Neoplasie Mieloproliferative Croniche
Report dei gruppi di lavoro

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9° EDITION
Highlights from EHA
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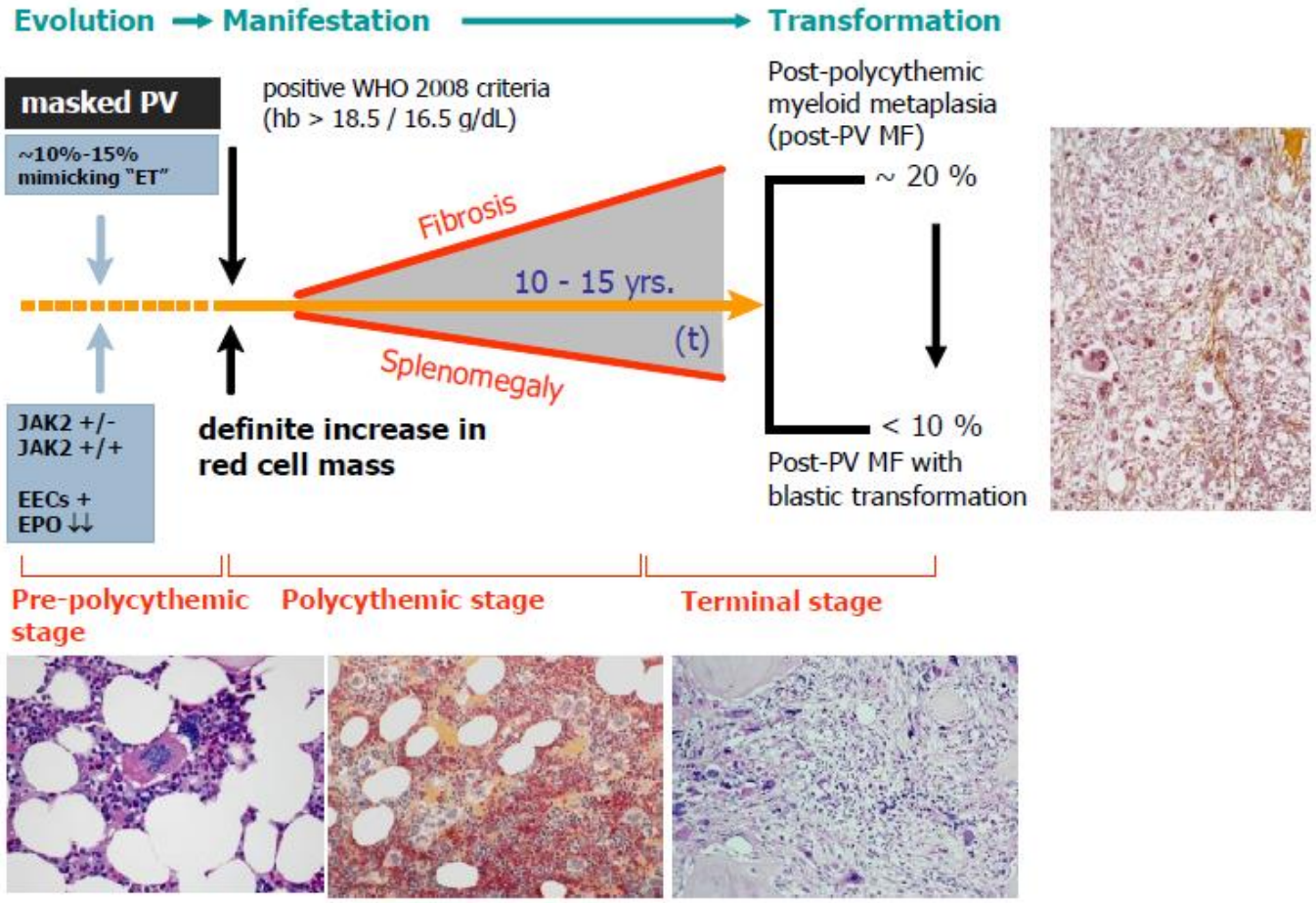
Domande del gruppo di lavoro

- La classificazione WHO 2016
- Inserire le nuove conoscenze nella terapia
  - ET
  - PV
  - MF

Dynamics of the disease process in PV



Dopo la classificazione WHO 2008 le nuove scoperte genetiche e i risultati di studi epidemiologici hanno consentito di descrivere una nuova epidemiologia delle MPN

- earlier diagnosis,
- different clinical and hematologic features at presentation
- different rates of thrombo-hemorrhagic event, progression to myelofibrosis or transformation to blast phase .

- Consequently, the relevant clinical outcomes registered in contemporary cohorts of patients with MPN enrolled in several observational studies, were not concordant with the findings obtained before the 2008 WHO.

Underdiagnosis of PV

RCM demonstrated PV (RCM> 25% of predicted value) **in patients with hemoglobin or hematocrit below WHO 2008 requirement**

- **Johansson et al 2005**

  Hemoglobin: male 65% ; female 37%
- **Cassinat et al 2008**

  Hemoglobin or hematocrit: 46%
- **Alvarez-Larrán et al 2012**

  Hemoglobin: male 42%; female 52%
- **Silver et al 2013**

  Hemoglobin or hematocrit 29%

- Johansson et al Br J Haematol 129 (5):701-705.2005
- Alvarez-Larrán et al Haematologica 97 (11):1704-1707, 2012
- Cassinat et al 2008 Leukemia 22 (2):452-453.
- Silver et al 2013 Blood 122 (11):1881-1886

Bone marrow morphology was consistent with WHO-PV but hemoglobin or hematocrit were below WHO 2008 criteria in 397 JAK2 mutated patients classified as PV.

(centrally re-reviewed by JT completely blinded to outcome data)

- **257 (65%)** met the full WHO-2008 criteria.

- **140 (35%)** were classified and treated as PV, although they did not meet the hemoglobin level threshold that is required for the diagnosis of WHO-defined PV.

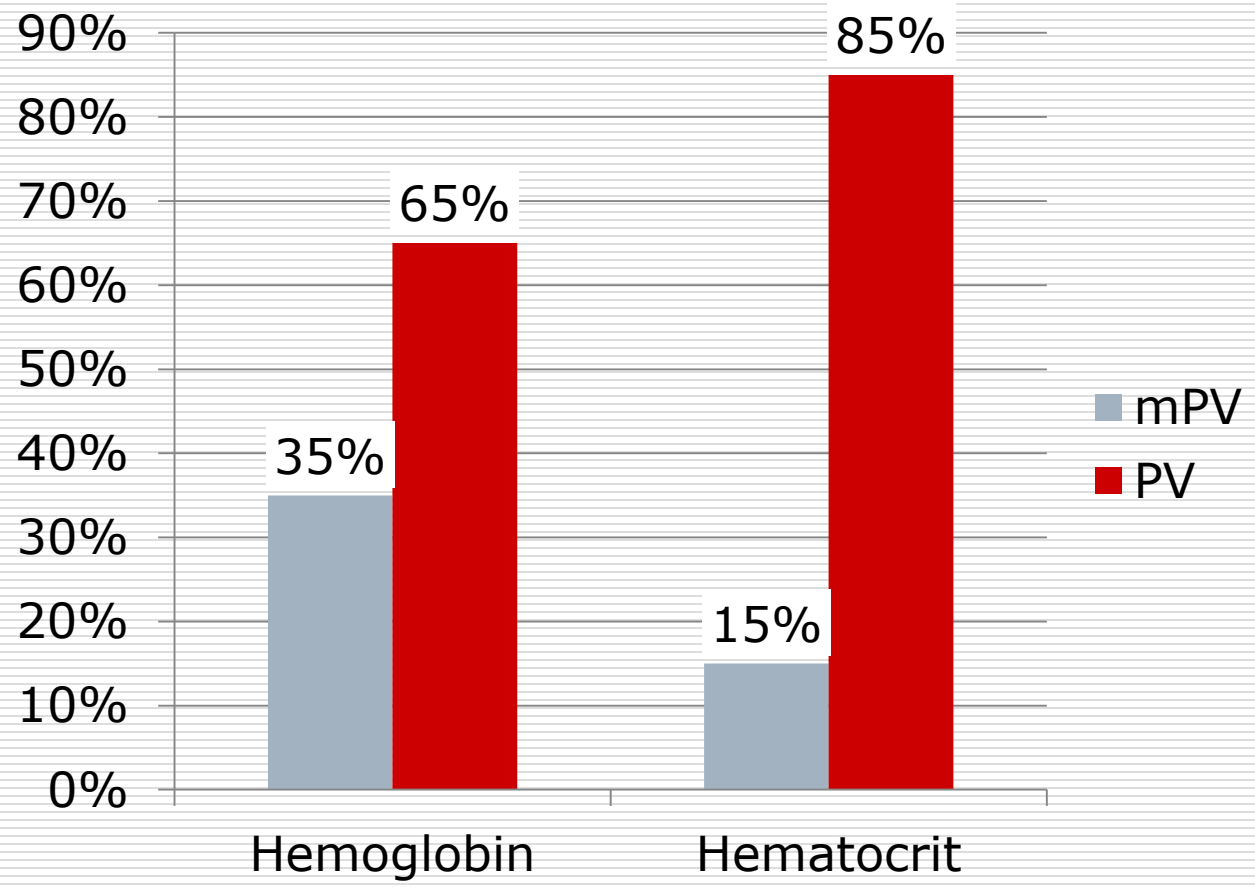
These patients were operationally defined as «**masked PV**».

* International study including patients from Italy, Austria and Mayo Clinic

Barbui T et al, Leukemia 2013

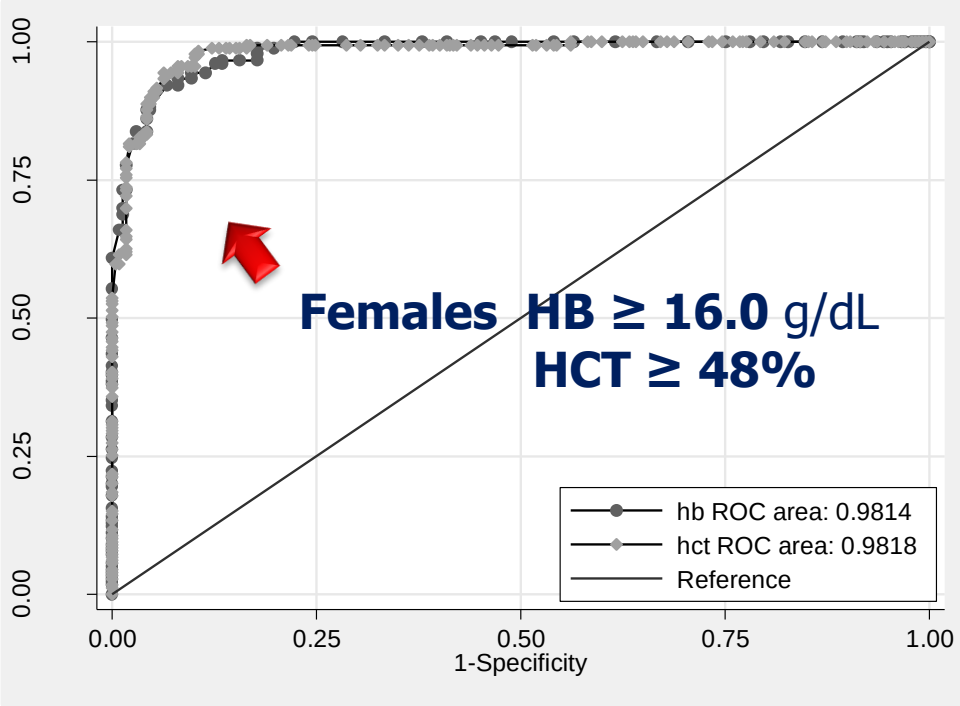
Hematocrit is a better indicator of raised RCM than Hemoglobin

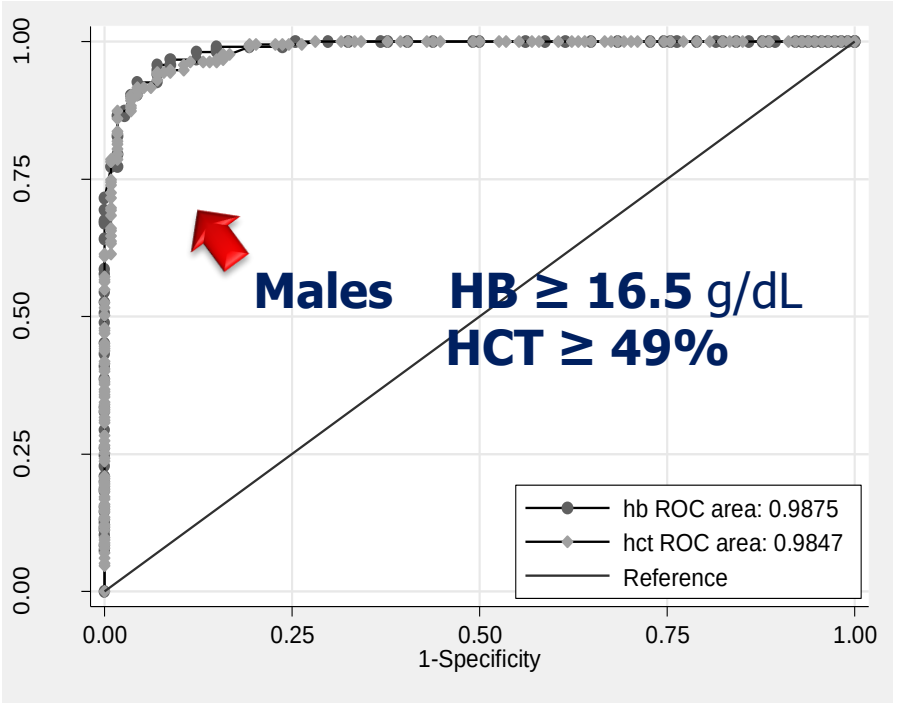
A1: High haematocrit (>0.52 in men;> 0.48 in women) OR raised red cell mass(>25% above predicted) and Presence of *JAK2* mutation



Barbui et al, Leukemia 2014

The best cut-off of Hb and HCT in males and females for the discrimination between PV and ET JAK2 positive patients

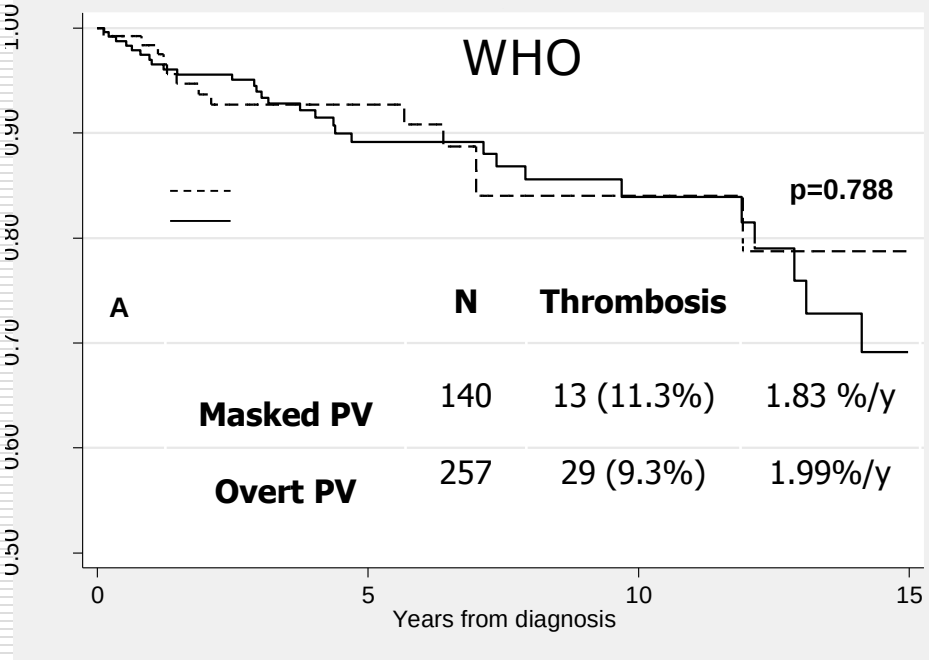


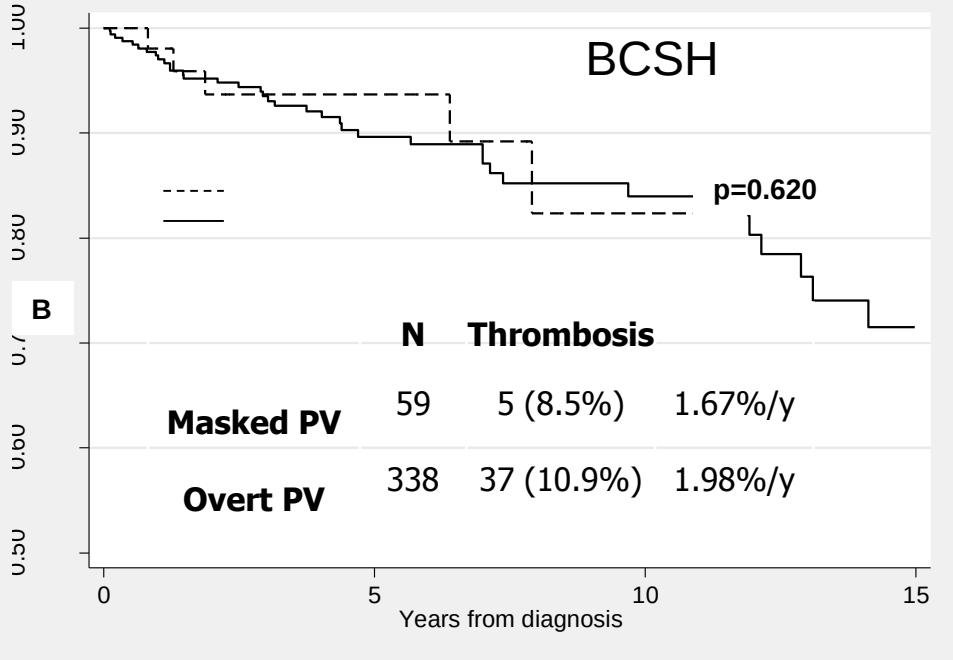


Barbui T et al, AJH 2013

Thrombosis-free in masked and overt PV patients by WHO and BCSH classification

All patients were treated as overt PV

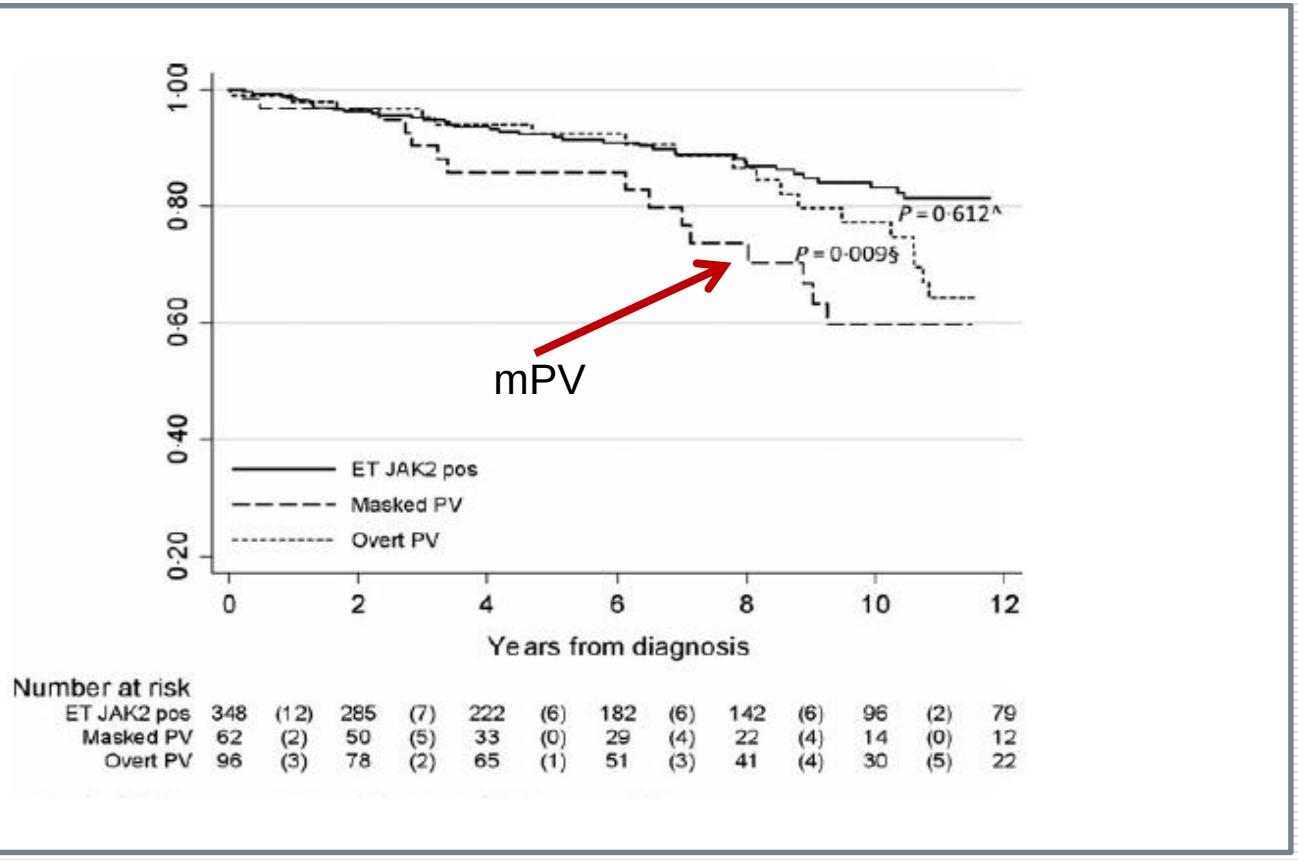




Barbui T et al, AJH 2013

Therapeutic relevance of recognizing mPV

An excess of thrombosis in 62 patients with mPV and age < 40 years was associated to less intensive therapy



Lussana et al, BJH 2014

UPDATE - Polycythemia vera (PV)

Major criteria:

1. Hb > 16.5 g/dL in men , Hb > 16.0 g/dL in women OR,
   Hct > 49% in men, Hct >48% in women OR,
   Increased red cell mass
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic megakaryocytes (differences in size)
3. Presence of *JAK2* mutation

Minor criterion:

Subnormal serum EPO level

Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion

UPDATE - WHO criteria for PV

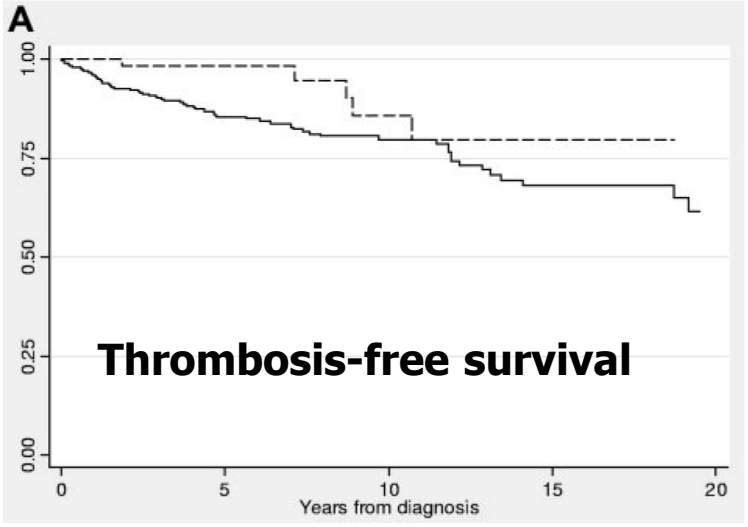
- In **cases with sustained absolute erythrocytosis** (Hb levels >18.5 g/dL, Hct >55.5 % in men or >16.5 g/dL, 49.5% in women, **bone marrow biopsy may not be necessary for diagnosis** if major criterion 3 and the minor criterion are present.

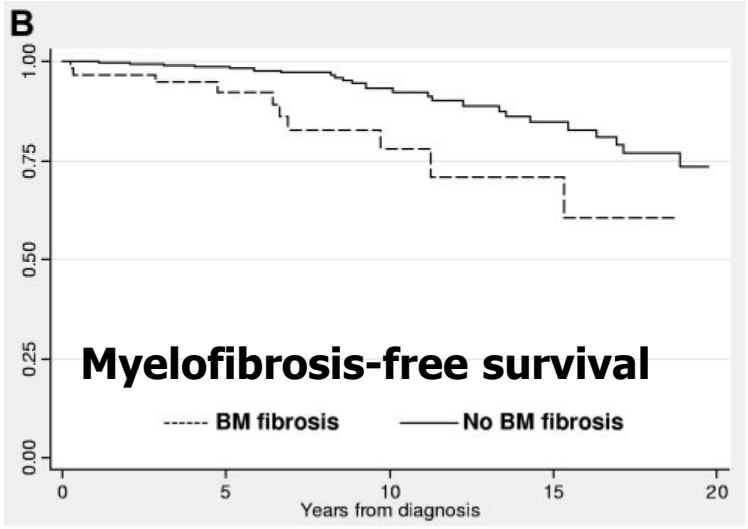
- However, only by performing a bone marrow biopsy an **initial myelofibrosis** (up to 20%) may be detected that indicates a more rapid progression to overt myelofibrosis (post-PV MF). (Barbui T et al. Blood 2012;119:2239-2241)

Initial bone marrow reticulin fibrosis in PV exerts an impact on clinical outcome (Barbui et al. Blood, 2012, 119)

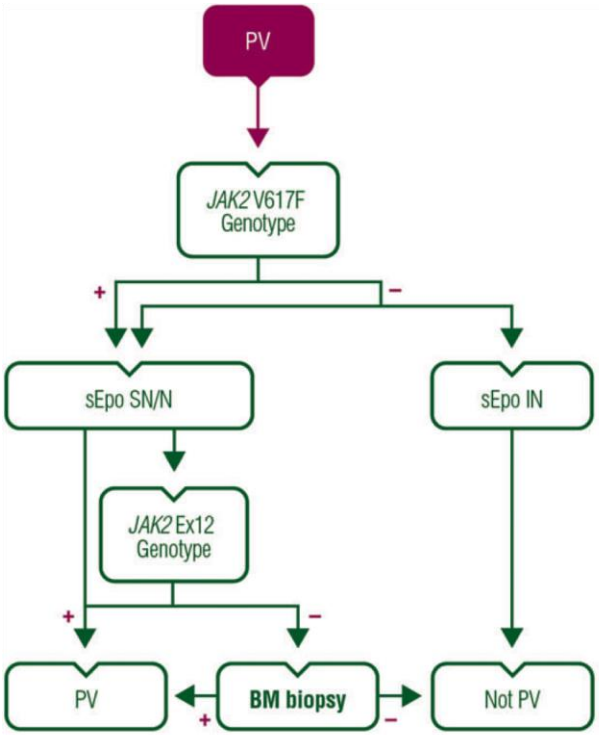
Progression to overt MF in PV

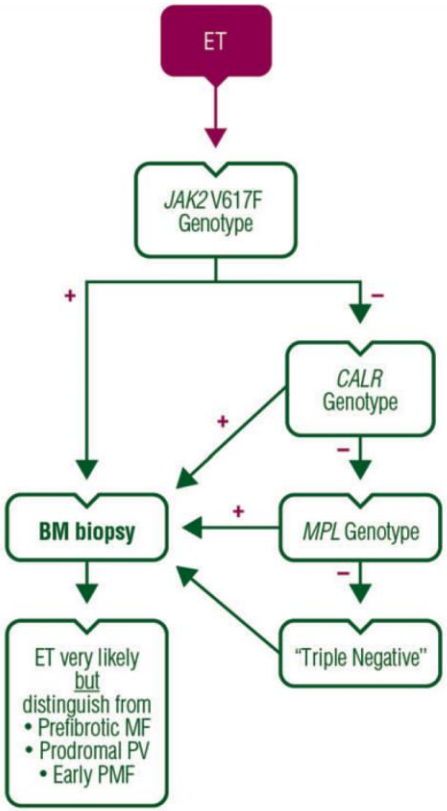
Grade at diagnosis	**Incidence** per 100 pts./yrs.	IRR	**cumulative incidence**		
			5 yrs.	10 yrs.	15 yrs.
MF-0	0.8	2.7	1.3	6.9	15.4
≥ MF-1	2.2		7.8	22.0	20.1

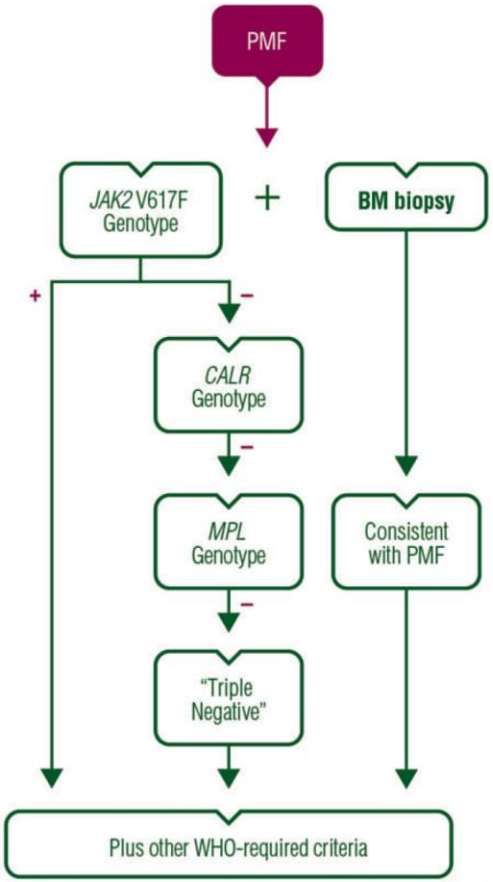




ESMO Practical Guidelines for MPN







Vannucchi AM et al, 2015

Domande del gruppo di lavoro

- La classificazione WHO 2016
- **Inserire le nuove conoscenze nella terapia**
  - ET
  - PV
  - MF

La terapia della ET nel 2016

Valuta il rischio cardiovascolare

Basso Rischio

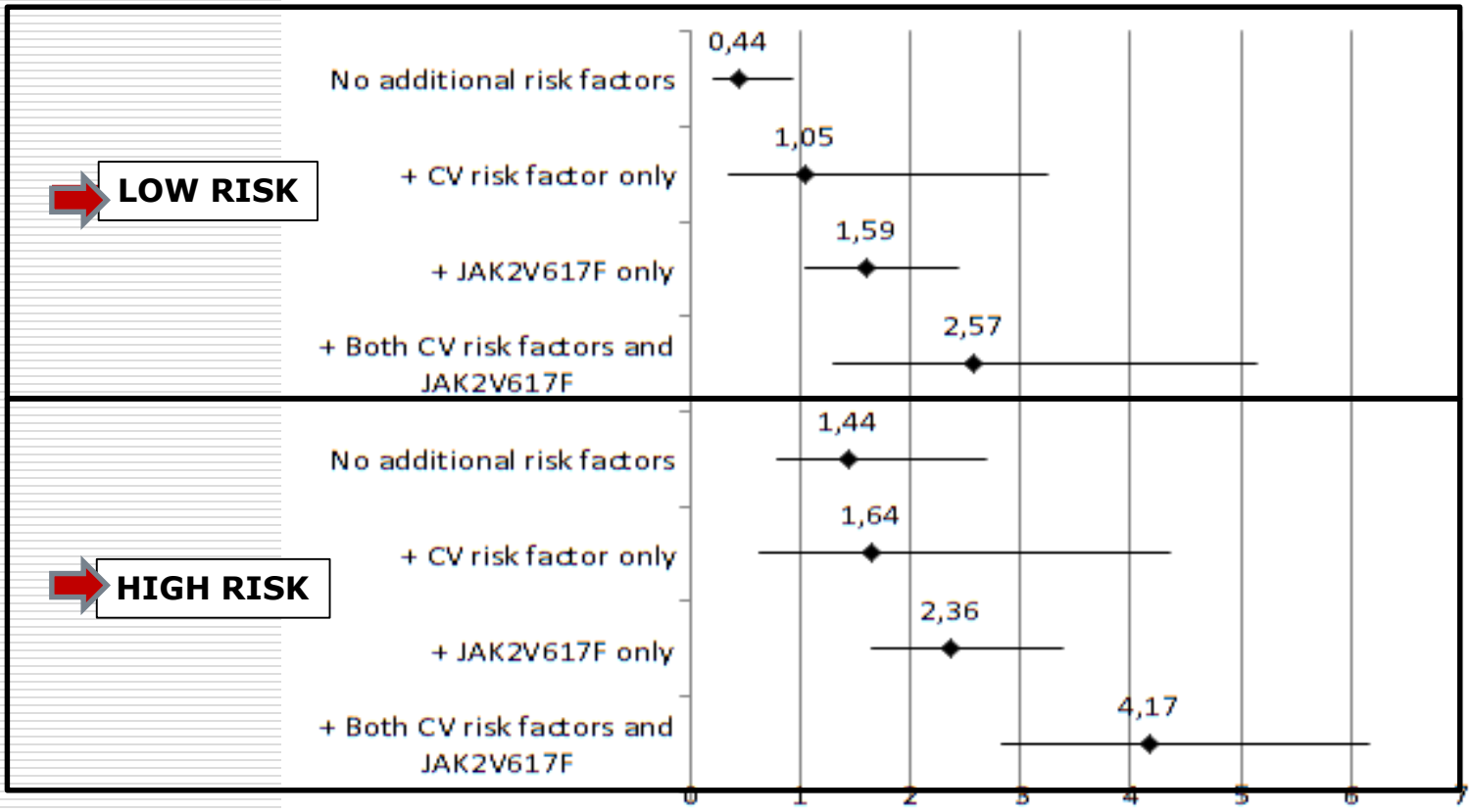
- Observation only
- LD-Asa (case-by-case)

Alto Rischio

- **First line cytoreduction**
  - HU
  - IFN-α
- Asa or anticoagulants (if prior venous event)
- **Second line** (IFN-α, HU, anagrelide or busulphan)
- Consider clinical trials for resistant/ refractory to conventional agents

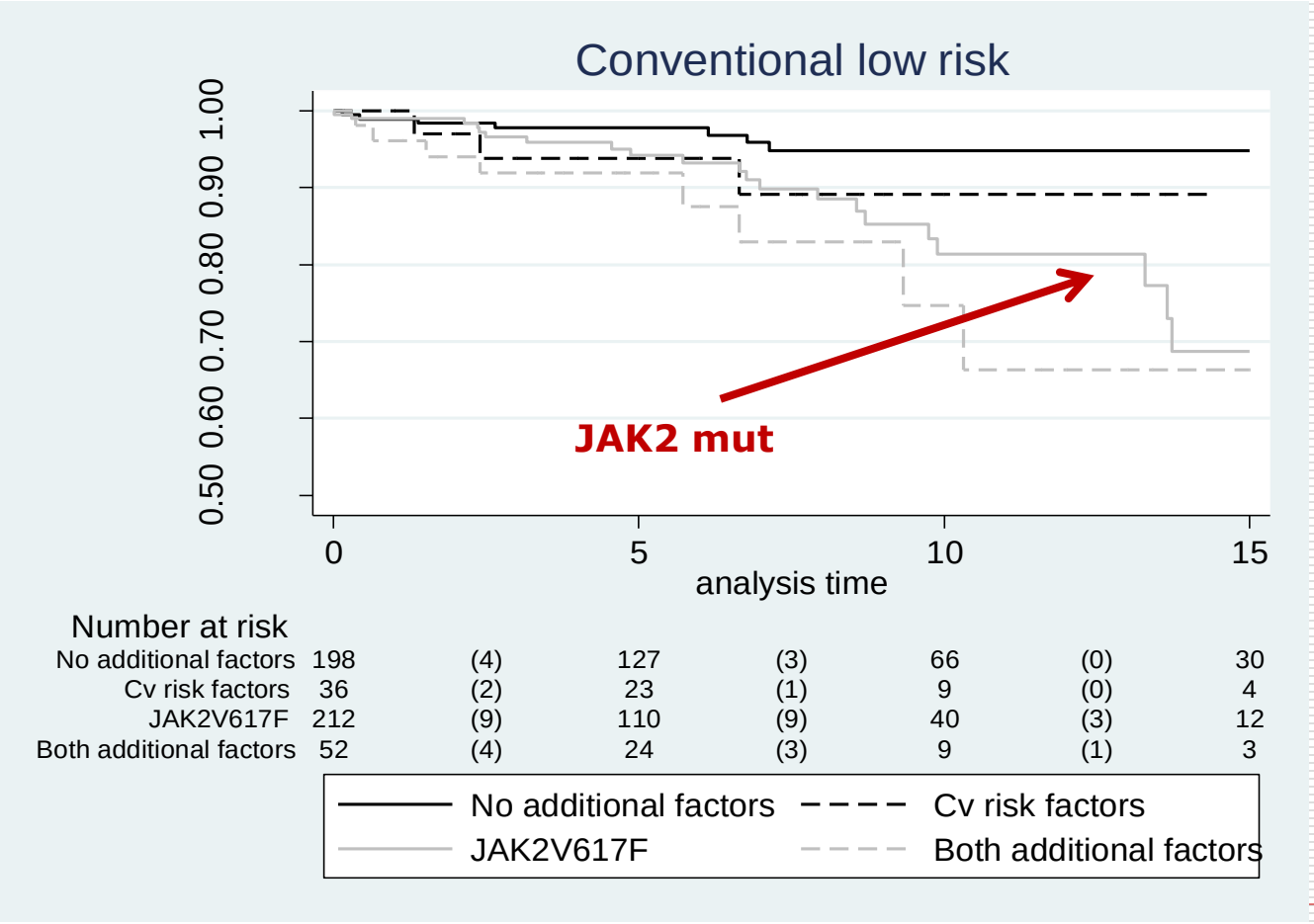
Vannucchi A et al, Linee guida ESMO 2015

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

La terapia della PV nel 2016

Valuta il rischio cardiovascolare

Basso Rischio

- Phlebotomy
- LD-Asa (all)

Alto Rischio

- Phlebotomy
- LD-Asa
- **First line cytoreduction**
  - HU
  - IFN-α
- Anticoagulants (if prior venous event)
- **Second line** (IFN-α, HU or busulphan)
- Consider *Jak*-inhibitors (for resistant/ refractory to conventional agents)

Vannucchi A et al, Linee guida ESMO 2015

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

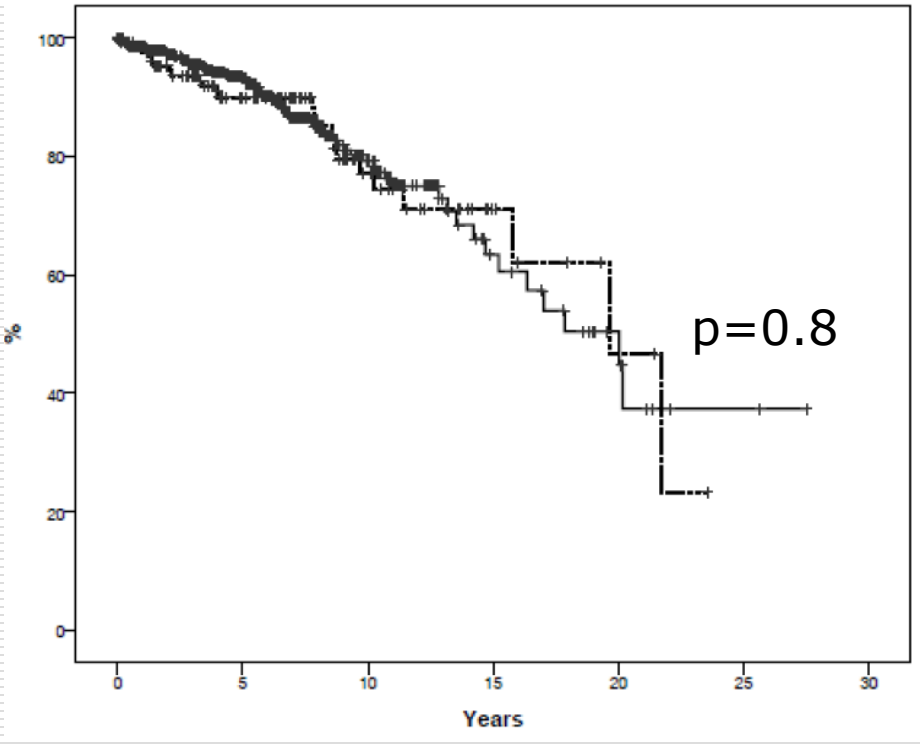
	LOW RISK N=	HIGH RISK N=
Dx before 2005 IR per 100 person/yrs	IR: 2.03 % pts/yr; 95% CI: 1.58-2.61	**IR: 4.01 %** pts/yr; 95% CI: 3.28-4.90
Dx after 2005 IR per 100 person/yrs	IR: 2.24 % pts/yr; 95% CI: 1.33-3.78	**IR: 2.93 %** pts/yr; 95% CI: 1.89-4.54

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

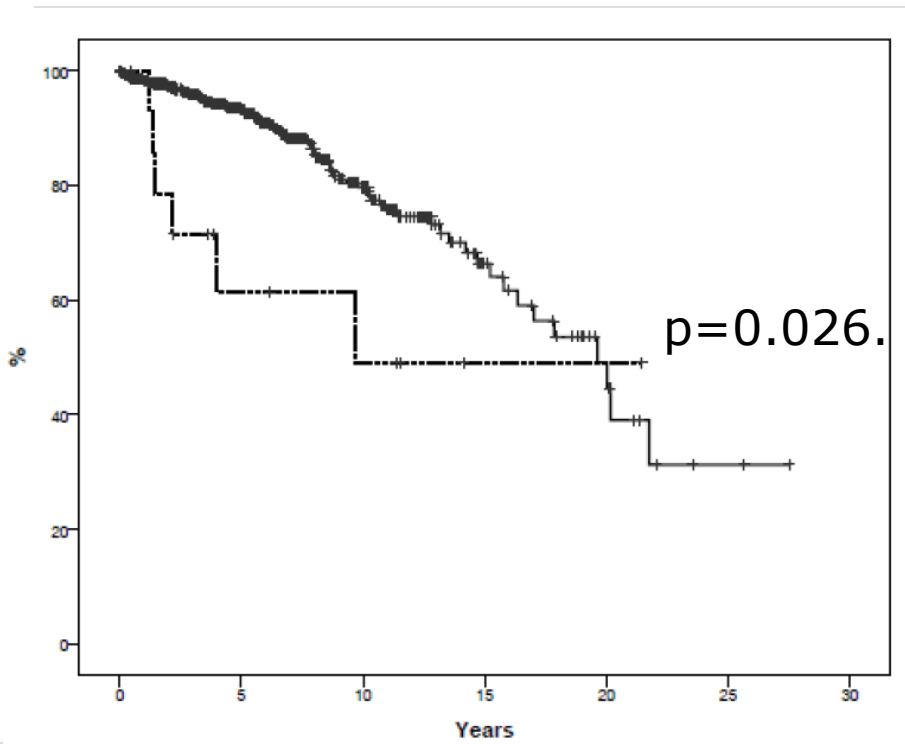
Overall survival in PV with criteria of resistance/intolerance

1A: resistance / intolerance to HU (dotted line) or not (solid line) p=0.8.
1B: development **of cytopenia** (dotted line) or not (solid line) p=0.026.

1A



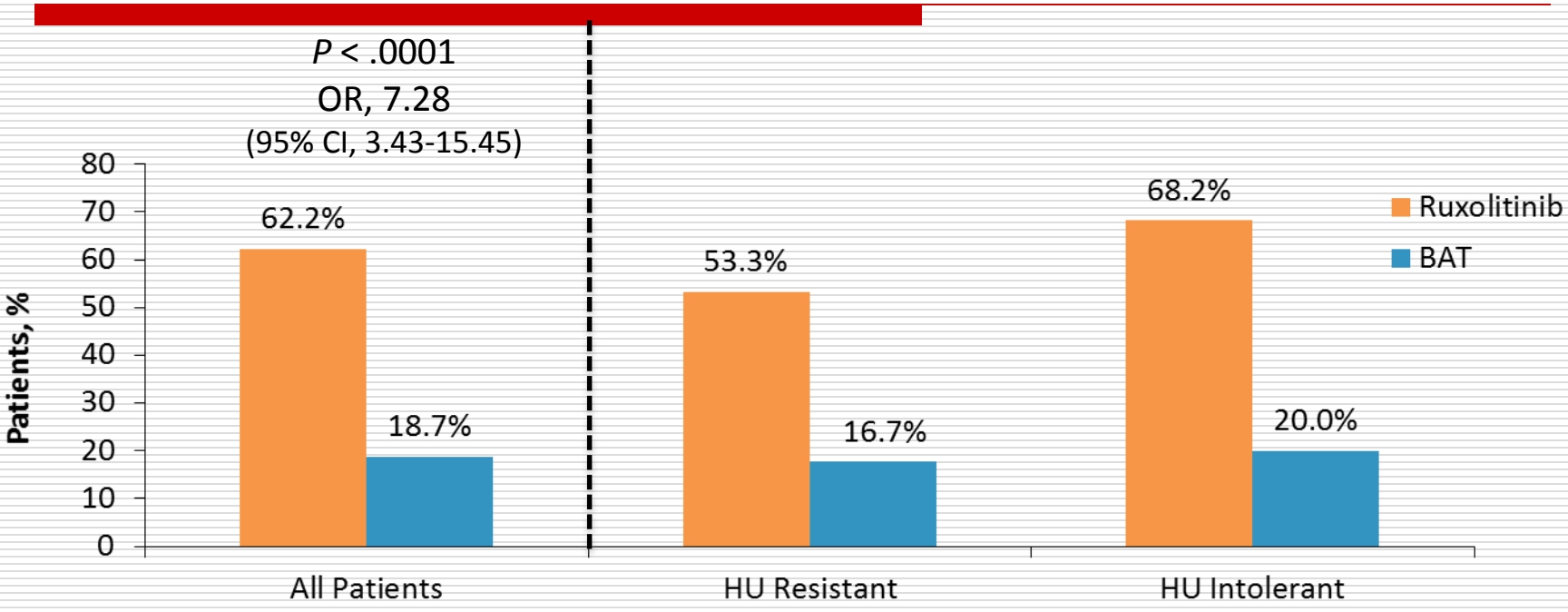
1B



Development of cytopenia was defined as an absolute neutrophil count < 1 x109/L or Hb level < 100 g/L or platelet count < 100 x 109/L at the lowest dose of HU required to achieve a complete or a partial response

Alvarez-Larràn A, Brit J Haematol 2016,172,786-703

Primary Response: Hct Control at Week 28



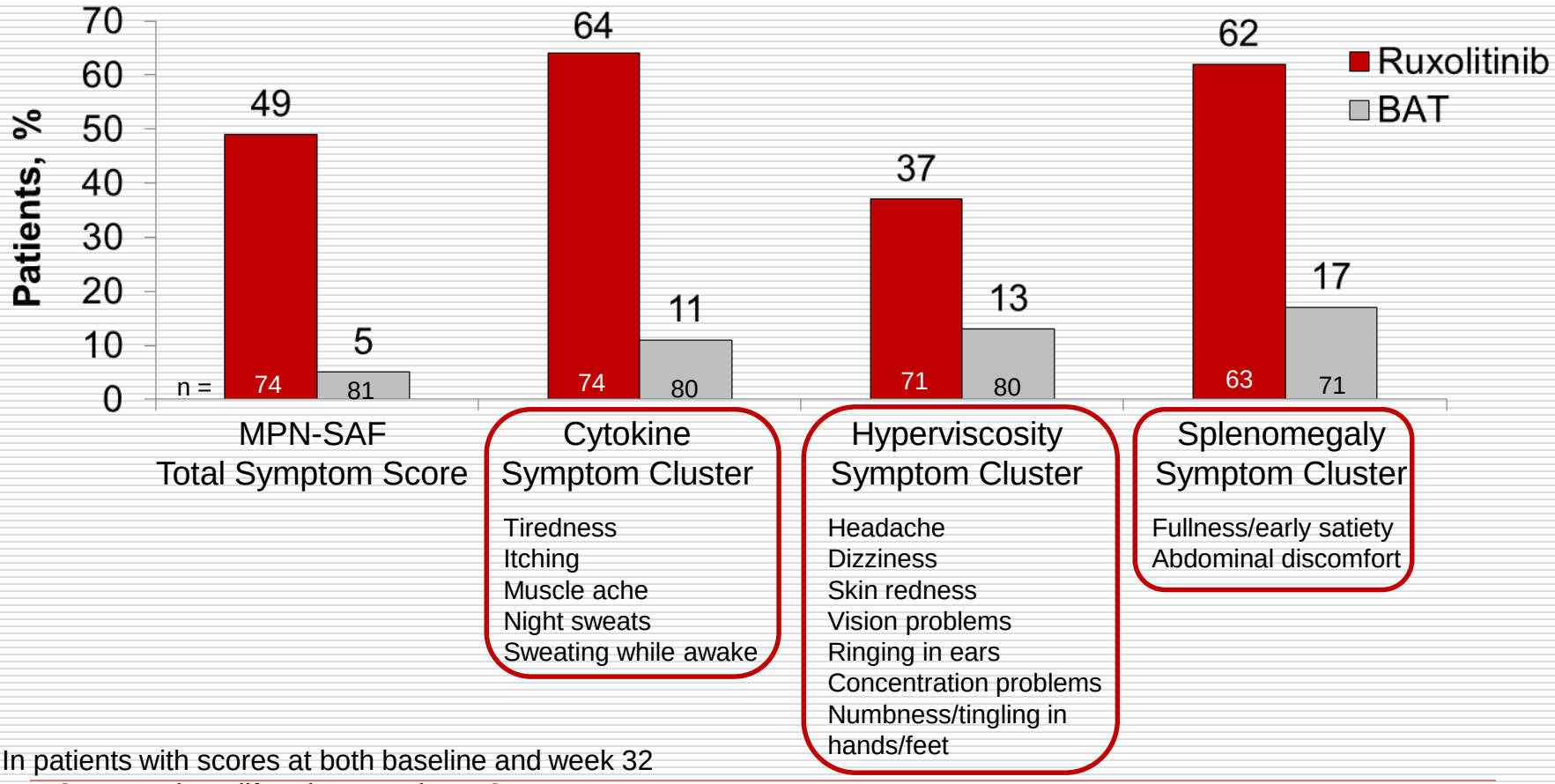
Significantly more patients randomized to ruxolitinib achieved Hct control without phlebotomy (primary endpoint) compared with those randomized to BAT

OR, odds ratio.

RESPONSE Study

Improvement in symptoms (week 32)

Percentage of Patients with a ≥ 50% Improvement in MPN-SAF Symptom Score at Week 32[a]



[a] In patients with scores at both baseline and week 32

MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form

Vannucchi *et al*, N Engl J Med 2015;372(5):426-435

Preliminary evidence shows that ruxolitinib may reduce the rate of thromboembolic events

RESPONSE study

Treatment Group	Ruxolitinib (n = 110)		BAT (n = 111[a])	
Exposure, Patient-Years	227.7		73.6	
Number of Patients (Rate per 100 Patient-Years of Exposure)	All Grades	Grade 3/4	All Grades	Grade 3/4
All thromboembolic events	4 **(1.8)**	2 (0.9)	6 **(8.2)[b]**	2 (2.7)

Preliminary evidence of the **lower rate of thromboembolic events observed in the ruxolitinib arm** vs the BAT arm. Consistent with the observed effects of ruxolitinib on hematocrit, WBC counts, and C-reactive protein levels, which are all associated with thromboembolic risk

Kiladjian et al, EHA 20th Congress, Vienna 2015, abstract 5447

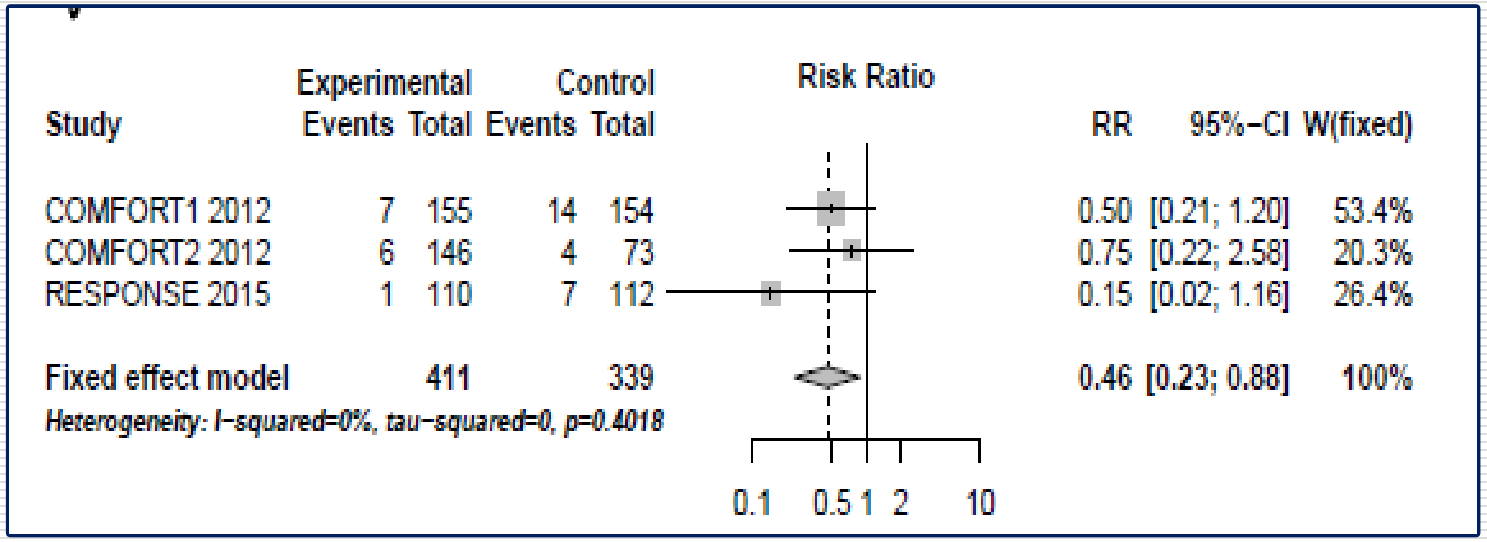
The impact of ruxolitinib on thrombosis in patients with polycythemia vera and myelofibrosis: a meta-analysis.

Method

Comfort-1 and2, Response 1 were identified.

In Comfort-1 and 2 trials rates of thrombosis were provided by Incyte.

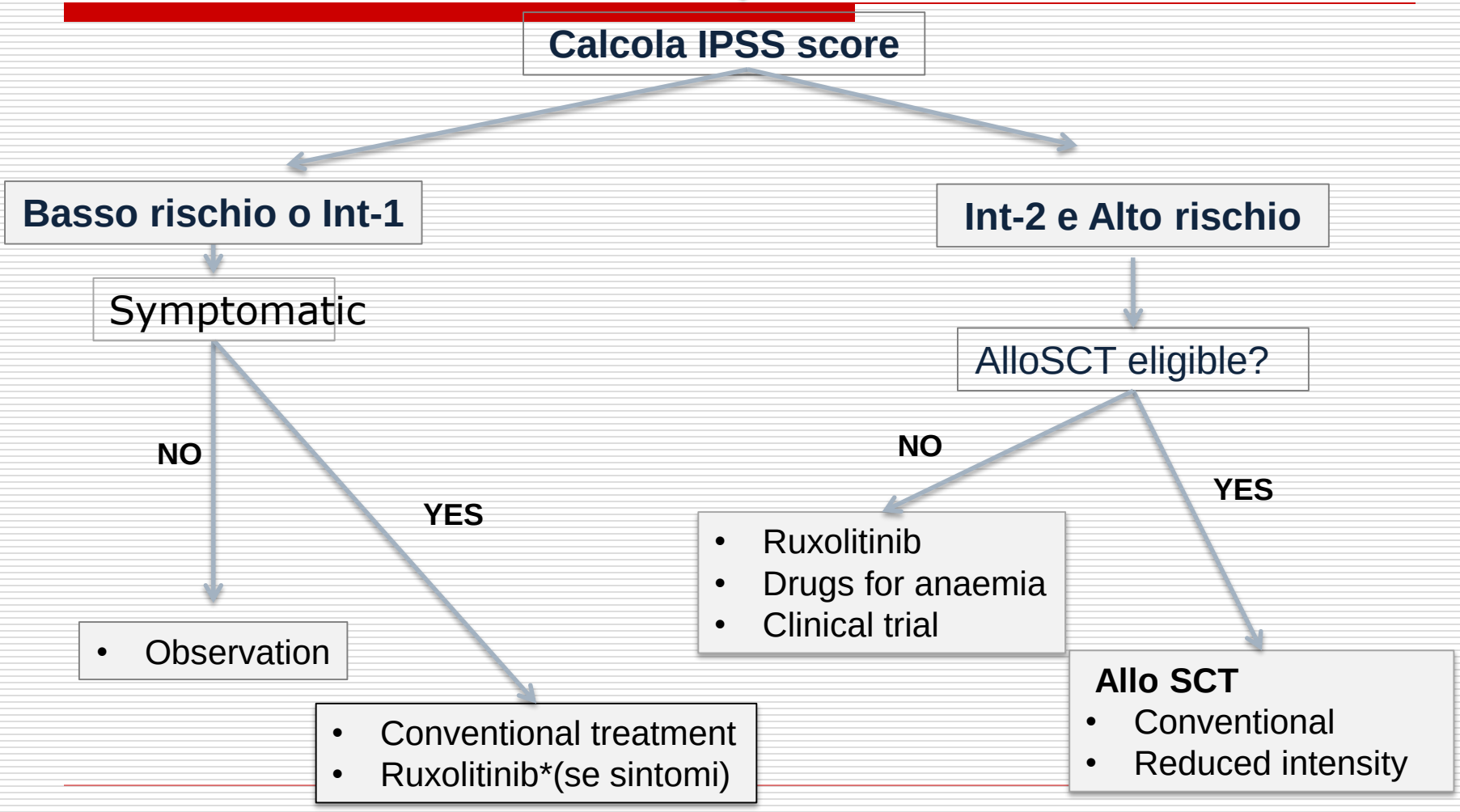
Primary outcomes: thrombosis (arterial, venous as defined by investigators.



Conclusion JAK1/JAK2 inhibition may reduce the risk of thrombosis in MPN. This finding warrants prospective trials

Samuelson BT al Blood Coagul Fibrinolysis. 2014 Nov 13. [Epub ahead of print]

La terapia della mielofibrosi primaria e dopo ET/PV nel 2015



Vannucchi A et al, Linee guida ESMO 2015

SYMPTOMS, RISK CLASSIFICATION, AND SPLEEN SIZE IN JAK2 INHIBITOR-NAÏVE MYELOFIBROSIS: IMPLICATIONS FOR JAK2 INHIBITOR TREATMENT

Questionario per la valutazione dei sintomi nelle malattie mieloproliferative croniche- 10
(MPN-10)

Sintomo	**Da 1 a 10 (0 se assente): il voto 1 è il più favorevole e 10 il meno favorevole**
Per favore, attribuisca un punteggio alla sua stanchezza (affaticamento, spossatezza) tracciando un cerchio attorno al numero che meglio descrive il suo **peggior** livello di stanchezza **durante le ultime 24 ore**	(Nessuna stanchezza) 0 1 2 3 4 5 6 7 8 9 10 (La peggior stanchezza immaginabile)
Per favore, tracci un cerchio attorno al numero che descrive l'intensità dei seguenti sintomi nell'ultima 24 ore:	
• Sensazione immediata di pienezza durante i pasti (sazietà precoce)	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Senso di ingombro addominale	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Rimanere senza fare nulla durante la giornata	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Problemi di concentrazione, rispetto a prima che Le venisse diagnosticata questa malattia	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Sudorazione notturna	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Prurito	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Dolore osseo (dolore osseo diffuso, non dolore articolare)	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Febbre (>37°C)	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
• Perdita di peso negli ultimi sei mesi senza aver fatto dieta dimagrante	(Assente) 0 1 2 3 4 5 6 7 8 9 10 (Il peggio immaginabile)
Per favore tracci un cerchio attorno al numero che meglio descrive come lei valuta la sua qualità di vita globale?	(La migliore possibile) 0 1 2 3 4 5 6 7 8 9 10 (La peggiore possibile)

- A cutoff criteria of the worst single symptom being >5/10 may differentiate between which patients will most benefit from symptom-based treatment.
- We propose that JAK2 inhibitor treatment be strongly considered in any JAK2-inhibitor naïve MF patient with an individual symptom score >5.

Robyn Scherber et al. EHA 2016

Which patients with myelofibrosis should receive ruxolitinib therapy? ELN-SIE evidence-based recommendations

Marchetti Monia[1], Barosi Giovanni[2], Cervantes Francisco[3], Birgegård Gunnar[4], Griesshammer Martin[5], Harrison Claire[6], Hehlmann Rüdiger[7], Kiladjian Jean-Jacques[8], Kröger Nicolaus[9], McMullin Mary Frances[10], Passamonti Francesco[11], Vannucchi Alessandro[12], Barbui Tiziano[13].

Leukemia, accepted 2016

Ruxolitinib was **strongly recommended**

- for improving symptomatic or severe (>15 cm below the costal margin) splenomegaly in patients with an IPSS/DIPSS risk INT2 or high
- for improving systemic symptoms in patients with a MPN10 score higher than 44, refractory severe itching, unintended weight loss not attributable to other causes or unexplained fever.
- because **of weak evidence**, the panel does not recommend ruxolitinib therapy for improving survival.
- the recommendations given above do not necessarily apply to patients who are candidates for allogeneic stem cell transplant.