Katedra i Klinika
Hematologii i Transplantacji
Szpiku

Szpital Kliniczny
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Risk stratification and treatment decisions in Philadelphia-negative myeloproliferative neoplasms

The classical myeloproliferative neoplasms (MPNs)

- the most frequent diseases among the myeloproliferative disorders
- MPN are characterized by excessive production of terminally differentiated blood cells that are fully functional
- classical MPNs have been classified into 3 entities: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), which have frequent disease-related complications, such as venous and arterial thrombosis, hemorrhages, and transformation to acute myeloid leukemia
- all MPN entities arise from a single somatically mutated hematopoietic stem cell that clonally expands and gives rise to virtually all myeloid cells, and B and natural killer cells

	Overall MPN	PV	ET	PMF
Incidence	1.15-4.99/100.000	0.01-2.61/100.000	0.21-2.27/100.000	0.22-0.99/100.000
Prevalence		0.49-46.88/100.000	11.00-42.51/100.000	1.76-4.05/100.000
5-year survival (%)	56.7 (USA) 88.6 (UK)	84.8	89.9	39 (Sweden)

Anderson LA, et al. Curr Hematol Malig Rep DOI 10.1007/s11899-014-0228-z

The classical myeloproliferative neoplasms (MPNs)

- The clonal expansion of the MPN hematopoietic stem cells is accompanied by single or multilineage hyperplasia

- *PV is characterized not only by an excess of erythrocytes and predominant erythroid lineage involvement, but is also associated with a variable hyperplasia of the megakaryocytic/granulocytic lineages*
- *ET is characterized by an increased platelet count with a megakaryocytic hyperplasia, whereas PMF is a more heterogeneous disorder both by its clinical and biological characteristics, defined by the presence of bone marrow fibrosis (excess of collagen fibers) and megakaryocytic hyperplasia*
- *in PMF myeloproliferation initially predominates in the bone marrow and later expands to extramedullary sites, such as the spleen and liver*

MPN symptoms by MPN subtype

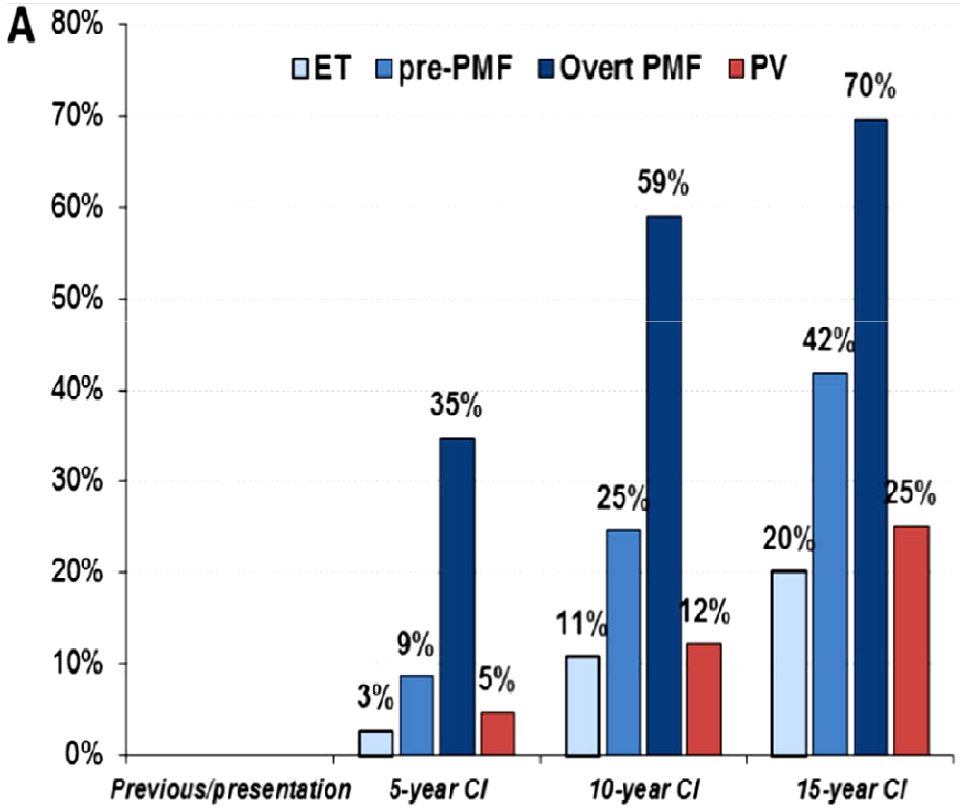
	ET (n=874)		PV (n=729)		MF (n=486)		Total (n=2089)	
Symptom	**Mean (SD)**	**Incidence (%)***	**Mean (SD)**	**Incidence (%)***	**Mean (SD)**	**Incidence (%)***	**Mean (SD)**	**Incidence (%)***
Worst fatigue (one-item BFI)	3.9 (2.9)	84	4.2 (2.9)	85	4.9 (2.8)	94	4.3 (2.9)	87
Early satiety	2.1 (2.6)	56	2.4 (2.7)	60	3.2 (3.0)	74	2.4 (2.8)	61
Abdominal discomfort	1.6 (2.3)	48	1.6 (2.3)	48	2.6 (2.8)	65	1.8 (2.5)	52
Inactivity	1.9 (2.5)	54	2.4 (2.8)	60	3.3 (3.0)	76	2.4 (2.7)	61
Concentration	2.2 (2.7)	58	2.6 (2.8)	62	2.8 (2.9)	68	2.5 (2.8)	62
Night sweats	1.9 (2.7)	47	2.1 (2.8)	52	2.9 (3.2)	63	2.2 (2.9)	53
Itching	1.7 (2.6)	46	2.7 (3.1)	62	2.1 (2.9)	52	2.1 (2.9)	53
Bone pain	1.7 (2.6)	45	2.0 (2.8)	48	2.2 (2.9)	53	1.9 (2.7)	48
Fever	0.4 (1.2)	17	0.4 (1.2)	19	0.6 (1.6)	24	0.5 (1.3)	19
Weight loss	0.9 (2.0)	28	1.2 (2.2)	33	2.2 (3.1)	47	1.3 (2.4)	34
MPN - 10	**18.3 (15.4)**	**---**	**21.6 (16.7)**	**---**	**26.6 (18.0)**	**---**	**21.4 (16.8)**	**---**

ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera

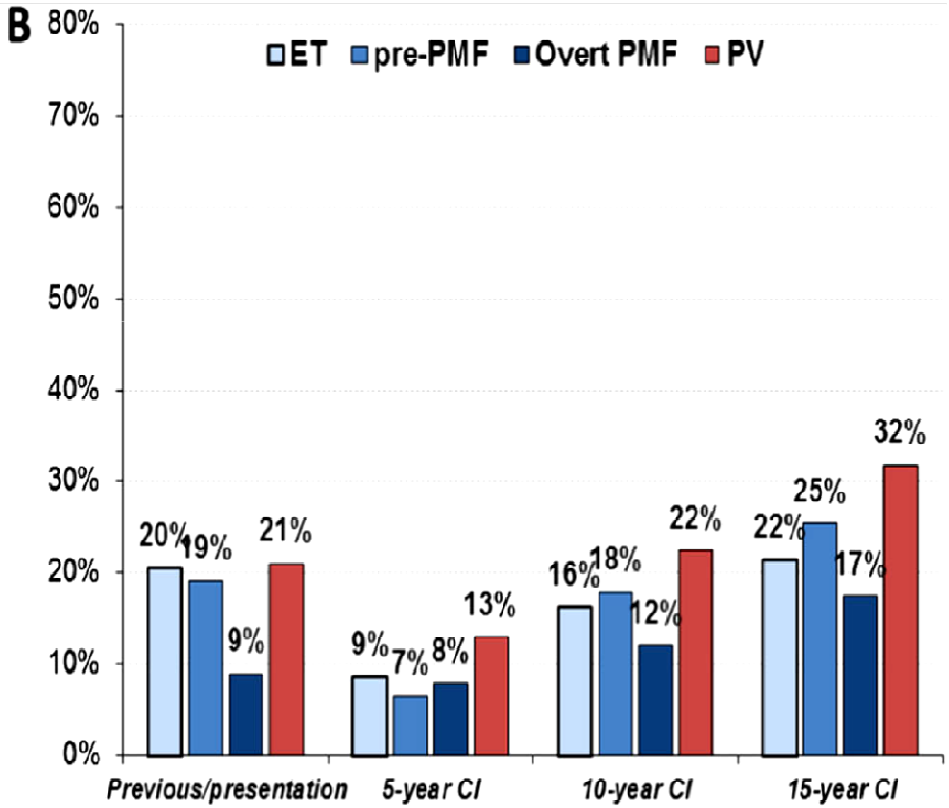
Geyer HL, et al. Hematology 2014;

MPN

Mortality



Major arterial and venous thrombotic complications



Barbui et al. Blood Cancer Journal (201

European consensus on the grading of myelofibrosis (MF)

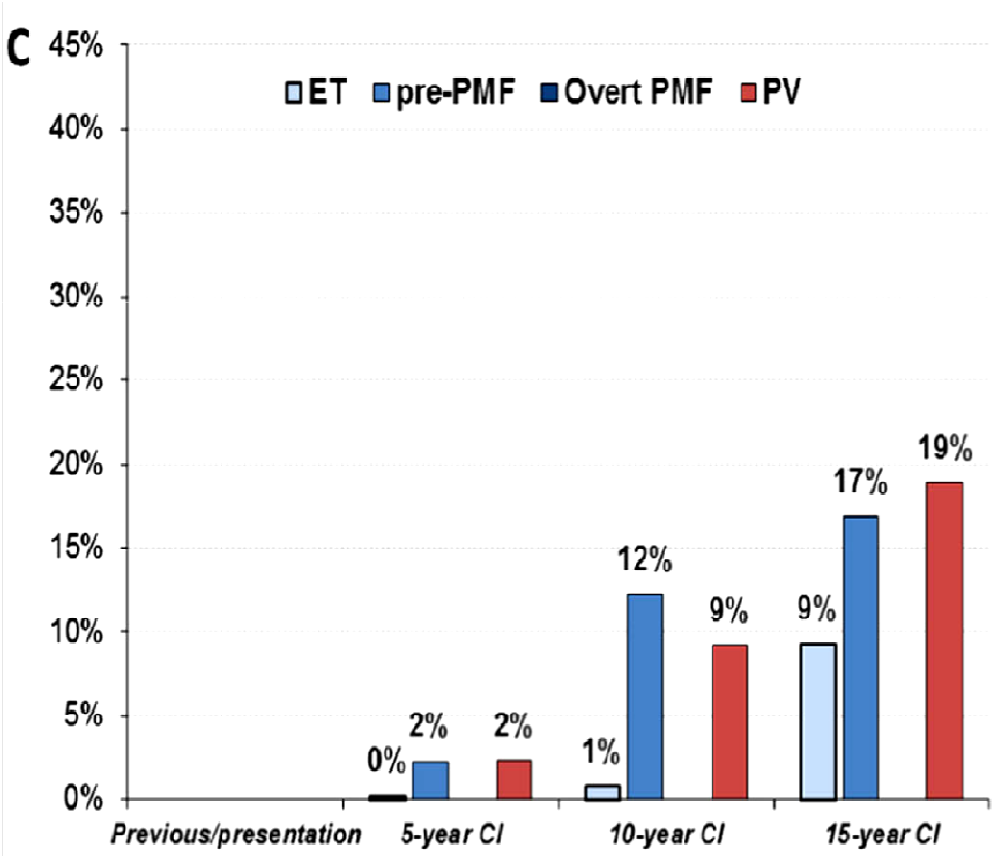
MF—0 Scattered linear reticulin with no intersection (cross-overs) corresponding to normal bone marrow
MF—1 Loose network of reticulin with many intersections, especially in perivascular areas
MF—2 Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF—3 Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Fibre density should be assessed in haematopoietic (cellular) areas.

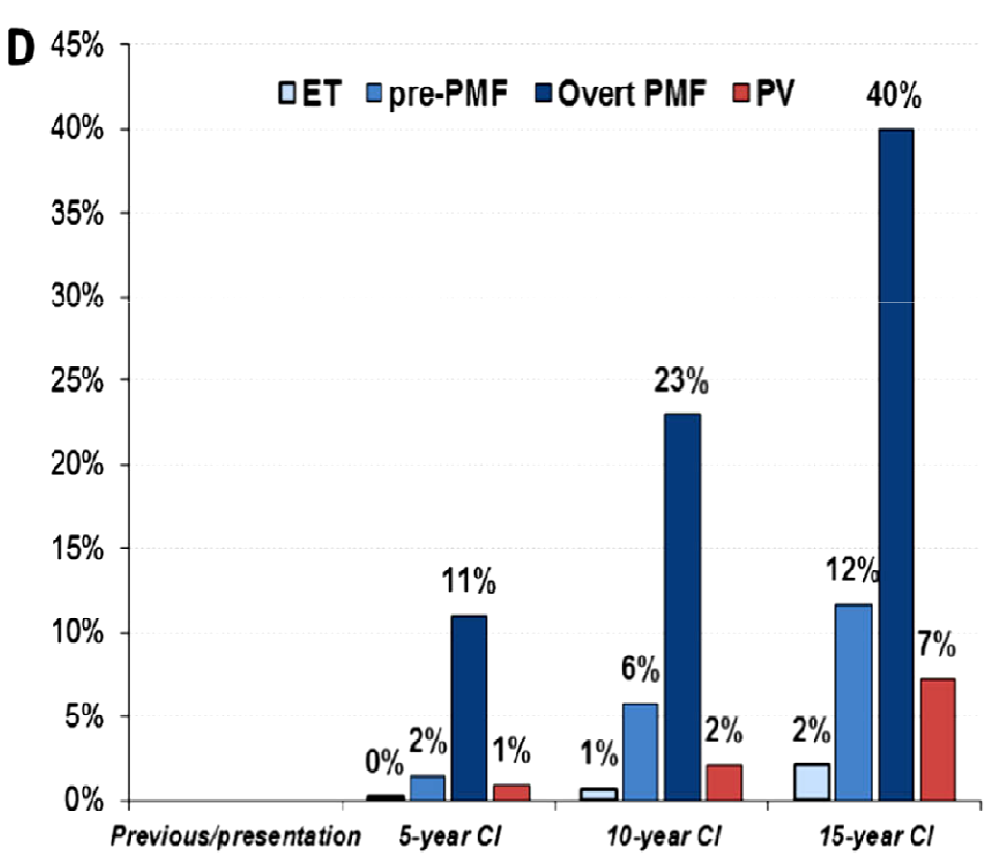
Thiele J, et al. Haematologica 2005; 90:1128–1132

MPN

Fibrotic transformation

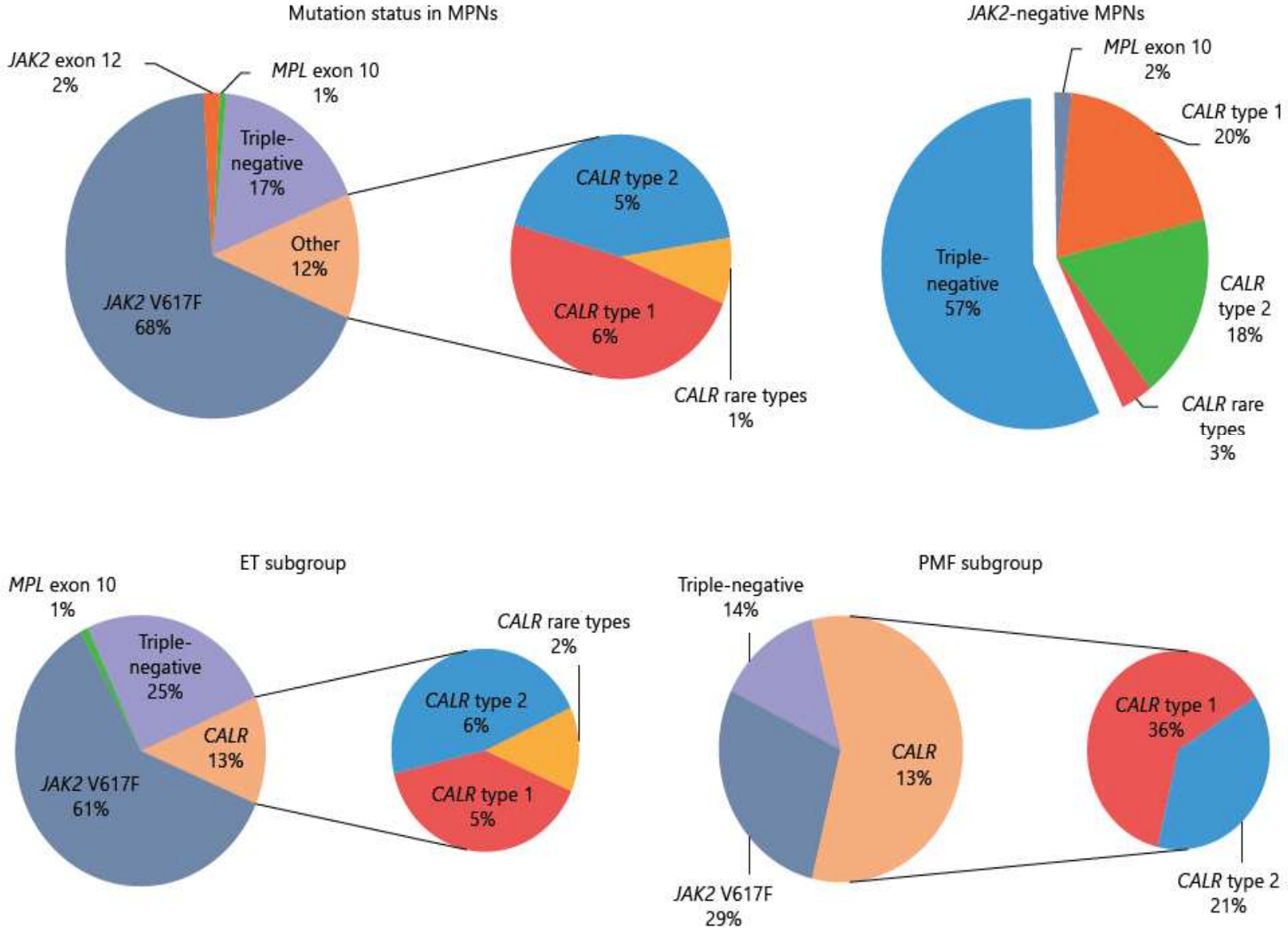


Blast transformation

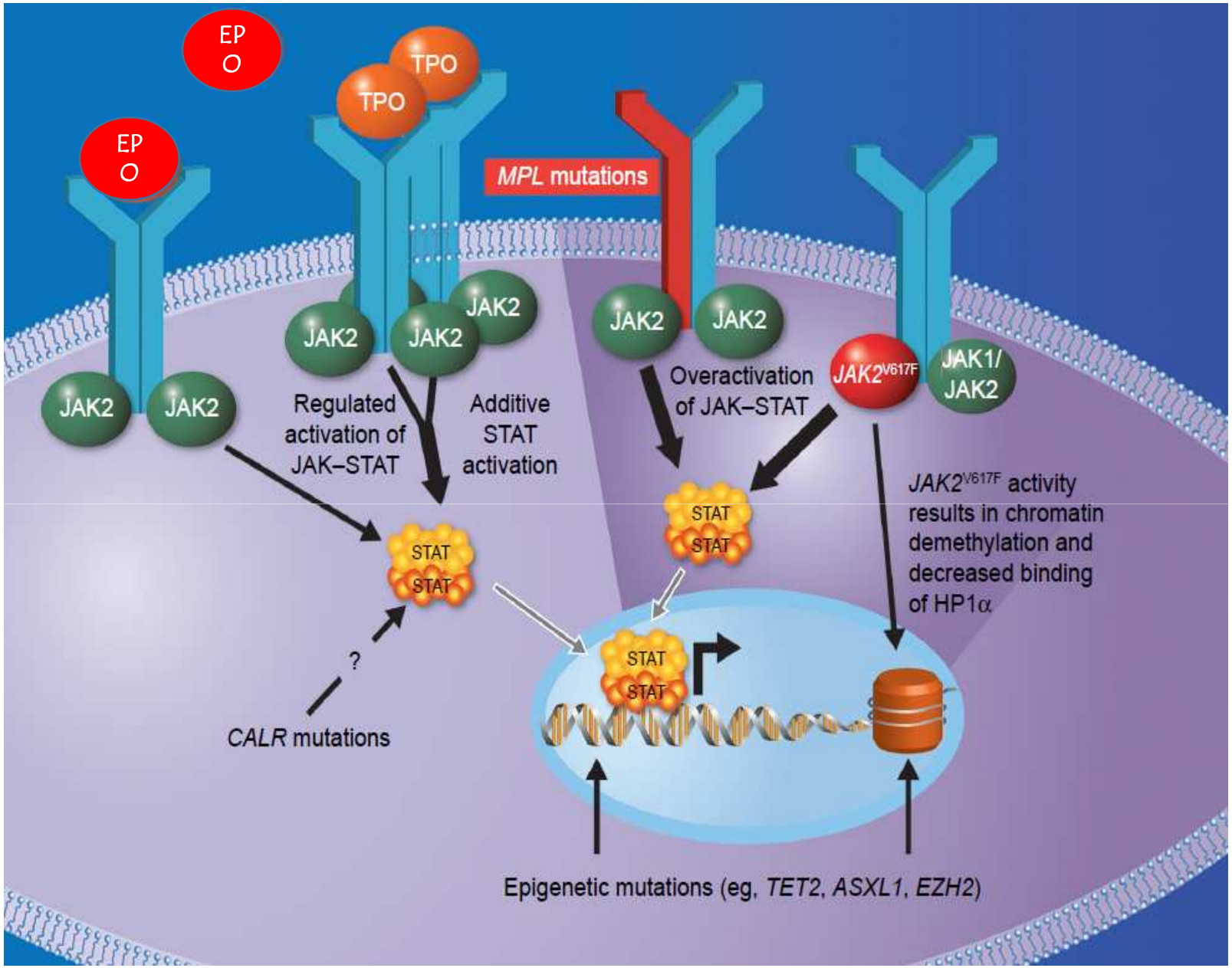


Barbui et al. Blood Cancer Journal (20

Distribution of recurrent mutations of the (*JAK2*, *MPL* and *CALR)* in Philadelphia-negative MPNs



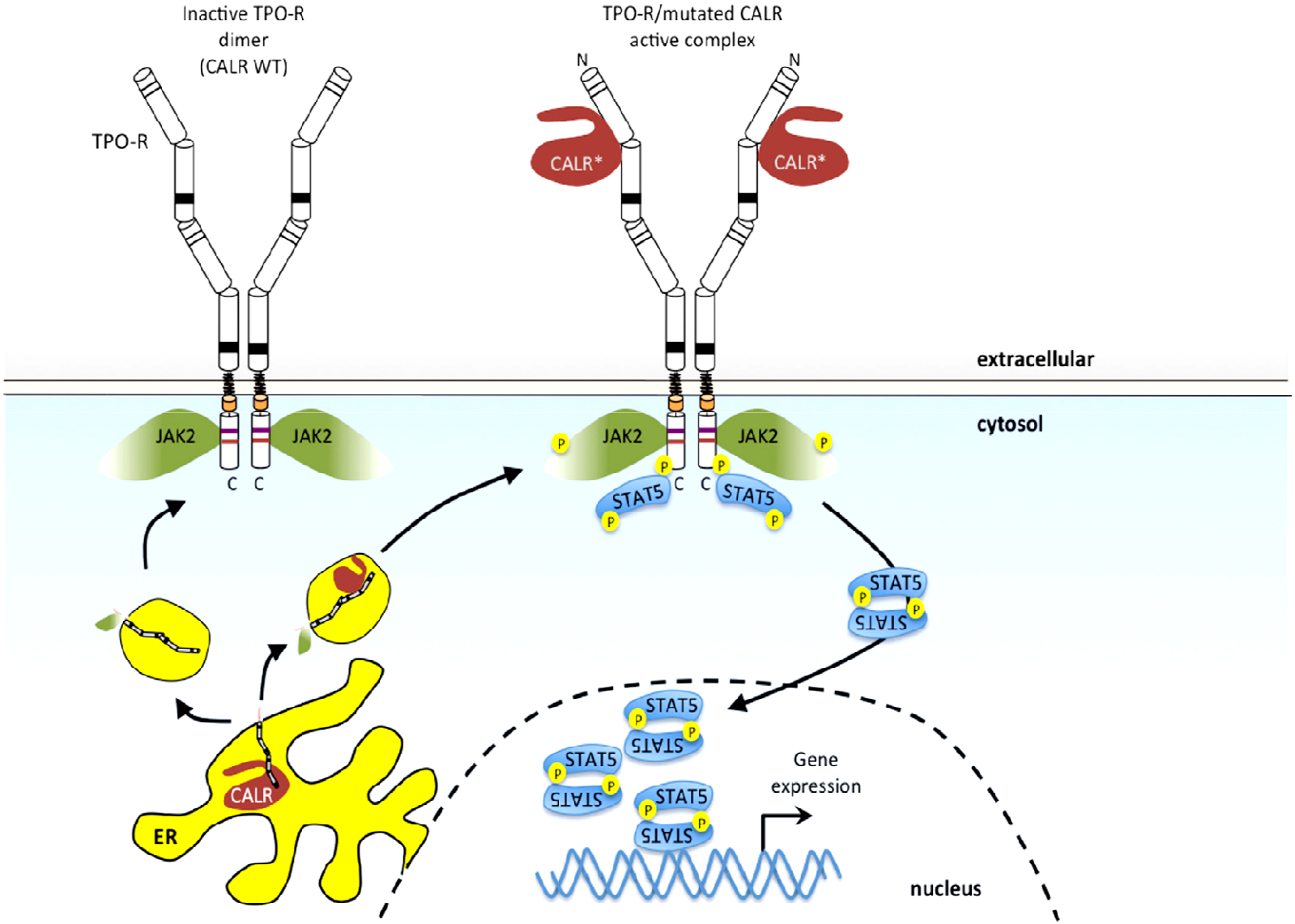
Wojtaszewska M, Iwoła M, Lewandowski K. Acta Haematol. 2015;



EPO- erythropoietin, TPO- thrombopoietin, JAK2- Janus kinase 2
CALR- calreticulin, STAT- signal transducer and activator of transcription

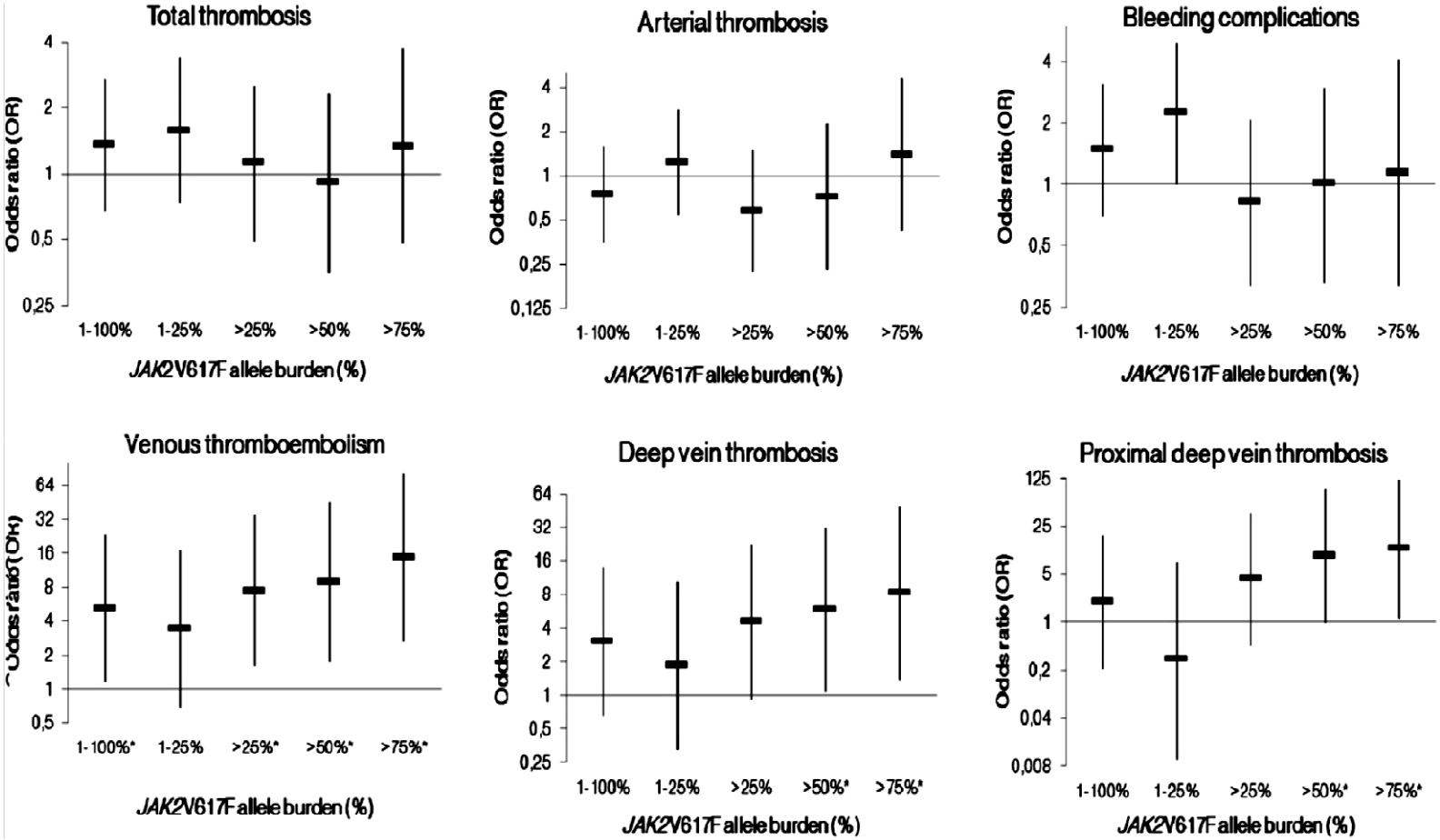
According :Savona MR. *Leuk Res 2014*; 38(9):1001–1012
Javier Pinilla-Ibarz, et al. OncoTargets and Therapy 2016:9 4937–4957, modified

MPN-associated calreticulin (CALR) mutants bind to TPO-R and activate JAK2 signaling in the absence of thrombopoietin (TPO) ligand



Leila N. Varghese, et al. Front Endocrinol (Lausanne)

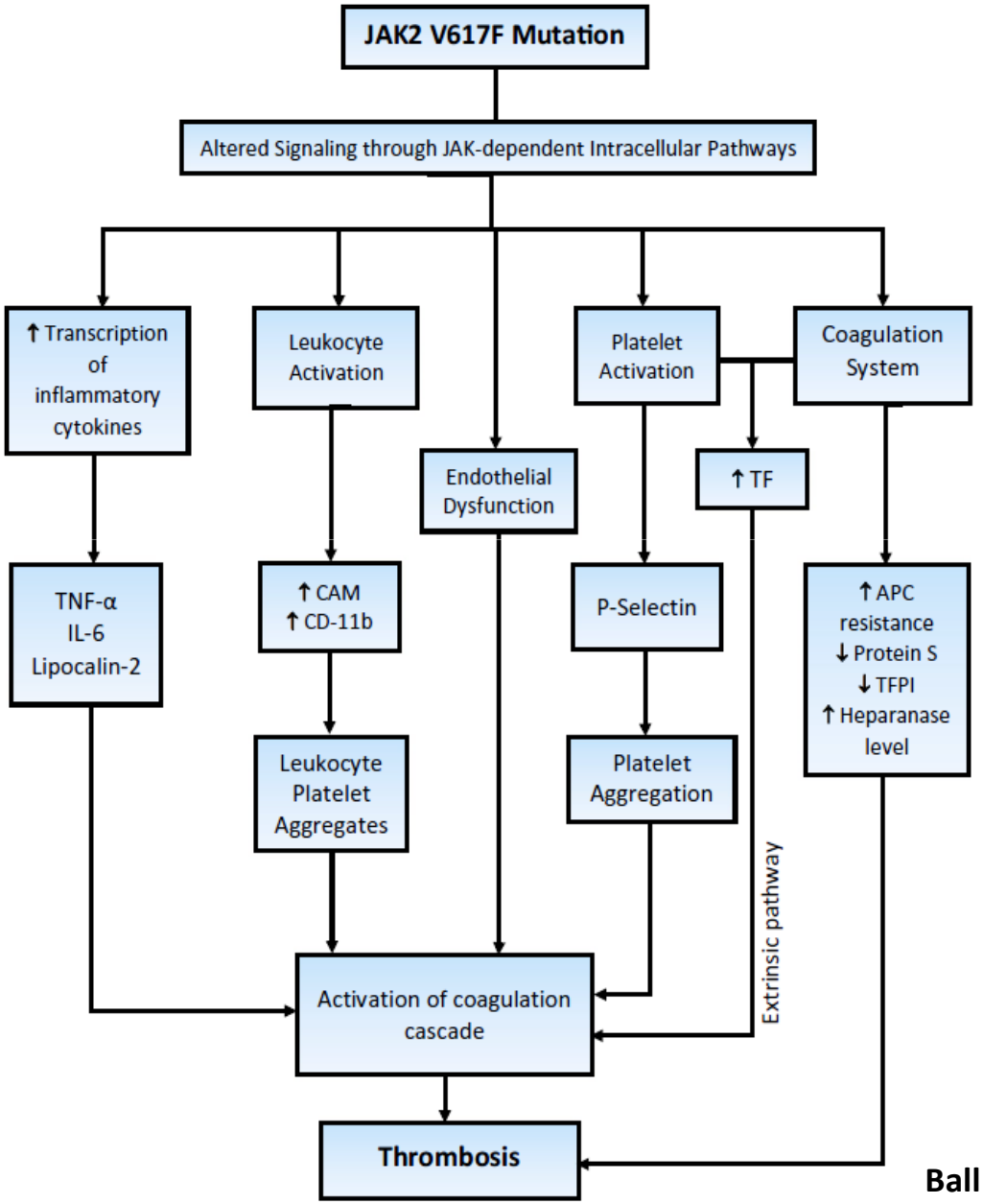
Effects of the JAK2 V617F mutant allele burden on the risk of vascular complications in patients with Ph- MPNs



The group of MPN patients with JAK2 V617F allele burden higher than 20% may benefit the most from
vigilant monitoring and appropriate prophylaxis against vascular events

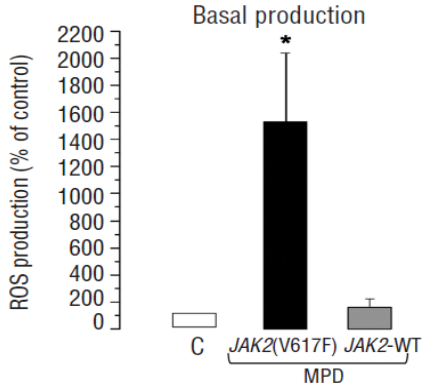
Borowczyk M, Wojtaszewska M, Lewandowski K. Thrombosis Research 135

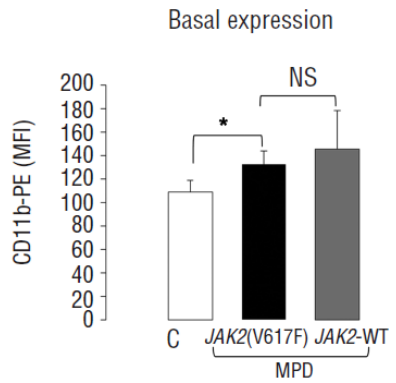
Role of JAK2 mutation in thrombosis

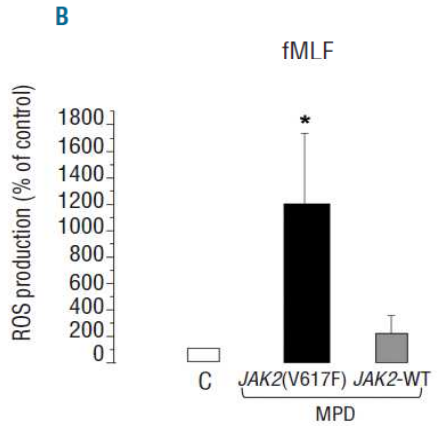


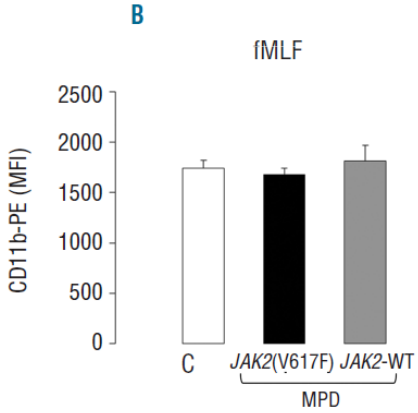
Ball S, et al. Journal of Thrombosis and Thrombolysis 2018;45:51

Increased reactive oxygen species production and p47phox phosphorylation in neutrophils from myeloproliferative disorders patients with *JAK2* (V617F) mutation









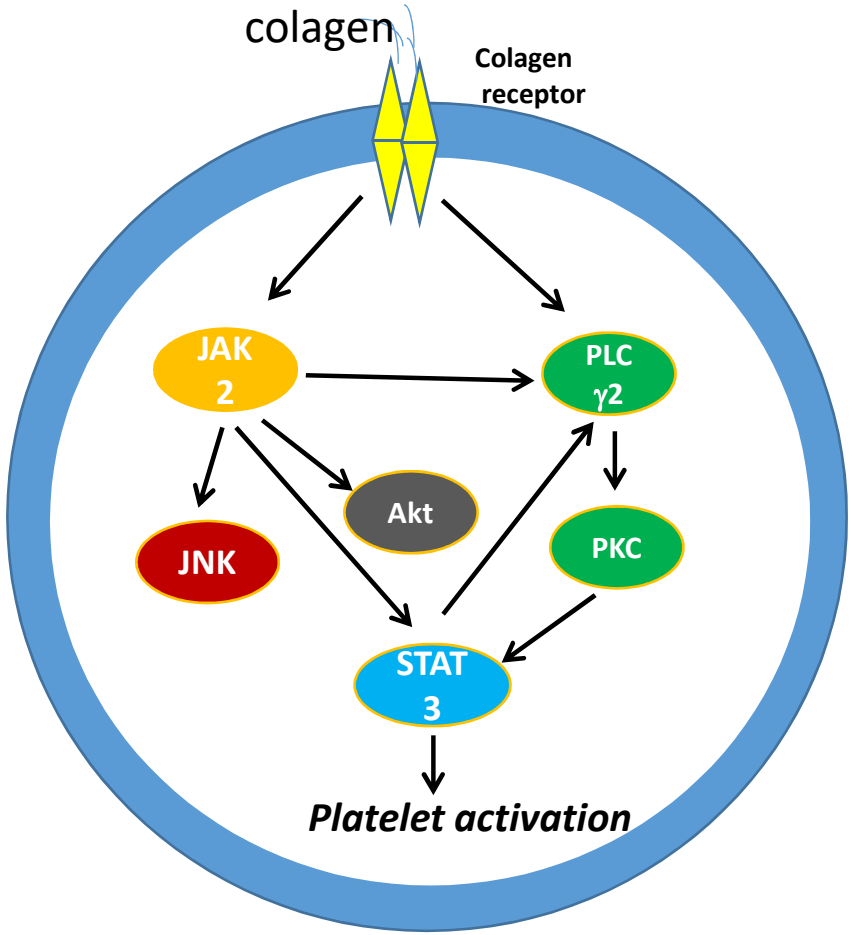
Basal and fMLF-induced ROS production by neutrophils from controls and patients with myeloproliferative disorders with or without the *JAK2* V617F mutation

Basal and fMLF-induced CD11b expression by neutrophils from controls and patients with myeloproliferative disorder without the *JAK2* V617F mutation

Neutrophil hyperactivation could be implicated in the thrombophilic status of patients with myeloproliferative neoplasm

Hurtado-Nedelec M et al. Haematologica 2013 Oct;98(1(

The JAK2-STAT3 pathway is involved in collagen-induced platelet activation through the activation of JAK2-JNK/PKC-STAT3 signaling



JAK2 inhibitor AG490 (Tyrphostin) attenuated collagen-induced platelet aggregation and calcium mobilization in a concentration-dependent manner (25 and 50 μM).

Lu W-J, et al. Thrombosis Research 133 (2014) 1088–109

PV

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Daniel A. Arber, et al. Blood. 2016;

ET

WHO ET criteria
Major criteria
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

Daniel A. Arber, et al. Blood. 2016;

Pre-PMF

WHO prePMF criteria

Major criteria
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting the WHO criteria for *BCR-ABL1*$^{+}$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of minor reactive BM reticulin fibrosis‡
Minor criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^{9}/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 8.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Daniel A. Arber, et al. Blood. 2016;

Overt PMF

WHO overt PMF criteria

Major criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*$^{+}$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive myelofibrosis‡
Minor criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^{9}/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
e. Leukoerythroblastosis
Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 8.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Daniel A. Arber, et al. Blood. 2016;

The International Working Group forMyelofibrosis Research and Treatment (IWGMRT) criteria for post-essential thrombocythemia and post-polycythemia vera myelofibrosis

Criteria for post-essential thrombocythemia myelofibrosis (PE MF)

Diagnosis of post-ET MF entails meeting both required criteria and at least two additional criteria

Required criteria

1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria
2. Bone marrow fibrosis grades 2–3 (on 0–3 scale)* or grades 3–4 (on 0–4 scale)**

Additional criteria

1. Anemia and a ≥ 2 g/dL decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased LDH (above reference level)
5. Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5 °C)

*Grades 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain); or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain)

**Grades 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Curr Hematol Malig Rep. 2018 Apr 30. doi: 10.1007/s11899-018-0453-y. [Epu

The International Working Group forMyelofibrosis Research and Treatment (IWGMRT) criteria for post-essential thrombocythemia and post-polycythemia vera myelofibrosis

Criteria for post-polycythemia vera myelofibrosis (PPV MF)

Diagnosis of post-PV MF entails meeting both required criteria and at least two additional criteria

Required criteria

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria
2. Bone marrow fibrosis grades 2–3 (on 0–3 scale)* or grades 3–4 (on 0–4 scale)**

Additional criteria

1. Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive ther cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5 °C)

*Grades 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain); or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain)

**Grades 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Curr Hematol Malig Rep. 2018 Apr 30. doi: 10.1007/s11899-018-0453-y. [Epu

MPN complication rates, prognosis and risk scoring algorithms

	ET	PV	PMF
Thrombotic events	10%–29%[23]	34%–39%[23]	7.2–13.2%[65,66]
Bleeding events	0.3%[67]	2.9[68]	–
Leukemic transformation	2% at 15 y[69,70]	5.5% at 15 y[27]	6%–18%[71]
Overall survival	14.7 y[70]	6.5–24 y[72,73]	6–10 y[28,74,75]
Risk algorithms	IPSET[26]	Tefferi criteria[27]	DIPSS PLUS[2]
Age	≥60 (2 pts) vs <60	≥67 (5 pts) 57–66 (2 pts)	≥65 (1 pt) vs <65
Leukocytes	≥11 (1 pt) vs <11 × 10^9/L	≥15 (1 pt) vs <15 × 10^9/L	>25 (1 pt) vs ≤25 × 10^9/L
Prior vascular events	Yes (1 pt) vs no	Yes (1 pt) vs no	
Anemia			<10 (2 pts) vs ≥10g/dL
Constitutional symptoms			Present* (1 pt) vs absent
Peripheral blood blasts			≥1% (1 pt) vs <1%
Unfavorable karyotype			Present (1 pt) vs absent
RBC transfusion requirement			Present (1 pt) vs absent
Platelet count <100 000 × 10^9/L			Present (1 pt) vs absent
High risk	3–4 points	4 points	>4 points
Intermediate 2 risk	N/A	3 points	3–4 points
Intermediate 1 risk	1–2 points	1–2 points	1–2 points
Low risk	0	0 points	0 points

* Constitutional symptoms were defined as weight loss over 6 months, night sweats, unexplained fever.[29]

Geyer HL, et al. Hematology 2014;2

Cardiovascular risk in Philadelphia negative MPN (n=258)

Risk Factor	Thrombosis				Arterial Thrombosis			Venous Thrombosis		
	Present	Absent	OR (CI)	P	Present	OR (CI)	P[a]	Present	OR (CI)	P[b]
Patients	36 (26.9)	98 (73.1)			29 (21.6)			10 (7.5)		
FV Leiden mutation heterozygote	2 (5.6)	4 (4.1)	1.4 (0.2-7.9)	.659[c]	1 (3.4)	0.8 (0.1-7.8)	1.000[c]	1 (10.0)	2.6 (0.3-25.9)	.391[c]
FII G20210A heterozygote	0 (0.0)	3 (3.1)	0.4 (0.0-7.4)	.564[c]	0 (0.0)	0.5 (0.0-9.2)	1.000[c]	0 (0.0)	1.3 (0.1-26.9)	1.000[c]
JAK2 V617F mutation positive	28 (77.8)	56 (57.1)	2.6 (1.1-6.3)	.047[d,*]	24 (82.8)	3.6 (1.3-10.2)	.015[d,*]	7 (70.0)	1.8 (0.4-7.1)	.517[d]
JAK2 V617F burden allele (%), median (first-third quartile)	19.3 (10.4-27.7)	16.7 (9.2-24.7)		.253[e]	19.8 (11.2-30.2)		.140[e]	18.7 (8.8-24.9)		.948[e]
WBC ($\times 10^9$/L), median (first-third quartile)	10.2 (8.6-13.5)	8.5 (7.0-10.9)		.010[e,*]	10.6 (9.7-14.0)		< .001[e,*]	8.6 (5.9-10.4)		.840[e]
RBC ($\times 10^{12}$/L)	4.68 ± 0.89	4.68 ± 0.66		.964[f]	4.82 ± 0.90		.500[f]	4.50 (±0.90)		.517[f]
HGB (g/L)	136 ± 27	136 ± 19		.938[f]	136 ± 29		.940[f]	135 ± 20		.823[f]
PLT ($\times 10^9$/L), median (first-third quartile)	657 (543-850)	617 (526-745)		.576[e]	700 (571-910)		.050[e,*]	492 (444-707)		.074[e]
Age (years), median (range)	65 (23-92)	52 (18-90)		.008[e,*]	65 (23-92)		.009[e,*]	63 (38-82)		.079[e]
Male	14 (38.9)	26 (26.5)	1.8 (0.8-3.9)	.241[d]	12 (41.4)	2.0 (0.8-4.6)	.168[d]	3 (30)	1.2 (0.3-4.9)	1.000[c]
Smoking	8 (22.2)	13 (13.3)	1.9 (0.7-5.0)	.319[d]	8 (27.6)	2.5 (0.9-6.8)	.088[d]	1 (10)	0.7 (0.1-6.2)	1.000[c]
Alcoholism	0 (0.0)	0 (0.0)	2.7 (0.1-138.5)	1.000[c]	0 (0.0)	3.3 (0.1-171.9)	1.000[c]	0 (0.0)	9.5 (0.2-502.7)	1.000[c]
Hypertension	26 (72.2)	40 (40.8)	3.8 (1.6-8.7)	.003[d,*]	19 (65.5)	2.8 (1.2-6.5)	.021[d,*]	10 (100)	30.3 (1.7-532.4)	< .001[d,*]
Diabetes	6 (16.7)	10 (10.2)	1.8 (0.6-5.2)	.470[d]	6 (20.7)	2.3 (0.8-7.0)	.139[d]	1 (10.0)	1.0 (0.1-8.5)	1.000[c]
Hyperlipidemia	11 (30.6)	9 (9.2)	3.1 (1.2-8.1)	.005[d,*]	9 (31.0)	4.5 (1.6-12.6)	.006[d,*]	3 (30.0)	4.2 (0.9-19.3)	.081[c]
At least one CV risk factor	31 (86.1)	54 (55.1)	5.1 (1.8-14.1)	.001[d,*]	24 (82.8)	3.9 (1.4-11.1)	.009[d,*]	10 (100)	17.1 (1.0-300.8)	.005[c,*]

Data are presented as n (%) or mean standard deviation unless otherwise indicated.
Abbreviations: ET L' essential thrombocythemia; CI L' confidence interval; CV L' cardiovascular; HGB L' hemoglobin; OR L' odds ratio; PLT L' platelets; RBC L' red blood cell count; WBC L' white blood cell count.
aFor comparison of ET patients with arterial thrombosis to ET patients with no thrombosis.
bFor comparison of ET patients with venous thrombosis to ET patients with no thrombosis.
cFisher's exact test.
d$\chi 2$ test.
eMann Whitney test.
ft test for unpaired samples.
Statistically significant are P values <.050.

Hgorvat I, et al. Clin Lymphoma Myeloma Leuk. 2019 Jan;19(1):53-63. doi: 10.1016/j.clml.2018.08.(

Risk assessment model—IPSET thrombosis study

IPSET thrombosis model[a]

Risk factor	HR	Score
Age > 60 years	1.50	1 point
CV risk factors	1.56	1 point
Prior thrombosis	1.93	2 points
JAK2V617F	2.04	2 points

Distribution and event rate[b]

Risk category	Points	Distribution	Event rate
Low risk	0–1 points	39%	1.03% pts/year
Intermediate risk	2 points	39%	2.35% pts /year
High risk	≥ 3 points	23%	3.56% pts /year

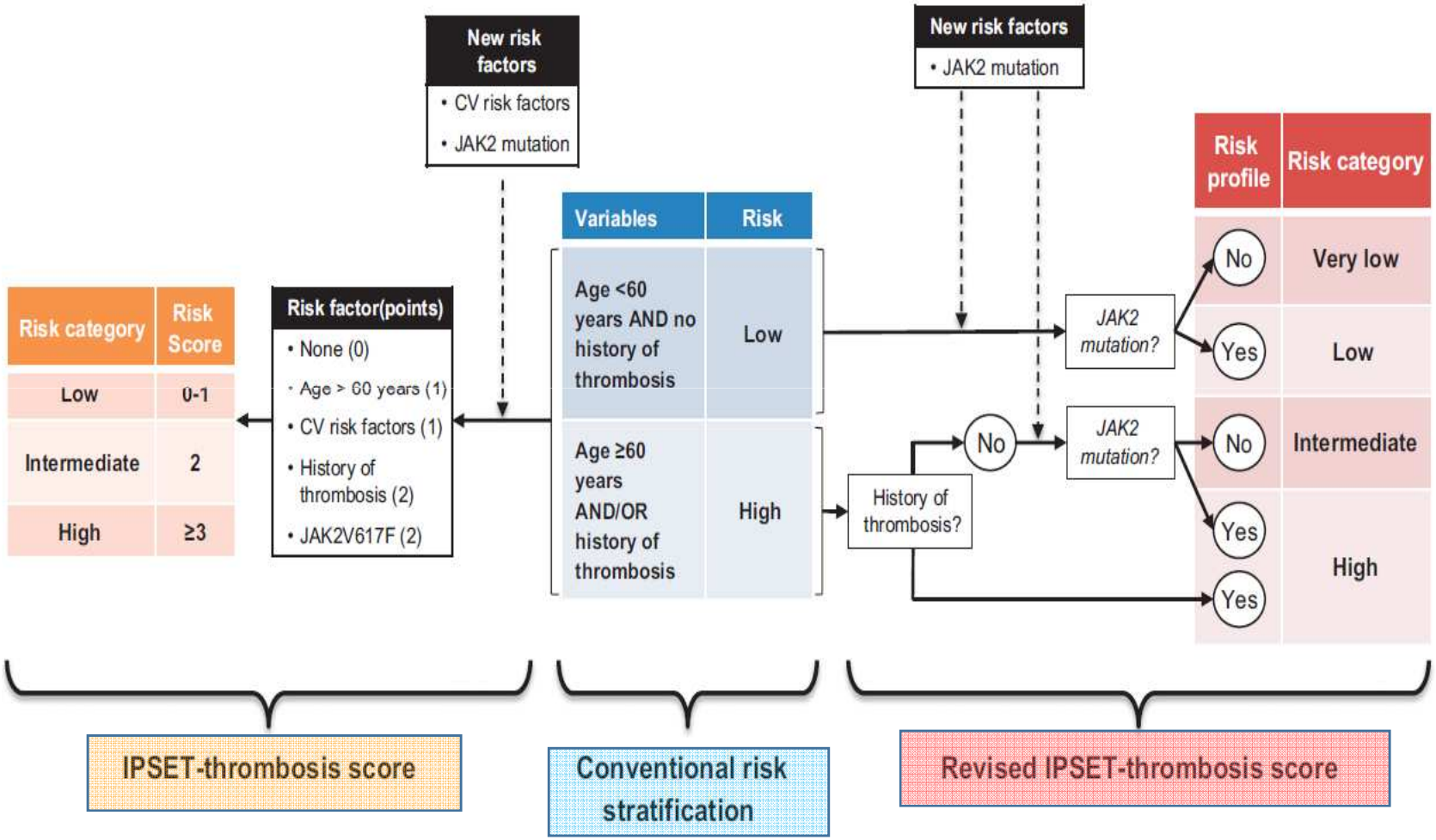
IPSET International Prognostic Score of Thrombosis, *CV* cardiovascular, *% pts/y* percentage of patients per year]

[a]891 patients

[b]1220 patients

Barbui T, A et al. Blood 2012;120:51

Essential thrombocythaemia thrombotic risk assessement



CV, czynniki ryzyka sercowo-naczyniowego, IPSET, International Prognostic Score for Thrombosis in Essential Thrombocythemia

Falchi L, Kantarjian HM, Verstovsek S. Leukemia 2017;Sep;31(9):1845-1

Recommendations for second-line therapy in PV

Current drug options

Interferon-α, *if hydroxyurea resistant / intolerant*

Hydroxyurea, *if Interferon-α resistant / intolerant*

Busulfan, for patien[illegible]th short life expectancy

Pipobroman, ^{32}P (not frequently used)

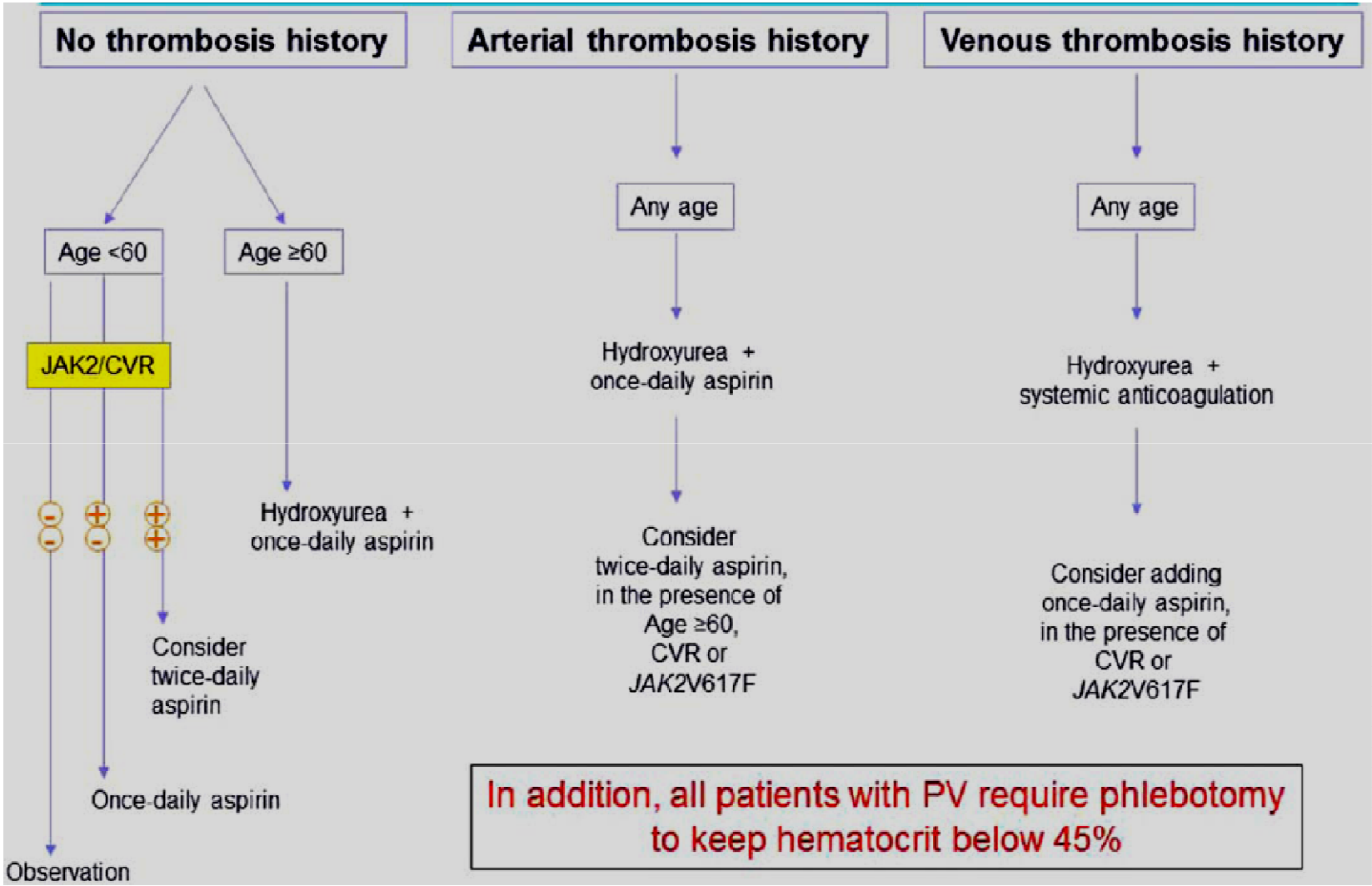
Barbui *et al*, J Clin Oncol 2011;29(6):761-70

Ruxolitinib, in patients with inadequate response or intolerant to hydroxyurea

FDA

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202192s008lbl.pdf

Contemporary treatment algorithm in essential thrombocytopenia and polycythaemia vera



Aspirin is used in the absence of treatment contraindications including clinically significant acquired von Willebrand syndrome. We recommend performing ristocetin cofactor activity in patients with over 1 million platelets per microliter and holding aspirin if the activity level is below 20%.

Tefferi A, Barbui T. Am J Hematol. 2015 Apr 14. doi: 10.1002/ajh.24037. [Epub ahead of print

Currently used cytoreductives in ET and PV: benefits, risks, patient selection, and candidacy for up-front use

Interferons

Benefits
- Control of myeloproliferation
- Reduction in thrombosis risk?
- Anticlonal activity

Concerns
- Impact on short-term QoL
- Long-term tolerability

Patient selection
- Early in disease course
- Preserved fitness/limited comorbidities
- Modest if any splenomegaly
- Absence of additional nondriver mutations

Compelling data for early use

Hydroxyurea

Benefits
- Control of myeloproliferation
- Reduction in thrombosis risk (high-risk ET)

Concerns
- Mucocutaneous toxicity, skin cancer risk, myelosuppression

Patient selection
- High-risk ET and PV
- Caution in those aged ≤40 y
- Lower-risk patients with symptomatic thrombocytosis, intolerance of phlebotomy, progressive leukocytosis, uncontrolled symptoms/splenomegaly

No compelling data to advise in low-risk patients without indications

Ruxolitinib

Benefits
- Reduction in phlebotomy needs
- Reduction in spleen size
- Improvement in symptom burden

Concerns
- Infection, weight gain, cholesterol change, skin cancer risk, myelosuppression

Patient selection
- Later disease course
- Moderate to high symptom burden
- Hydroxyurea resistant or intolerant PV

Data only support use as a second-line agent in PV; no frontline data or support for use in ET

Sankar K et al. J Natl Compr Canc Netw. 2018 Dec;16(12):1539-1545. doi: 10.6004/jn

Primary myelofibrosis

Prognostic Scoring Systems

Variable	IPSS [2]	DIPSS [29]	DIPSS plus [30]
Age > 65 years	√	√	√
Constitutional symptoms[a]	√	√	√
Hb < 10 g/dL	√	√	√
WBC > 25,000/μL	√	√	√
Peripheral blood blasts ≥ 1%	√	√	√
Platelets < 10×10^4/μL			√
Red cell transfusion need[b]			√
Unfavorable karyotype[c]			√
Point per variable	1 point each	1 point each but Hb = 2	1 point each

IPSS, International Prognostic Scoring System;
DIPSS, Dynamic IPSS; DIPSS plus,
Dynamic IPSS plus additional prognostic factors

a Weight loss 10% of the baseline value in the year preceding primary myelofibrosis diagnosis and/or unexplained fever or excessive sweats persisting for more than 1 month.

b Red blood cell (RBC) transfusion at the time of referral and those with history of RBC transfusions, for myelofibrosis-associated anemia.

c Complex karyotype or si t w o or tow abnormalities including +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 rearrangements.

Takenaka K, et al. Korean J Intern Med. 2018 Apr 20. doi: 10.3904/kjim.2018.033. [Ep

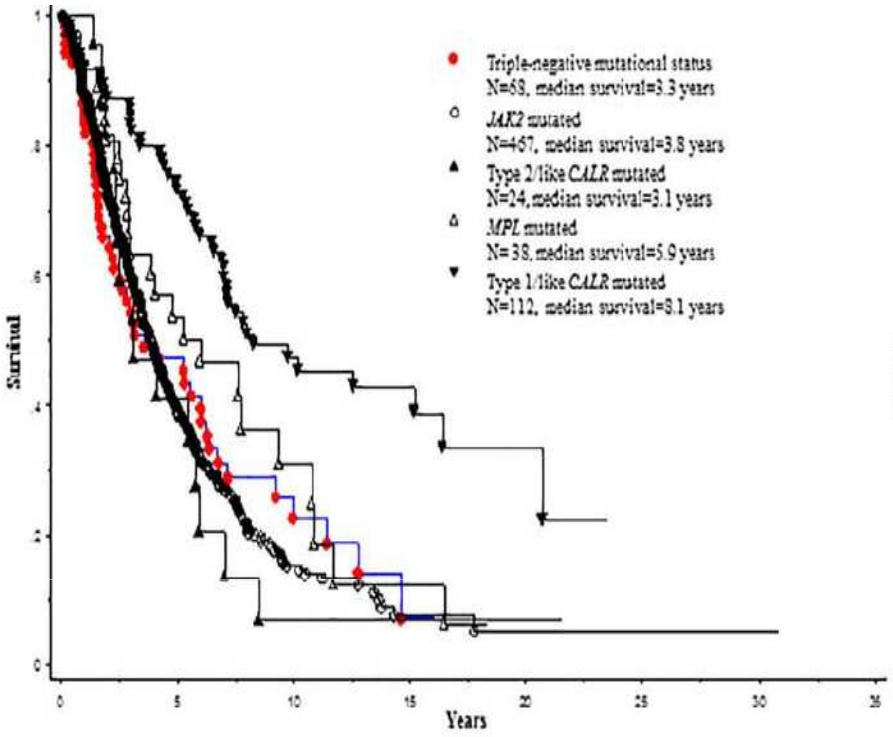
Summary of driver mutations and their implications in primary myelofibrosis

Mutation	Mutational frequency	Phenotypic implications	Prognostic implications
*JAK2*V617F	50–60%	Older age Higher hemoglobin level Higher WBC count Lower PLT count Highly thrombophilic	Compared with *CALR*+, *MPL*+, and triple-negative cohorts: Intermediate overall survival [6]
CALR	20–25% overall Up to 74% cases of *JAK2/MPL* unmutated [5▪]	Compared with *JAK2*V617F+: Less thrombophilic [26▪]	Compared with *JAK2*V617F+ and triple-negative cohorts (type 1/2 variants confounded): Lower DIPPS plus scores [5▪] Lower rates leukemic transformation [6,37] Superior overall survival [5▪]
CALR type 1/like Exon 9, 52-bp deletion	~70% of *CALR* mutations	Compared with *JAK2*V617F+: Younger age Less frequent anemia Less frequent leukocytosis Higher PLT count [28,36]	Compared with *JAK2*V617F/CALR type 2/MPL-mutated or triple-negative: Superior overall survival [50]
CALR type 2/like Exon 9, 5-bp insertion	~15% of *CALR* mutations	Compared with *CALR* type 1+: Higher WBC count Higher circulating blast% [28,36]	Compared with *CALR* type 1+: Higher DIPPS plus scores Inferior overall survival [6,36]
MPL Predominantly *MPL*W515L and W515K	6–7%	Compared with *JAK2*V617F+: Less thrombophilic	Compared with *JAK2*V617F+, *CALR*+ and triple-negative cohorts: Intermediate overall survival [6]
Triple-negative	10–15%	Older age Lower hemoglobin level Lower WBC count Lower PLT count [26▪,39] Compared with *JAK2*V617F+: Less thrombophilic	Compared with *JAK2*V617F/*CALR*/*MPL*+ cohorts: Higher IPSS scores [26▪,39] Higher rates leukemic transformation and inferior overall survival [5▪,6,50]

Bp, base pair; CALR, calreticulin; DIPPS plus, dynamic international prognostic scoring system plus; IPSS, international prognostic scoring system; JAK2, Janus kinase 2; MPL, myeloproliferative leukemia; PLT, platelet; WBC, white blood cell.

Szuber N, et al. Curr Opin Hematol 2018, 25

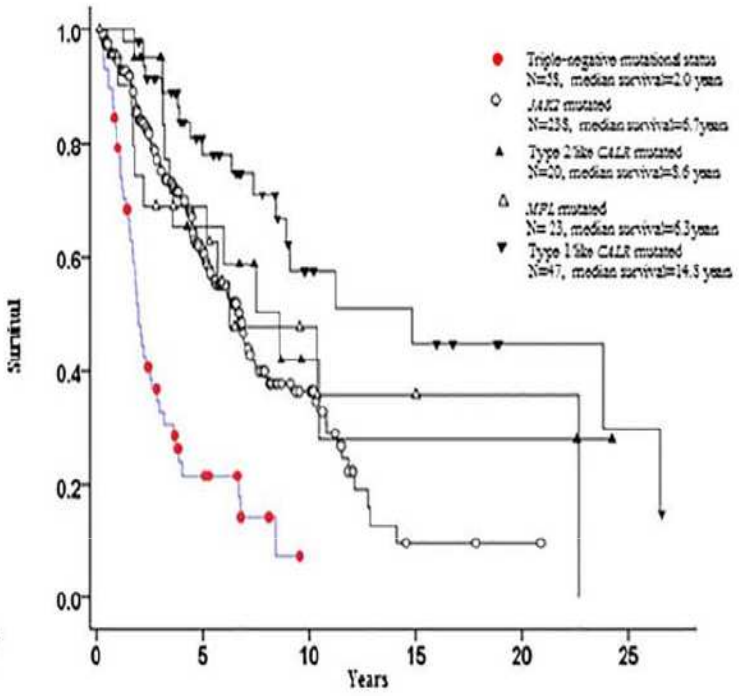
Overall survival in PMF (Mayo-Careggi MPN alliance study, n=1095)



a: Overall survival of 709 primary myelofibrosis patients from the Mayo Clinic, stratified by driver mutational status

P=<0.0001
HR 2.6 (95% CI 1.9-3.5) JAK2 vs type 1/like CALR
HR 2.5 (95% CI 1.4-4.5) Type 2/like CALR vs type 1/like CALR
HR 1.8 (95% CI 1.1-3.0) MPL vs type 1/like CALR
HR 2.4 (95% CI 1.6-3.6) Triple-negative vs type 1/like CALR

P=0.41
JAK2 vs type 2/like CALR vs MPL vs triple-negative



b: Overall survival of 386 primary myelofibrosis patients from Florence group, stratified by driver mutational status

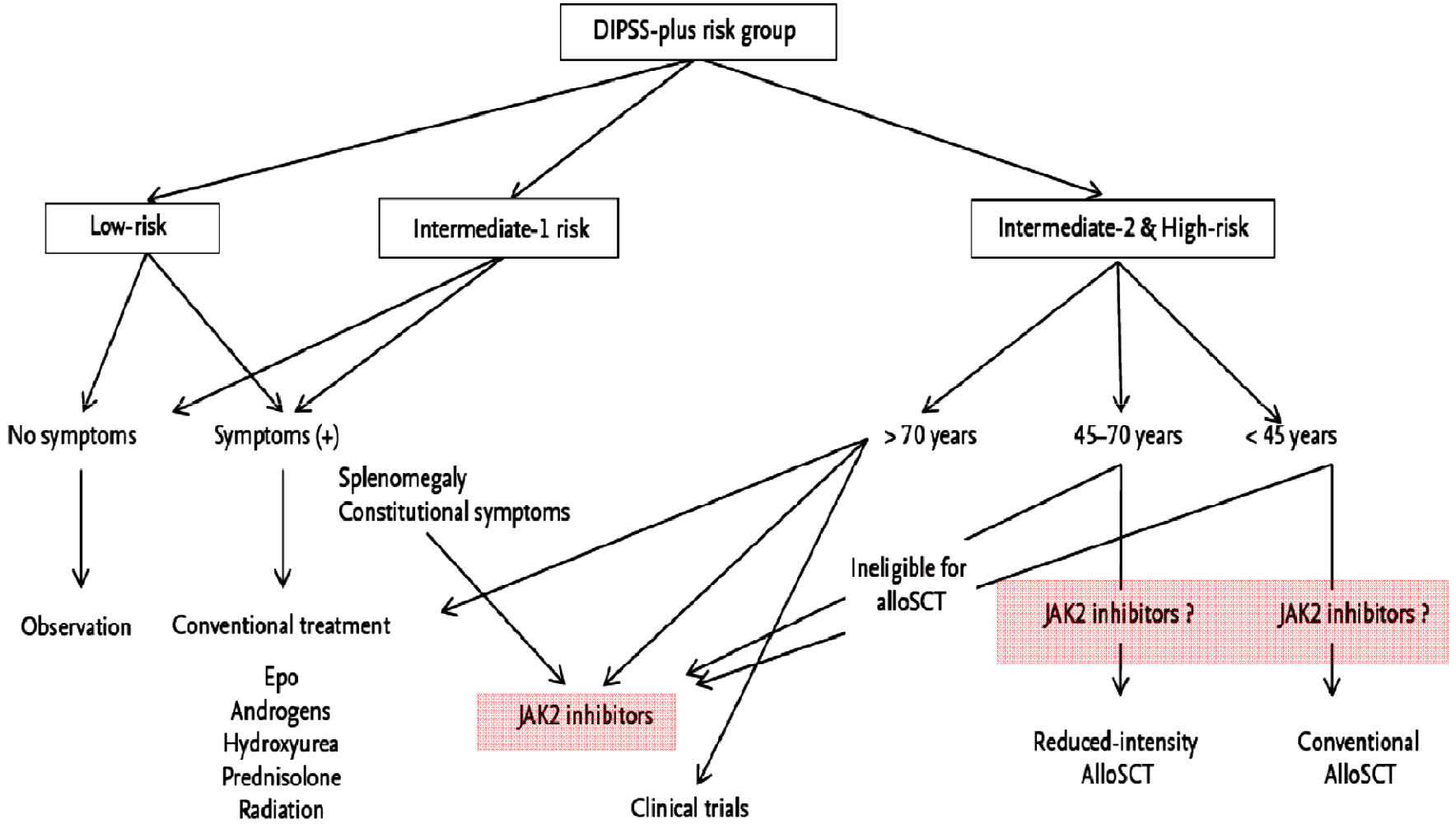
HR 2.4 (95% CI 1.4-4.0) JAK2 vs type 1/like CALR P=.001
HR 1.6 (95% CI 0.9-3.5) Type 2/like CALR vs type 1/like CALR P=.051
HR 2.1 (95% CI 1.0-4.5) MPL vs type 1/like CALR P=.048
HR 7.5 (95% CI 4.2-13.5) Triple-negative vs type 1/like CALR P<.0001

JAK2 vs type 2/like CALR P=.397
JAK2 vs MPL P=.529
JAK2 vs triple-negative P<.0001

Tefferi A, et al. Am J Hematol. 2018 Mar;93(3):3

Treatment algorithm for primary myelofibrosis

DIPSS plus, Dynamic International Prognostic Scoring System plus additional prognostic factors



Takenaka K, et al. Korean J Intern Med. 2018 Apr 20. doi: 10.3904/kjim.2018.033. [Ep

PMF: clinical and molecular risk stratification and risk-adapted therapy; modified]

		Molecular risk		
		High type1/like CALR$^-$ and ASXL1$^+$/SRSF2$^+$	**Intermediate** not classifiable as high or low risk	**Low** type1/like CALR$^+$ and ASXL1$^-$/SRSF2$^-$
DIPPS-plus risk	High	SCT/IDT	SCT/IDT	SCT/IDT
	Intermediate-2	SCT/IDT	SCT/IDT	IDT
	Intermediate-1	SCT/IDT	OBSERVATION/IDT	OBSERVATION
	Low	SCT/IDT	OBSERVATION	OBSERVATION

SCT (*stem cell transplant*), IDT (*investigational drug therapy*)

Tefferi A, Am J Hematol. 2016 Dec;91(12):1262-1271. doi: 10.1002/ajh.24592

PMF - Current Recommendations to Consider Transplantation

Based on baseline characteristics
- DIPSS/DIPSS plus:
  - Intermediate-2 and high risk
  - Intermediate-1/low risk—dependent on mutations, patient age, response to JAK2 inhibitor therapy (see below)
- Transfusion dependence
- Leukemic transformation, if responsive to induction therapy
- Patients without excessive comorbidity (HCT-specific comorbidity index < 4)
- Up to eighth decade of life

Based on disease course
- Disease progression
  - Increasing DIPSS/DIPSS plus scores
  - Loss of response to *JAK2* inhibitor therapy
  - Clonal evolution on *JAK2* therapy

Based on mutational characteristics*
- Triple negative
- *ASXL1* (In PMF)
- *SRSF2*
- *IDH1/2*
- *TP53*
  - *SF3B1 + IDH*

* As discussed in the text, data on additional mutations are evolving, and decisions will need to be reassessed on an ongoing basis.

Salit RB, et al. Biol Blood Marrow Transplant 2

The molecular status and transplantation outcome

- Early reports evaluating the impact of mutational status on allo-SCT outcomes suggested a favorable survival effect of *JAK2*V617F mutations as compared with *JAK2* wild-type disease
- Moreover, achievement of *JAK2*V617F negativity after allo-SCT may be associated with a lower incidence of relapse [1]
- Later studies demonstrated respectively favorable and detrimental effects of a *CALR*-positive versus triple-negative status [2], with presence of *CALR* mutation representing an independent factor for lower non-relapse mortality and improved progression-free and overall survival (OS)
- Significantly, in this context, type 1 and type 2 *CALR* mutations resulted in similar posttransplant outcomes [3]

1. Alchalby H, et al. Blood 2010; 116:3572–3581
2. Panagiota V, et al. Leukemia 2014; 28:1552–1555
3. Kroger N, et al. Biol Blood Marrow Transplant 2017; 23

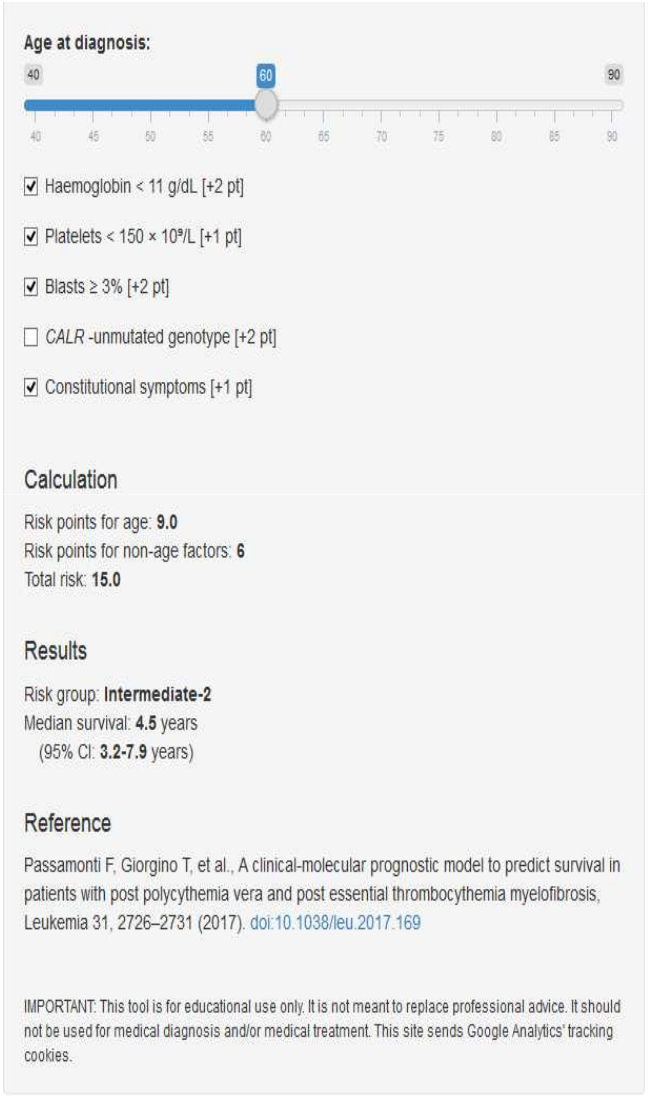
Sum of differences between primary and post-PV and post-ET myelofibrosis

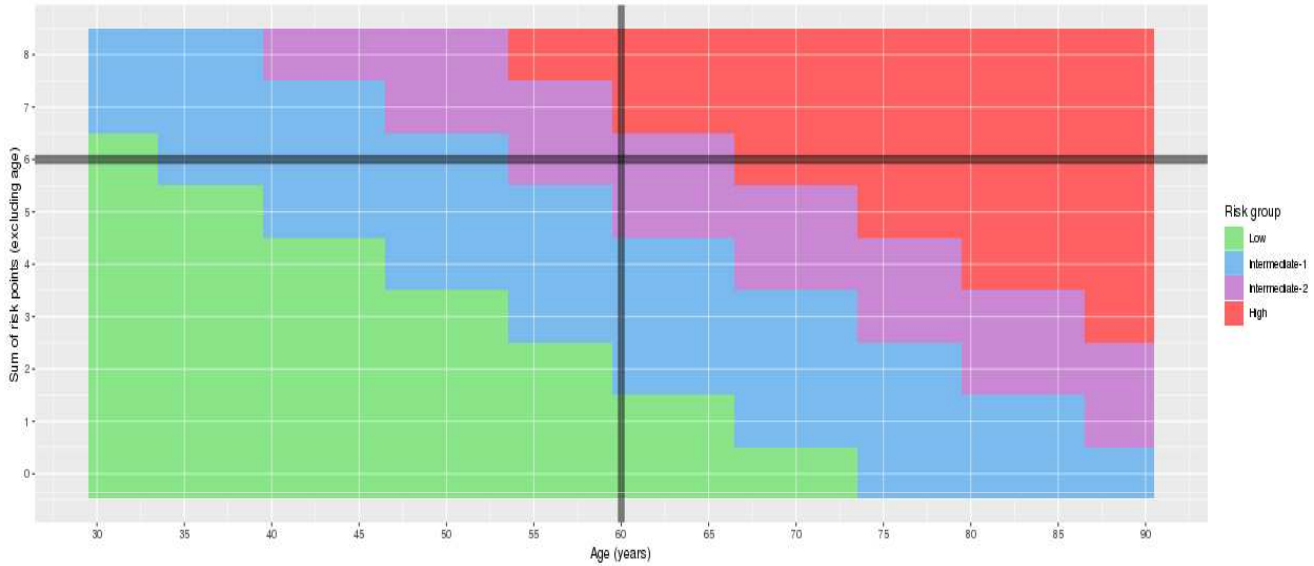
	Primary myelofibrosis	Secondary myelofibrosis
Diagnostic criteria	WHO 2016	IWG-MRT (2008)
Phenotype	Higher transfusion dependence	
Cytogenetics		Higher % of complex karyotype
High molecular risk mutations	*ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*	*SRSF2*
Treatment guidelines	ELN 2018	ELN 2018
JAK2 inhibitors		Possible higher efficacy
Prognostic scores	IPSS/DIPSS/DIPSS-plus/MIPSS70	MYSEC-PM
Median survival	69 months (IPSS study)	112 months (MYSEC study)
Most frequent cause of death	Blast phase progression	Non-clonal progression

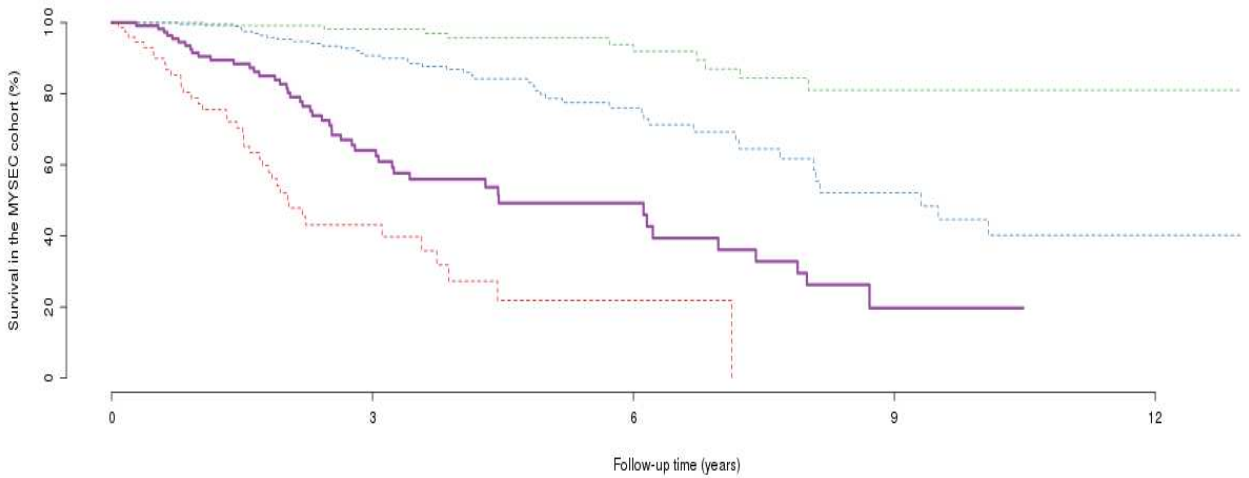
Curr Hematol Malig Rep. 2018 Apr 30. doi: 10.1007/s11899-018-0453-y. [Epu

A clinical-molecular prognostic model to predict survival in patients with post PV and post ET-myelofibrosis

(MYSEC Prognostic Model Risk Calculator (MYSEC-PM)







Passamonti F, et al. Leukemia 2017;31, 2726–2731. doi:10.1038/l

Treatment of PMF and SMF

- With regard to available JAK-inhibitor trial data, evidence of a differential response according to MF subtype derives from a multivariate analysis of COMFORT-2 suggesting a higher response to ruxolitinib in PET MF with respect to PMF
- **A pooled analysis of overall survival in COMFORT-1 and COMFORT-2 showed that SMF was associated with a better prognosis than PMF independently of treatment**

Vannucchi AM, et al. Haematologica. 2015;100(9):1139–45