Ripensare al trattamento dei bassi rischi della Trombocitemia e Policitemia Vera

T. Barbui

Foundation for Clinical Research (FROM)
Hospital Papa Giovanni XXIII
Bergamo, Italy

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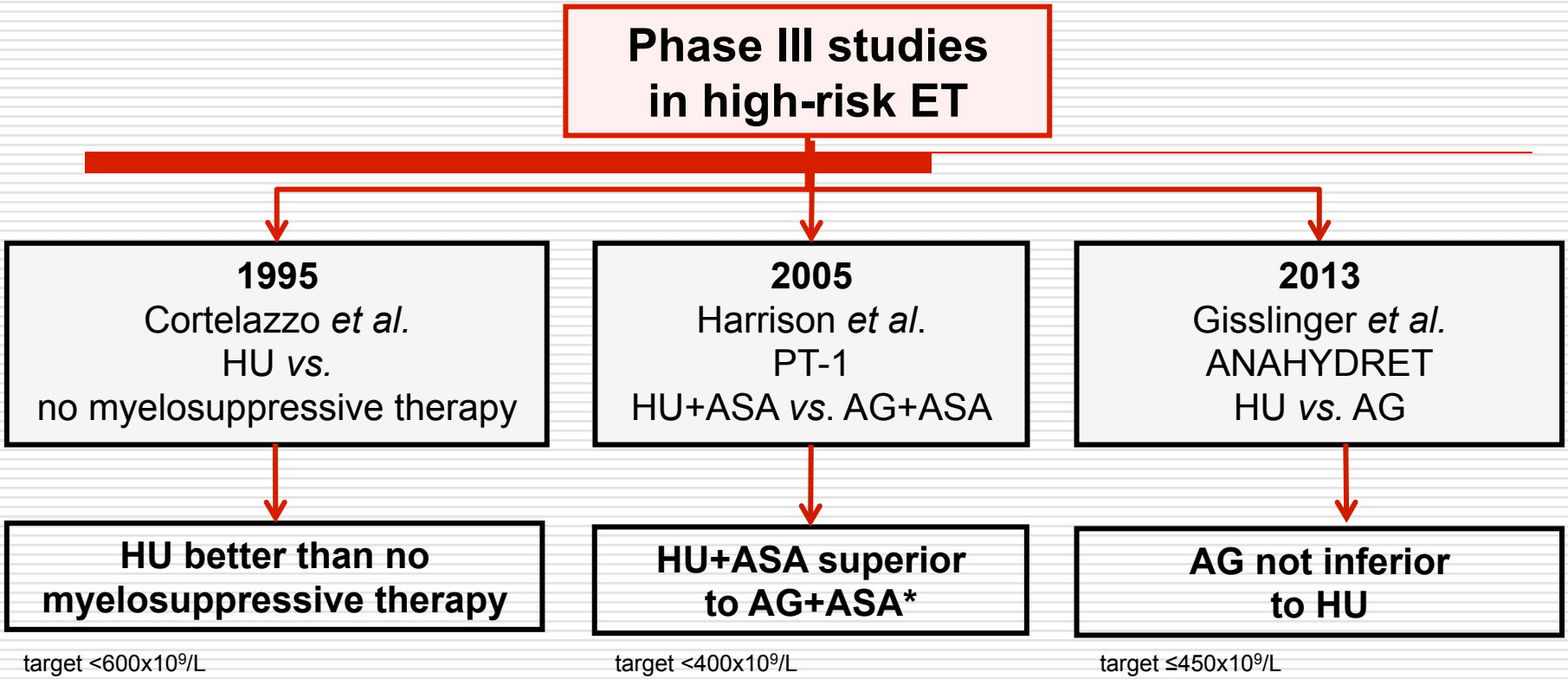
Prospective Randomized Clinical Trials in ET



* composite primary end point: arterial or venous thrombosis, serious hemorrhage, or death from vascular causes

HU: hydroxyurea
AG: anagrelide
ASA: acetylsalicylic acid

Cortelazzo *et al.* N Engl J Med 1995;332:1132
Harrison *et al.* N Engl J Med 2005;353:33
Gisslinger *et al.* Blood 2013;121:1720

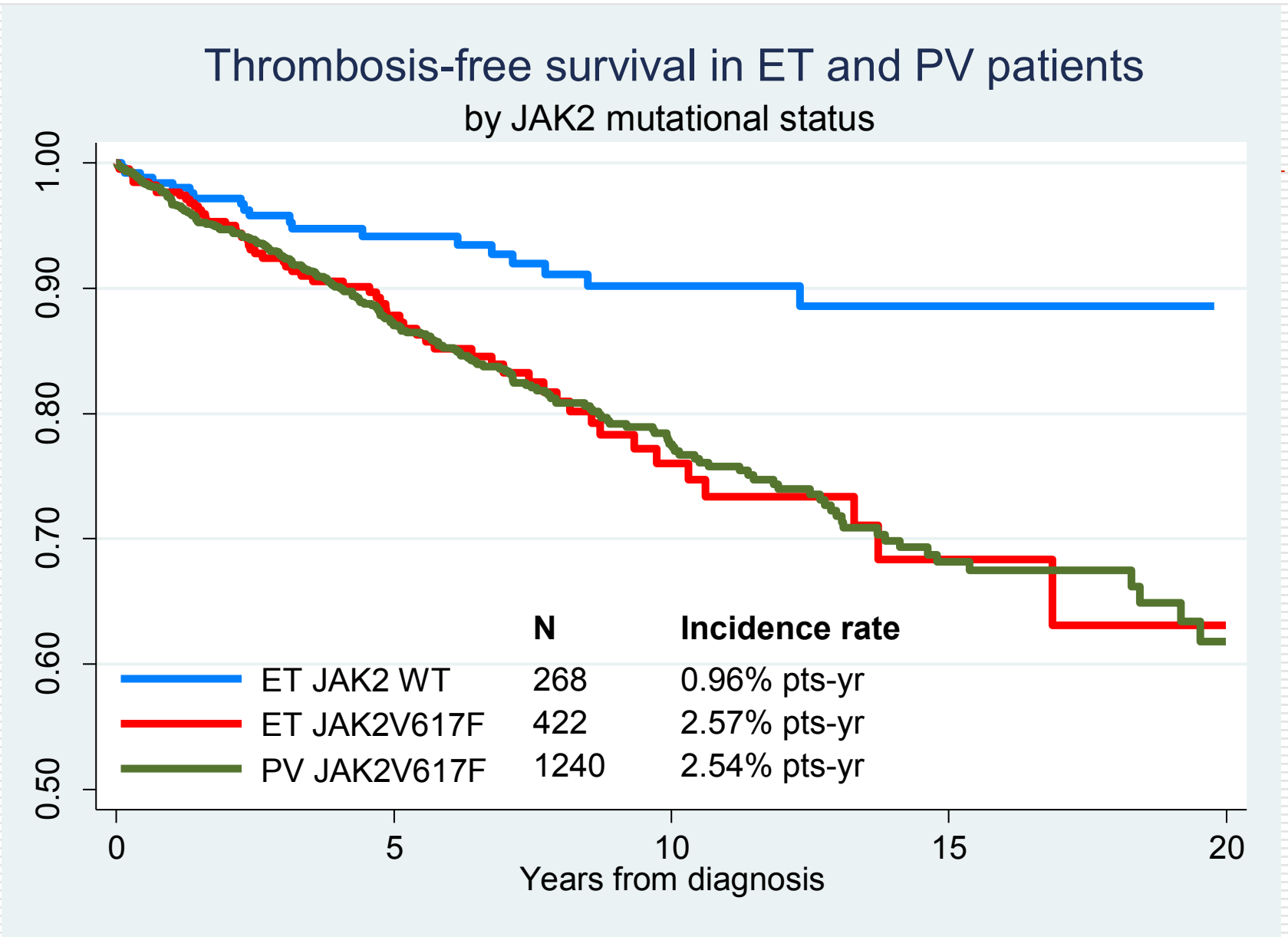
Jak2 mutation status is an independent factor for total thrombosis in ET (n= 891)*

Risk factor	HR	
Age > 60	1.50	
CV risk factors	1.56	
Previous thrombosis	**1.93**	
JAK2 V617F	**2.04**	

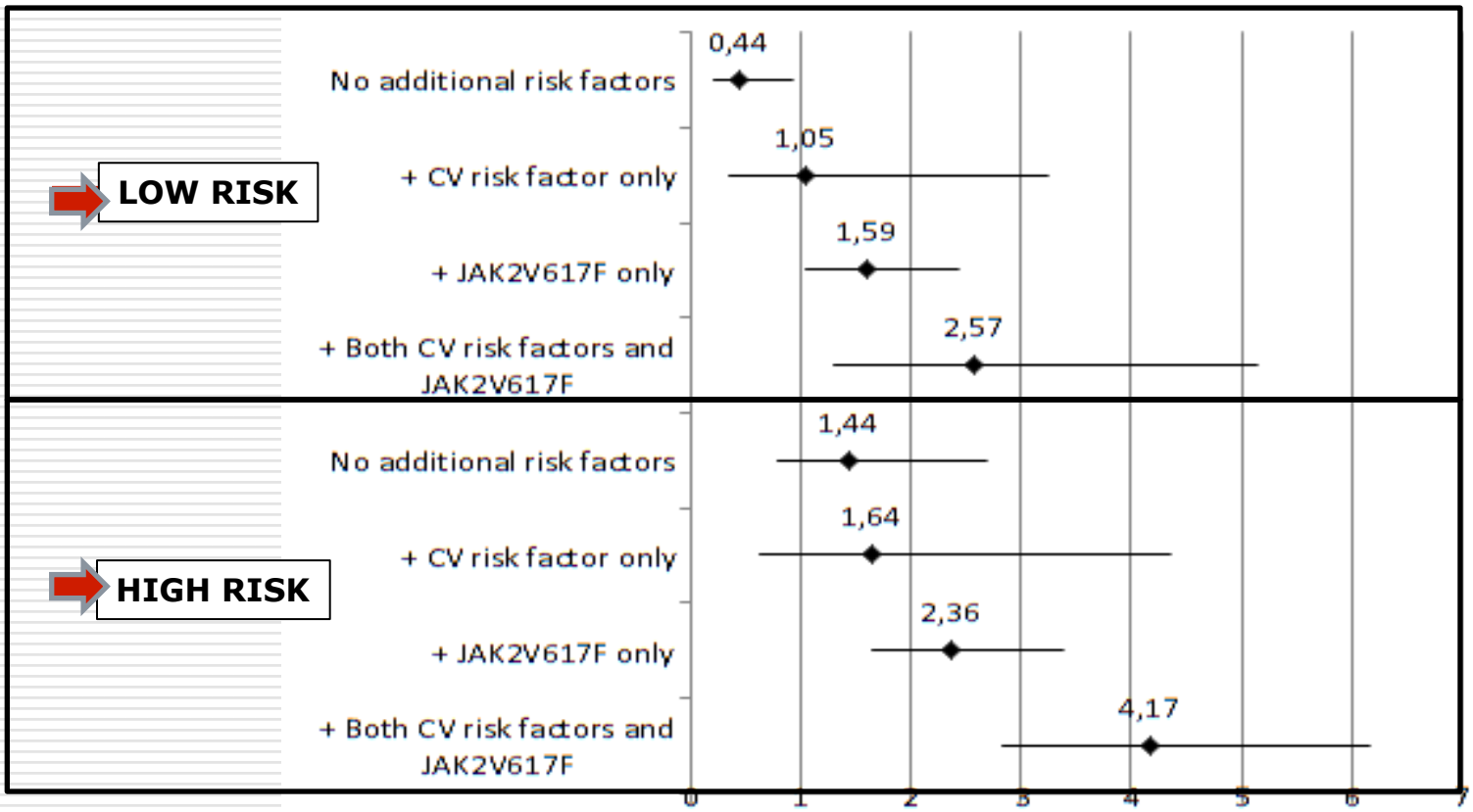
* Multivariate model adjusted for: sex, Hb, WBC and plt counts, HU and aspirin

*Leukocytosis associated with arterial and not venous thrombosis
HR=

Carobbio A *et al, Blood.* 2011;117:5857-9; Barbui T et al, Blood 2012.

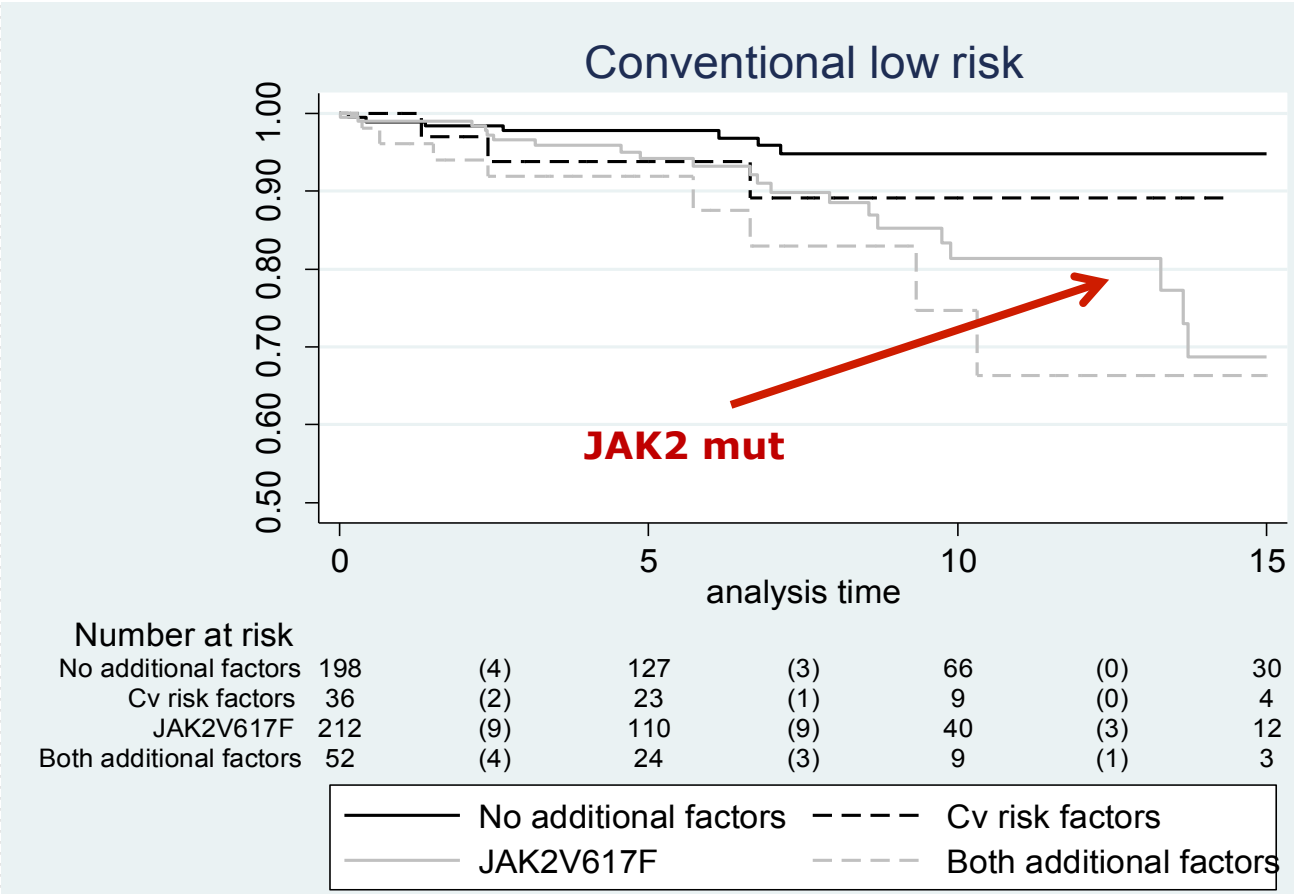

Thrombosis-free survival in ET and PV patients
by JAK2 mutational status
1.00
0.90
0.80
0.70
0.60
0.50
N
Incidence rate
ET JAK2 WT
268
0.96% pts-yr
ET JAK2V617F
422
2.57% pts-yr
PV JAK2V617F
1240
2.54% pts-yr
0
5
10
15
20
Years from diagnosis

Influence JAK2 mutation status on the rate of vascular events in a cohort of 1019 conventionally defined low and high risk patients with ET



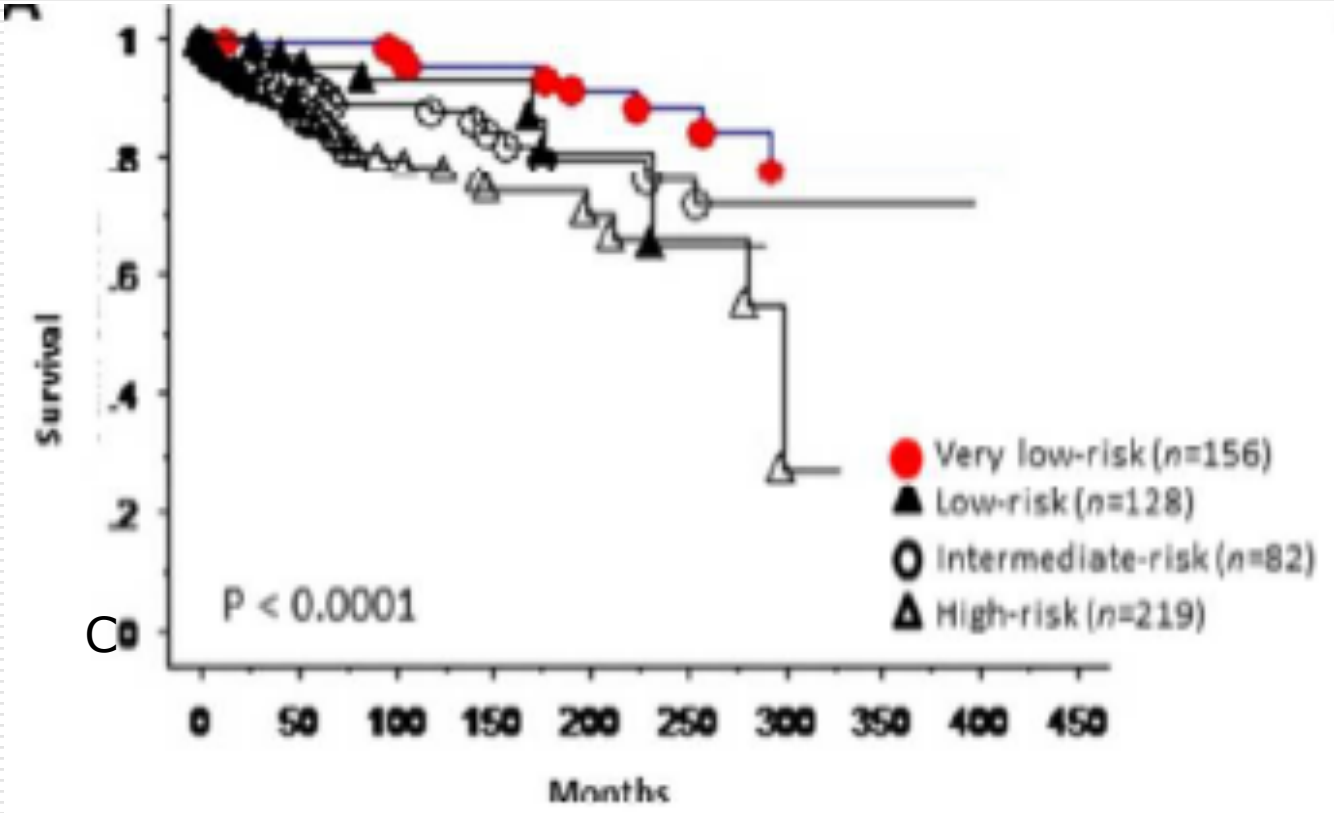
Barbui T et al, Blood Cancer J. 2015; Barbui T. AJH 2016

Conventionally defined low risk patients subgroups according to the presence or absence of cardiovascular risk factors and JAK2 mutation)



Barbui T et al, BCJ 2015

Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients



Mahnur Haider et al, AJH 2016

Stratification of the risk of thrombosis and prophylaxis in patients with ET

Very low thrombotic risk

- No history of thrombosis
- Age <60 years
- JAK2V617F-unmutated
- No cardiovascular risk factors (CVR)

Annual rate 0,44%

Low thrombotic risk

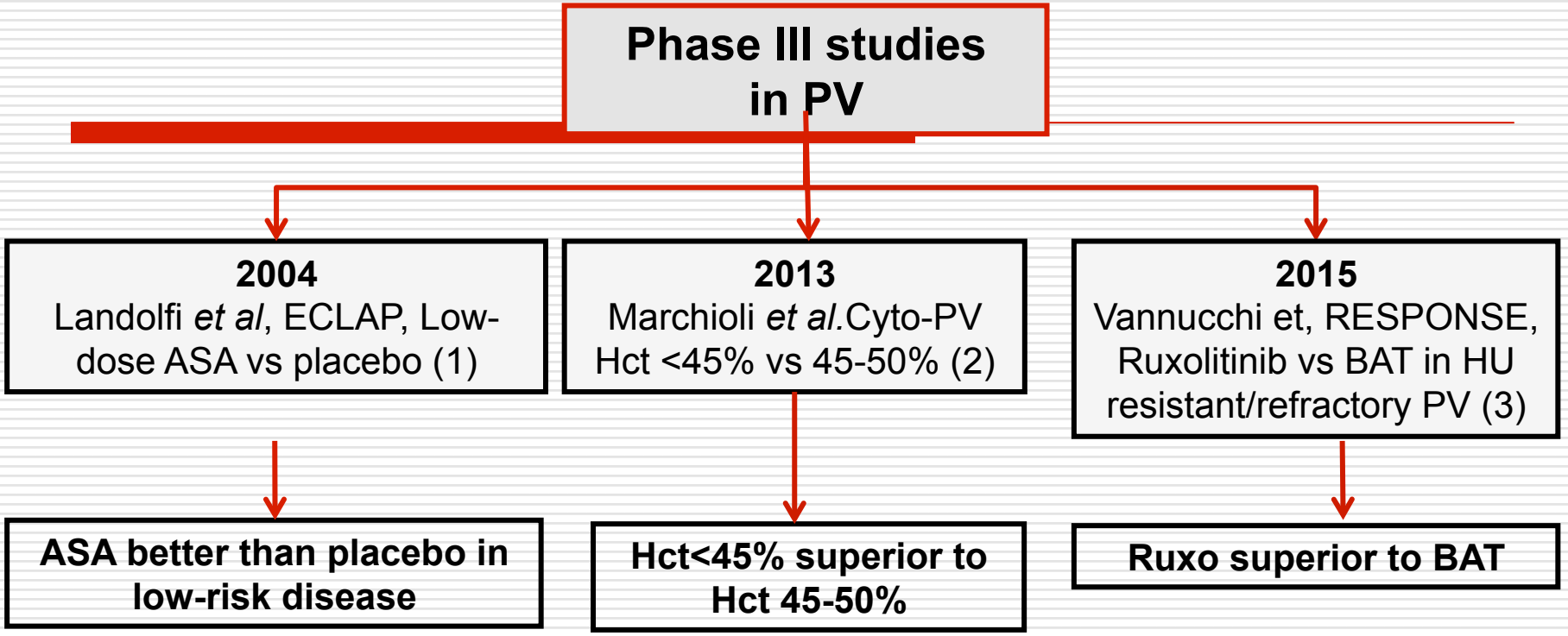
- No history of thrombosis
- Age <60 years
- JAK2V617F-mutated and/or CVR present

Annual rate 2,57%

High thrombotic risk

- History of thrombosis and/or Age ≥ 60 year
- JAK2V617F-mutated and/or CVR present

Recent Randomized Clinical Trials in PV



Prinary end-point Thrombosis incidence	Primary end-point Thrombosis incidence	Primary end-point Hct control and reduction of splenomegaly
3.2% *vs.* 7,9%	2,7% *vs.* 9,8%	21% vs 1%

1.N Engl J Med 2004;350:114-24; 2. N Engl J Med 2013;368:22-33. 3. N Engl J Med 2015;372:426-35..

Rates of thrombosis in low and high risk PV patients in ECLAP compared with CYTO-PV trial

Cyto-PV Study period: 2008-2012 *NEJM 2013;368(1):22-33.*
ECLAP Study period: 1997-2002 *NEJM 2004;350(2):114-24.*

	No Previous Thrombosis		Previous Thrombosis		Overall
	Age <65	**Age ≥65**	**Age <65**	**Age ≥65**	
CYTO-PV	4 (3.4)	9 (6.4)	3 (6.8)	3 (4.9)	19 (5.2)
IR per 100 person/yrs	**2.0**	**4.4**	3.8	**2.9**	**3.2**
ECLAP	34 (7.0)	62 (12.0)	29 (13.6)	101 (**24.1**)	226 (**13.8**)
IR per 100 person/yrs	**2.5**	**4.9**	**5.0**	**10.9**	**5.5**

Barbui T et al, Blood 2015

Rates of incident thrombosis in conventionally defined low and high risk PV by calendar period of diagnosis (N= 1,545)

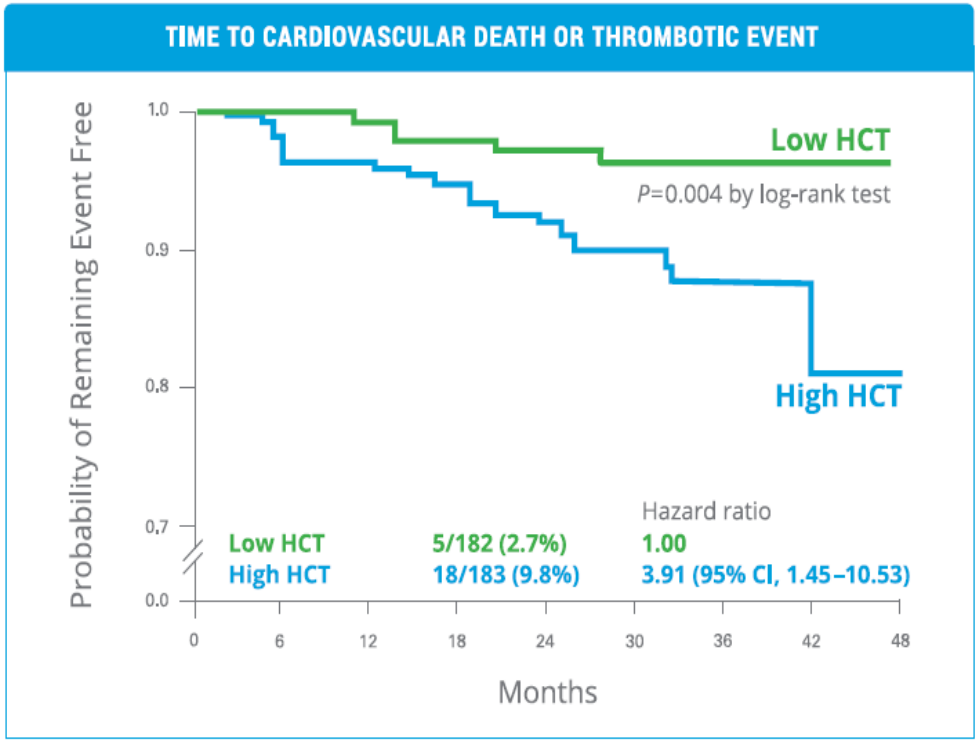
	LOW RISK N=	HIGH RISK N=
Dx before 2005 IR per 100 person/ yrs	IR: 2.03 % pts/ yr; 95% CI: 1.58-2.61	**IR: 4.01 %** pts/yr; 95% CI: 3.28-4.90
Dx after 2005 IR per 100 person/ yrs	IR: 2.24 % pts/ yr; 95% CI: 1.33-3.78	**IR: 2.93 %** pts/yr; 95% CI: 1.89-4.54

Barbui T et al, AJH 2015, Feb 14, Epub, ahead of print

How to reduce the residual rate of thrombosis in PV (rates from 2 to 4%/pts/y)

- earlier establishment of PV diagnoses
- more precocious prescription of therapy
- appropriate use of cytoreductive drugs and prophylactic low-dose aspirin
- more stringent criteria of phlebotomy
- better management of cardiovascular risk factors and diminishing tobacco smoking
- Jak2 inhibitors
- Peg-IFN

Time to cardiovascular death and thrombosis according to intensive therapy

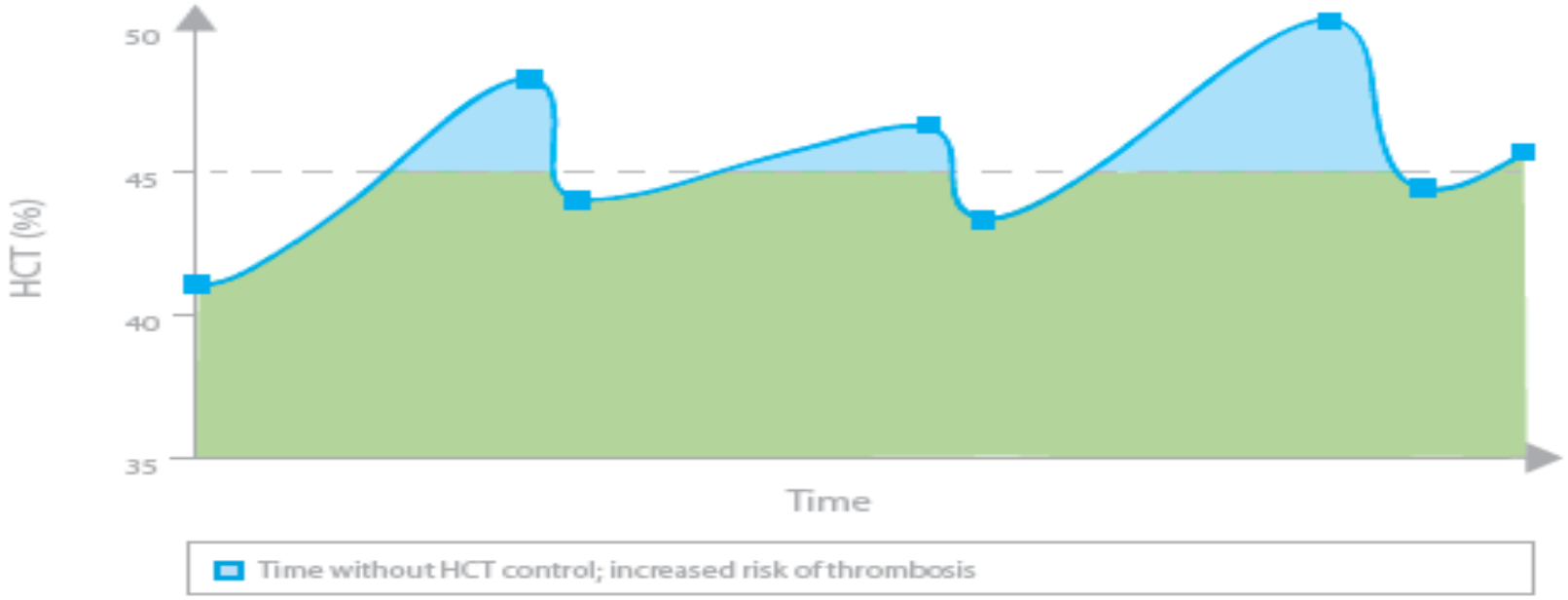


WBC (x10^9/L)	Events / patients (%)	Hazard ratio (95%CI), p-value
<7.0	4/100 (4.0)	1.00
7.0-8.4	4/84 (4.8)	1.58 (0.39-6.43), 0.52
8.5-11.0	8/88 (9.1)	2.69 (0.80-9.05), 0.11
≥11.0	**12/93 (12.9)**	**3.90 (1.24-12.3), 0.023**

1. Marchioli R, et al. N Engl J Med. 2013;368:22-33; Barbui et al,Blood 2015.

Hypothetical representation of HCT fluctuation in patients with phlebotomy or with HU resistance

Does time without HCT control increase risk of thrombosis?

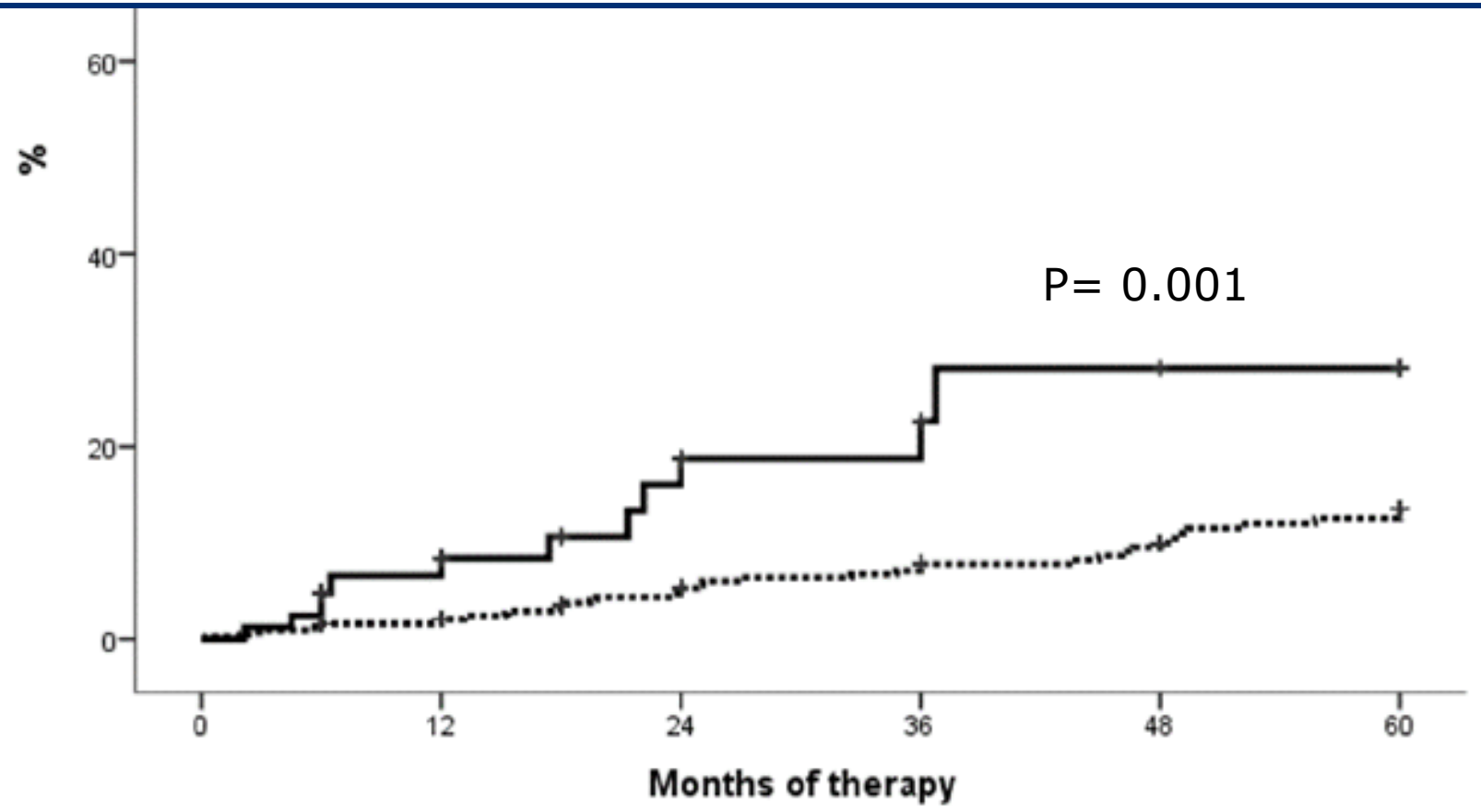


Multivariate analysis of factors predicting thrombosis in 533 patients with polycythemia vera treated with hydroxyurea

	HR	95%CI	P value
Male sex	0.5	0.25-1.1	0.08
Cardiovascular risk factors	2.2	0.8-5.6	0.1
Thrombosis at PV diagnosis	4.7	2.3-9.8	<0.0001
HU with 3 or more PHL per year	3.3	1.5-6.9	0.002

Alvarez-Larran A. et al Haematologica September 2016

Time to thrombosis in PV patients treated with HU and 3 or more phlebotomy per year (solid line) or with HU and 0-2 phlebotomies per year (dotted line)



Alvarez-Larran A. et al Haematologica September 2016

The combination hematocrit <45% and WBC < 11 x10^9/L meets the definition of surrogate end-point of thrombosis

Requirements

- The treatment significantly affects the "marker" and the "true" endpoint.
- The "marker" significantly correlates with the "true" endpoint
- After adjustment for the "marker", no additional effect should be observed

Then and only then "biomarkers" qualify as surrogate endpoints

Prentice 2009

Clinical trials of pegylated IFNs in MPNs

High rates of hematological response

	PVN-1 (PV n=40)	PV MD Anderson (n=40)	PV Peginvera (n=47)	ET (n=36)
CR	91%	78%	53%	86%
PR	9%	3%	45%	6%
Failure	0%	18%	2%	8%

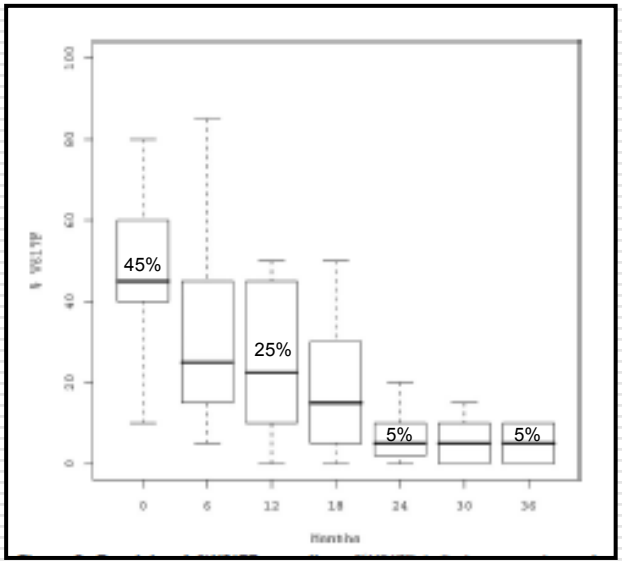
Stop for toxicity

	PVN-1 (PV n=40)	PV + ET (n=76)
Stop for toxicity - 1 year	8%	10%

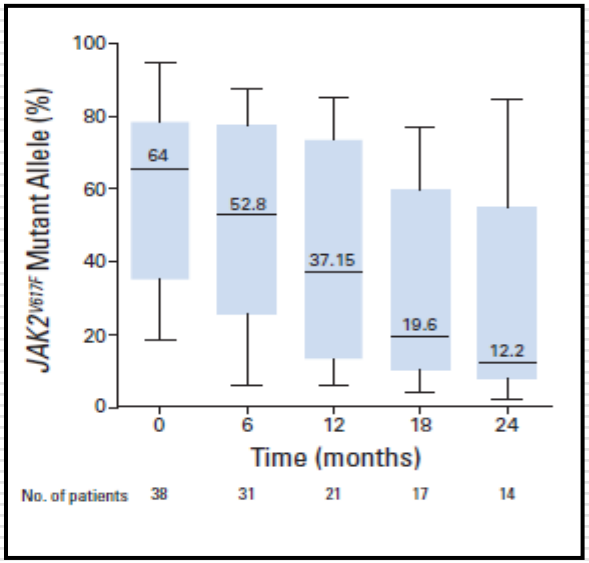
Kiladjian et al, Blood, 2008 *Quintas Cardama et al, JCO, 2009* *Them et al, Am J Hematol, 2015*

Clinical Trials of Pegylated IFNs in PV

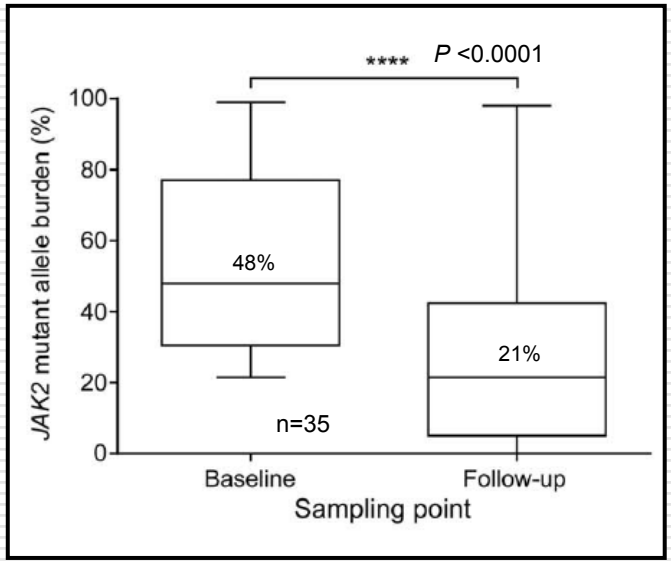
Dynamics of *JAK2*V617F allele burden



Kiladjian *et al*, 2008



Quintas-Cardama *et al*, 2009



Them *et al*, 2015

Kiladjian *et al*, Blood 2008;112(8):3065-3072
Quintas-Cardama *et al*, J Clin Oncol 2009;27(32):5418-5424
Them *et al*, Am J Hematol 2015;90(4):288-294

PVN-1 Long-term Analyses of Peg-IFNα-2a

- Cumulative incidence of molecular CR:
  - 14% at 2 years
  - 30% at 4 years
- Clinical remissions without cytoreductive therapy
  - 27% of patients could stop Peg-IFNα-2a and remained in hematological CR without cytoreductive treatment for a median time of 31 + months (up to 66+ months)
- Additional findings:
  - No vascular events reported (expected: 6-10)
  - In some patients histological complete remission was observed

courtesy of JJ Kiladjian; EHA 2015

Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera

Key Points

- The novel IFNα-2b, ropeginterferon alfa-2b, administered once every 2 weeks has low toxicity and induces high and sustained response rates in polycythemia vera patients.
- Ropeginterferon alfa-2b induces significant partial and complete molecular response rates, as reflected by reduction of *JAK2* allelic burden.

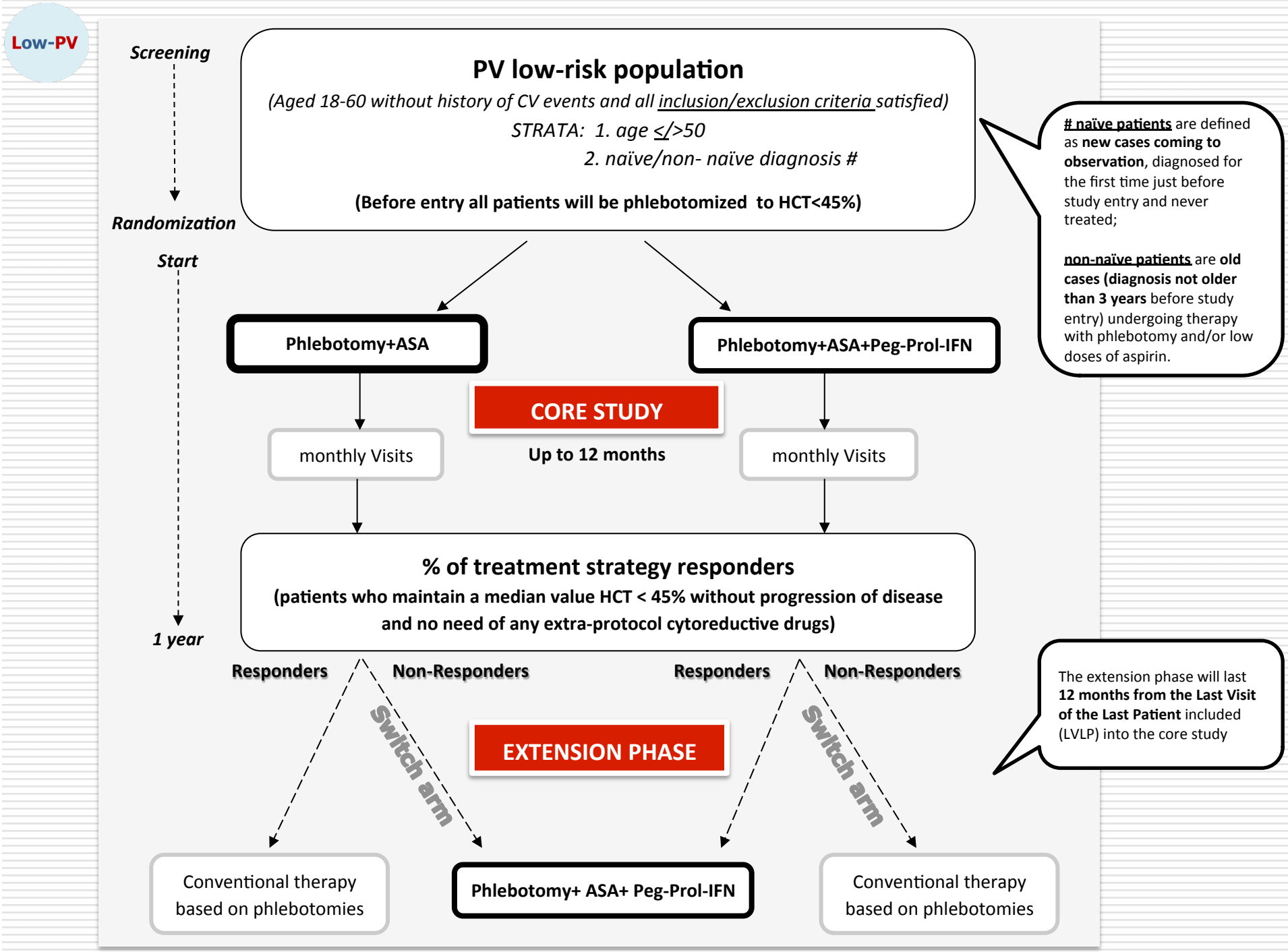
Gisslinger et al, Blood 2015

Low-PV

Low-PV phase II randomized trial

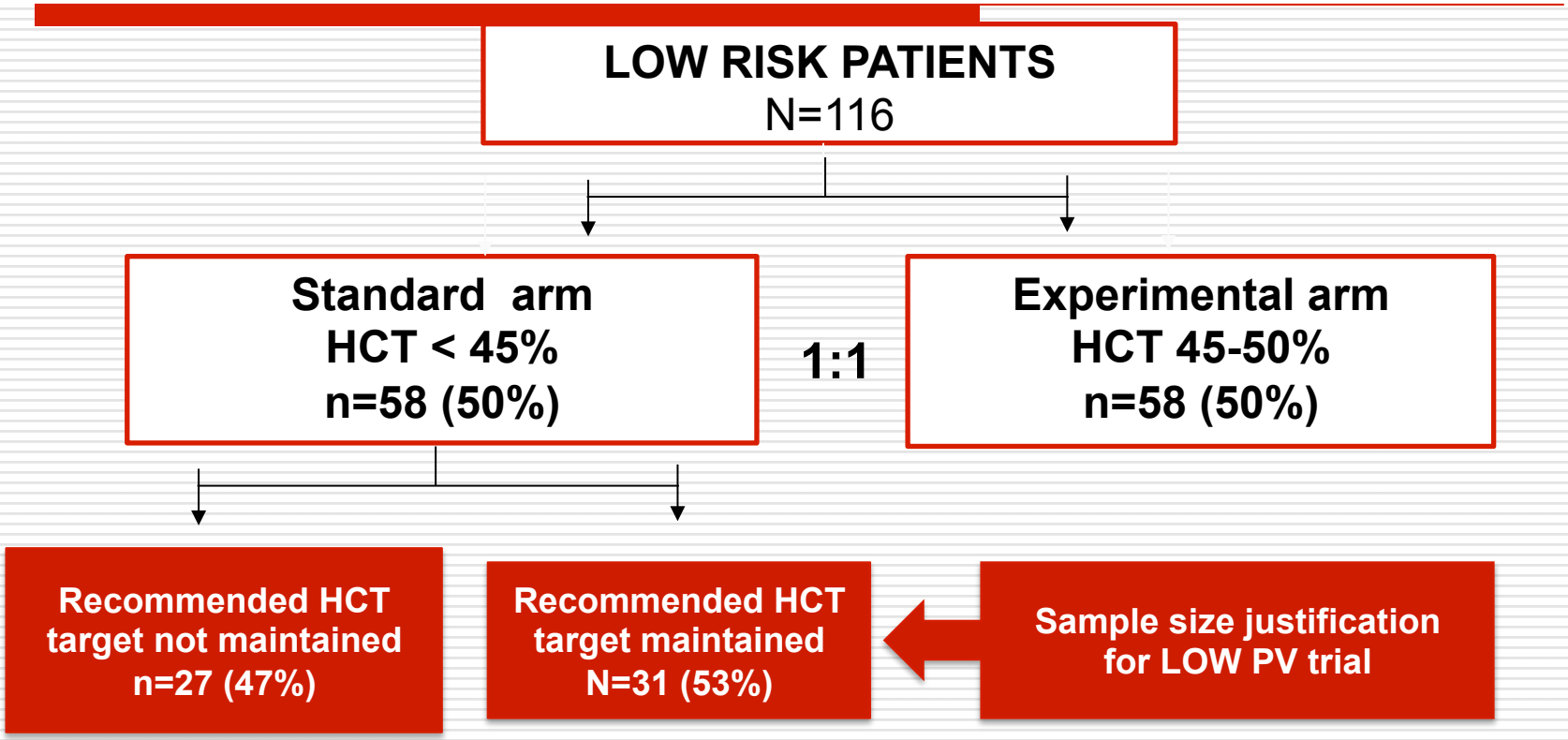
RCT testing the benefit/risk profile of pegylated-proline-Interferon-alpha-2b (AOP2014) added to phlebotomy + low-dose aspirin in low-risk patients with WHO-Polycythemia Vera (PV)

Promoter: Foundation for Clinical Research (FROM)
Principal Investigator: Alessandro Rambaldi (USC Hematology)
Ospedale Papa Giovanni XXIII- Bergamo, Italy


Low-PV
Screening
Randomization
Start
1 year
PV low-risk population
(Aged 18-60 without history of CV events and all inclusion/exclusion criteria satisfied)
STRATA: 1. age ≤/>50
2. naïve/non- naïve diagnosis #
(Before entry all patients will be phlebotomized to HCT<45%)
naïve patients are defined as new cases coming to observation, diagnosed for the first time just before study entry and never treated;
non-naïve patients are old cases (diagnosis not older than 3 years before study entry) undergoing therapy with phlebotomy and/or low doses of aspirin.
Phlebotomy+ASA
Phlebotomy+ASA+Peg-Prol-IFN
CORE STUDY
Up to 12 months
monthly Visits
monthly Visits
% of treatment strategy responders
(patients who maintain a median value HCT < 45% without progression of disease and no need of any extra-protocol cytoreductive drugs)
Responders
Non-Responders
Responders
Non-Responders
Switch arm
Switch arm
EXTENSION PHASE
The extension phase will last 12 months from the Last Visit of the Last Patient included (LVLP) into the core study
Conventional therapy based on phlebotomies
Phlebotomy+ ASA+ Peg-Prol-IFN
Conventional therapy based on phlebotomies

Low-PV

The sample size calculation in Low-PV trial derives from the CYTO-PV results in low-risk subgroup



CONCLUSION

- The prevention of venous and arterial vascular complications still represents **an unmet clinical need** both in low and high risk ET/ PV patients.
- An annual rate of thrombosis around **2% in low risk and greater than 3-4% in high risk cases** was documented in recent studies.
- These figures **exceed the estimates in non MPN controls** where the annual rates of arterial and venous thrombosis are around 0.5% and 0.1% respectively.
- The possibility exists that **different subgroups of low risk ET/ PV** patients might be identified suggesting the opportunity of different personalized treatment.