Policitemia Vera
Nuovi approcci terapeutici

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SIMTI

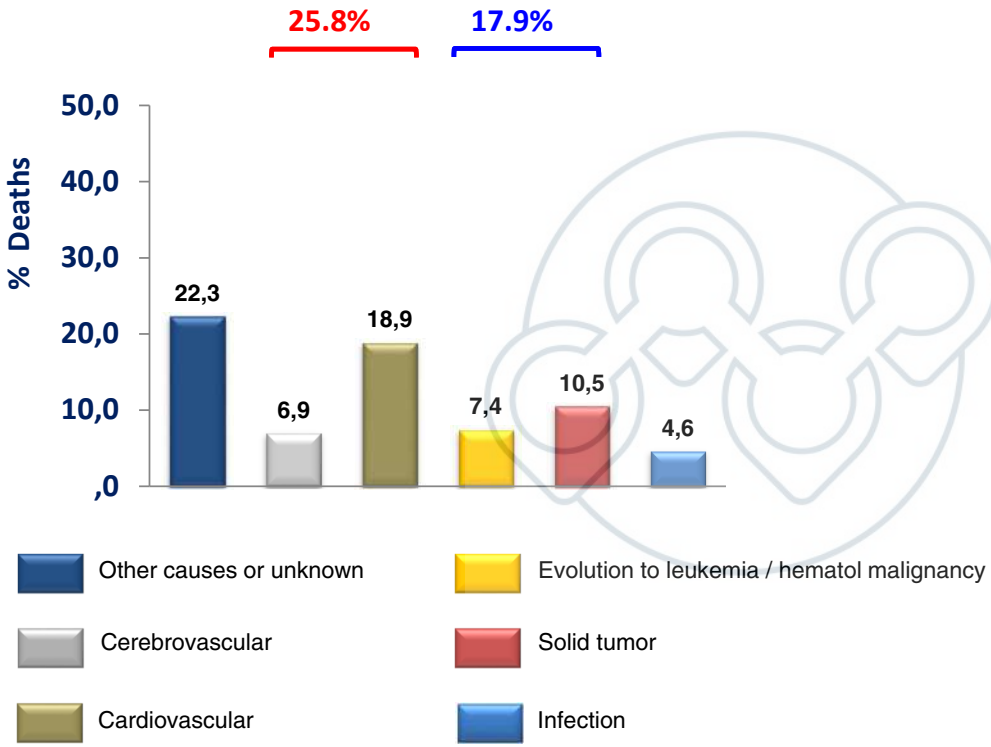
Il/La sottoscritto/a, in qualità di Relatore
dichiara che

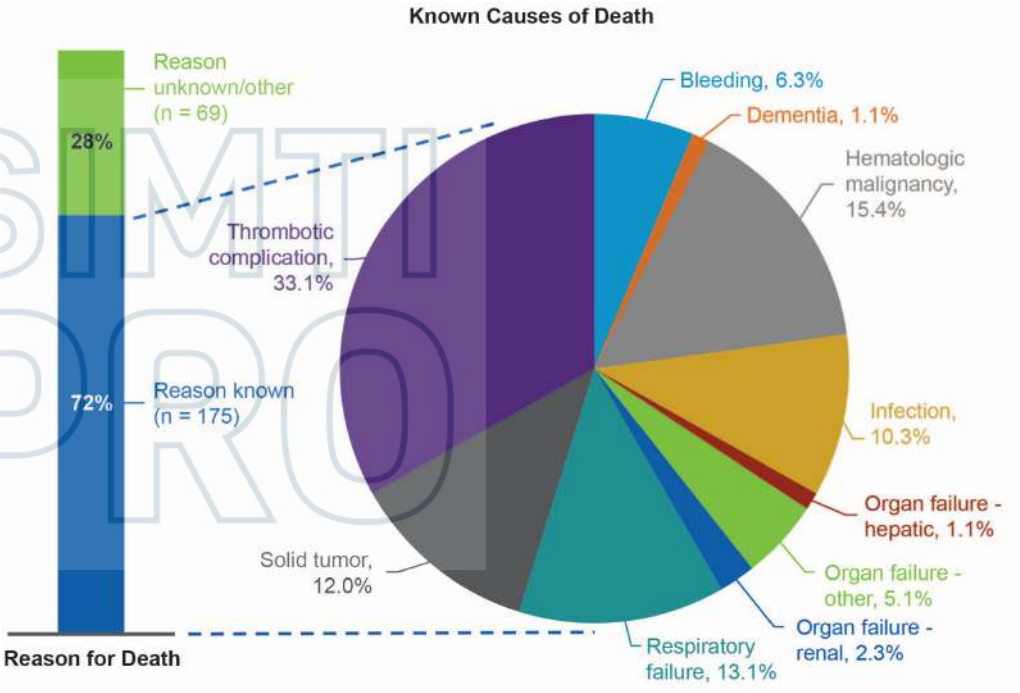
nell’esercizio della Sua funzione e per l’evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

Open issues in the management of Polycythemia Vera

- Reduce the rate of thromboembolic and hemorrhagic events
- Improve quality of life
- Prevent the evolution of the disease to post-PV myelofibrosis and acute leukemia

Causes of death in PV patients

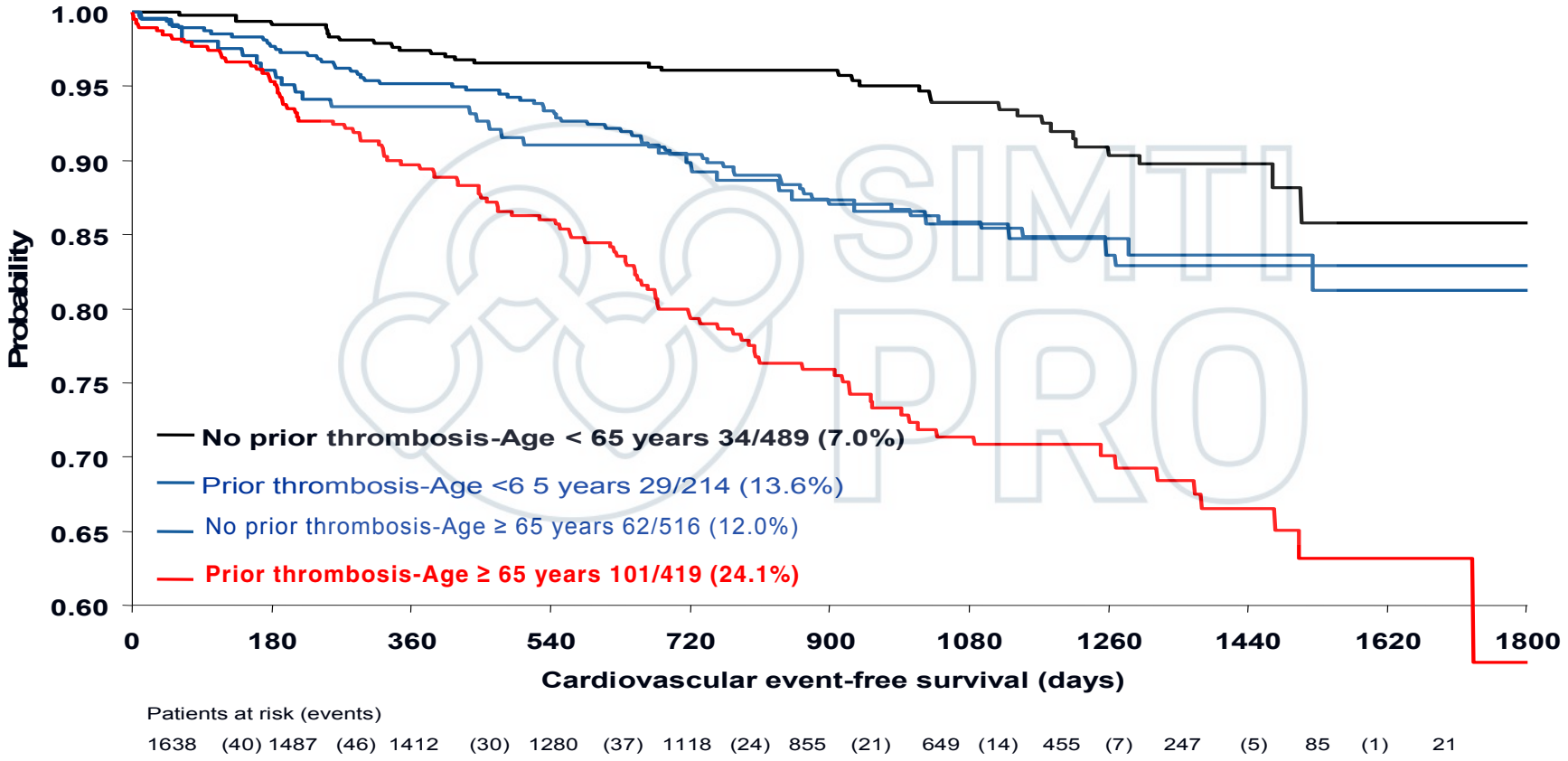




[1] Hultcrantz et al. *J Clin Oncol* **2015**;33:2288-2295. [2] Stein et al. *ASH annual meeting* **2020**;abs#484.

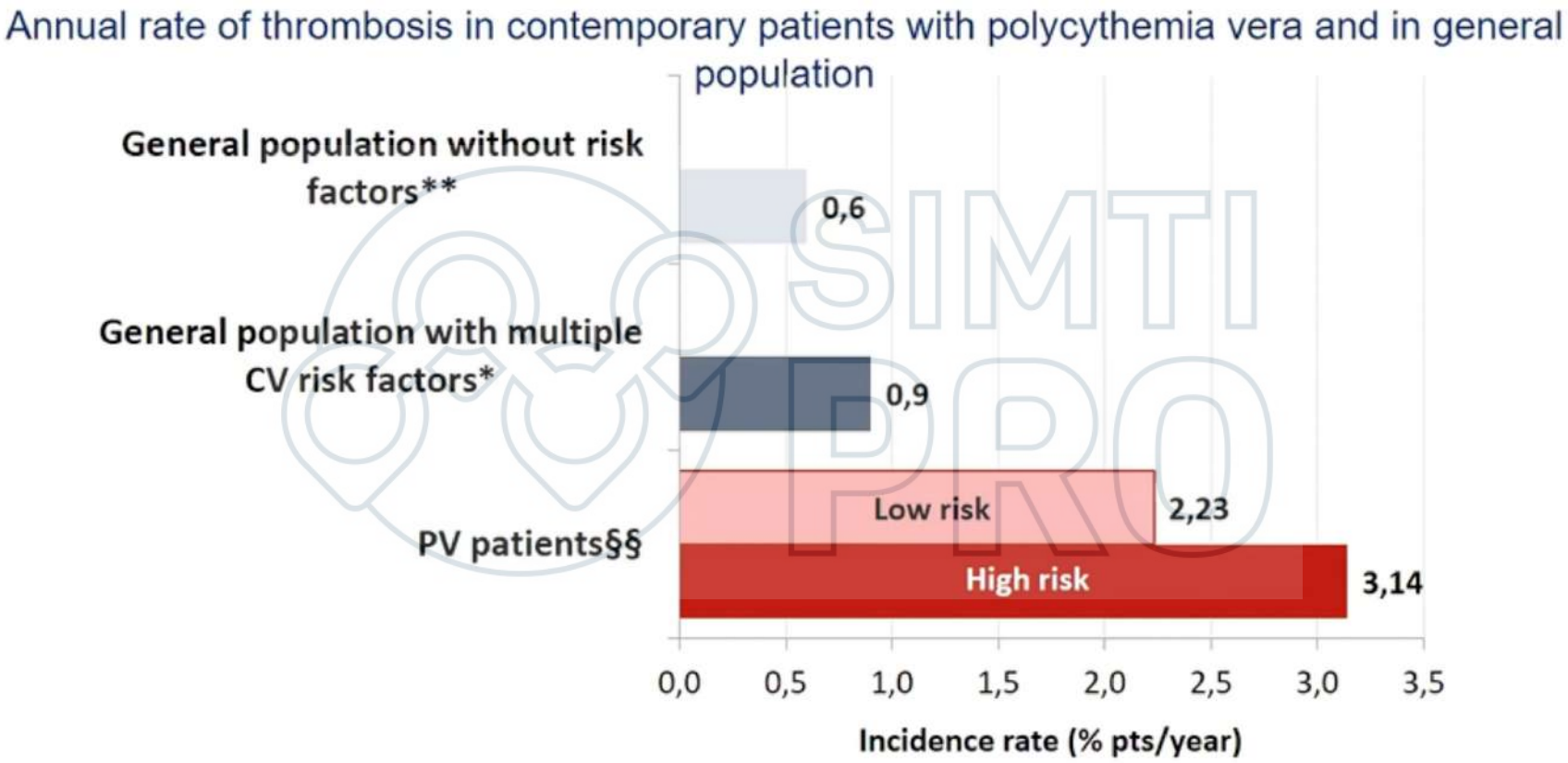
«Classic» risk factors: age and history of thrombosis

Determinant of thrombosis in 1,638 patients enrolled in the ECLAP study



Marchioli et al. *J Clin Oncol* **2005**;23:2224-2232.

Rates of thrombosis in low-risk PV are higher than in non-MPN population



Barbui et al. *Blood* **2014**;124:3021-3023.

Factors associated with thrombosis risk in PV

General factors

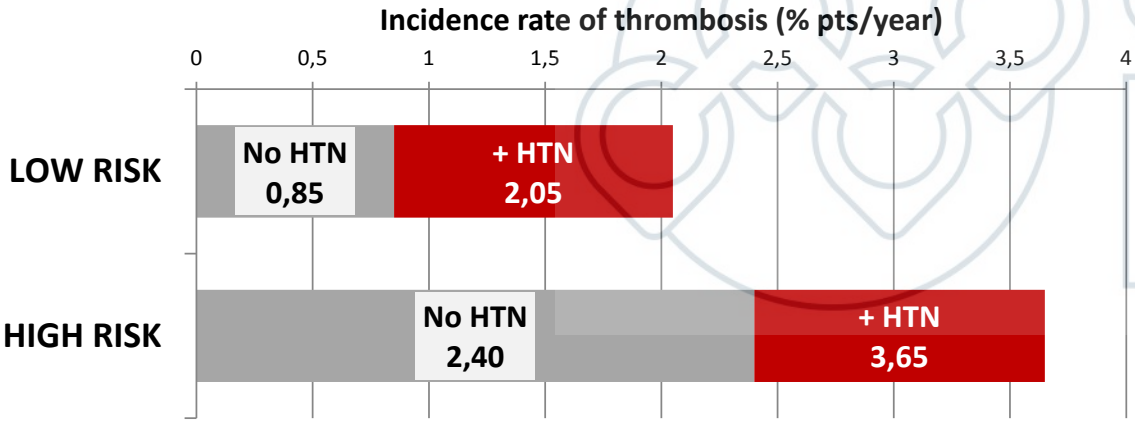
- Advanced age (> 60 years)
- History of thrombosis
- Cardiovascular risk factors (smoking, hypertension, dislypidemia, diabetes)
- Inherited or acquired thrombophilia

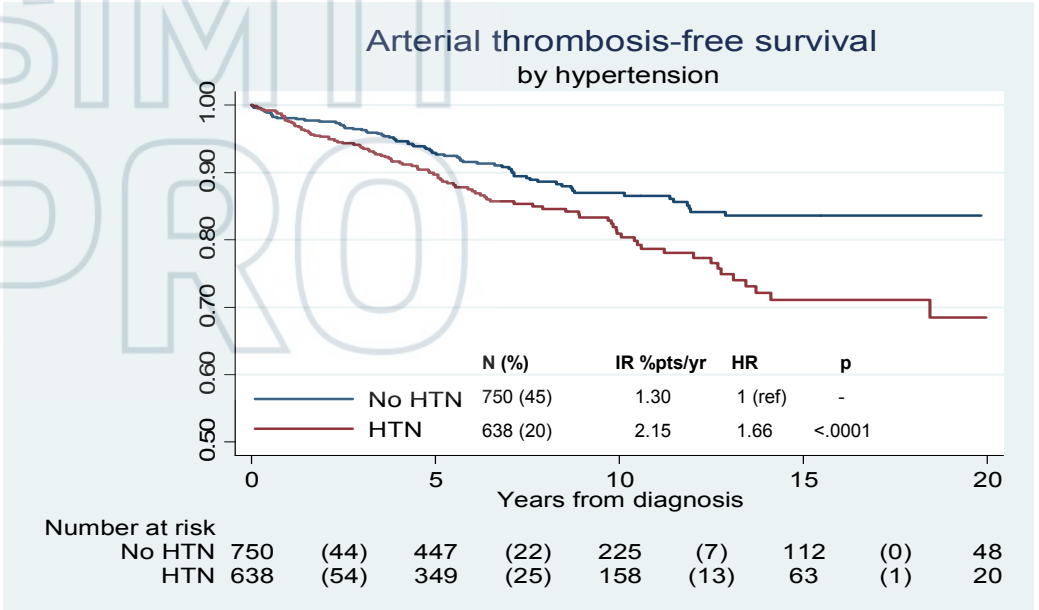
PV-specific factors

- Hypercythemia (high hematocrit, leukocytosis, *but not thrombocytosis*)
- Higher $JAK2^{V617F}$ mutation allele burden
- Platelet biochemical and functional abnormalities
- Coagulation activation
- Leukocyte and platelet activation

Cardiovascular risk factors

Additional effect of hypertension (HTN)
in Low and High risk PV cases enrolled in ECLAP trial





Barbui et al. *Am J Hematol* **2017**;92:e5.

Hypercythemia: the role of hematocrit

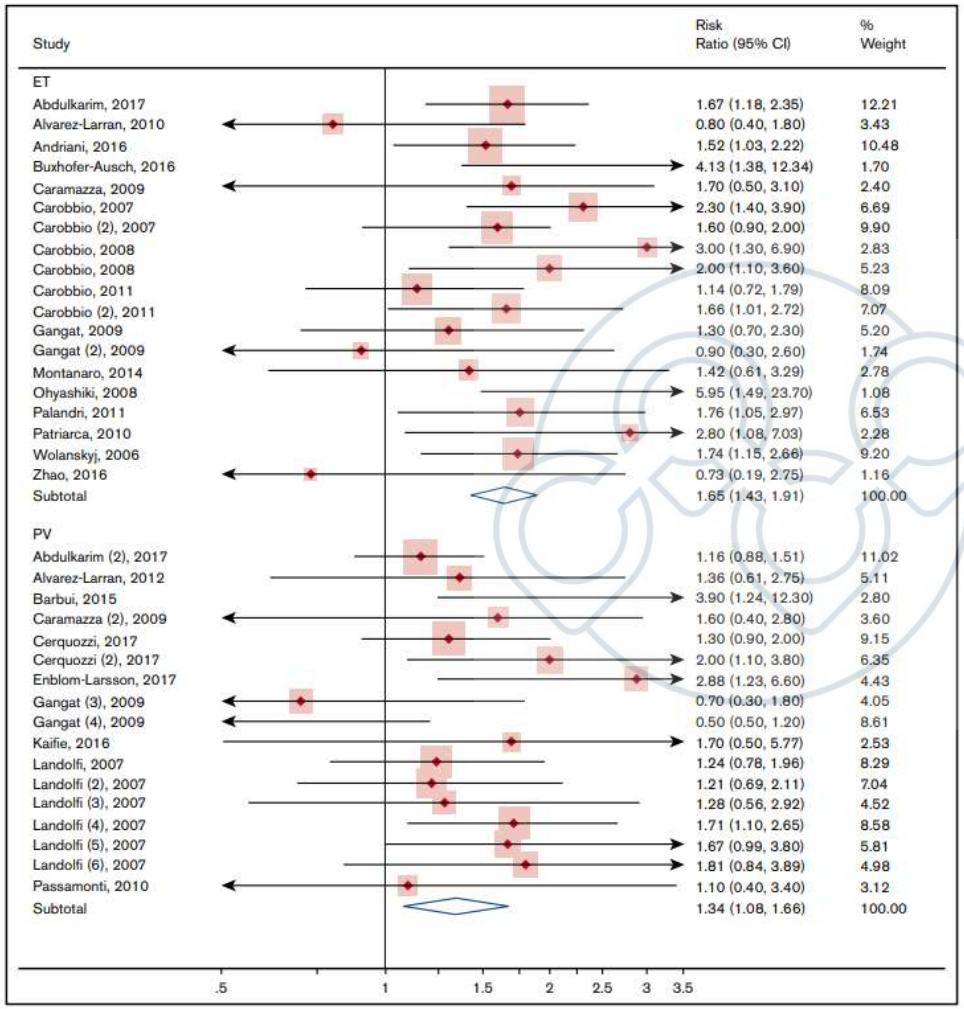
In PV patients with **Ht levels ≥45%**, the risk of CV-related **death or major thrombosis** was increased approximately **4 times** vs patients with Ht<45%

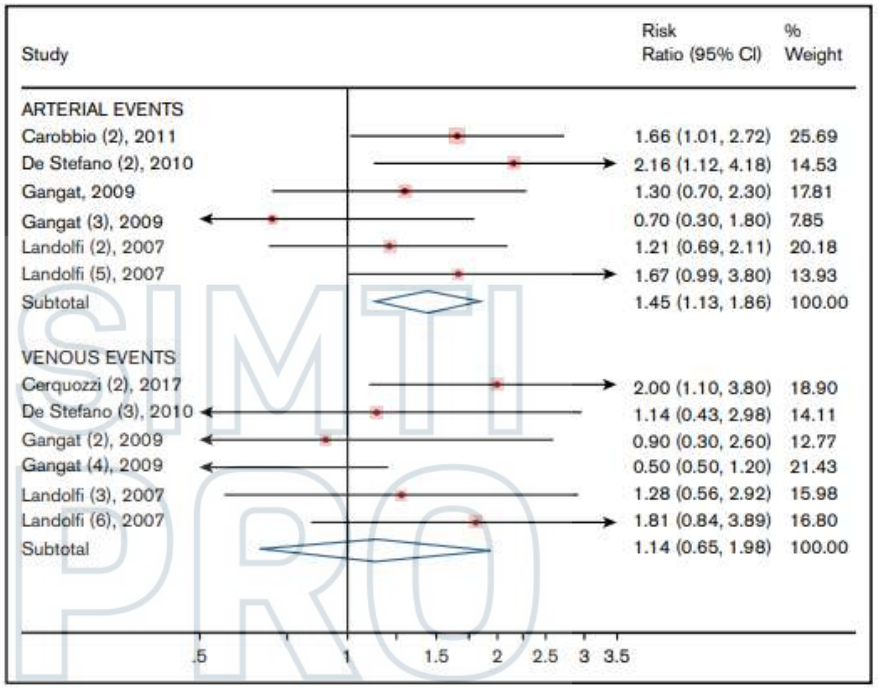
	HCT< 45% *n* = 182	HCT 45-50% *n* = 183	Total *n* = 365	HR (95% CI)	*p*
Primary Endpoint*, *n* (%) (CV death, MI, stroke, PAT, DVT, PE, TIA and abdominal thrombosis)	**5 (2.8)**	**19 (10.4)**	24 (6.6)	4.12 (1.54-11.0)	0.005
IR person/year	**1.1**	**4.7**	2.9		
Total CV events*, *n* (%) (Primary Endpoint plus superficial thrombosis)	**8 (4.4)**	**21 (11.5)**	29 (8.0)	2.83 (1.25-6.38)	0.012
IR person/year	**1.9**	**5.2**	3.5		

* After a median of 31 months of follow-up.

Marchioli et al. *N Engl J Med* **2013**;368:22-33.

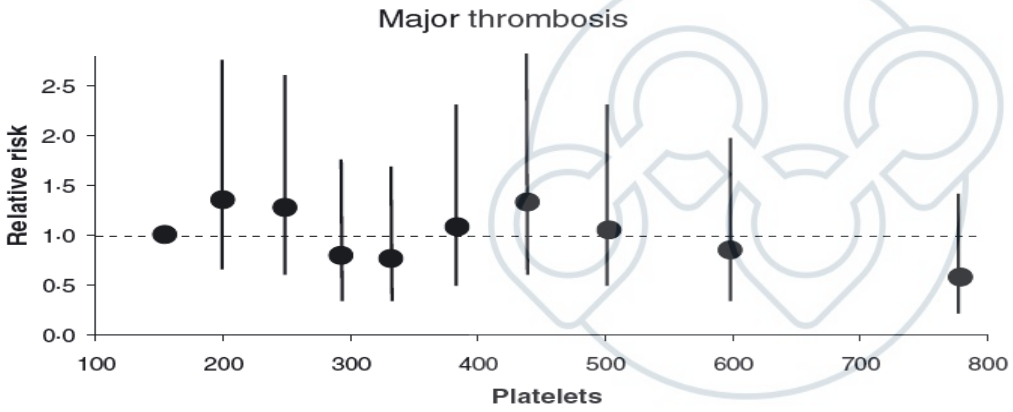
Hypercythemia: the role of WBC

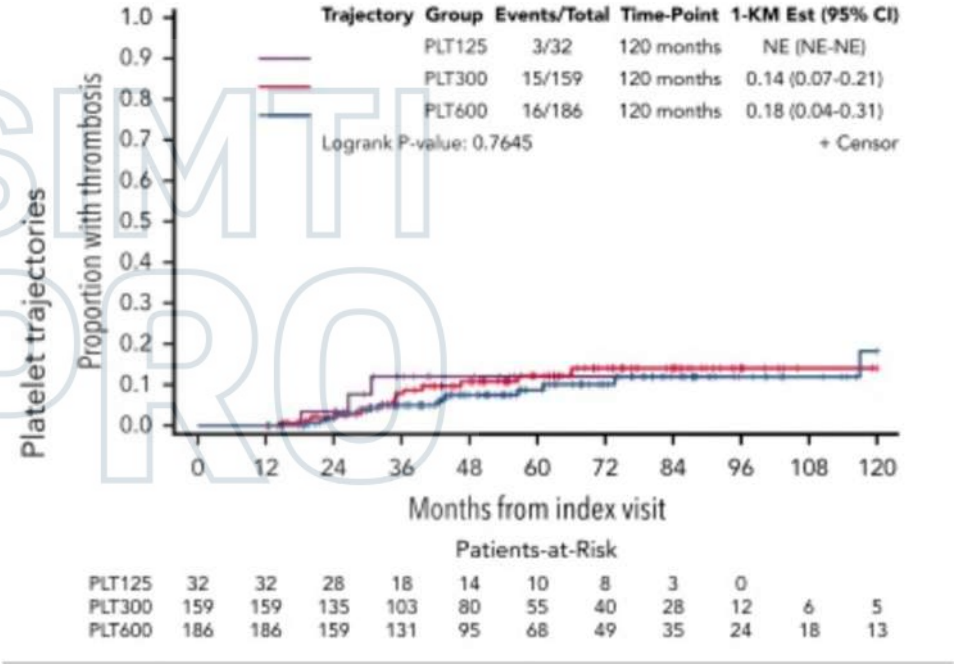




Carobbio et al. *Blood Adv* **2019**;3:1729-1737

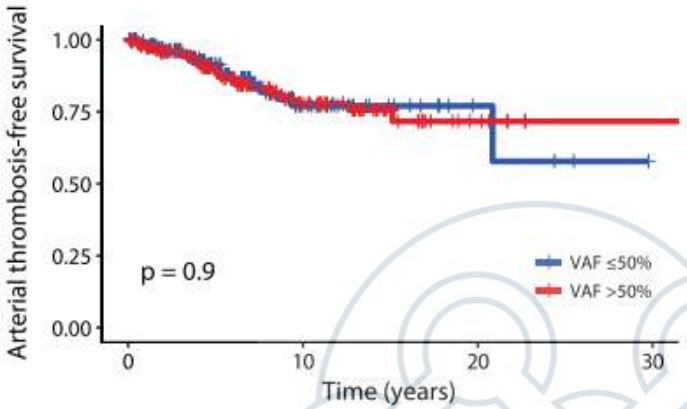
Hypercythemia: the role of platelets

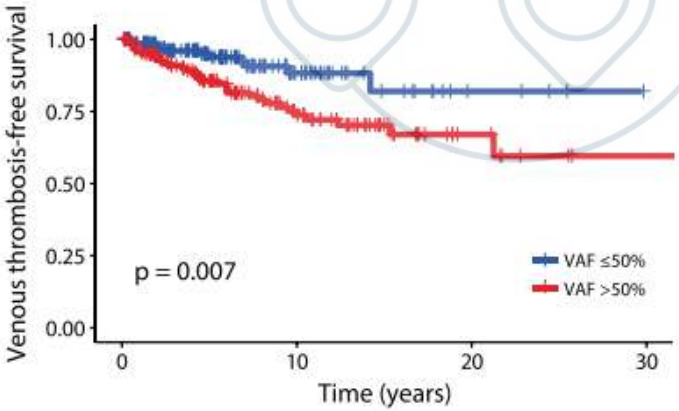




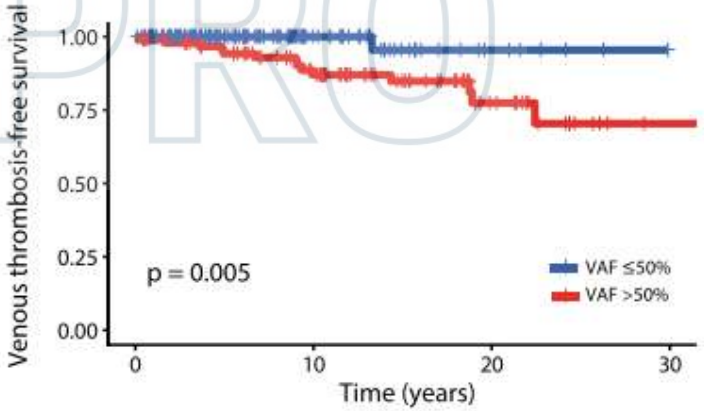
[1] Di Nisio et al. *Br J Haematol* **2007**;136:249-259. [2] Ronner et al. *Blood* **2020**;135:1696-1703.

JAK2 allele burden and thrombotic risk





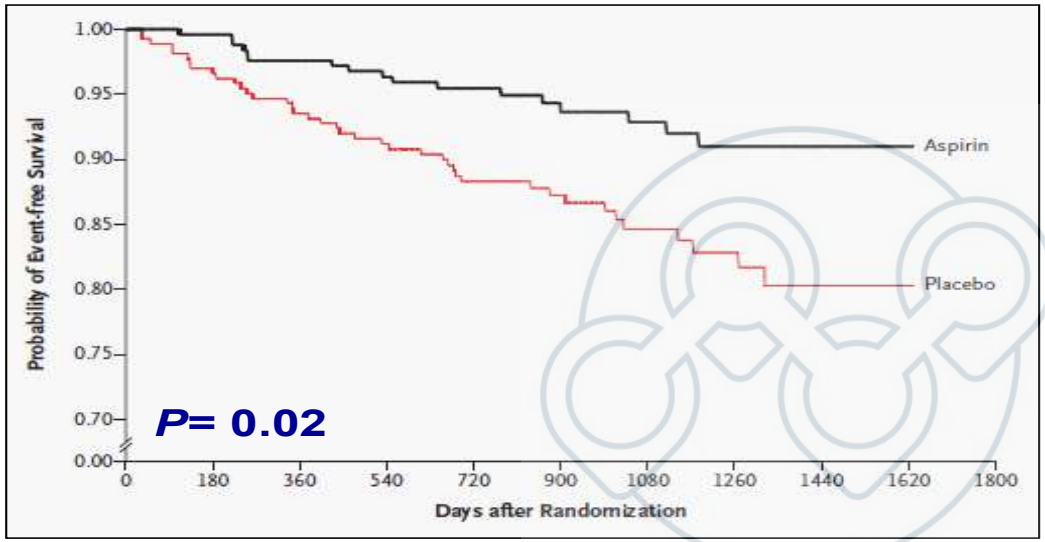
Low-risk patients



Guglielmelli et al. *Blood Cancer J* **2021**;11:199.

Treatment backbones: low dose aspirin and hematocrit Level <45%

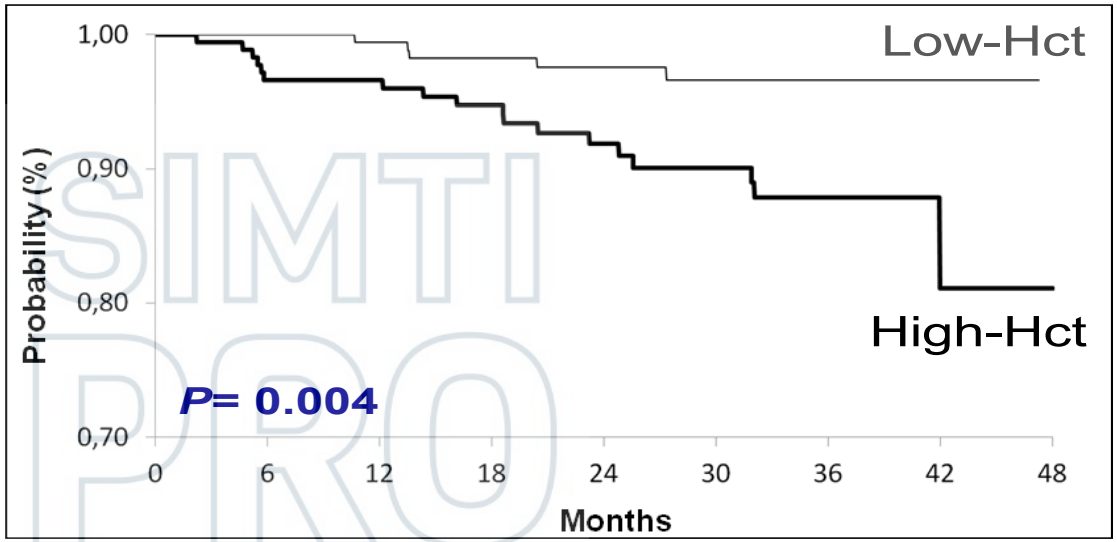
ECLAP Trial



- **Probability of survival free** of myocardial infarction, stroke, and death from cardiovascular causes, pulmonary embolism and DVT

  HR: 0.40 (95% CI, 0.18 to 0.91)

Cyto-PV Trial



Hct target level	Low Hct <45%	High Hct 45-50%
IR %person/year	1.1	4.4

P< 0.005

Primary Endpoint
(CV death, MI, stroke, PAT, DVT, PE, TIA, SVT)

Landolfi R et al. *N Engl J Med* **2004**;350:114-124. Marchioli R et al. *N Engl J Med* **2013**;365:22-33.

Cytoreduction therapy in PV: ELN guidelines

Category	Characteristics
Low risk	Age <60 years and no history of thrombosis
High risk	Age ≥60 years or history of thrombosis

European LeukemiaNet Indications for Cytoreduction

- **High-risk PV**, but also in **low-risk** in specific situations:
  - Frequent phlebotomy requirement or poor tolerance to phlebotomy
  - Severe disease-related symptoms
  - PLT >1,500 x 10^9/L
  - Progressive leukocytosis
  - Symptomatic and progressive splenomegaly

Options for first-line cytoreduction include HU and IFN (and busulfan for very eldely patients)

Barbui et al. *Leukemia* **2018**;32:1057-1069.

Recommendations for cytoreduction in LOW-RISK patients

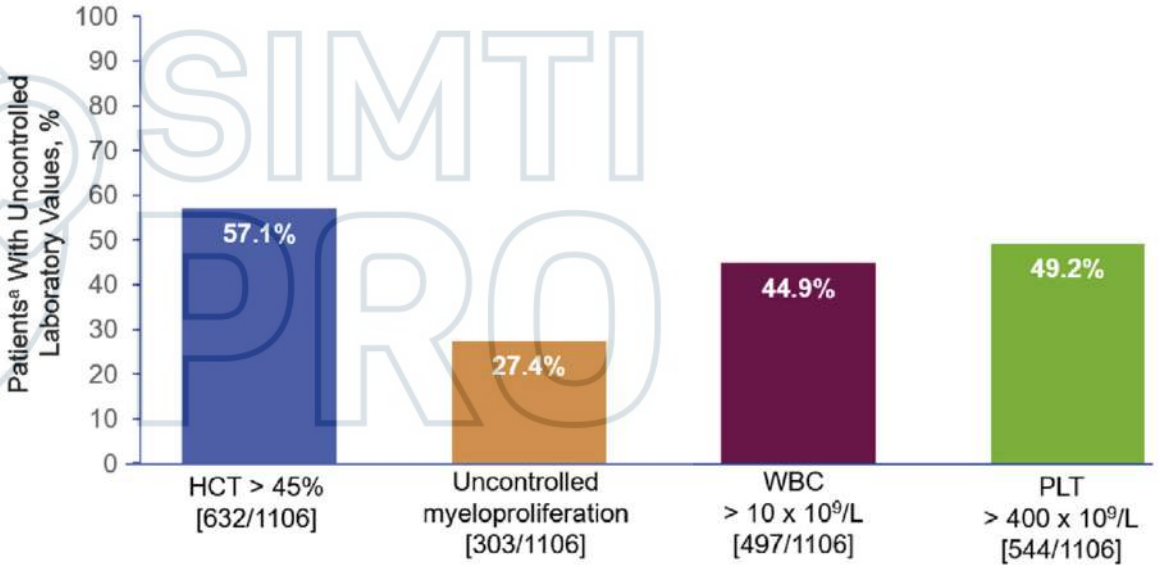
Cytoreduction is recommended	• poor tolerance to **phlebotomy**, strictly defined • symptomatic progressive **splenomegaly** (increase by >5 cm in the past year) • persistent **leukocytosis** (leukocyte count >20 × 10^9 cells per L confirmed at 3 months
Cytoreduction should be considered	• progressive (at least 100% increase if baseline count is <10 × 10^9 cells per L or at least 50% increase if baseline count is >10 × 10^9 cells per L) and persistent (leukocyte count >15 × 10^9 cells per L confirmed at 3 months) **leukocytosis** • extreme **thrombocytosis** (>1500 × 10^9 platelets per L), bleeding manifestations related to the disease irrespective of the platelet count, or both • **inadequate haematocrit control** with phlebotomies, i.e. a need for at least six phlebotomies per year for at least 2 years in the maintenance phase
Cytoreduction can be considered	• high **symptom burden** (total symptom score ≥20) or severe itching (itching score ≥5) that are not ameliorated by phlebotomy, antiplatelet therapy, or antihistamines • on an individual basis in patients reporting a **relevant cardiovascular risk**, provided that primary prevention strategies have been implemented

Marchetti et al. *Lancet Haematol* **2022**;9:e301-311.

Dose intensity and efficacy of hydroxyurea in the real world (REVEAL study)

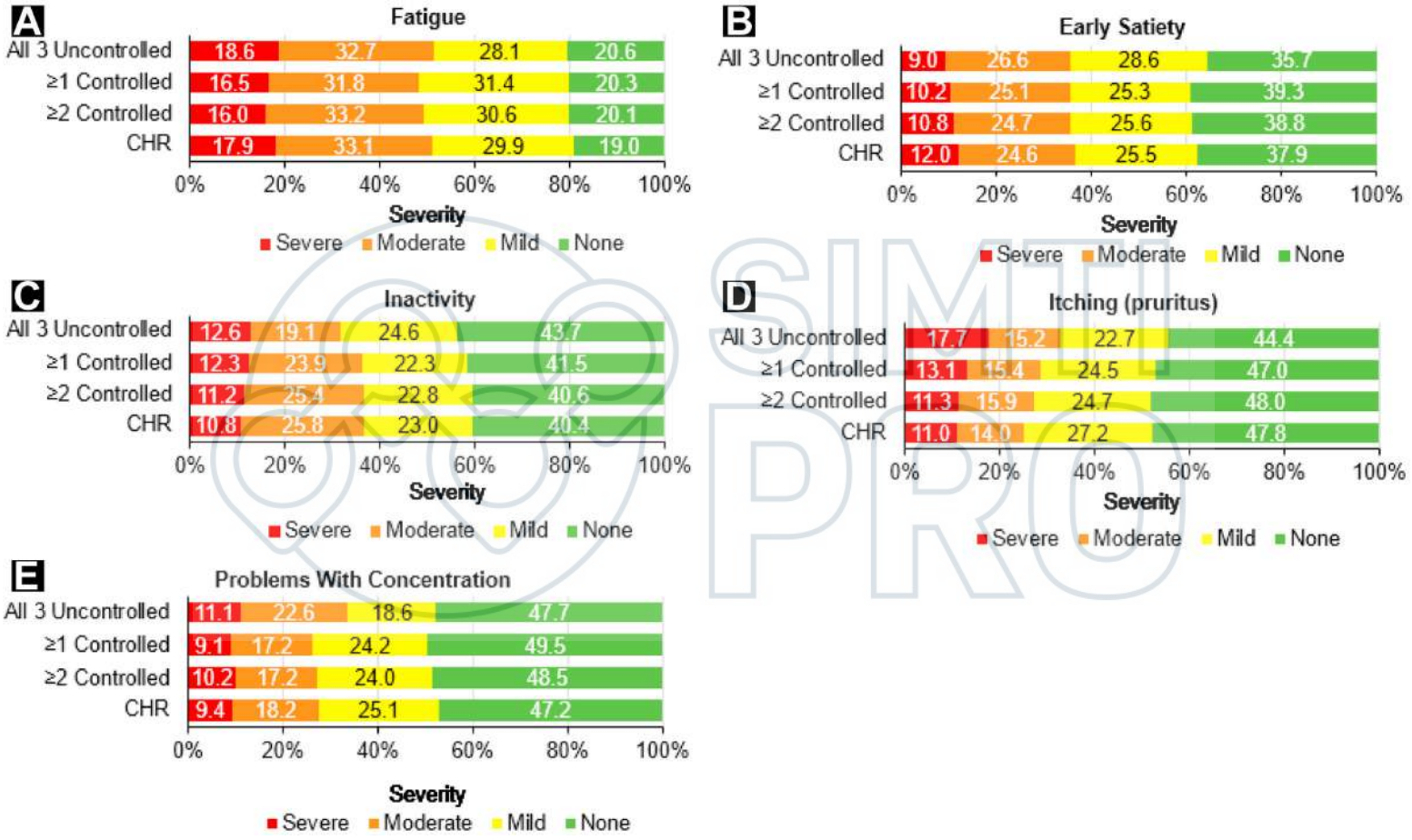
Table 3 HU Dose Intensity and Exposure

	Received HU for ≥ 3 Months (n = 1381)
Median maximum daily dose (range), mg/d	1000.0 (71.4-5571.4)
Maximum daily dose, mg/d, n (%)	
< 400	91 (6.6)
500	415 (30.1)
750	159 (11.5)
1000	423 (30.6)
1500	204 (14.8)
2000	61 (4.4)
> 2000	28 (2.0)
Median duration of maximum daily dose, (range), mos	19.6 (0.0-38.5)
Median HU exposure post-index (range), mos	23.6 (3.1-38.5)



Grunwald et al. *Clin Lymphoma Myeloma Leuk* **2020**;20:219-225.

Blood count control does not imply symptom control



Grunwald et al. *Clin Lymphoma Myeloma Leuk* **2019**;19:579-584.

Predictors of complete response to hydroxyurea

Characteristics before treatment	CR (n. 195)	SubOR (n. 467)	p value
Age, median (range), years	71 (43-89)	65 (21-89)	**<0.001**
Male sex, %	43.1%	55.7%	**0.003**
JAK2^{V617F}≥50%, % on 426 evaluable	39.0%	54.1%	**0.004**
Platelet count, median (range), x 10^9/L	497 (159-1279)	457 (138-1209)	0.03
Leukocytes, median (range), x 10^9/L	10 (3.3-30)	10 (1-38)	0.93
Hemoglobin, median (range), g/dL			
Male	18.6 (12-23.6)	18.6 (12-24.8)	0.93
Female	17.8 (15.3-22)	17.5 (13.2-21.9)	0.05
Hematocrit, median (range), %			
Male	55.5 (38-72.5)	56.3 (38-73)	0.94
Female	54 (47.6-71.7)	54 (39-72)	0.81
Palpable spleen, % of 645 evaluable	16.6%	40%	**<0.001**
Spleen palpable at ≥5 cm BLCM	1.0%	7.7%	**0.001**
Symptoms, no. (%)	92 (47.1%)	315 (67.5%)	**<0.001**
Pruritus, no. (%)	31 (16.0%)	188 (40.3%)	**<0.001**
BMI ≥25, % of 398 evaluable	43.8%	49.9%	0.35
At least one CVRF, no. (%)	154 (79.0%)	362 (77.5%)	0.68
Thromboses pre-/at diagnosis, no. (%)	47 (24.1%)	122 (26.1%)	0.59

Compared to SubOR patients, at diagnosis CR patients were characterized by:

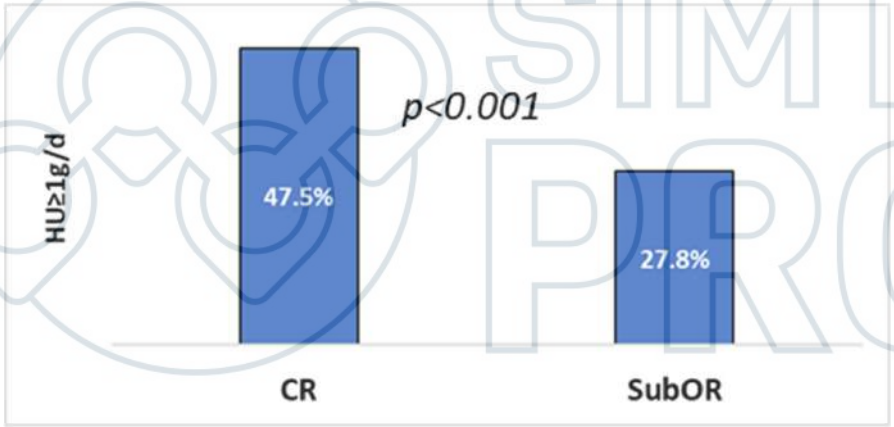
- Older age
- Female sex
- Less frequent occurrence of
  - *JAK2*^{V617F} ≥50%
  - palpable spleen, spleen ≥5 cm BLCM
  - symptoms and pruritus

Suboptimal response (SubOR) included ≥1 of the following criteria after at least 3 months of HU: leukocyte count >10 x10^9/l and platelet count 400 x10^9/l; need for phlebotomy to keep HCT<45%; persistence/occurrence of palpable splenomegaly; failure to completely relieve PV-related symptoms

Palandri et al. *SIE* **2021**;abs#C097.

Hydroxyurea dose is associated with response

- In 593 patients, median HU dose was reported
- Median dose was 0.5 g/d (range, 0.2-2) and was ≥2 g/d in 3.1% of patients. 192 patients (32.4%) received median HU doses ≥1 g/d
- CR patients received more frequently HU ≥1 g/d compared to SubOR patients, with no significant difference between PR and NR patients (p=0.08).



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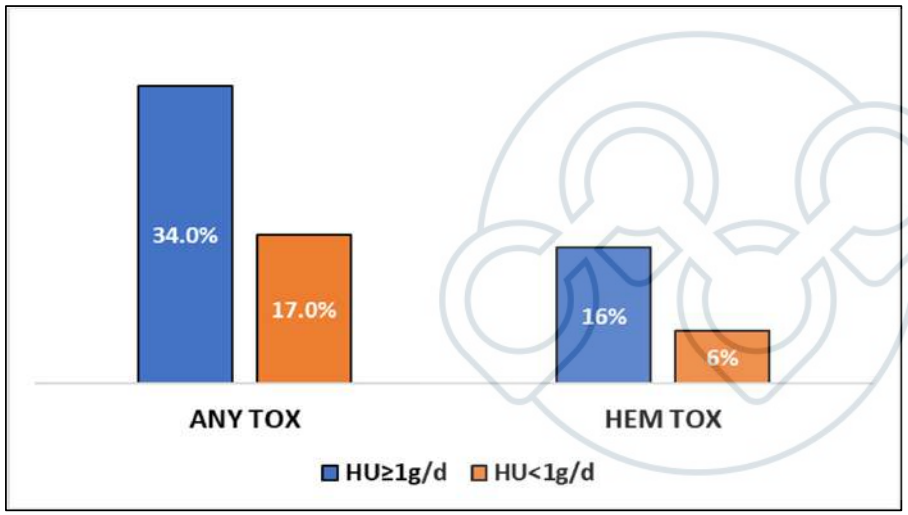
- In the 192 patients who received HU ≥1 g/d, $JAK2^{V617F}$ <50% & absence of palpable spleen/symptoms confirmed their association with CR

Palandri et al. *SIE* **2021**;abs#C097.

Hydroxyurea dose is associated with toxicity

- At least one HU-related AE occurred in 152/662 patients (23%) and was hematological in 59 patients (8.9%).
- HU dose ≥1 g/d was associated with increased incidence of HU-related AEs

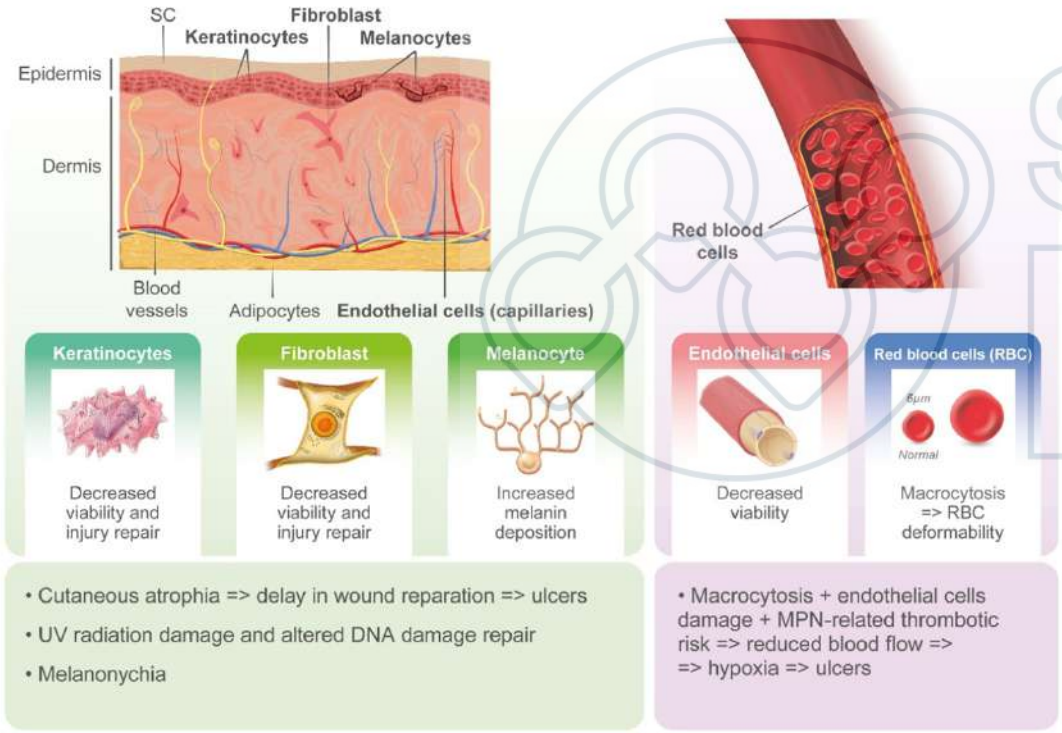


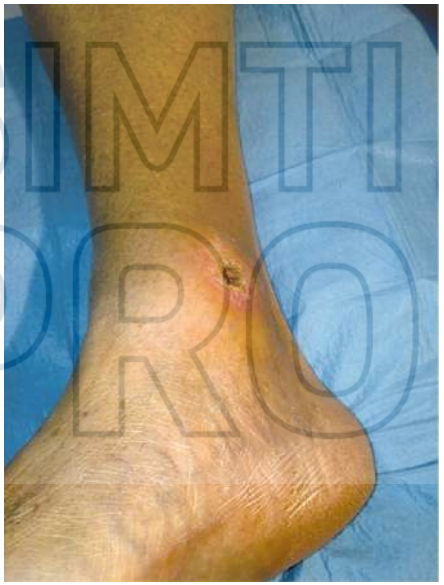
Toxicity	HU <1 g/d (n. 401)	HU ≥1 g/d (n. 192)
Anemia/thrombocytopenia	24 (6.0%)	30 (15.6%)
Skin ulcers	21 (5.2%)	24 (12.5%)
Oral aftosis	11 (2.7%)	5 (2.6%)
Gastrointestinal disturbances	6 (1.5%)	4 (2.1%)
Fever	2 (0.5%)	1 (0.5%)
Mialgia	3 (0.7%)	0
Zoster reactivations	1 (0.2%)	1 (0.5%)

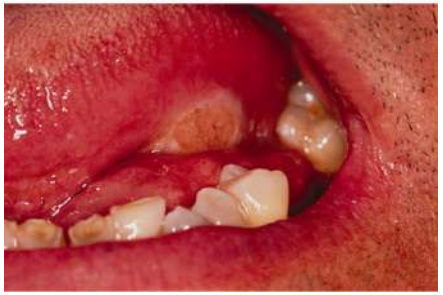
- Among non hematological adverse events, there was a significant excess of skin ulcers in HU ≥1 g/d (p=0.002).
- A total of 14 NMSC occurred during or after HU, with no impact of HU dose (p=0.22)

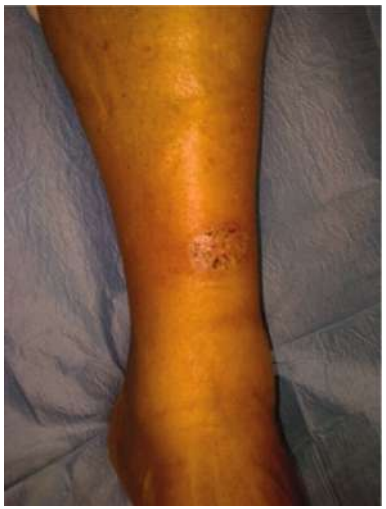
Palandri et al. *SIE* **2021**;abs#C097.

Hydroxyurea skin toxicity



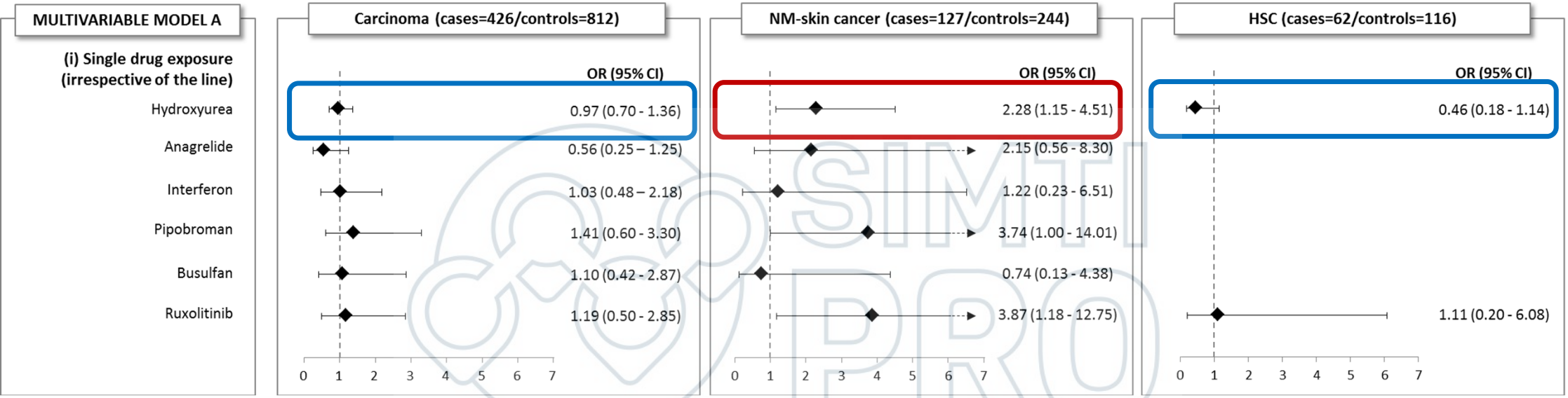






Latagliata et al. *Cancer* **2012**;118:404-409.

Risk of second malignancies



1881 pts, 647 with second cancer and 1234 without SC (nested case-control study)

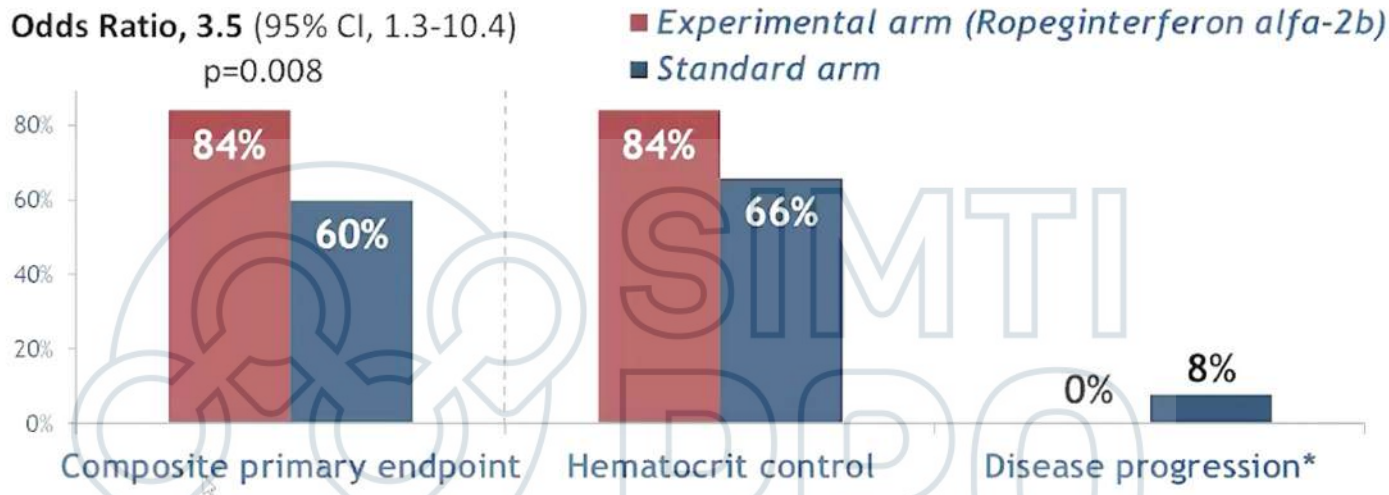
HU significantly associated with the appearance of non-melanoma skin cancer

Interferon did not increase the risk of carcinoma and non-melanoma skin cancer

Barbui et al. *Leukemia* **2019**;33:1996-2005.

Low-PV: Ro-PEG-IFN α2b vs phlebotomies only in low-risk PV patients

PRIMARY ENDPOINT

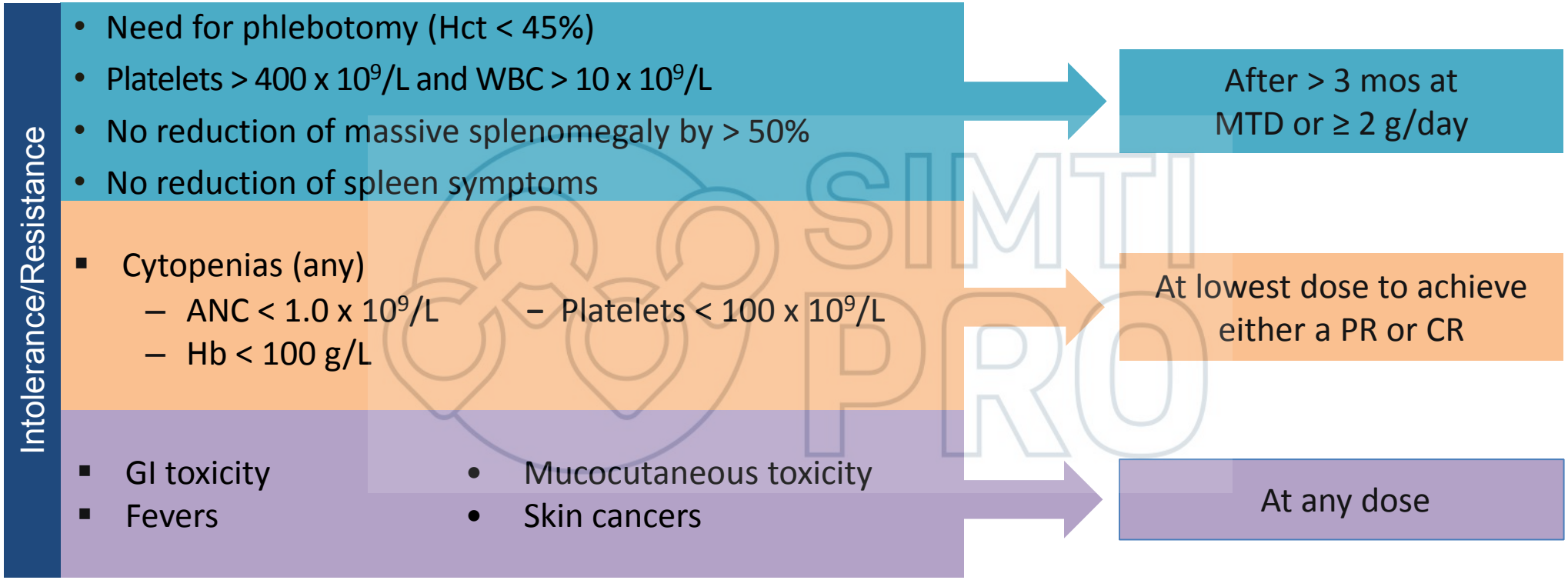


**Disease progression was observed in 4 patients (all in standard arm), as platelet count progression >1500x10⁹/L or >1000x10⁹/L according to baseline values (higher or lower than 600x10⁹/L, respectively, confirmed after 30 days). In one patient progression was due to splenic infarction.*

Additional efficacy	▪ **10% allele burden reduction in experimental group (vs 1% in standard)** ▪ **8/37 were molecular responders**
Safety	▪ No difference in rate of grade ≥3 toxicities ▪ Neutropenia (4/50) in experimental group noted ▪ "Skin symptoms" (2/50) in standard group ▪ 1 thrombotic event (splenic vein) in standard group

Barbui et al. *Lancet Hematol* **2021**;8:e175.

Inadequately controlled PV: when switching to a second-line therapy?



Barosi et al. *Br J Haematol* **2010**;148:961-963.

ELN 2021 recommendations for second-line cytoreduction in PV

Switching is recommended	• intolerance to hydroxyurea because of grade 3-4 or prolonged grade 2 **non-hematological toxicity** (eg, mucocutaneous manifestations, gastrointestinal symptoms, fever, or pneumonitis) at any dose • intolerance to hydroxyurea because of **hematological toxicity** (Hb <100 g/L, platelet count <100 × 10^9 cells per L, or neutrophil count <1 × 10^9 cells per L) at the lowest dose of hydroxyurea to achieve a response • development of **non-melanoma skin cancers** • development of **vascular events** (either clinically relevant bleeding, venous thrombosis, or arterial thrombosis)
Switching should be considered	Insufficient clinical response to hydroxyurea (at >1.5 g per day for at least 4 months and without reporting intolerance), as defined by at least one of the followings: • **persistent disease-related symptoms**: a total symptom score of at least 20 or an itching score of at least ten for at least 6 months • **persistent thrombocytosis**: a platelet count >1000 × 10^9 cells per L, microvascular symptoms, or both, persisting for more than 3 months • **symptomatic or progressive splenomegaly**: increased in spleen size by more than 5 cm from the left costal margin in 1 year • **progressive** (at least 100% increase if baseline count is <10 × 10^9 cells per L or at least 50% increase if baseline count is >10 × 10^9 cells per L) **and persistent leukocytosis** (leukocyte count >15 × 10^9 cells per L confirmed at 3 months) • **insufficient hematocrit control**: need for six or more phlebotomies per year to keep haematocrit below 45%

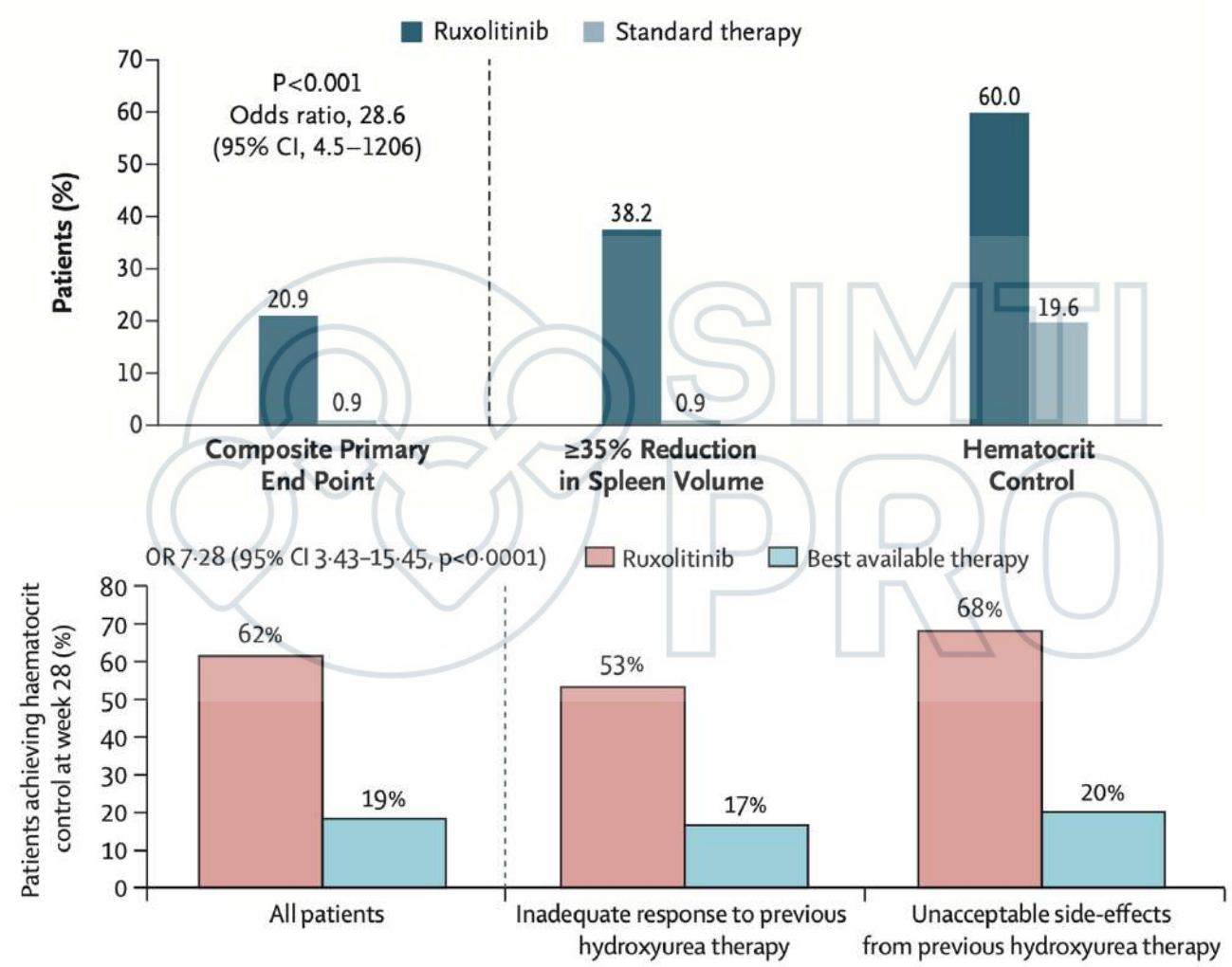
Marchetti et al. *Lancet Haematol* **2022**;9:e301-311.

Recommendations for second-line cytoreduction in patients with PV

	Favoured shift to interferon alfa?	Quality of evidence	Favoured shift to ruxolitinib?	Quality of evidence
Disease transformation*	Yes	Moderate[26,37]	Yes	Low†[14,17]
Vascular events*	Yes	Low[36–38]	Yes	Moderate[50,51,60]
Symptoms*	Yes	Moderate[45]	Yes	High[17,19]
Haematocrit control	Yes	Moderate[37,38]	Yes	Moderate[14,16,60]
Phlebotomy frequency	Yes	High[37,38]	Yes	High[14]
Haematological response	Yes	Moderate[36,38]	Yes	High[16]
Quality of life	Yes	Moderate[15]	Yes	High[32,61]
Adverse effects	No	High[7,37,41,62]	No	High[7,41,62,63]
Secondary malignancies	Yes	Moderate[8,37,40,48]	No	Moderate[8,14,16,38,48]
Molecular response	Yes	High[15,37]	Yes	Moderate[14,16]
Overall survival	Yes	Low[26,37]	Yes	Low[16,64]

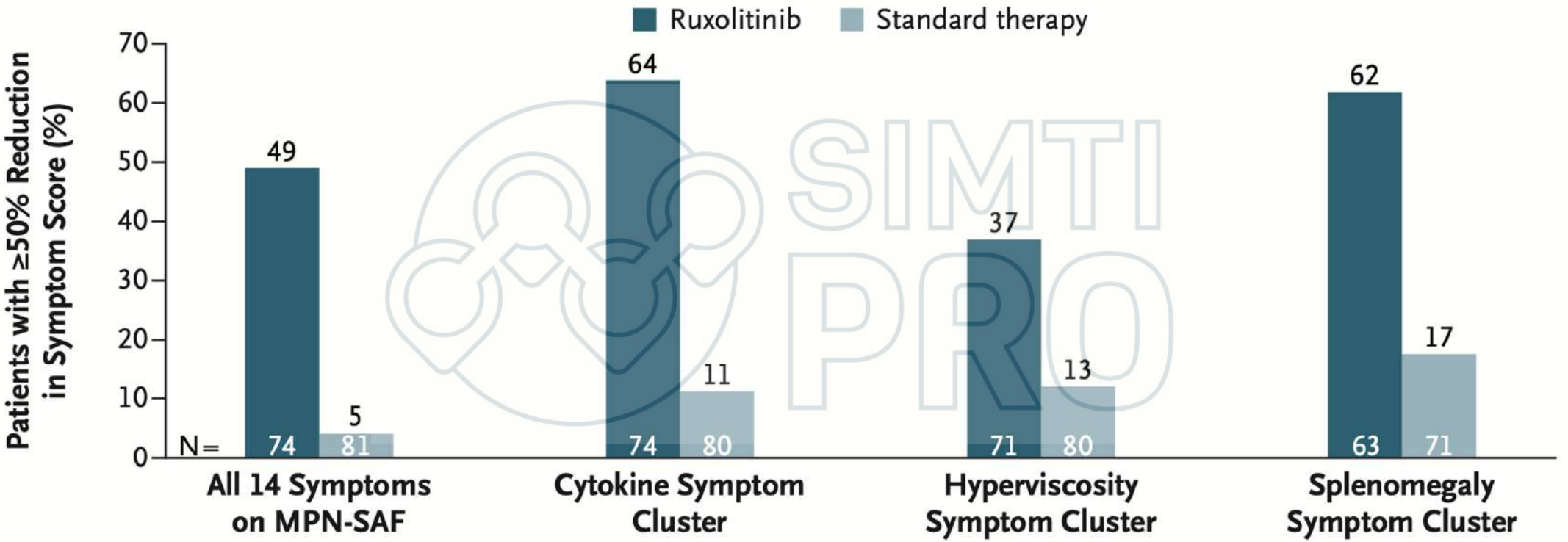
Marchetti et al. *Lancet Haematol* **2022**;9:e301-311.

Ruxolitinib vs best available treatment in resistant/intolerant PV patients



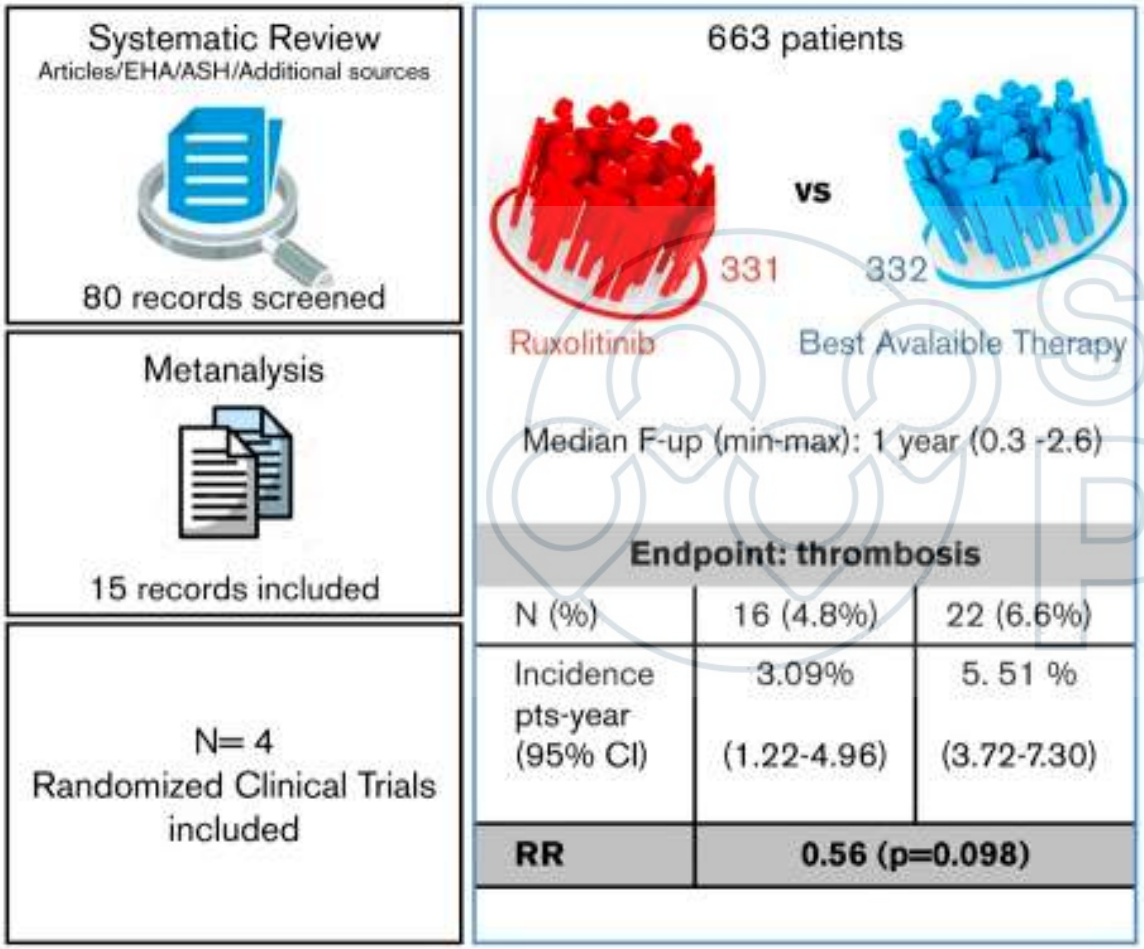
[1] Vannucchi et al. *N Engl J Med* **2015**;372:426-435. [2] Passamonti et al. *Lancet Oncol* **2017**;18:88-98.

RESPONSE: improvement of symptoms



Vannucchi et al. *N Engl J Med* **2015**; 372:426

Reduction of thrombosis risk with ruxolitinib

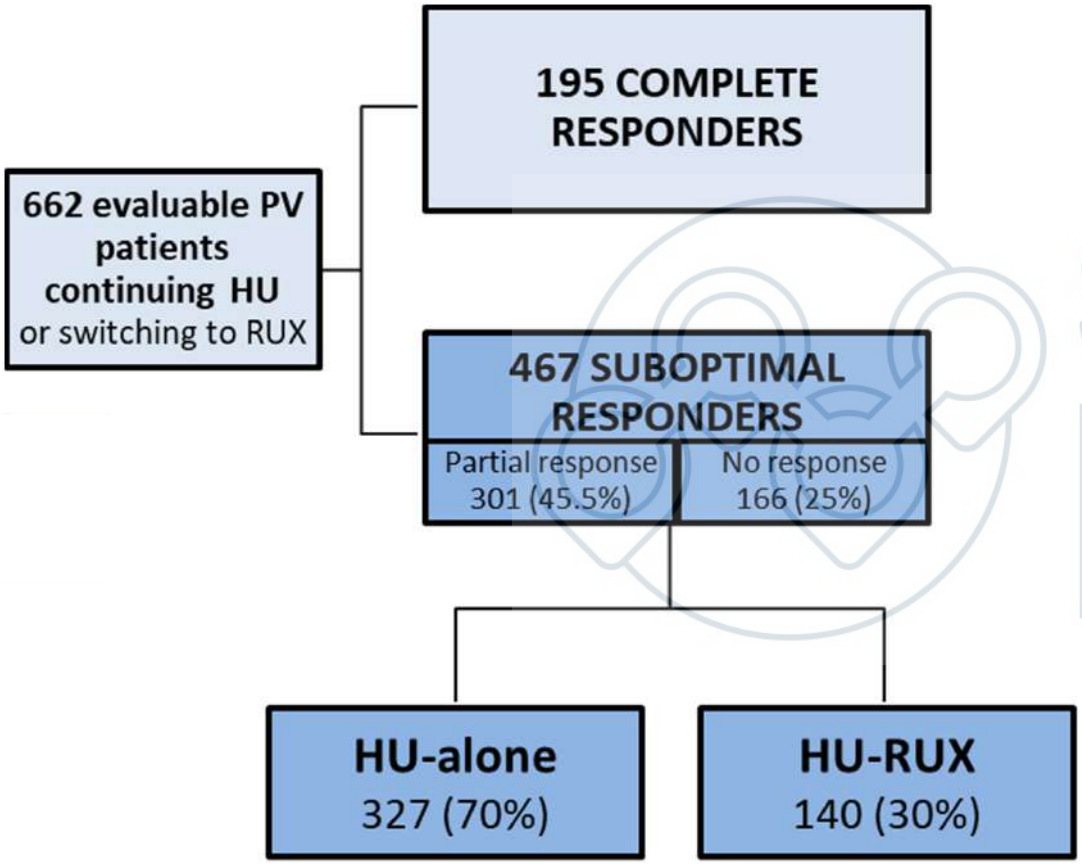


Endpoint: thrombosis		
N (%)	16 (4.8%)	22 (6.6%)
Incidence pts-year (95% CI)	3.09% (1.22-4.96)	5. 51 % (3.72-7.30)
RR	**0.56 (p=0.098)**	

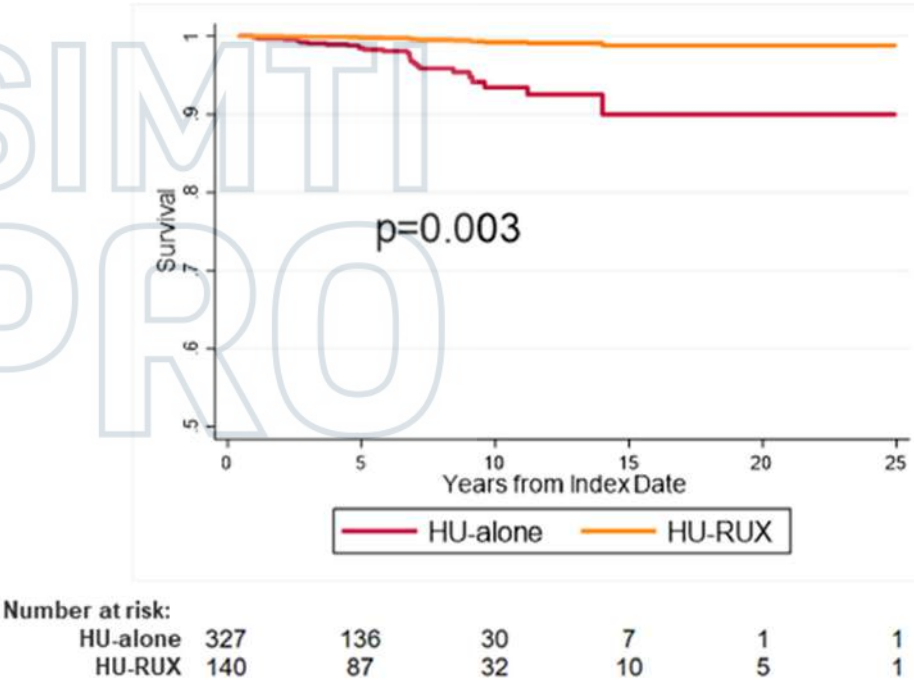
Even though not formally confirmed, results suggest an efficacy of Ruxolitinib to prevent thrombosis in patients with PV.

Masciulli et al. *Blood Adv* **2020**;4:380-386.

Possible survival benefit with ruxolitinib after HU failure



- In the 467 SubOR patients, RUX switch was associated with improved OS compared to HU-alone



Survivor functions of CR, PR and NR patients were plotted after the Cox proportional hazards multivariable regression model adjusting for age
Survivor functions of HU-RUX and HU-alone SubOR patients were plotted after the Cox proportional hazards multivariable regression model adjusting for age and splenomegaly.

Palandri et al. *SIE* **2021**;abs#C097.

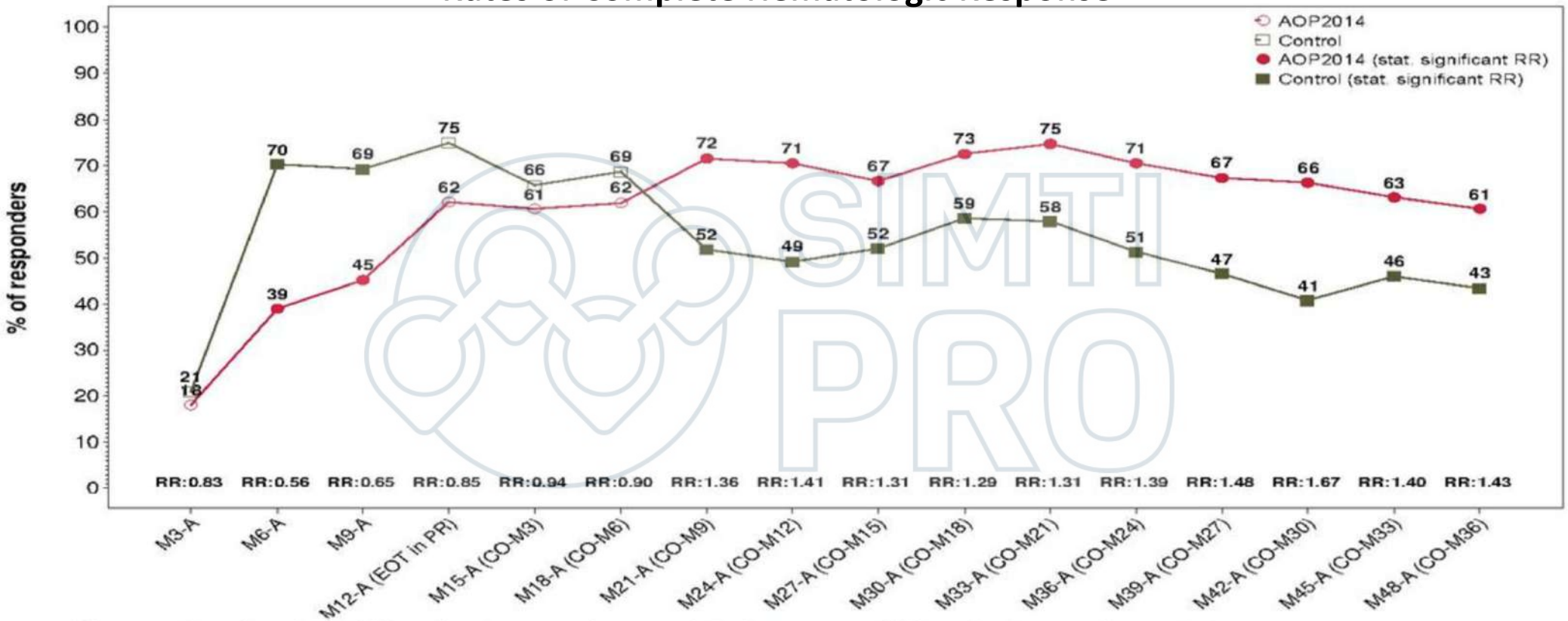
Recommendations for second-line cytoreduction in patients with PV

	Favoured shift to interferon alfa?	Quality of evidence	Favoured shift to ruxolitinib?	Quality of evidence
Disease transformation*	Yes	Moderate[26,37]	Yes	Low†[14,17]
Vascular events*	Yes	Low[36–38]	Yes	Moderate[50,51,60]
Symptoms*	Yes	Moderate[45]	Yes	High[17,19]
Haematocrit control	Yes	Moderate[37,38]	Yes	Moderate[14,16,60]
Phlebotomy frequency	Yes	High[37,38]	Yes	High[14]
Haematological response	Yes	Moderate[36,38]	Yes	High[16]
Quality of life	Yes	Moderate[15]	Yes	High[32,61]
Adverse effects	No	High[7,37,41,62]	No	High[7,41,62,63]
Secondary malignancies	Yes	Moderate[8,37,40,48]	No	Moderate[8,14,16,38,48]
Molecular response	Yes	High[15,37]	Yes	Moderate[14,16]
Overall survival	Yes	Low[26,37]	Yes	Low[16,64]

Marchetti et al. *Lancet Haematol* **2022**;9:e301-311.

PROUD-PV: Ro-PEG-IFN α2b vs HU in high-risk PV patients

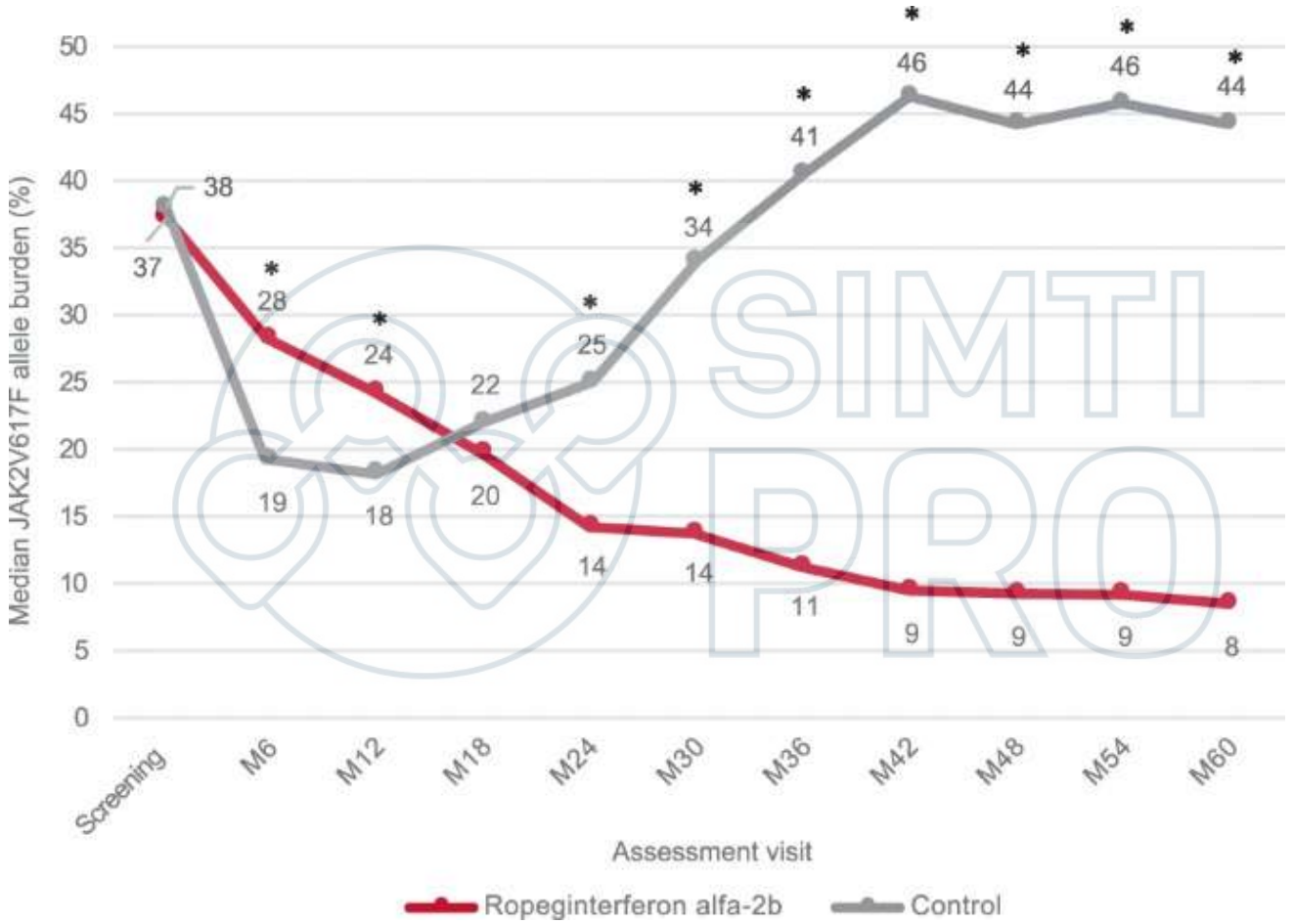
Rates of Complete Hematologic Response



- Observational period: 419 patients-years in ropeginterferon arm, 338 patient-years in control arm
- Rate of patients with major thromboembolic events over the entire treatment period: **3.1% in both arms**
- Incidence of thrombotic events: 1.4% patient-year for ropeginterferon and 1.2% for the control arm

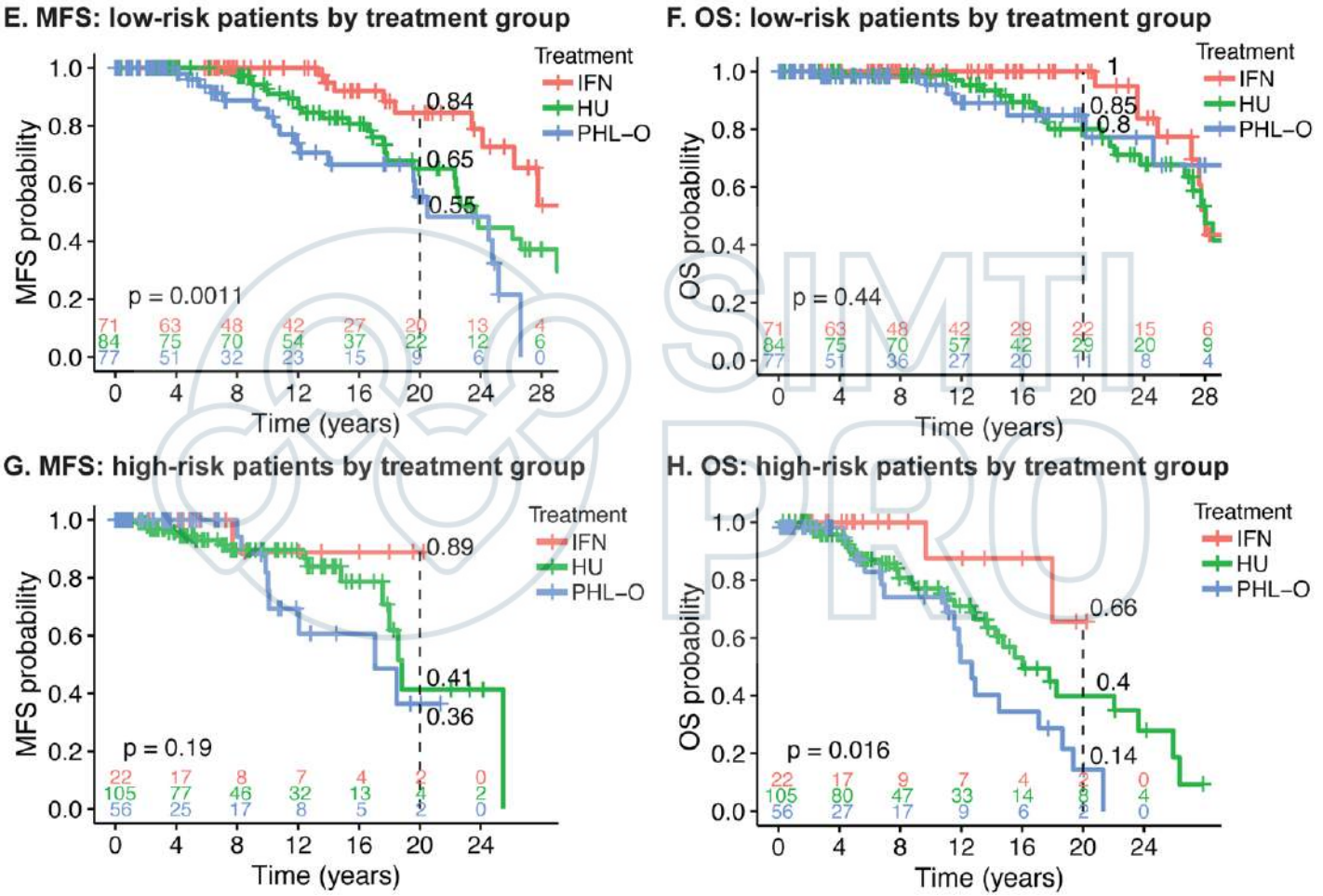
Kiladjian et al. *Leukemia* **2022**;36:1408-1411.

PROUD-PV: Ro-PEG-IFN α2b molecular responses



Kiladjian et al. *Leukemia* **2022**;36:1408-1411.

IFN treatment is associated with improved MFS and OS in PV



Abu-Zeinah et al. *Leukemia* **2021**;35:2592-2601.

Take home messages

- Arterial and/or venous thromboses represent the main cause of morbidity and mortality in PV.
- Treatment should be mainly focused on reduction of thrombotic risk, myeloproliferation control, improvement of symptomatic burden, and management of disease-associated complications.
- Hydroxyurea and interferons are suitable options for the front-line treatment of PV; prolonged treatment with interferon is associated to a progressive reduction of JAK2 V617F allele burden.
- Interferon and Ruxolitinib may be used as second-line treatment in patients with resistance and/or intolerance to hydroxyurea.