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

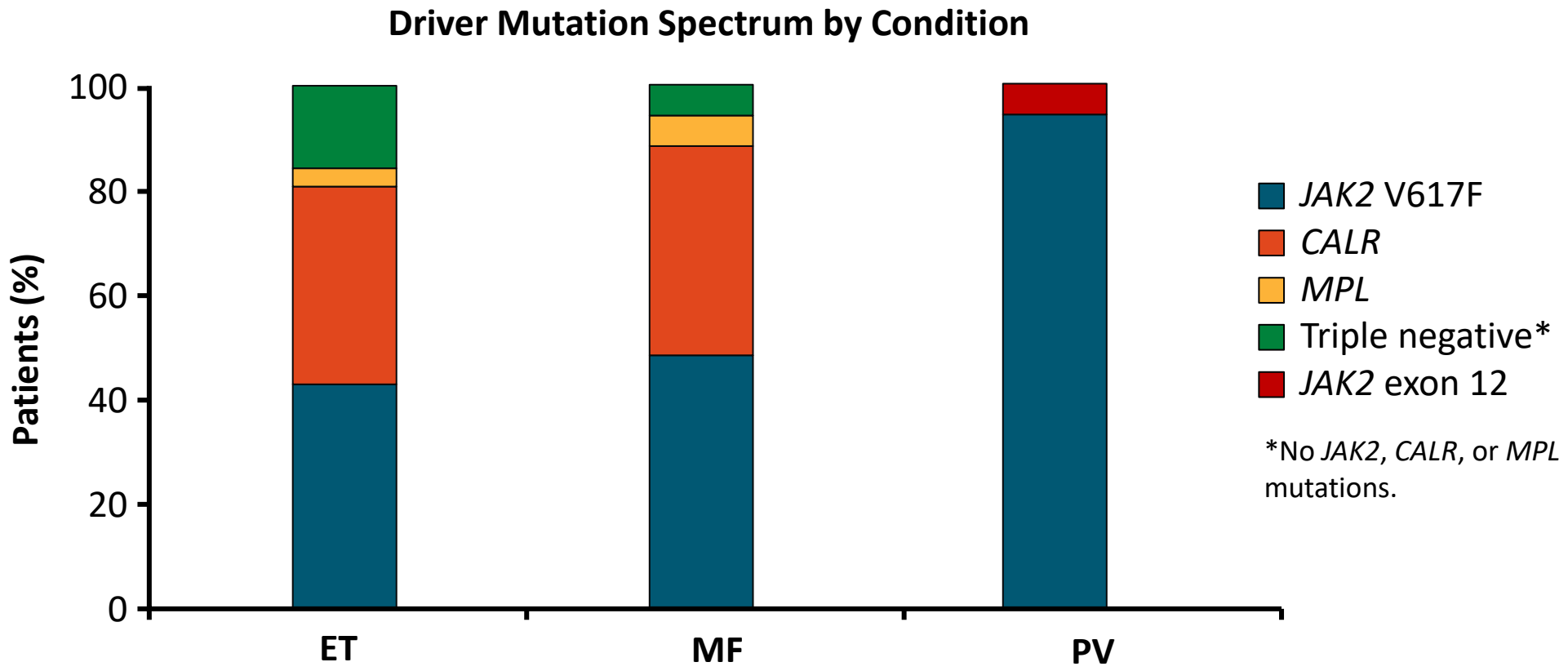
The most common *BCR-ABL1*-negative MPNs: PMF, PV and ET

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



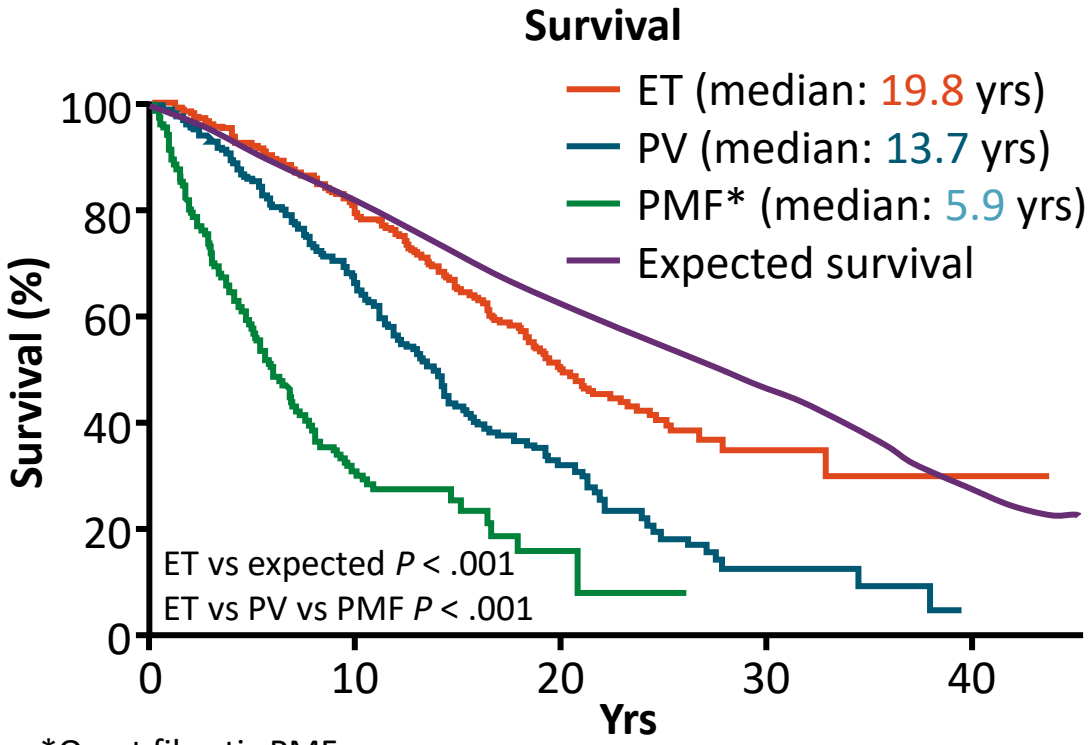
- A very small percentage of PV patients may have *LNK* or *CALR* driver mutations
- Nondriver mutations mostly frequently occurring in MPNs: *TET2, ASXL1, DNMT3A*

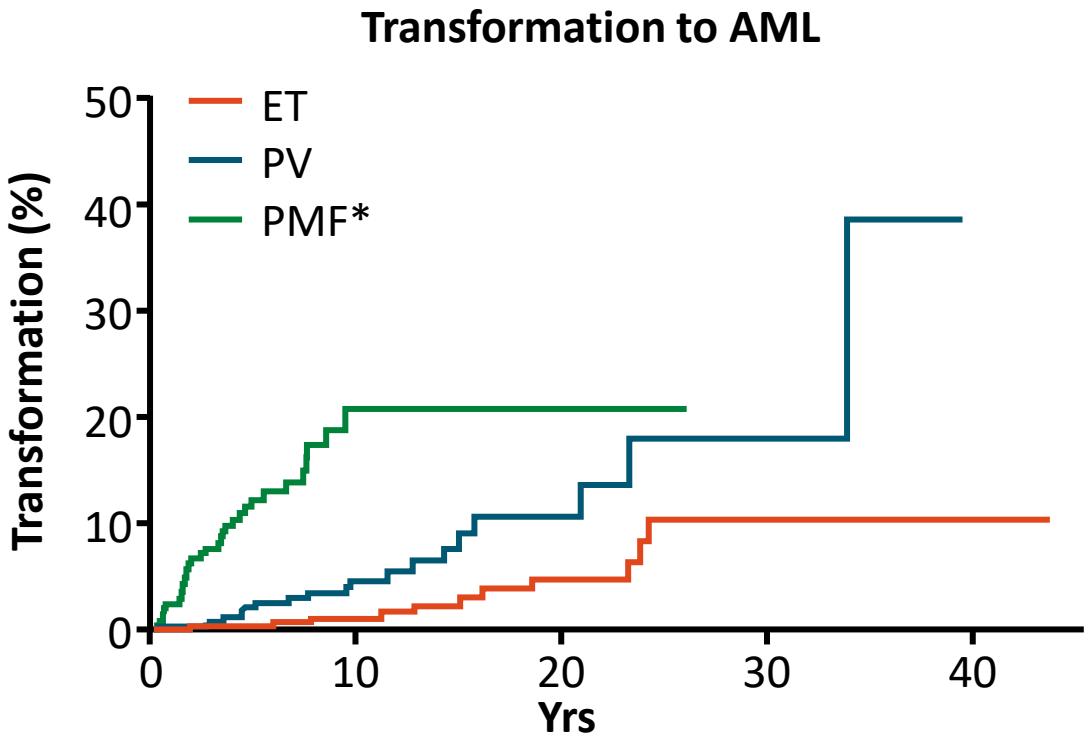
Grinfeld. Haematologica. 2017;102:7.

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.

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*.

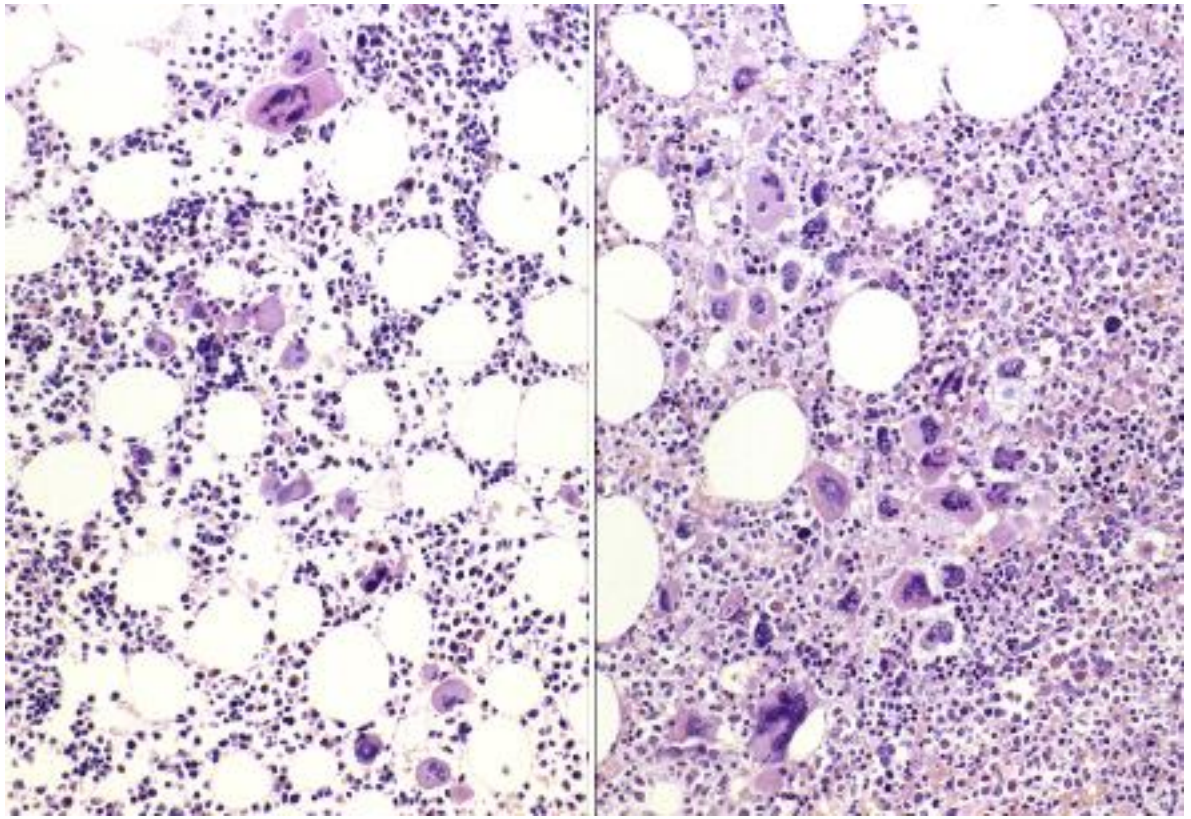
Arber. Blood. 2016;127:2391.

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

ET 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

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

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

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

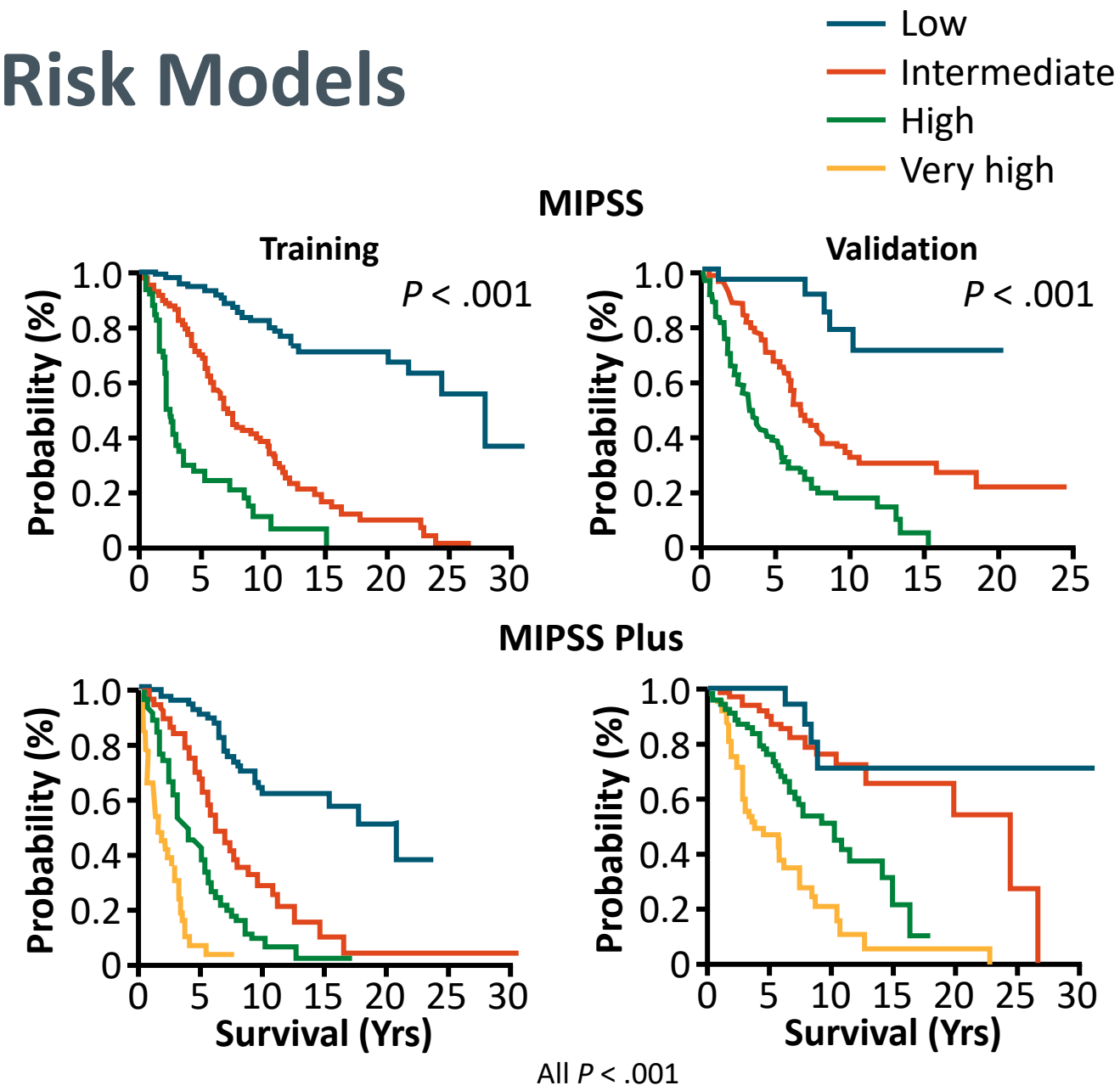
- Analysis of association between set of **nondriver mutations** (*IDH, EZH2, ASXL1, SRSF2*) and survival in patients with primary MF (N = 797)[2]
  - Presence of mutations predicted decreased survival; ≥ 2 mutations predicted worst survival

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*.

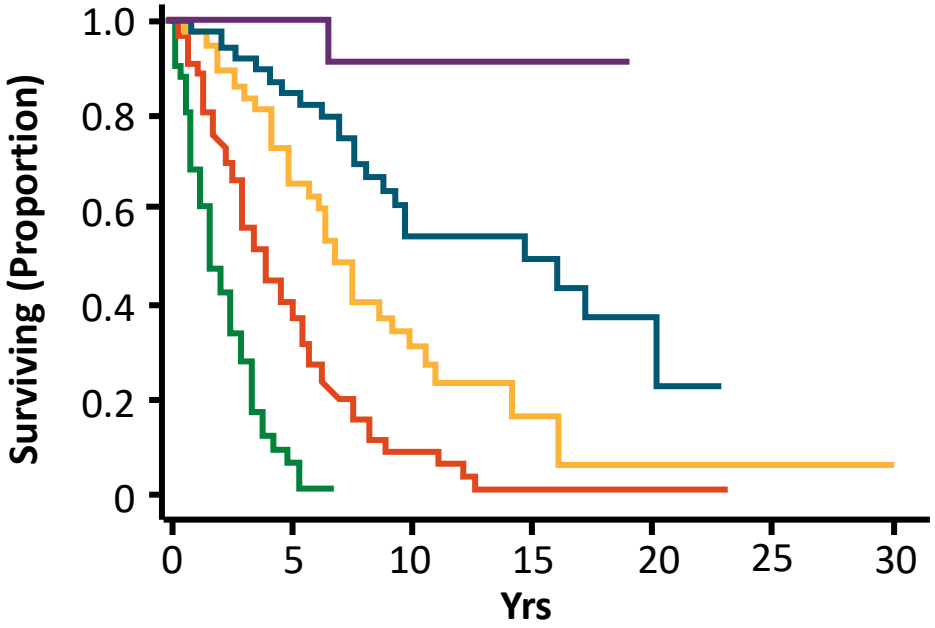


Guglielmelli. JCO. 2018;36:310. http://www.mipss70score.it/index.html.

MIPSS70-Plus v2.0 Risk Model

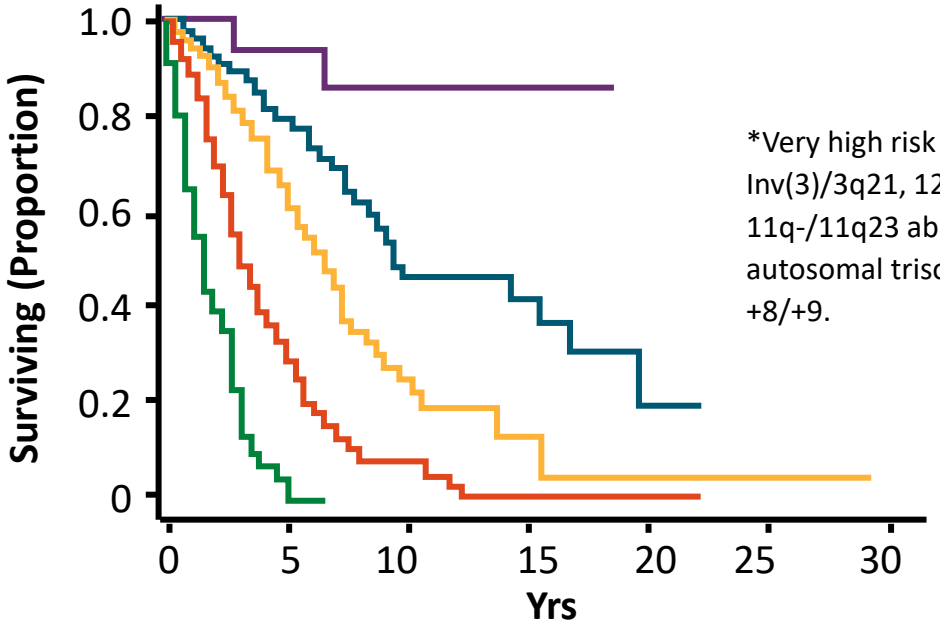
- Also incorporates very high–risk karyotype,* U2AF1 Q157 mutation status, sex- and severity-adjusted Hb thresholds (vs MIPSS70-Plus) and defines 5 prognostic categories, from very low to very high risk

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

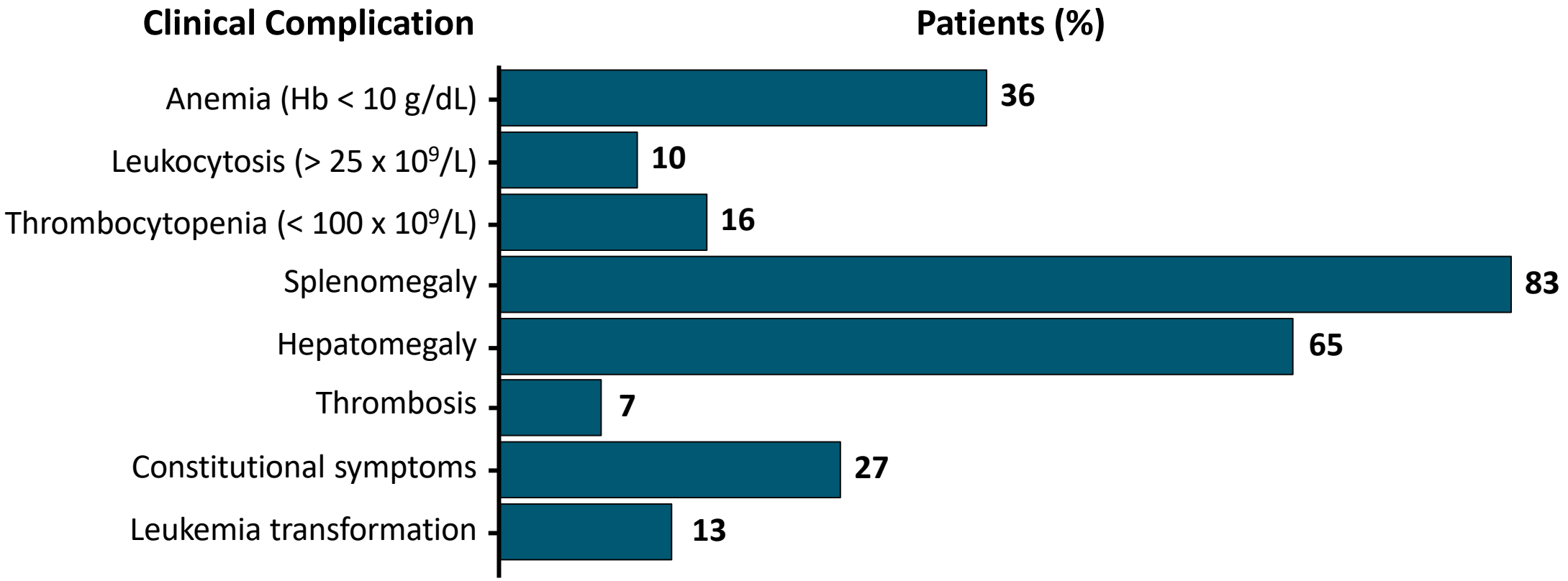
Mesa. Leuk Lymphoma. 2013;54:242. Geyer. Hematology Am Soc Hematol Educ Program. 2014;2014:277.

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**	

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)

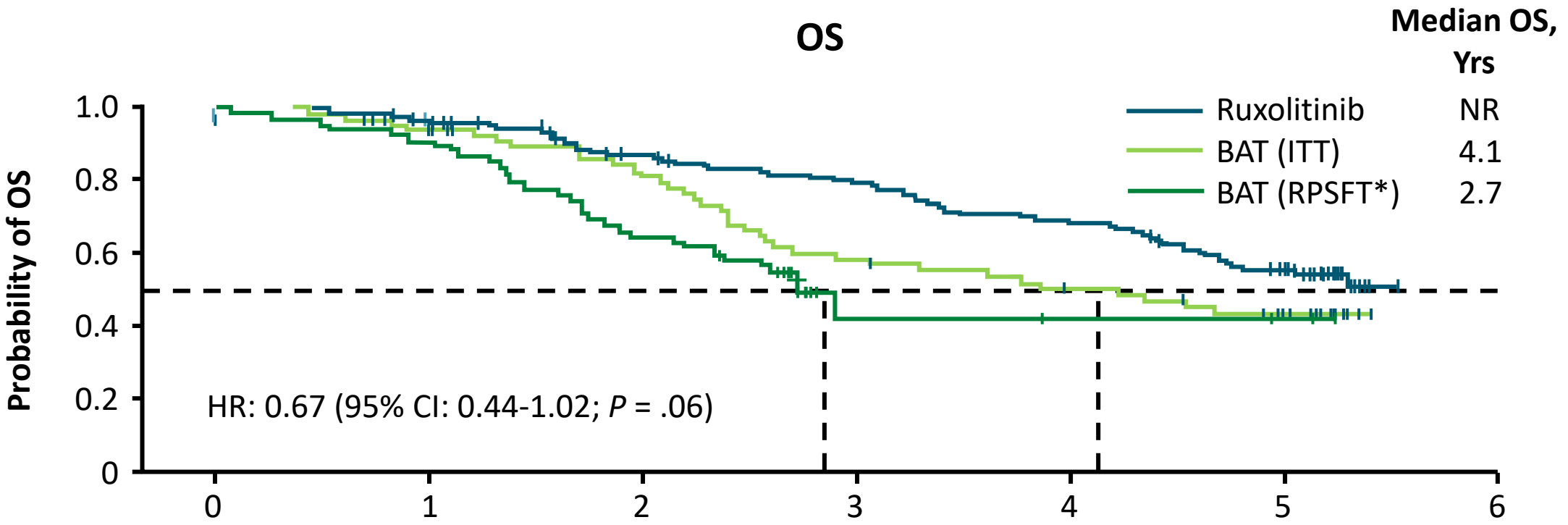
Outcome	COMFORT-I, Wk 24[1]		*P* Value	COMFORT-II, Wk 48[2]		*P* Value
	Ruxolitinib (n = 155)	Placebo (n = 154)		Ruxolitinib (n = 144)	BAT (n = 73)	
Spleen volume reduction ≥ 35%,* %	41.9	0.7	< .001	28	0	< .001
≥ 50% reduction in MF-SAF TSS, %	45.9	5.3	< .001	NR	NR	NR
D/c for AEs	11.0	10.6	NR	8	5	NR

*Primary endpoint. †n = 151.

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

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

COMFORT-II: 5-Yr OS 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

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

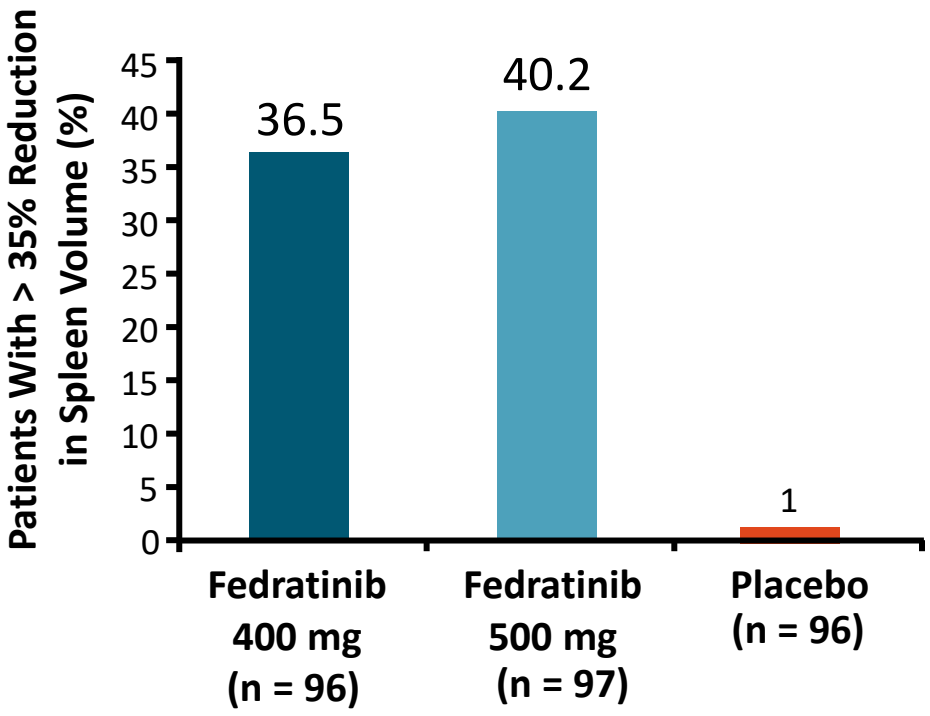
Ruxolitinib Dosing Recommendations	
Starting dose	***Determined by platelet count:*** ▪ > 200 x 10^9/L: 20 mg BID PO ▪ 100 to 200 x 10^9/L: 15 mg BID PO ▪ 50 to < 100 x 10^9/L: 5 mg BID PO
Monitoring	Monitor CBC every 2-4 wks until doses stabilized, then as clinically indicated
Dose adjustment	Modify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

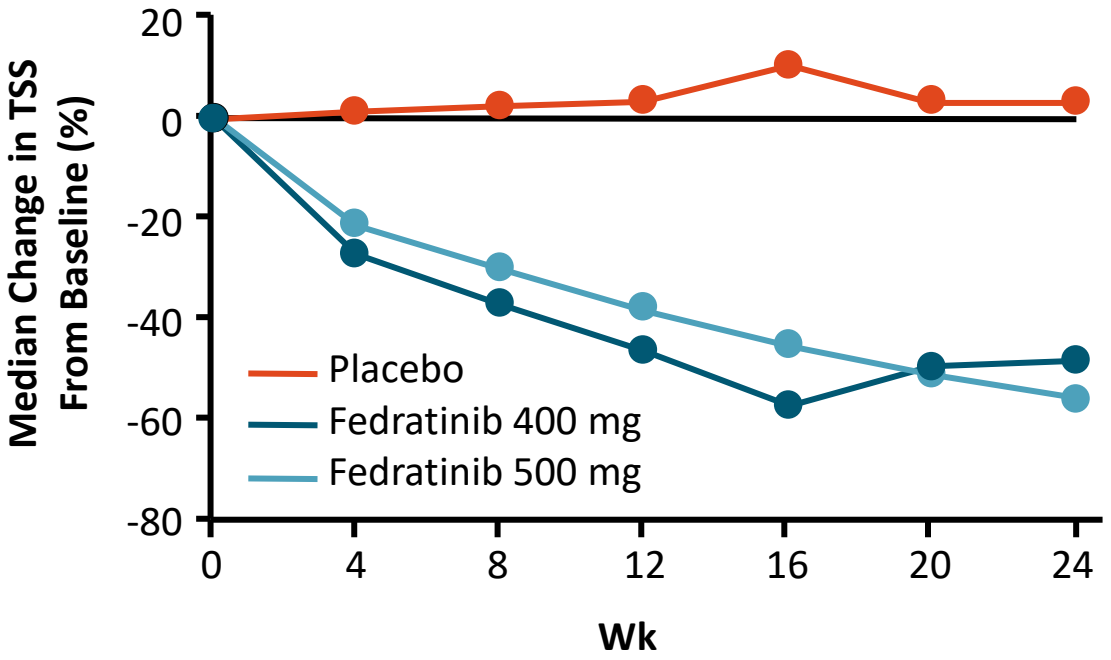
Mesa. Int J Hematol. 2016;104:420. Ruxolitinib PI. Porpaczy. Blood. 2018;132:694. Pemmaraju. Blood. 2019;133:2348. Cervantes. EHA 2019. Abstr PS1465..

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.

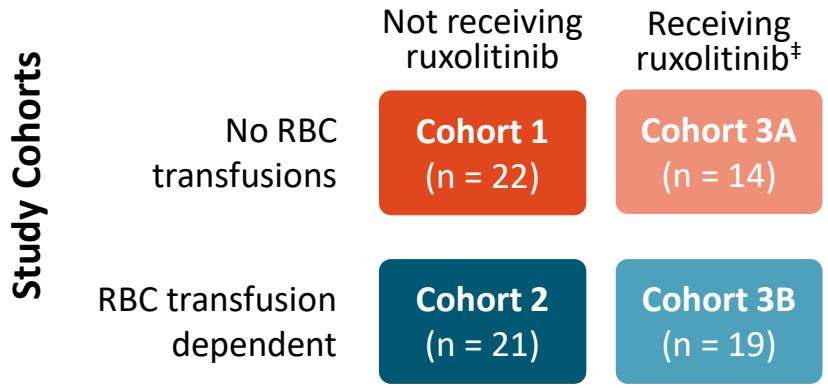
Fedratinib Indication in MF

- 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 QD in patients with platelets ≥ 50 x 10^9/L
  - Reduce dose to 200 mg QD 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 Pacakge Insert.

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)

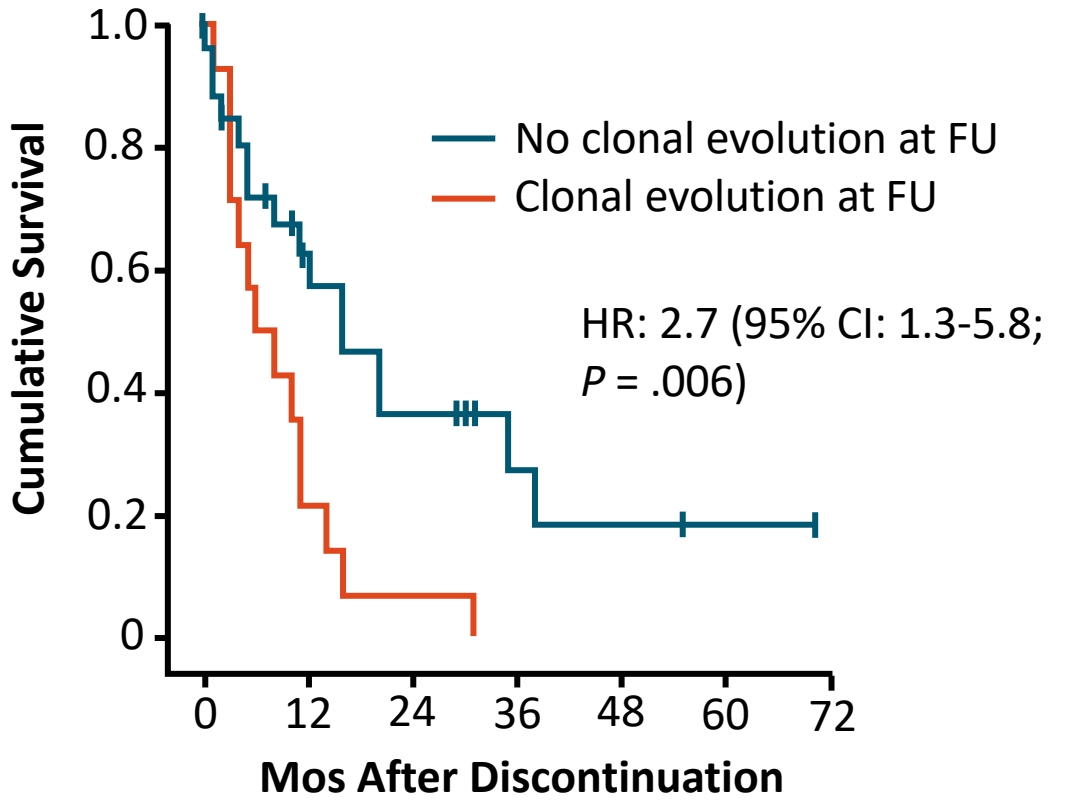
Hb Increase ≥ 1.5 g/dL From BL for ≥ 12 Consecutive Wks†	No RBC Transfusions	
	No RUX (Cohort 1; n = 22)	RUX (Cohort 3a; n = 14)
Hb increase ≥ 1.5 g/dL at every assessment, n (%)	3 (14)	3 (21)
Mean Hb increase ≥ 1.5 g/dL, n (%)	4 (18)	9 (64)

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

Gerds. ASH 2019. Abstr 557.

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 overall survival: 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*

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)

*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.

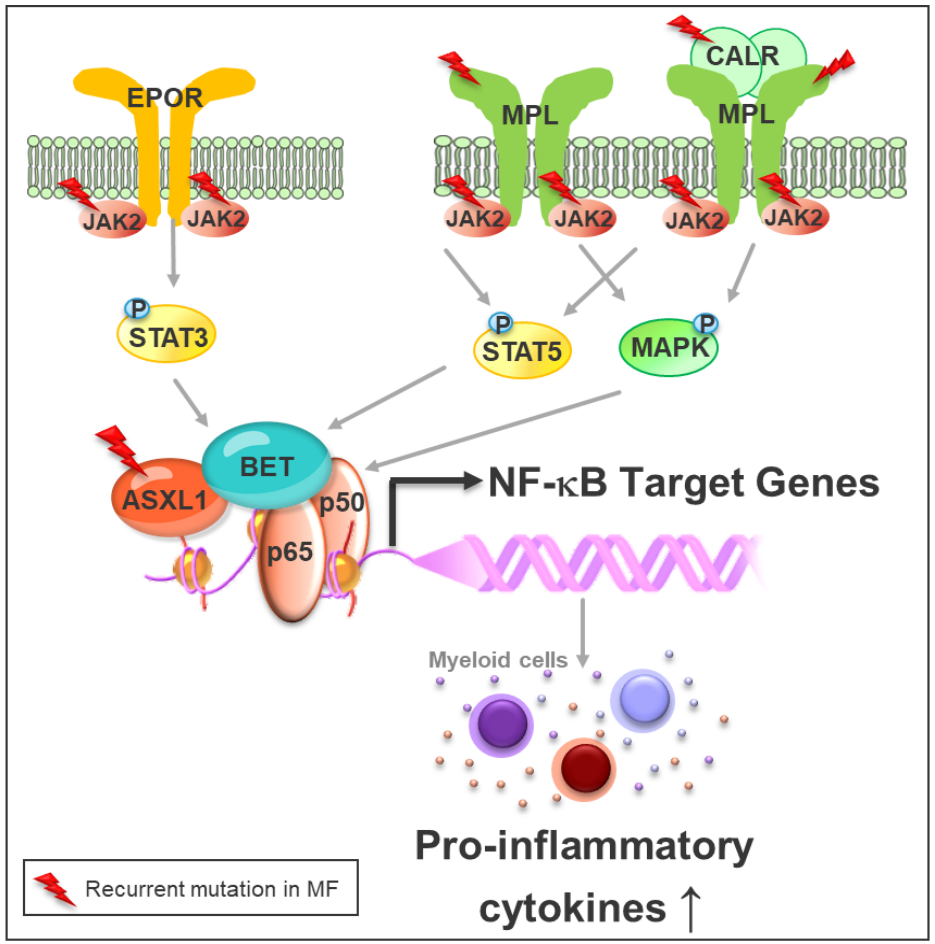
Novel agents in clinical trials for MF

	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

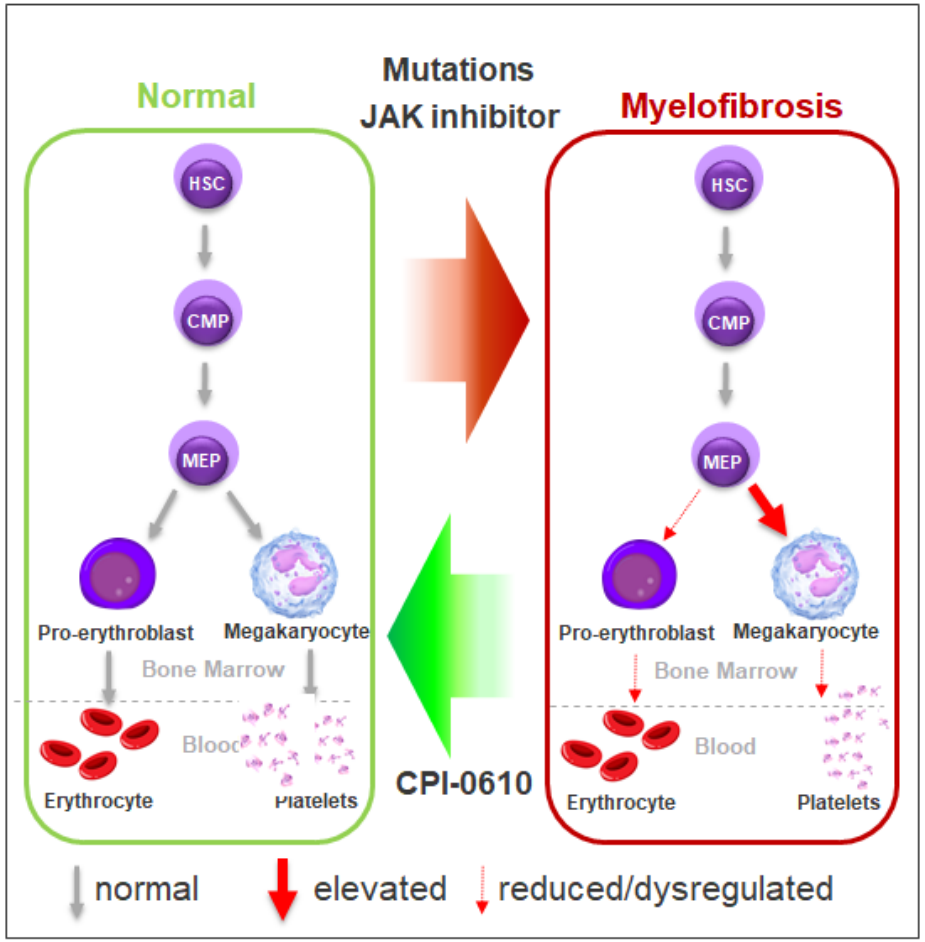
Modified from Economides MP, et al. *Curr Hematol Malig Rep*. 2019 Aug 1.

Manifest Study- CPI-0610

CPI-0610 reduces inflammatory cytokines

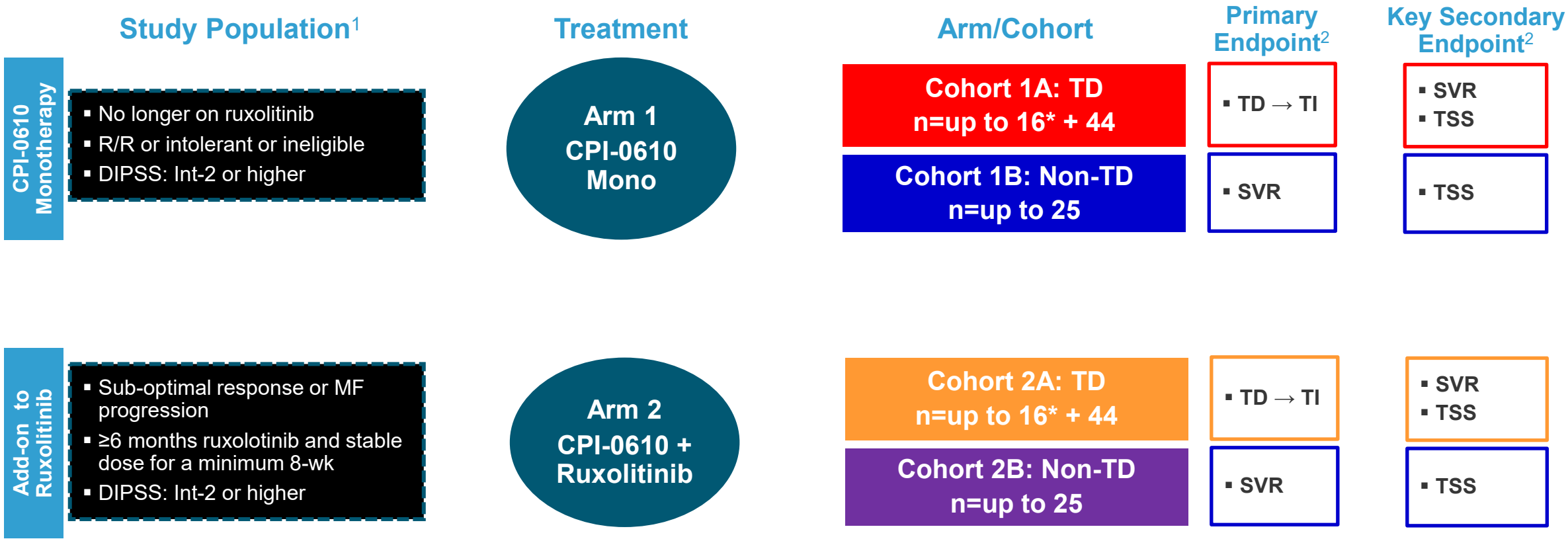


CPI-0610 affects megakaryocyte differentiation



- Reduce inflammation and suppress cells in the bone marrow that drive myelofibrosis (MF)

MANIFEST Study Design



DIPSS: Dynamic International Prognostic Scoring System, TD = Transfusion Dependent; TI = Transfusion Independent; SVR = Spleen Volume Response; R/R: Resistant/Refractory; PLT: Platelets; RBC: Red Blood Cell

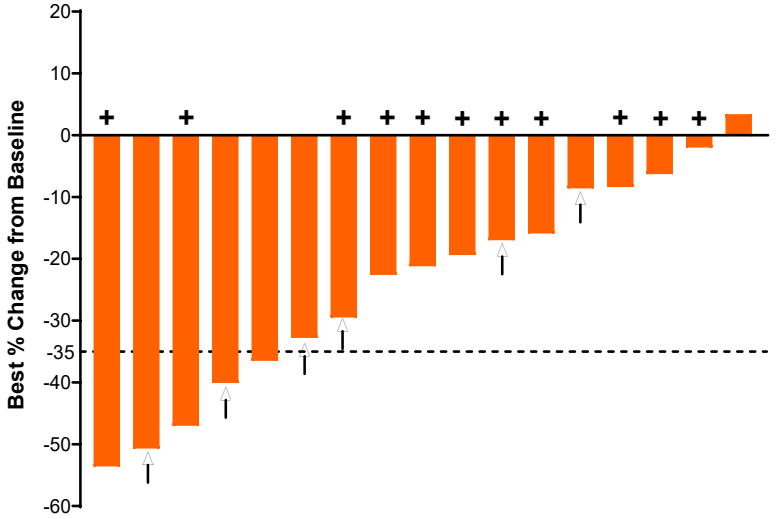
[1] ClinicalTrials.gov Identifier: NCT02158858 for further details on study design and patient population per last protocol amendment.

[2] Other endpoints: Anemic response, RBC transfusion rate, safety, PK, proinflammatory cytokine levels, bone marrow morphology and mutant allele burden

* Will follow Simon 2-stage design

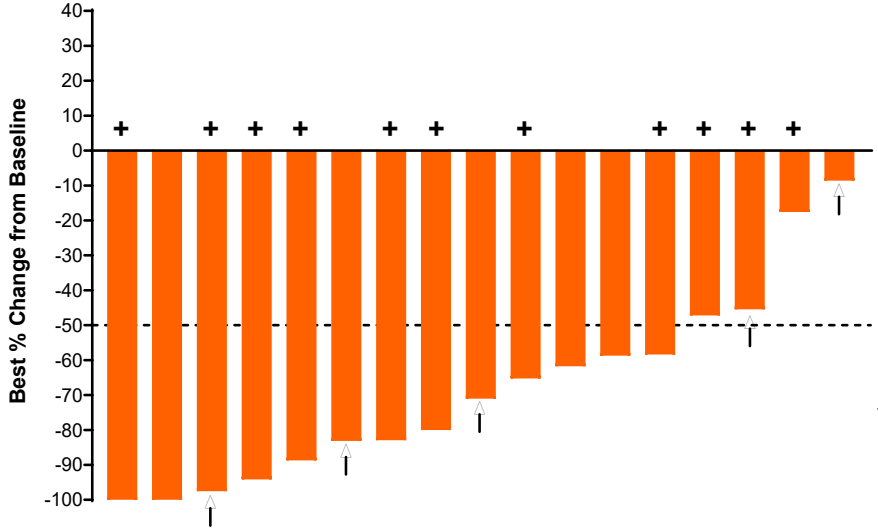
Cohort 2A: CPI-0610 Add-On to Ruxolitinib in R/R MF TD Patients
Efficacy Results – Best Response

Best % Spleen Volume Reduction (n=17)[1]



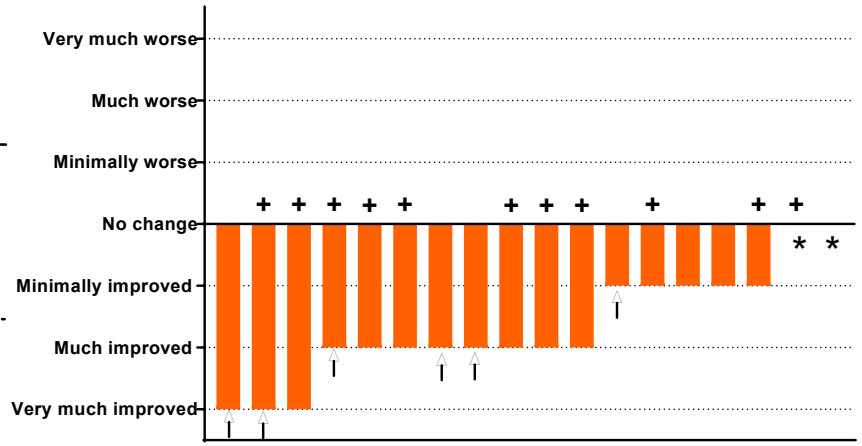
- SVR35 Response: 29% (5/17)
- Median Best Change: -21.2%

Best % TSS Improvement (n=17)[1,2]



- TSS ≥50% Response: 76.5% (13/17)
- Median Best Change: -71%

Best PGIC Score (n=18)[1]



- PGIC: 89% (16/18) had improvement in overall status
  - 61% (11/18) much or very much improved

[1] Evaluable patients: Patients received at least 12 week of treatment, have baseline and at least one post-baseline assessment available. SVR and TSS: Best % change from baseline at any time during the study. PGIC: Best status reported at any time during the study.
[2] One patient not included due to missing baseline converted from TD to TI
Preliminary data as of 17 October 2019

+ HMR

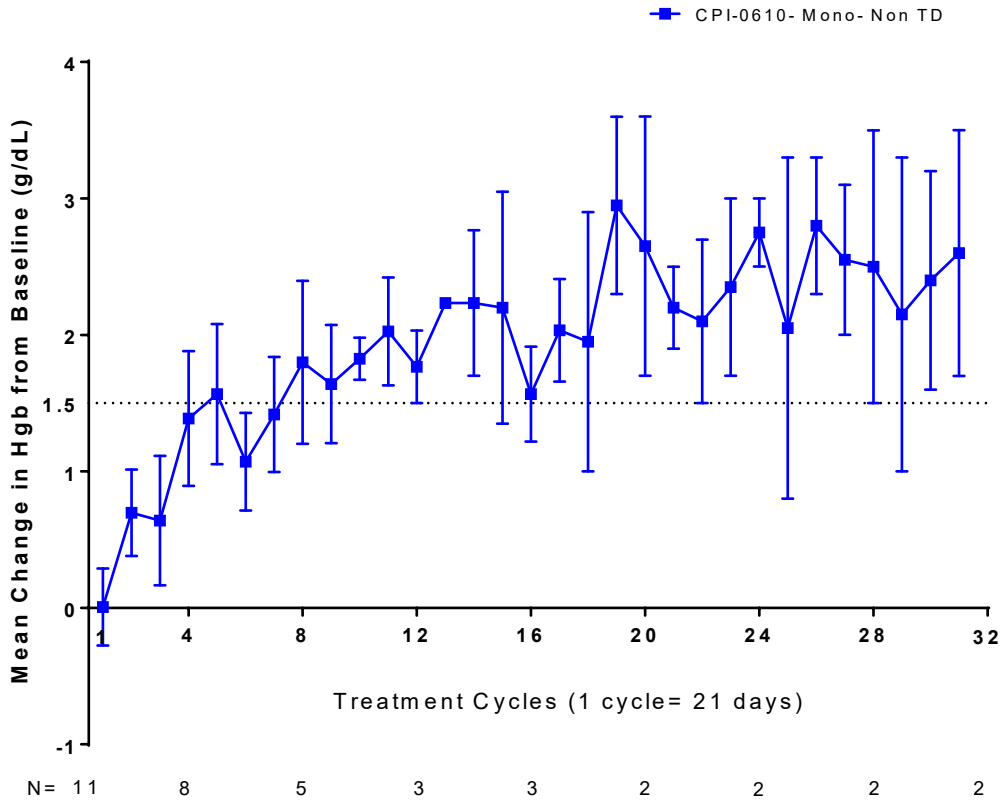
↑ TD→TI Conversion

*** Patients with no change**

Cohorts 1B & 2B: Hemoglobin Improvement by CPI-0610 Monotherapy

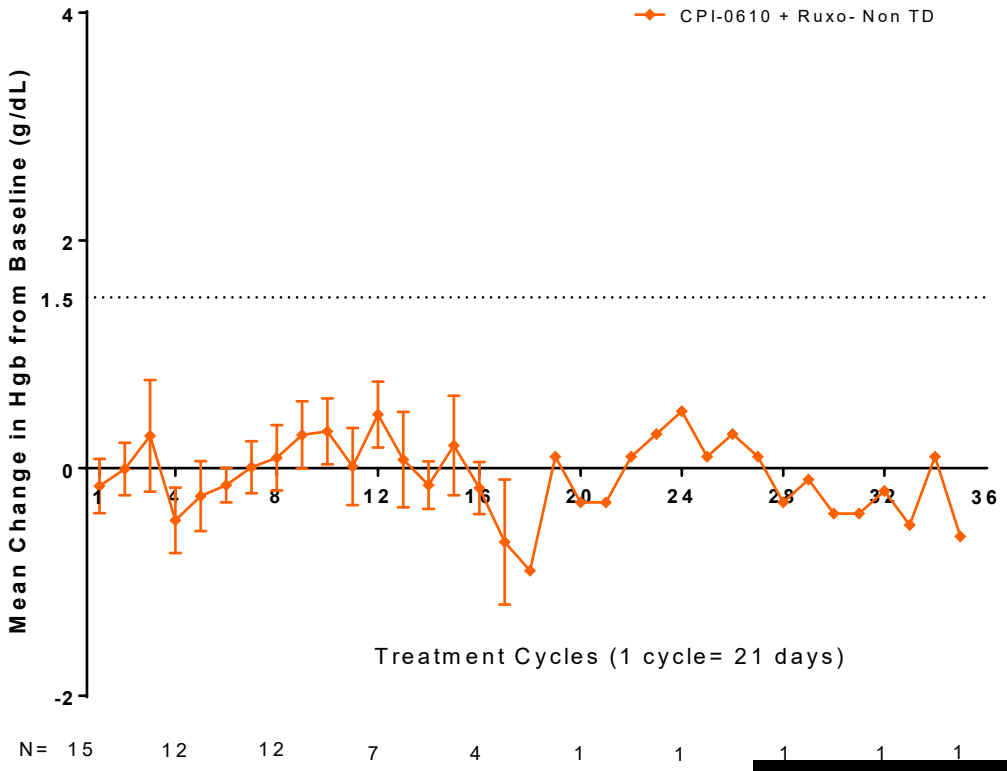
CPI-0610 Monotherapy (n=11)[1]

- 55% (6/11) patients had ≥1.5 g/dL increase in hemoglobin[2]
- 64% (7/11) (patients had ≥1.0 g/dL increase in hemoglobin[2]



CPI-0610 + Ruxolitinib (n=15)[1]

- 13% (2/15) patients had ≥1.5 g/dL increase in hemoglobin[2]
- 20% (3/15) (patients had ≥1.0 g/dL increase in hemoglobin[2]

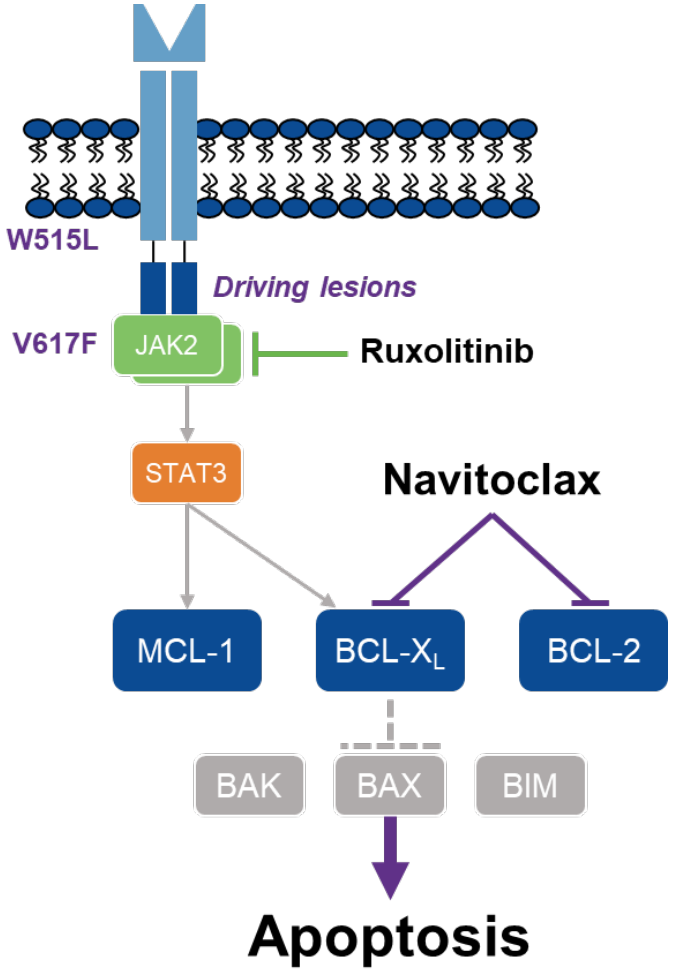


[redacted]

[1]Hemoglobin change in evaluable population: Received treatment for ≥12-wk, without any transfusion.
[2]The increases in hemoglobin from baseline, confirmed within 6-wk with a second assessment.
Mean+/-SEM. Preliminary data as of 17 October 2019

Ruxolitinib and Navitoclax

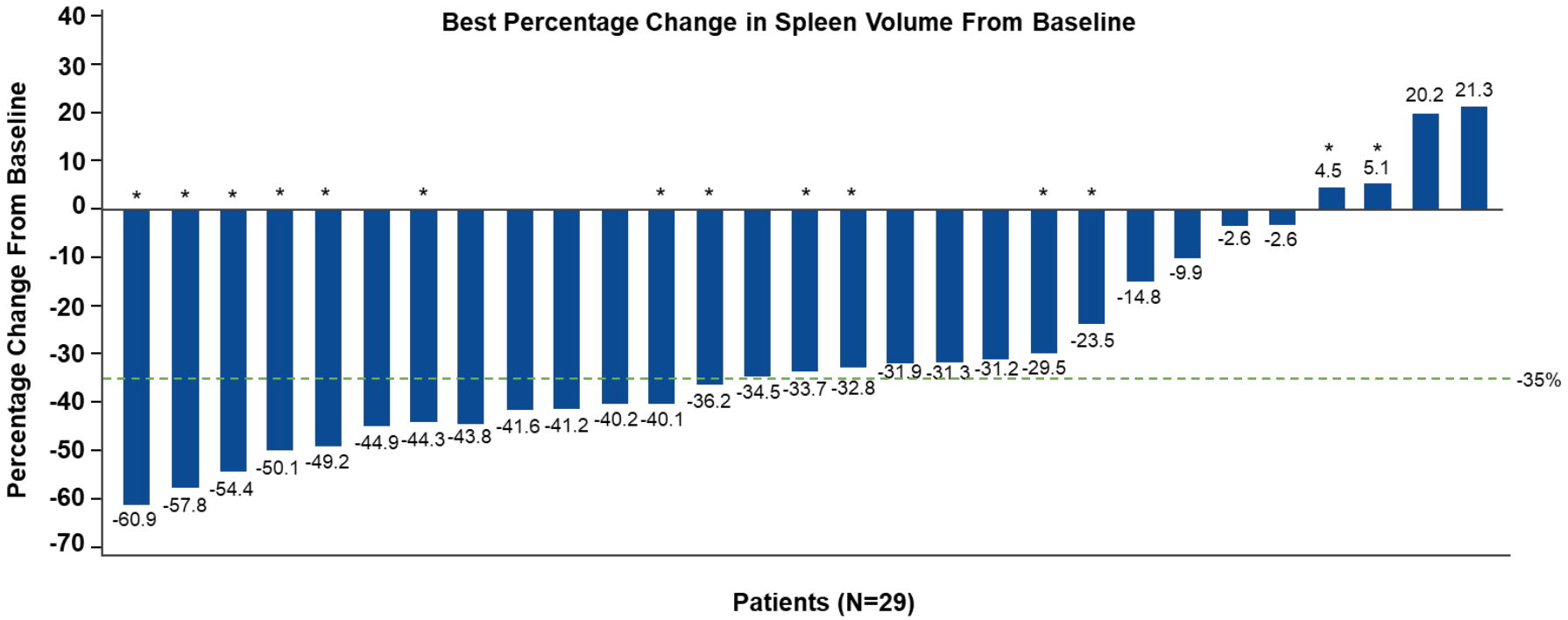
- **Navitoclax** is a novel small molecule that binds with high affinity to BCL-X_L, BCL-2, and BCL-W, causing cell death by apoptosis[1]
  - It has demonstrated cytotoxic activity in myeloproliferative neoplasm (MPN)-derived cell lines[2-4]
- Preclinical rationale
  - BCL-X_L inhibition has the potential to prevent fibrosis growth in the bone marrow[2]
  - The combination (JAK2 + BCL-X_L / BCL-2 inhibition) works synergistically to kill *JAK2*-mutated cells[2]
  - BCL-X_L inhibition overcomes resistance to JAK2 inhibition[3]
  - Navitoclax has demonstrated killing of activated myofibroblasts[5]
- **Hypothesis:** Combining navitoclax with ruxolitinib overcomes resistance to JAK-2 inhibition



BCL, B-cell lymphoma; JAK2, janus kinase 2; MCL, myeloid leukemia cell; MPN, myeloproliferative neoplasm; STAT3, signal transducer and activator of transcription 3.

1. Tse C, et al. *Cancer Res*. 2008;68:3421-3248; 2. Zeuner A, et al. *Blood*. 2009;113:1522-1525; 3. Waibel M, et al. *Cell Rep*. 2013;5:1047-1059; 4. Guo J, et al. *PLoS One*. 2015;10:e0114363; 5. Lagares D, et al. *Sci Transl Med*. 2017;9.

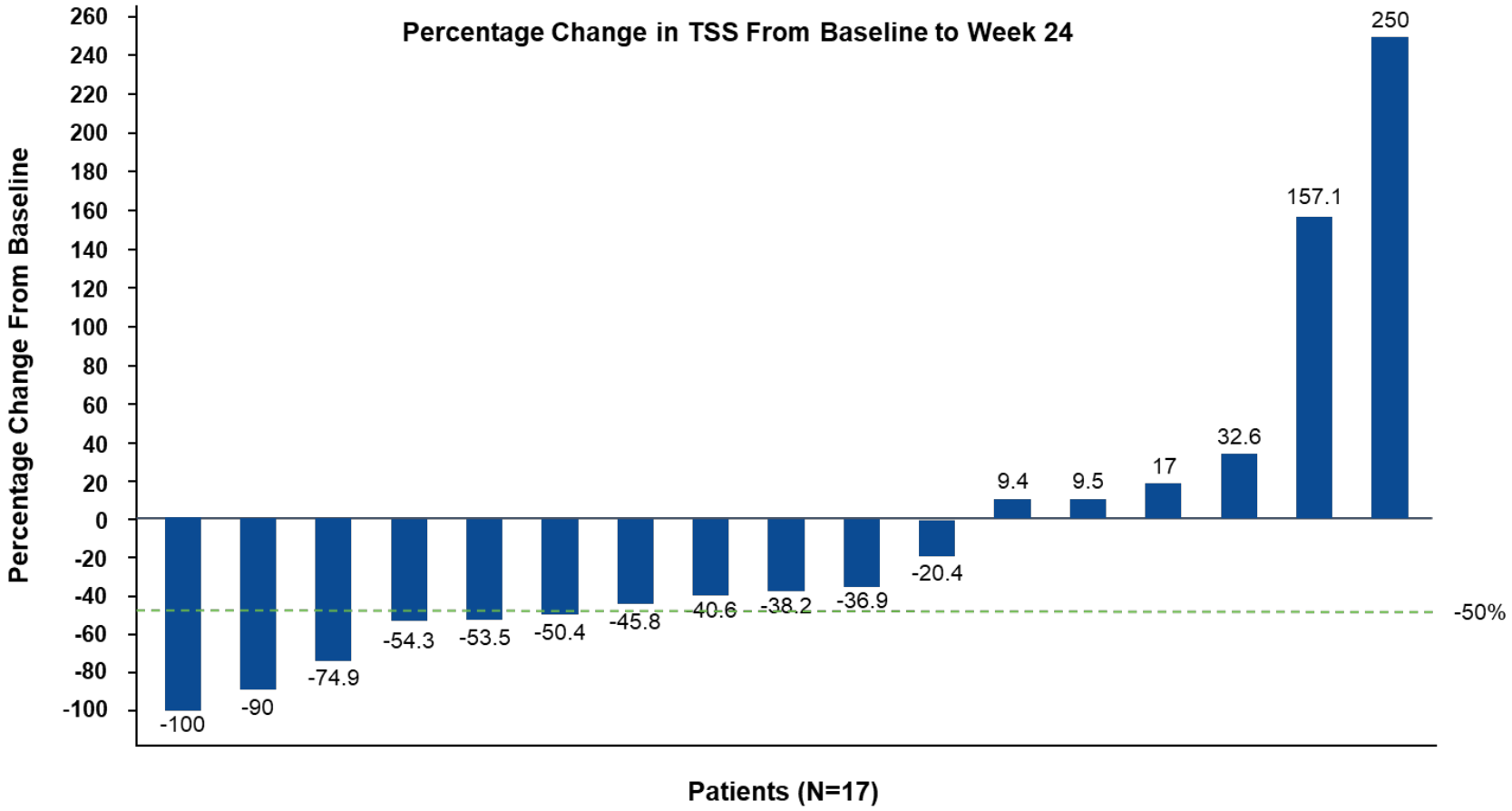
Navitoclax Overcomes Ruxolitinib Resistance Resulting in Splenomegaly Improvement for Most Patients



- SVR_{35} best on study: 43% (13/30)
- SVR_{35} at week 24: 30% (9/30)
- 53% (16/30) of patients resolved palpable splenomegaly during study treatment
- 25% (8/32) of patients demonstrated reduction in bone marrow fibrosis (local assessment)
  - 13% (4/32) with 1 grade reduction
  - 13% (4/32) with 2 grade reduction

Data cut: November 18, 2019.
Percentages calculated on the basis of efficacy analysis set (N=30).
N = number of patients with non-missing maximum spleen volume reduction across visits.
Baseline is defined as the last non-missing observation collected on or prior to the date of the first dose of any component of study treatment.
*Denotes patients with high molecular risk (defined by the presence of mutations within *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*, *U2AF1*).
ASXL1, additional sex combs like 1; *EZH2,* enhancer of zeste homolog 2; *IDH1/2*, isocitrate dehydrogenase 1/2; MF, myelofibrosis; *SRSF2*, serine/arginine-rich splicing factor 2; SVR_{35}, spleen volume reduction of 35%; *U2AF1*, U2 small nuclear RNA auxiliary factor 1.

Navitoclax Overcomes Ruxolitinib Resistance Resulting in Total Symptom Score Improvement for Most Patients

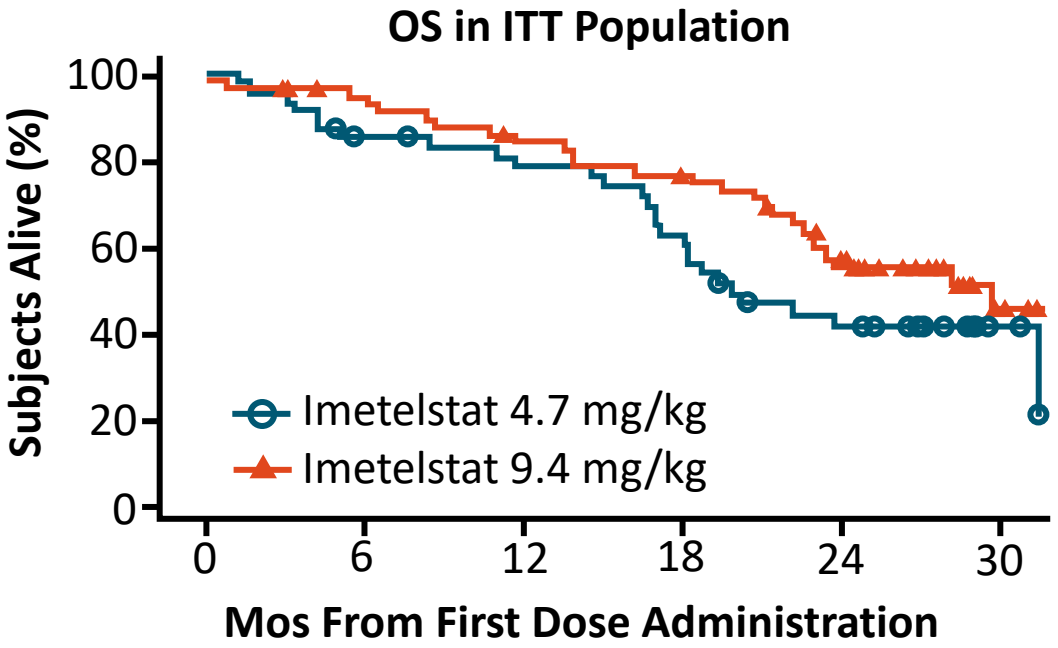


- 65% (11/17) of patients experienced reduction in symptoms
- 35% (6/17) of patients experienced ≥50% reduction in symptoms
- Baseline median TSS: 12 (range, 0–30)
- Week 24 median TSS: 7 (range, 0–23)

Data cut: November 18, 2019.
N = number of patients with non-missing percentage change in TSS from baseline at week 24 (missing baseline TSS: N=5; missing week 24 TSS: N=7; baseline TSS=0: N=1)
Baseline is defined as the average value of the observation collected on or prior to the date of the first dose of any component of study treatment.
MF-SAF, Myelofibrosis Symptom Assessment Form; TSS, Total Symptom Score.

Imetelstat for Patients With MF

- **Imetelstat:** 13-mer oligonucleotide that competitively inhibits telomerase (IC_{50}: 0.5-10 nM)
- IMbark/MYF2001: randomized phase II trial of imetelstat 4.7 mg/kg Q3W (n = 48) or imetelstat 9.4 mg/kg Q3W (n = 59)* for patients with relapsed/JAKi-refractory MF



- Median follow-up: 27.4 mos
- Median OS
  - 4.7 mg/kg: 19.9 mos (95% CI: 17.1-NE)
  - **9.4 mg/kg: 29.9 mos** (95% CI: 22.8-NE)
- In 9.4-mg/kg arm at Wk 24, 10% had SVR ≥ 35%; 32% had ≥ 50% symptom response

*After interim analysis, 4.7 mg/kg arm recruitment closed and dose escalation permitted.

Mascarenhas. ASH 2018. Abstr 685.

Polycythemia Vera and Essential Thrombocythemia in Focus

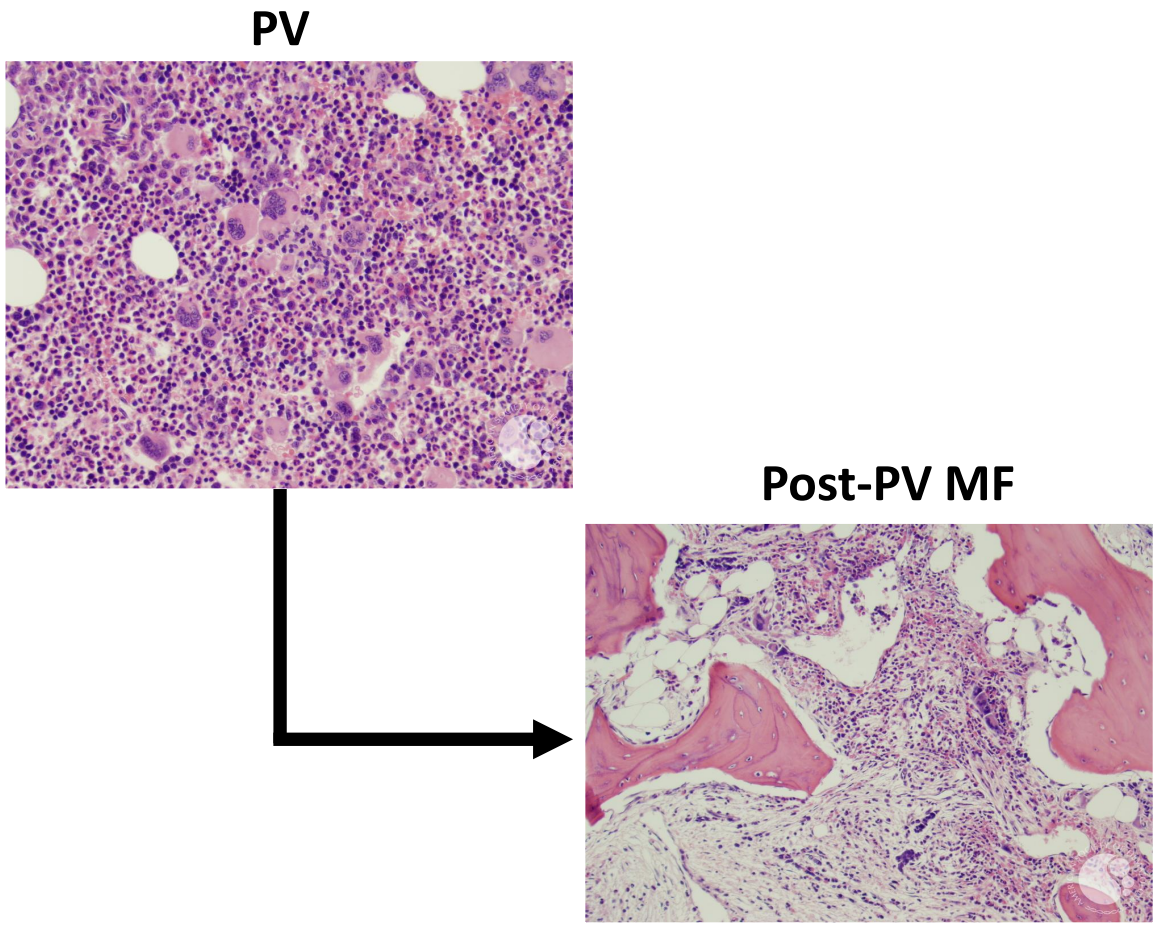
Evolution of WHO PV Diagnostic Criteria

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

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

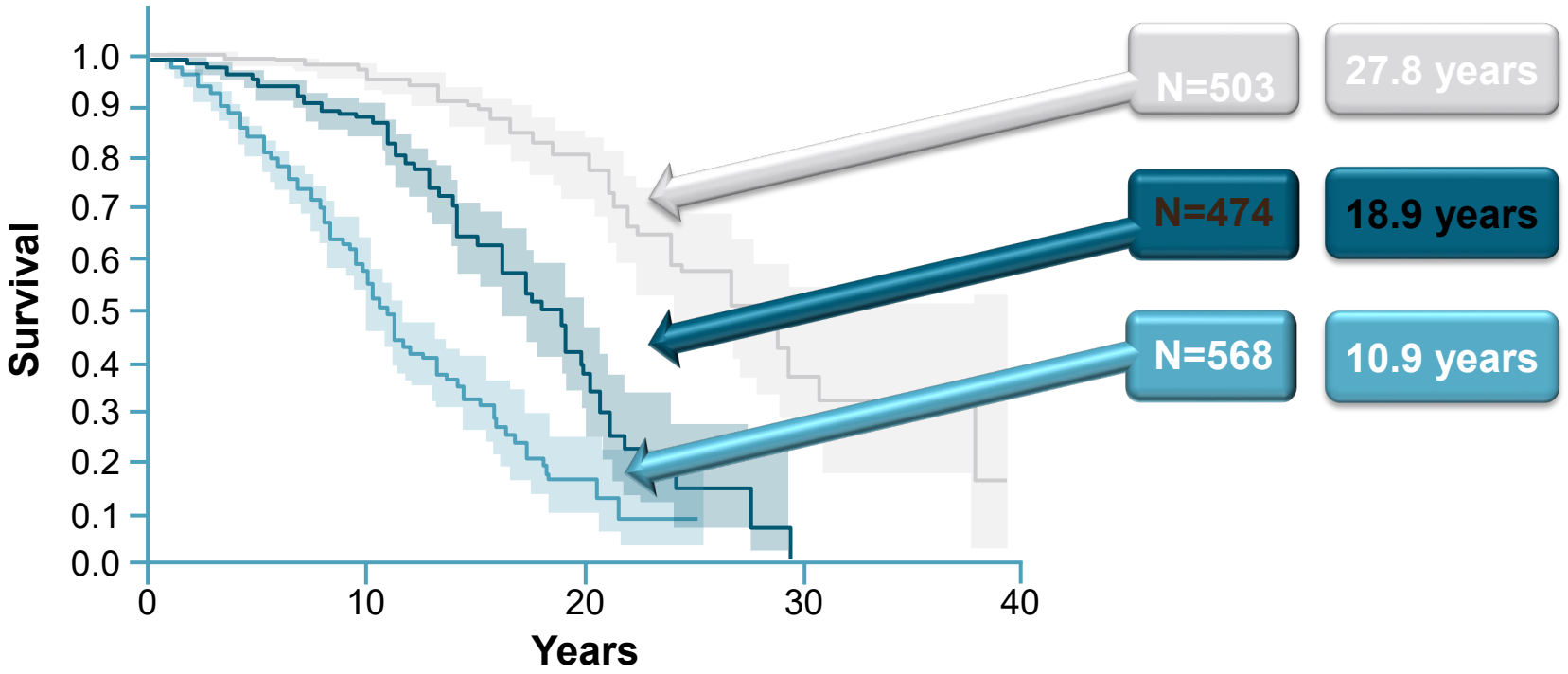
Bone Marrow Testing in PV Diagnosis

- **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.
These images were originally published in ASH Image Bank. Elizabeth L. Courville, MD. Polycythemia vera (PV), polycythemic phase, core biopsy 2; Post-polycythemic myelofibrosis, bone marrow core 1. ASH Image Bank. 2019; #00060162; #00060155. © the American Society of Hematology.

Prediction of Survival in 1545 WHO-based PV



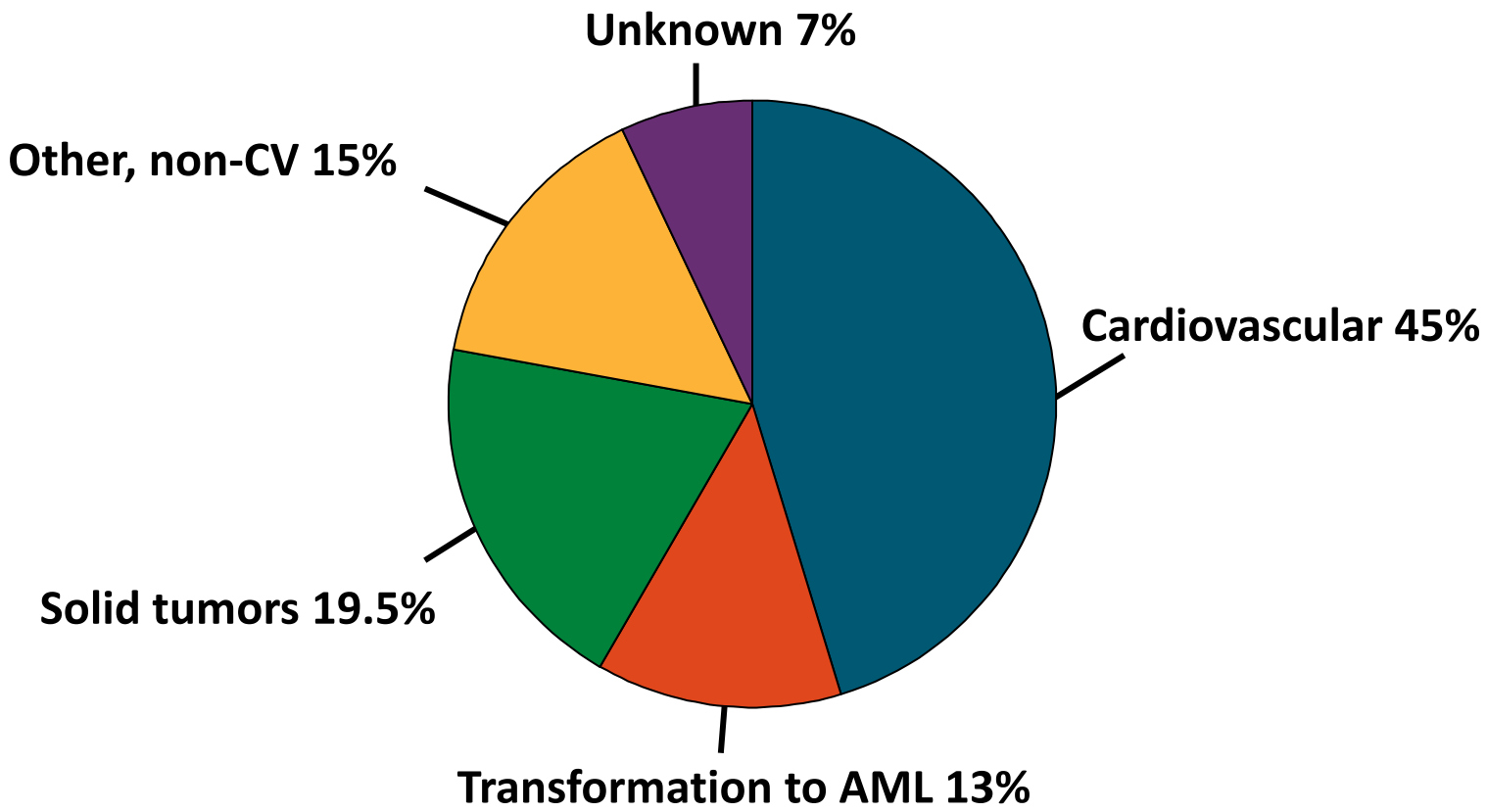
Risk factors	
Age > 67 years	5 points
Age 57-66	2 points
WBC > 15 x10^9/L	1 point
Venous thrombosis	1

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

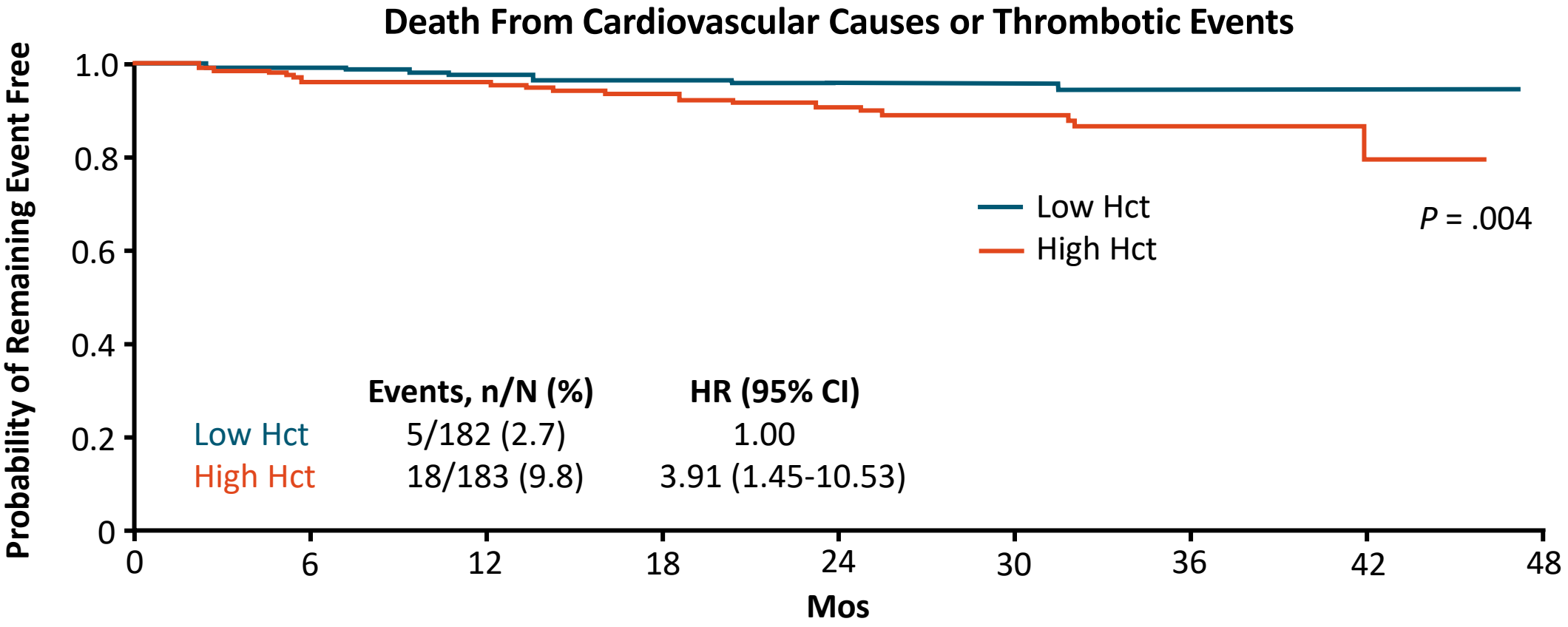
<table>
<tr><th>Category</th><th>Characteristics</th><th colspan="2">Treatment</th></tr>
<tr><td>Low risk</td><td>Age ≤ 60 yrs AND no history of thrombosis</td><td colspan="2">▪ Therapeutic phlebotomy (goal Hct < 45%) in PV
▪ Aspirin 81 mg/day for ET/PV*
▪ Address CV modifiable risk factors for ET/PV</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>▪ 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.

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

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

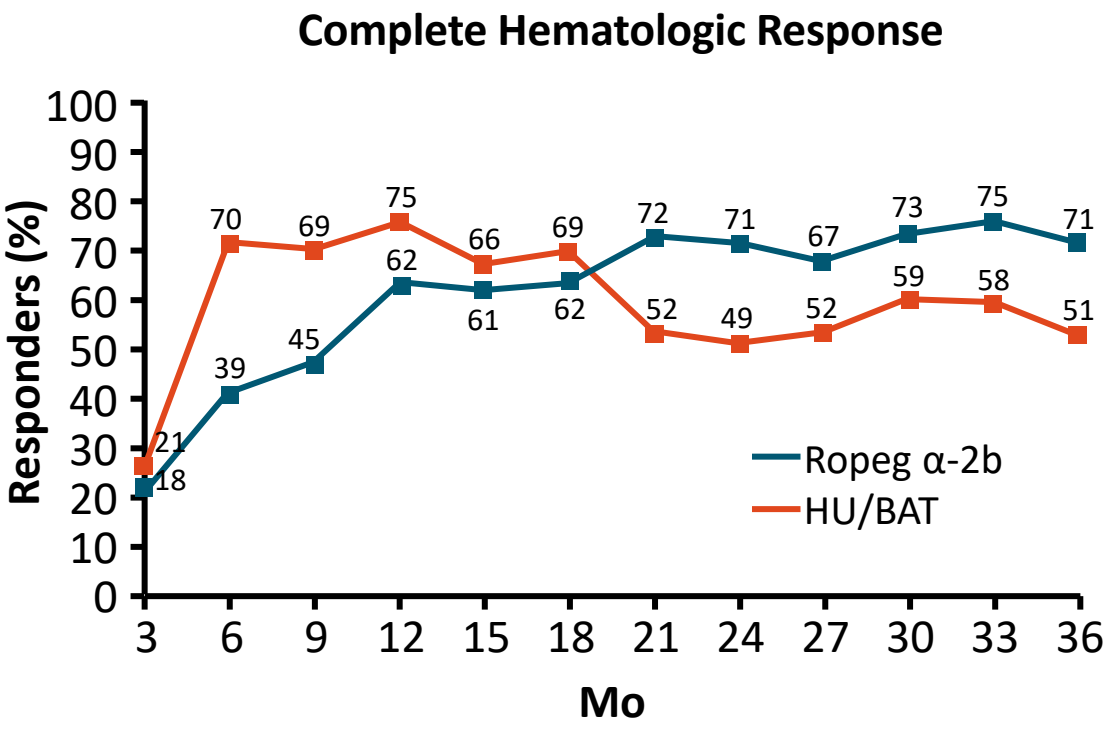
- Randomized, open-label phase III trial in which PV patients were treated to a lower (< 45%) or higher (45% to 50%) Hct target with ASA + phlebotomy ± cytoreductives (N = 365)



Marchioli. NEJM. 2013;368:22.

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.

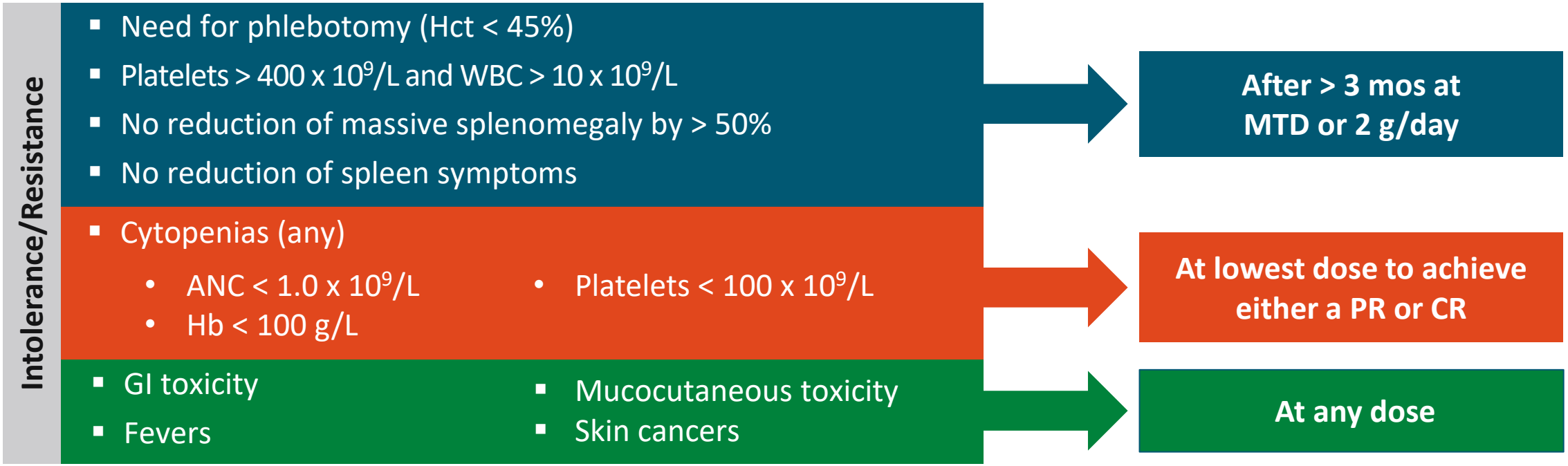
Gisslinger. ASH 2018. Abstr 579.

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 modest ▪ 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

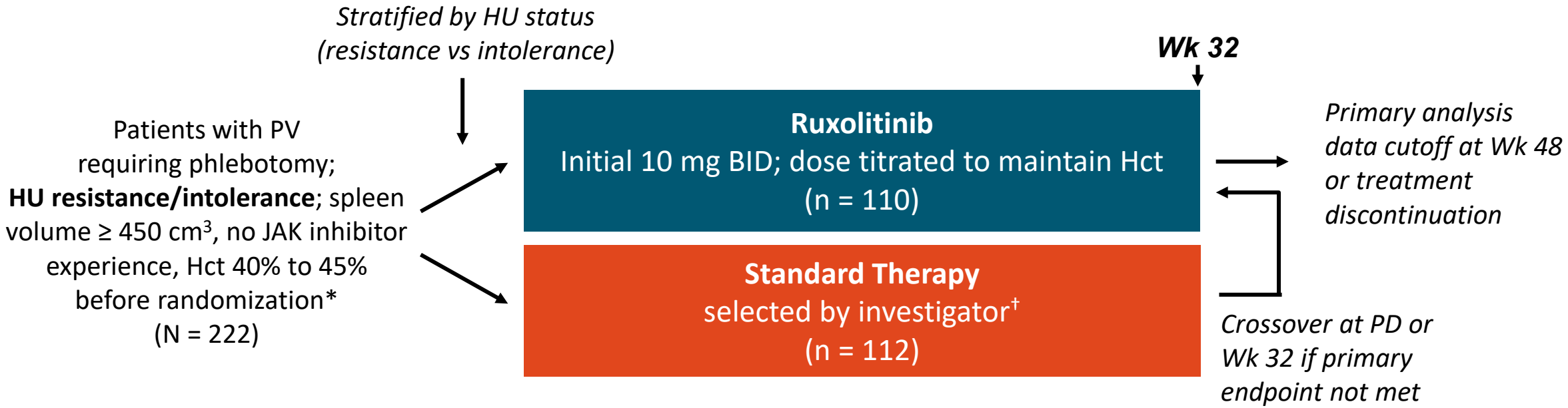


- Prevalence of HU resistance/intolerance: up to 25%
- Among individual criteria, development of cytopenia at the lowest required HU dose associated with increased risk of MF/AML progression and death
- Uncontrolled PV symptoms can be a trigger to re-evaluate therapeutic strategy

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

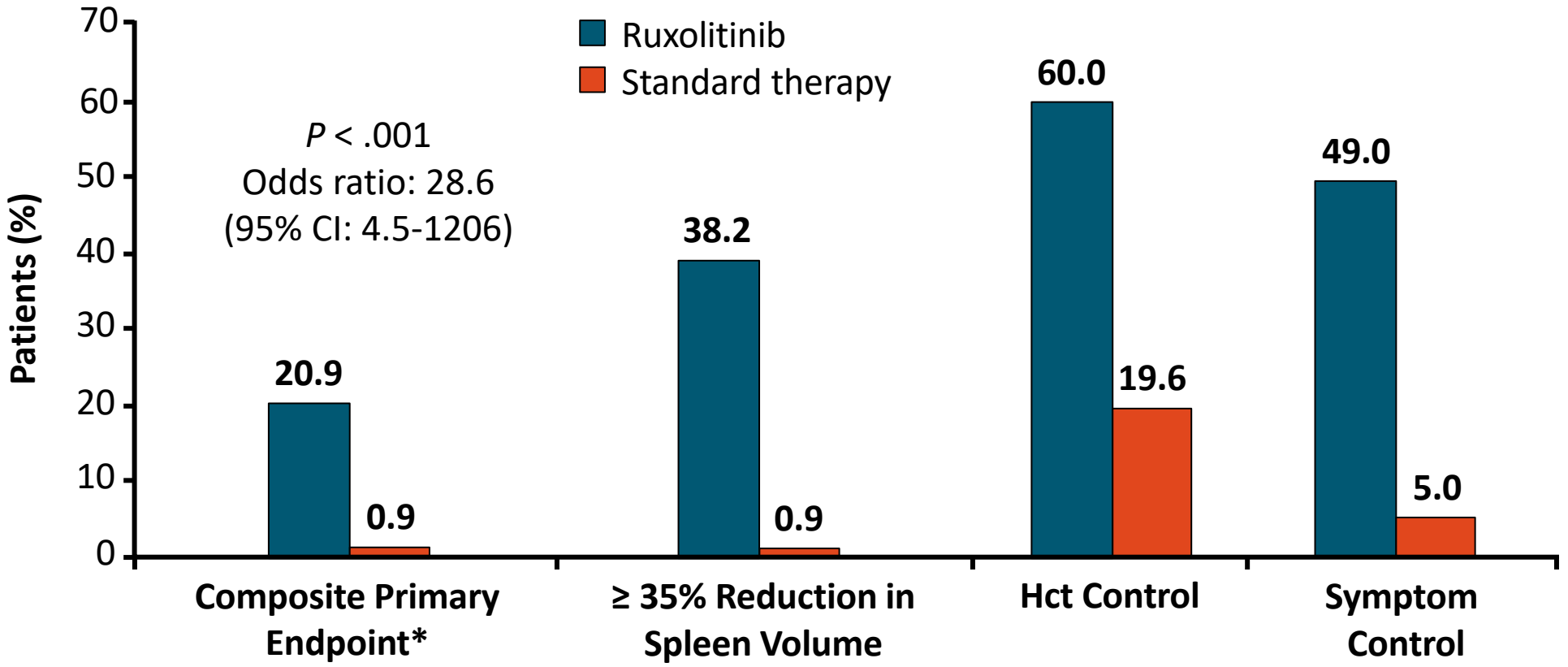
- International, multicenter, randomized, open-label phase III study
  - **Ruxolitinib:** JAK 1 and 2 inhibitor



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

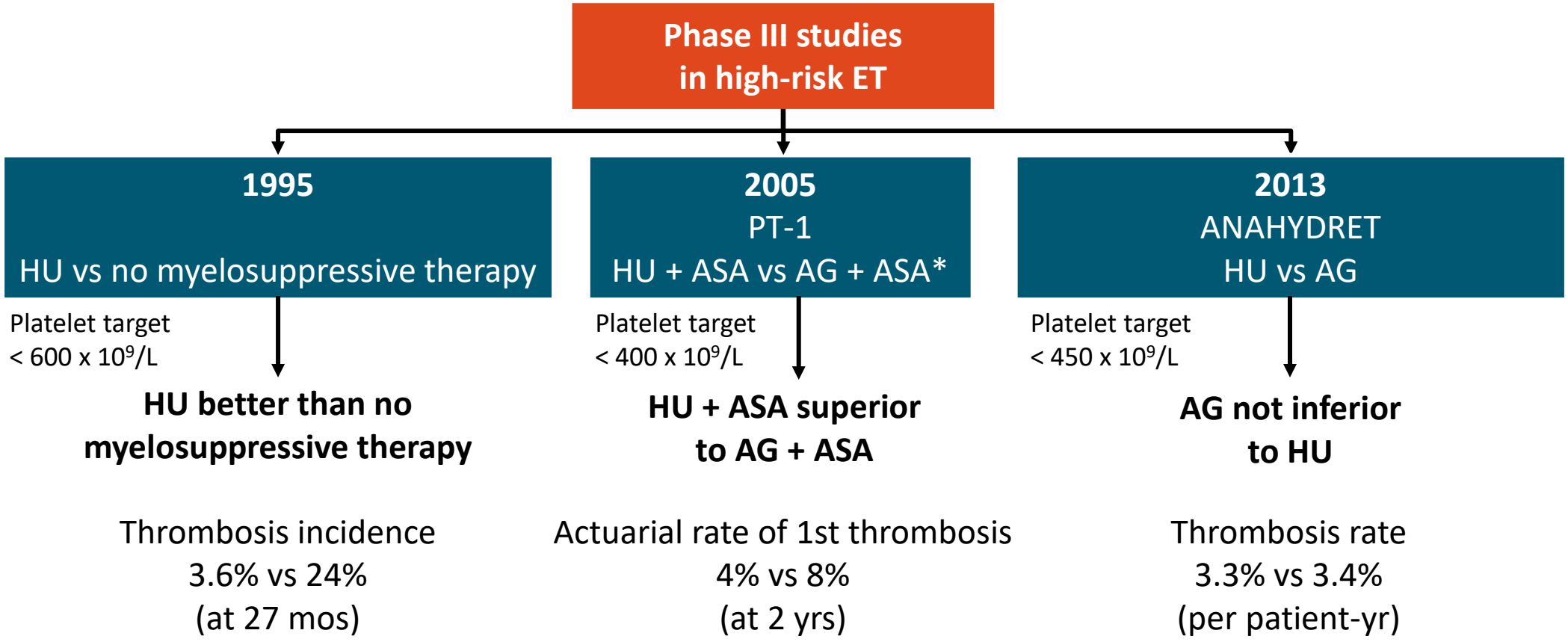
- Multicenter, randomized, open-label phase IIIb study in which patients with HU-resistant/intolerant PV who required phlebotomy and had **no splenomegaly** were treated with **ruxolitinib** or **best available therapy** (N = 149)

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.

Passamonti. Lancet Oncol. 2017;18:88.

Prospective Randomized Clinical Trials in ET

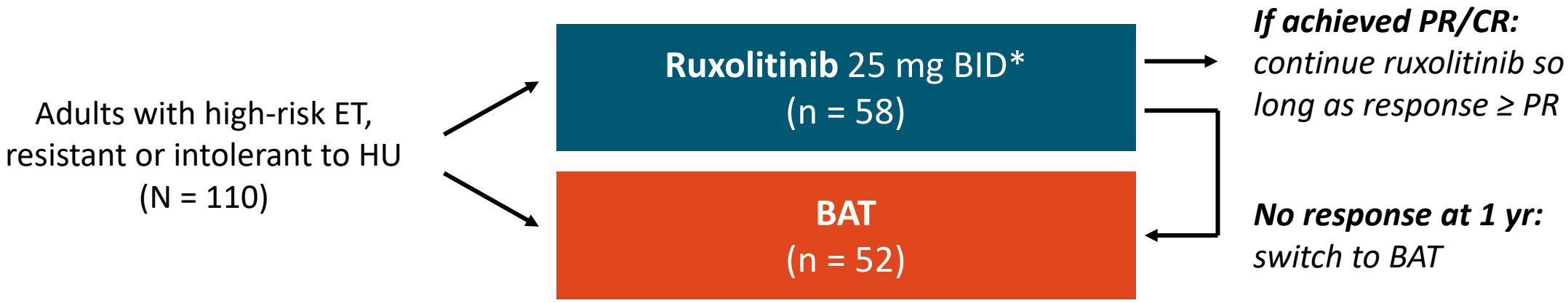


*Composite primary endpoint: arterial or venous thrombosis, serious hemorrhage, or death from vascular causes.

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



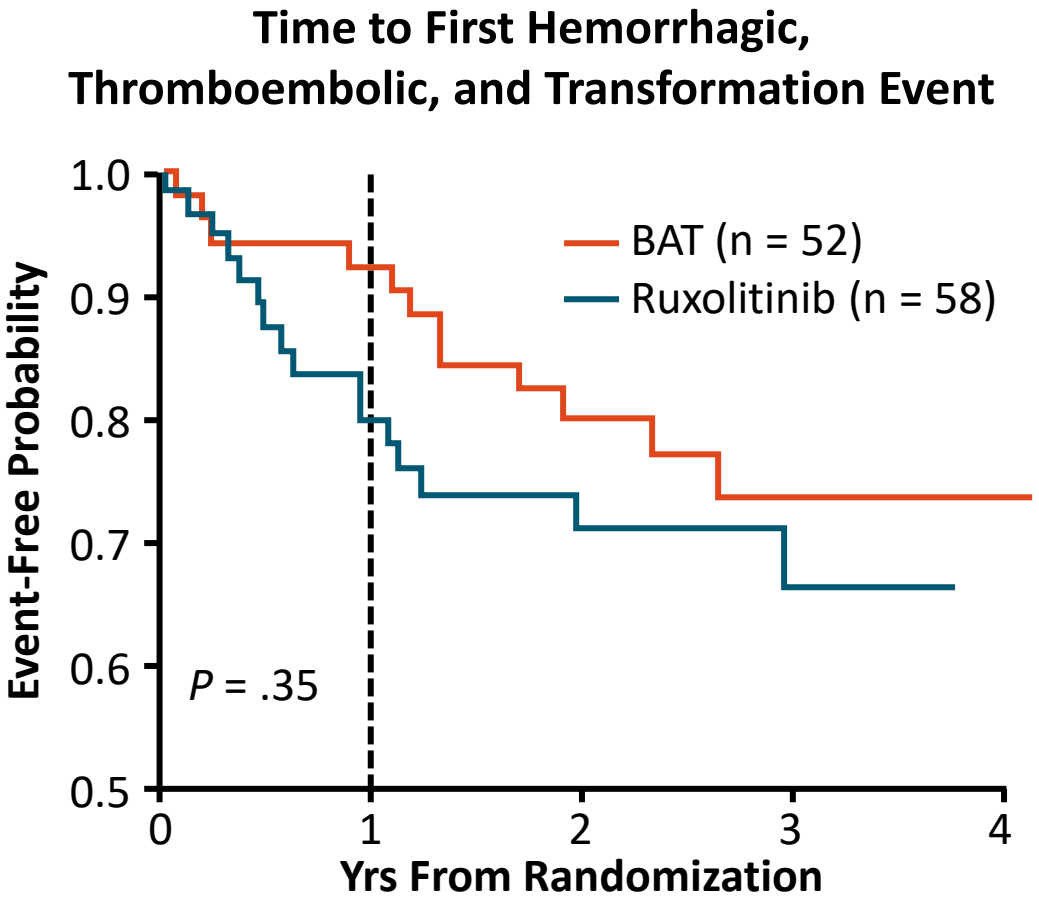
*If platelets 100-200 x 10^9/L, ruxolitinib dosed at 20 mg BID.

- 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.

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