Current Treatment Strategies of Myeloproliferative Neoplasms

Rami Komrokji, MD

Senior Member & Professor of Oncologic Sciences

Section Head – Leukemia & MDS

Vice Chair - Malignant Hematology Department

H Lee Moffitt Cancer Center & Research Institute

Tampa, Florida

COI disclosure

- Speaker Bureau: Celgene/BMS, JAZZ, AbbVie, Agios.
- Honoraria/consultancy: Celgene/BMS, JAZZ, AbbVie, Agios, Acceleron, Geron.

2016 WHO classification of chronic myeloid neoplasms

1	2	3	4	5	6
Myeloproliferative neoplasms	Mastocytosis	Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1*, or with *PCM1-JAK2*	Myelodysplastic/ myeloproliferative neoplasms (MDS/MPNs)	Myelodysplastic syndromes (MDS)	Myeloid neoplasms with germ line predisposition

- Chronic myelogenous leukemia (CML), *BCR-ABL1*-positive
- Chronic neutrophilic leukemia
- Primary myelofibrosis (PMF)
  - Prefibrotic/early stage
  - Overt fibrotic stage
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified
- MPN, unclassifiable

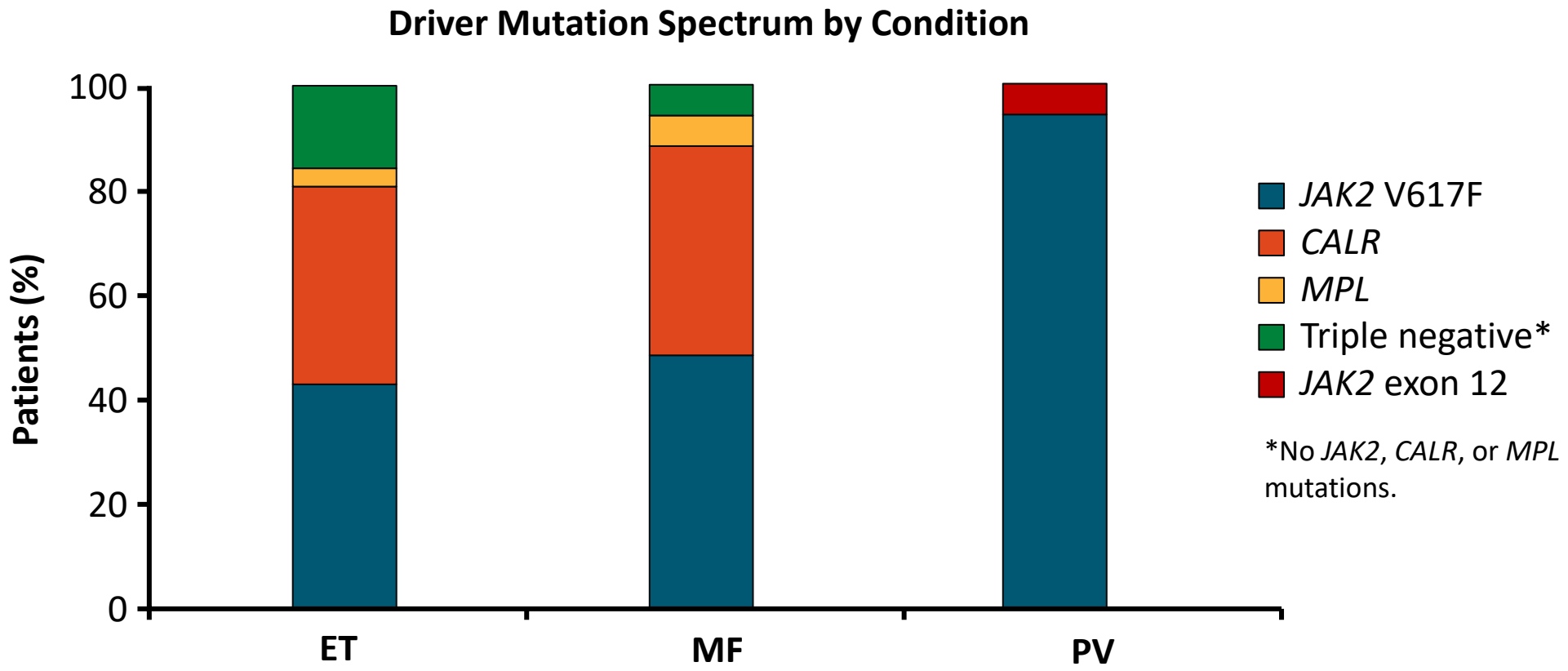
The most common *BCR-ABL1*-negative MPNs: PMF, PV and ET

Arber et al. Blood 2016;127:2391–405

Tefferi et al. Am J Hematol 2017;92:95–108

WHO, World Health Organization

Phenotype Driver Mutations Activating the JAK-STAT Pathway in MPNs



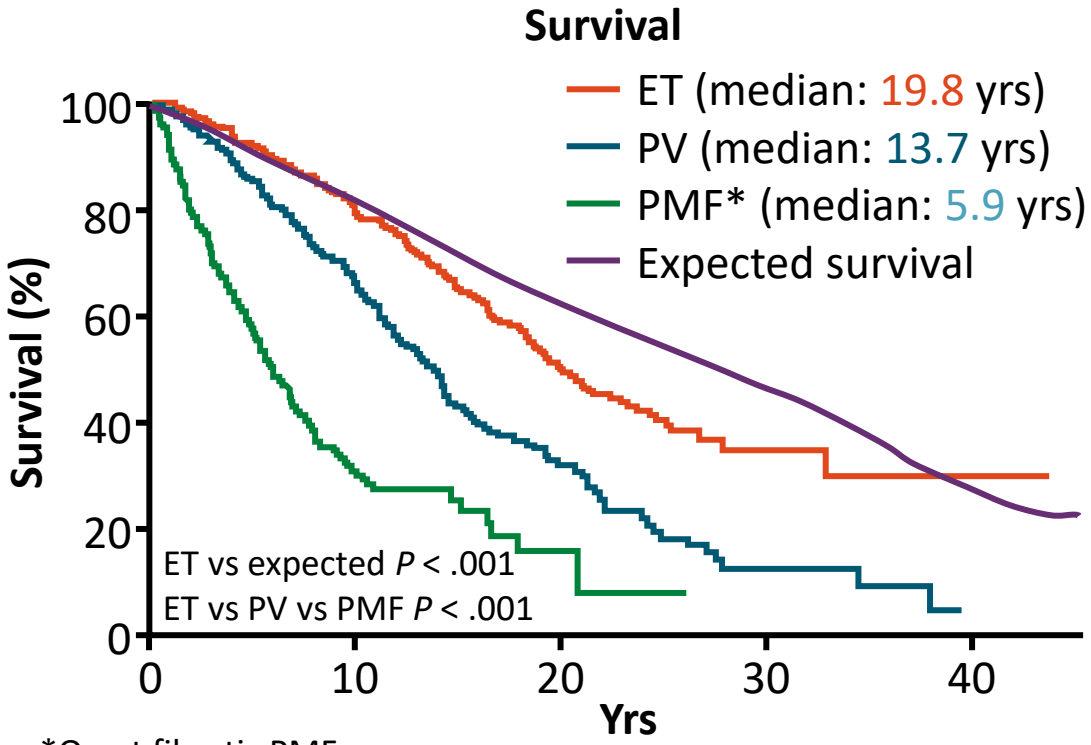
- A very small percentage of PV patients may have *LNK* or *CALR* driver mutations
- Nondriver mutations mostly frequently occurring in MPNs: *TET2, ASXL1, DNMT3A*

Grinfeld. Haematologica. 2017;102:7.

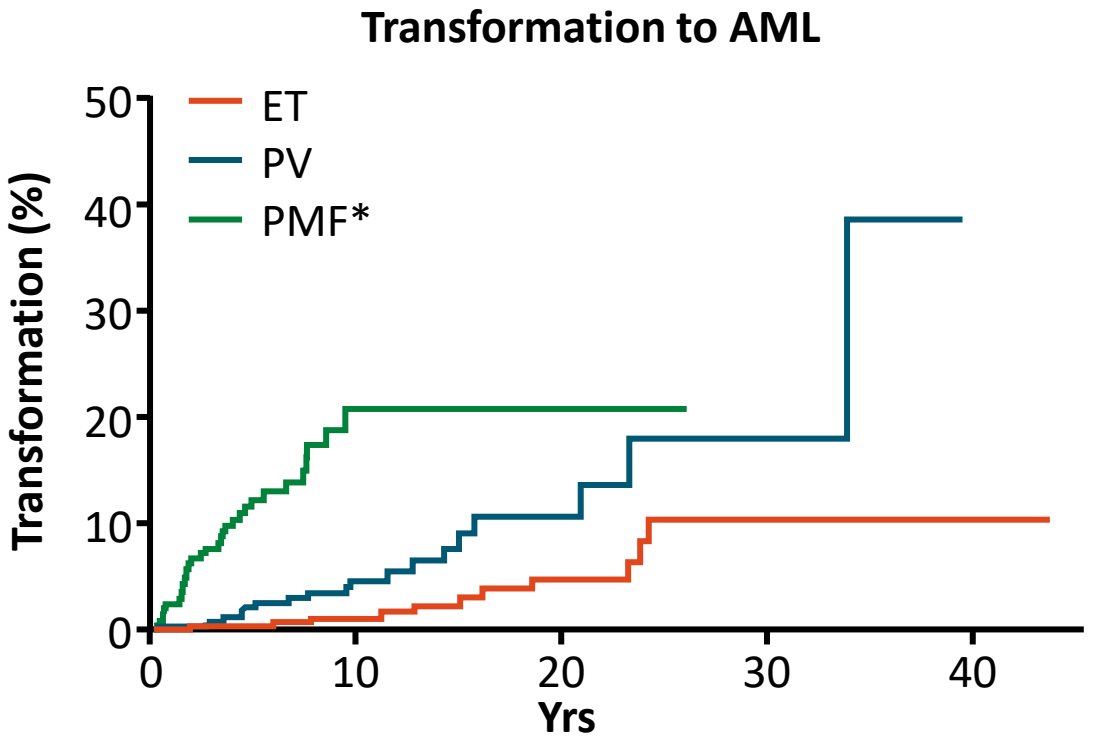
ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

Survival and Disease Progression With PV, MF, and ET

- Although similarities exist in the molecular signature and presentation of PV, MF, and ET, important to distinguish among these conditions as prognosis and management can differ
- Assessment of survival and progression in patients with PV, MF, or ET at Mayo Clinic (N = 826)



*Overt fibrotic PMF.



Tefferi. Blood. 2014;124:2507.

AML, acute myeloid leukemia; ET, essential thrombocythemia; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera.

Contemporary Management of Myelofibrosis

WHO Diagnostic Criteria: MF

Primary MF Diagnosis	
Requirement for diagnosis	
▪ All 3 major criteria AND ≥ 1 minor criteria	
Major criteria	
1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1 (prefibrotic PMF)** or **with reticulin and/or collagen fibrosis grade 2/3 (overt fibrotic PMF)**	
2. *JAK2*, *CALR*, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF	
3. Not meeting WHO criteria for other myeloid malignancies	
Minor criteria	
1. Anemia not attributed to a comorbid condition	3. Palpable splenomegaly
2. Leukocytosis ≥ 11 x 10^9/L	4. LDH increased above ULN
	5. **Leukoerythroblastosis (overt fibrotic PMF)**

*eg, *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*.

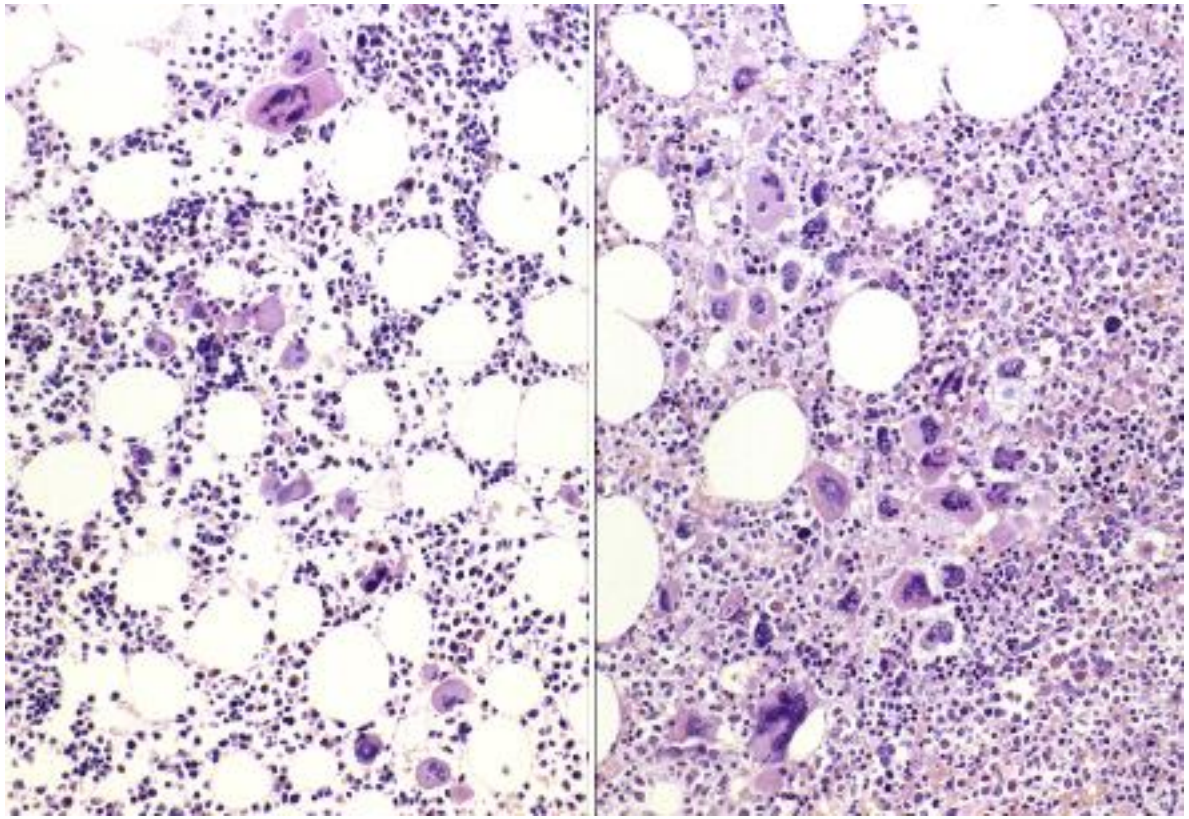
Arber. Blood. 2016;127:2391.

LDH, lactate dehydrogenase; MF, myelofibrosis; PMF, primary myelofibrosis; ULN, upper limit of normal; WHO, World Health Organization.

Essential thrombocytosis versus pre-fibrotic PMF

MF at 15 y: 9.3%
AML at 15 y: 2.1%
15-y survival: 80%

Large, mature MK's with hyperlobation



MF at 15 y: 16.9%
AML at 15 y: 11.8%
15-y survival: 59%

Atypical MK proliferation, ↑cellularity (granulocytic proliferation)

Michiels, Jan Jacques et al. *Maedica* vol. 11,1 (2016): 5-25.

Clinicohematologic-Based Prognostic Models of MF

Comparison of IPSS, DIPSS, and DIPSS-Plus[1]

Parameter	IPSS	DIPSS	DIPSS-Plus
Age > 65 yrs	Yes (1 point)	Yes (1 point)	Yes*
Hb < 10 g/dL	Yes (1 point)	Yes (2 points)	Yes*
WBC > 25 x 10^9/L	Yes (1 point)	Yes (1 point)	Yes*
PB blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes*
Constitutional symptoms	Yes (1 point)	Yes (1 point)	Yes*
Unfavorable karyotype	NA	NA	Yes (1 point)
RBC transfusion dependence	NA	NA	Yes (1 point)
Platelets < 100 x 10^9/L	NA	NA	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

Survival by Risk Group and Prognostic Model

Risk Group ▪ Points	Median OS, Yrs		
	IPSS[2]	DIPSS[3]	DIPSS-Plus[4]
Low ▪ 0	11.3	NR	15.0
Intermediate 1 ▪ IPSS/DIPSS-Plus: 1 ▪ DIPSS: 1-2	7.9	14.2	6.6
Intermediate 2 ▪ IPSS: 2 ▪ DIPSS: 3-4 ▪ DIPSS-Plus: 2-3	4.0	4.0	2.9
High ▪ IPSS: ≥ 3 ▪ DIPSS: ≥ 5 ▪ DIPSS-Plus: ≥ 4	2.3	1.5	1.3

DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; IPSS, International Prognostic Scoring System; MF, myelofibrosis; NA, not applicable; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell.

*0-3 points for each based on DIPSS risk categories; features not individually weighted.

1. Bose. Cancer. 2016;122:681. 2. Cervantes. Blood. 2009;113:2895. 3. Passamonti. Blood. 2010;115:1703. 4. Gangat. JCO. 2011;29:392.

Prognostic Impact of Driver and High Molecular Risk Nondriver Mutations in Primary MF

- Analysis of association between **driver mutations** and survival in patients with primary MF (N = 617)[1]

Driver Mutation	Patients, %	Median OS, Yrs
CALR mutated	22.7	17.7
JAK2 mutated	64.7	9.2
MPL mutated	4.0	9.1
Triple negative	8.6	3.2

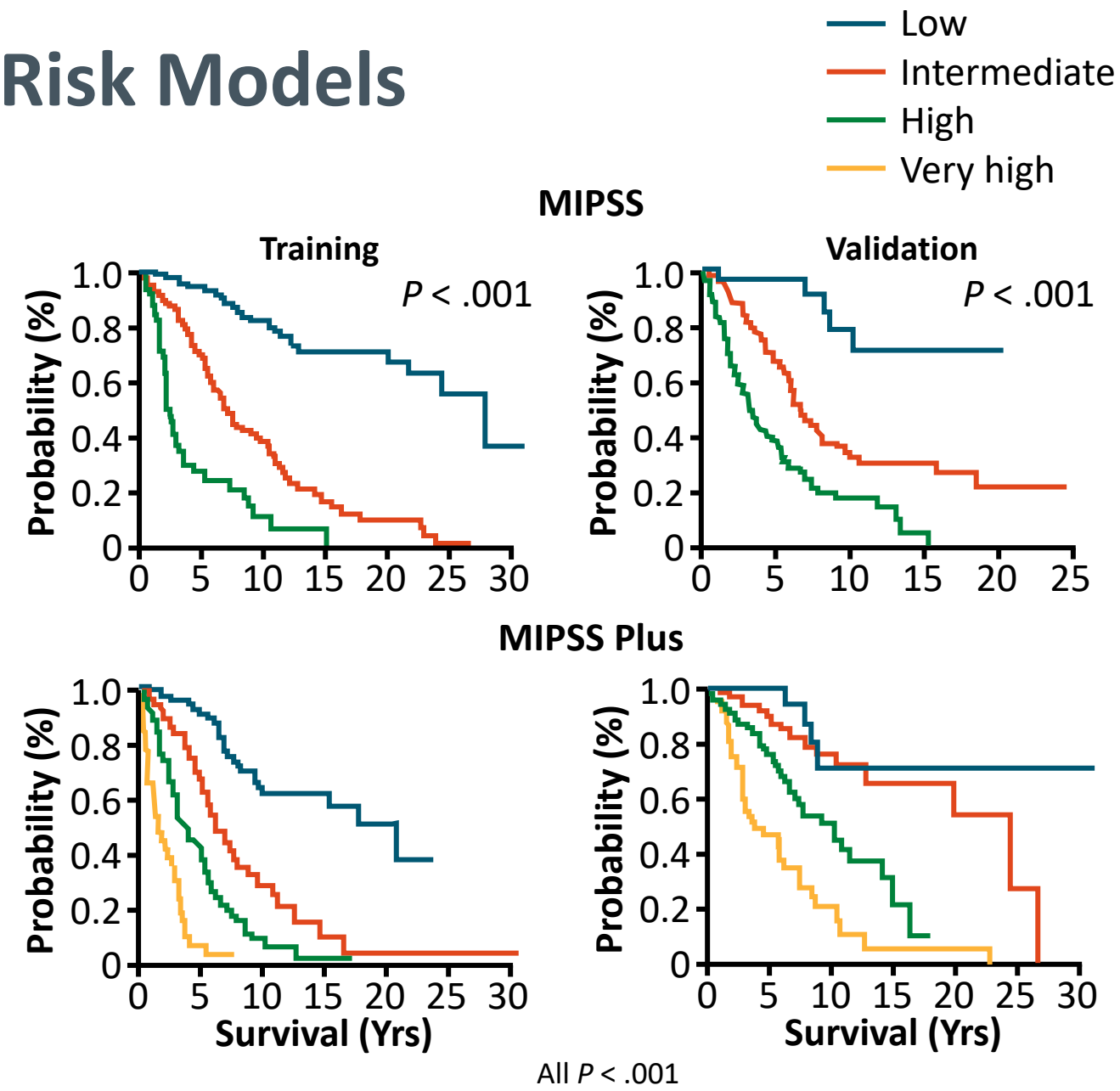
- Analysis of association between set of **nondriver mutations** (*IDH, EZH2, ASXL1, SRSF2*) and survival in patients with primary MF (N = 797)[2]
  - Presence of mutations predicted decreased survival; ≥ 2 mutations predicted worst survival

1. Rumi. Blood. 2014;124:1062. 2. Guglielmelli. Leukemia. 2014;28:1804.

MIPSS70/MIPSS70-Plus Risk Models

Variables	Rank
Hb < 100 g/L	1
WBC > 25 x 10^9/L	2
Platelets < 100 x 10^9/L	2
PB blasts ≥ 2%	1
Constitutional symptoms	1
Grade ≥ 2 BM fibrosis	1
Absence *CALR* type 1	1
HMR category*	1
≥ 2 HMR mutations	2

*HMR category, any mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*.

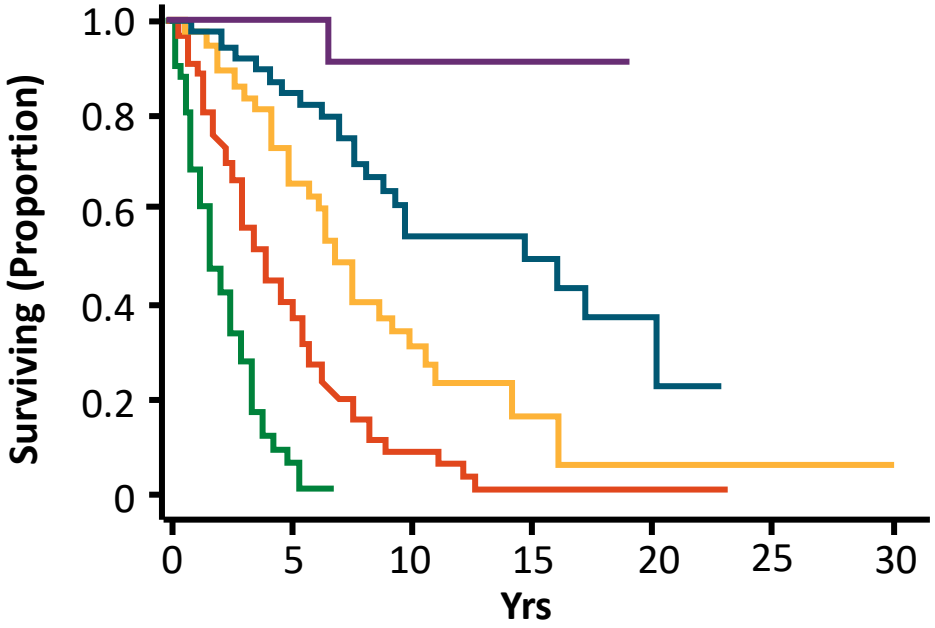


Guglielmelli. JCO. 2018;36:310. http://www.mipss70score.it/index.html.

MIPSS70-Plus v2.0 Risk Model

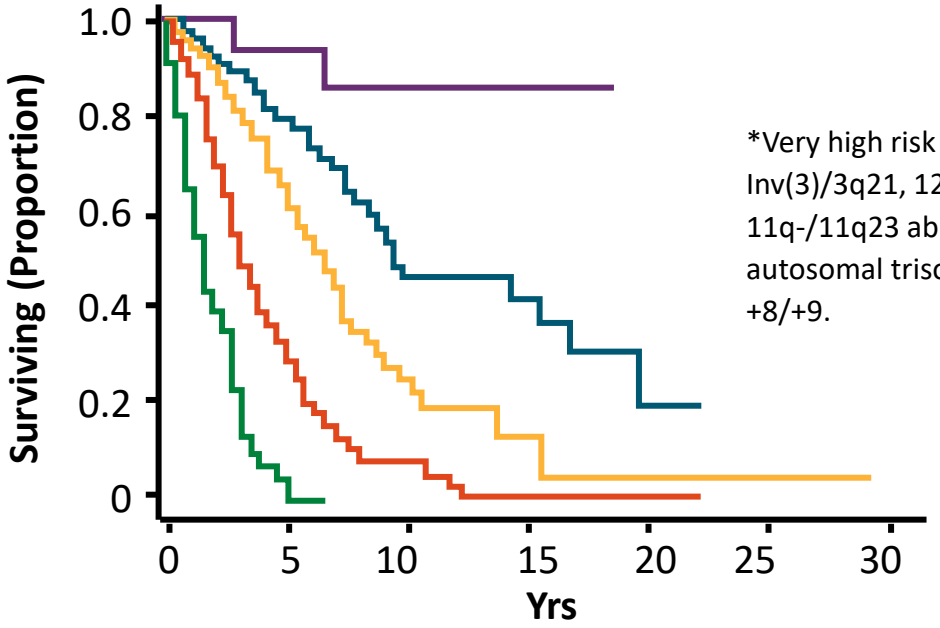
- Also incorporates very high–risk karyotype,* U2AF1 Q157 mutation status, sex- and severity-adjusted Hb thresholds (vs MIPSS70-Plus) and defines 5 prognostic categories, from very low to very high risk

Patients Aged ≤ 70 Yrs (n = 311)



- Very high risk; n = 44; median 1.8 yrs; 10-yr survival < 5%
- High risk; n = 124; median 4.1 yrs; 10-yr survival 13%
- Intermediate risk; n = 64; median 7.7 yrs; 10-yr survival 37%
- Low risk; n = 61; median 16.4 yrs; 10-yr survival 56%
- Very low risk; n = 18; median not reached; 10-yr survival 92%

Patients of All Age Groups (n = 406)



- Very high risk; n = 69; median 1.8 yrs; 10-yr survival < 3%
- High risk; n = 172; median 3.5 yrs; 10-yr survival 10%
- Intermediate risk; n = 76; median 7 yrs; 10-yr survival 30%
- Low risk; n = 70; median 10.3 yrs; 10-yr survival 50%
- Very low risk; n = 19; median not reached; 10-yr survival 86%

*Very high risk karyotype: -7, i(17q), Inv(3)/3q21, 12p-/12p11.2, 11q-/11q23 abnormalities; other autosomal trisomies not including +8/+9.

Tefferi. JCO. 2018;17:1769.

MF Treatment: Based on Risk and MF-Related Symptoms/Signs

Low Risk	Minimally symptomatic → observation or IFN Many symptoms → consider JAK inhibitor
Intermediate-1 Risk	→ Ruxolitinib or anemia treatment and/or allogeneic HSCT
Intermediate-2 Risk	→ Allogeneic HSCT or JAK inhibitor and/or anemia treatment
High Risk	→ Allogeneic HSCT or JAK inhibitor and/or anemia treatment

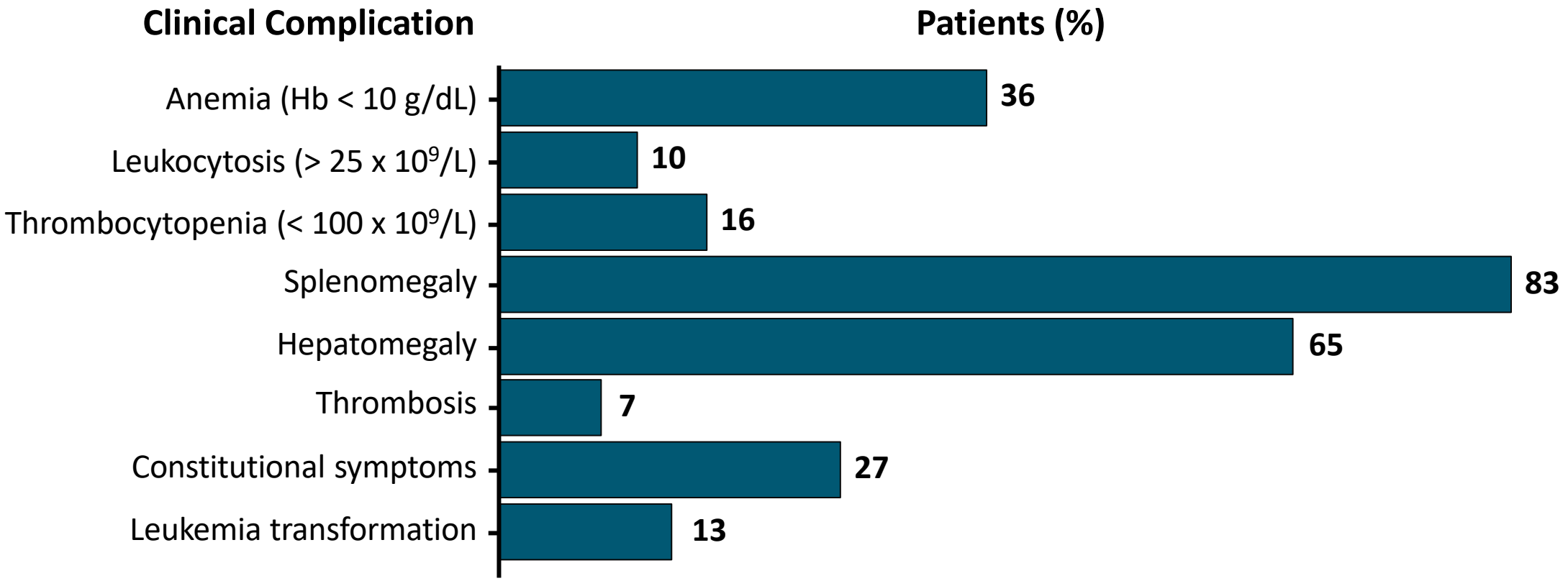
Mesa. Leuk Lymphoma. 2013;54:242. Geyer. Hematology Am Soc Hematol Educ Program. 2014;2014:277.

Allogeneic HSCT for Patients With MF

- **Who**: consider HSCT in **younger patients whose survival is expected to be < 5 yrs** (int-2–risk/high-risk patients < 70 yrs of age but also int-1–risk patients < 65 yrs of age with refractory, transfusion-dependent anemia, circulating blasts >2%, adverse cytogenetics (as defined in the DIPSS+), triple negativity or *ASXL1* mutation[1]
- **But**: **very few MF patients undergo HSCT**
  - Traditionally **limited to younger patients** < 60 yrs of age and those with HLA-identical sibling match (although now possible up to 75 yrs of age)
  - **High transplant-related mortality and morbidity** associated with transplantation due to acute and chronic GvHD[1]
    - 1-yr NRM rate: 12% (completely matched donors) to 38% (mismatched)
    - 5-yr survival rate: 56% (matched sibling donors) to 34% (partially matched/ mismatched)

1. Kröger. Leukemia. 2015;29:2126.

Main Clinical Complications in MF



- Common symptoms derived from complications: bone pain, pruritus (myeloproliferation), night sweats, weight loss, fever (constitutional), early satiety, abdominal discomfort (splenomegaly), fatigue, insomnia

Passamonti. Blood. 2010;115:1703. Barbui. Blood. 2010;115:778. Passamonti. Blood. 2010;116:2857. Scherber. Blood. 2011;118:401.

Needs-Oriented Therapy for MF

Clinical Issue	Treatments	
Anemia	▪ ESAs ▪ Corticosteroids ▪ Danazol	▪ Thalidomide, lenalidomide (IMiDs)
Symptomatic splenomegaly	▪ **Ruxolitinib, fedratinib** ▪ Hydroxyurea	▪ Cladribine, IMiDs ▪ Splenectomy
Constitutional symptoms/QoL	▪ **Ruxolitinib, fedratinib** ▪ Corticosteroids	
Extramedullary hematopoiesis	▪ Radiation therapy	
Hyperproliferative (early) disease	▪ Interferon	
Risk of thrombosis	▪ Low-dose aspirin	
Accelerated/blastic phase	▪ Hypomethylating agents	
Improved survival	▪ Allogeneic HSCT ▪ **Ruxolitinib**	

ESA, erythropoiesis-stimulating agent; HSCT, hematopoietic stem cell transplantation; IMiD, immunomodulatory drug; MF, myelofibrosis; QoL, quality of life.

COMFORT-I and -II: Ruxolitinib for Patients With Intermediate-2–Risk/High-Risk MF

- Randomized phase III studies in which patients with intermediate 2–risk/high-risk MF were treated with **ruxolitinib** (15 or 20 mg BID) vs **placebo** (COMFORT-I, N = 309) or **best available therapy** (COMFORT-II, N = 149)

Outcome	COMFORT-I, Wk 24[1]		*P* Value	COMFORT-II, Wk 48[2]		*P* Value
	Ruxolitinib (n = 155)	Placebo (n = 154)		Ruxolitinib (n = 144)	BAT (n = 73)	
Spleen volume reduction ≥ 35%,* %	41.9	0.7	< .001	28	0	< .001
≥ 50% reduction in MF-SAF TSS, %	45.9	5.3	< .001	NR	NR	NR
D/c for AEs	11.0	10.6	NR	8	5	NR

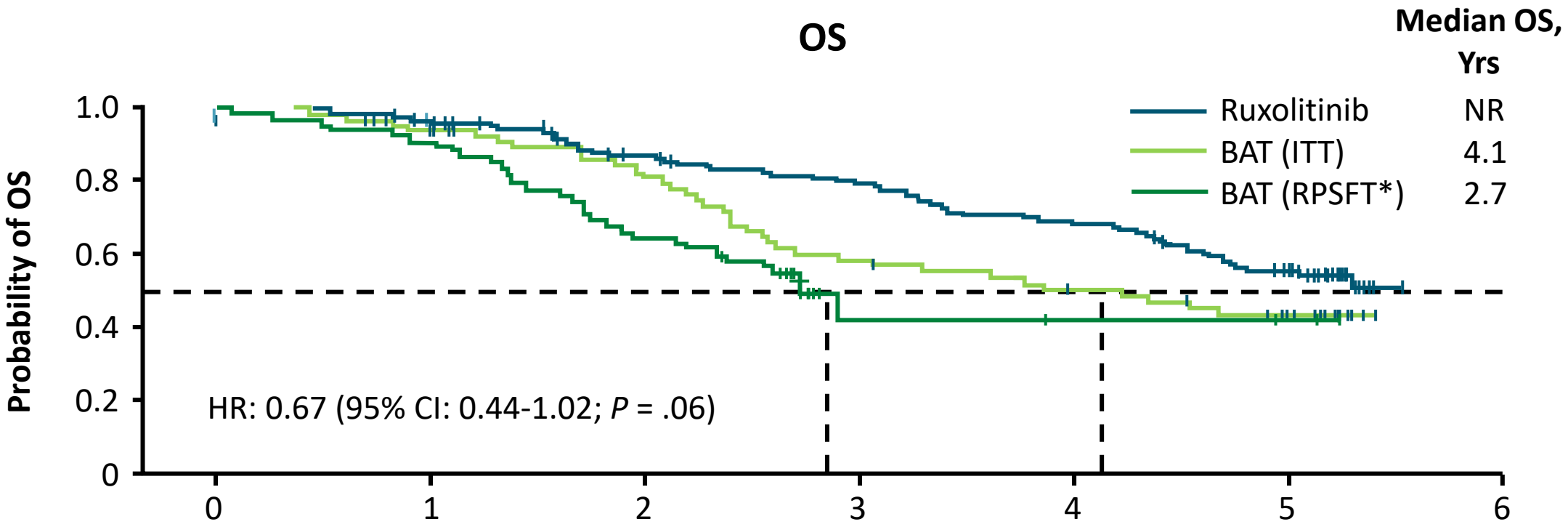
*Primary endpoint. †n = 151.

- Grade 3/4 anemia/thrombocytopenia/neutropenia in COMFORT-I, %: **ruxolitinib**, 45/13/7; **placebo** 19/1/2†

AE, adverse event; BAT, best available therapy; D/c, discontinued; MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; NR, not reported.

1. Verstovsek. NEJM. 2012;366:799. 2. Harrison. NEJM. 2012;366:787.

COMFORT-II: 5-Yr Overall Survival With Ruxolitinib vs BAT



*RPSFT modeling estimates treatment effect corrected for crossover.

- Median follow-up: 4.3 yrs; majority crossed over from BAT to ruxolitinib

BAT, best available therapy; ITT, intention-to-treat; NR, not reached; RPSFT, rank-preserving structural failure time.

Harrison. Leukemia. 2016;30:1701.

Ruxolitinib in IPSS-1 Patients: Higher Response Rate and Lower Toxicities

Rate, %	Category	Spleen Response at Wk 24	Grade 3/4 Anemia	Grade 3/4 Thrombocytopenia	Discontinuations
COMFORT-I[1] (n = 155)	Int-2–risk and high-risk patients	41.9	45.2	12.9	21.0[6]
COMFORT-II[2] (n = 146)	Int-2–risk and high-risk patients	32.0	42.0	8.0	38.0
JUMP INTM-1[3] (n = 163)	Int-1–risk patients	63.8	24.5	11.0	19.6
ROBUST[4] (n = 14)	Int-1–risk patients	57.1	NA	NA	NA
Italian study[5] (n = 70)	Int-1–risk patients	54.7	21.7*	2.9*	17.1

*Grade 3 only.

1. Verstovsek. NEJM. 2012;366:799. 2. Harrison. NEJM. 2012;366:787. 3. Al-Ali. Haematologica. 2016;101:1065.
4. Mead. Br J Haematol. 2015;170:29. 5. Palandri. Hematol Oncol. 2018;36:285. 6. Verstovsek. Haematologica. 2015;100:479.

Tips for Using Ruxolitinib to Treat Patients With MF

- Effective regardless of patient's mutational profile (not specific for *JAK2* V617F mutation)
- **Starting dose selected based on platelet count**; anemia is **NOT** contraindication for use, can consider 10 mg BID x 12 weeks before escalating in anemic patients
- Development of anemia **DOES NOT** affect benefits of ruxolitinib
- Avoid abrupt interruption of ruxolitinib in patients responding well to therapy
  - Decision to stop ruxolitinib will depend on benefit and presence/absence of toxicity

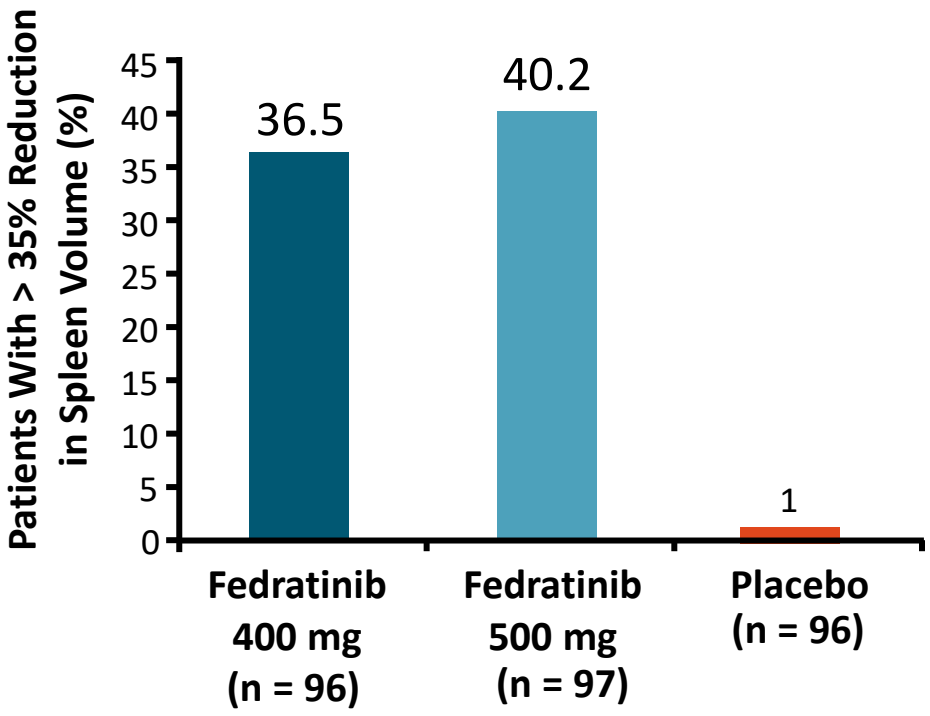
Ruxolitinib Dosing Recommendations	
Starting dose	***Determined by platelet count:*** ▪ > 200 x 10^9/L: 20 mg BID PO ▪ 100 to 200 x 10^9/L: 15 mg BID PO ▪ 50 to < 100 x 10^9/L: 5 mg BID PO
Monitoring	Monitor CBC every 2-4 wks until doses stabilized, then as clinically indicated
Dose adjustment	Modify or interrupt dosing for thrombocytopenia

- Dose should be modified to the maximum tolerated when response not adequate, and treatment should be continued for ≥ 6 mos
- NHL risk appears unsubstantiated

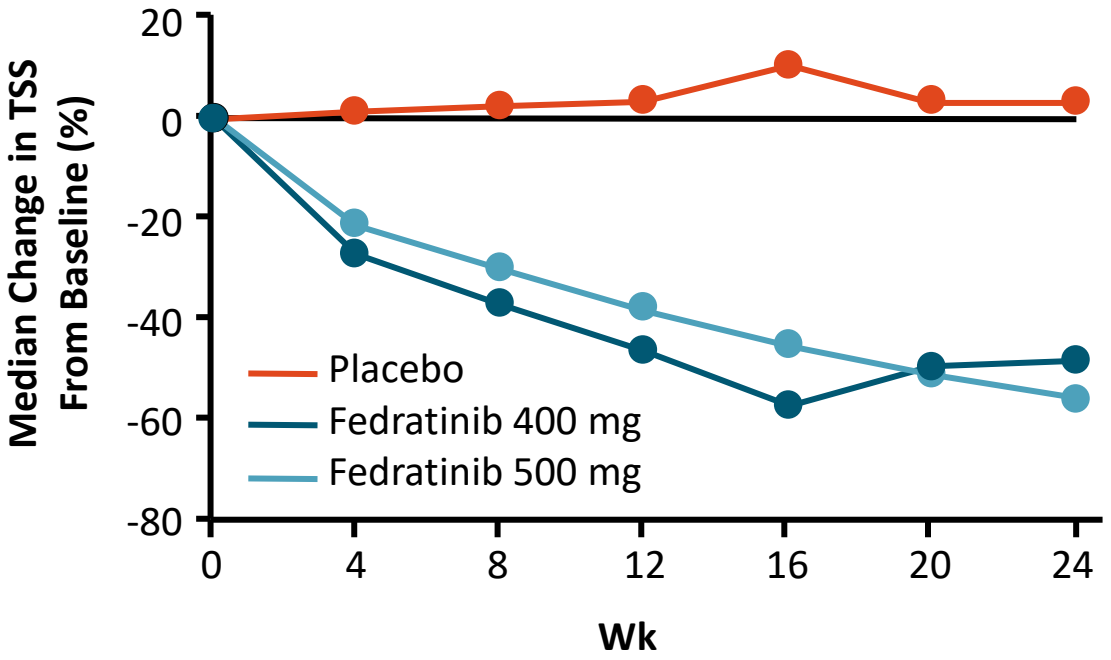
Mesa. Int J Hematol. 2016;104:420. Ruxolitinib PI. Porpaczy. Blood. 2018;132:694. Pemmaraju. Blood. 2019;133:2348. Cervantes. EHA 2019. Abstr PS1465..

JAKARTA: Efficacy

Spleen Response (Primary Endpoint)



Change in Total Symptom Score



Pardanani. JAMA Oncol. 2015;1:643.

JAKARTA: Hematologic and Nonhematologic Events

Adverse Events, n (%)	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
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
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. JAMA Oncol. 2015;1:643.

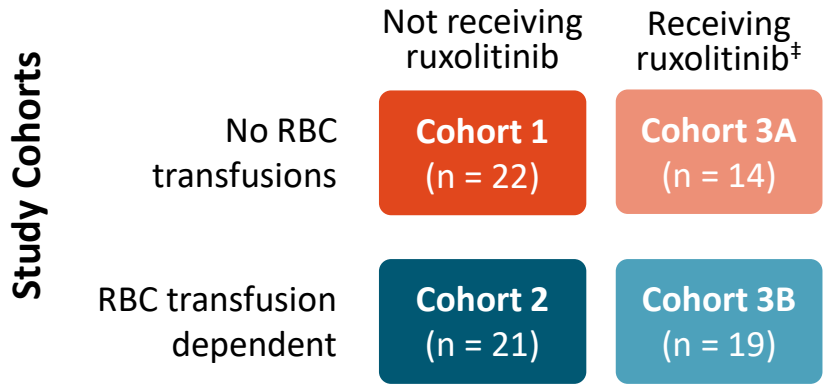
Fedratinib Indication in MF

- Approved by FDA in August 2019 for treatment of adults with intermediate-2–risk or high-risk primary or secondary MF
- Recommended dose 400 mg daily in patients with platelets ≥ 50 x 10^9/L
  - Reduce dose to 200 mg daily in patients receiving strong CYP3A inhibitors or if severe renal impairment
- Black box warning: Wernicke's encephalopathy (ataxia, AMS, ophalmoplegia) occurred in 8/608 (1.3%) patients receiving fedratinib in trials
  - Measure and replace thiamine levels prior to treatment initiation
  - Do not start fedratinib in patients with thiamine deficiency

Fedratinib Package Insert infromation.

Luspatercept for Treating Anemia in MF

- Open-label, nonrandomized, multicohort phase II trial of **luspatercept** 1 mg/kg every 21 days for patients with primary or post-ET/ post-PV MF and anemia (planned N = 100)



Parameter	RBC Transfusion Dependent	
	No RUX (Cohort 2; n = 21)	RUX (Cohort 3b; n = 19)
RBC transfusion-free ≥ 12 consecutive wks, n (%)*	2 (10)	6 (32)
▪ Median duration of response, wks (range)	32 (16-49)	39 (12-77)
≥ 50% reduction in RBC transfusion burden from BL, n (%)	8 (38)	10 (53)

Hb Increase ≥ 1.5 g/dL From BL for ≥ 12 Consecutive Wks†	No RBC Transfusions	
	No RUX (Cohort 1; n = 22)	RUX (Cohort 3a; n = 14)
Hb increase ≥ 1.5 g/dL at every assessment, n (%)	3 (14)	3 (21)
Mean Hb increase ≥ 1.5 g/dL, n (%)	4 (18)	9 (64)

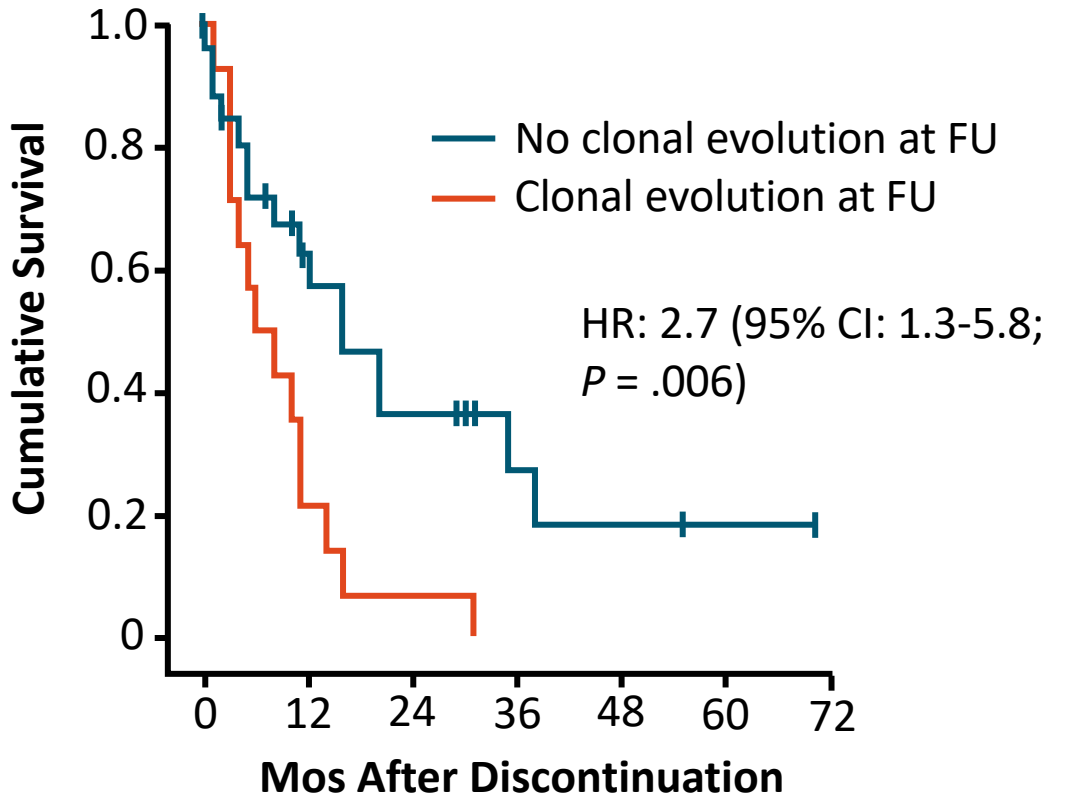
*Primary endpoint, cohorts 2, 3b. †Primary endpoint, cohorts 1, 3a. ‡Stable dose for ≥ 16 wks at enrollment

Gerds. ASH 2019. Abstr 557.

ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; MDS, myelodysplastic syndromes; MF, myelofibrosis; PS, performance status; RBC, red blood cell.

Outcomes After Ruxolitinib Discontinuation

- Retrospective analysis of clonal evolution and outcomes after ruxolitinib discontinuation in an open-label phase I/II study (N = 56)



- Median OS: 14 mos
- Survival improved if baseline platelets ≥ 260 vs < 260 × 10^9/L (HR: 2.7; *P* = .006)
- Survival improved if follow-up platelets ≥ 100 vs < 100 × 10^9/L (HR: 4.1; *P* = .001)
- 35% of patients acquired a new mutation while on ruxolitinib, most commonly *ASXL1*

FU, follow-up., OS overall survival, HR hazard ratio

Newberry. Blood. 2017;130:1125.

JAKARTA-II Reanalysis: Fedratinib for Patients With MF Previously Treated With Ruxolitinib

- Aim: confirm efficacy of **fedratinib** in ITT analysis in all enrolled patients, and in subgroups defined using **rigorous definitions of prior ruxolitinib response**

Criteria for Ruxolitinib Failure			
ITT Population		**Ruxolitinib Failure Cohort**	
Resistant	RUX ≥ 14 days with no response or stable disease, disease progression, or loss of response per investigator	Relapsed	RUX ≥ 3 mos with regrowth (defined as < 10% SVR or < 30% decrease in spleen size from BL following an initial response)
		Refractory	RUX ≥ 3 mos with < 10% SVR or < 30% decrease in spleen size from BL
Intolerant	RUX ≥ 14 days before d/c tx due to unacceptable toxicity	Intolerant	RUX ≥ 28 days complicated by development of RBC transfusion requirement (≥ 2 units/mos for 2 mos); or grade ≥ 3 thrombocytopenia, anemia, hematoma/hemorrhage while on RUX

- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%); median prior RUX duration in RUX failure cohort, 11.5 mos (range: 1.0-62.4)
- In RUX failure cohort: median number of FEDR cycles, 7; **spleen volume RR 30%** (95% CI: 21-42); median spleen response duration, NE (95% CI 7.2-NE); **symptom RR 27%** (95% CI: 17-39)

Harrison. ASCO 2019. Abstr 7057.

Momelotinib for Patients With MF

- **Momelotinib:** JAK1/2 inhibitor with potential to improve anemia, possibly via suppression of hepcidin[1]

Key Trial	Type	Key Findings
SIMPLIFY 2[2]	Phase III RCT in MF previously treated with ruxolitinib (N = 156)	▪ SVR ≥ 35% at Wk 24*: **momelotinib, 7%; BAT, 6%** (*P* = .90)
SIMPLIFY 1[3]	Phase III RCT in JAKi-naive patients with MF (N = 432)	▪ SVR ≥ 35% at Wk 24*: **momelotinib, 26.5%; ruxolitinib, 29%** (noninferior)

- Ongoing double-blind, randomized **phase III MOMENTUM trial** (NCT04173494) of **momelotinib vs danazol** for **symptomatic patients with MF who have anemia** (Hb < 10 g/dL) and previous JAKi experience
  - Primary endpoint, symptom response; secondary endpoints, transfusion independence and spleen response)

BAT, best available therapy; MF, myelofibrosis; SVR, spleen volume reduction.

*Primary endpoint(s).

1. Asshoff. Blood. 2017;129:1823. 2. Harrison. Lancet Haematol. 2018;5:e73. 3. Mesa. JCO. 2017;35:3844.

Pacritinib for Patients With MF

- **Pacritinib**: selective inhibitor of JAK2, JAK2 V617F, and FLT3

Key Trial	Type	Key Findings
PERSIST-1[1]	Phase III RCT in higher-risk, JAKi-naive MF with any degree of anemia/thrombocytopenia (N = 327)	▪ SVR ≥ 35% at Wk 24*: **pacritinib, 19%; BAT (no JAK2i), 5%** (*P* = .0003)
PERSIST-2[2]	Phase III RCT in MF (prior JAKi allowed) with platelet count ≤ 100,000/µL (N = 311)	▪ SVR ≥ 35%*: **pacritinib, 18%; BAT, 3%** (incl RUX) (*P* = .001); TSS reduced ≥ 50%*: **pacritinib, 25%; BAT, 14%** (*P* = .08)
PAC203[3]	Phase II dose-finding trial in higher-risk MF with previous ruxolitinib (N = 164)	▪ **200 mg BID dose** most effective: SVR ≥ 35%, 9.3%; TSS reduced ≥ 50%, 7.4%

- Development of pacritinib put on hold by FDA in 2016 due to reports of patient deaths related to intracranial hemorrhage, cardiac failure, and cardiac arrest; **clinical hold removed in 2017**
- Ongoing randomized **phase III PACIFICA trial** of pacritinib vs physician's choice treatment for pts with limited (90 days)/no previous JAKi treatment and intermediate- or high-risk **MF and platelet count < 50,000/µL**[4]

*Primary endpoint(s).

1. Mesa. Lancet Haematol. 2017;4:e225. 2. Mascarenhas. JAMA Oncol. 2018;4:652.
3. Gerds. ASH 2019. Abstr 667. 4. Harrison. ASH 2019. Abstr 4175.

Novel agents in clinical trials for MF

	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
JAKi		Itacitinib
PI3Kδi		Parsaclisib

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

Polycythemia Vera and Essential Thrombocythemia in Focus

Evolution of WHO PV Diagnostic Criteria

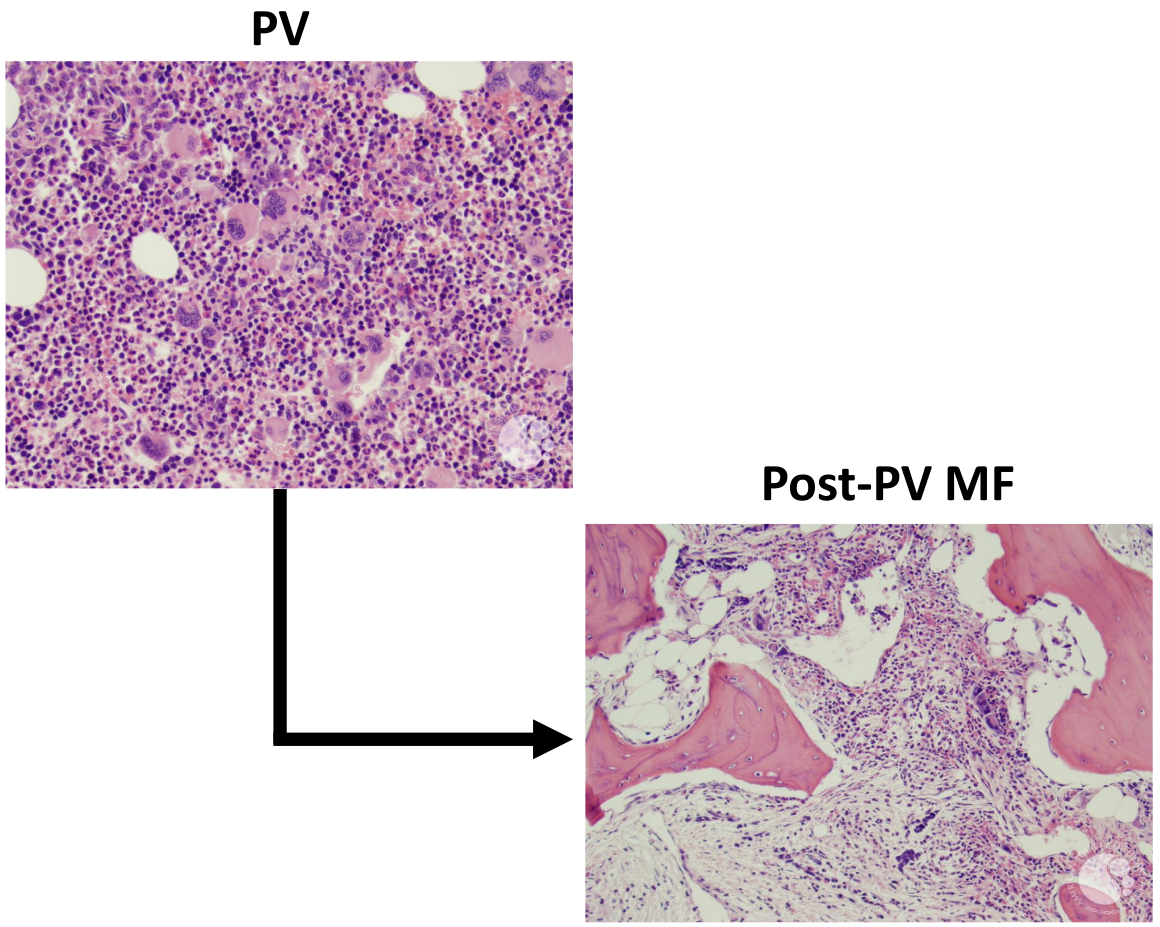
WHO 2008[1]	WHO 2016[2]
Requirement for diagnosis	
▪ 2 major and 1 minor criteria OR first major and 2 minor criteria	▪ All 3 major criteria OR first 2 major criteria and the minor criterion
Major criteria	
1. Hb > 18.5 g/dL (men); > 16.5 g/dL (women) 2. *JAK2* V617F mutation or similar (*JAK2* exon 12)	1. Hb > 16.5 g/dL or Hct > 49% (men); Hb > 16.0 g/dL or Hct > 48% (women) 2. BM biopsy showing hypercellularity, trilineage growth (panmyelosis) with erythroid, granulocytic, and pleomorphic, mature megakaryocytic proliferation 3. *JAK2* V617F or *JAK2* exon 12 mutation
Minor criteria	
1. Subnormal serum EPO level 2. BM trilineage proliferation 3. Endogenous erythroid colony growth	1. Subnormal serum EPO level

BM, bone marrow; EPO, erythropoietin; Hb, hemoglobin; Hct hematocrit; PV, polycythemia vera; WHO, World Health Organization.

1. Thiele. Curr Hematol Malig Rep. 2009;4:33. 2. Arber. Blood. 2016;127:2391.

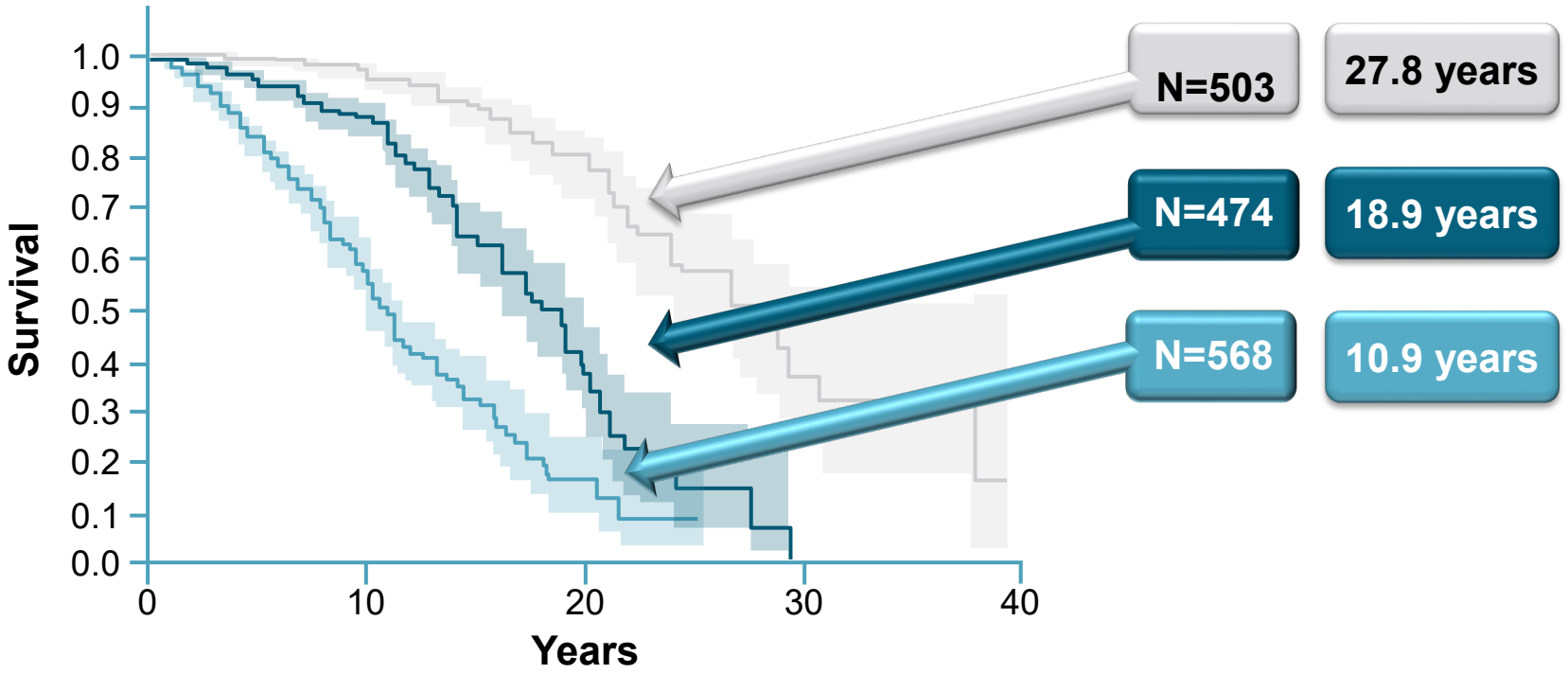
Bone Marrow Testing in PV Diagnosis

- **Bone marrow biopsy may not be required for diagnosis** if sustained Hb levels > 18.5 g/dL (men) or > 16.5 g/dL (women) where *JAK2* mutated and EPO suppressed[1]
- **Biopsy may identify fibrosis at diagnosis**
  - Prevalence: 14% to 48% with grade 1 fibrosis at diagnosis; consequences include a higher rate of overt, fibrotic progression[2,3]
- **Biopsy required to diagnose post-PV MF**[4]
  - Progression prevalence: 5% to 19% at 15 yrs
  - Note that high-grade bone marrow fibrosis alone not enough to diagnose post-PV MF



1. Arber. Blood. 2016;127:2391. 2. Barbui. Blood. 2012;119:2239. 3. Barraco. Blood Cancer J. 2017;7:e538. 4. Cerquozzi. Blood Cancer J. 2015;5:e366.

Survival among 1545 patients with WHO-based PV



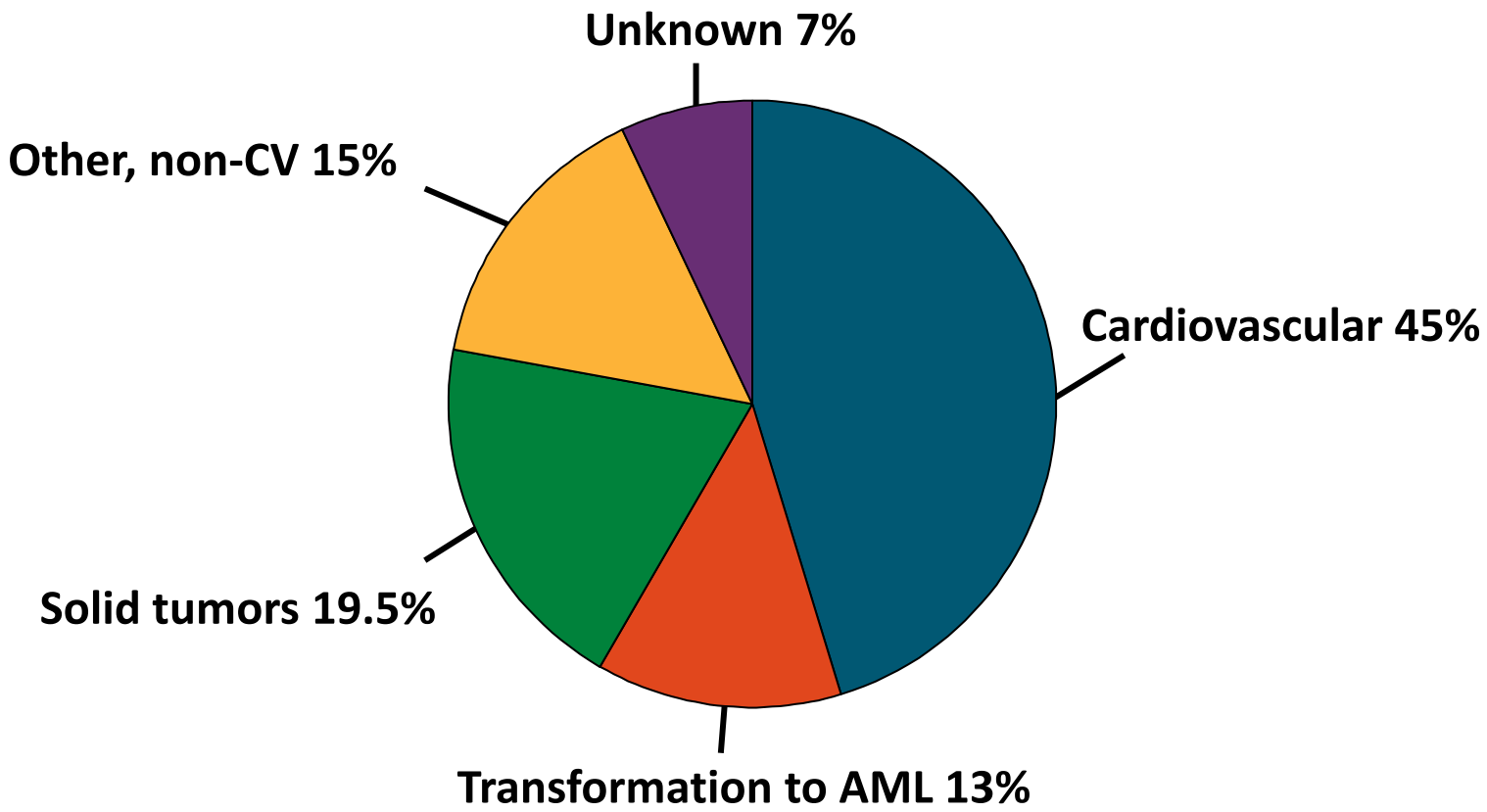
Risk factors	
Age > 67 years	5 points
Age 57-66	2 points
WBC > 15 x10^9/L	1 point
Venous thrombosis	1

Risk Categories/score	
LR	0
Int	1-2
HR	≥3

Tefferi A, et al. *Leukemia* (2013) 27, 1874-1881

Thrombosis: A Major Cause of Mortality in PV

- Data from large prospective multicenter project in PV (ECLAP trial); 164 of 1638 patients deceased at time of analysis



Marchioli. JCO. 2005;23:2224.

Thrombosis Risk–Adapted Management of ET and PV

<table>
<tr><th>Category</th><th>Characteristics</th><th colspan="2">Treatment</th></tr>
<tr><td>Low risk</td><td>Age ≤ 60 yrs AND no history of thrombosis</td><td colspan="2">▪ Therapeutic phlebotomy (goal Hct < 45%) in PV
▪ Aspirin 81 mg/day for ET/PV*
▪ Address CV modifiable risk factors for ET/PV</td></tr>
<tr><td rowspan="3">High risk</td><td rowspan="3">Age > 60 yrs OR history of thrombosis</td><td colspan="2">▪ All the above AND cytoreductive therapy</td></tr>
<tr><td colspan="2">Cytoreductive therapy</td></tr>
<tr><td>First line</td><td>Second line</td></tr>
<tr><td></td><td></td><td>▪ Hydroxyurea for ET/PV
▪ Anagrelide for ET
▪ PegIFN for ET/PV</td><td>• Ruxolitinib for PV
• PegIFN for ET/PV
• Busulfan (age > 70 yrs) for ET/PV</td></tr>
</table>

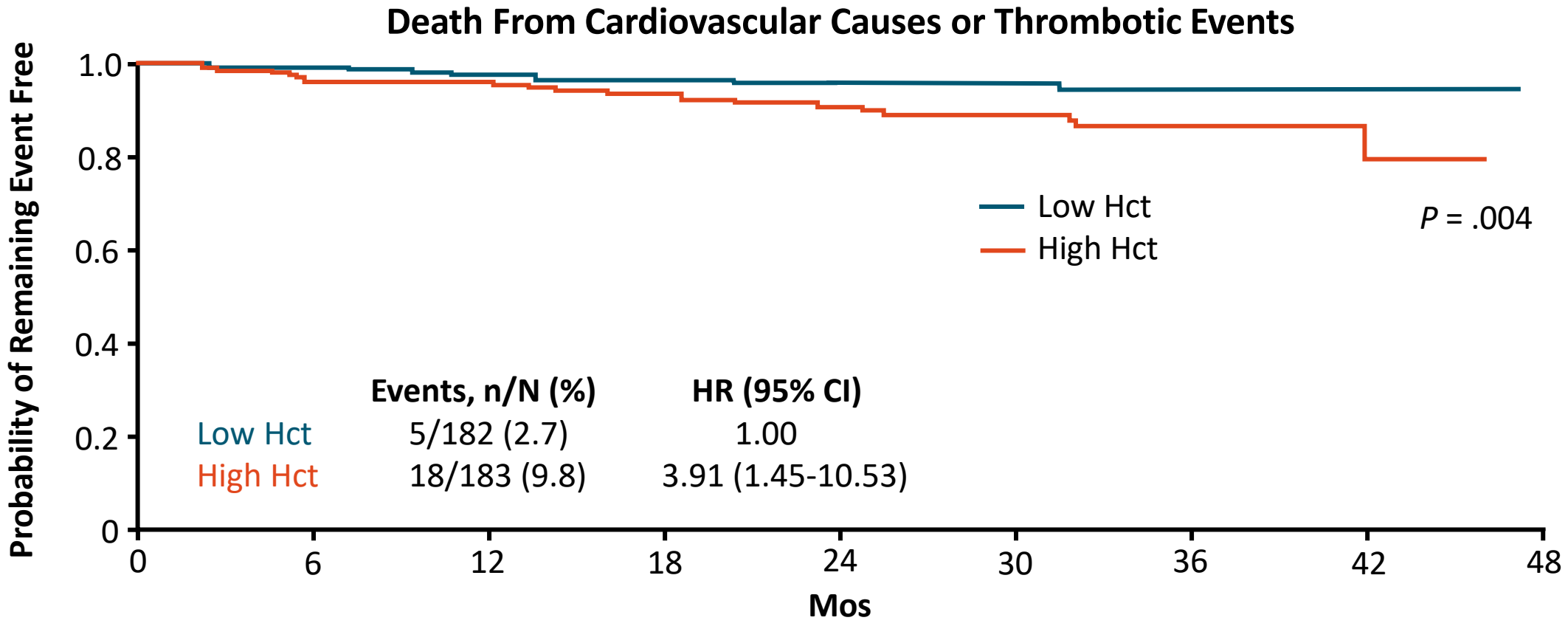
*ASA may not be needed for CALR-mutant ET patients ≤ 60 yrs AND no history of thrombosis.

CV, cardiovascular; ET, essential thrombocythemia; Hct, hematocrit; PegIFN, peginterferon; PV, polycythemia vera.

Barbui. JCO. 2011;29:761. Tefferi. Am J Hematol. 2015;90:162.

CYTO-PV: Death From CV or Thrombotic Events by Hematocrit Target

- Randomized, open-label phase III trial in which PV patients were treated to a lower (< 45%) or higher (45% to 50%) Hct target with ASA + phlebotomy ± cytoreductives (N = 365)

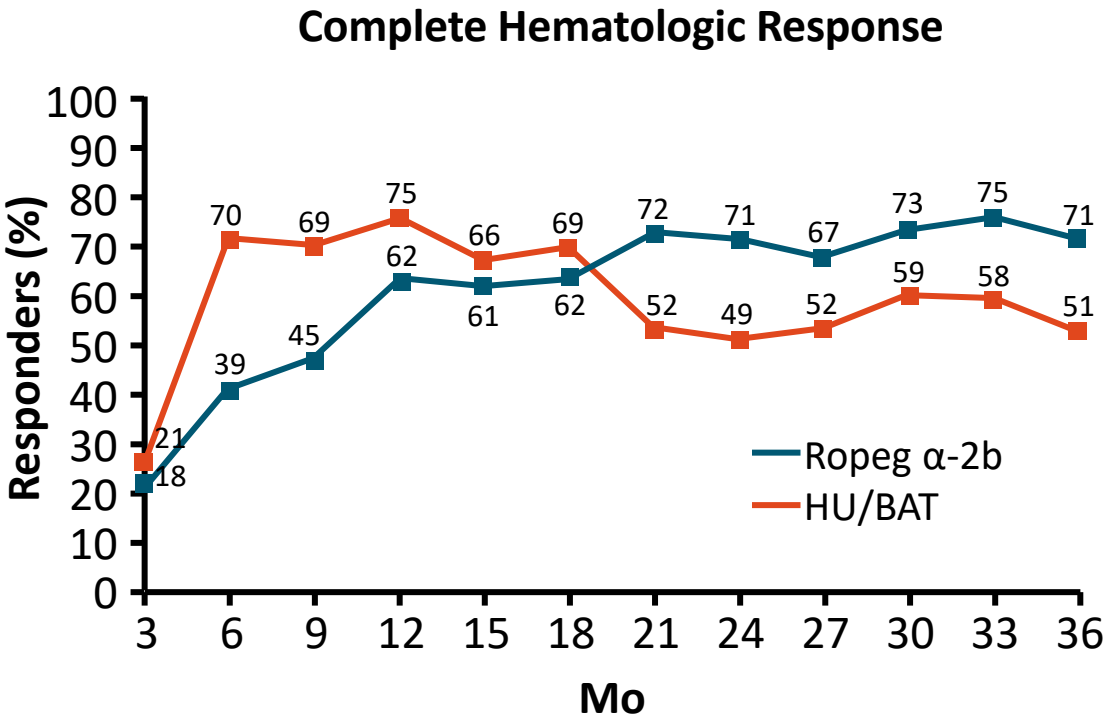


Marchioli. NEJM. 2013;368:22.

ASA, aspirin; CV, cardiovascular; Hct, hematocrit; PV, polycythemia vera.

PROUD-PV/CONTI-PV: Ropeginterferon α-2b for Patients With PV

- Randomized phase III study of **ropeginterferon α-2b** vs **HU*** for cytoreductive-naive or previously HU-treated patients† with PV (N = 254)



Study Mo	Responder, n/N (%)		*P* Value	RR (95% CI)
	Ropeg α-2b (n = 95)	HU/BAT (n = 76)		
12 (EOT in PR)	59/95 (62.1)	57/76 (75.0)	.1201	0.85 (0.70-1.04)
24	67/95 (70.5)	33/67 (49.3)	.0111	1.42 (1.08-1.87)
36	67/95 (70.5)	38/74 (51.4)	.0122	1.38 (1.07-1.79)

*After 12 mos, could switch to BAT. †Could not have HU resistance.

BAT, best available therapy; EOT, end of treatment; HU, hydroxyurea; PV, polycythemia vera; Ropeg, ropeginterferon; RR, relative risk.

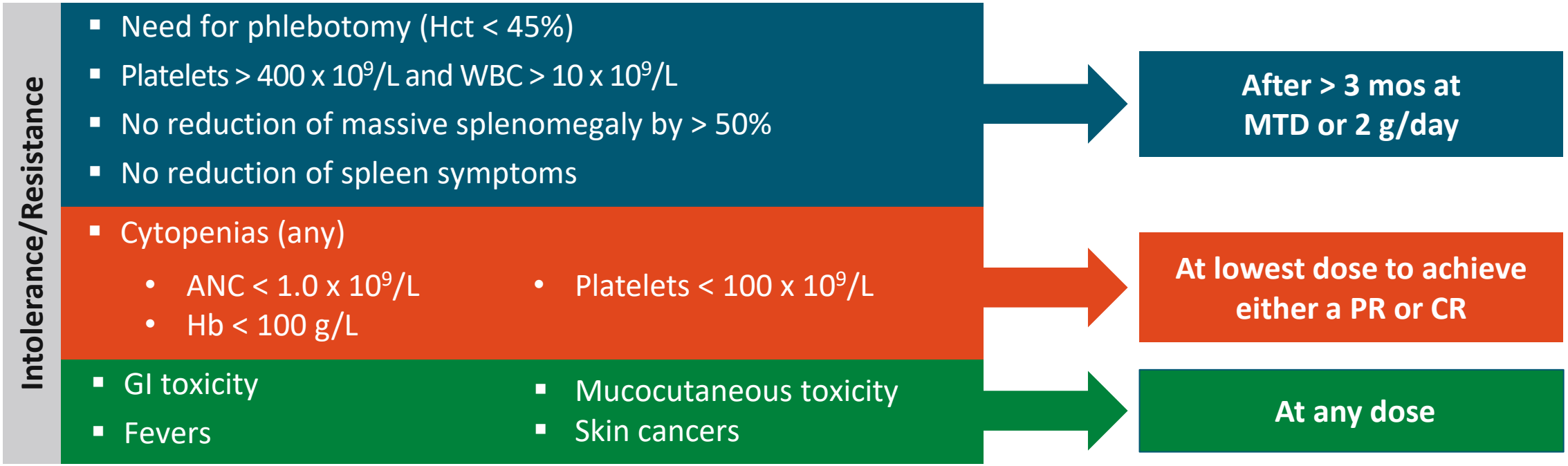
Gisslinger. ASH 2018. Abstr 579.

IFN for First-line PV Treatment

Parameter	Considerations	
Patients in whom IFN may be considered	▪ Preserved performance status and limited comorbidities ▪ Earlier in disease course ▪ Modest splenomegaly No additional non-*JAK2* mutations (?)	
Limitations	▪ Potential for short-term negative impact on QoL ▪ Tolerable in the long term?	
Impact of use	Early	▪ Blood count control ▪ Address splenomegaly, when modest ▪ Reduction in thrombosis risk
	Late	▪ Anticlonal activity ▪ Potential for regression of histologic changes, delayed transformation

Foucar. Curr Hematol Malig Rep. 2017;12:406.

HU Resistance and Intolerance: ELN Criteria

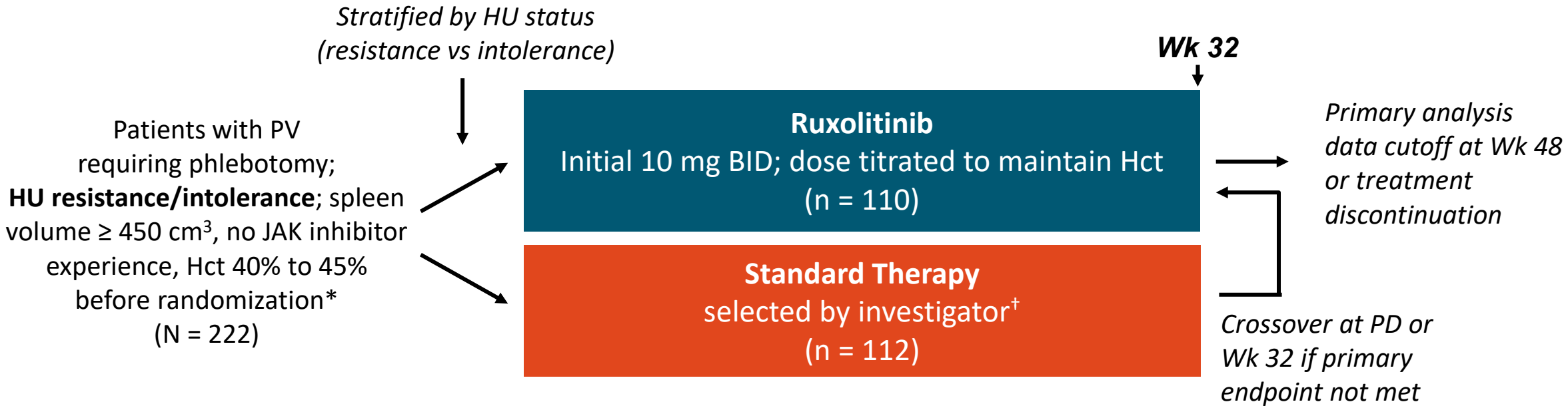


- Prevalence of HU resistance/intolerance: up to 25%
- Among individual criteria, development of cytopenia at the lowest required HU dose associated with increased risk of MF/AML progression and death
- Uncontrolled PV symptoms can be a trigger to re-evaluate therapeutic strategy

Barosi. Br J Haematol. 2010;148:961. Griesshammer. Ann Hematol. 2015;94:901. Alvarez-Larrán. Br J Haematol. 2016;172:786.

RESPONSE: Ruxolitinib vs Standard Therapy in Patients With PV and HU Resistance/Intolerance

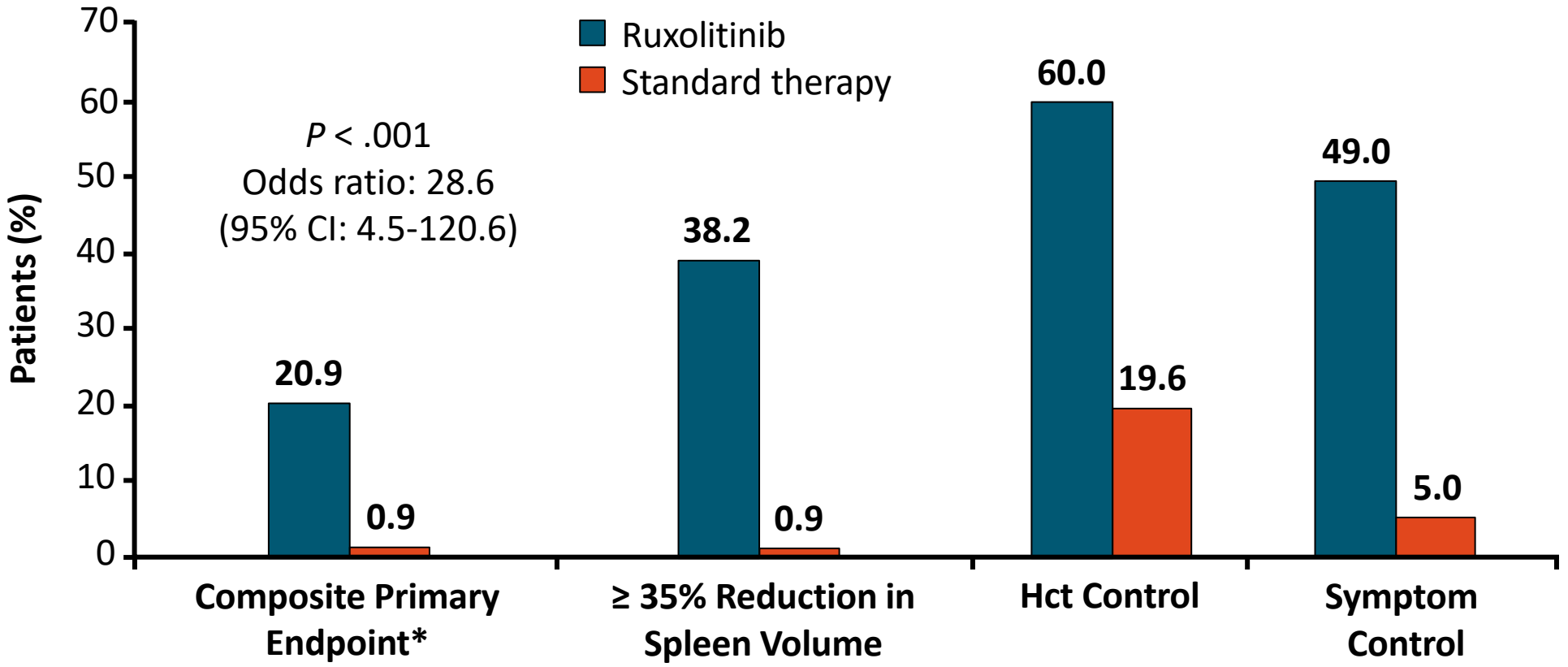
- International, multicenter, randomized, open-label phase III study
  - **Ruxolitinib:** JAK 1 and 2 inhibitor



All patients received low-dose ASA.
*Patients with Hct < 40% or > 50% entered Hct control period prior to randomization. †Excluding ^{32}P, busulfan, and chlorambucil.

Vannucchi. NEJM. 2015;372:426.

RESPONSE: Key Efficacy Findings at Wk 32



*Proportion with Hct control + spleen volume reduction ≥ 35%.

- Complete hematologic response also significantly improved with ruxolitinib vs standard therapy (23.6% vs 8.9%; *P* = .003)

Vannucchi. NEJM. 2015;372:426.

RESPONSE: 256-Wk Follow-up Data

- For patients randomized to **ruxolitinib** (n = 110)
  - Median exposure: 255 wks
  - Remained on or completed treatment: 66%
  - For patients achieving response at 32 wks (n = 25), KM estimate of maintaining response for 224 wks:
    - Primary endpoint*: 0.74
    - Hct control: 0.73
    - Spleen reduction: 0.72

Events/100 PY	Ruxolitinib (n = 110)
Thromboembolic events	1.2
Grade 3/4 thrombocytopenia	1.2
Zoster	4.7
Nonmelanoma skin cancer	5.1
Increased weight	6.1

Kiladjian. ASH 2018. Abstr 1753.

RESPONSE-2: Ruxolitinib vs Best Available Therapy in Patients Without Splenomegaly

- Multicenter, randomized, open-label phase IIIb study in which patients with HU-resistant/intolerant PV who required phlebotomy and had **no splenomegaly** were treated with **ruxolitinib** or **best available therapy** (N = 149)

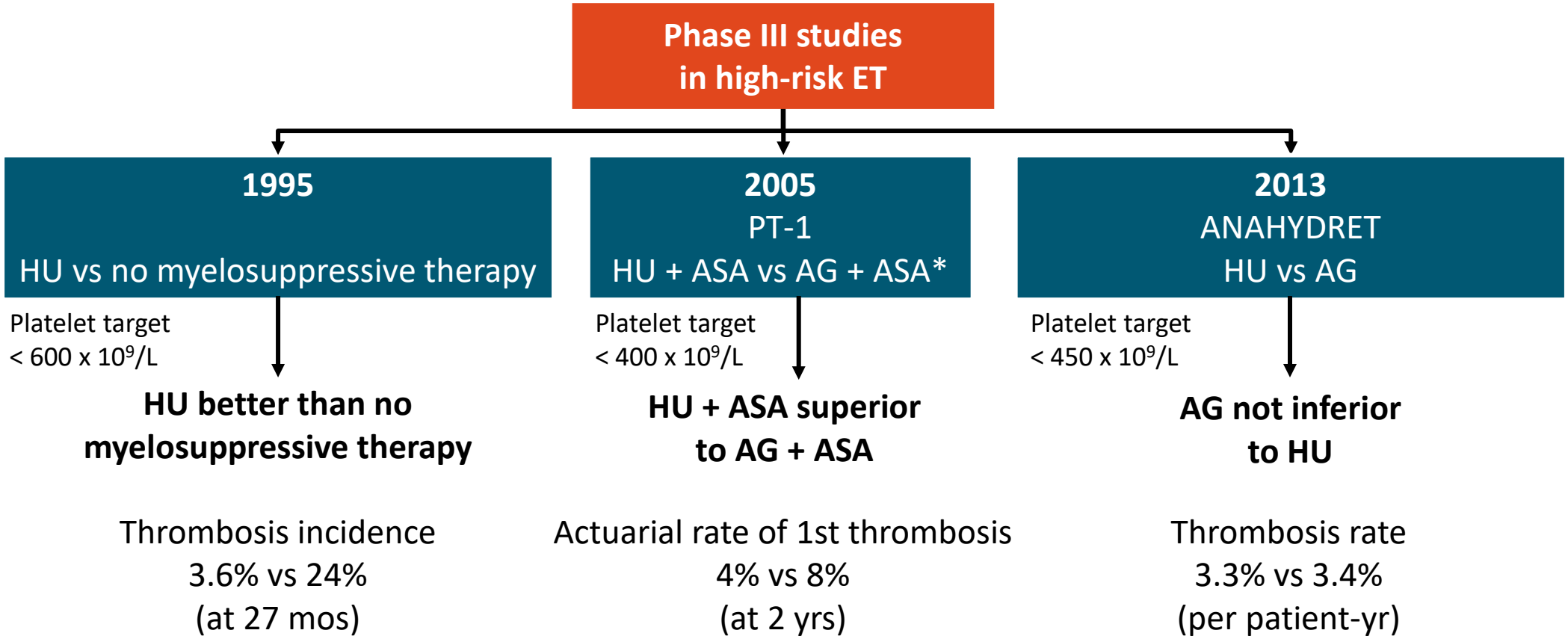
Outcome, Wk 28	Ruxolitinib (n = 74)	BAT (n = 75)	*P* Value
Hct control,* n (%)	46 (62)	14 (19)	< .0001
Complete hematologic response, n (%)	17 (23)	4 (5)	.0019
Complete resolution in symptoms, n/N† (%)	17/34 (50)	2/26 (8)	NR
▪ ≥ 50% reduction in MPN-SAF TSS, n/N (%)	29/64 (45)	5/22 (23)	NR

*Primary endpoint. †Patients with baseline MPN-SAF TSS of ≥ 20.

BAT, best available therapy; Hct, hematocrit; HU, hydroxyurea; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; NR, not reported; PV, polycythemia vera.

Passamonti. Lancet Oncol. 2017;18:88.

Prospective Randomized Clinical Trials in ET



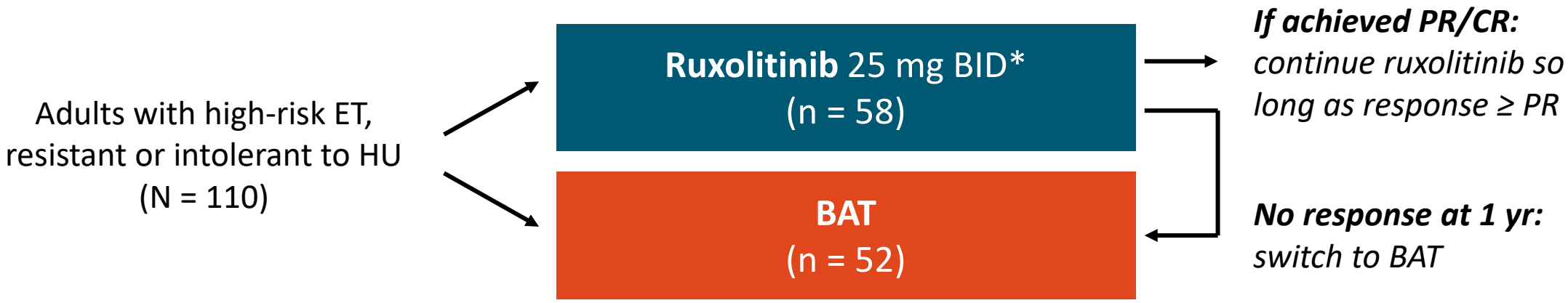
*Composite primary endpoint: arterial or venous thrombosis, serious hemorrhage, or death from vascular causes.

AG, anagrelide; ASA, aspirin; ET, essential thrombocythemia; HU, hydroxyurea; Plt, platelet.

Cortelazzo. NEJM. 1995;332:1132. Harrison. NEJM. 2005;353:33. Gisslinger. Blood. 2013;121:1720.

MAJIC-ET: Ruxolitinib vs BAT in Patients With ET Resistant or Intolerant to HU

- Randomized, open-label phase II study



*If platelets 100-200 x 10^9/L, ruxolitinib dosed at 20 mg BID.

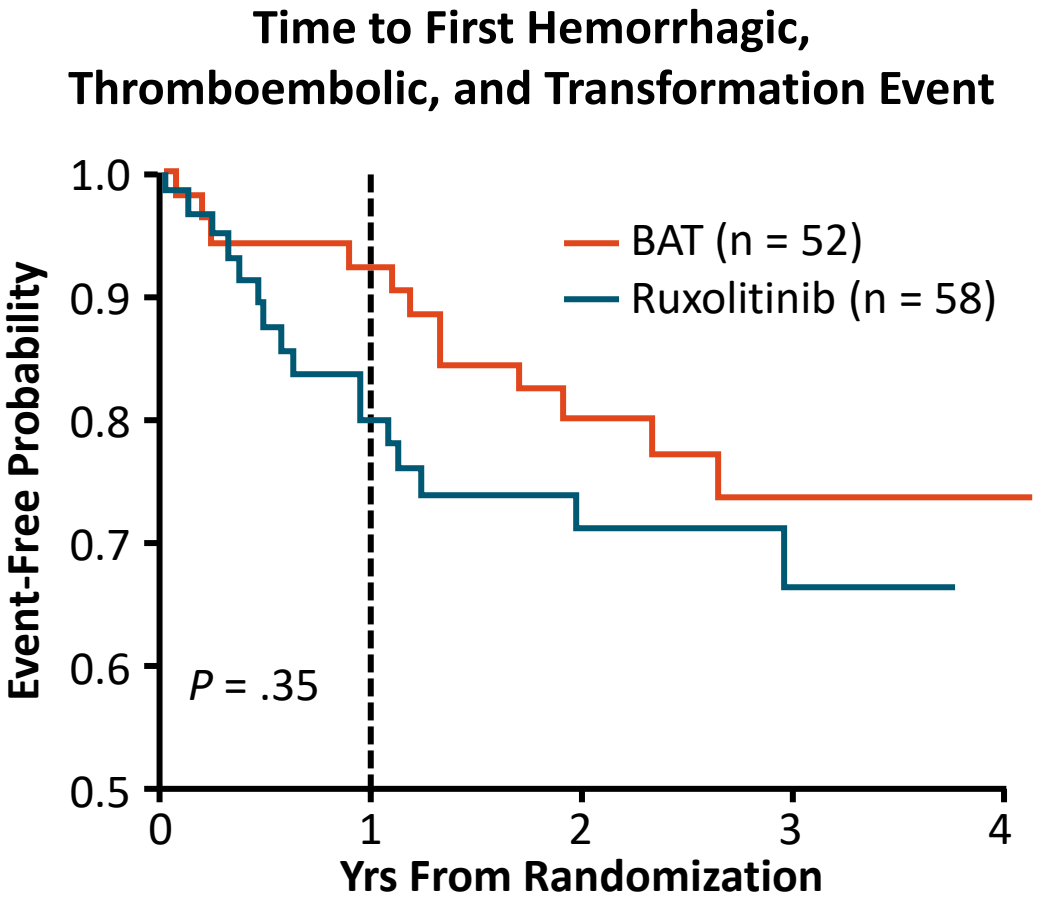
- Baseline: resistant to HU, 48.2%; intolerant to HU, 51.8%; both, 22.7%
- Primary endpoint: CR rate within 1 yr of treatment (ELN criteria)
- Secondary endpoints: PR rate within 1 yr of treatment, DoR, ORR, histologic response, molecular response, hemorrhagic and thromboembolic events, disease transformation, OS, PFS, QoL, disease symptom burden, safety

Harrison. Blood. 2017;130:1889.

BAT, best available therapy; DoR, duration of response; ELN, European LeukemiaNet; ET, essential thrombocythemia; HU, hydroxyurea; QoL, quality of life.

MAJIC-ET: No Difference in Outcomes With Ruxolitinib vs BAT in ET

- No difference in CR, PR within first yr of treatment
  - CR: ruxolitinib, 46.6%; BAT, 44.2% (*P* = .40)
- Rates of thrombosis, hemorrhage, or transformation not different between arms at 2 yrs
- More grade 3/4 anemia, thrombocytopenia, and grade 3 infections with ruxolitinib vs BAT
- More d/c with ruxolitinib vs BAT (60% vs 19%)
- Some molecular responses in ruxolitinib-treated patients with *JAK2* V617F or *CALR* positivity
- Better improvement of some disease-related symptoms with ruxolitinib



Harrison. Blood. 2017;130:1889.


Fly Emirates
Fly Emirates
Fly Emirates
Fly Emirates
Fly Emirates
only perfect counts
Moffitt MDS Team