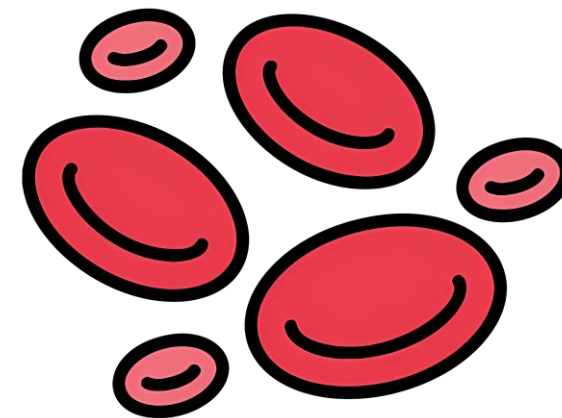




Risk-adapted treatment for Polycythemia Vera

Sunisa Kongkiatkamon, MD

Division of Hematology, Department of Medicine
Faculty of Medicine, Chulalongkorn University





Disclosure

- No conflict of interest to disclose



Outline

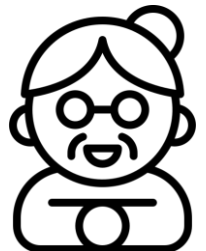
- Overview
- Risk assessment in PV
- Management of polycythemia vera



Ph-negative MPNs

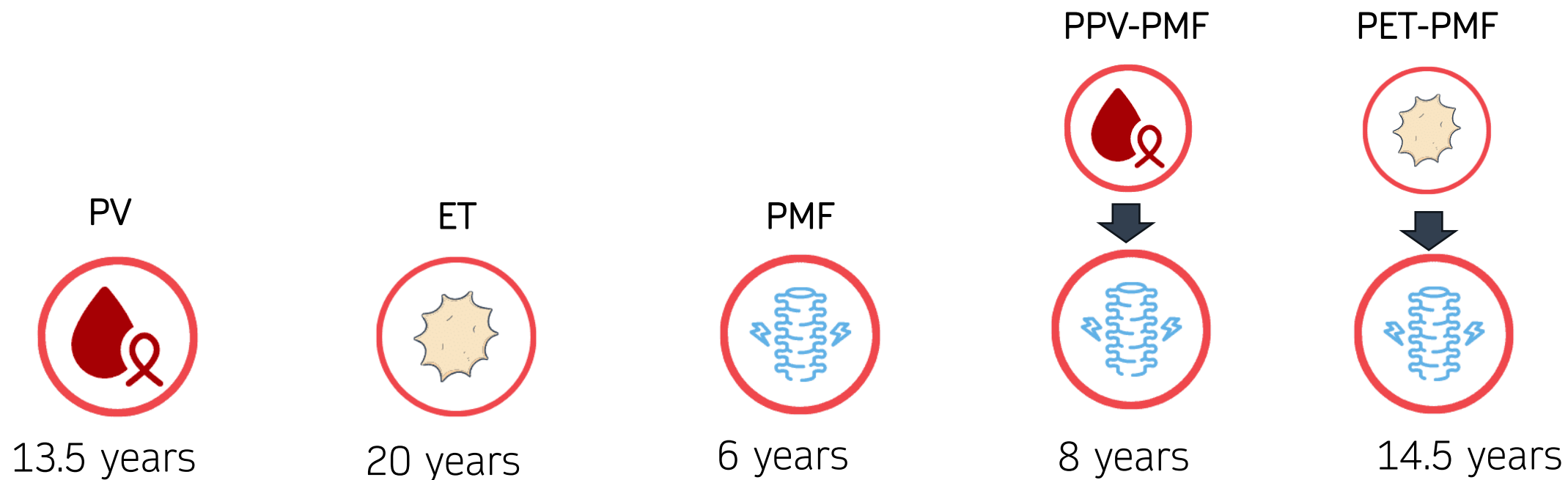


- *BCR::ABL1*-negative myeloproliferative neoplasms (MPNs) are recognized as chronic hematologic malignancies.
- These diseases are caused by the proliferation of mature myeloid cells owing to a constitutive activation of the JAK-STAT pathway.
- Risk assessment is quite challenging because of the long natural history of these diseases



Overall survival of different MPN subtypes

- Overall survival and disease complications varies according to the MPN subtype





Disease complications in PV

Reference	No of patients	All thrombosis (%)	At diagnosis		During F/U		Bleeding	MF transformation	Leukemic transformation
			Arterial	venous	arterial	Venous			
Marchioli et al	1638	38.6	28.7	13.7	2.5	2.4	NS	0.85	0.52
Tefferi et al	1545	23	68	32	1.5	1.1	NS	1.09	0.57
Pasquer et al	364	28	8.8	18.9	0.7	0.8	0.4	1.45	0.43
Cherdchoo et al	48	22	12.5	10.4	0.48	0.24	0.36	0.48	0.06

J Clin Oncol. 2005;23(10):2224-2232
Leukemia. 2013;27(9): 1874-1881
Leukemia. 2024;38(2):326-339.
Hematology, 28(1).

Conventional risk score in PV

Low risk

Age < 60 years and
No history of thrombosis

High risk

Age > 60 years *and / or*
history of thrombosis



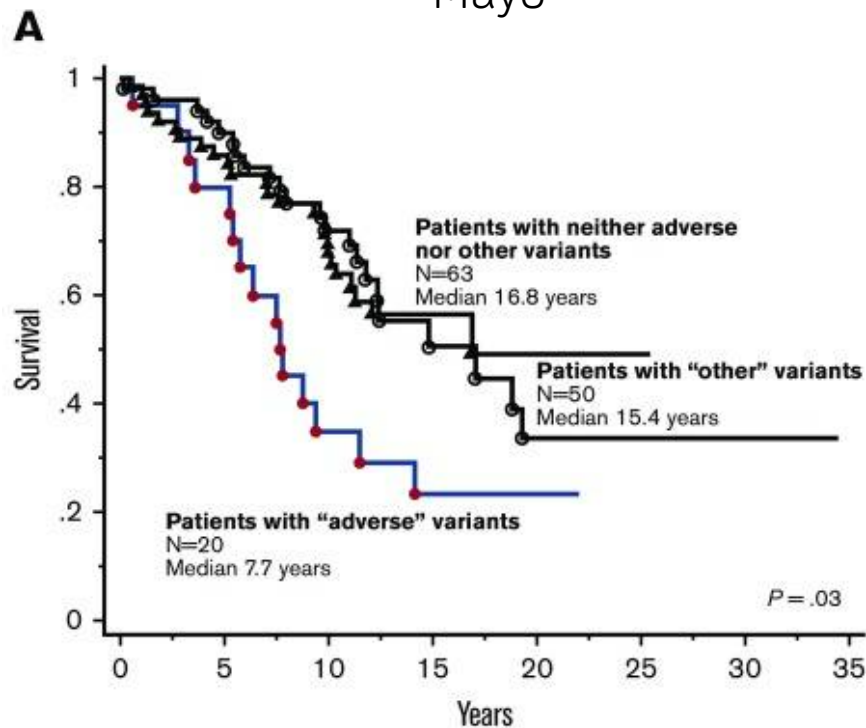
Molecular integrated prognostication in MPN

End-point	Score	ET	PV	PMF	sMF
Thrombosis	Conventional	Thrombosis score	Thrombosis score	-	-
	Molecular	IPSET-r	-	IPSET	
Survival	Conventional			IPSS,DIPSS, DIPSS-plus	
	Molecular	MIPSS-ET	MIPSS-PV	MIPSS70/plus v2.0 GIPSS Oxford	MYSEC-PM

Adverse variants in PV

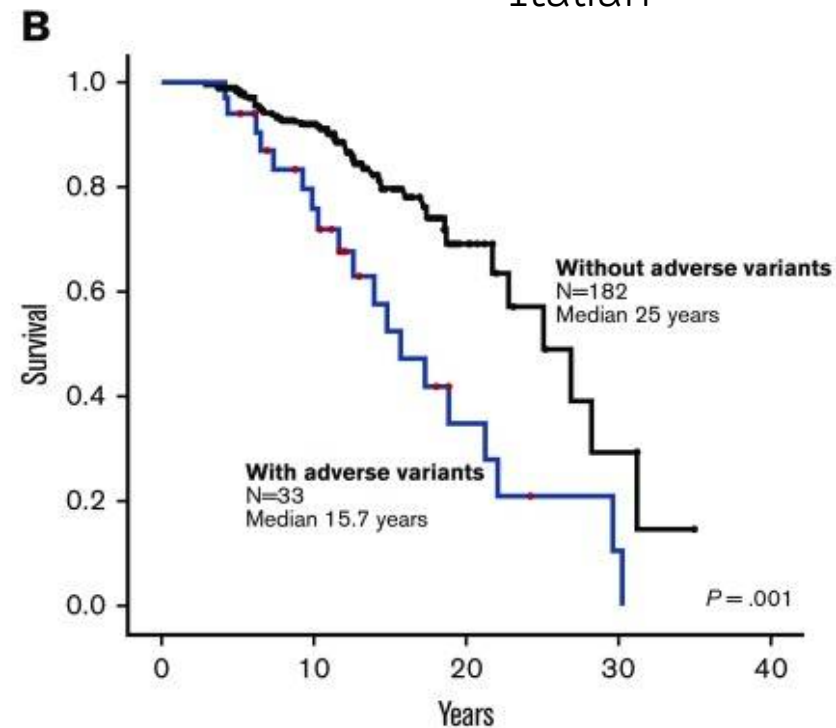
N=133

Training cohort
Mayo



N=215

Validation cohort
Italian



SRSF2
ASXL1
IDH2

MIPSS-PV, a molecular scoring system for (ET) and PV

Mayo



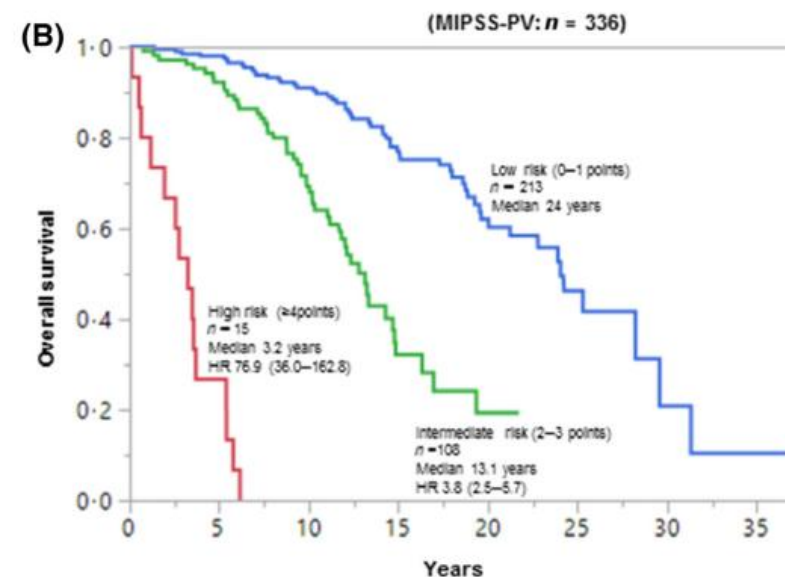
N=146

Italy



N=258

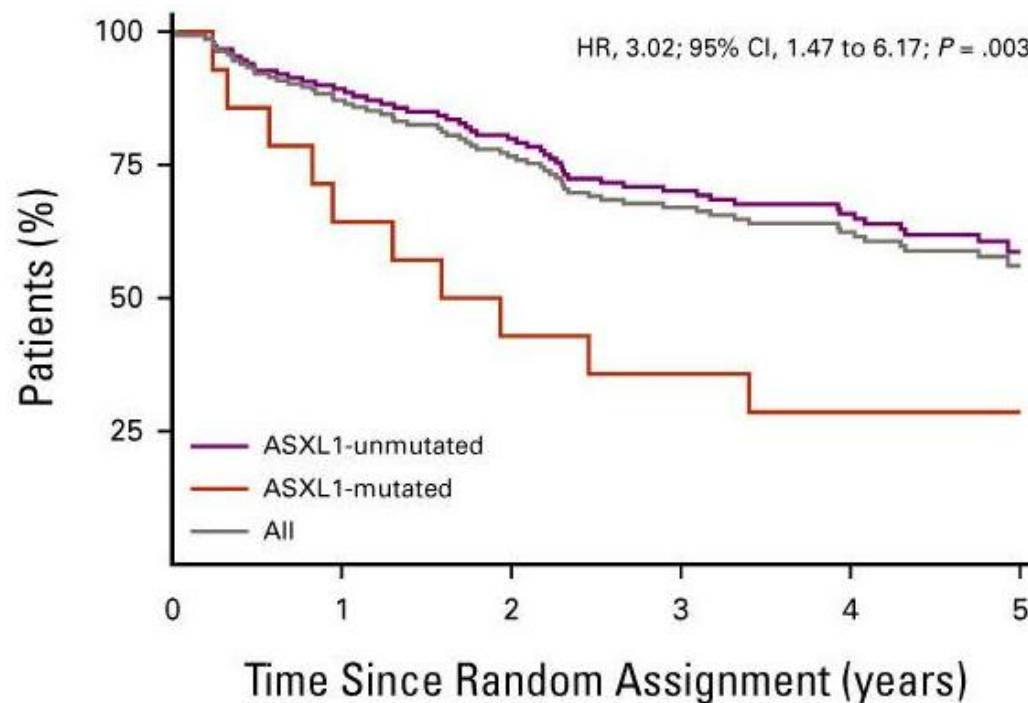
Median F/U 12 yrs



Prognostic Score [Reference]	Clinical Variables (Points)	Molecular Variables (Points)	Risk Categories (Points)	Survival *
MIPSS-PV, Tefferi et al. [95]	Leukocyte count $\geq 15 \times 10^9 / L$ (1); thrombosis history (1); age > 67 years (2)	<i>SRSF2</i> mutation (3)	Low (0-1) Intermediate (2-3) High (4-7)	24 13.1 3.2

EFS stratified according to *ASXL1* mutational status

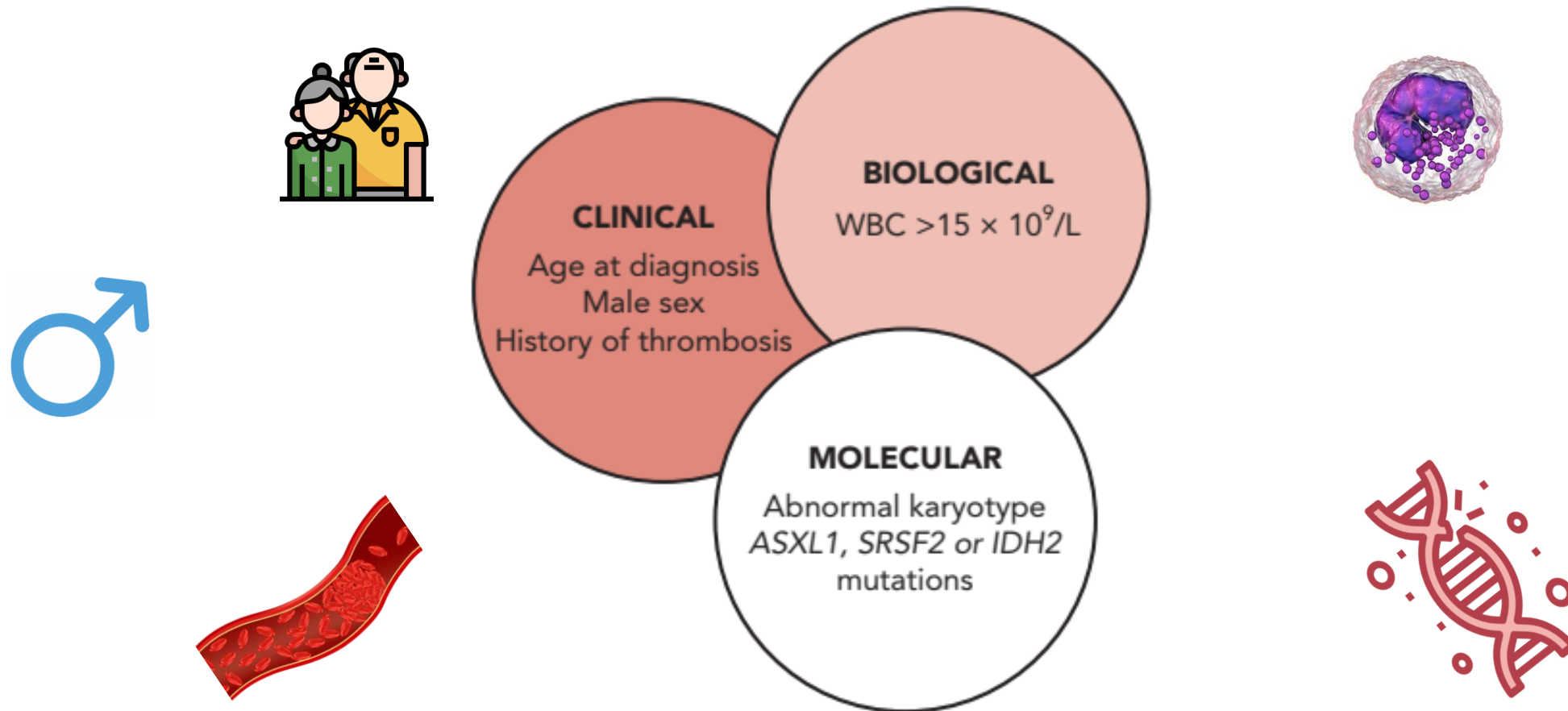
Data from MAJIC-PV study



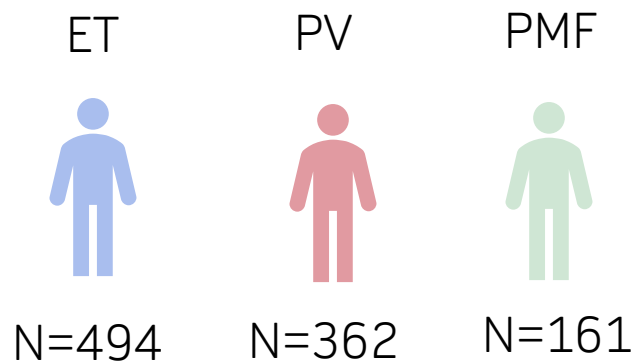
No. at risk:

ASXL1-unmutated	153	128	110	87	72	20
ASXL1-mutated	14	9	6	5	4	2
All	167	137	116	92	76	22

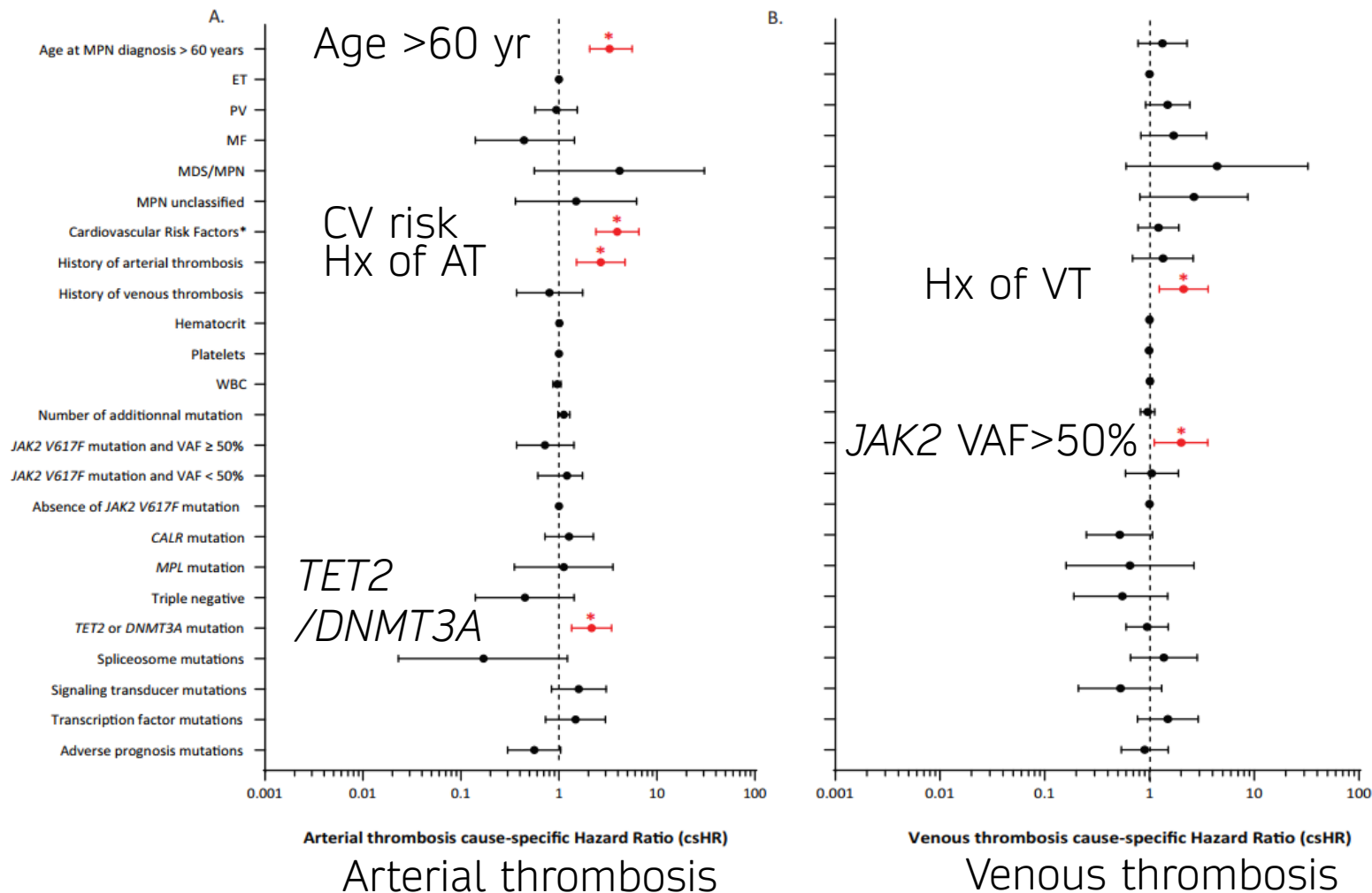
Factor associated with OS in PV



Distinct clinico-molecular arterial and venous thrombosis scores for MPN risk stratification



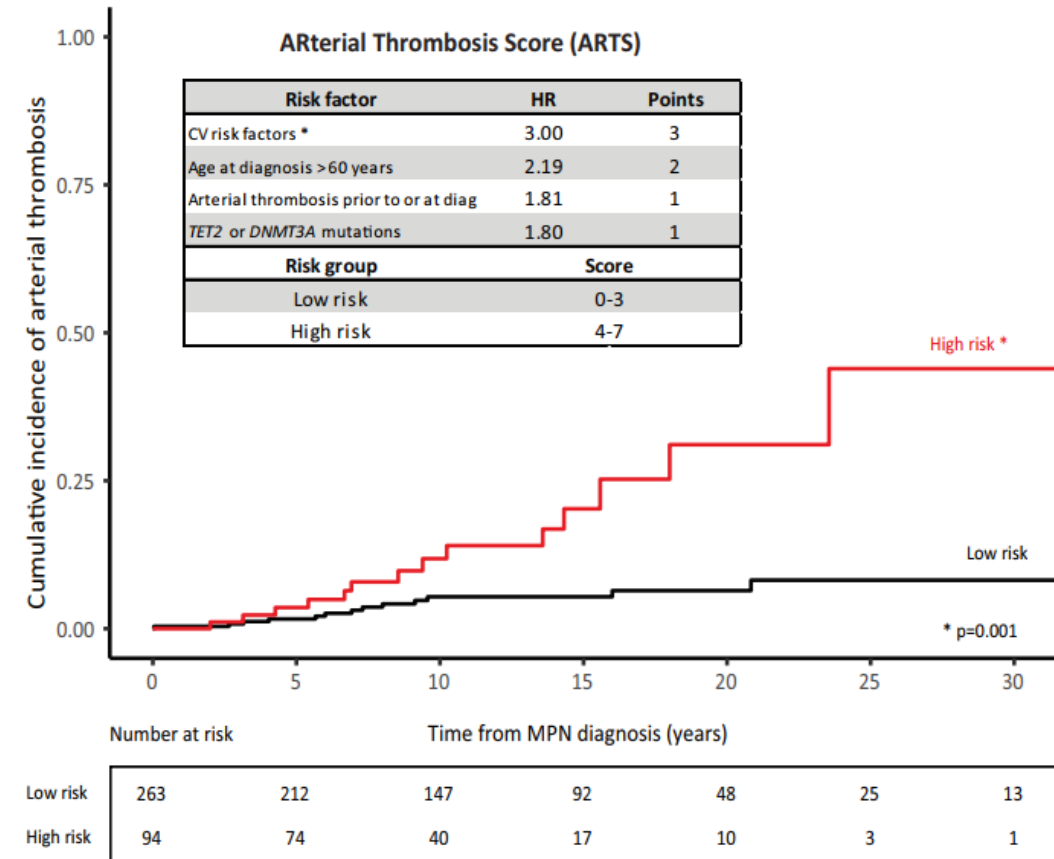
Median F/U 9.45 yrs



Arterial Thrombosis Score

ARterial Thrombosis Score (ARTS)

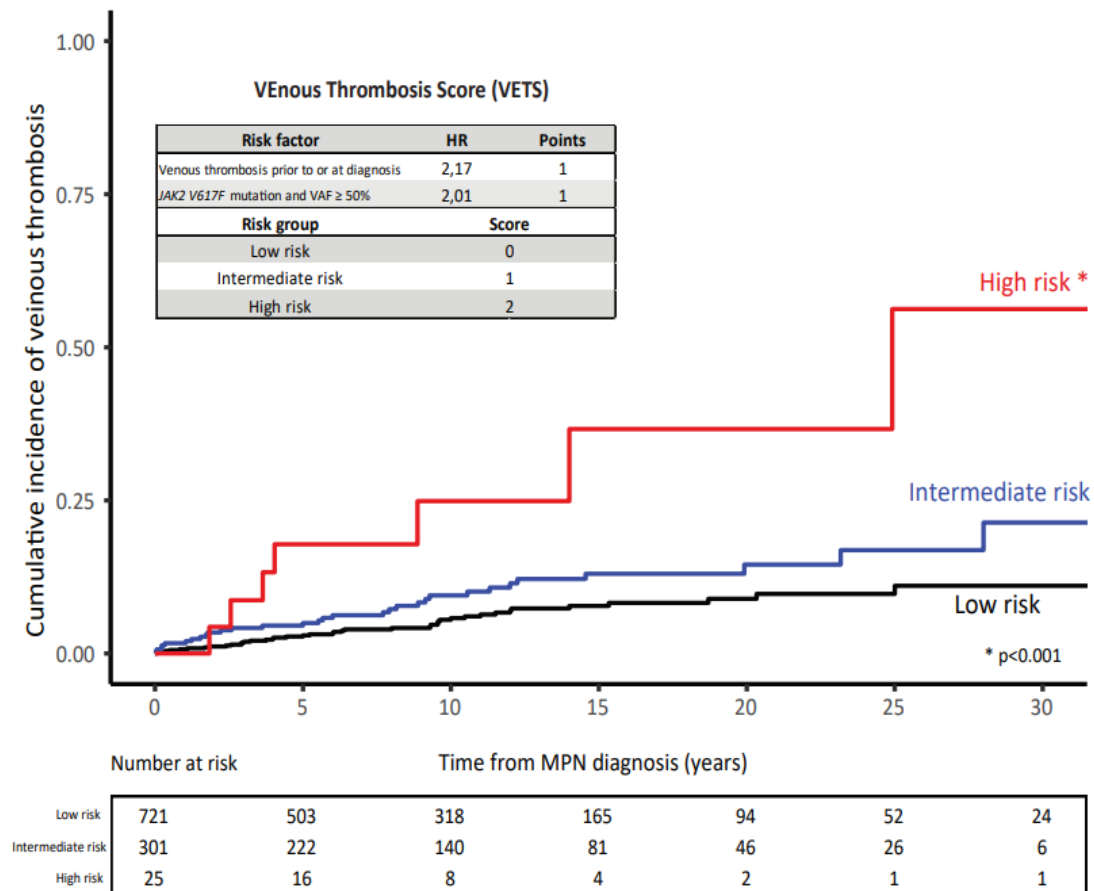
Risk factor	HR	Points
CV risk factors *	3.00	3
Age at diagnosis > 60 years	2.19	2
Arterial thrombosis prior to or at diag	1.81	1
TET2 or DNMT3A mutations	1.80	1
Risk group		Score
Low risk		0-3
High risk		4-7



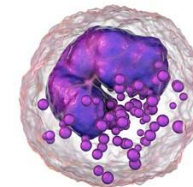
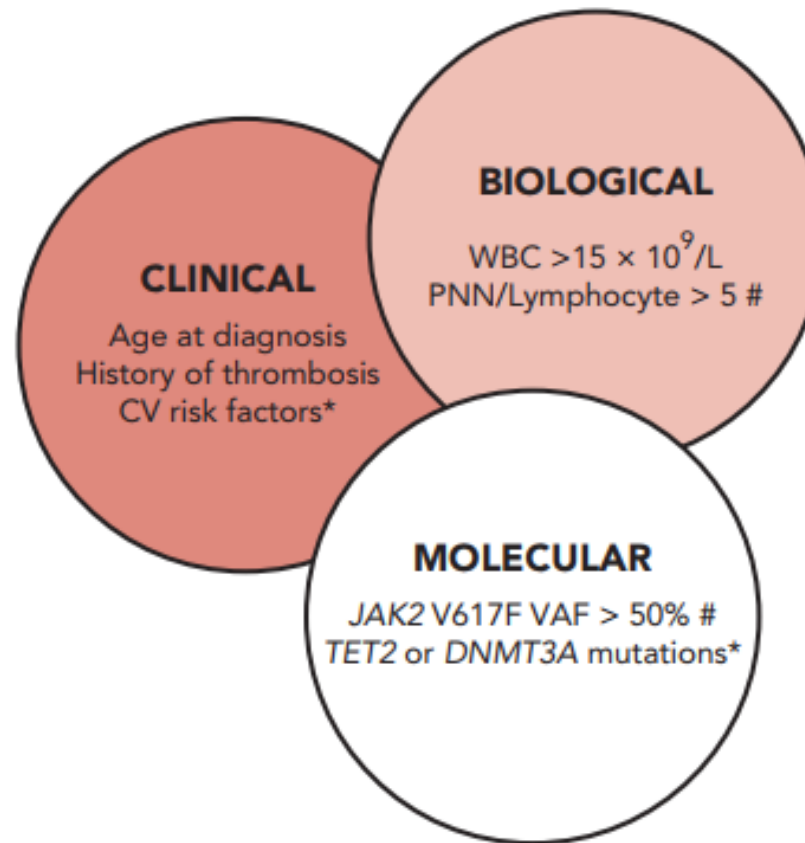
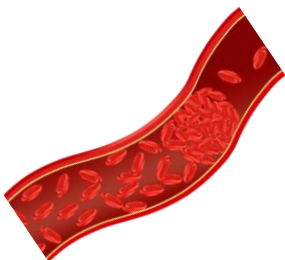
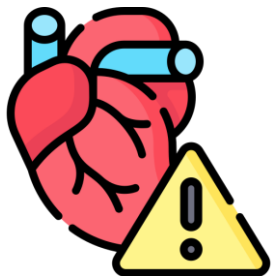
Venous Thrombosis Score

VENous Thrombosis Score (VETS)

Risk factor	HR	Points
Venous thrombosis prior to or at diagnosis	2,17	1
JAK2 V617F mutation and VAF $\geq$ 50%	2,01	1
Risk group		Score
Low risk		0
Intermediate risk		1
High risk		2

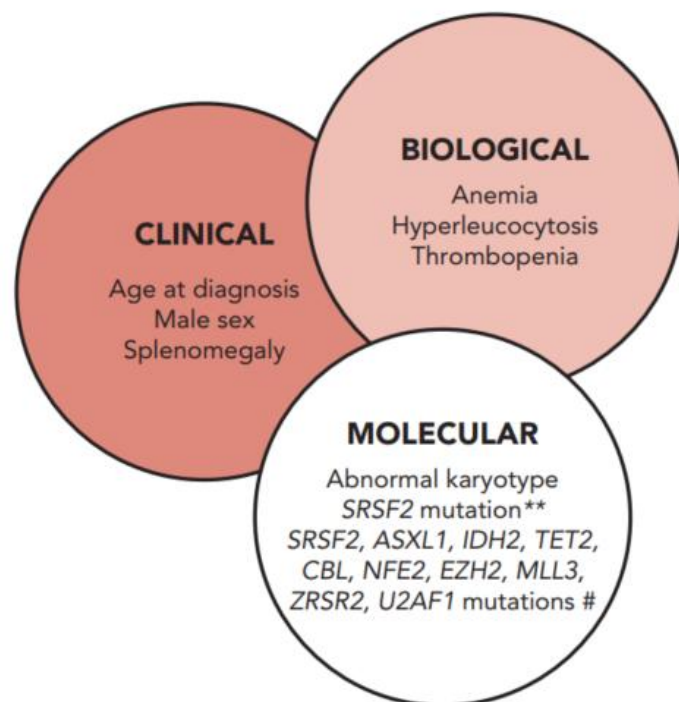


Factor associated with thrombosis in PV

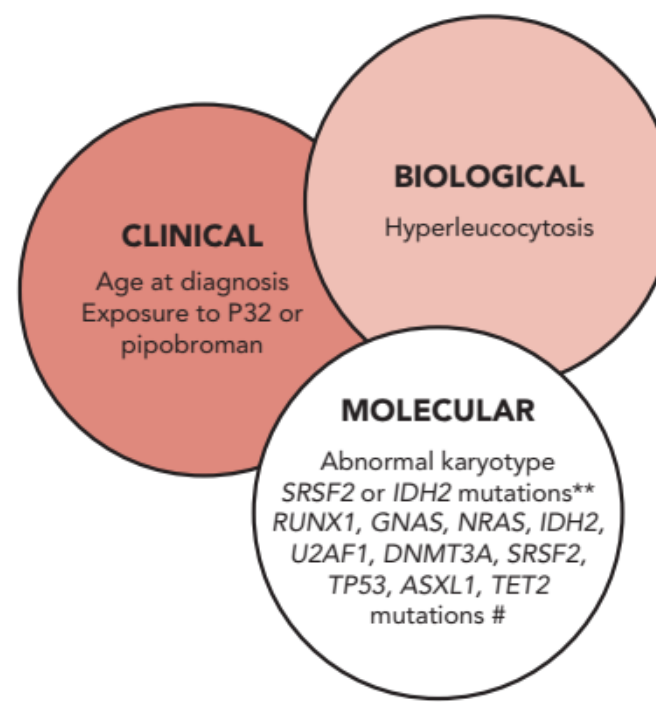


*Indicates risk factors associated with arterial thrombosis.
#Indicates risk factors associated with venous thrombosis.

MF transformation



Leukemia transformation

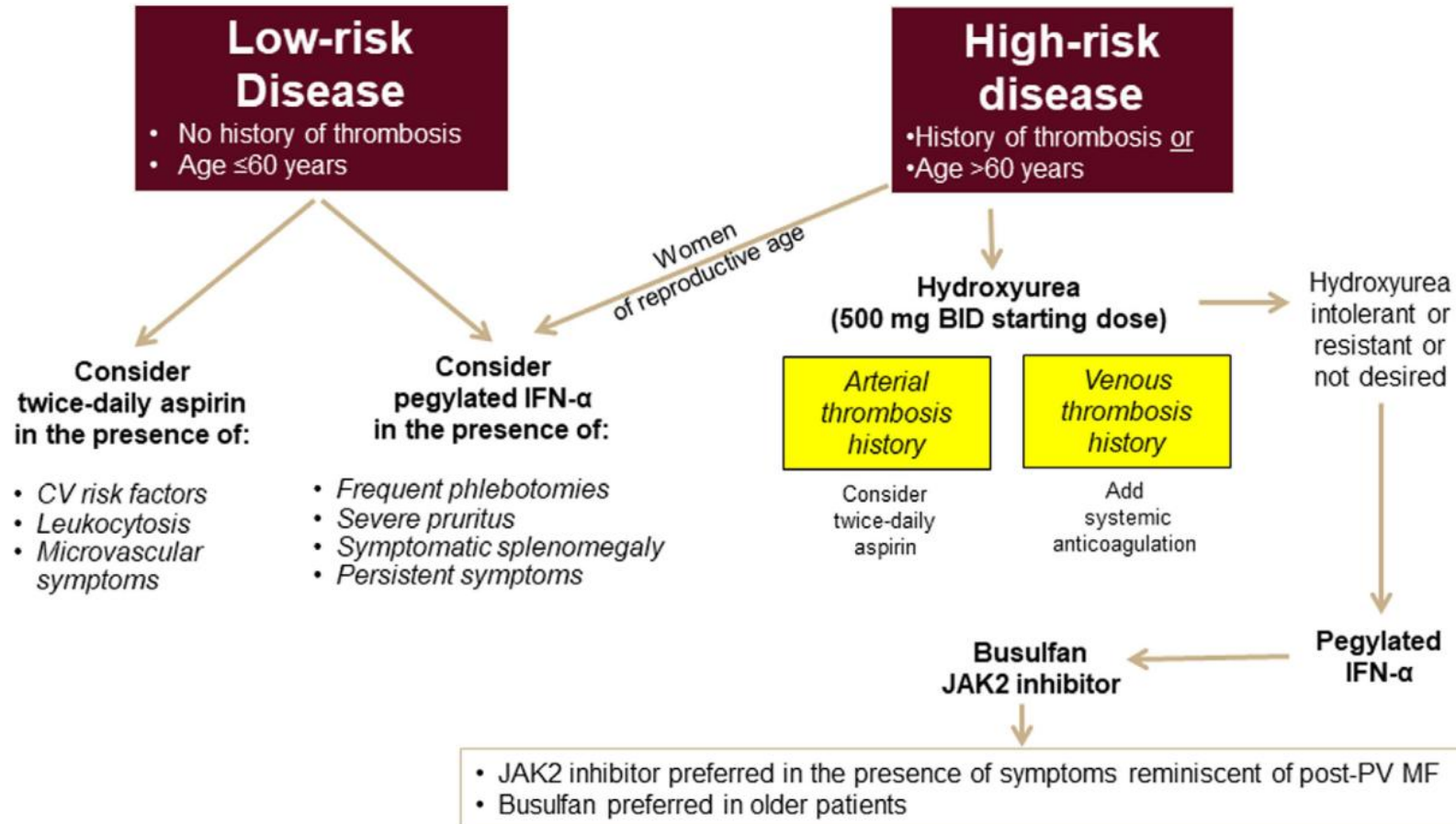




Risk adapted therapy in PV

Current Treatment Approach in Polycythemia Vera

Periodic phlebotomy to keep hematocrit <45% in all patients
+
Once-daily low-dose aspirin (40–100 mg) in all patients



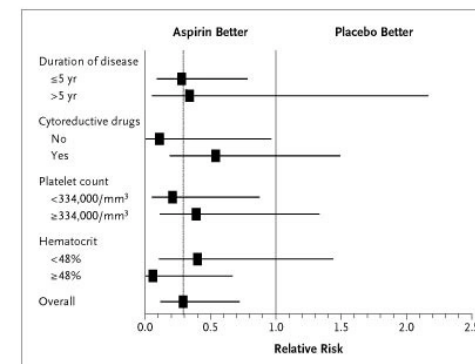
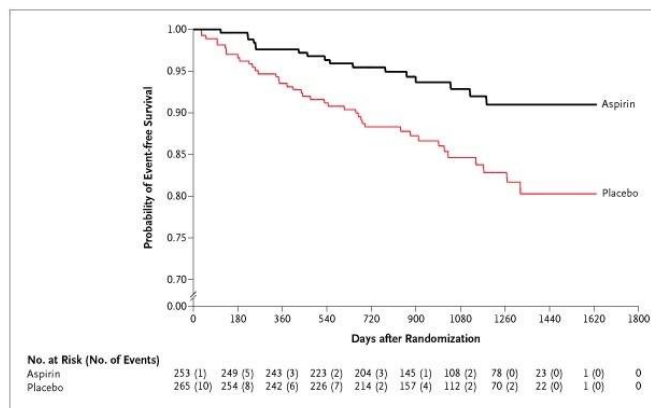
Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

N= 518
PV patients

ASA
100 mg/day

cumulative rate of
nonfatal myocardial
infarction, nonfatal stroke,
or death from
cardiovascular causes

Placebo

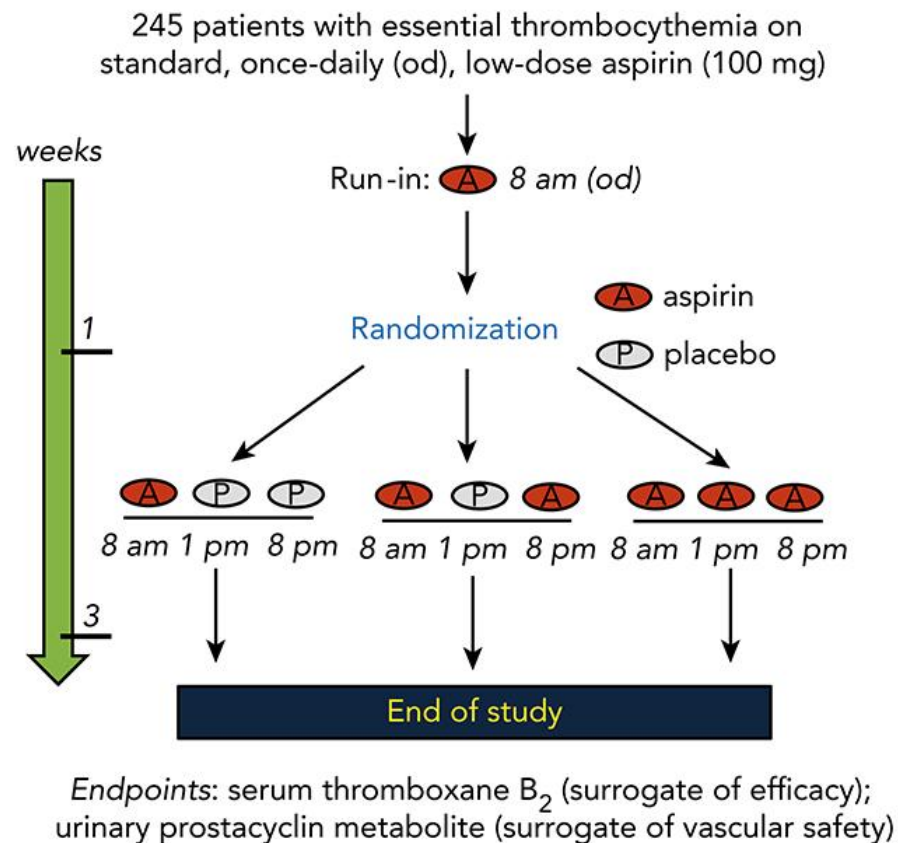


age ≥ 70 = 26%
Previous thrombosis ~ 10%
Cardiovascular risk factors 35%

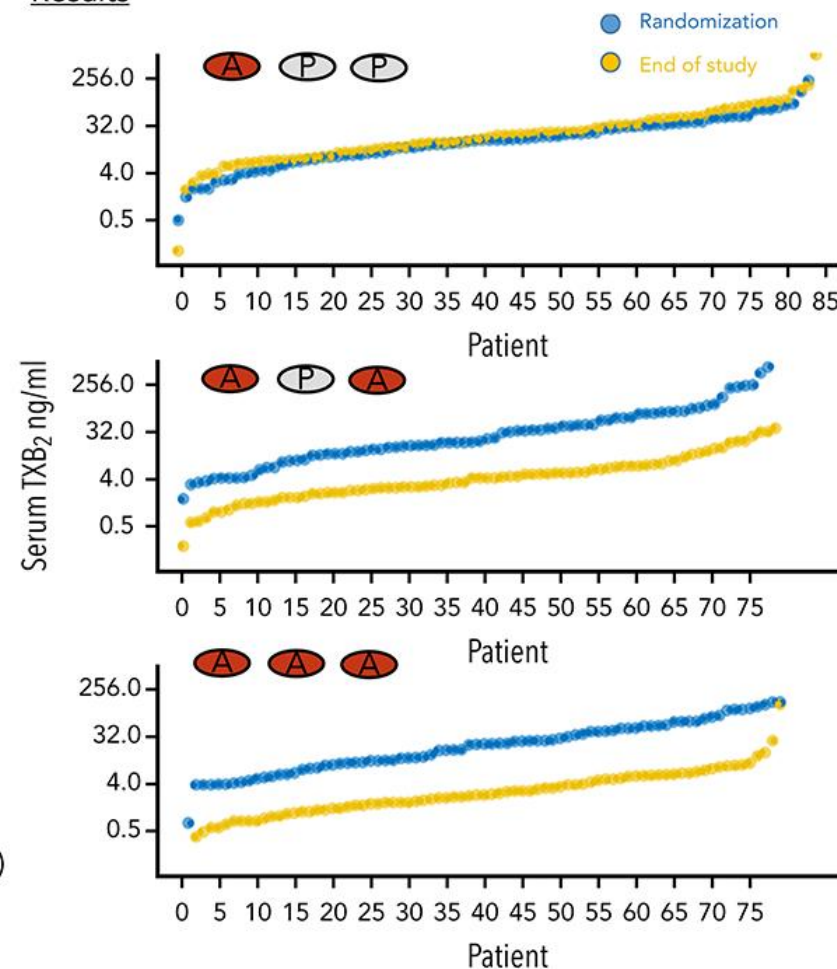
End Point	Aspirin Group (N=253) no. (%)	Placebo Group (N=265) no. (%)	Relative Risk (95% CI)	P Value
Primary end points				
Nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes	5 (2.0)	13 (4.9)	0.41 (0.15–1.15)	0.09
Nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes	8 (3.2)	21 (7.9)	0.40 (0.18–0.91)	0.03

A RCT of 3 aspirin regimens to optimize antiplatelet therapy in ET

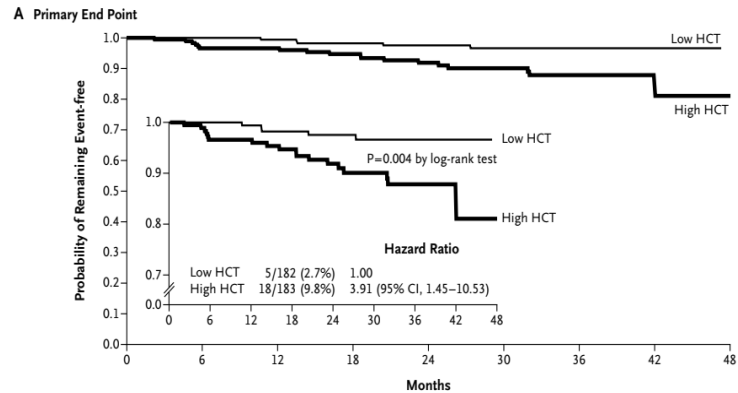
Design



Results

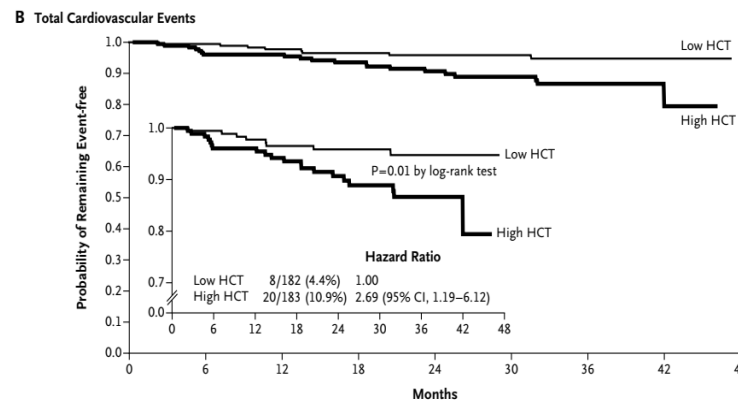


Optimal Hct control to reduce major thrombotic events (CYTO-PV)



Low Hct (Hct <45%)
Median Hct =44.4%

No. at Risk	0	6	12	18	24	30	36	42	48
Low HCT	182 (0)	177 (1)	168 (2)	154 (1)	129 (1)	95 (0)	62 (0)	18 (0)	0
High HCT	183 (6)	168 (0)	160 (3)	143 (4)	110 (2)	92 (2)	54 (1)	12 (0)	1



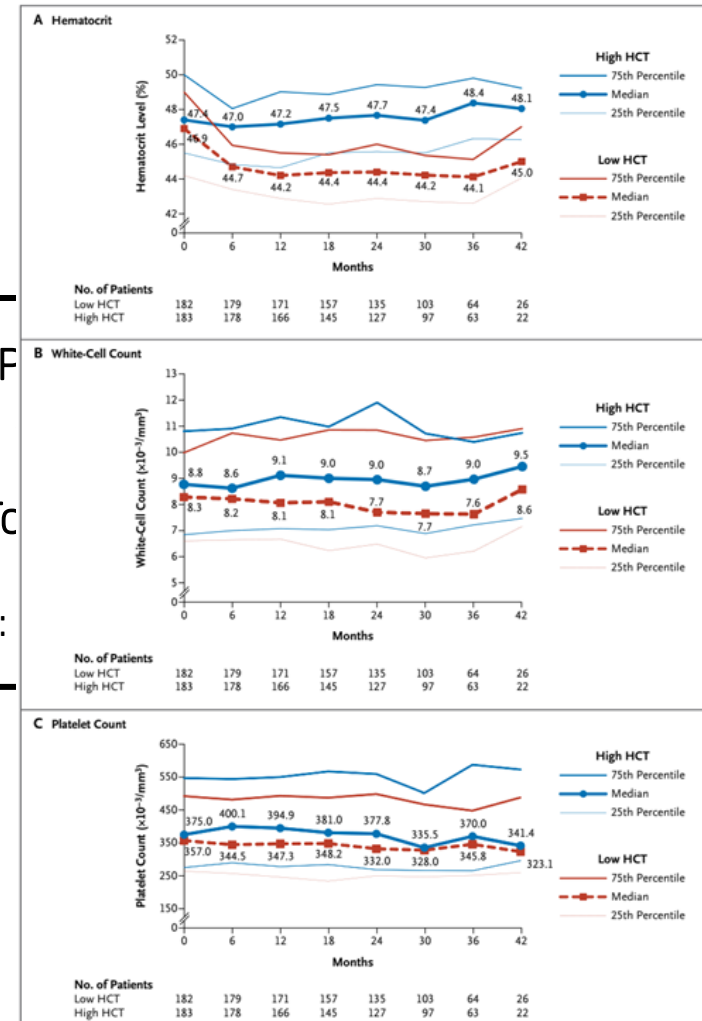
High Hct (Hct ≥45%)
Median Hct =47.5%

No. at Risk	0	6	12	18	24	30	36	42	48
Low HCT	182 (1)	176 (3)	165 (2)	151 (1)	127 (0)	94 (1)	60 (0)	18 (0)	0
High HCT	183 (7)	167 (0)	159 (4)	141 (4)	108 (2)	91 (2)	53 (1)	11 (0)	0

HR:

Tc

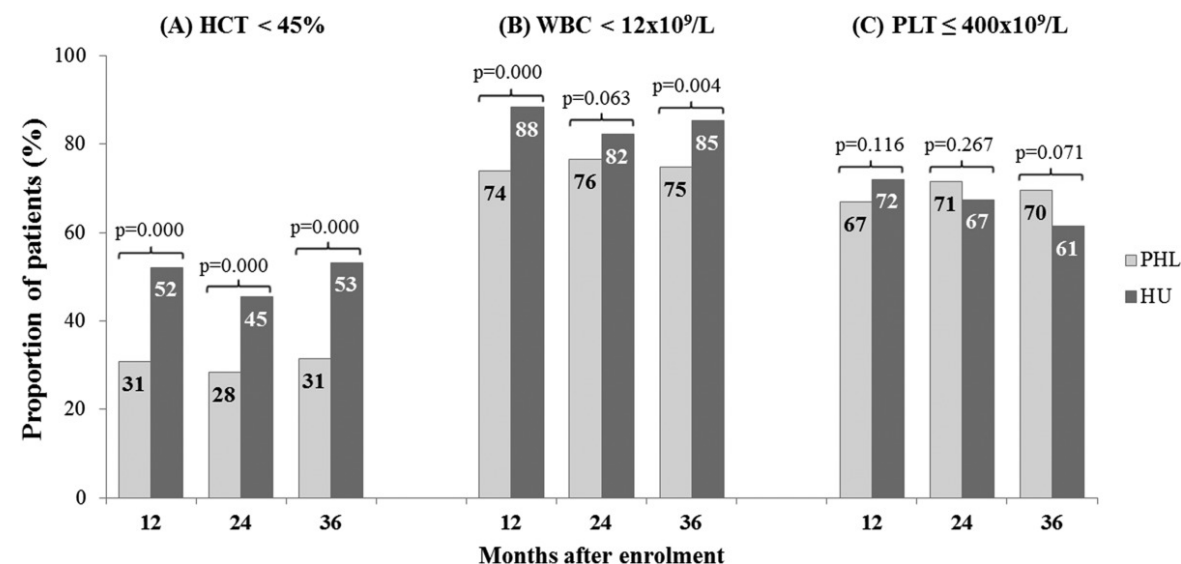
HR:



The benefit of HU in polycythemia vera

Data from ECLAP study

1:2 random-sample matched cohort (n = 1,023)			
	PHL (n = 342)	HU (n = 681)	P
Median total follow-up (IQR), months	29.9 (15.1, 41.0)	34.7 (24.1, 45.3)	0.001
Median treatment duration (IQR), months	25.8 (12.7, 37.3)	24.0 (12.0, 36.0)	0.696
1. CV events (fatal/non-fatal)	45 (13.2%)	54 (7.9%)	0.006
2. Hematologic transformation	9 (2.6%)	1 (0.2%)	0.006
3. Overall death	31 (9.1%)	24 (3.5%)	0.000



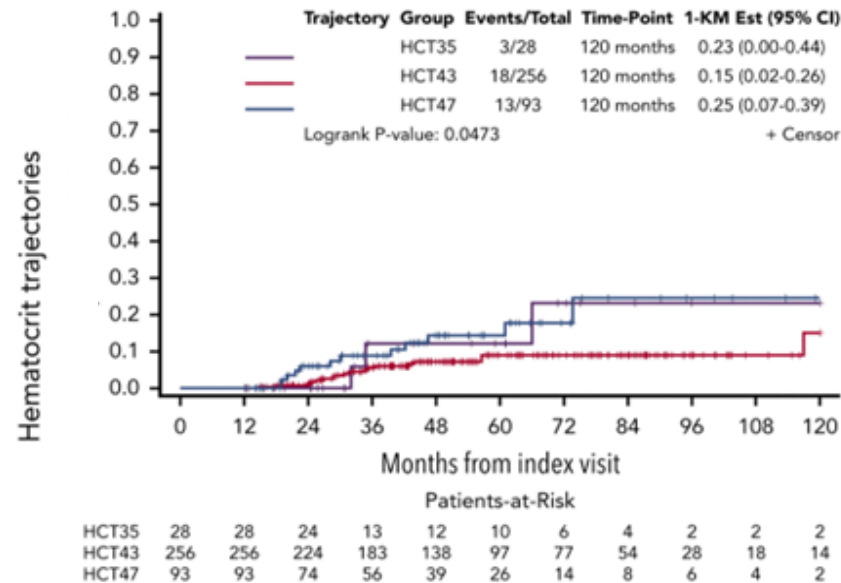
Response criteria for PV

	Criteria
Complete remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND
B	Durable* peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$, AND
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND
D	Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of >grade 1 reticulin fibrosis
Partial remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND
B	Durable* peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$, AND
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND
D	Without bone marrow histological remission defined as persistence of trilinear hyperplasia.
No response	Any response that does not satisfy partial remission
Progressive disease	Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia‡

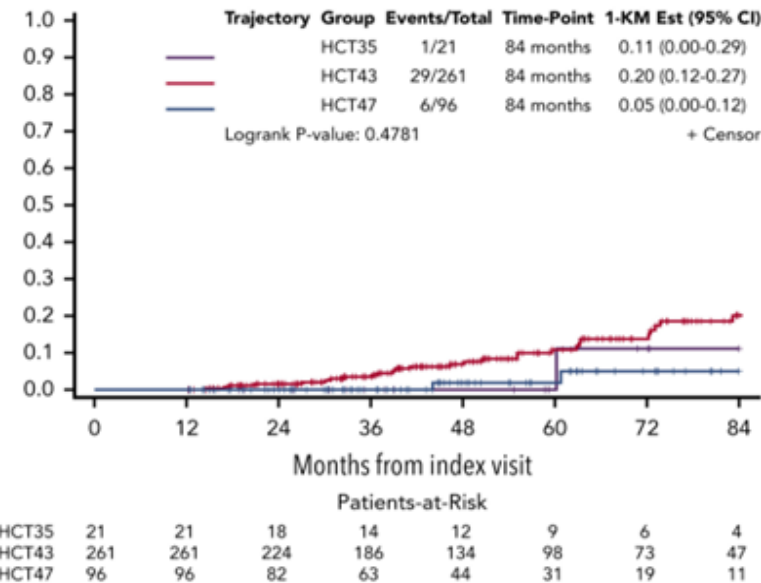
Trajectories of hematologic laboratory values and outcomes of thrombosis and disease evolution

N=520 PV patients across 10 centers in US

Thrombosis



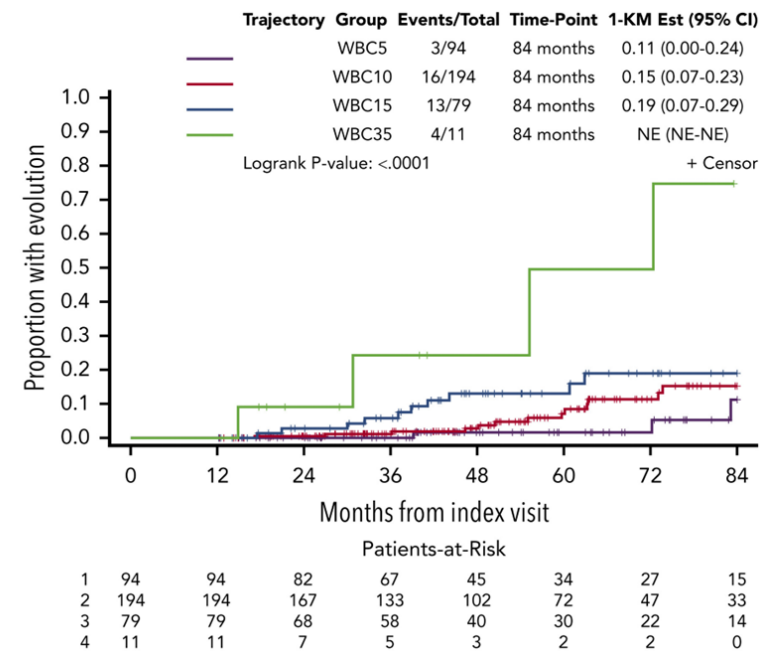
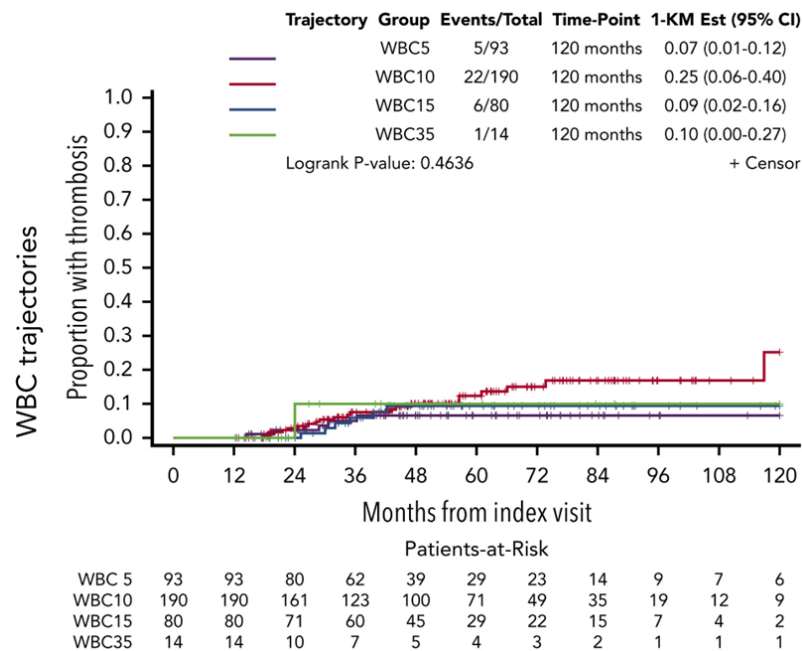
Evolution



Multivariable Cox proportional hazards model examining the association between hematocrit and thrombosis, there was no statistically significant association between hematocrit trajectory and thrombosis ($P = .1849$). Hematocrit trajectory was also not significantly associated with hazard of disease evolution ($P = .5407$)

Trajectories of hematologic laboratory values and outcomes of thrombosis and disease evolution

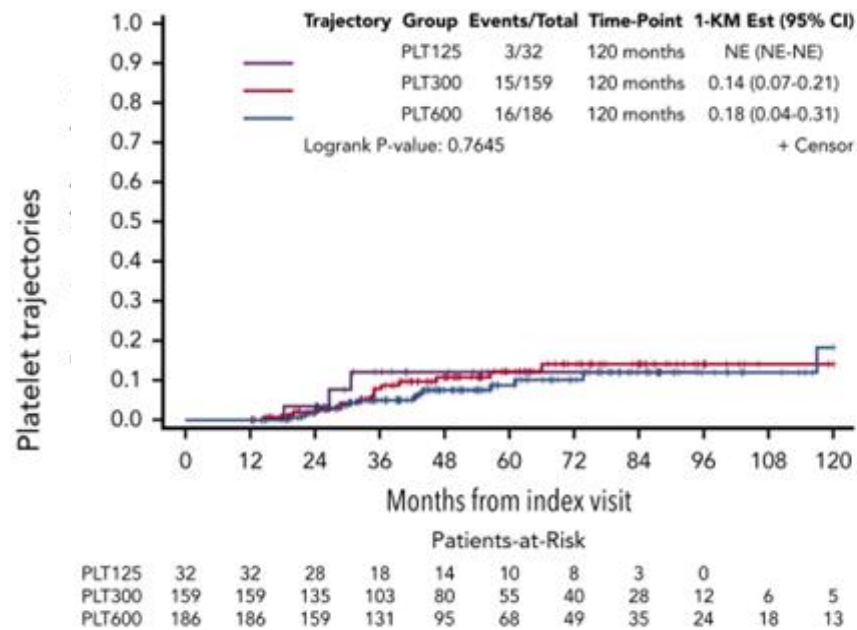
N=520 PV patients across 10 centers in US



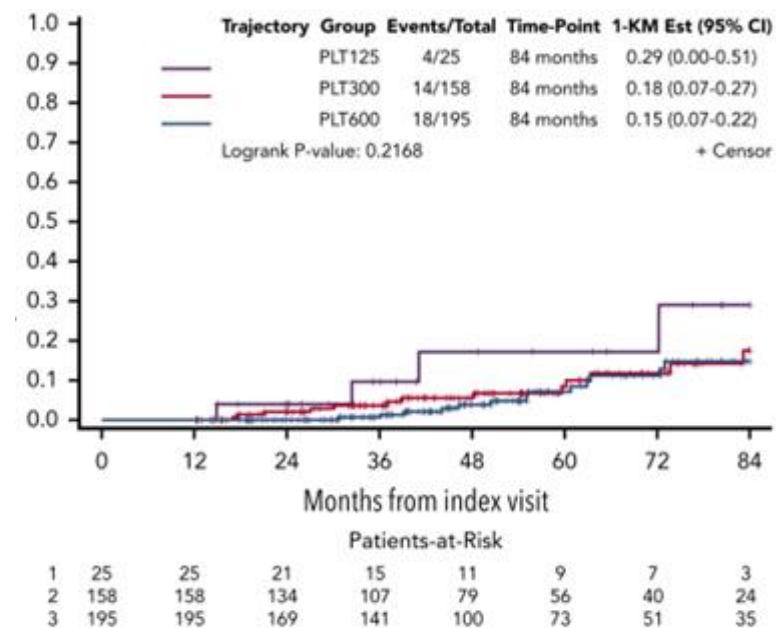
Multivariable Cox proportional hazards model examining the association between leukocyte trajectory and thrombosis, no significant association between them was found ($P = .4163$). There was, however, a significant association between leukocyte trajectory and hazard of disease evolution ($P = .0002$).

Trajectories of hematologic laboratory values and outcomes of thrombosis and disease evolution

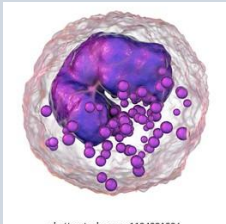
Thrombosis



Evolution



No significant association between platelet trajectory and thrombosis ($P = .9501$) or disease evolution ($P = .1670$)

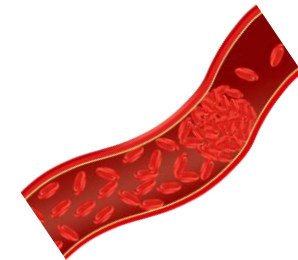
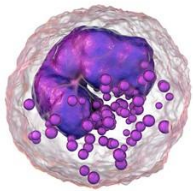


Persistently elevated leukocyte trajectories were not associated with the hazard of a thrombotic event but were significantly associated with increased hazard of disease evolution in an ascending stepwise manner



Neither hematocrit nor platelet count was significantly associated with the hazard of thrombosis or disease evolution.

JAK2 allele burden in PV



JAK2^{V617F}
Clone size >50%

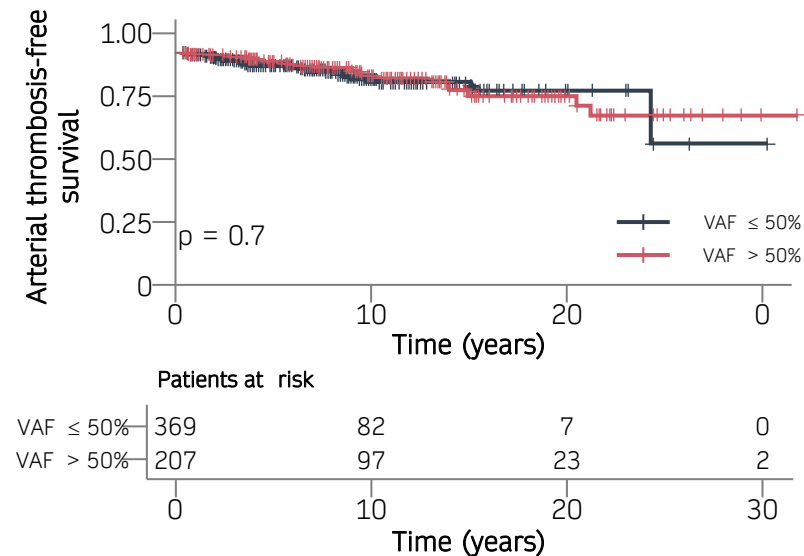
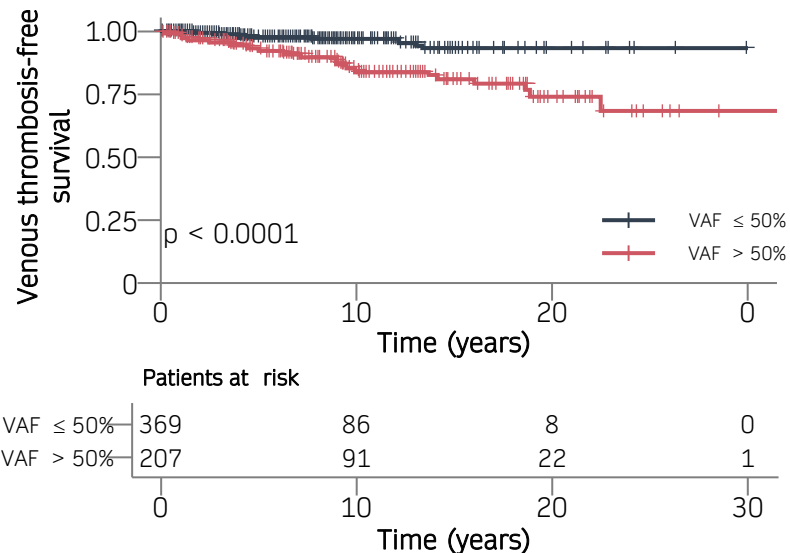
- Recent data have demonstrated the ability of some therapies to significantly decrease not only peripheral blood cell counts but also. *JAK2*^{V617F} mutant allele burden





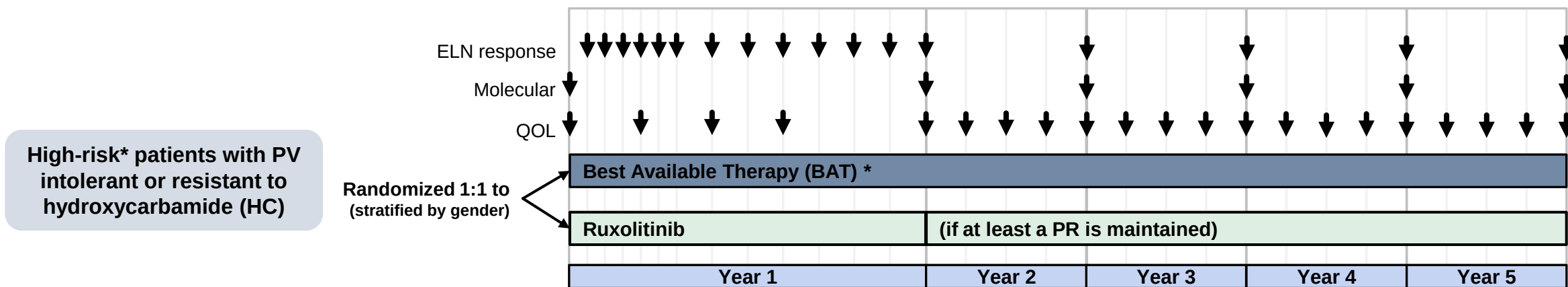
$JAK2^{V617F}$ VAF to identify patients with PV at high risk for venous thrombosis

Venous + arterial thrombosis-free survival for $JAK2^{V617F}+$ patients with PV
Training cohort stratified by their $JAK2^{V617F}$ VAF ($> 50\%$ vs $\leq 50\%$)



$JAK2^{V617F}$ VAF $> 50\%$ identifies patients at high risk for venous thrombosis

MAJIC-PV is a phase 2, randomized open-label, two-arm, multicenter clinical trial

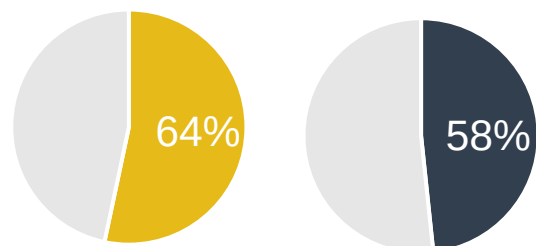


*In common with the RESPONSE trials patients could receive HC on the BAT arm

MAJIC PV was designed to assess **long-term benefit** of **ruxolitinib** and also specific clinical targets such as comprehensive **blood count control** and **molecular response** in patients with **high-risk** PV

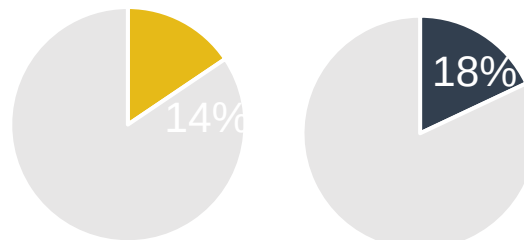
Molecular analysis from MAJIC-PV

At baseline:



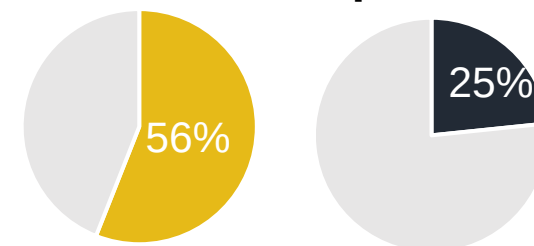
JAK2V617F VAF did not differ at baseline (64% for ruxolitinib vs 58% BAT)

At 12 months:



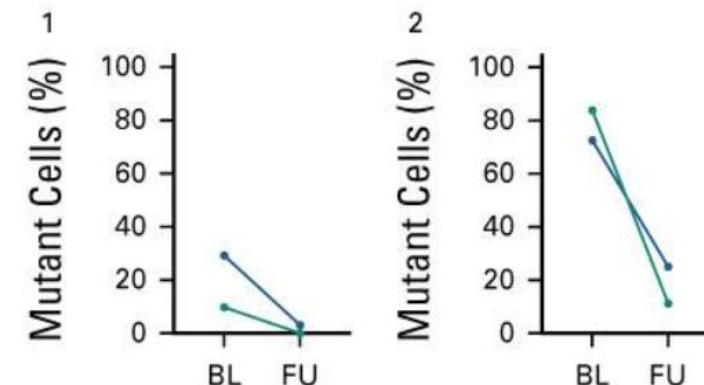
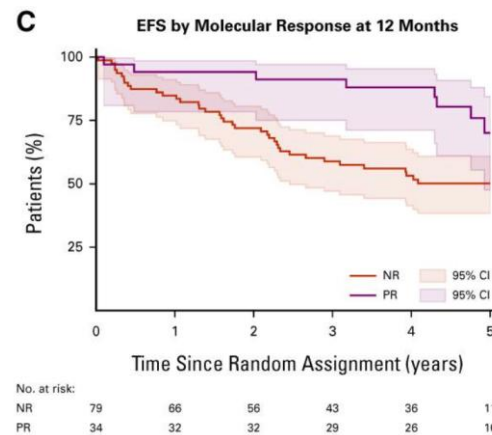
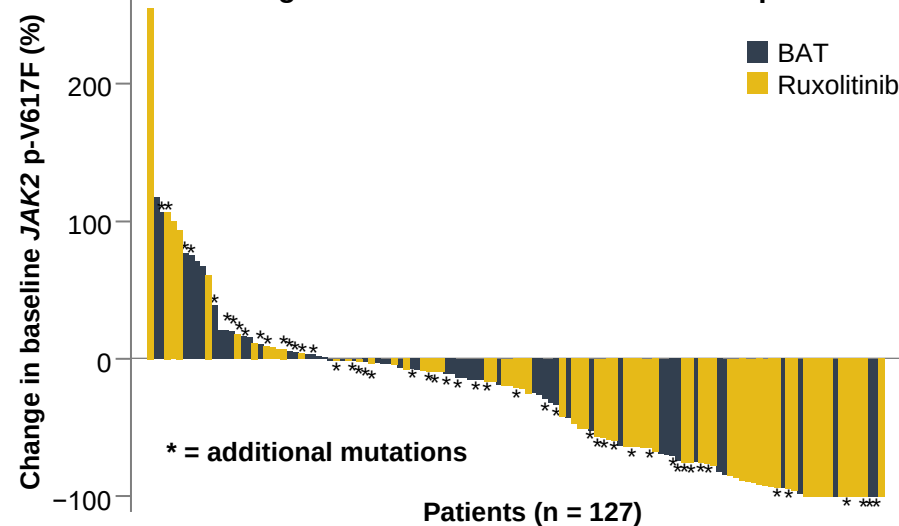
Molecular response (> 50% reduction) was similar at 12 months in 14% for ruxolitinib and 18% for BAT

Final timepoint:



Molecular response (> 50% reduction) at the final timepoint was 56% for RUX and 25% for BAT

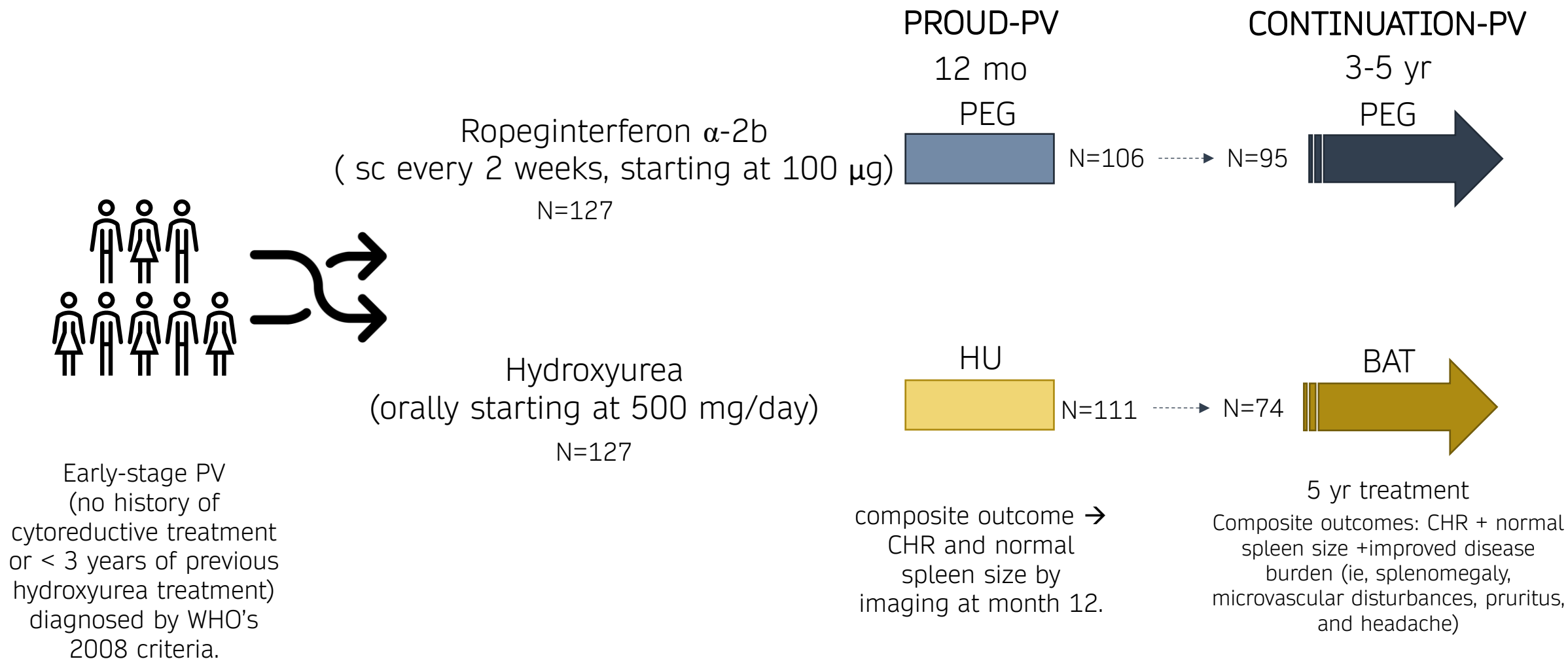
Change in JAK2 raw value at latest timepoint



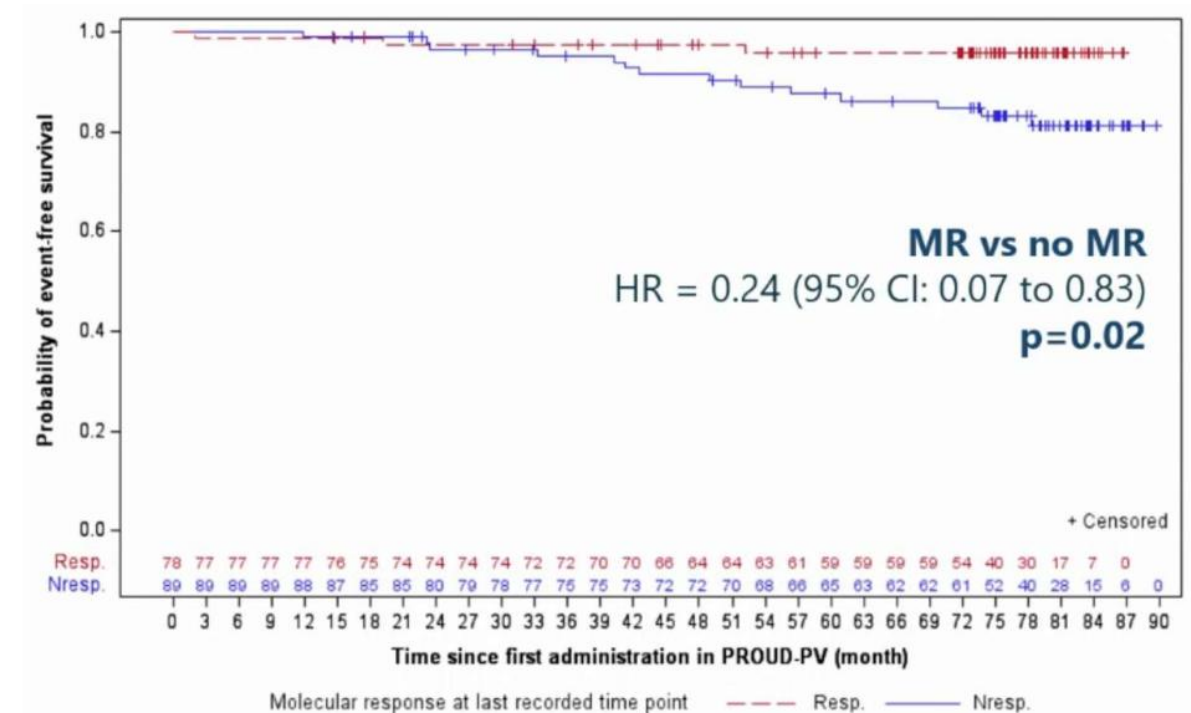
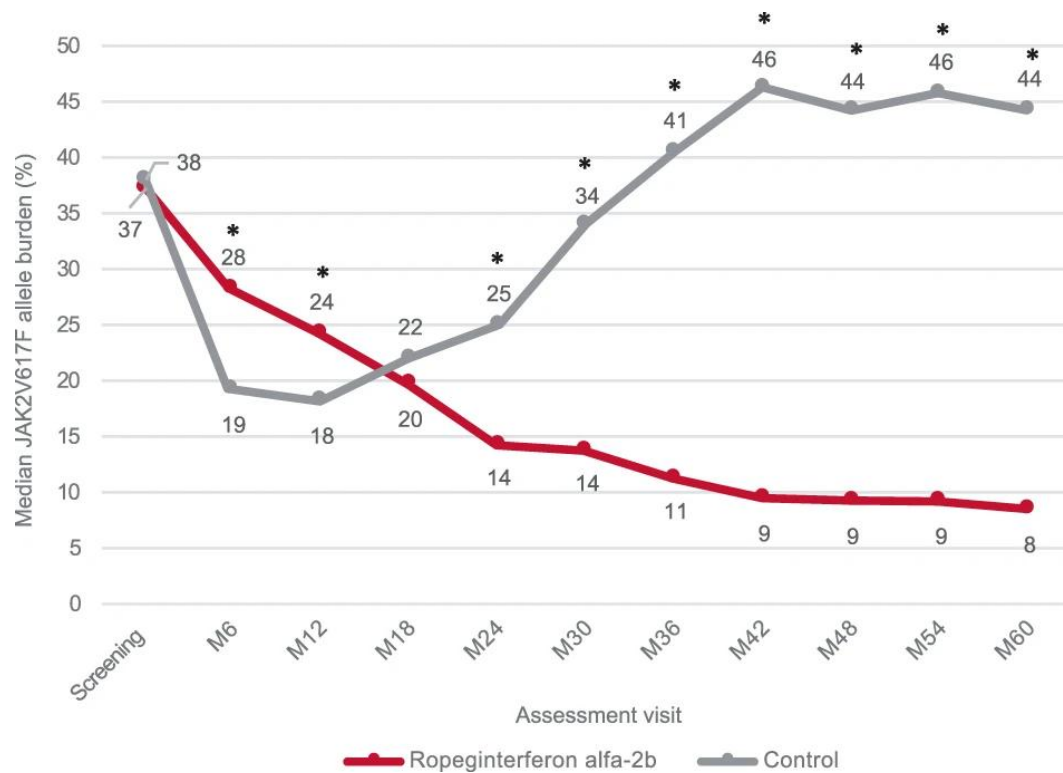


Molecular response in early lines of PV treatment

Ropeginterferon α -2b vs standard therapy for PV

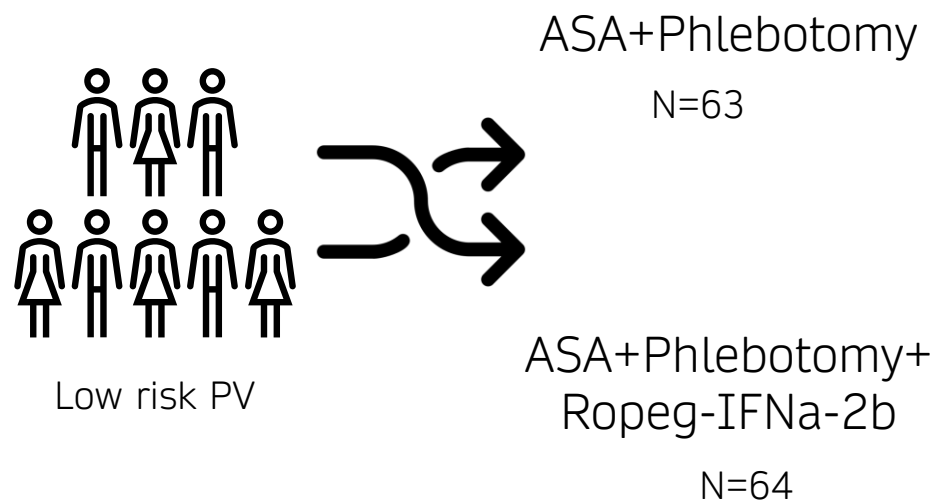


Molecular response impacts on EFS



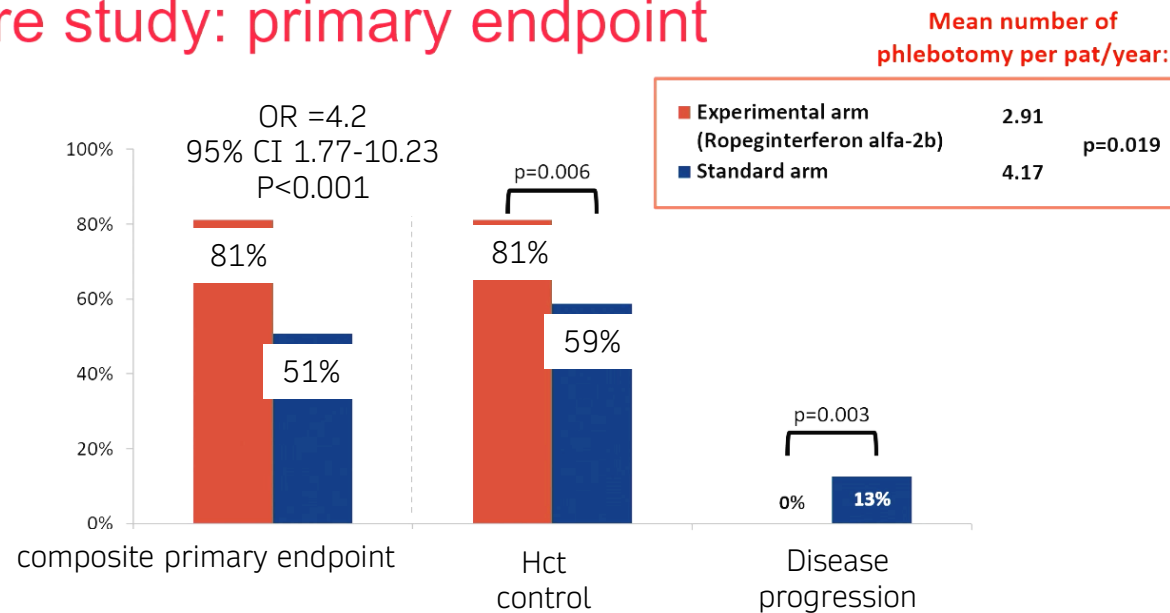
. Kiladjian et al, EHA, 2024

Ropeginterferon Alfa-2b vs Standard Therapy for LR-PV



	EXP (n=55) 12 mo	EXP (n=29) 24 mo	STD (n=43) 12 mo	STD (n=5) 24 mo
Absolute JAK2 ^{V617F} VAF change from baseline — %, mean (SD)	-11.9 (20.7)	-23 (28.9)	1.8 (9.0)	15.4 (30.5)
PMR— n (%)	16 (29.1)	16 (55.2)	0	1

Core study: primary endpoint



13% (N=8)
6→ Platelet progression
2→splenic infarction, TIA

The composite primary endpoint :% of patients maintaining Hct ≤45% over 12 months in the absence of progressive disease (i.e., thrombosis, bleeding, progressive leukocytosis, symptomatic thrombocytosis, symptomatic splenomegaly or other uncontrolled symptoms).



Conclusions

- The implementation of molecular data, in addition to clinical and biologic risk factors, enabled better stratification of estimated OS and the risk for vascular events in MPN patients
- Better blood count control and $JAK2^{V617F}$ allele burden reduction contribute to lower thrombosis risk and improve long term outcomes in PV patients
- A forward-looking approach to systematically studying newer agents should be applied to reflect meaningful health outcomes.



Thank you