Ospedale di Circolo

Fondazione Macchi

Prognostic models in PV and ET

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Current risk stratification in PV and ET:
statement from European LeukemiaNet consensus

- Age over 60 years
- Previuos thrombosis

Low risk
No factor

High risk
≥ 1 factor

No cytoreduction

Cytoreduction

Barbui et al, JCO 2011

Potential candidate parameters

- Leukocyte count
- Bone marrow histopathology
- *JAK2* (V617F) and allele burden
- Other molecular abnormalities

Leukocytes and thrombosis

Relationship of WBC count (x10^9/L) at diagnosis

- >15 and thrombosis in 332 ET (Wolanskyj, MCP 2006)
- >15 and myocardial infarcion in 1638 PV (Landolfi, Blood 2007)
- >8.7 and thrombosis in 439 ET (Carobbio, Blood 2007)
- No in 605 ET not stratified (Tefferi, Blood, 2007)
- >9.4 and thrombosis in 341 low-risk ET (Carobbio, JCO 2008)
- >11, PLT <1000 and thrombosis in 1063 ET (Carobbio, Blood 2008)
- No in 605 ET not stratified (Passamonti, Haematologica, 2008)
- >9.5 and thrombosis in 187 PV/ET (Caramazza, AH 2009)
- No in 407 low-risk ET and PV (Gangat, Cancer 2009)
- >12.4 and a. thr. recurrence in 253 PV/ET <60 yrs (De Stefano, AJH 2010)
- > 11 and thrombosis in 532 ET (Palandri et al, AJH 2011)

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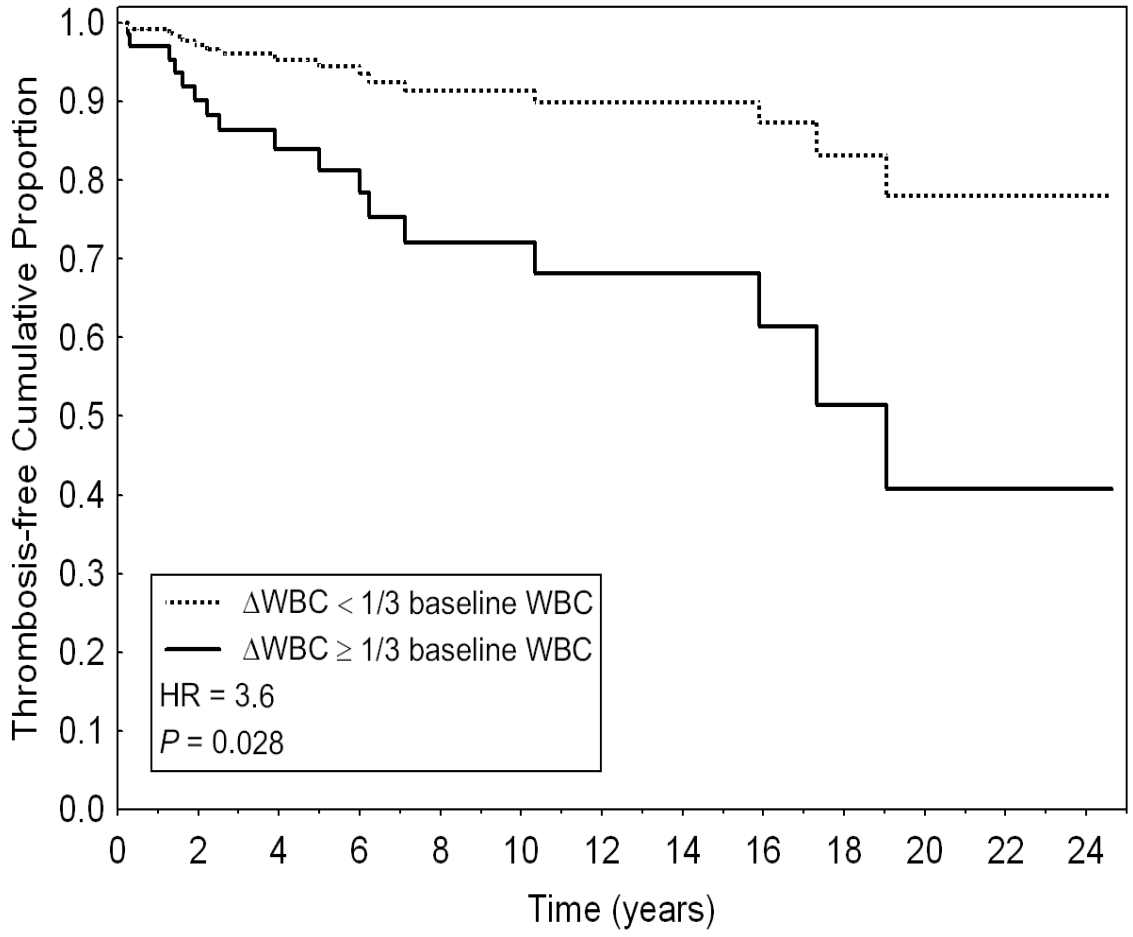
Thrombosis-free survival estimate in 194 patients with LR-ET



Patients with a ΔWBC > 1/3 of the baseline WBC count within two years from diagnosis have a 3.6 fold higher risk to develop thrombosis during follow-up compared to those with a ΔWBC < 1/3

ΔWBC represents the difference between the two numerical evaluations of white blood cell (WBC) count

Passamonti et al, JTH 2009

Leukocytes and other events

Relationship with post-PV MF

- >15 x10^9/L at diagnosis

647 PV (Passamonti, Blood 2008)

Relationship with survival

- >15 x10^9/L, age over 60 years

459 PV (Gangat, Leukemia 2007)

- >15 x10^9/L, age over 60 years, anemia

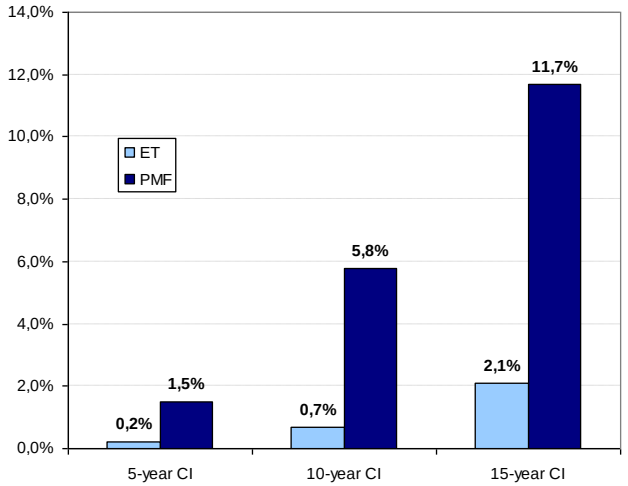
605 ET (Gangat, Leukemia 2007)

- > 11 x10^9/L, age over 60 years, anemia

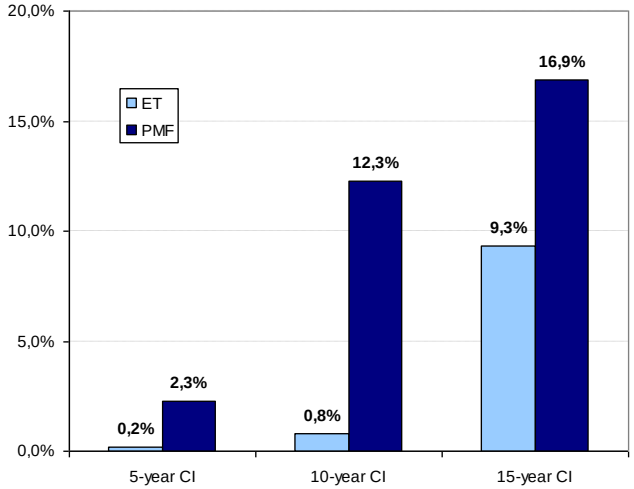
311 ET (Girodon, Leukemia 2010) 532 ET (Palandri, AJH 2011)

The impact of BM histopathology on events in 1104 ET patients

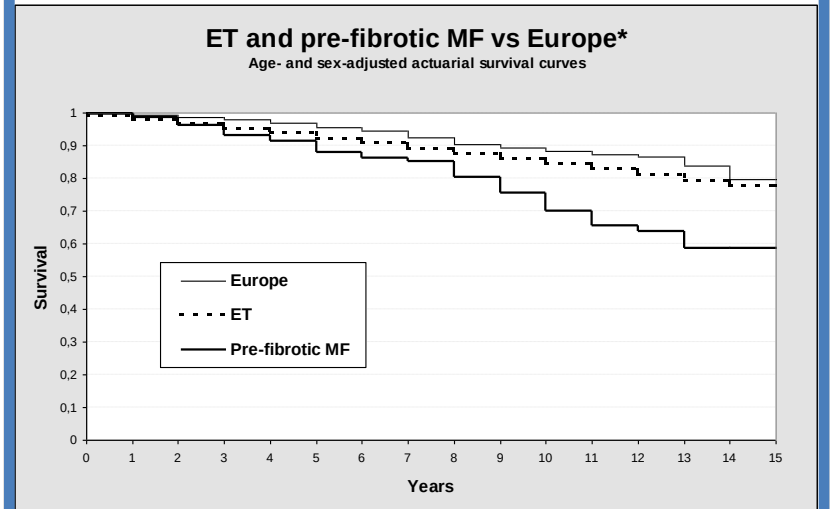
Incidence of AML



Incidence of MF



OS



Barbui et al, JCO 2011 in the press

Risk factors for thrombosis in WHO-defined ET

Arterial

- Age > 60 years
- History of thrombosis
- Cardiovascular risk factors
- WBC > 11 x 10^9/L
- JAK2 (V617F)

Venous

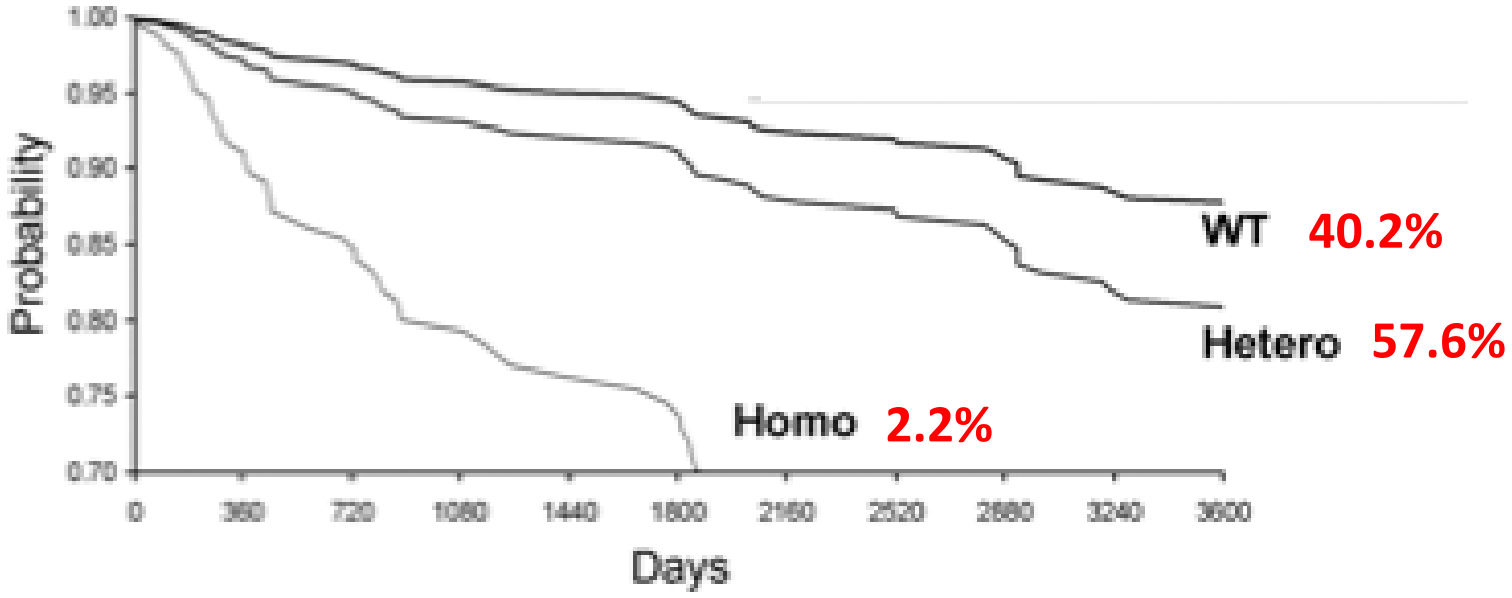
- Male gender

Carobbio et al, Blood prepub 2011

JAK2 (V617F) and thrombosis in ET

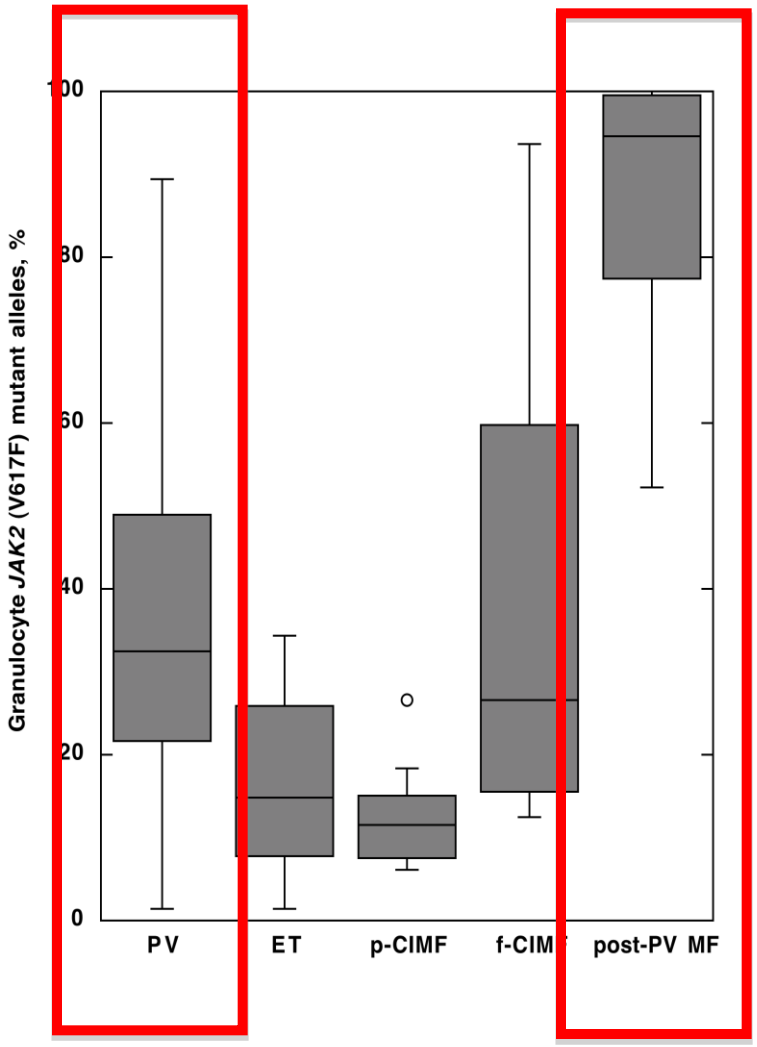
• Medline- and Embase-guided meta-analyses showed that V617F increases the risk of thrombosis

Dahabreh *et al*, Leuk Res 2009; Lussana *et al*, TR 2009



Vannucchi *et al*, Blood 2007

Proportion of *JAK2* mutant alleles in PV



Passamonti et al, Blood 2006

Significant different mutant alleles between PV and post-PV MF

Transformation to MF is more frequent in PV patients with higher mutant burden

Tefferi et al, Cancer 2005
Vannucchi et al, Blood 2007

Study of *JAK2* allele burden in PV

Patients with PV enrolled in the study (N=338)

JAK2 (V617F)-pos (N=320, 94.7%)

JAK2 exon 12-pos (N= 14, 4.1%)

JAK2-negative (N=4, 1.2%)

Excluded from the analysis

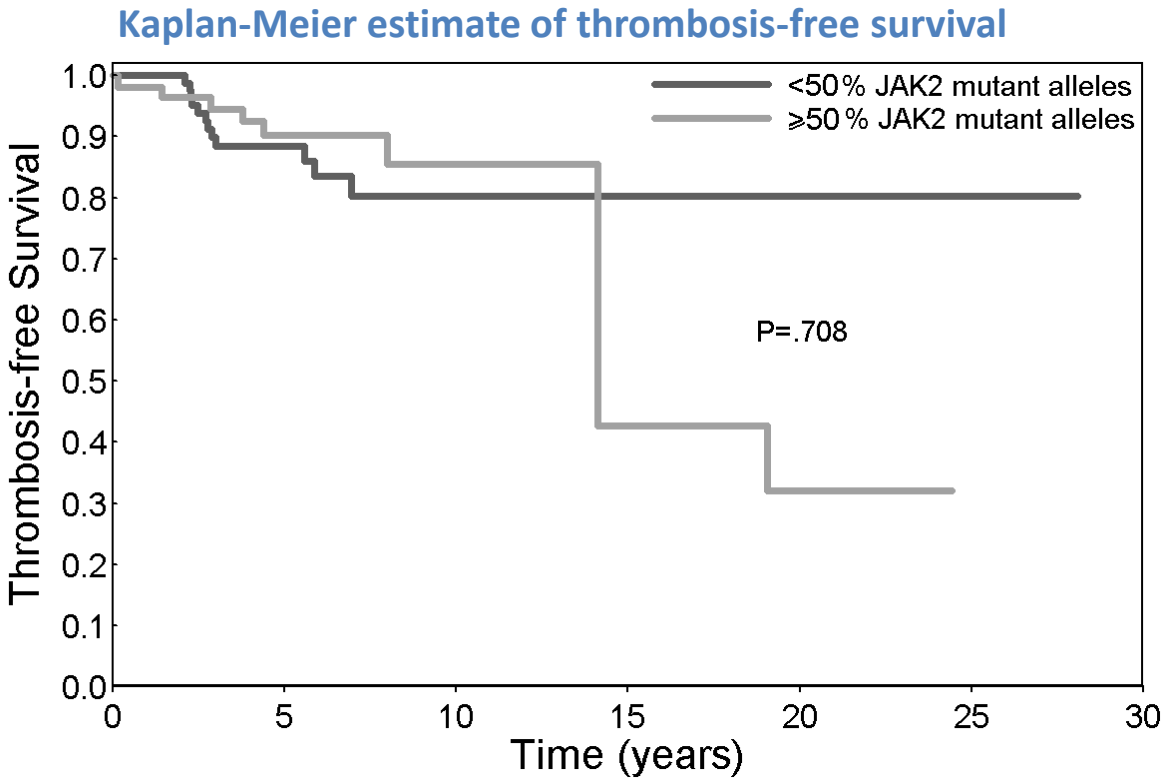
JAK2 (V617F) allele burden

< 50%: 152 (47%)

≥ 50%: 168 (53%)

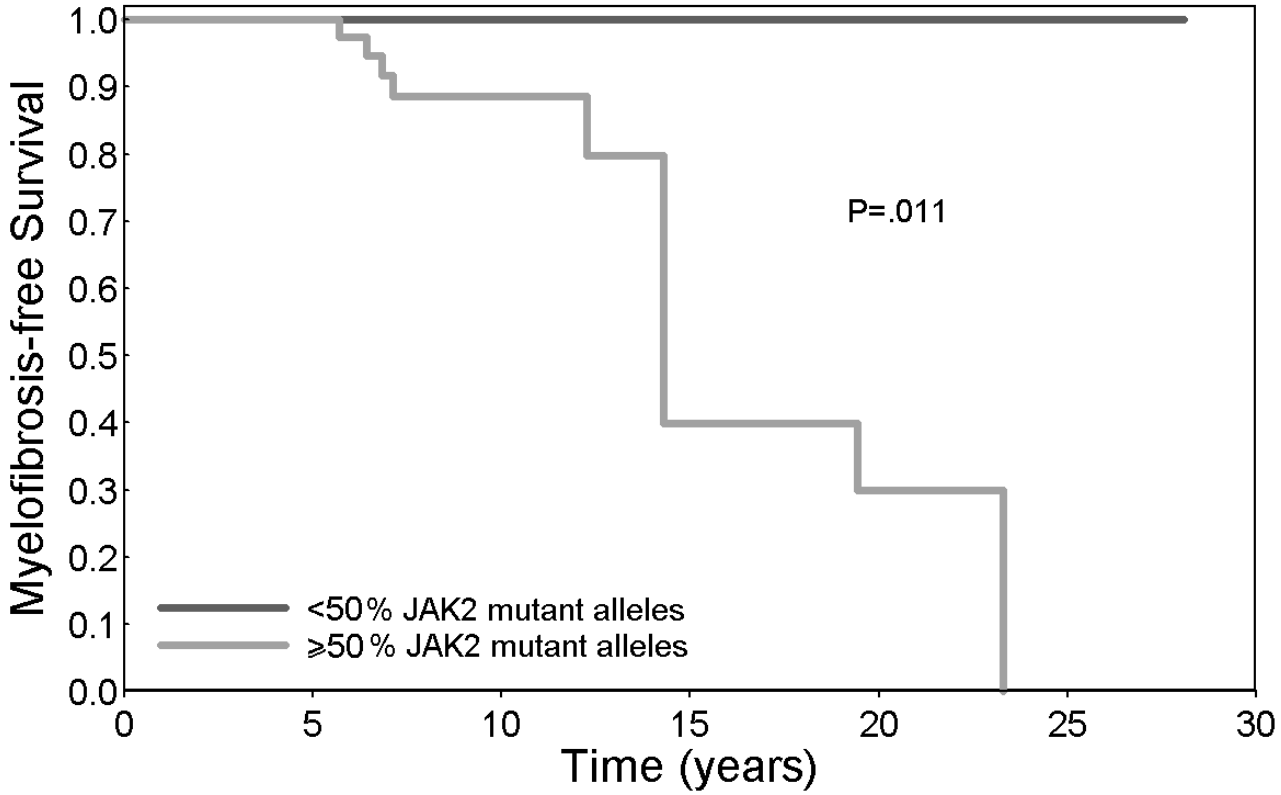
JAK2 allele burden and thrombosis

• *JAK2* mutant allele burden (continuous or categorical variable) does not affect the risk of thrombosis during follow-up (Cox proportional hazard regression)



Passamonti et *al*, Leukemia 2010

JAK2 allele burden and MF

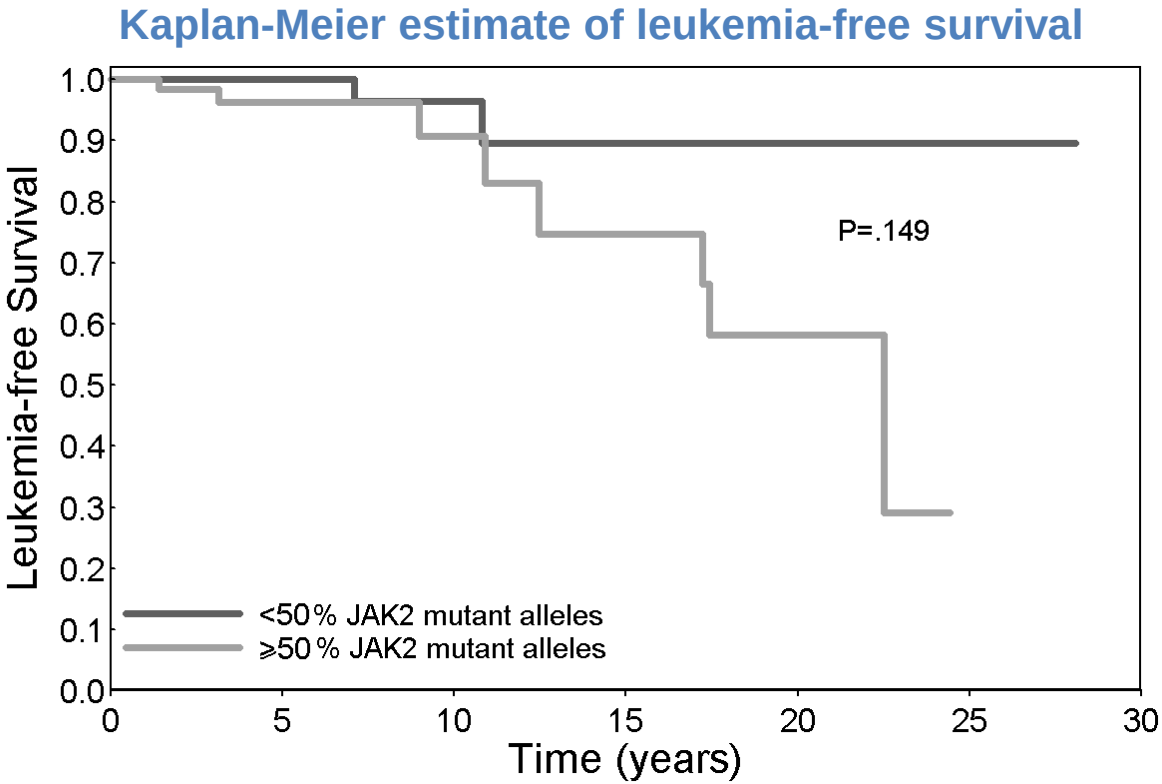


PV patients with more than 50% mutant alleles have a significantly shorter myelofibrosis-free survival

Passamonti e*t al*, Leukemia 2010

JAK2 allele burden and AML

• *JAK2* mutant allele burden (continuous or categorical variable) is not associated to a different occurrence of leukemia (Cox proportional hazard regression)



Passamonti e*t al*, Leukemia 2010

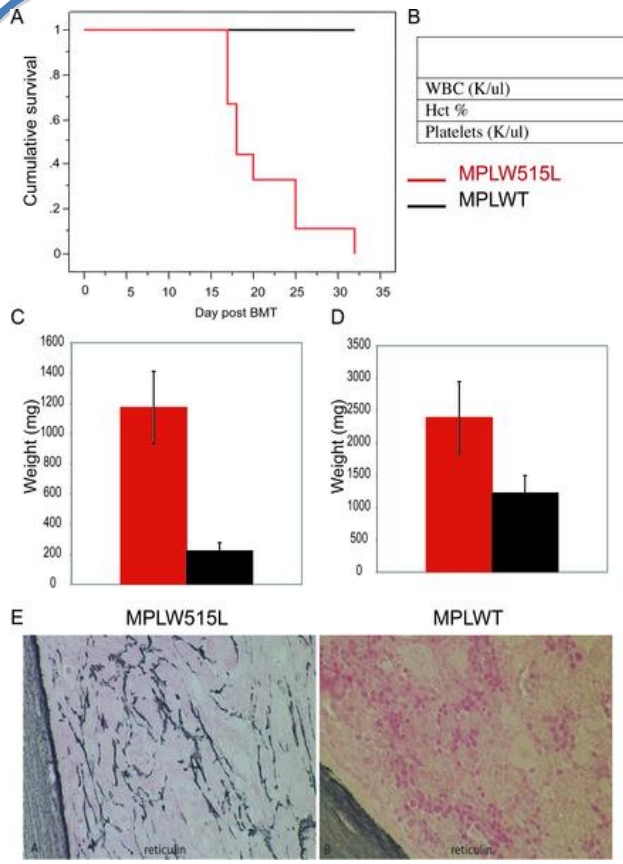
JAK2 exon 12 mutations

A collaborative European study including 13 centers

- 106 patients with PV carrying exon 12 mutations of *JAK2*; 17 different mutations
- Most frequent mutation: N542-E543del (30%)
- Clinical phenotype irrespective of mutation
- 64% had isolated erythrocytosis, 15% + leukocytosis, 12% + thrombocytosis, 9% trilieage myeloproliferation
- No differences in term of events (thrombosis, MF, AML) when compared with V617F-positive PV patients
- Age over 60 years and prior thrombosis predicted thrombosis

Passamonti et al. Blood 2011

MPL mutations



- In Chr.1p34; Different mutations within exon 10

ET (1-4%):
MPL^{+} vs *V617F*$^{+}$: lower Hb, higher PLT, reduced BM cellularity, expansion of megakaryocytic lineage

PMF (5-9%):
MPL^{+} vs *V617F*$^{+}$: lower Hb, more transfusional need

- No impact on events

Pikman *et al*, Plos 2006; Pardanani *et al*, Blood 2006; Beer *et al*, Blood 2008, Guglielmelli *et al* BJH 2007; Vannucchi et al, Blood 2008

TET2 mutations

MPN

PV 14/98 (14%)

ET 8/73 (11%)

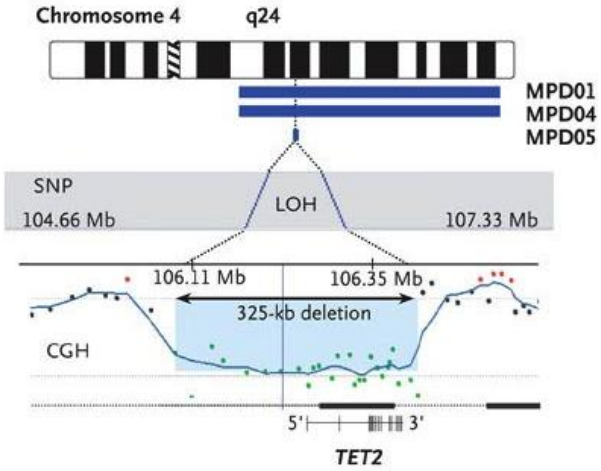
PMF 3/10 (30%)

MDS

15/81 (18%)

AML

5/21 (25%)

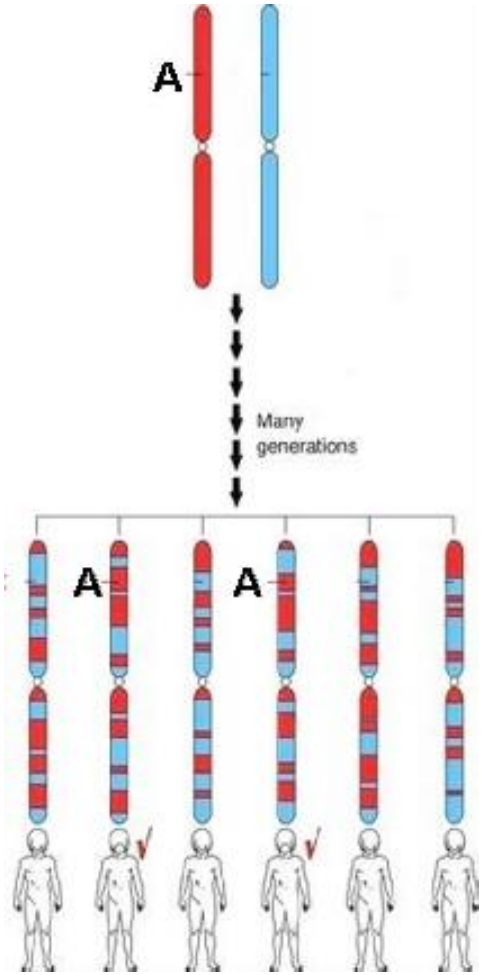


- In Chr. 4q24
- Deletions, frameshift, stop codons, AA substitutions
- *TET2* may precede *JAK2* mutations, viceversa
- *TET2* and *JAK2* mutations may be two separate clones

- No impact on OS in PV and PMF

Delhommeau *et al*, NEJM 2009; Tefferi et al, Leukemia 2009 Schaub *et al* Blood 2010; Olcaydu et al, Haematologica 2011

Germline genetic variation: haplotype



- Association between a specific *JAK2* haplotype (46/1 or GGTT) and *JAK2* (V617F)$^{+}$ or *JAK2* exon 12^{+} MPN (Kilpivaara, Nat Gen 2009; Olkaydu, Nat Gen 2009, Leukemia 2009; Jones, Nat Gen 2009)
- *JAK2* haplotype affects MPN susceptibility regardless of *JAK2* status (Tefferi, Leukemia 2009)
- *JAK2* haplotype predispose to the acquisition of JAK2 in familial MPN (Olcaydu, Haematologica 2011)
- *JAK2* haplotype affects survival in PMF and not in ET (Tefferi, Leukemia 2009)

Conclusions

- Current PV and ET risk stratification is based on advanced age and prior thrombosis
- But WBC count, mutational status and BM fibrosis should be considered as additional tests