THE UNIVERSITY OF TEXAS
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Management of Myelofibrosis

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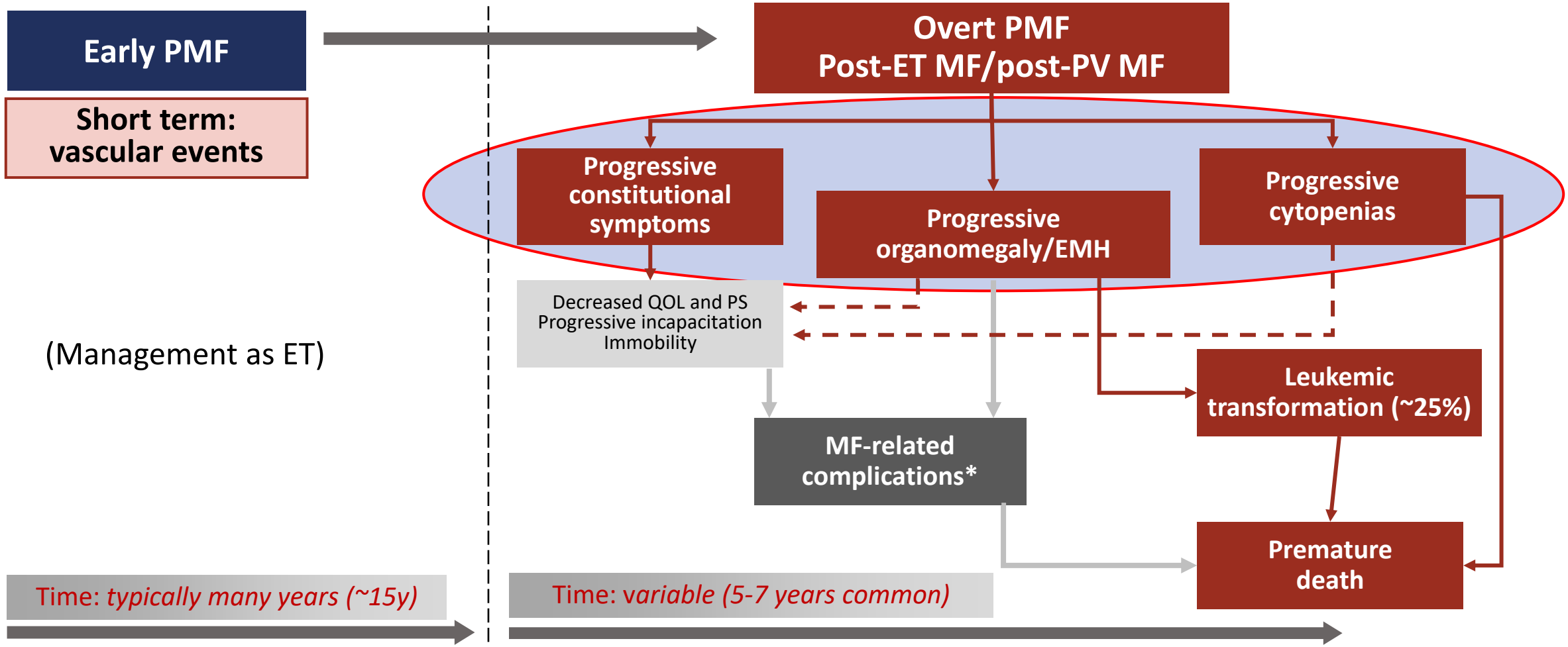
Myelofibrosis: Disease Course and Complications

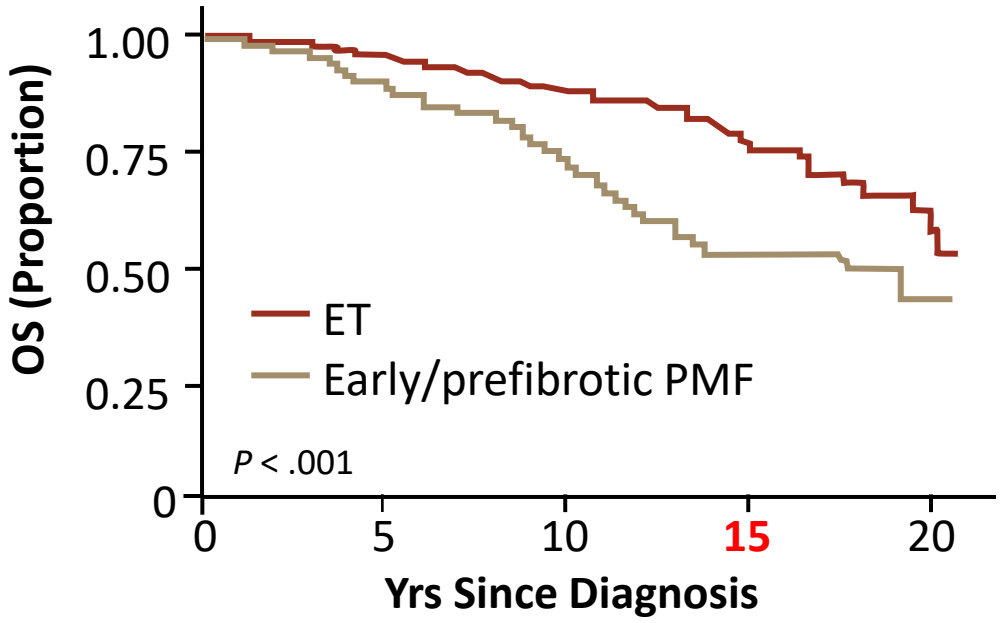


Abbreviations: EMH, extramedullary hematopoiesis; ET, essential thrombocythemia; PMF, primary myelofibrosis; PS, performance status; PV, polycythemia vera; QOL, quality of life.

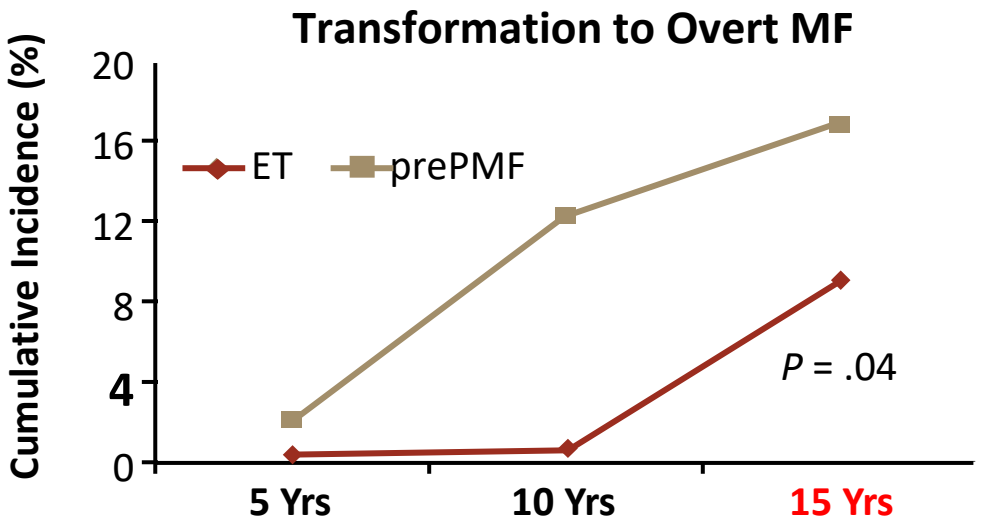
1. Mughal TI, et al. *Int J Gen Med.* 2014;7:89-101; 2. Haybar H, et al. *Cardiovasc Hematol Disord Drug Targets*. 2017;17(3):161-166.

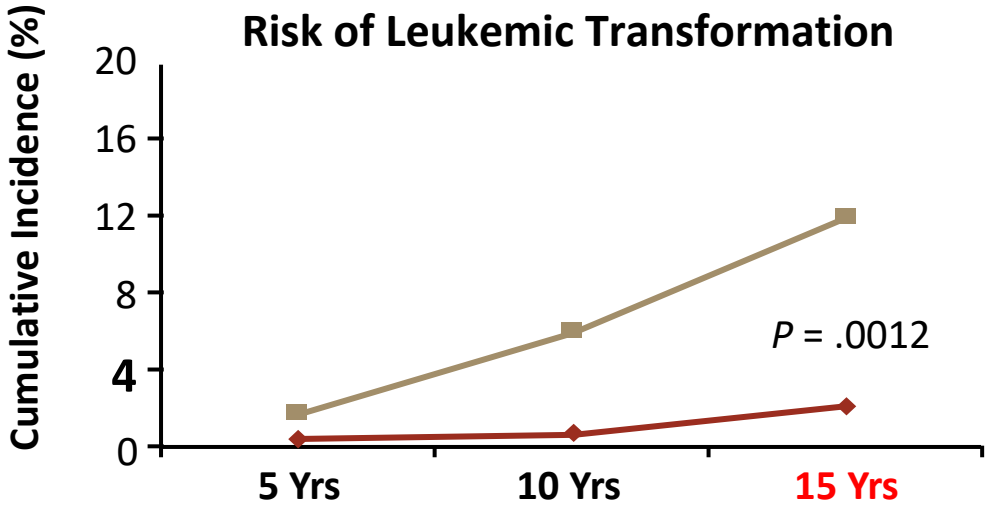
Early/Prefibrotic Primary Myelofibrosis:
Not So Aggressive Neoplasm

- International, observational study in which patients with ET or rediagnosed prePMF were followed for disease progression (N = 1,104)



Events	32	47	31	13
No. at risk	628	326	157	57





Barbui T, et al. *J Clin Oncol.* 2011;29:3179-84.

The Heterogeneous Clinical Spectrum of Prefibrotic Myelofibrosis

Mimicking essential thrombocytopenia

Progression towards overt myelofibrosis

Time

Bleeding and thrombosis

Symptoms of myelofibrosis

Life expectancy

Finazzi. Blood Cancer J. 2018;8:104.

Classic Prognostic Models for Myelofibrosis

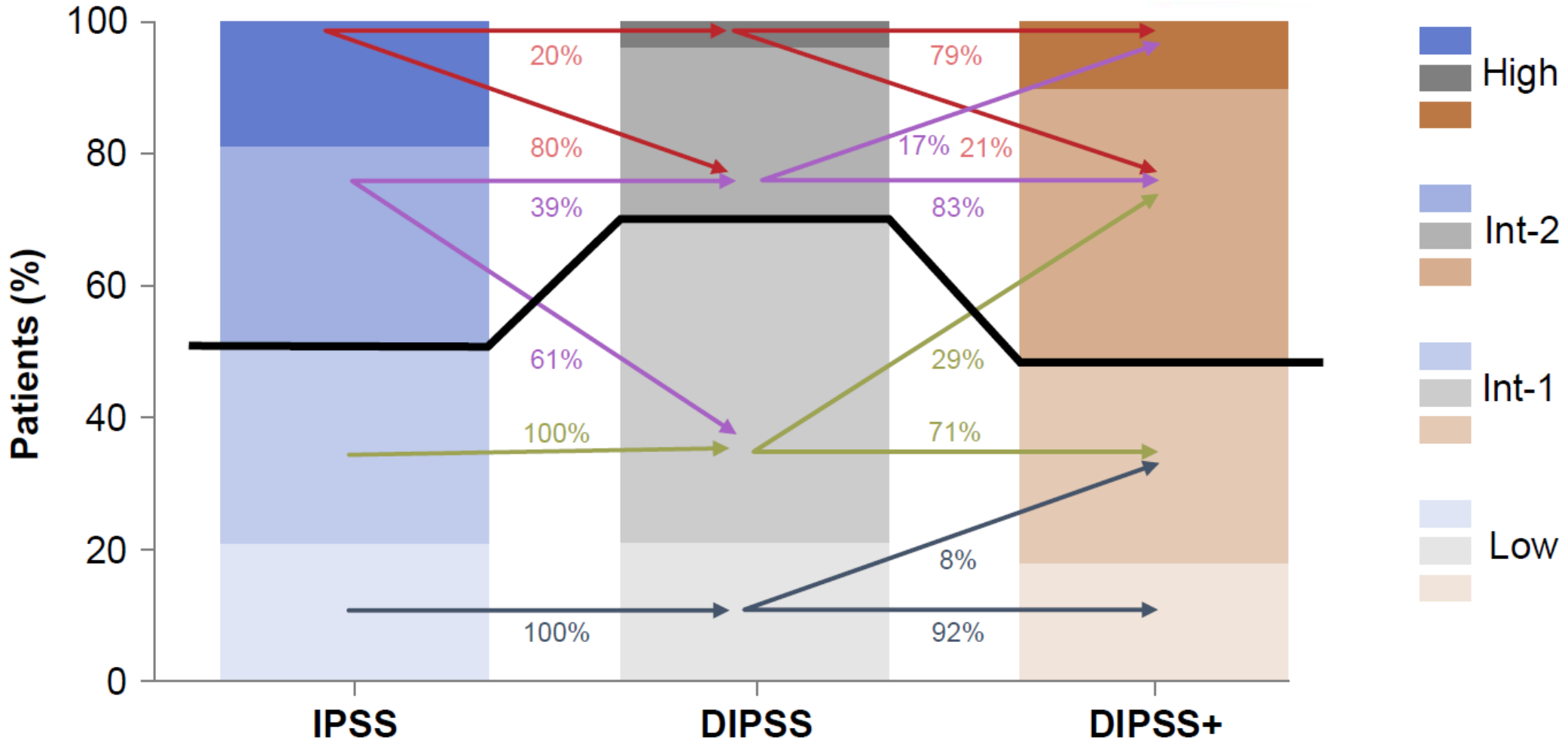
Parameter	Included in IPSS[2]	Included in DIPSS[3]	Included in DIPSS-Plus[4]
Age > 65 y	Yes (1 point)	Yes (1 point)	Yes[a]
Hgb < 10 g/dL	Yes (1 point)	Yes (2 points)	Yes[a]
WBC > 25×10^9/L	Yes (1 point)	Yes (1 point)	Yes[a]
PB blood blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes[a]
Constitutional symptoms	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, Interational Prognostic Scoring System; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell count.
[a]Zero, I, 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.

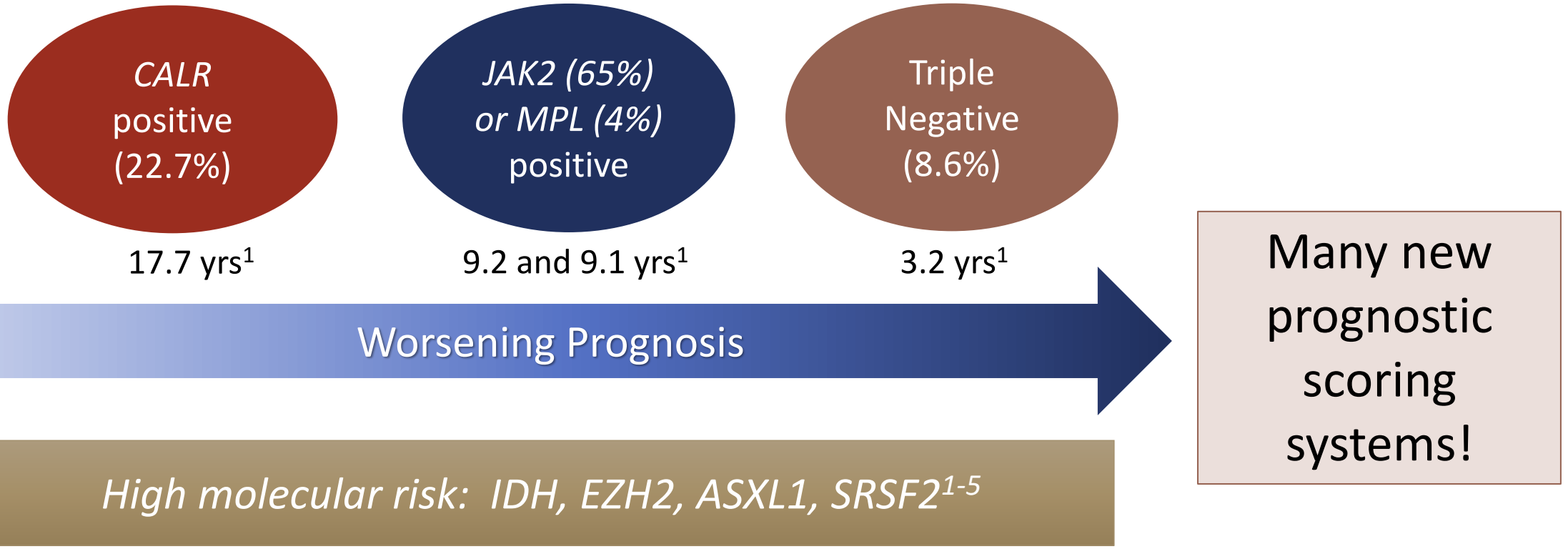
1. Bose P, Verstovsek S. *Cancer*. 2016;122:681-92; 2. Cervantes F, et al. *Blood*. 2009;113:2895-2901; 3. Passamonti F, et al. *Blood*. 2010;115:1703-1708; 4. Gangat N, et al. *J Clin Oncol.* 2011;29:392-397

Distribution of Myelofibrosis Patients by Different Prognostic Models



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

Impact of Driver and "High Molecular Risk" Mutations in Primary Myelofibrosis



- Worst prognosis in *CALR* neg/*ASXL1* positive[3]
- 2 or more HMR mutations also worsens survival[4]

1. Rumi E et al. *Blood*. 2014;124:1062-1069; 2. Vannucchi AM et al. *Leukemia*. 2013;27:1861-9; 3. Tefferi A. et al. *Leukemia*. 2014;28:1472-7; 4. Guglielmelli P, et al. *Leukemia*. 2014;28:1804-10; 5. Lee YC, et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:558-568.

Once we are done with prognostication: "Clinical needs" oriented current therapy for MF

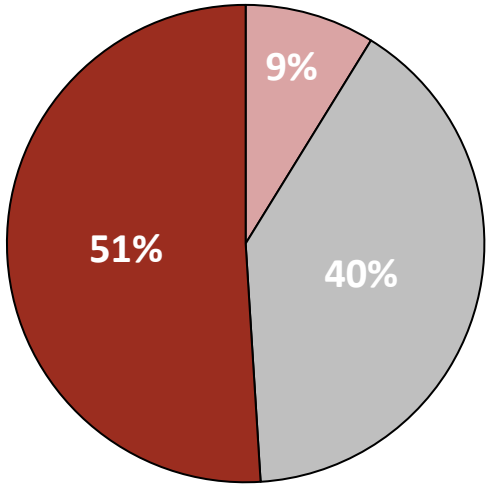
Clinical need	Drugs / Intervention	
Anemia	• Corticosteroids • Danazol • erythropoietin	• Thalidomide • Lenalidomide
Symptomatic splenomegaly	• Ruxolitinib, fedratinib • Hydroxyurea	• Cladribine, IMIDs • Splenectomy
Extramedulary hematopoiesis	• Radiation therapy	
Hyperproliferative (early) disease	• Interferon, hydroxyurea	
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.

MPN Patient Treatment-Watch and Wait
2016 International Landmark Study

- 23% of patients managed with watch and wait had high to moderate symptom burden
- Only 36% reported not currently experiencing symptoms

MF
(n = 194)



Despite a significant symptom burden in some untreated patients, around half of the physicians would still observe > 25% of patients at diagnosis

Observe > 25% of patients

Observe 1%-25% of patients

Active treatment

From Koschmieder S, et al. *Congress of the European Hematology Association*; June 22 - 25, 2017; Madrid, Spain [poster 706].

MPN10

Total Symptom Score [MPN-SAF]

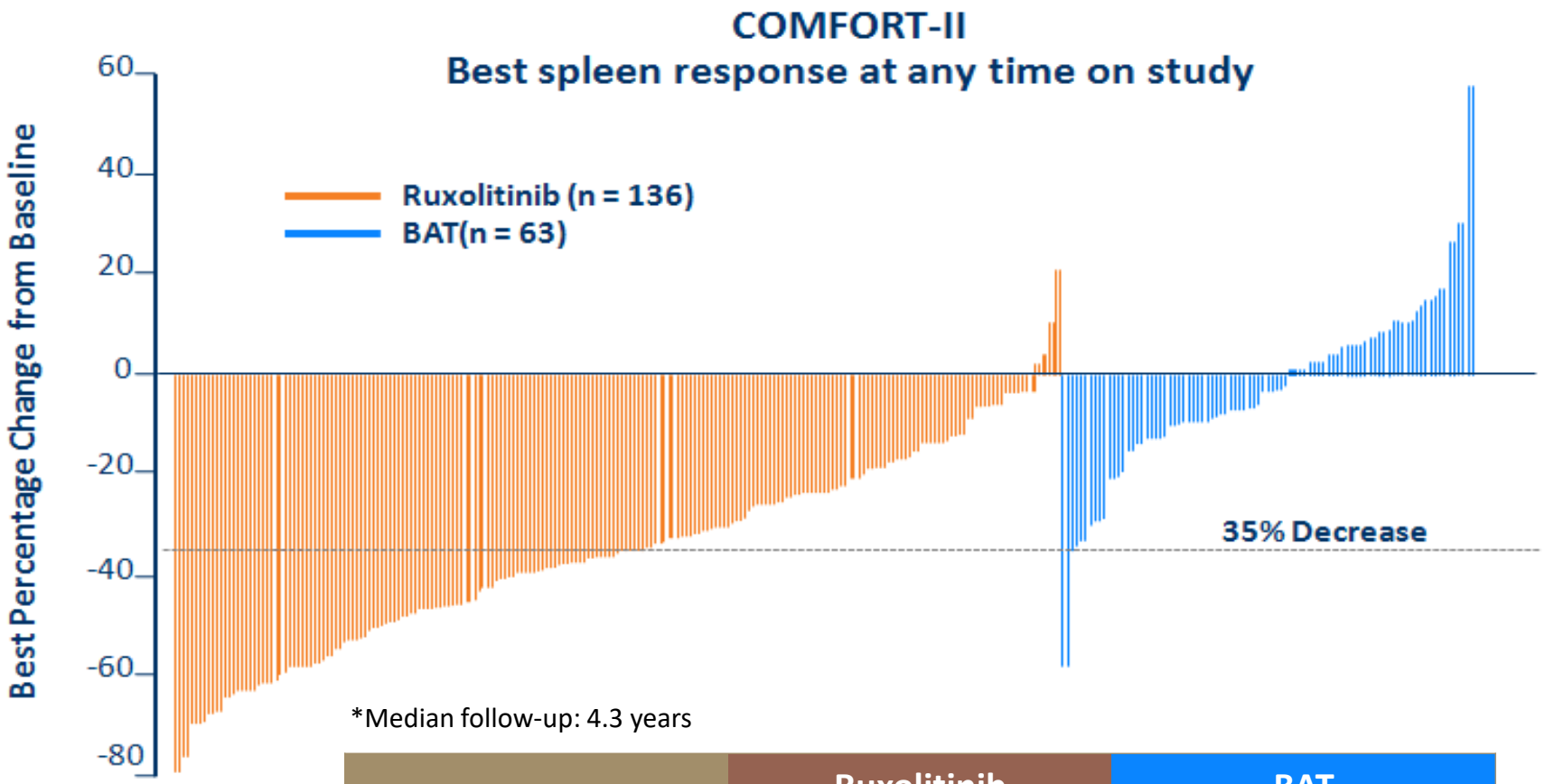
An easy tool to assess symptoms in MPNs

- Inflammation
- Splenomegaly
- Anemia

	Value	Prognostic variable
Fatigue	0	1 to 10 ranking (0 if absent; 1 most favorable; 10 least favorable)
Early satiety	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Unintentional weight loss last 6 months	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
MPN10 score	0	

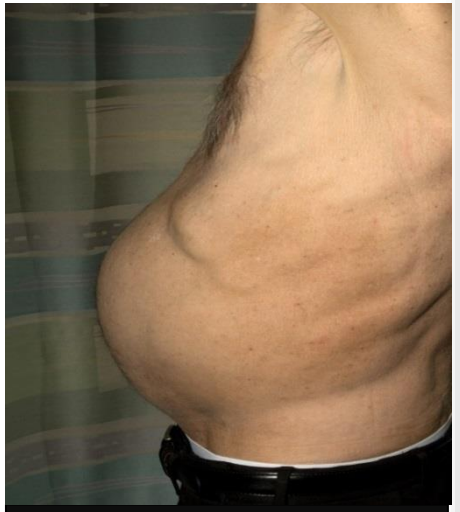
Scherber R, et al. *Blood*. 2011;118:401-408.

Spleen Volume Response: Ruxolitinib vs. BAT

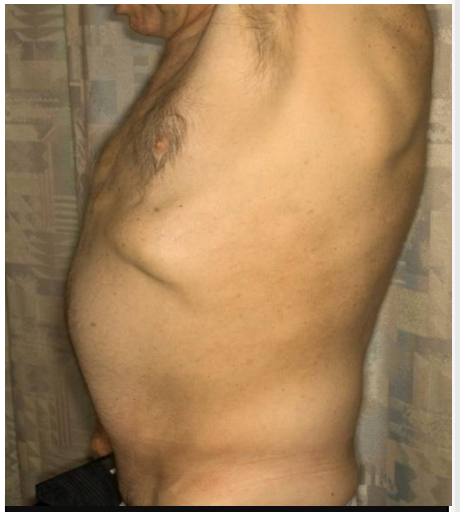


*Median follow-up: 4.3 years

	Ruxolitinib	BAT
↓ Spleen volume	132 (97%)	35 (56%)
↑ Spleen volume	4 (3%)	28 (44%)



MF Patient Pre-Ruxolitinib Therapy

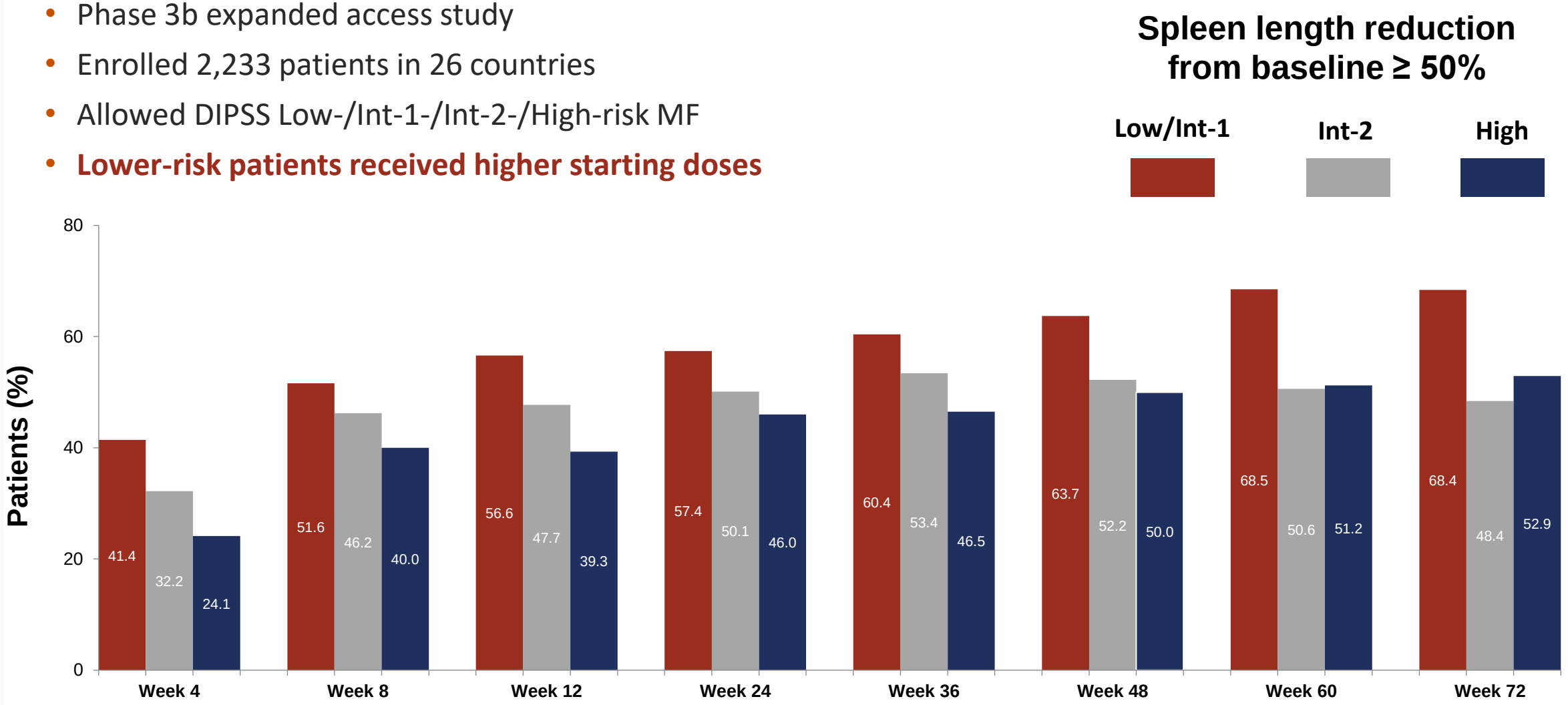


After 2 Months of Therapy

Harrison C, et al. *N Engl J Med*. 2012;366(9):787-98. *Images courtesy of Srdan Verstovsek, MD, PhD*

JUMP study: lower the risk, better the spleen response to ruxolitinib

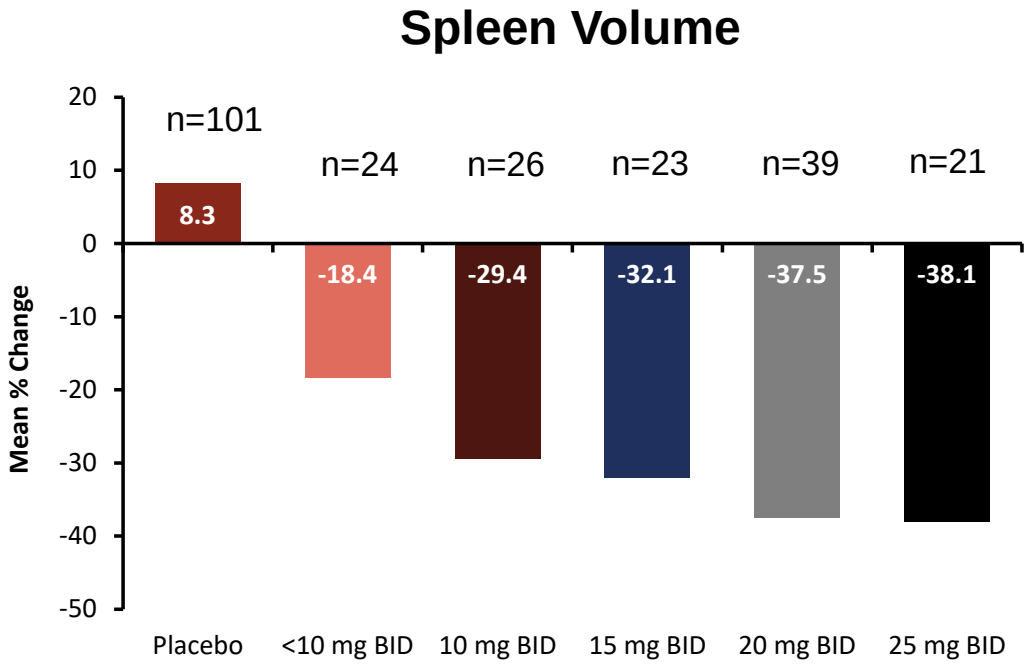
- Phase 3b expanded access study
- Enrolled 2,233 patients in 26 countries
- Allowed DIPSS Low-/Int-1-/Int-2-/High-risk MF
- **Lower-risk patients received higher starting doses**

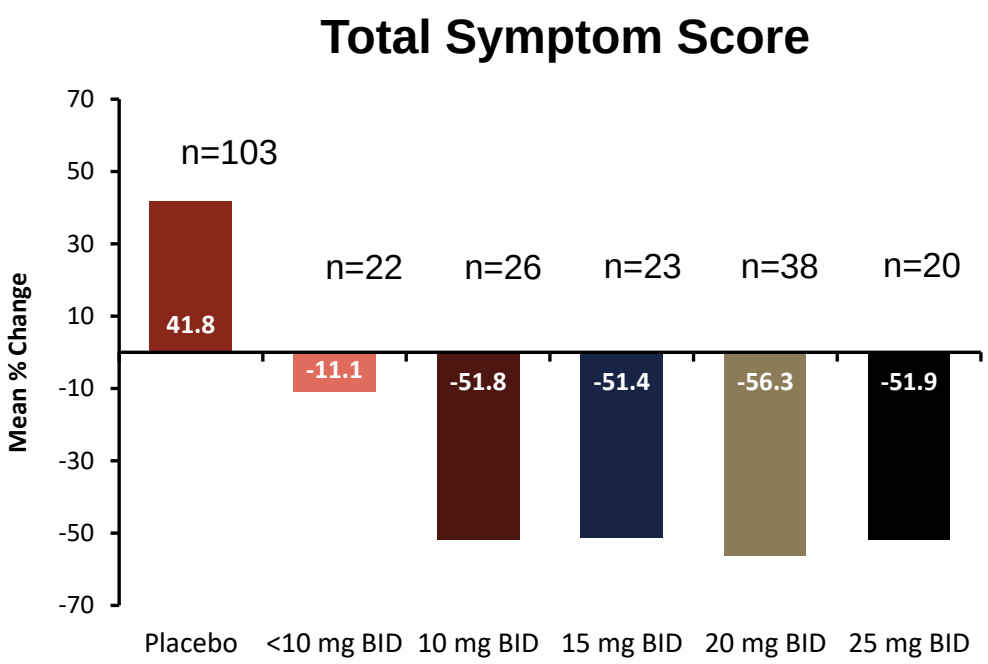


Passamonti F, et al. Poster presented at EHA 2017. Haematologica. 2017;102:abstract E1333.

Ruxolitinib Efficacy by Titrated Dose: COMFORT-I

Week 24





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

Verstovsek S, et al. *OncoTargets and Therapy*. 2014;7:13-21.

Rationale for earlier use of ruxolitinib for MF patients – a retrospective Italian study (N = 408)

The influence of disease stage on quality of response

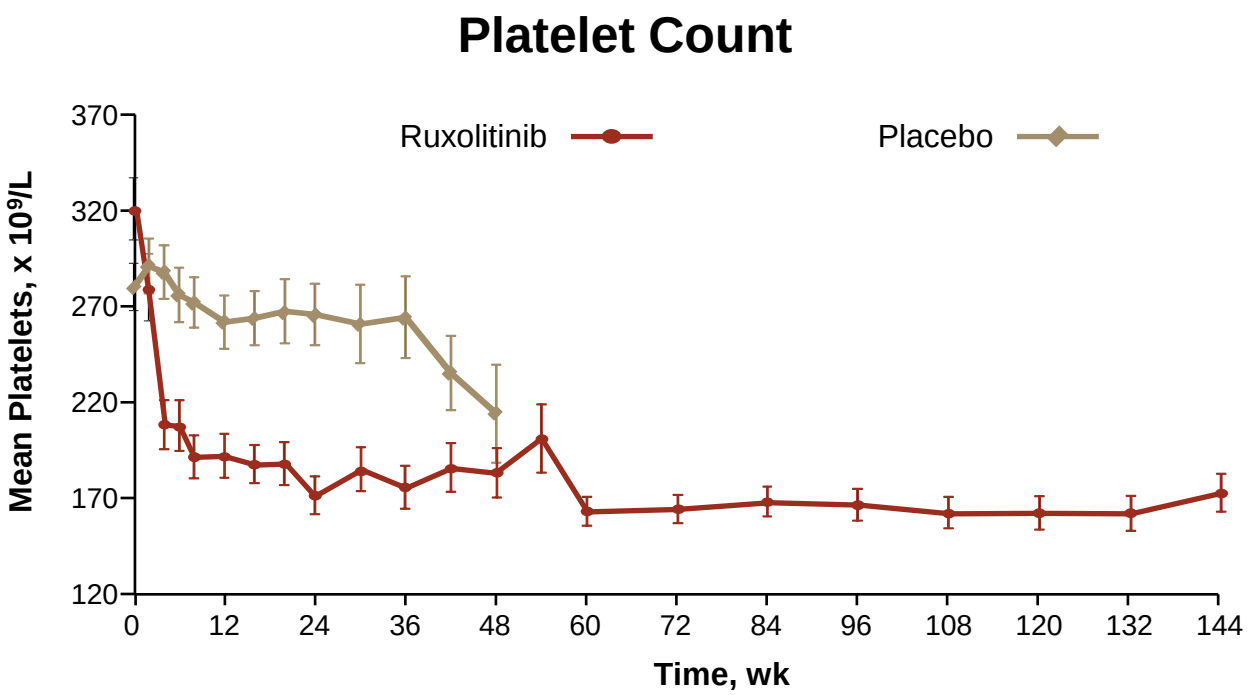
- Spleen/symptom responses are lower if
  - Time interval between MF diagnosis and start of ruxolitinib > 2 years
  - Larger splenomegaly/higher total symptom score
  - Transfusion dependency/lower PLT count
  - IPSS Int-2/High risk

The influence of ruxolitinib dose

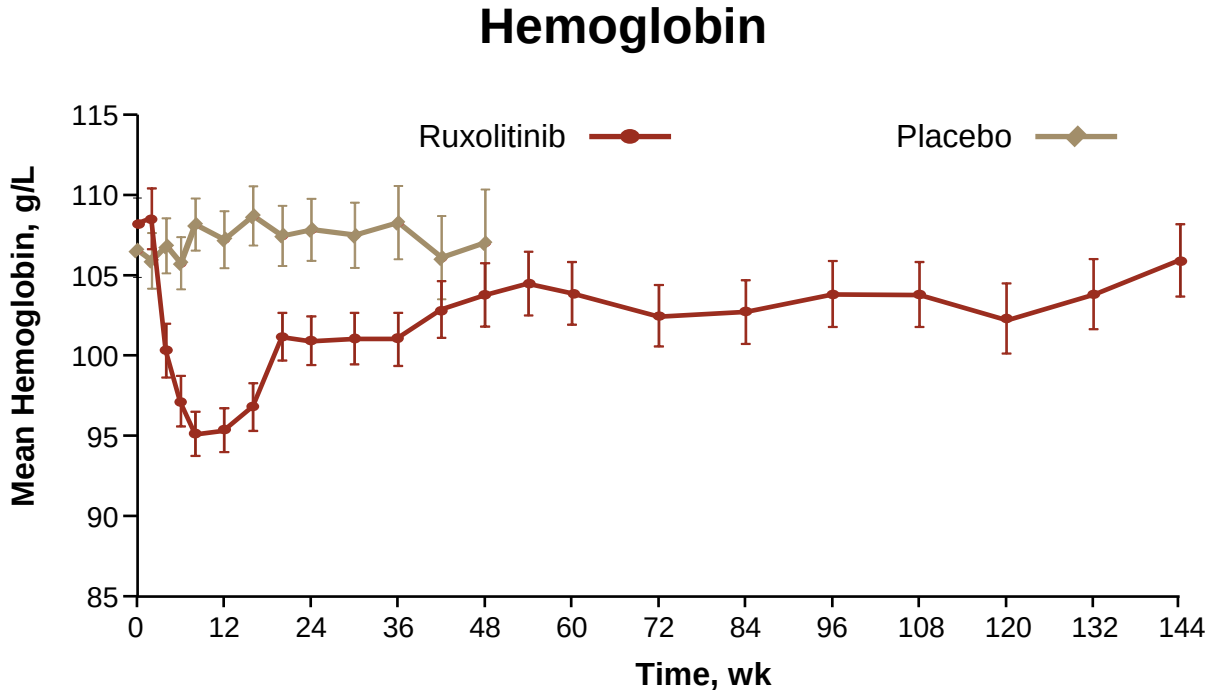
- Early MF patients may tolerate a higher ruxolitinib dose
- Patients starting with higher doses have a higher rate of spleen response
- Use of lower ruxolitinib doses may also result in reduced efficacy

Palandri F, et al. Oncotarget. 2017;8:79073-86.

Mean Platelet Count and Hemoglobin over Time COMFORT-I[1]



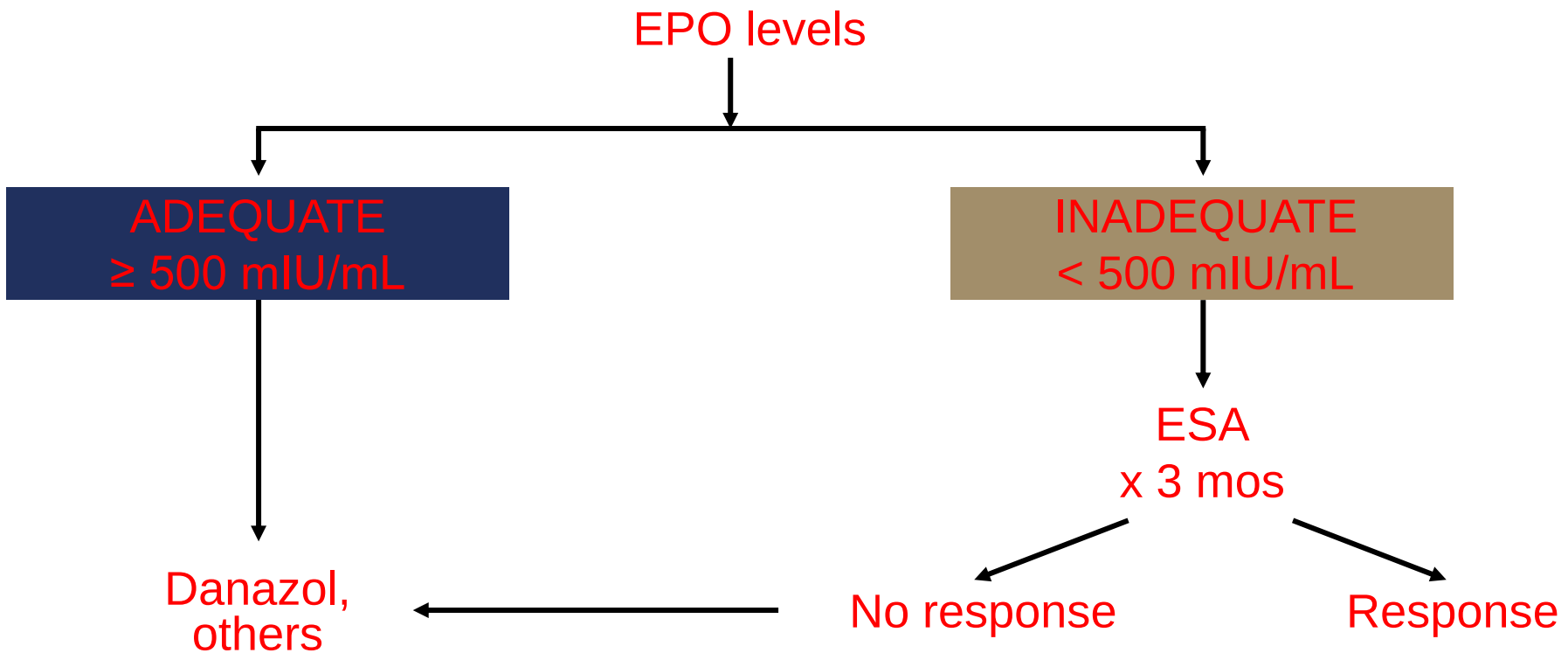
No. of Patients													
RUX	155	144	143	136	124	112	110	107	104	100	94	88	79
Placebo	151	128	112	82	37								



No. of Patients													
	155	145	143	136	124	113	110	107	104	100	94	88	79
	151	132	113	83	37								

Verstovsek S, et al. *Haematologica*. 2015;100:479-488.

Approach to the Treatment of Anemia in MF



NCCN guidelines, 2017

JAKARTA:
Fedratinib for Int-2/High-Risk Myelofibrosis[1,2]

- 289 patients with int-2 or high-risk MF, post-PV MF, or ET MF with splenomegaly
- Fedratinib 500 mg (n = 97); 400 mg (n = 96); or placebo (n = 96) once daily for ≥6 cycles

Fedratinib 400 mg (recommended dose)*:

- 37% achieved ≥35% reduction in spleen volume vs. 1% with placebo ($p < 0.0001$)
- 40% had ≥ 50% reduction in MF-related symptoms, vs. 9% with placebo

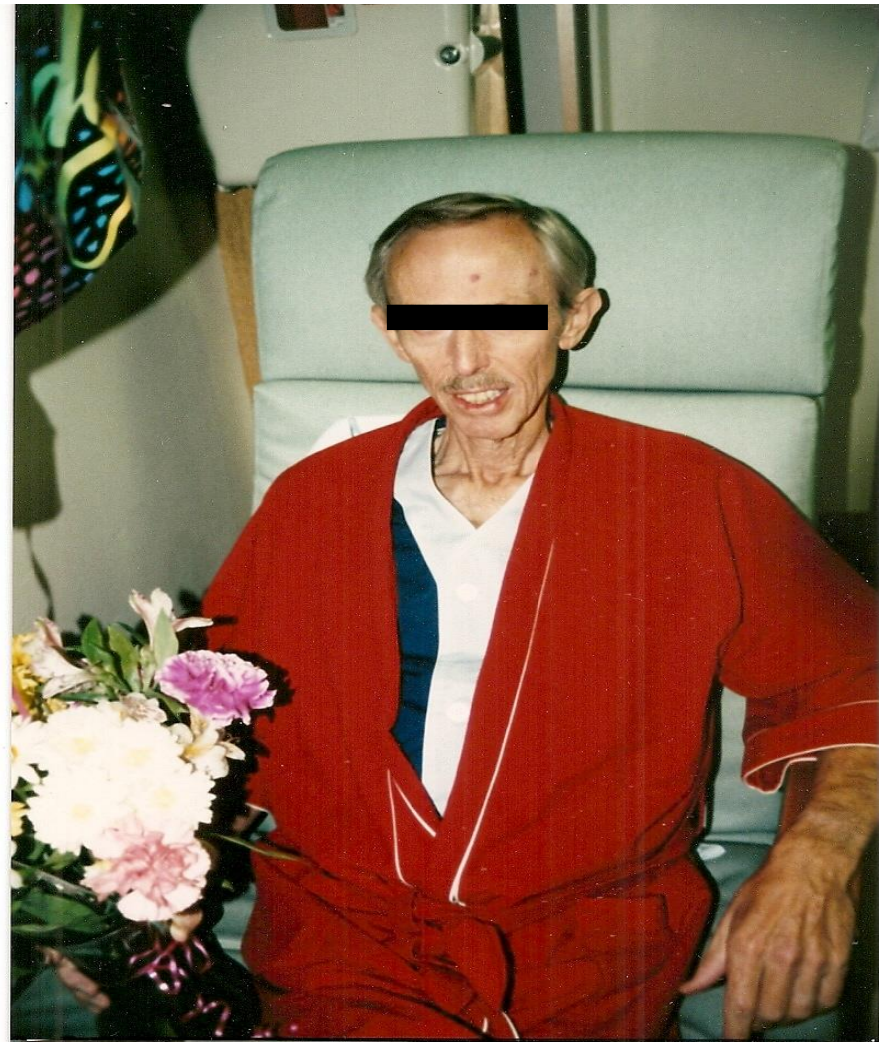
Safety:

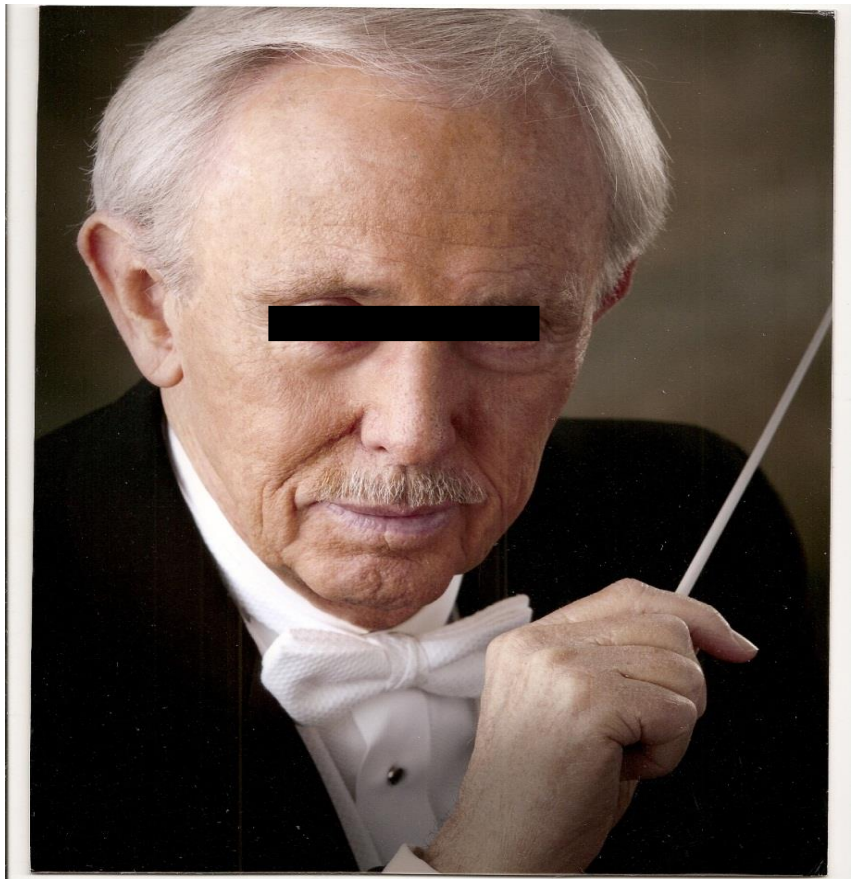
- Boxed warning about the risk **Wernicke encephalopathy**
  - Assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. If encephalopathy is suspected, fedratinib should be immediately discontinued and parenteral thiamine initiated
- The most common adverse reactions were diarrhea, nausea, anemia, and vomiting

***Recommended dose of fedratinib is 400 mg orally once daily (baseline platelet count of ≥50 x 10^9/L)[2]**

1. Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651; 2. Inrebic® (fedratinib) prescribing information; Aug 2019.

Lets talk about something else…





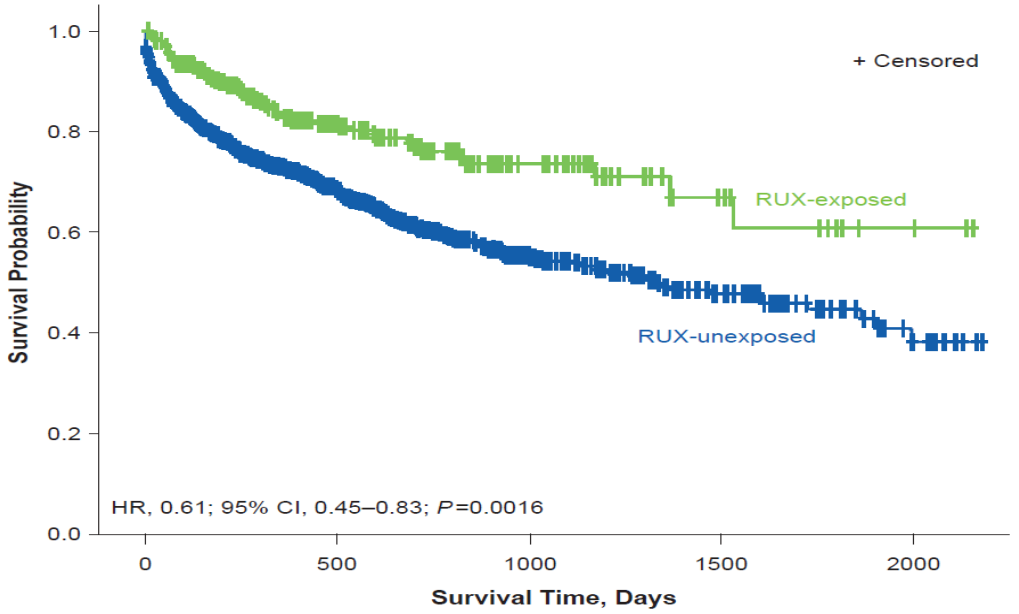
Real-World Survival in Elderly Patients With Myelofibrosis in the United States: Ruxolitinib Exposed vs Unexposed

OS Outcomes*

Parameter	Patients Exposed to RUX (n=272)	Patients Unexposed to RUX (n=1127)
Follow-up, median, mo	14	10
OS, median (95% CI), mo	**NR**	**44.4**
Survival, % (95% CI)		
1-y	82	72
2-y	76	61

- Patients in the ruxolitinib-exposed group had a significantly lower risk of mortality compared with the ruxolitinib-unexposed group (adjusted **HR, 0.61**; 95% CI, 0.45–0.83; *P*=0.0016)
- Medicare FFS Claims Database (Parts A/B/D)

Kaplan-Meier Analysis of OS*

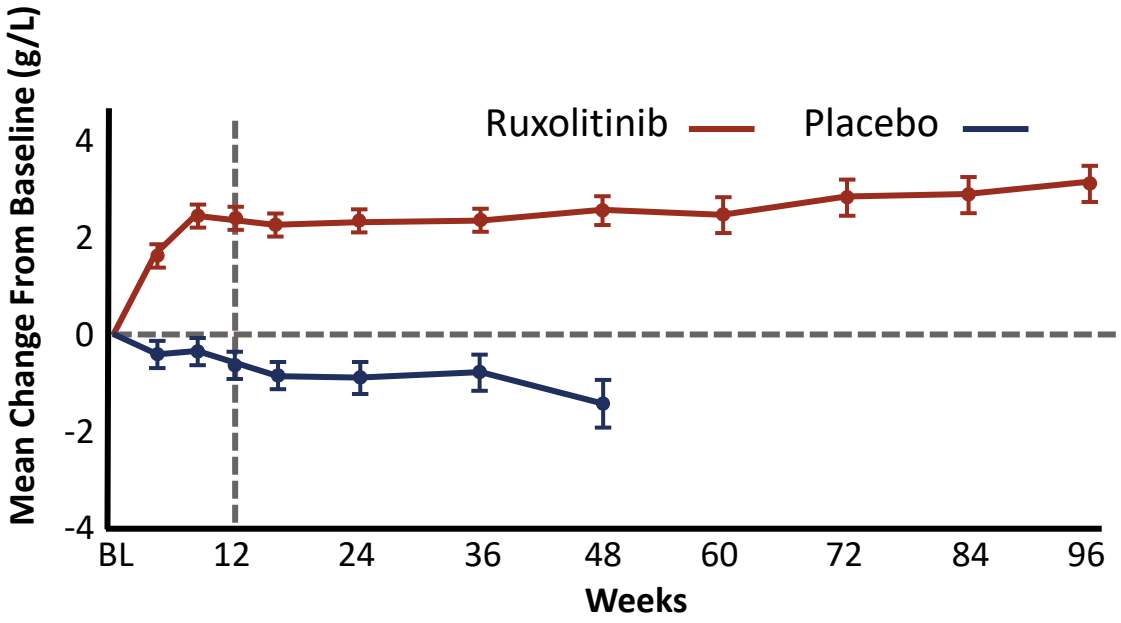


HR, hazard ratio; NR, not reached.
* In patients newly diagnosed with intermediate- or high-risk MF after exclusion of patients with MDS, hematologic malignancies (excluding AML), solid tumors, and AML ≤12 months before, on, or any time after the index date.

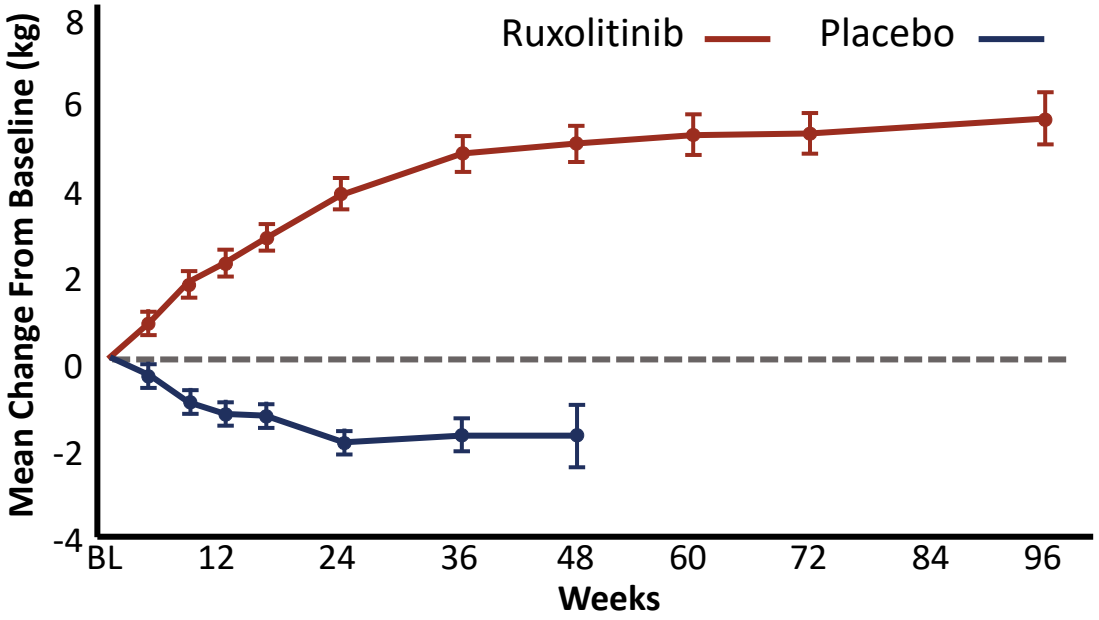
Verstovsek, EHA 2020, abstract EP1124

COMFORT-I: Effects of Ruxolitinib on Metabolic and Nutritional Parameters in Patients with MF

Mean Change in Serum Albumin

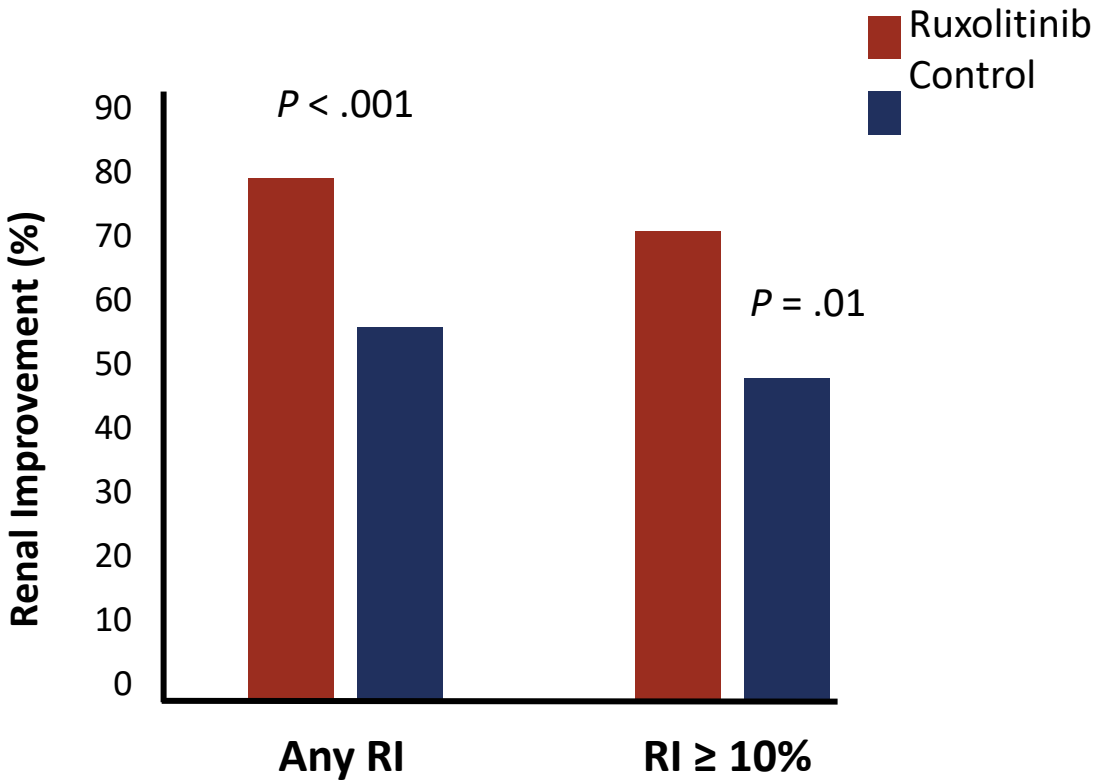


Mean Change in Body Weight

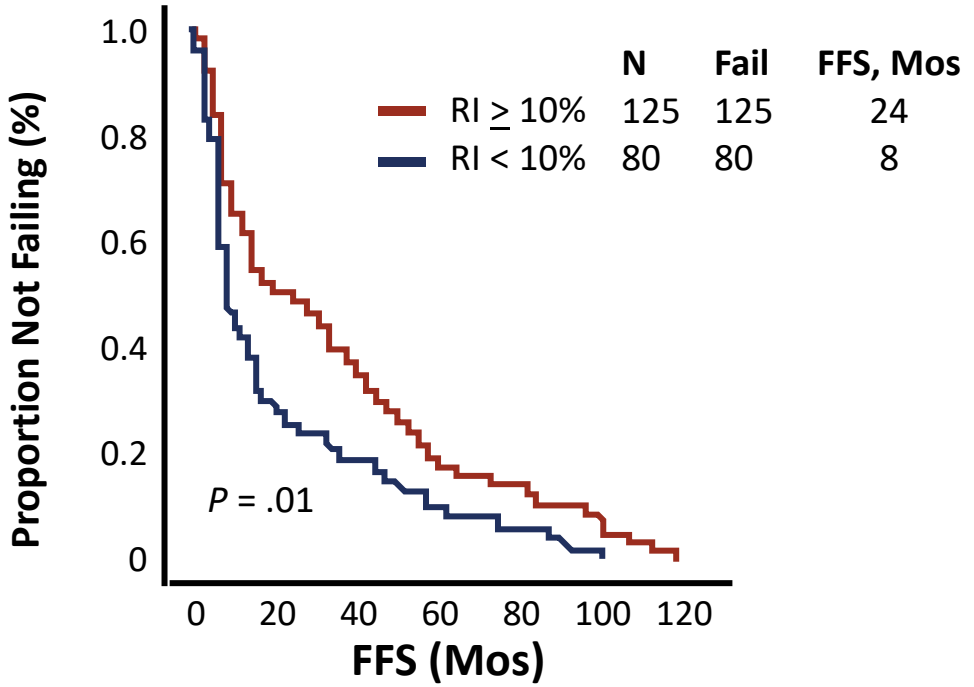


Ruxolitinib Improves Renal Function in MF

Renal Improvement* in Ruxolitinib-Treated Pts vs Matched Controls

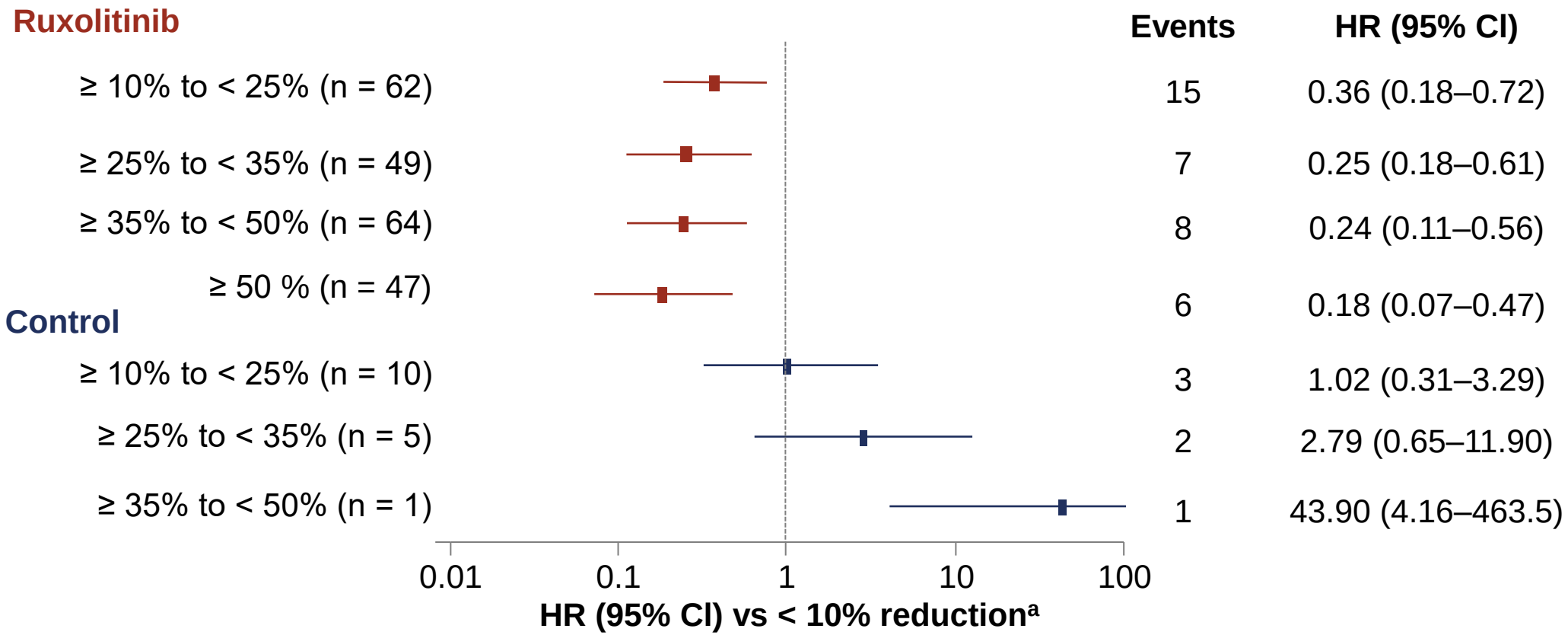


Relationship Between Quality of Renal Improvement and FFS



*Best percentage change in eGFR during treatment vs baseline.

Pooled analysis COMFORT-I and COMFORT-II: Correlation of spleen volume reduction at Week 24 and OS

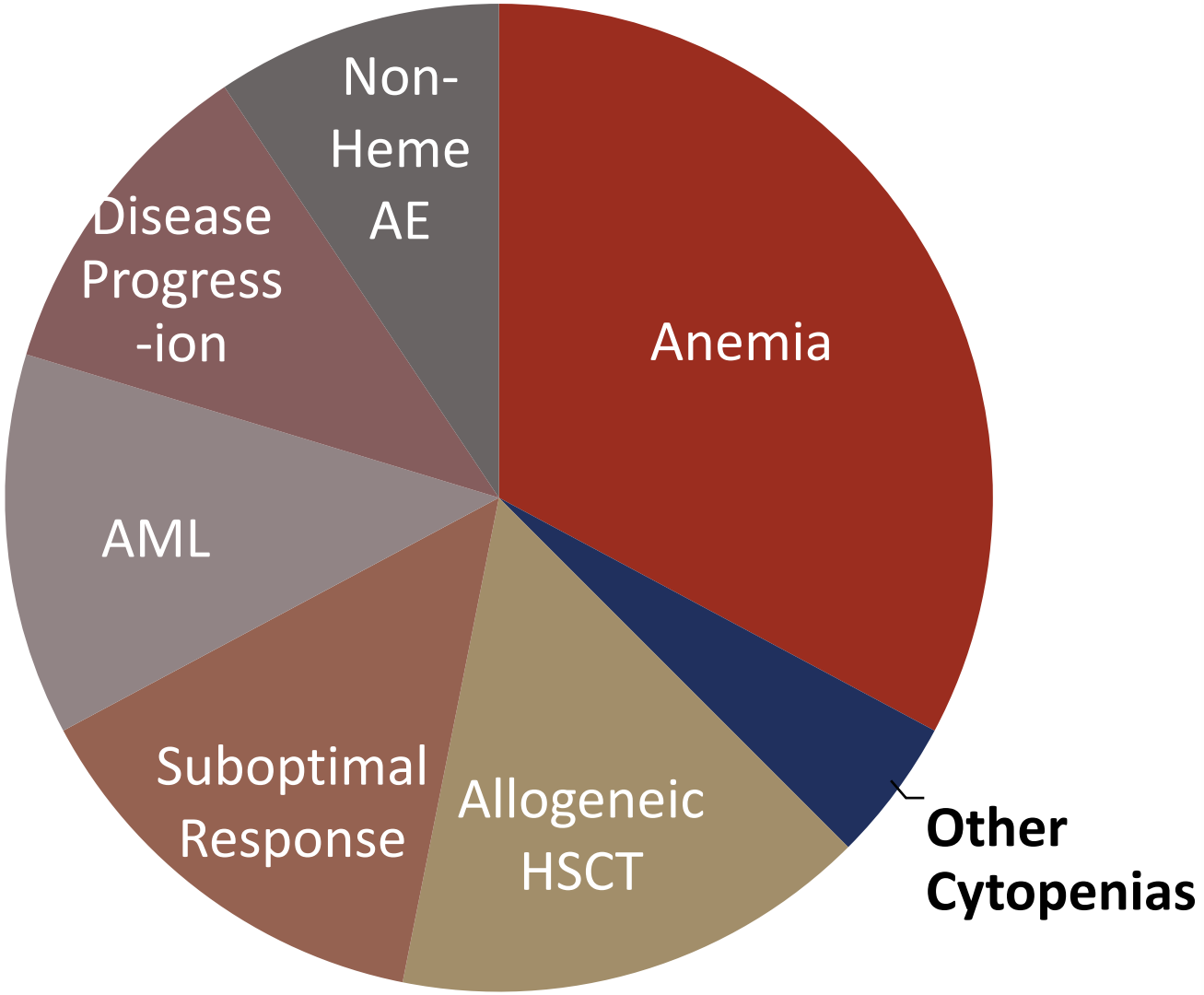


"… Each 10% reduction from baseline in spleen length at Week 24 was associated with a 9% reduction in the risk of death for ruxolitinib-treated patients (HR 0.91, 95% CI 0.84–0.99; p = 0.02)…"

[a] Category includes patients with a < 10% reduction from baseline in spleen volume at Week 24 or no assessment (ruxolitinib 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.

Reasons for stopping Ruxolitinib

Anemia appears to be the leading cause of ruxolitinib discontinuations



Kuykendall AT, et al., *Annals of Hemotology* (2018) 97: 435-441.

JAKARTA-2: Fedratinib after ruxolitinib
Re-Analysis Using More Stringent Criteria for Ruxolitinib 'Failure'

- **Reanalysis employed a more stringent definition of RUX failure[1]**
- 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

Ongoing phase III studies of fedratinib in MF patients previously treated with RUX[2]

FREEDOM

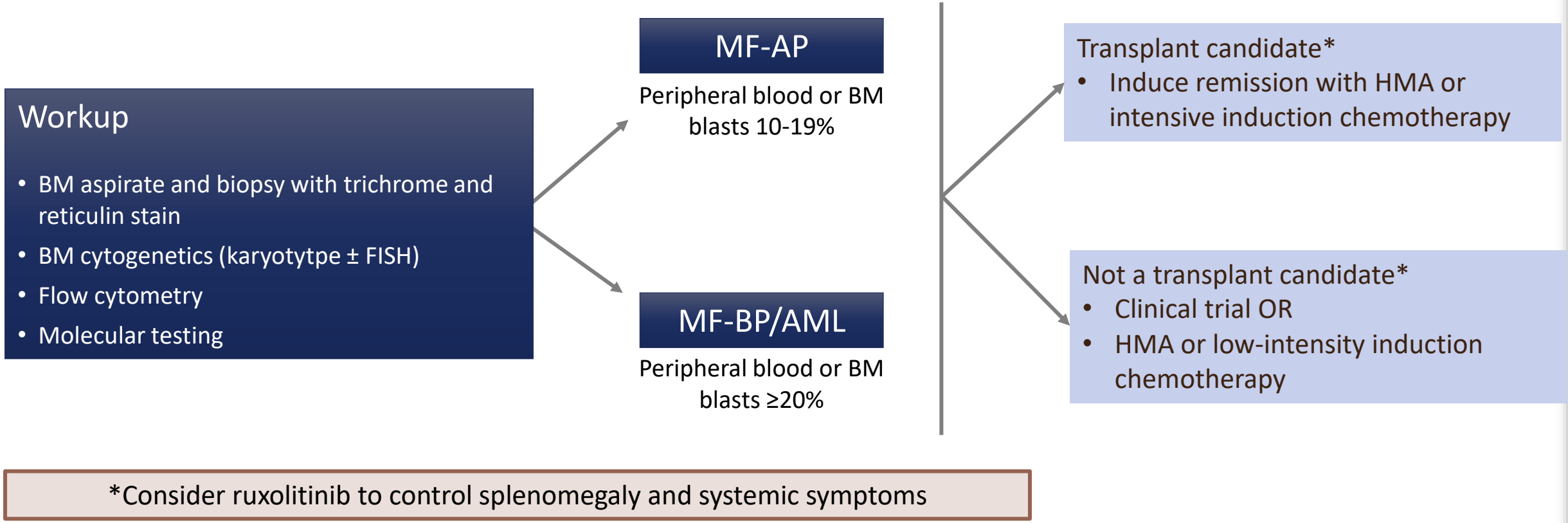
Single group assignment
(NCT03755518)

FREEDOM2

Fedratinib vs BAT
(NCT03952039)

1. Harrison CN, et al. *Am J Hematol*. 2020 Mar 4. [Epub ahead of print]; 2. clinicaltrials.gov. Accessed Mar 23, 2020.

NCCN Guideline for Treatment of MF-AP or MF-BP/AML



*Consider ruxolitinib to control splenomegaly and systemic symptoms

MF-AP: myelofibrosis in accelerated phase; MF-BP/AML – myelofibrosis in blast phase or transformation to AML; HMA – hypomethylating agents (azacitidine and decitabine)

Thank You

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