or for progression of splenomegaly
- Patients were randomized 1:1:1 to pacritinib 400 mg once daily, pacritinib 200 mg twice daily, or BAT
- Coprimary endpoints:
  - Rate of patients achieving 35% or more spleen volume reduction at week 24
  - Rate of patients achieving 50% or more reduction in total symptom score at week 24

Response at Week 24	Pacritinib arms combined	BAT
Spleen Size		
Patients with ≥35% reduction in spleen size by MRI, n/N	27/149 (18%)	2/72 (3%)
Symptoms		
Patients with ≥50% reduction in total symptom score, n/N	37/149 (25%)	10/72 (14%)

AXIS Medical Education

BAT, best available therapy; MRI, magnetic resonance imaging.
Mascarenhas J, et al. JAMA Oncol. 2018;4(5):652-659.

Pacritinib Is a Potent ACVR1 Inhibitor With Significant Anemia Benefit in Patients With Myelofibrosis

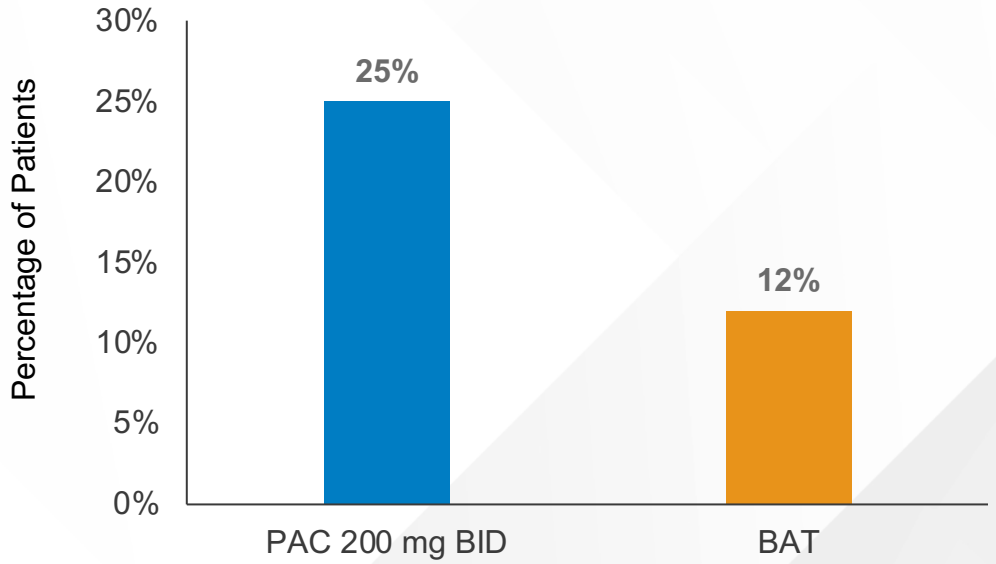
ACVR1, activin A receptor, type I.
Oh ST et al. ASH 2022. Abstract 628.

Pacritinib in Cytopenic Myelofibrosis

- Approved in patients with MF who have a platelet count <50x10^9/L
- Able to be administered at the full approved dose (200 mg BID) regardless of cytopenias[1-3]
- Demonstrated hemoglobin improvement in randomized PERSIST-2 study[2]
- The underlying mechanism and extent of anemia benefit has not been fully described
- Diarrhea is a common side effect

Clinical Improvement in Hemoglobin[2]

PERSIST-2, Week 24



IWG criteria: among patients with baseline hemoglobin <10 g/dL, increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks

BAT, best available therapy; BID, twice daily; IWG, International Working Group; MF, myelofibrosis; RBC, red blood cell.

1. Mesa R, et al. *Lancet Oncology*. 2017. 2. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. 3. Gerds A, et al. *Blood Advances*. 2020;4(22):5825-5835.

Pacritinib Is a Potent ACVR1 Inhibitor

Pacritinib is ~4x more potent than momelotinib against ACVR1

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	**20.4**	**22.6**	**70.2**	**312.0**	**>1000**
Replicate 2 ACVR1 IC_{50} (nM)	**32.4**	**10.8**	**34.9**	**235.0**	**>1000**
Mean ACVR1 IC_{50} (nM)	**26.4**	**16.7**	**52.6**	**273.5**	**>1000**
Potency[b] (C_{max}:IC_{50})	**N/A**	**12.7**	**3.2**	**1.0**	**<0.01**

Legend

Higher potency

Lower potency

[a]LDN 193189 is an ACVR1 inhibitor.
[b]Cmax is the maximum unbound plasma concentration at the clinical recommended dose in humans.
ACVR1, Activin A receptor type 1; Cmax, peak drug concentration; FED, fedratinib; IC50, inhibitory concentration 50%; MMB, momelotinib; PAC, pacritinib; RUX, ruxolitinib.
Oh ST, et al. ASH 2022. Abstract 628.

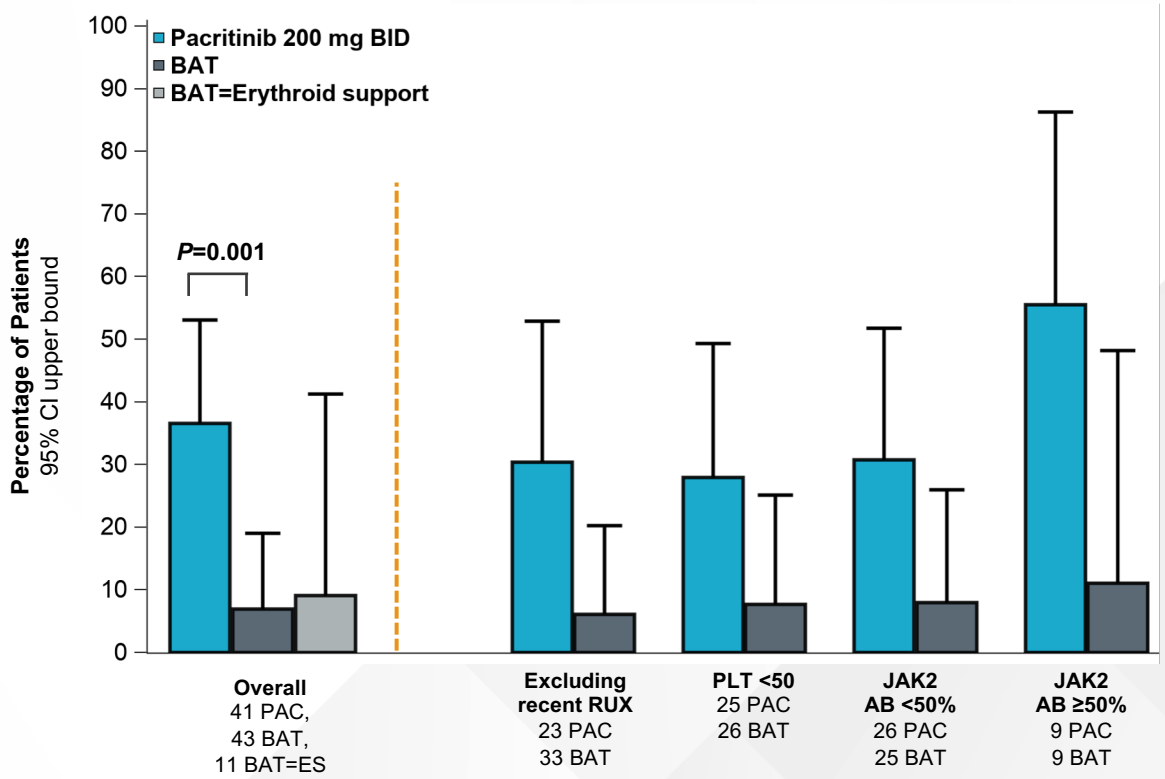
More Pacritinib Patients Achieved TI: PERSIST-2 Post-Hoc Analysis

TI Conversion Rate

Pacritinib N=41	BAT N=43	P-value
37%	7%	0.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
  - Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



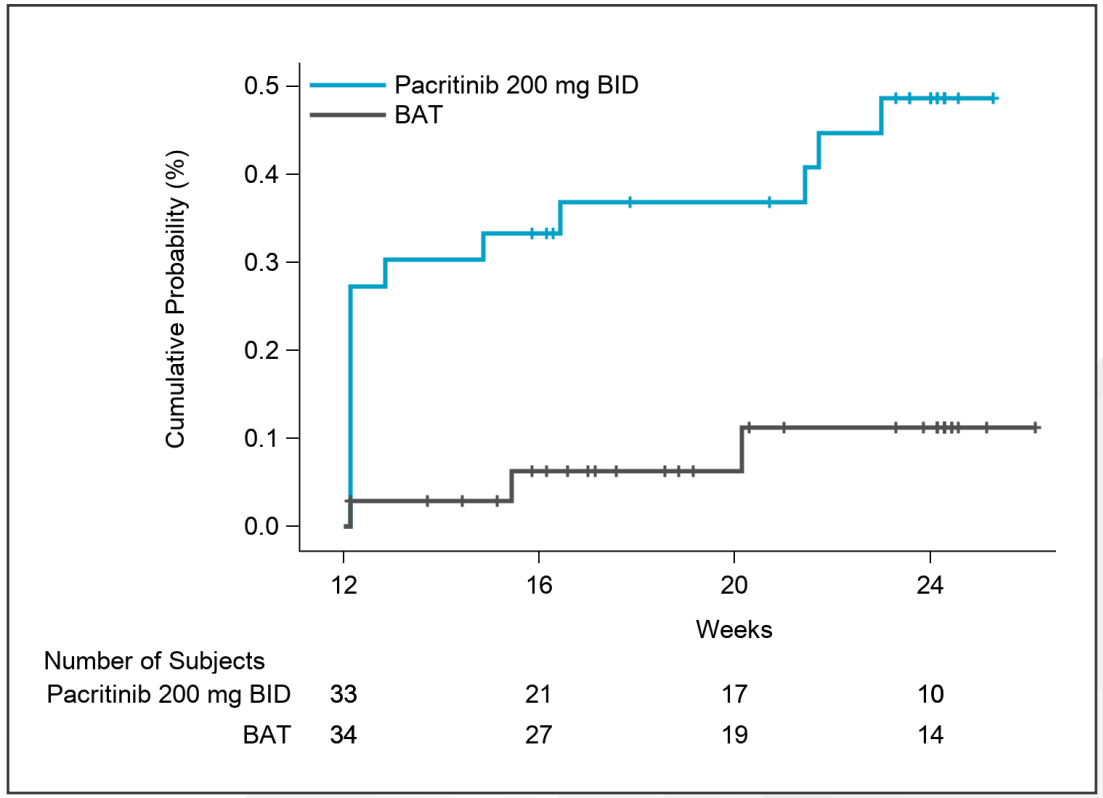
AB, allele burden; BAT, best available therapy; BID, twice daily; ES, erythroid support; JAK, Janus-associated kinase; PAC, pacritinib; PLT, platelets; recent RUX, no ruxolitinib in prior 30 days; TI, transfusion independence

Oh ST, et al. ASH 2022. Abstract 628.

TI Conversion Can Occur Late in Treatment

- Many responses occurred early during treatment
- Some responses occurred after several months on treatment

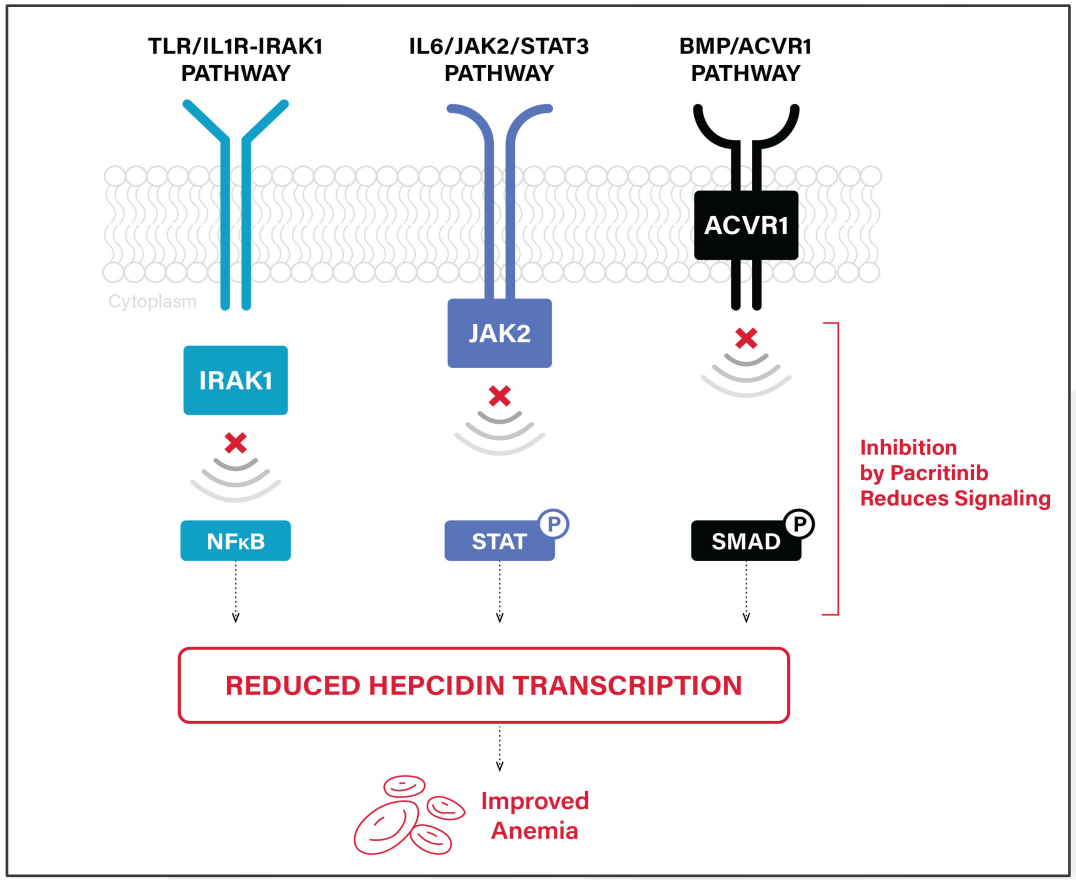
Cumulative Incidence of TI (Gale criteria)



BAT, best available therapy; BID, twice daily; TI, transfusion independence.
Oh ST, et al. ASH 2022. Abstract 628.

Hypothesized Mechanism of Anemia Benefit

- Potent, 24-hour inhibition of ACVR1 may function in conjunction with IRAK1 and JAK2 inhibition to reduce levels of hepcidin
- Hepcidin reduction ameliorates anemia of inflammation that occurs in myelofibrosis



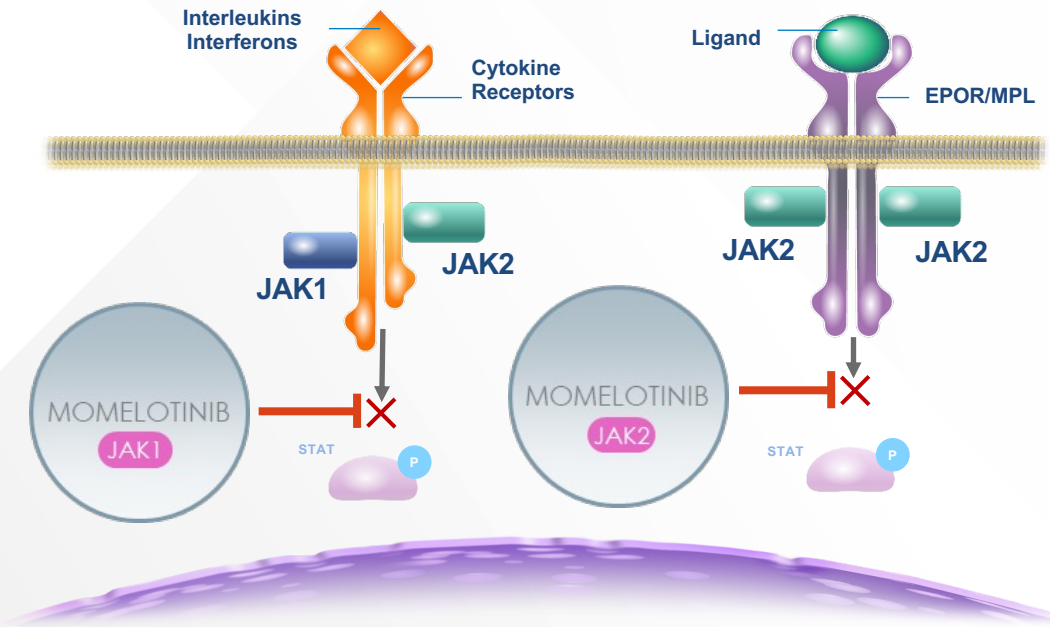
ACVR1, Activin A receptor type 1; BMP, bone morphogenetic protein; JAK2, Janus-associated kinase 2; IL6, interleukin-6; IRAK, interleukin receptor-associated kinase; STAT, signal transducers and activators of transcription; SMAD, suppressor of mother against decapentaplegic; TLR/IL-1R, toll-like receptor/Interleukin (IL)-1 receptor. Oh ST, et al. ASH 2022. Abstract 628.

Momelotinib – FDA accepted NDA application for MF August 17, 2022

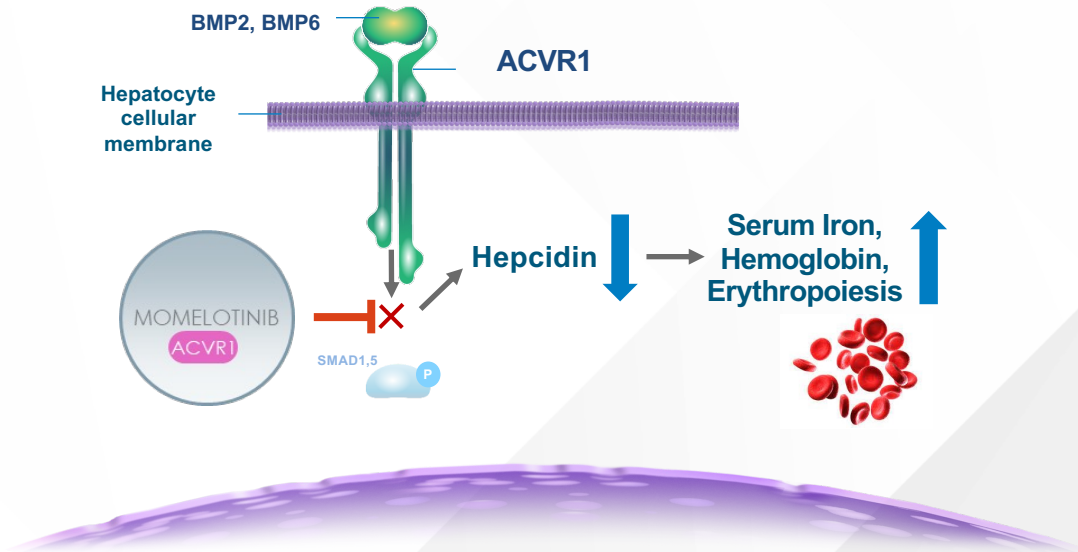
FDA, US Food and Drug Administration; NDA, new drug application; MF, myelofibrosis.

GSK.com. https://www.gsk.com/en-gb/media/press-releases/us-fda-accepts-new-drug-application-for-gsk-s-momelotinib-for-the-treatment-of-myelofibrosis/.

Momelotinib Inhibits JAK1, JAK2, and ACVR1 to Address MF Symptoms, Spleen, and Anemia



Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**.[1,2]



Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF.[3,4]

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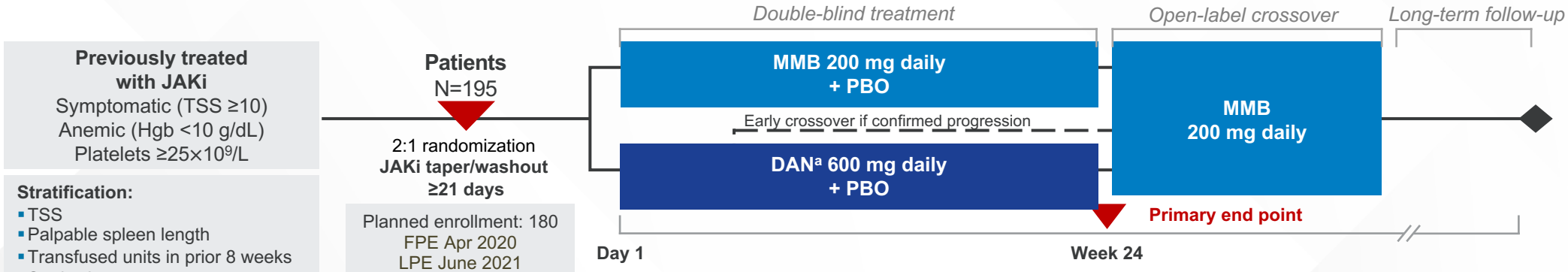
ACVR1, activin A receptor type 1; BMP, bone morphogenic protein; EPOR, erythropoietin receptor; JAK, Janus-associated kinase; MF, myelofibrosis; MMB, momelotinib; MPL, myeloproliferative leukemia protein; SMAD, mothers against decapentaplegic homolog; STAT, signal transducer and activator of transcription.

1. Chifotides HT, et al. *J Hematol Oncol*. 2022;15(1):7. 2. Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458. 3. Asshoff M, et al. *Blood*. 2017;129(13):1823-1830; 4. Oh S, et al. *Blood Adv*. 2020;4(18):4282-4291.

MOMENTUM Is an Ongoing Phase 3 Study of Momelotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients

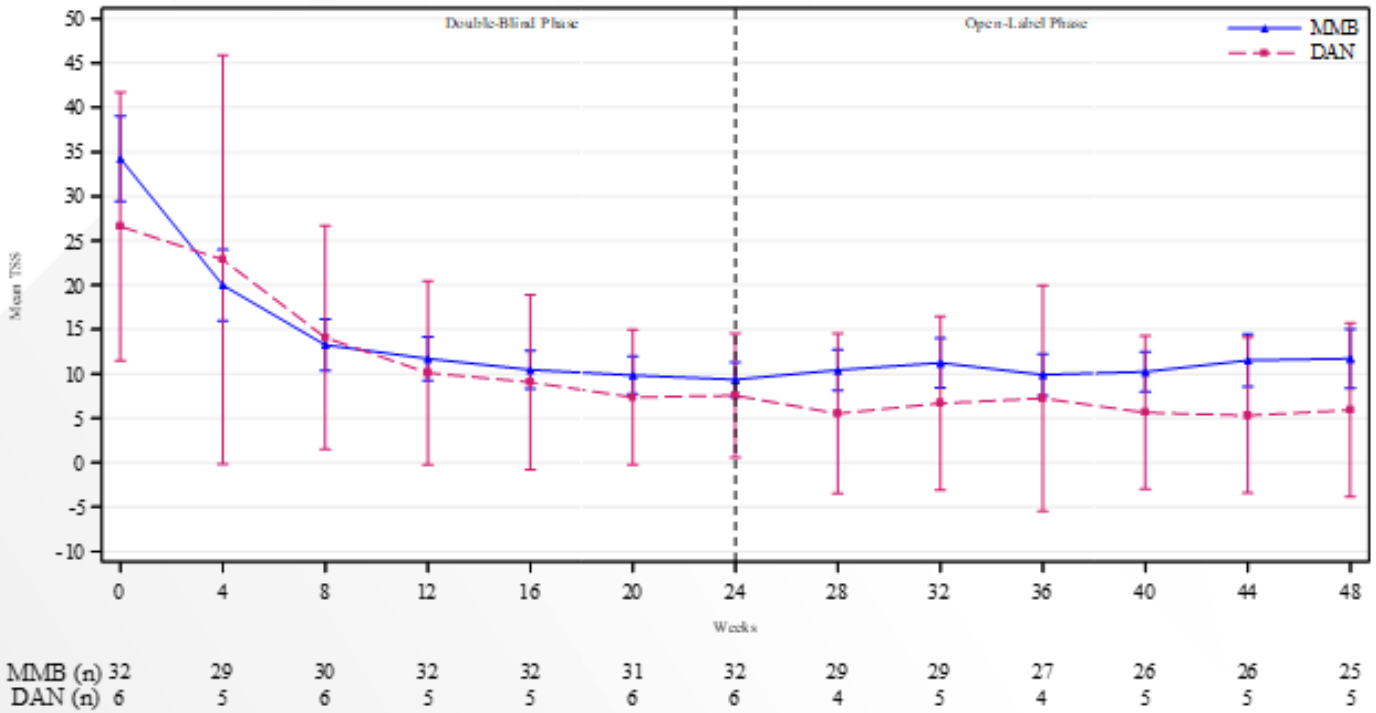


MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P =.0095 (superior)	1-sided *P* =.0064 (noninferior)	*P* =.0006 (superior)

ClinicalTrials.gov: NCT04173494.
[a]Danazol was selected as an appropriate comparator given its use to ameliorate anemia in patients with MF.[3-5] [b]TSS response defined as achieving ≥50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline. [c]TI response defined as not requiring red blood cell transfusion in the last 12 weeks of the 24-week randomized period, with all Hgb levels during the 12-week interval of ≥8 g/dL. [d]SRR defined as achieving a ≥25% or ≥35% reduction in spleen volume from baseline.
DAN, danazol; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; PBO, placebo; SRR, splenic response rate; TI, transfusion independence; TSS, total symptom score.
1. Mesa R et al. ASCO 2022. Abstract 7002. 2. Verstovsek S et al. EHA 2022. Abstract S195.

Sustained Responses Were Observed in Week 24 Symptom Responders[a]

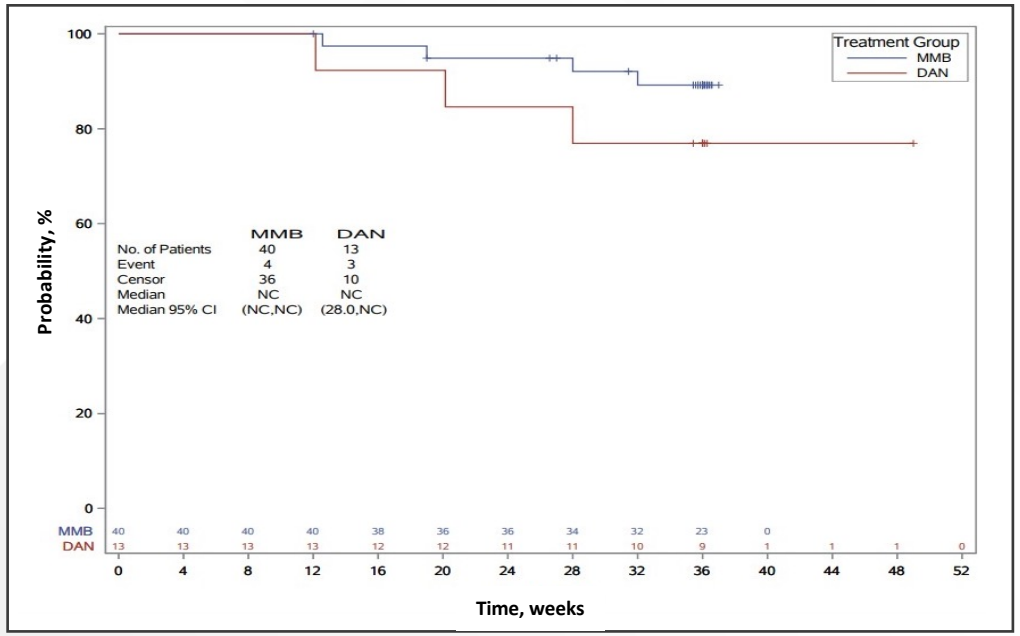


Of TSS responders at week 24, 1 of 32 (3%) MMB→MMB patients and 0 of 6 (0%) DAN→MMB patients had TSS ≥baseline in OL

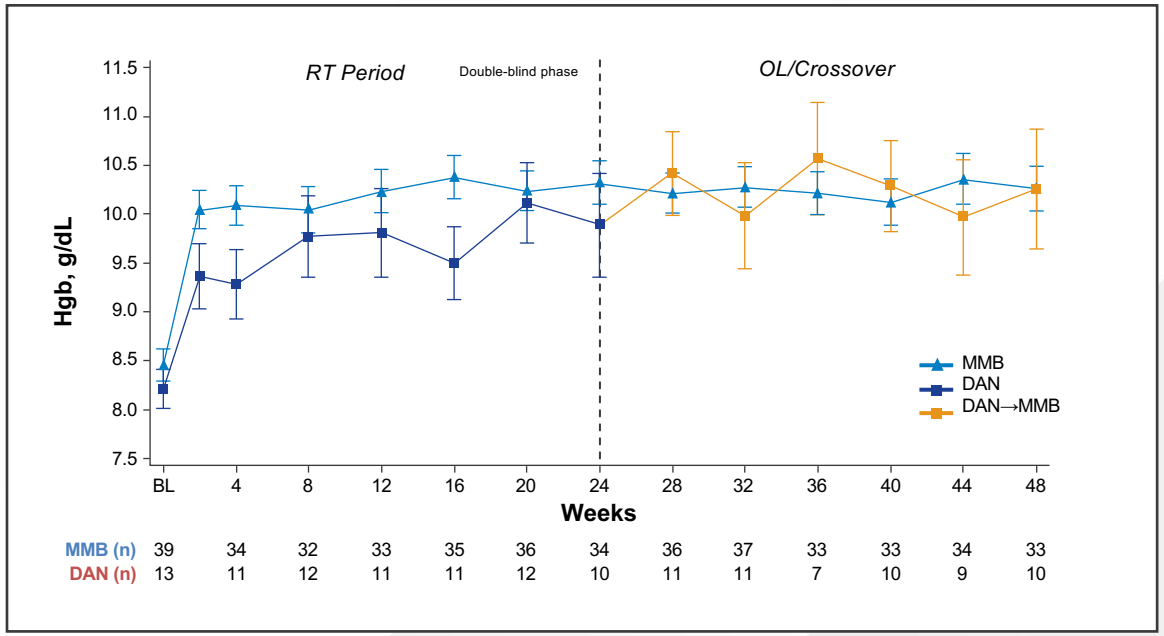
[a]Defined as the proportion of patients who achieve ≥50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline.
DAN, danazol; MMB, momelotinib; OL, open-label; TSS, total symptom score.
Gerds AT, et al. ASH 2022. Abstract 627.

Sustained Responses Were Observed in Week 24 TI Response[a]

TI Duration of Response in ITT Population



Mean Hgb Over Time in TI Responders



Of TI responders at week 24, 4 of 40 (10%) MMB→MMB patients and 3 of 13 (23%) DAN→MMB patients had an RBC transfusion or Hgb <8 g/dL in OL

[a]Defined as not requiring RBC transfusion in the prior 12 weeks and Hgb levels ≥8 g/dL.
BL, baseline; DAN, danazol; Hgb, hemoglobin; ITT, intention-to-treat; MMB, momelotinib; OL, open-label; RBC, red blood cell; RT, randomized treatment; TI, transfusion independence.
Gerds AT, et al. ASH 2022. Abstract 627.

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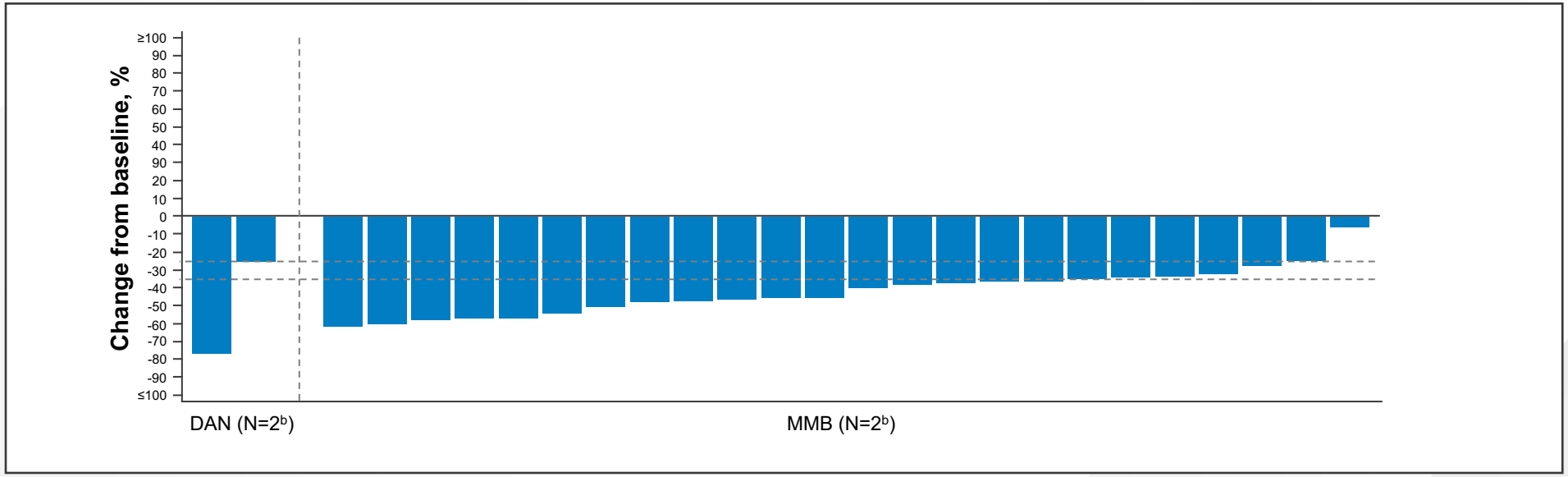
Sustained Responses Were Observed in Week 24 Spleen Responders[a]

Change From Baseline in Spleen Volume at Week 24 in Spleen Responders



Of SRR35 responders at week 24 who had a week 48 scan, 0 of 24 (0%) MMB→MMB patients and 0 of 2 (0%) DAN→MMB patients had splenic volume ≥ baseline at week 48

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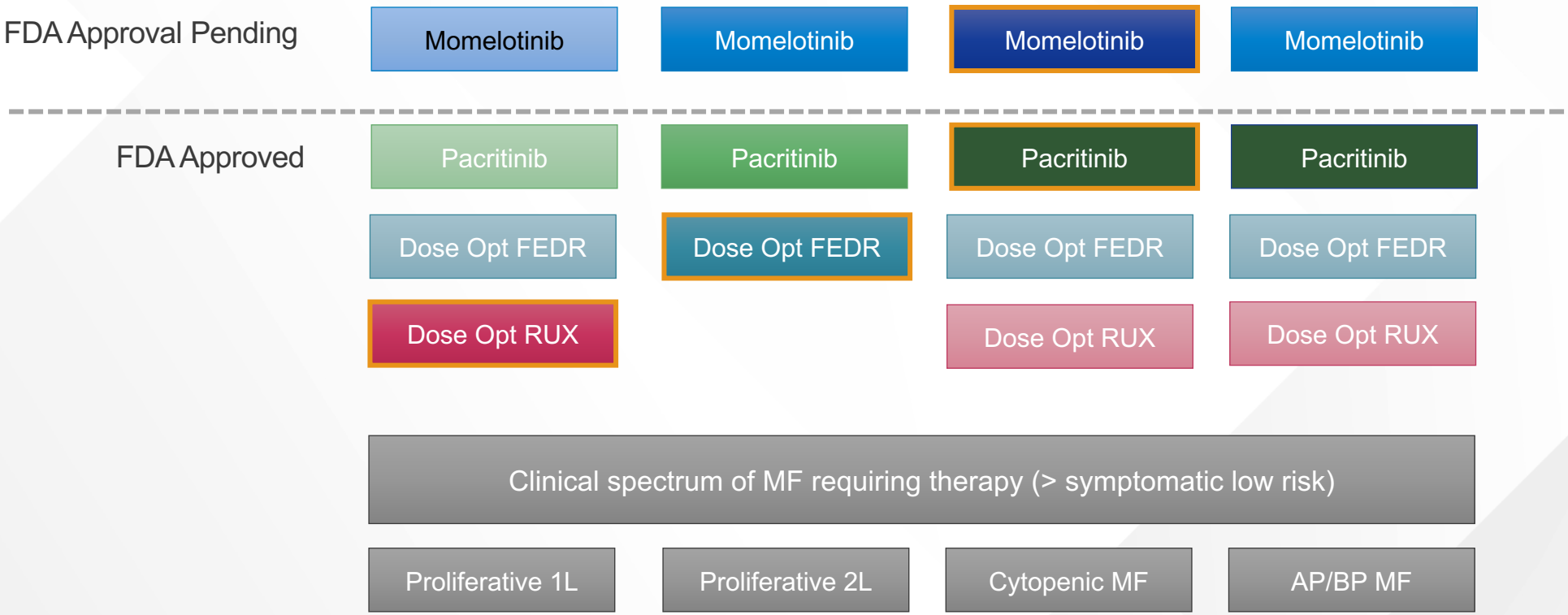
[a]Defined as the proportion of patients who have a reduction in spleen volume of ≥35% from baseline. [b]N is the number of patients with percent change in spleen volume at week 48 available.
DAN, danazol; MMB, momelotinib; SRR35, splenic response rate >35%.
Gerds AT, et al. ASH 2022. Abstract 627.

Step 1 for MF Management: Optimize JAK Inhibition



R Mesa developed Slide
1L, first-line; 2L, second-line; AP, accelerated phase; BP, blast phase; dose opt., dose optimized; FDA, US Food and Drug Administration; JAK, Janus-associated kinase; FEDR, fedratinib; MF, myelofibrosis; RUX, ruxolitinib.

A Selection of Novel Agents/Targets Being Developed in Myeloproliferative Neoplasms, Particularly Myelofibrosis

Cell-Cycle Checkpoint

- P2 Imetelstat | Telomerase Inhibitor
- P1 Alisertib | Aurora Kinase Inhibitor

Anti-fibrotic

- P2 PRM-151 | Pentraxin-2

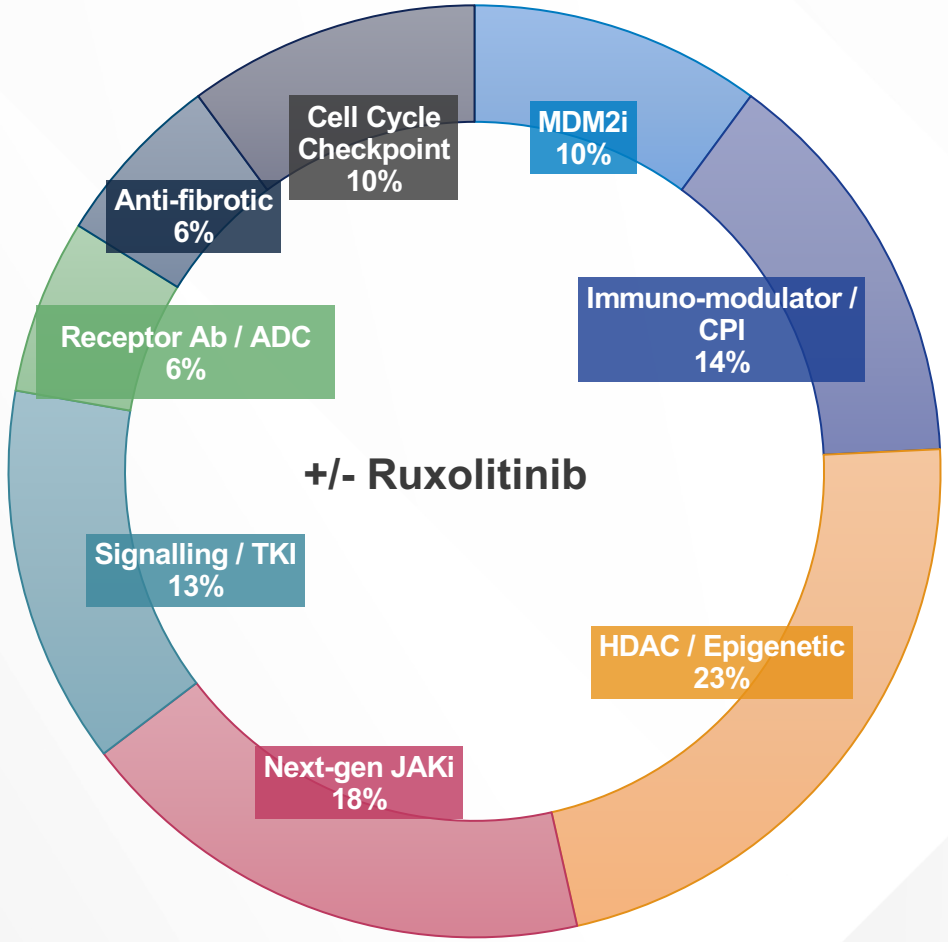
Receptor Ab / ADC

- P2 SL-401 | CD123-toxin

Signaling / TKI

- P2 Glasdequib | Hedgehog
- P2 Sonideqib | Hedgehog
- P2 INCB'465 | PI3Ki
- P2 LCL1 | SMAC/IAP

- P3 Fedratinib | JAK2
- P3 Pacritinib | JAK2/FLT3
- P3 Momelotinib | JAK2/1/ACVR1
- P2 Itacitinib | JAK1



- MDM2i
- Immuno-modulator / CPI
- HDAC / Epigenetic
- Next-gen JAKi
- Signalling / TKI
- Receptor Ab / ADC
- Anti-fibrotic
- Cell Cycle Checkpoint

Apoptosis/MDM2/BCL

- P1 KRT-232
- P2 Idasanutlin | RG7388
- P1 Navitoclax | BCL2 inhibition

Immuno-modulator / CPI

- P3 Pegasys | IFN- α2a
- P3 Ropeg-IFN-α2a
- P2 Nivolumab / Pembrolizumab | PD-1

HDAC Epigenetic

- P3 Azacytidine | HMA
- P3 Panobinostat | HDAC
- P2 Givinostat I HDAC
- P2 IMG-7289 | LSD1
- P1 CPI-0610 | BETi
- P1 PU-H71 | HSP90i

Phase of development (in MPN):

- P1 Phase 1
- P2 Phase 2
- P3 Phase 3

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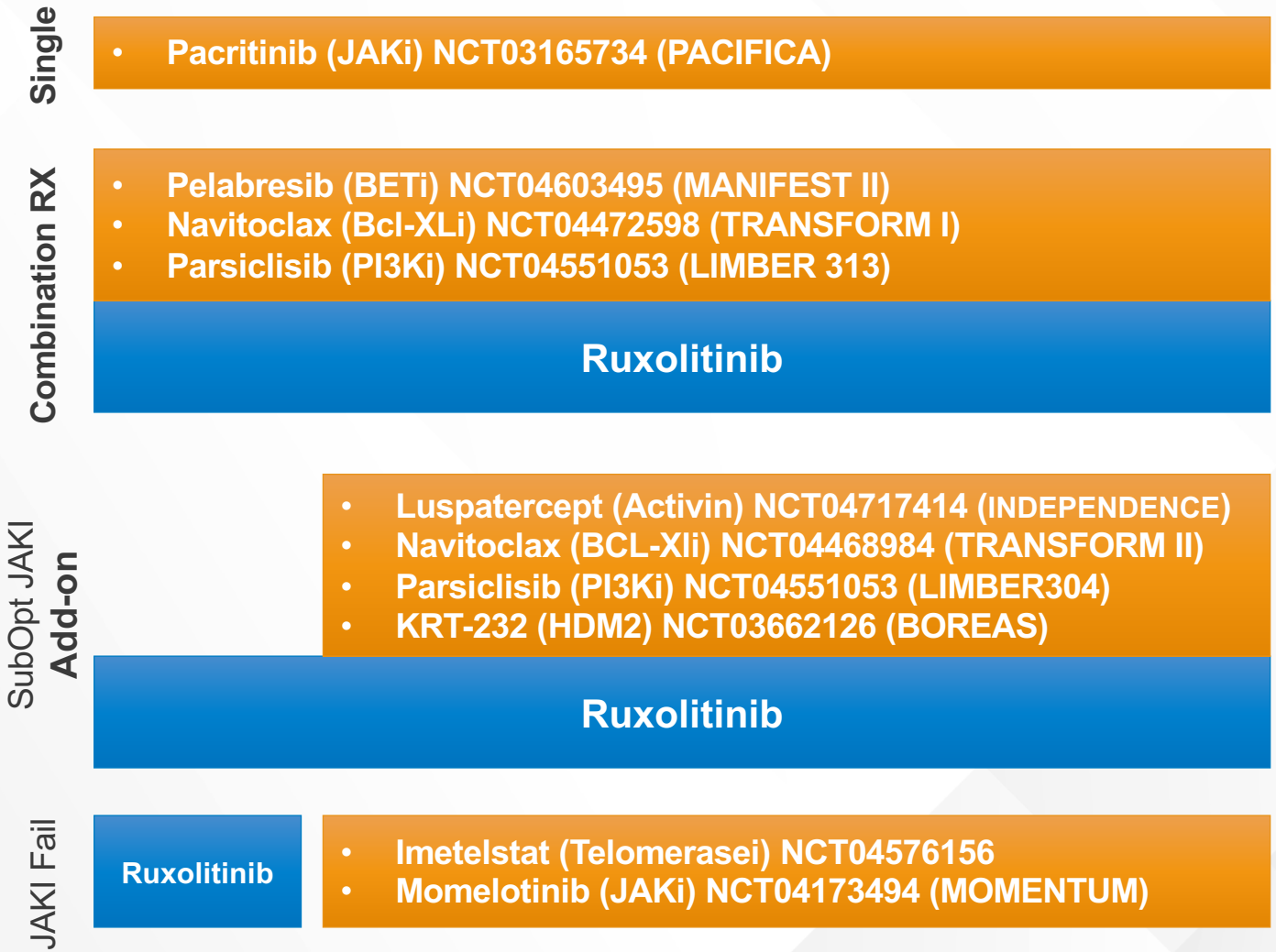
Slide Courtesy of Prof Claire Harrison

Ab, antibody; ADC, antibody drug conjugate; BETi, bromodomain and extraterminal domain inhibitor; BCL, B-cell lymphoma; CPI, checkpoint inhibitor; HDAC, histone deacetylase; HMA, hypomethylating agent; JAKi, Janus kinase inhibitor; LSD1, Lysine-specific demethylase-1; MDM2i, murine double minute 2 inhibitor; MPN, myeloproliferative neoplasm; TKI, tyrosine kinase inhibitor.

Current Phase 3 Trials in MF



MF Management Take-Home Points

- Management of MF is based on estimation of risk and starts with decision for medical therapy (majority) versus allogeneic SCT
- Ruxolitinib and fedratinib both approved first-line medical therapies
- Fedratinib with both second line efficacy and in those with modest thrombocytopenia
- Momelotinib and pacritinib both JAK inhibitors in advanced phase 3 programs
- Robust pipeline of additional agents in development for MF

MF, myelofibrosis; JAK, Janus-associated Kinase; SCT, stem cell transplantation.

Chapter 4
Case Study

Case: Introduction

- 2020: 72-year-old patient with MF
  - Primary MF
  - JAK2 mutated
  - MPN-10: 45 (out of 100)
  - 6 kg (13 lb) weight loss
  - Night sweats
  - Fatigue
- Spleen: 14 cm BLCM
- Hemoglobin: 9.5 g/dL
- White blood cell count: 14 x 10^9/L
- Platelets: 140 x 10^9/L

BLCM, below left costal margin; MF, myelofibrosis; JAK, Janus-associated Kinase; MPN, myeloproliferative neoplasm

Case (cont.)

MF Risks - DIPSS	Present
Age ≥65 years	X
Leukocytosis >25x10^9/L	
Hb <10 g/dL	X
Symptoms	X
Blasts >1% PB	

MF Patient Burden	Present
Symptoms (MPN-10: 30)	X
Splenomegaly	X
Anemia	X
Signs of progression	
Movement toward AML	

Intermediate 2 Risk MF

Symptomatic Intermediate 2 MF With Splenomegaly

Initiated Ruxolitinib

AML, acute myeloid leukemia; DIPSS, dynamic international prognostic scoring system; Hb, hemoglobin; MF, myelofibrosis; PB, peripheral blasts.

Case: 2023

- Initially had a IWG clinical improvement in
  - Splenomegaly (14 to 2 cm BLCM)
  - Symptoms (MPN-10: from 45 to 10)
  - Developed transfusion dependence
  - Moved away to live near grandkids

- Returns to see you
  - Taking ruxolitinib 5 mg BID
  - Spleen 14 cm BLCM
  - Symptoms MPN-10: 35
  - Hb 7.6 g/dL
    (last transfusion 3 weeks ago)
  - Platelets 40 x 10^9/L
    - > Marrow
    - > 3+ reticulin fibrosis
    - > Karyotype 13q-
    - > Blasts 6%
    - > NGS: *JAK2, ASXL1, IDH1* mutation

BID, twice daily; BLCM, below left costal margin; IWG, International Working Group; Hb, hemoglobin; NGS, next-generation sequencing.

Case: 2023 (cont.)

MIPSS 70	Present
Hb <10 g/dL	X
WBC >25 x 10^9/L	
PLT <100 x 10^9/L	X
Blasts ≥2%	
Fibrosis >grade 1	X
Constitutional symptoms	X
Absence of CALR mutation	
HMR	
ASXL1	X
EZH2	
SRSF2	
IDH1/2	X
≥2 HMR	X

→ **High-risk MF**
5-yr overall survival: 34%

MF Patient Burden	Present
Symptoms (MPN-10: Score 30)	X
Splenomegaly	X
Anemia	X
Signs of progression	X
Movement toward AML	

→ **What now?**

AML, acute myeloid leukemia; CALR, calreticulin; Hb, hemoglobin; HMR, high mutation rate; MF, myelofibrosis; MIPSS, Mutation-enhanced International Prognostic Scoring System; Hb, hemoglobin; MF, myelofibrosis; PLT, platelets; WBC, white blood cell.

Case Study Question

Which of the following would be appropriate second-line therapy based on NCCN guidelines?

a) Prescribe fedratinib instead of ruxolitinib
b) Increase dose of ruxolitinib to 10mg BID
c) Add venetoclax and azacitidine
d) Prescribe pacritinib instead of ruxolitinib
e) Unsure

BID, twice daily; NCCN, National Comprehensive Cancer Network.

Case: 2023 Alternative Labs

- Initially had a IWG clinical improvement in
  - Splenomegaly (14 to 2 cm BLCM)
  - Symptoms (MPN-10: from 45 to 10)
  - Developed transfusion dependence
  - Moved away to live near grandkids
- Returns to see you
  - Taking ruxolitinib 5 mg BID
  - Spleen 14 cm BLCM
  - Symptoms MPN-10: 35
  - Hb 7.6 g/dL
    (last transfusion 3 weeks ago)
  - Platelets 95 x 10^9/L
    - Marrow
    - 3+ reticulin fibrosis
    - Karyotype 13q-
    - Blasts 6%
    - NGS: *JAK2, ASXL1, IDH1* mutation

BID, twice daily; BLCM, below left costal margin; Hb, hemoglobin; IWG, International Working Group; Hb, hemoglobin; NGS, next-generation sequencing.

Case: 2023 (cont.)

MIPSS 70	Present
Hb <10 g/dL	X
WBC >25 x 10^9/L	
PLT <100 x 10^9/L	X
Blasts ≥2%	
Fibrosis >grade 1	X
Constitutional symptoms	X
Absence of CALR mutation	
HMR	
ASXL1	X
EZH2	
SRSF2	
IDH1/2	X
≥2 HMR	X

High-Risk MF
5-yr overall survival: 34%

MF Patient Burden	Present
Symptoms (MPN-10: Score 30)	X
Splenomegaly	X
Anemia	X
Signs of progression	X
Movement toward AML	

What now?

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AML, acute myeloid leukemia; CALR, calreticulin; Hb, hemoglobin; HMR, high mutation rate; MF, myelofibrosis; MIPSS, Mutation-enhanced International Prognostic Scoring System; Hb, hemoglobin; MF, myelofibrosis; PLT, platelets; WBC white blood cell.

Case Study Question

Which of the following would be appropriate second-line therapy for the management of this patient?

a) Prescribe fedratinib in combination with ruxolitinib
b) Add venetoclax and azacitidine
c) Prescribe axitinib instead of ruxolitinib
d) Switch to momelotinib (pending approval)

Key Takeaways

- An accurate diagnosis, prognosis, and symptom burden assessment is needed to develop treatment plan for MF
- Molecular diagnostic panels very helpful in assessing MF diagnosis and prognosis
- JAK inhibition (ruxolitinib and fedratinib) is appropriate front-line therapy for MF
- Fedratinib approved and available as second line for ruxolitinib failures for those with minimal anemia or thrombocytopenia
- Pacritinib now approved for MF patients with thrombocytopenia (and/or cytopenic) MF in front or second line
- Momelotinib beneficial in front and second line for MF patients with anemia and may be available soon

JAK, Janus-associated kinase; MF, myelofibrosis.

AXIS Medical Education

Incorporating Scientific Advances into Myelofibrosis Treatment Plans:

A Quality Improvement Initiative