# *PV ed ET alla diagnosi: score prognostici e fattori biologici*

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# Disclosures

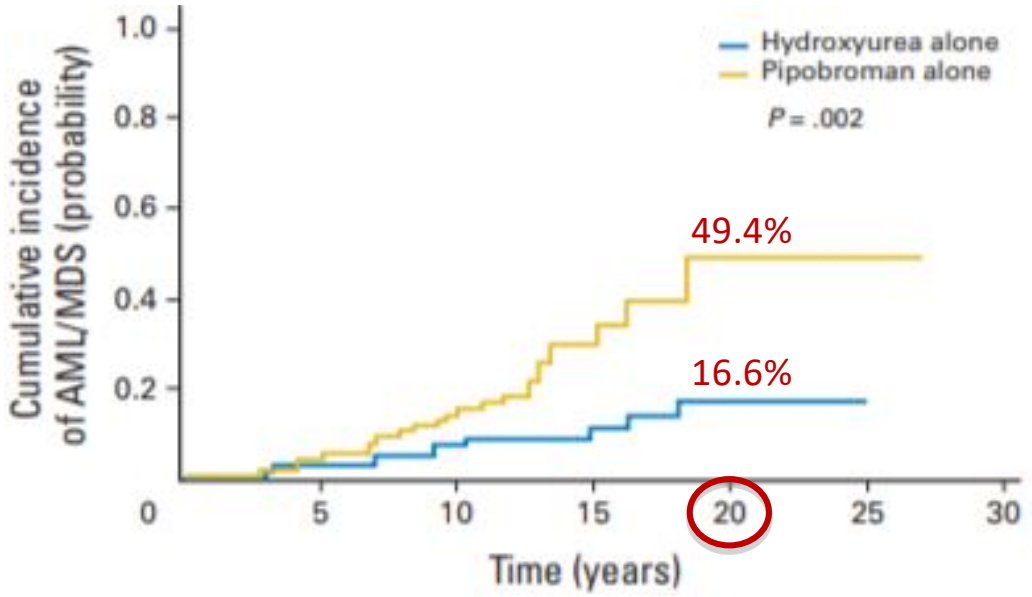
- Speaker bureau: Novartis, Celgene
- Advisory boards: Celgene, Novartis, Roche, Janssen, Incyte, Abbvie.

# Events in PV, results from a meta-analysis

- Incidence rate of thrombosis:
  - Median value: 3.3% persons/year
  - 1.9% at 60 years with no history of thrombosis (low risk patients)
  - 6.8% at a median age of 80 years
- Risk of myelofibrosis:
  - 0.9%, 5% and 34% at 1, 5 and 10 years
  - The odds increase on average 6% for each year of age
- Risk of blast phase
  - 0.4%, stable incidence over time

*Ferrari et al., Haematologica. 2019*

# Pipobroman/Hydroxyurea and AML occurrence in PV




- PV patients treated with HU alone (N=94 for 12 yrs) and PB alone (N=130 for 9.5 yrs)

*Kiladjian et al, J. Clin. Oncol. 2011*

# Abnormal karyotype impacts on AML-free survival in PV

| Predictors of leukemia-free survival | N | Univariate p-values | Age-adjusted p-values | Multivariate p-values (HR; 95% CI) [a] | Multivariate p-values (HR; 95% CI) [b] |
|---|---|---|---|---|---|
| Age | 1545 | 0.0002 | | | |
| Age > median (61y) | 1545 | 0.005 | | 0.007 (2.2;1.3-4.1) | 0.004 (6.3;1.8-22) |
| Abnormal karyotype | 631 | 0.03 | 0.03 | | 0.03 (3.9;1.2-13.1) |
| WBC ≥ $15X10^9/L$ | 1545 | 0.0003 | 0.0002 | 0.0004 (2.9;1.6-5.2) | 0.01 (3.9;1.3-11.6) |

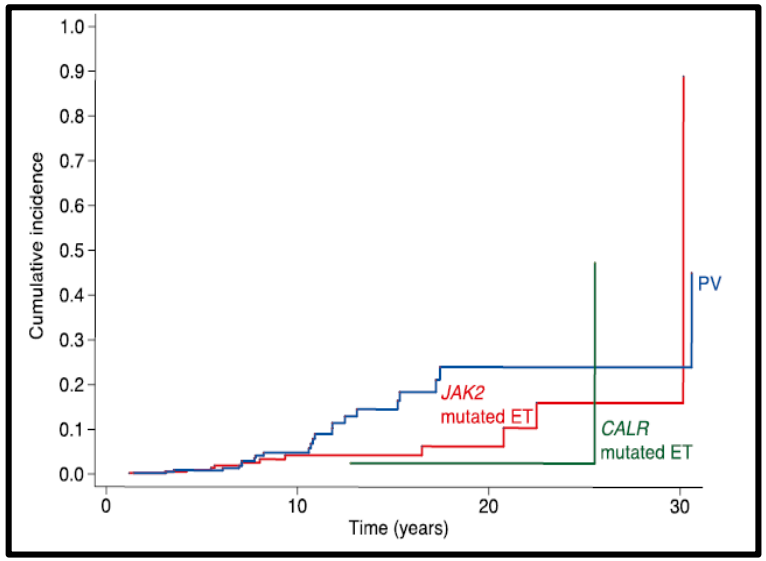
[a] karyotype excluded as a covariate; [b] Karyotype included as a covariate

Post-PV AML: 50/1545 (3%) at a median time of 10.8 yrs

*Tefferi et al., Leukemia. 2013*

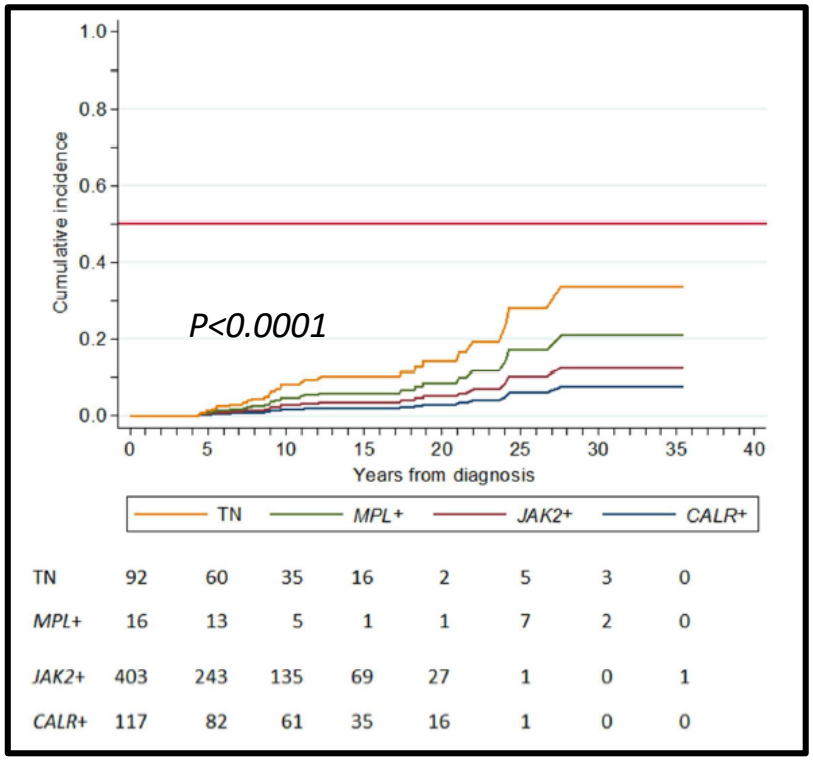
# Driver mutations' are predictive of post-MPN AML

*Median follow-up: 5.2 years*




***Rumi et al., Blood. 2014***

*Median follow-up: 7.2 years*




***Alvarez-Larran et al., BJH. 2017***

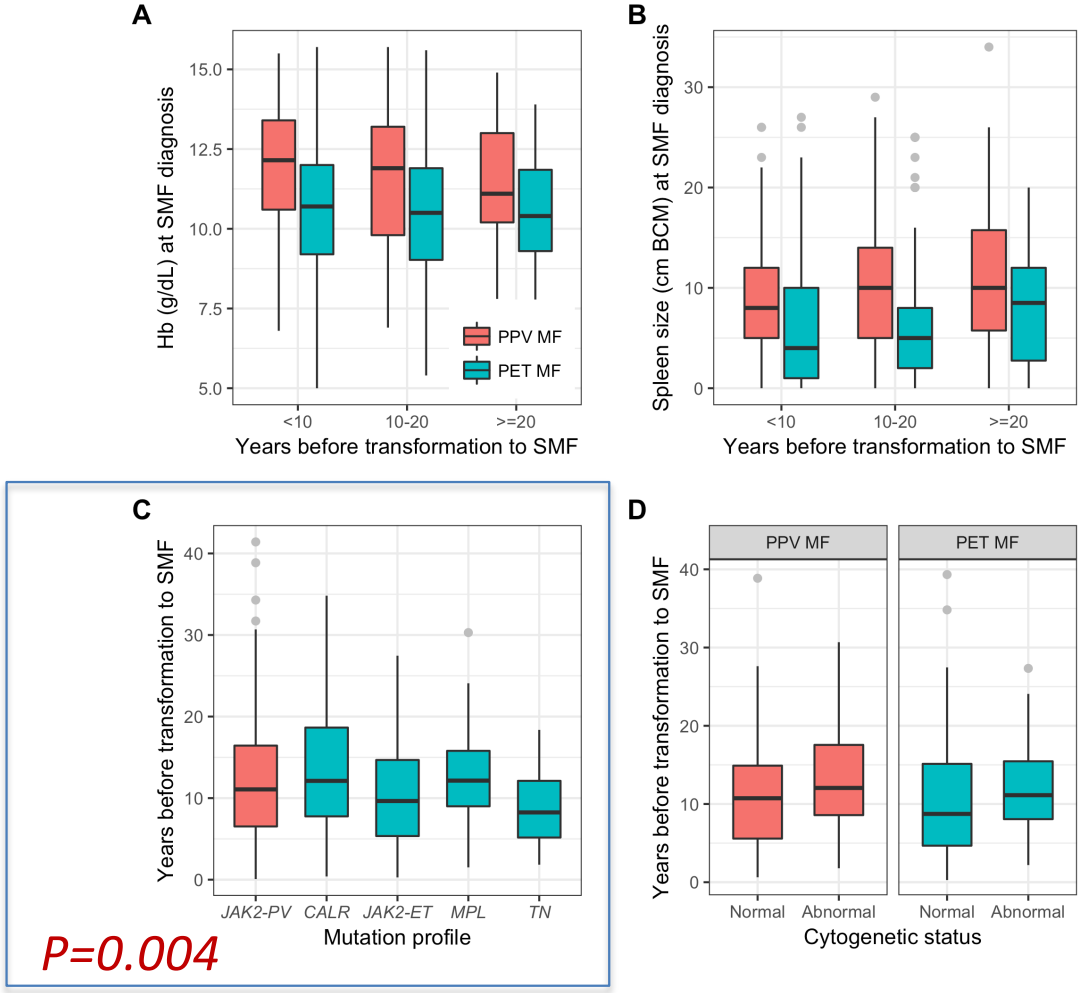
# Non-driver mutations' are predictive of post-MPN AML


HR 12.2 (95% CI 2.6-57.1, *P=0.001*) in multivariate analysis

- 13.5% risk of AML transformation at 15 years from first sample
- *ASXL1, TP53, SRSF2, IDH1/2, RUNX1*

***Senin et al., Ann. Hematol. 2017***

# Driver mutations and time to progression in PPV/PET MF




*Mora et al., Leuk. Res. 2018*

# NGS-enhanced prediction of survival in PV and ET

**ET**

- *SRSF2/SF3B1* mutations (HR 2.8)
- Age >60 years (HR 6.7)
- Male sex (HR 1.8)

**PV**

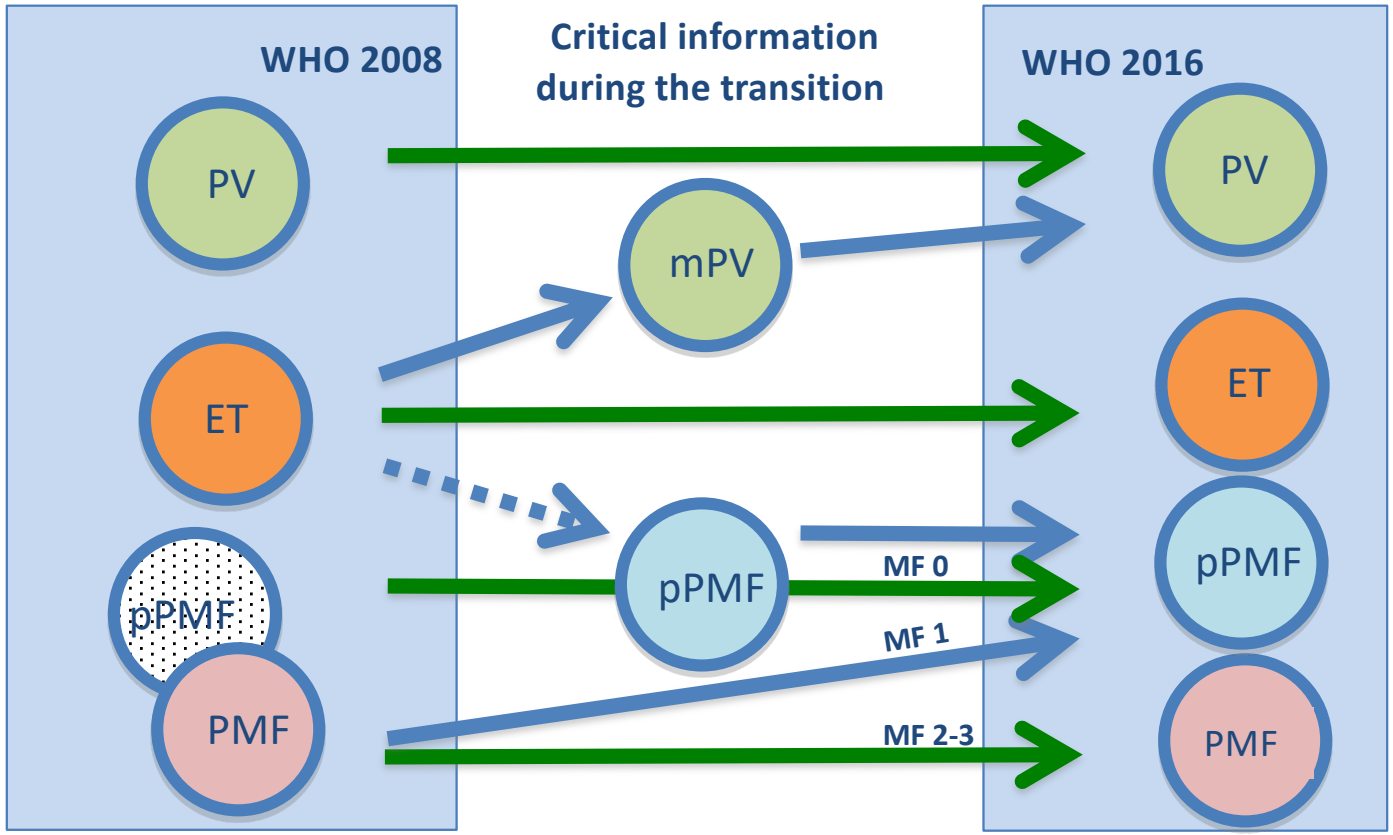
- *SRSF2* mutations (HR 7.0)
- Age >67 yrs (HR 5.7)
- Leukocytes ≥11 x $10^9$/l (HR 2.4)
- Abnormal karyotype (HR 2.1)

***ET and PV (N=906)***

*Tefferi et al., ASH 2018*

# *Essential thrombocythemia*

# What is ET: WHO 2008 → 2017

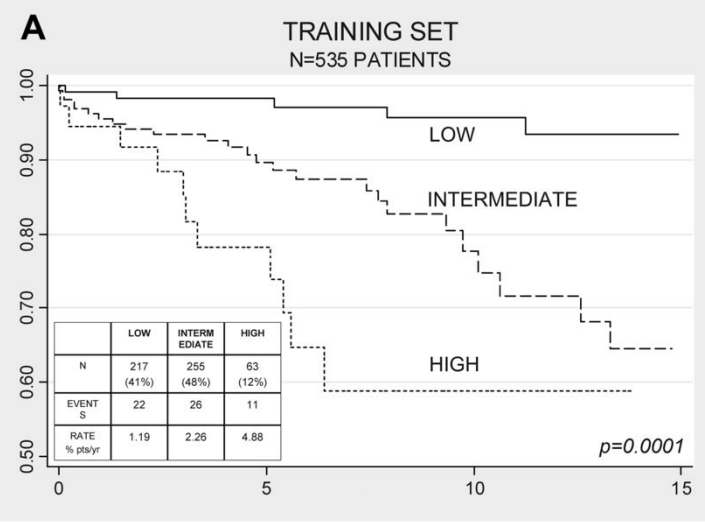



*Passamonti & Maffioli, ASH Educational 2016*

# *JAK2* assessment outperformes the two-tiered risk stratification for thrombosis: the IPSET-t model

(891 WHO-defined ET, follow-up 6.2 years)

- ***Prognostic factors***
  - Age > 60 years (1 point)
  - Thrombosis history (2 points)
  - Cardiovascular risk (1 point)
  - *JAK2* V617F (2 points)
- ***IPSET Model***
  - Low risk (< 2 points): 1.03% p/y
  - Intermediate risk (2 points): 2.35% p/y
  - High risk (> 2 points): 3.56% p/y



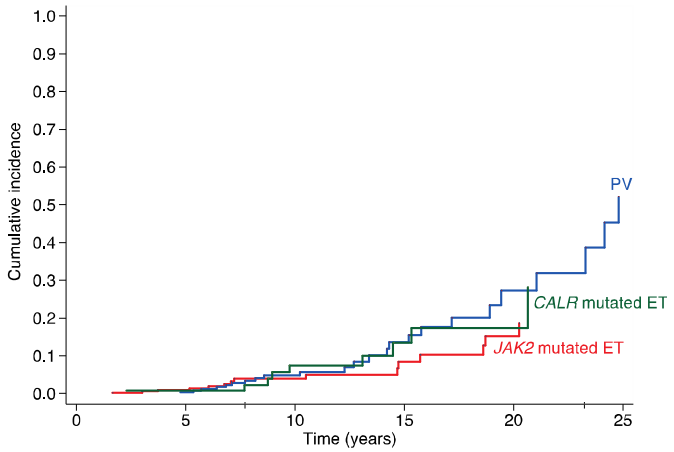

*Barbui et al. Blood 2012 Dec 20;120(26):5128-33*

**NO prognostic advantage of *CALR* mutation over IPSET-t in thrombosis prediction**

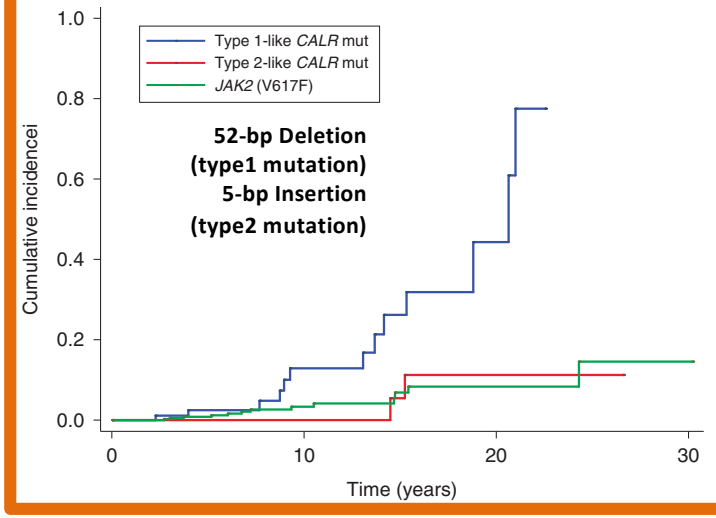
*Finazzi G. et al Blood. 2014 Oct 16;124(16):2611-2*

# Prediction of post-ET MF evolution

**Progression to post-ET MF per genotype**




**Progression to post-ET MF per *CALR***




- In the MYSEC study on post-ET MF, *CALR* T1/T1-like genotype was more frequent (61%) than *CALR* T2/T2-like
- In the Mayo series, no specific association with post-ET MF have been disclosed among *CALR* sutypes

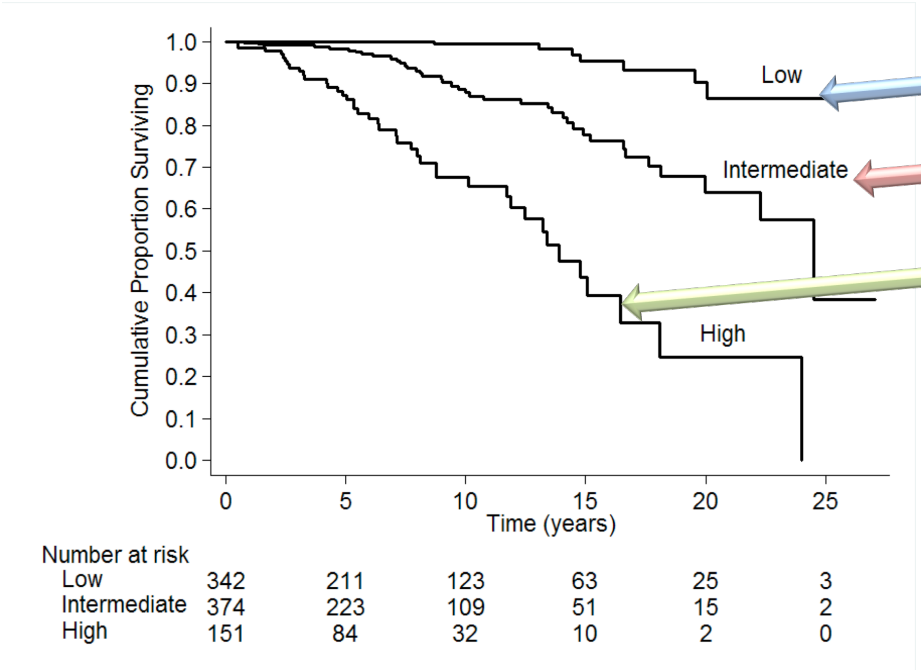
*Rumi E et al, Blood 2014;123(10):1544-51; Pietra et al. Leukemia. 2016 Feb;30(2):431-8;; Passamonti et al. Leukemia. 2017 Jan 3. doi: 10.1038/leu.2016.351; Elala et al. Am J Hematol. 2016 May;91(5):503-6.*

# Survival of WHO-based ET: the IPSET model

| Risk factors | |
|---|---|
| Age > 60 years | 2 points |
| Prior thrombosis | 1 point |
| WBC > 11 x$10^9$/L | 1 point |

→

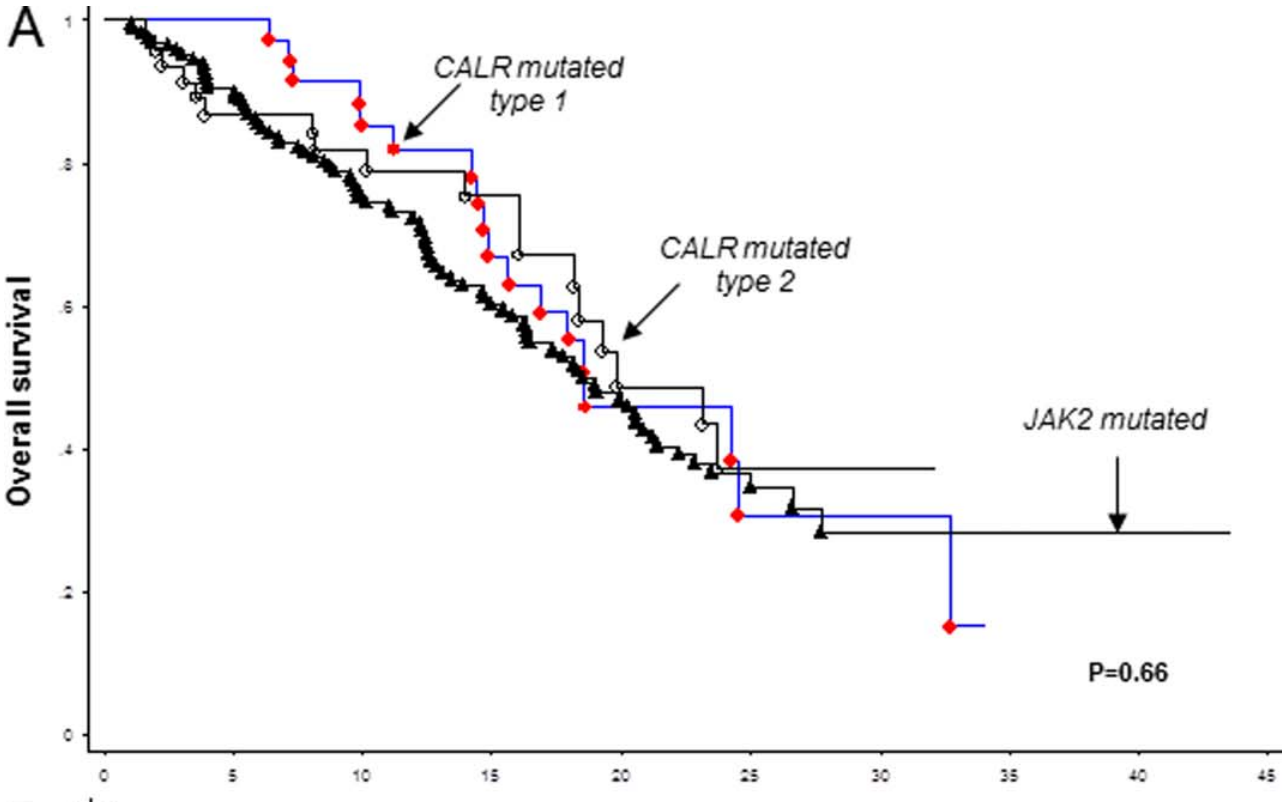
| Risk Categories/score | |
|---|---|
| LR | 0 |
| Int-1 | 1-2 |
| HR | 3-4 |




| | |
|---|---|
| N=342 | Not reach |
| N=374 | 24.5 years |
| N=151 | 15.1 years |

*Passamonti et al. Blood. 2012 Aug 9;120(6):1197-201*

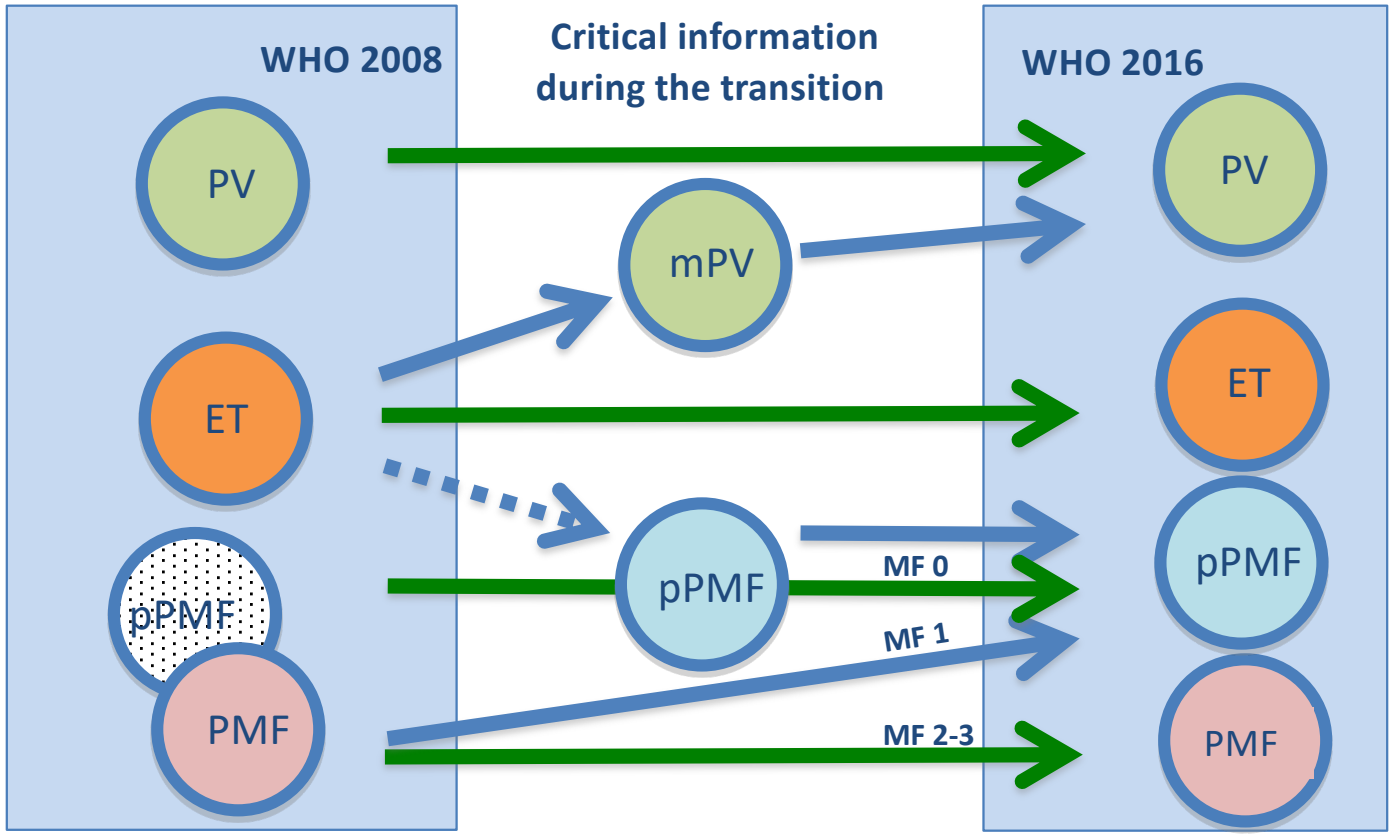
# No impact of genotype on survival in ET




*Tefferi et al, Am J Hematol. 2014 Aug;89(8):E121-4*


***polycythemia vera***

# What is PV: WHO 2008 → 2017




*Passamonti & Maffioli, ASH Educational 2016*

# Conventional prediction of thrombosis in PV

1. Age over 60 years
2. Previous thrombosis

**LR (no factor)** → Thrombosis incidence:
ET: 1.5 ×100 p/y
PV: 2.5 ×100 p/y

**HR (≥1 factor)** → Thrombosis incidence:
ET: 2.0 ×100 p/y
PV: 5.0-10.9 ×100 p/y

Cardiovascular risk factors to be corrected/prevented

Extreme thrombocytosis (PLT count >1,500 $\times 10^9$/L) implies a higher risk of bleeding

*Barbui T et al, J Clin Oncol 2011;29(6):761-70; Marchioli R et al, J Clin Oncol 2005;23(10):2224-32;; Carobbio A et al, Blood 2008;112(8):3135-7*

# Prediction of post-PV MF evolution

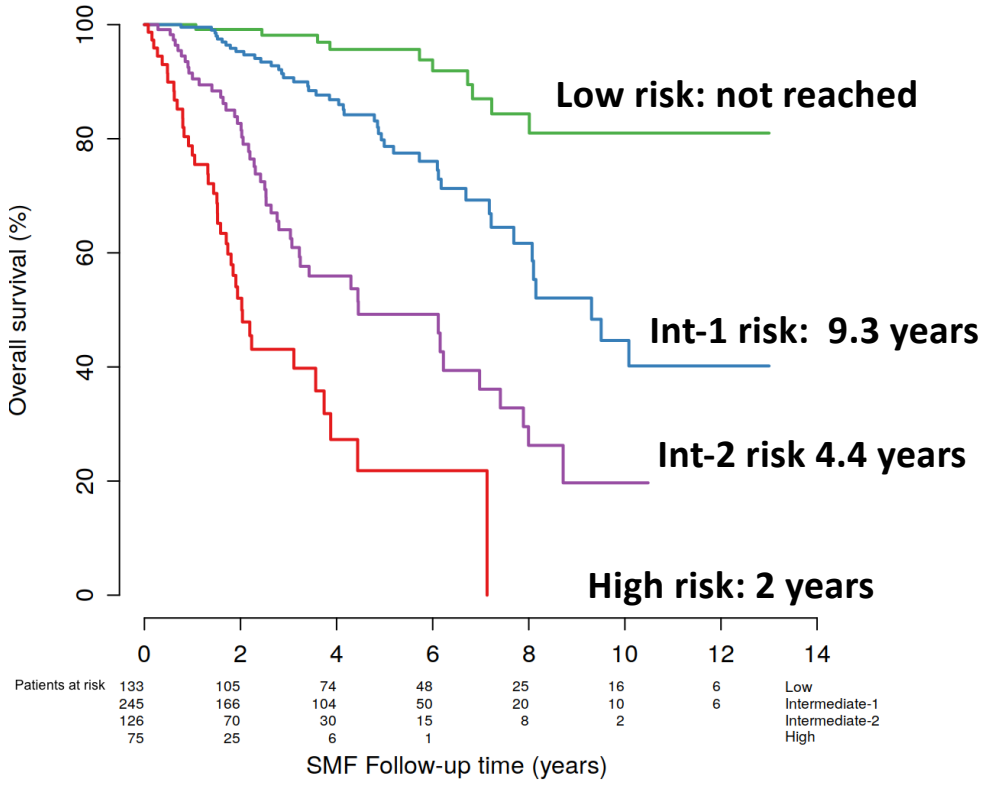
- SMF occur in 12-21% of PV
- Potential predictors of SMF evolution:
  - Detection of BM fibrosis in BM biopsy of PV at diagnosis
  - Some clinical parameters at diagnosis of PV (leukocytosis, splenomegaly, higher *JAK2* allele burden) or during PV course (HU-resistant splenomegaly)
  - *SRSF2*, DNMT3A mutations in PV; -2518 A/G polymorphism of MCP-1 (monocyte chemoattractant protein-1)
  - Abnormal cytogenetics

*Tefferi et al. Blood. 2014 Oct 16;124(16):2507-13; Barbui et al, J Clin Oncol. 2011 Aug 10;29(23):3179-84; Passamonti et al, Blood 2008; Tefferi et al; Leukemia 2013; Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-93; Passamonti et al, Blood 2006; Passamonti et al Leukemia Sep;24(9):1574-9; Rumi et al., Blood 2013; Rumi E et al, Blood 2014;123(10):1544-51; Pietra et al. Leukemia. 2016 Feb;30(2):431-8; Passamonti et al. Leukemia. 2017 Jan 3. doi: 10.1038/leu.2016.351; Elala et al. Am J Hematol. 2016 May;91(5):503-6; Lundberg et al, Blood 2014; Bartels et al, Leukemia 2017; Masselli et al, Leukemia 2018*

# Prediction of survival in post-PV/ET MF

## The integrated clinical-molecular model MYSEC-PM

| Covariates | Points |
|---|---|
| Age, years | 0.15 |
| Hemoglobin <11 g/dL | 2 |
| Platelet < 150 x$10^9$/L | 1 |
| Circulating blast cells ≥ 3% | 2 |
| *CALR*-unmutated genotype | 2 |
| Constitutional symptoms | 1 |




*Passamonti et al. Leukemia. 2017 May 31. doi: 10.1038/leu.2017.169*

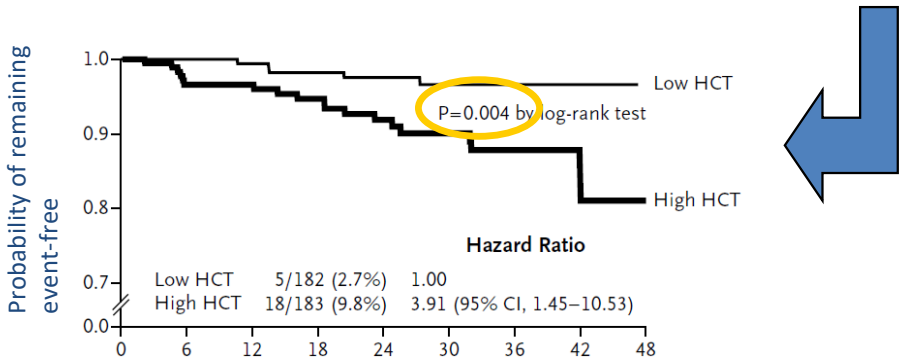
# HCT level is critical in PV management: the CYTO-PV trial

365 *JAK2*-pos. PV pts treated with phlebotomy ± HU

R 1:1

| | Primary endpoint achieved, n (%): | Secondary endpoint achieved, n (%): |
|---|---|---|
| Treated to Hct <45% n = 182 | 5* (2.7) | 8 (4.4) |
| Treated to Hct 45-50% n = 183 | 18* (9.8) | 20 (10.9) |

- 0 deaths in the Hct <45% arm,
- 4 deaths in the Hct 45-50% arm




***Primary composite end point:*** Death from CV cause or major thrombotic events (stroke, acute coronary syndrome, transient ischemic attack, PE, abdominal thrombosis, DVT, or peripheral arterial thrombosis)

***Secondary end point:*** Primary end point + superficial-vein thrombosis

*Marchioli R et al, N Engl J Med 2013;368(1):22-33*

# Inadequately controlled PV is a predictive factor

- Recorded in 137 patients (15.4%):
  - Need for phlebotomies (3.3%)
  - Uncontrolled myeloproliferation (1.6%)
  - Failure to reduce massive splenomegaly (0.8%)
  - Cytopenia at the lowest HU-dose to achieve response (1.7%)
  - Extra-haematological toxicity (9%)
- **Cytopenia affected survival, progression to MF, AML**
- **Splenomegaly affected MF**

*Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-93*

## Conclusions

- Driver mutations enter PV and ET process for diagnosis.
- *JAK2*, *CALR*, *MPL* variants can identify patients with different risk of thrombosis, and myelofibrosis.
- AML occurrence is more disease-based than expected.