Cytoreduction in low-risk PV: when, and which drug?

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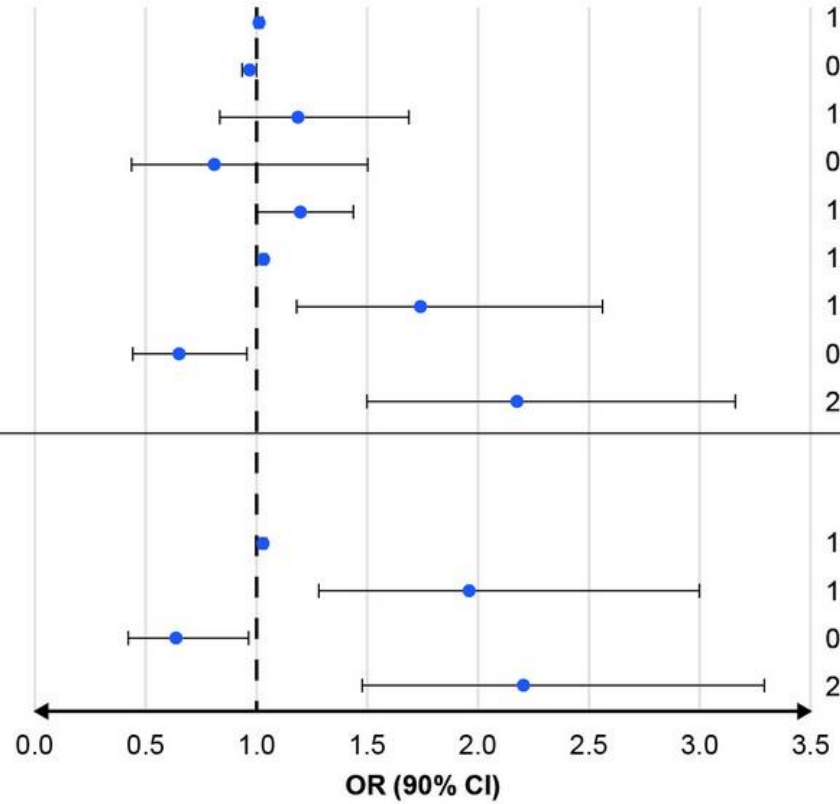
Disclosure Information Heinz Gisslinger

	Consultant	Research Funds (Institution)	Speakers Honorarium
AOP Orphan	+	+	+
Novartis	+	+	+
Celgene/BMS	+		+
GSK	+		+

Associations Between Patient Characteristics and PV Progression

Analysis	OR (90% CI)	*P* Value
Univariate logistic regression on PV disease progression		
Age, y	1.012 (0.997-1.027)	0.1323
BMI, lb/in^2	0.968 (0.936-1.001)	0.0580
Sex (female vs male)	1.187 (0.835-1.688)	0.3397
White (yes vs no)	0.809 (0.436-1.502)	0.5015
Charlson Comorbidity Index	1.198 (0.998-1.437)	0.0520
Time from PV diagnosis to enrollment	1.032 (1.020-1.045)	**<0.0001**
History of TE (yes vs no)	1.740 (1.182-2.562)	**0.0050**
HCT (>0.45 vs ≤0.45 L/L)	0.650 (0.442-0.956)	**0.0288**
WBC (>11 vs ≤11×10^9/L)	2.176 (1.498-3.161)	**<0.0001**
Multivariate logistic regression on PV disease progression with stepwise model selection		
Time from PV diagnosis to enrollment	1.030 (1.016-1.044)	**<0.0001**
History of TE (yes vs no)	1.960 (1.281-2.998)	**0.0019**
HCT (>0.45 vs ≤0.45 L/L)	0.637 (0.421-0.964)	**0.0330**
WBC (>11 vs ≤11×10^9/L)	2.205 (1.477-3.292)	**0.0001**



Significant values are indicated in bold font.
BMI, body mass index; CI, confidence interval; HCT, hematocrit; OR, odds ratio; PV, polycythemia vera; TE, thrombotic events; WBC, white blood cell.

Grunwald MR, et al, ASH 2023, Abstr. 385

Time-dependent multivariable analysis on the risk of major thrombosis in CYTO-PV study (N 5 365)

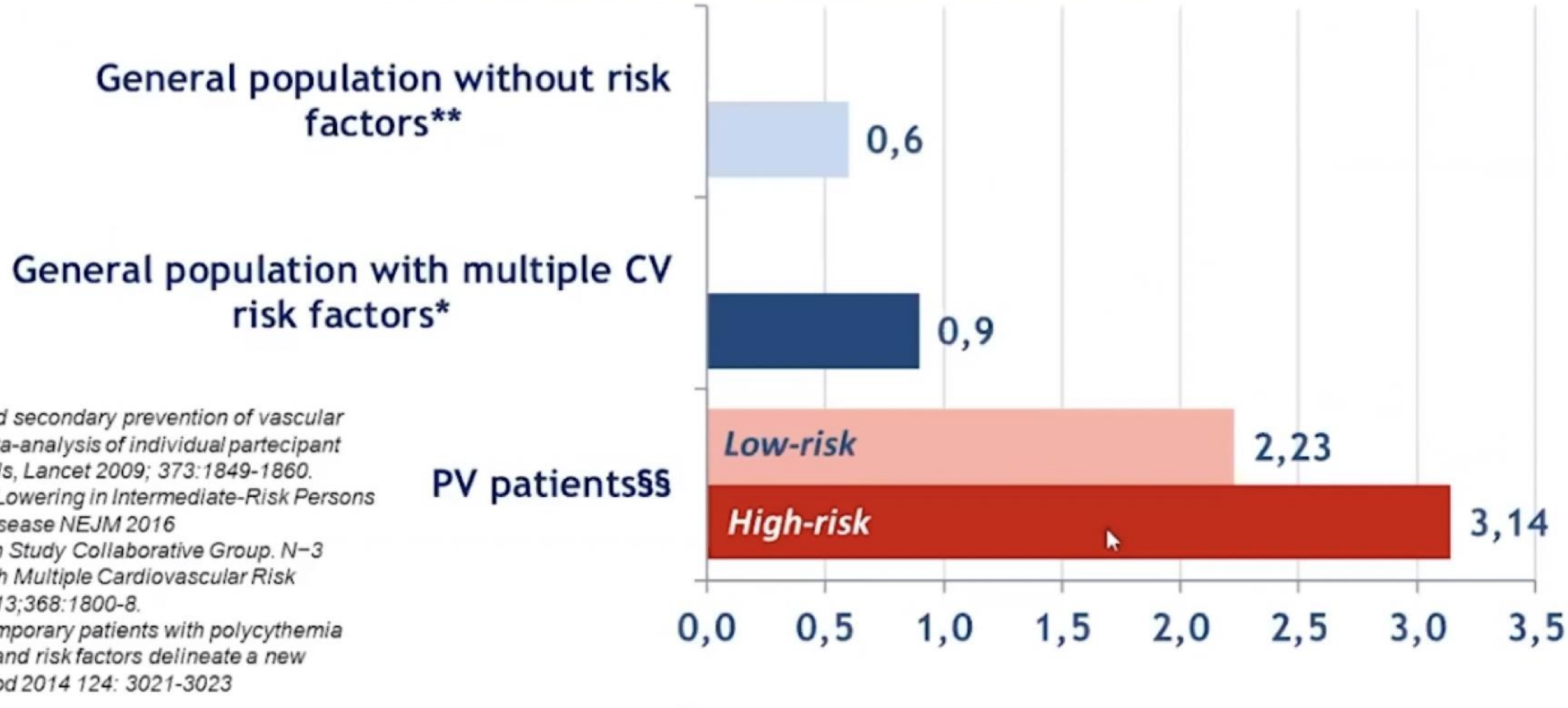
WBC class ($\times 10^9$/L)	Events/pts (%)	Hazard ratio (95% CI), *P*
<7.0	4/100 (4.0)	1.00
7.0-8.4	4/84 (4.8)	1.58 (0.39-6.43), .52
8.5-11.0	8/88 (9.1)	2.69 (0.80-9.05), .11
≥11.0	12/93 (12.9)	3.90 (1.24-12.3), .02

Adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and
hematocrit levels.
CI, confidence interval; pts, patients.

Barbui et al, Blood 2015

Patients with low risk PV have an elevated risk of thrombosis

Annual rate of thrombosis in contemporary patients with polycythemia vera and in general population

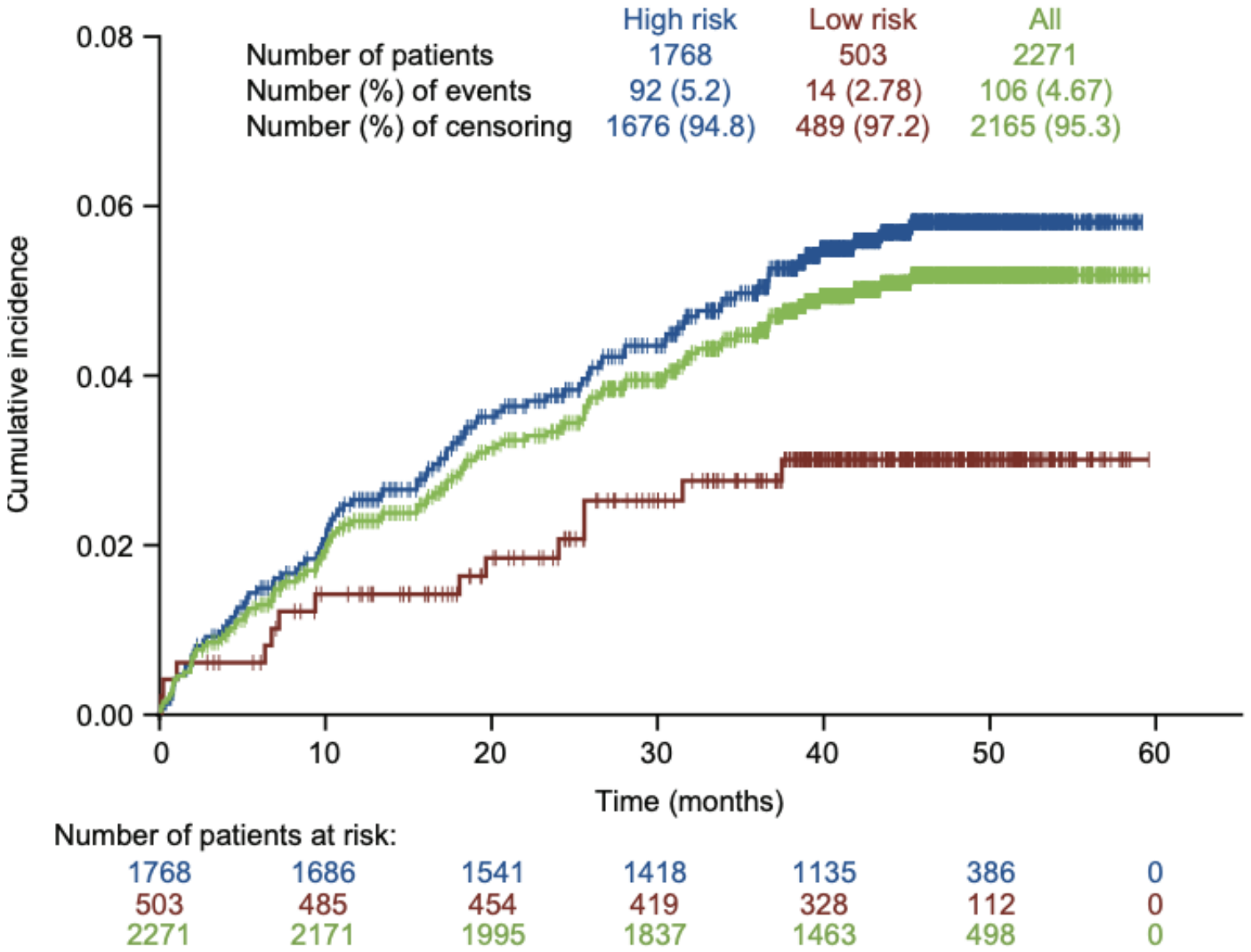


* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual partecipant data from randomized trials, Lancet 2009; 373:1849-1860.
Yusef S et al Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease NEJM 2016

**The Risk and Prevention Study Collaborative Group. N−3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. N Engl J Med 2013;368:1800-8.

§§ Barbui T, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood 2014 124: 3021-3023

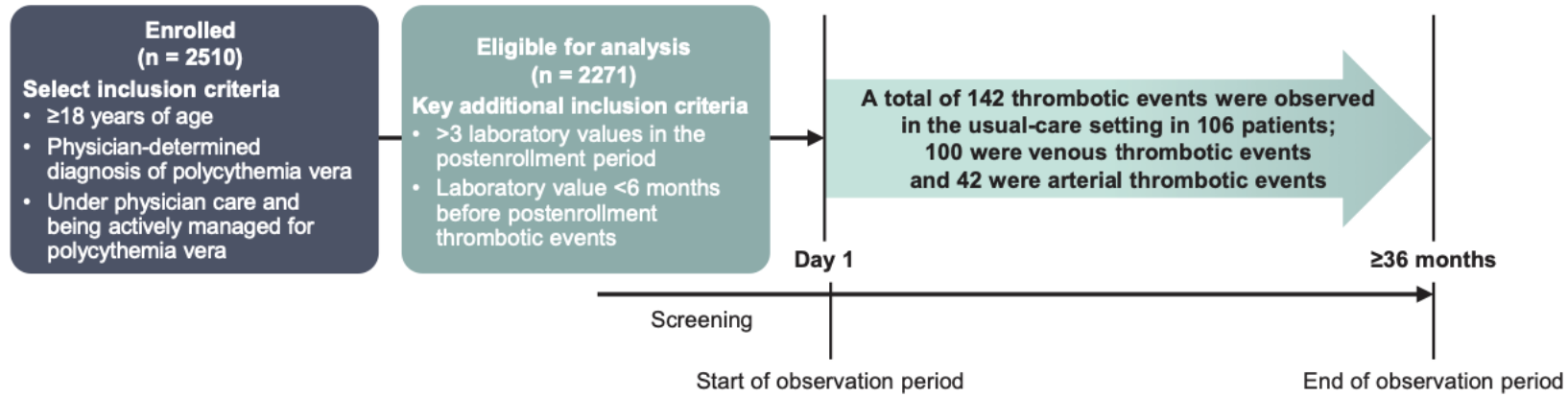
Cumulative incidence of TEs occurring during the study period

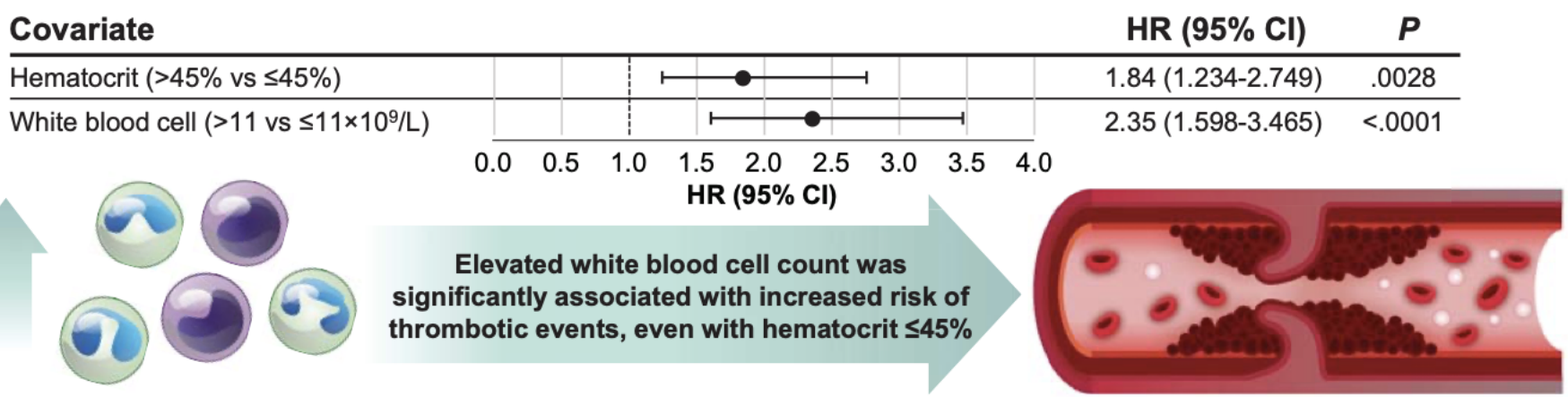


Gerds AT, et al, Blood 2023

Association between elevated white blood cell counts and thrombotic events in polycythemia vera: Analysis from REVEAL

REVEAL is the largest prospective observational study of patients with polycythemia vera in the United States



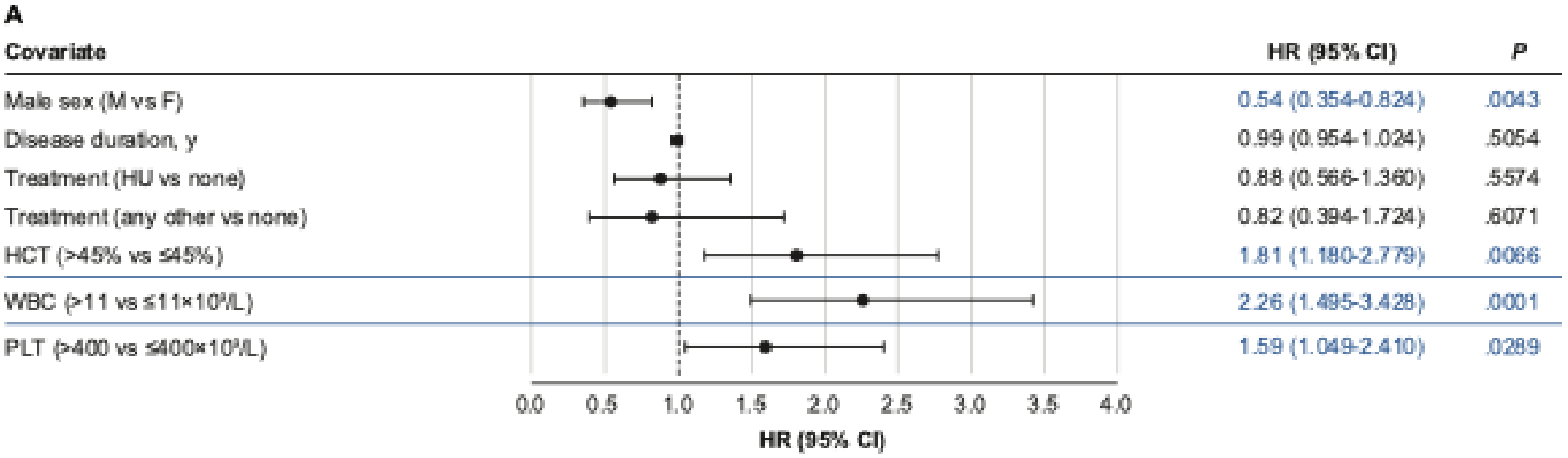


In addition to hematocrit, white blood cell count control is important in optimizing management and reducing thrombotic complications in patients with polycythemia vera.

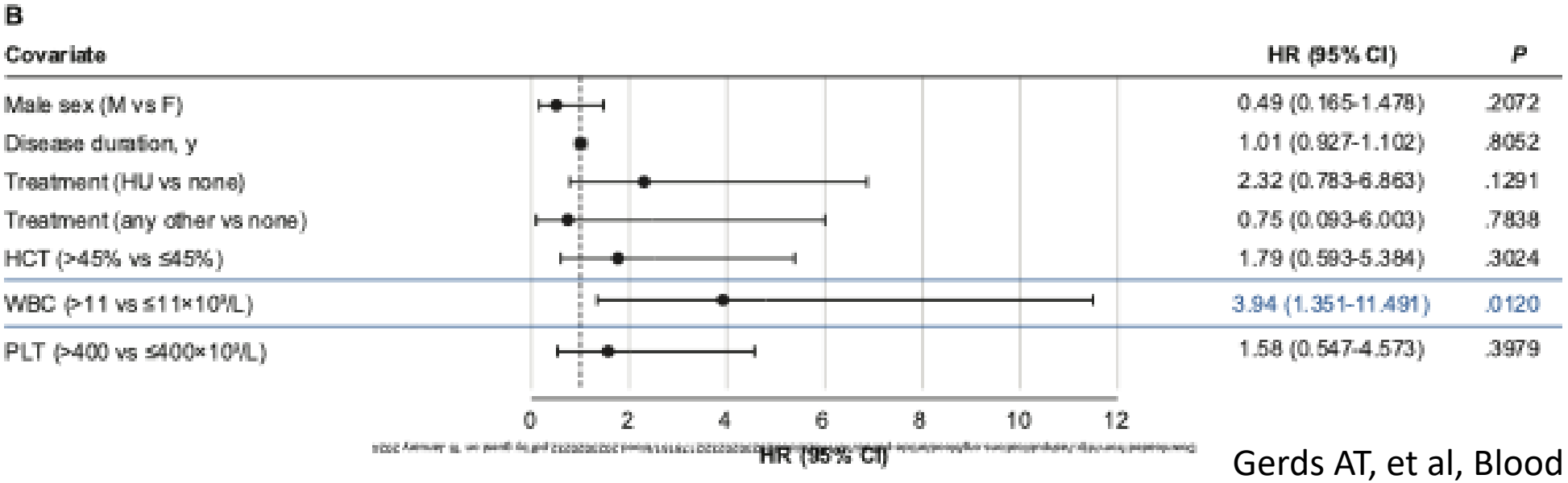
Gerds *et al, Blood, DOI* 10.1182/blood.XXXXX

Analysis of TE associations stratified by PV risk group

High risk

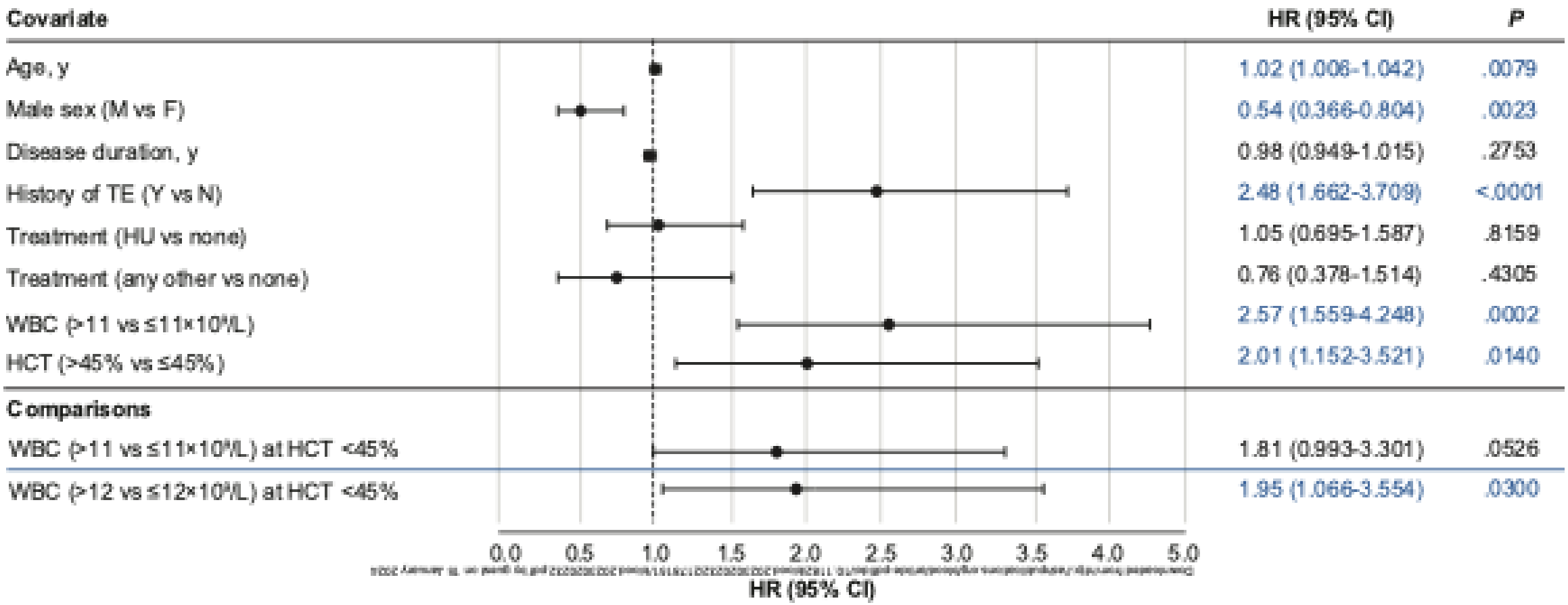


Low risk



Gerds AT, et al, Blood 2023

WBC count association with TEs at hematocrit levels ≤45% (WBC >11 and >12×109/L)



Gerds AT, et al, Blood 2023

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ORIGINAL ARTICLE

Ropeginterferon versus Standard Therapy for Low-Risk Patients with Polycythemia Vera

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Main efficacy results of the core study*

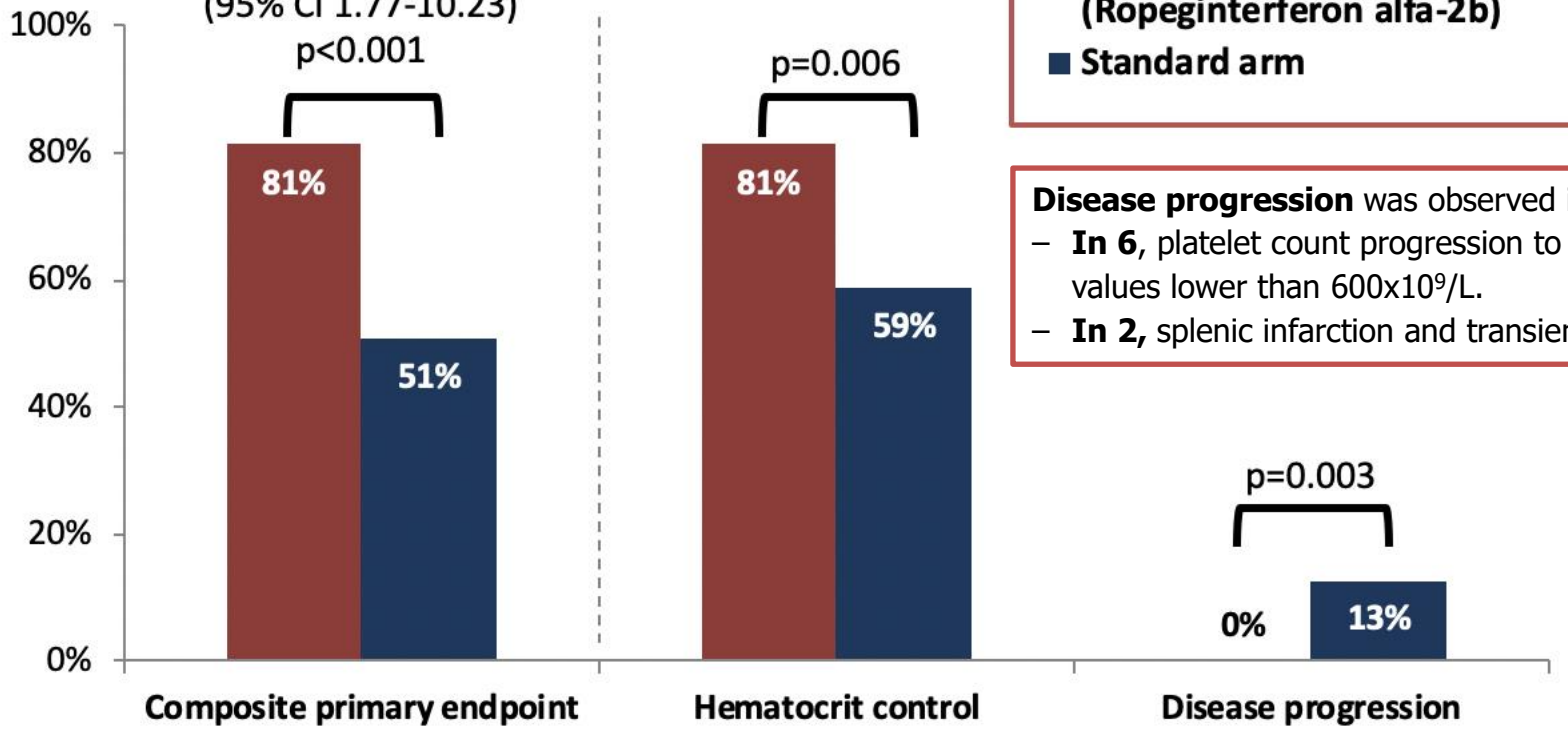
Core Study (12 Months)	Randomized Groups			
	EXP (n=64)	STD (n=63)	P Value	Effect Estimate† (95% CI)
Treatment response — n (%)	52 (81.3)	32 (50.8)	<0.001	4.20 (1.77–10.23)
Hematocrit control	52 (81.3)	37 (58.7)		3.05 (1.28–7.50)
Disease progression	0 (0.0)	8 (12.7)		—‡
No. of phlebotomies per patient year — mean (SD)	2.9 (2.4)	4.2 (3.2)		1.27 (0.27–2.26)
	EXP (n=55)	**STD (n=43)**		
Absolute *JAK2*V617F VAF change from baseline — %, mean (SD)	−11.9 (20.7)	1.8 (9.0)		13.73 (7.00–20.46)
Partial molecular response — n (%)	16 (29.1)	0 (0.0)		—‡

* Treatment response was obtained in the core study at 12 months by randomized groups. CI denotes confidence interval; EXP, experimental group; SD, standard deviation; STD, standard group; and VAF, variant allele frequency.

† For categorical and continuous end point estimates, odds ratios and mean differences are provided, respectively, with 95% CIs.

‡ Exact confidence levels are not possible with zero count cells.

Core study: primary endpoint



Mean number of phlebotomy per pat/year:

Experimental arm (Ropeginterferon alfa-2b)	2.91	p=0.019
Standard arm	4.17	

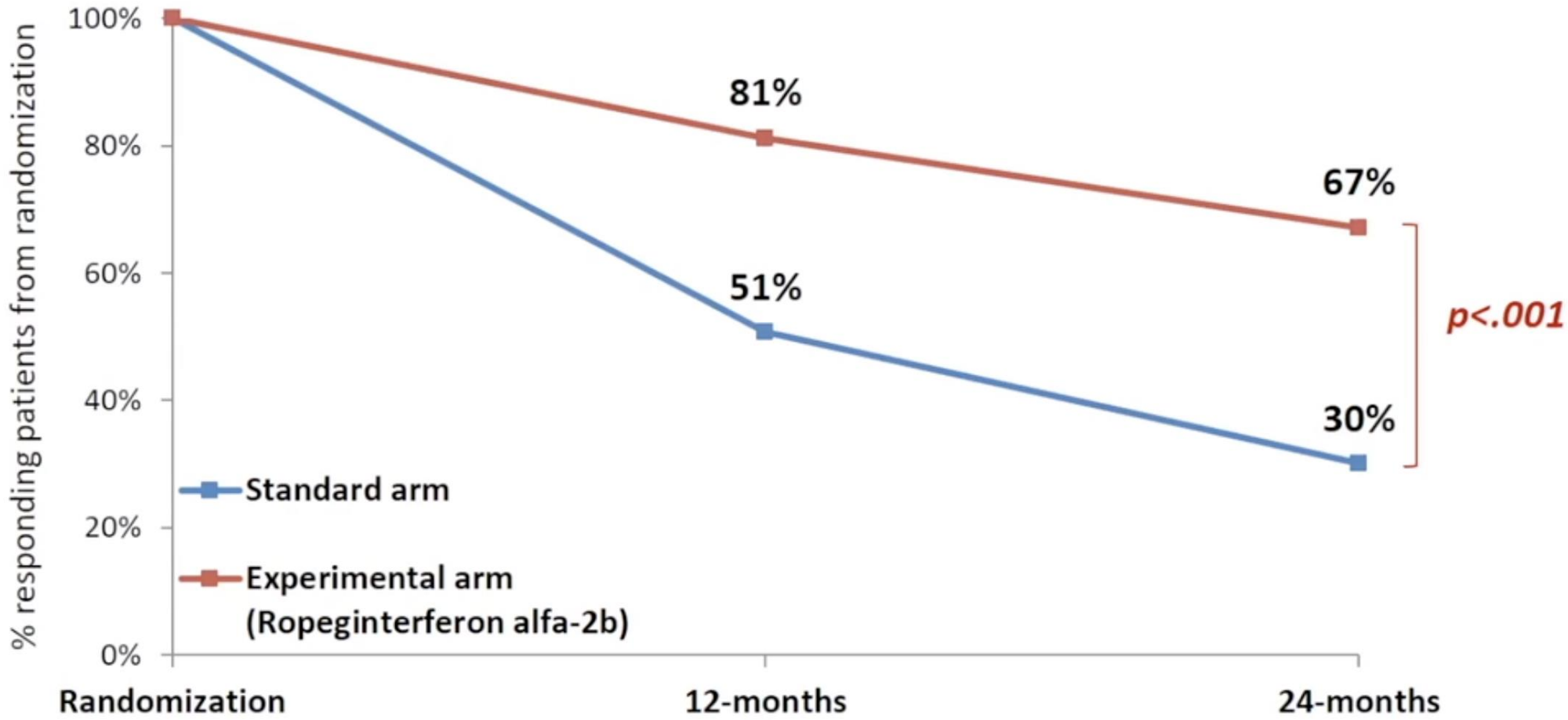
Disease progression was observed in **8 patients** (all in standard arm):

- **In 6**, platelet count progression to >1000x10^9/L in pts with baseline values lower than 600x10^9/L.
- **In 2,** splenic infarction and transient ischemic attack, respectively

Barbui et al, 2023, ASH 2022

Treatment response maintenance, by ITT*

- *All randomized patients included.*
- *Patients crossed-over were censored at 12 months as non-responders of the orginal arm*



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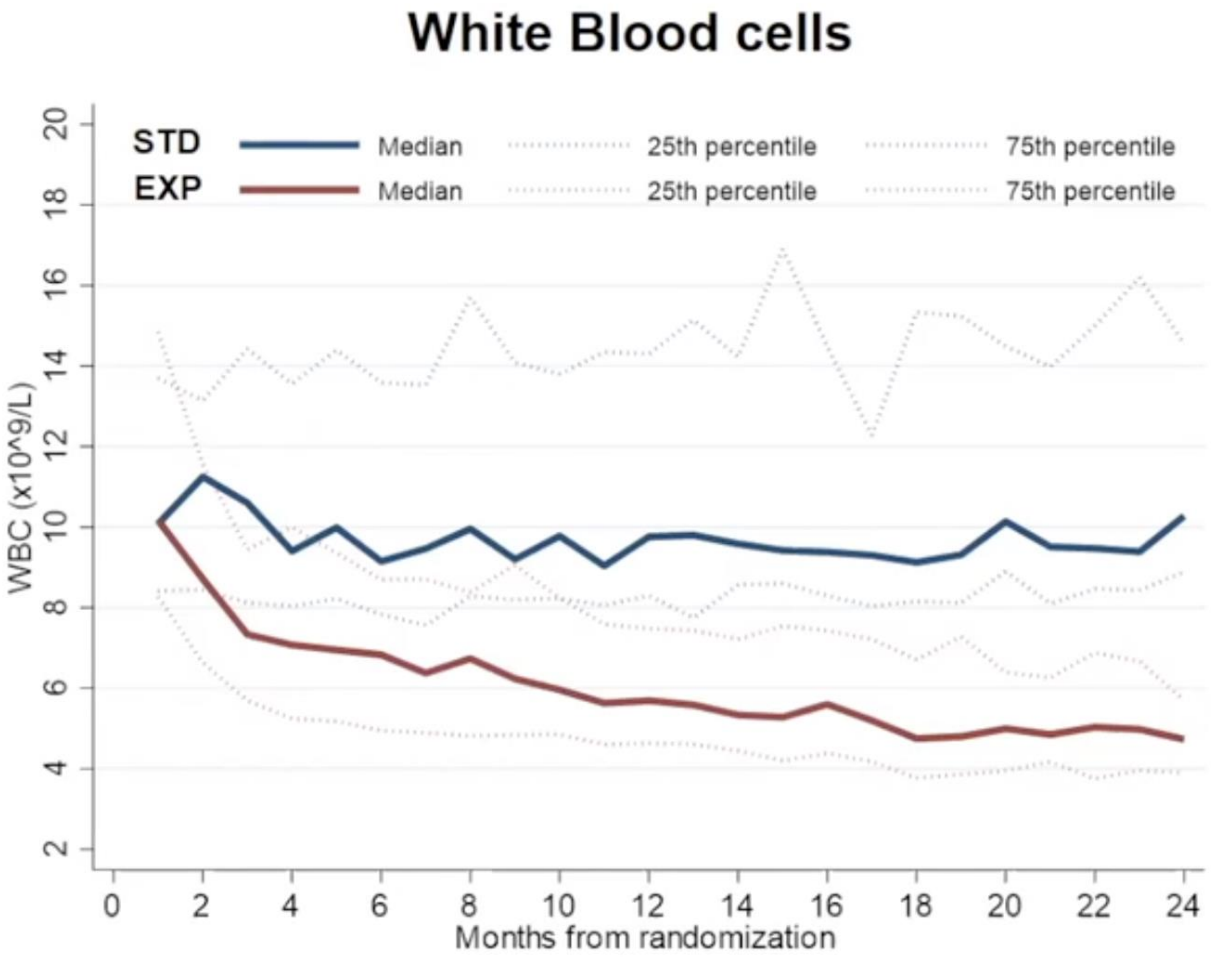
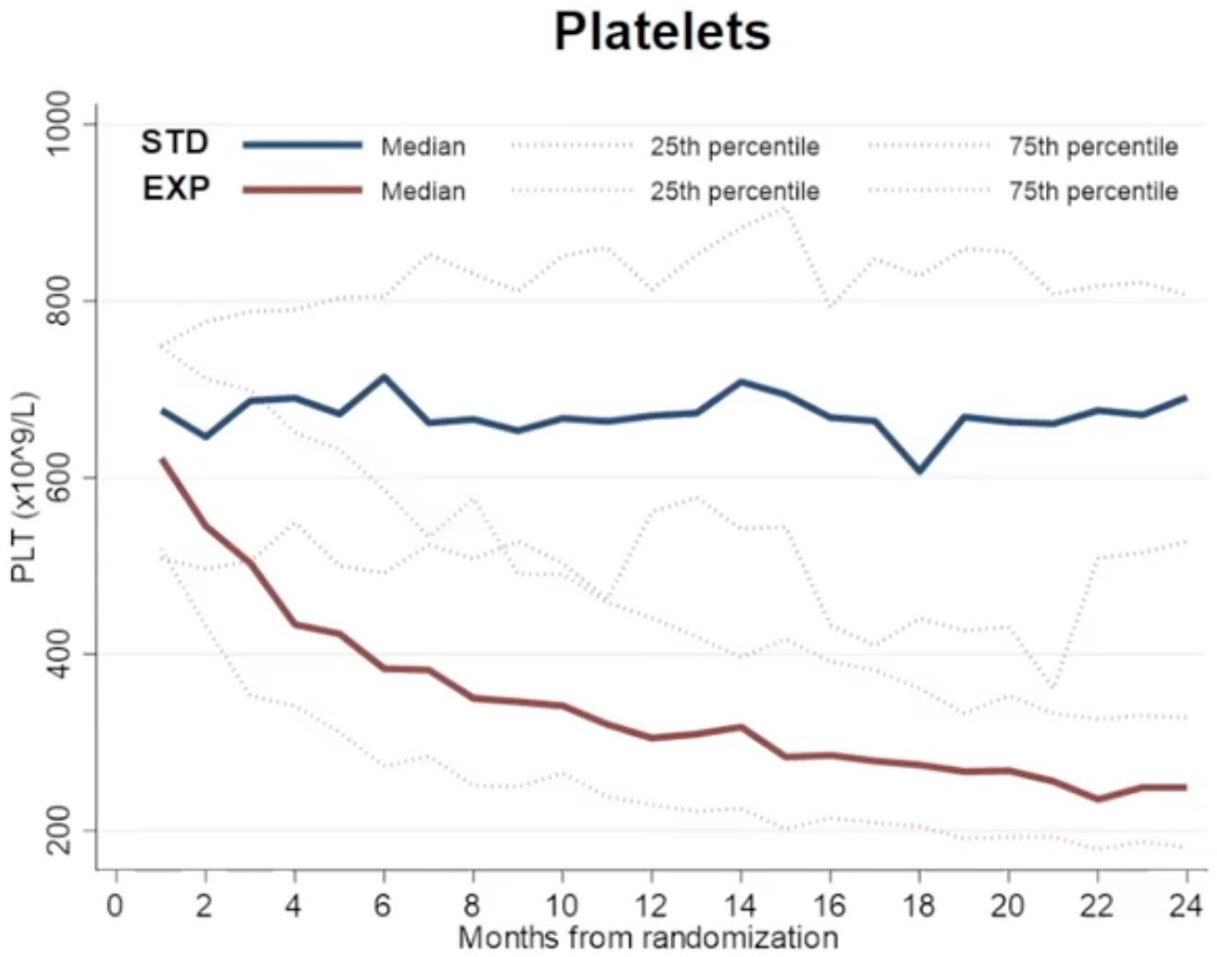
Responders: WBC and PLT





Barbui et al, 2023, ASH 2022

Conclusion: Ropeginterferon in low-risk PV

- Low-dose (100 µg every 2 weeks) Ropeginterferon alfa 2-b is **safe, well tolerated and more efficacious** in comparison to a strict therapeutic phlebotomy policy in steadily keeping the hematocrit at target levels in low-risk PV patients. This advantage was **maintained in the extension phase.**

- The drug had a significant **effect for all secondary end points** including quality of life, blood counts, ferritin levels, JAK2 allele burden and splenomegaly.

- During the core study, we identified **a subgroup of low-risk patients** who needed higher number of phlebotomies both in the core study and in the extension phase. These patients showed a significant lower *JAK2* VAF response.

- **In conclusion,** these findings **suggest significant advantages** of Ropeg over conventional treatment to control the natural history of PV disease in low-risk patients

Barbui et al, 2023, ASH 2022

Indications for cytoreductive therapy in low risk ET/PV

- Extreme thrombocytosis leading to clinical apparent acquired von-Willebrand is a key indication
- Microvascular symptoms may be particularly amenable to improvement with cytoreductive therapy
- Cytoreduction in patients with low symptom burden may exacerbate symptoms (TSS <20)[1]
- Treatment of low risk patients with leukocytosis is debatable

2021 ELN PV cytoreduction guidelines[2]

	Favours cytoreductive drug therapy?	Quality of evidence
Disease transformation*	Yes†	Moderate[22,26,35,37]
Vascular events*	Yes	Moderate[36,37,38]
Symptoms*	Yes	Moderate[13,33,37,42]
Haematocrit control and haematological response	Yes	High[22,37,42]
Phlebotomy frequency	Yes	High[13]
Quality of life	Yes	Very low[27-34]
Adverse events	No	High[36,38,41]
Secondary malignancies	Yes and no‡	Low[18,39,40]
Overall survival	Yes	Very low[22,26]
Molecular response	Yes	High[22,36,37,42]

1. Mazza et al Lancet Haem 2022
2. Marchetti et al Lancet Haem 2022

Summary of Randomized Clinical Trials Evaluating Pegylated Interferon and Ropeginterferon in Patients With MPN

Clinical Trial	Phase	Patients	Trial Arms	CHR		Molecular Response		Discontinuation Rate	
				IFN	Comparator	IFN	Comparator	IFN	Comparator
DALIAH[20]	III	Untreated MPN (n=205)	Pegylated IFN vs HU	21% (2-y)	26% (2-y)	16% (18-mo)	23% (18-mo)	30%/38%[a]	8%
MPN-RC 112[17]	III	High-risk ET (n=39) and PV (n=43)	Pegylated IFN vs HU	35% (1-y)	37% (1-y)	−10.7%[b]	−5.3%[b]	15%	10%
PROUD-PV CONTINUATION-PV[22]	III	PV with <3 y of cytoreduction (n=257)	Ropeginterferon vs HU	43% (1-y) 48% (2-y) 54% (3-y) 54% (4-y)	46% (1-y) 46% (2-y) 27% (3-y) 31% (4-y)	34% (1-y) 33% (2-y) 52% (3-y) 50% (4-y)	42% (1-y) 31% (2-y) 20% (3-y) 16% (4-y)	8%	4%
Low-PV[23]	II	Low-risk PV (n=100)	Ropeginterferon vs phlebotomy	84%[c] (1-y)	66%[c] (1-y)	NR	NR	NR	NR

Abbreviations: CHR, complete hematologic response; ET, erythrocythemia; HU, hydroxyurea; IFN, interferon; MPN, myeloproliferative neoplasm; NR, not reported; PV, polycythemia vera.

[a]Discontinuation rates with pegylated interferon alfa-2a/2b.

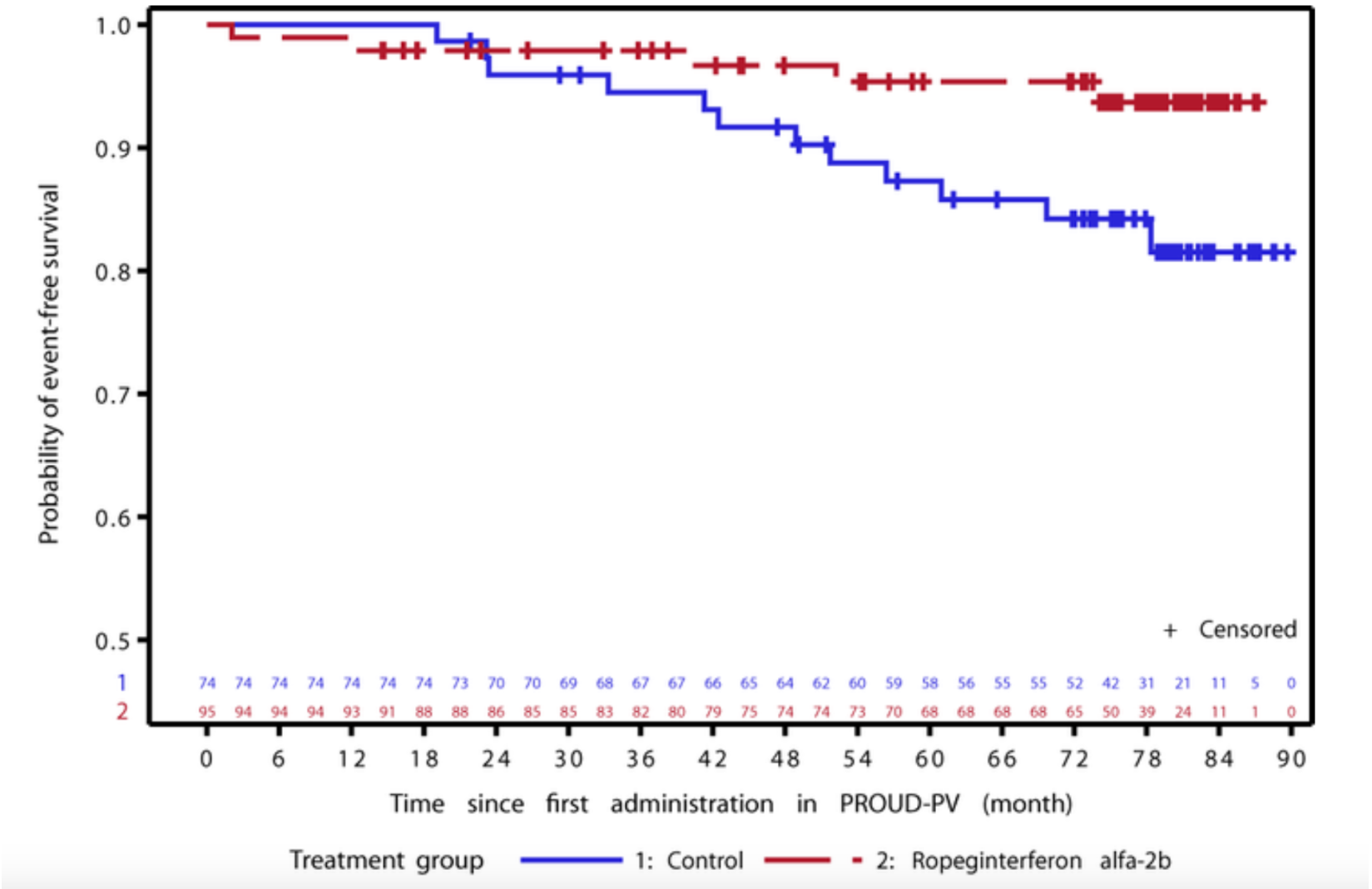
[b]Median decrease in *JAK2* V617F allele burden.

[c]Primary endpoint of Low-PV study was the percentage of patients meeting the hematocrit goal of <45% for 12 months.

How J and Hobbs G; 2022

Probability of event-free survival in patients with PV in the ropeginterferon alfa-2b arm and control arm (CONTINUATION-PV full analysis set)

Risk events were defined as thromboembolic events, disease progression or death



Gisslinger et al, Leukemia (2023) 37:2129–2132

Lessons learned from randomised trials of interferon in PV

- **Long-term treatment is mandatory**. The tolerability of the compound matters, withdrawal rates should be as low as possible. Treatment-emergent mutations may be important for interferon resistance.

- **The drug has less significant effect in later disease manifestations** e.g. in patients with excessive splenomegaly.

- **Long-term treatment increases rates of normal WBC-counts, of CHR and of MR, important to achieve disease modification**.

- **Low risk patients respond better**. A high proliferation rate (e.g. manifested by a high need of phlebotomies) even in low risk PV seems to impair the treatment effect of interferon.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Polycythemia Vera