prof. Lewandowski Krzysztof, MD, PhD

Myeloproliferative neoplasms (MPN): chronic myeloid leukaemia, Ph-negative MPN

Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

1. Myeloproliferative neoplasms (MPN)

- 1.1. Chronic myelogenous leukemia, *BCR-ABL1*–positive (CML)
- 1.2. Polycythemia vera (PV)
- 1.3. Essential thrombocythemia (ET)
- 1.4. Primary myelofibrosis (PMF)
- 1.5. Chronic neutrophilic leukemia (CNL)
- 1.6. Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
- 1.7. Mast cell disease (MCD)
- 1.8. MPN, unclassifiable

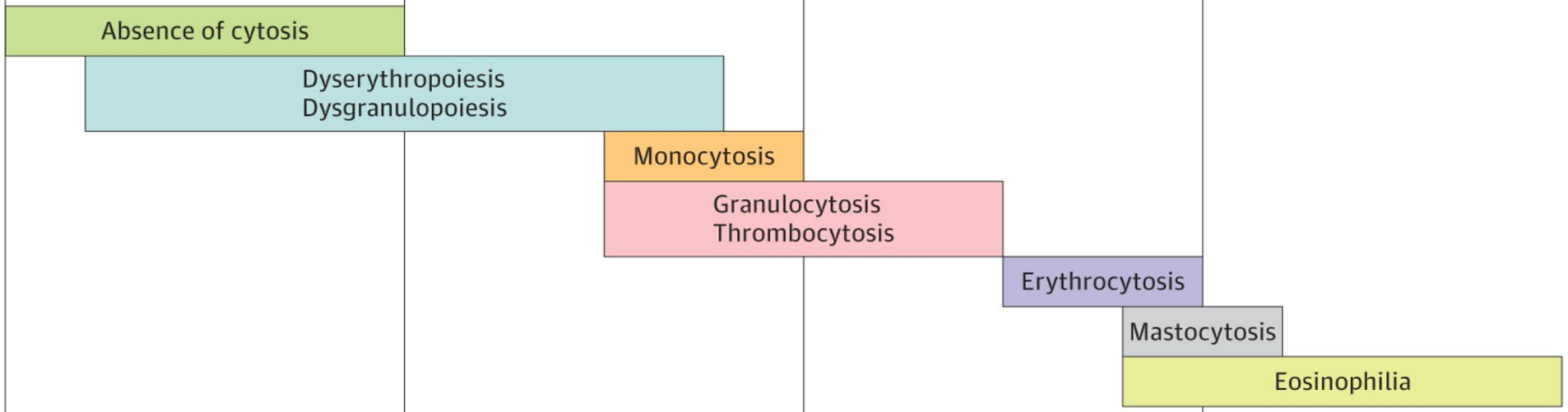
2. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1*

3. MDS/MPN

- 3.1. Chronic myelomonocytic leukemia (CMML)
- 3.2. Juvenile myelomonocytic leukemia (JMML)
- 3.3. Atypical chronic myeloid leukemia, *BCR-ABL*–negative (aCML)
- 3.4. MDS/MPN, unclassifiable

4. Myelodysplastic syndromes (MDS)

5. Acute myeloid leukemia (AML)

	Chronic myeloid neoplasms			
	Myelodysplastic syndromes	Myelodysplastic syndromes/ myeloproliferative neoplasms overlap	Myeloproliferative neoplasms	Myeloid and lymphoid neoplasms with eosinophilia and *PDGFR/FGFR1* mutation
Peripheral blood or bone marrow morphology				
Disease Associated mutation(s) (estimated frequency)	Myelodysplastic syndrome *TET2* (20%) Refractory anemia with ring sideroblasts *SF3B1* (80%-90%)	Chronic myelomonocytic leukemia *TET2* (40%-60%) *SRSF2* (30%-50%) *ASXL1* (40%) Refractory anemia with ring sideroblasts associated with marked thrombocytosis *SF3B1* (80%-90%) *JAK2*V617F (50%) Atypical chronic myeloid leukemia *SETBP1* (30%) Myelodysplastic/myeloproliferative neoplasm—unclassifiable	Chronic myeloid leukemia *BCR-ABL1* (100%) Polycythemia vera *JAK2* (99%) Essential thrombocythemia *JAK2/CALR/MPL* (85%) Primary myelofibrosis *JAK2/CALR/MPL* (90%) Chronic neutrophilic leukemia *CSF3R* (80%-100%) *SETBP1* (30%) Systemic mastocytosis *KIT*D816V (80%-100%) Chronic eosinophilic leukemia Myeloproliferative neoplasm—unclassifiable	Myeloid and lymphoid neoplasms with eosinophilia and *PDGFRA*, *PDGFRB*, or *FGFR1* mutations

CML

- results from a somatic mutation in a pluripotential lymphohematopoietic cell
- is a MPD characterized by increased granulocytic cell line, associated with erythroid and platelet hyperplasia
- the disease usually envolves into an accelerated phase that often terminates in acute phase

chronic phase	3-5 years
accelerated phase	
blastic phase	3-6 months

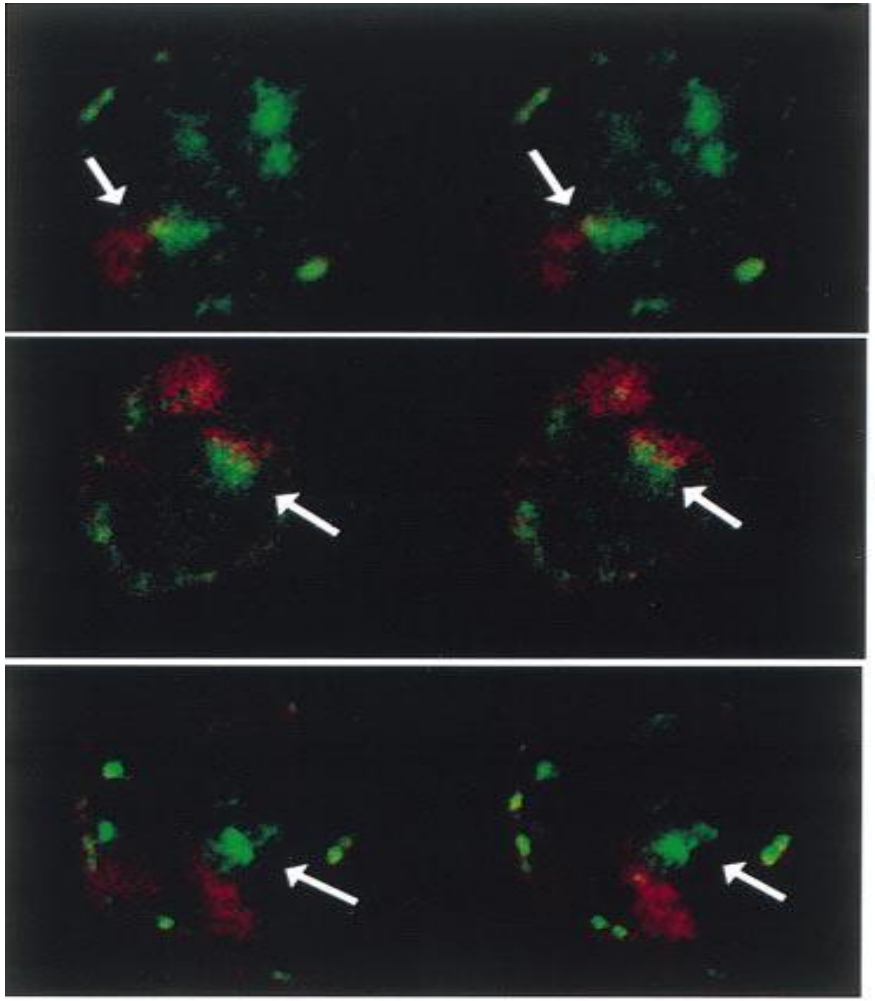
CML epidemiology

- accounts for approximately 15 percent of all cases of leukemia and approximately 3 percent of childhood leukemias
- The median age of onset is 53 years
- Frequency 1/100 000 people from general population

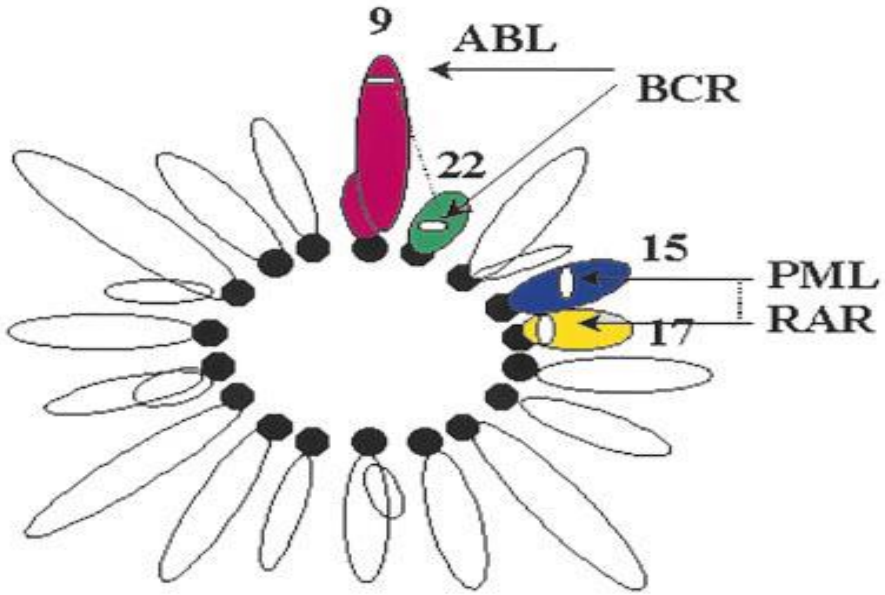
Pathogenesis

Genetic abnormality

- CML is the result of an acquired genetic abnormality
- A translocation between chromosome 9 and 22 [t(9;22)] – the Philadelphia chromosome
- The oncogene BCR-ABL encodes an enzyme – tyrosine phosphokinase (usually p210)



IM 9 - #9 (red) #22 (green)

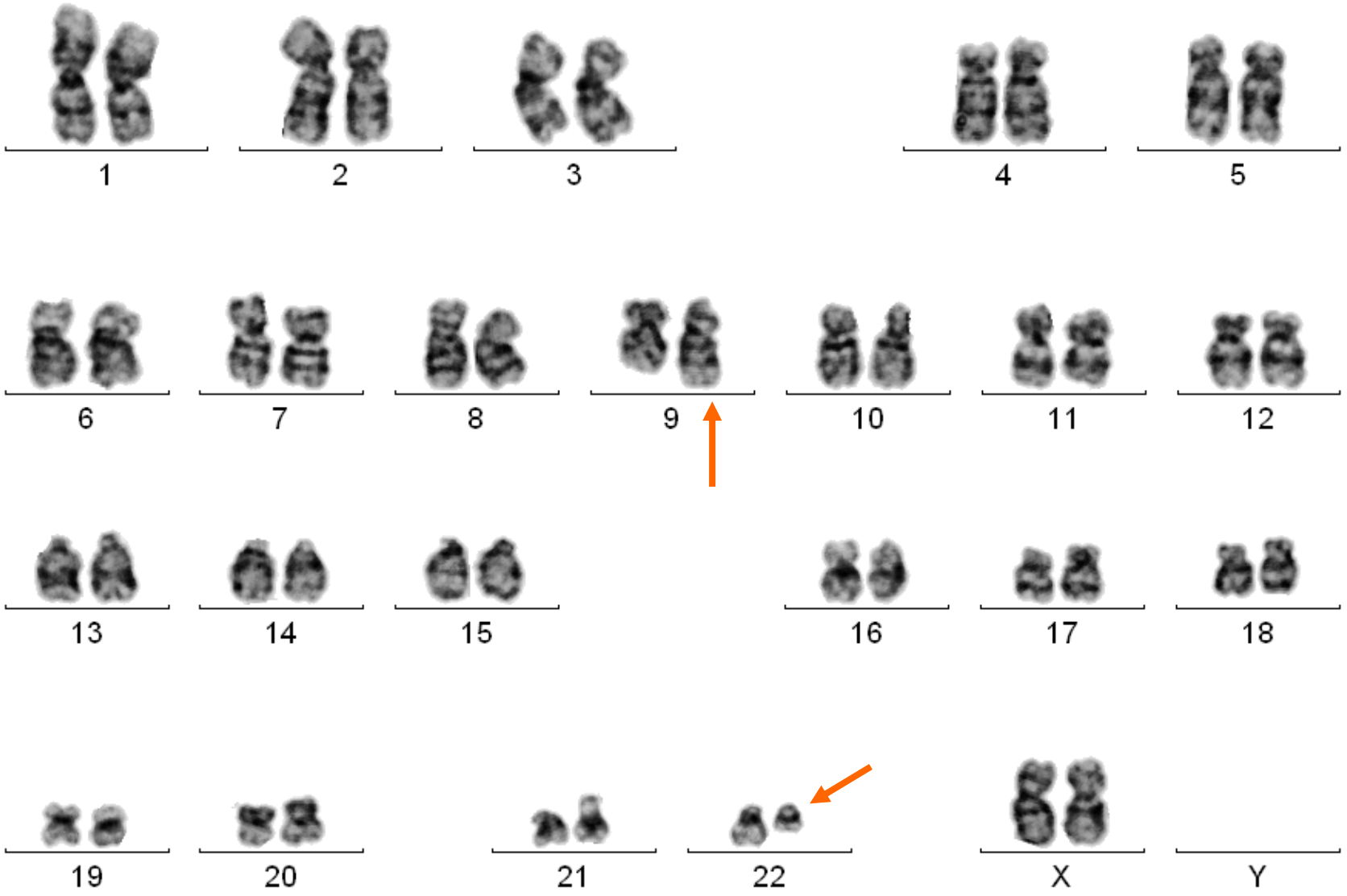


Optical sections from three IM-9 cells in metaphase hybridized with painting probes for chromosomes 9 (red) and 22 (green). Note that the signal corresponding to chromosome 22 is smaller and more centrally located than that of chromosome 9.
The diagram on the right represents the arrangement of chromosomes in a metaphase rosette and its potential effect on BCR-ABL and PML-RARa interdistances.

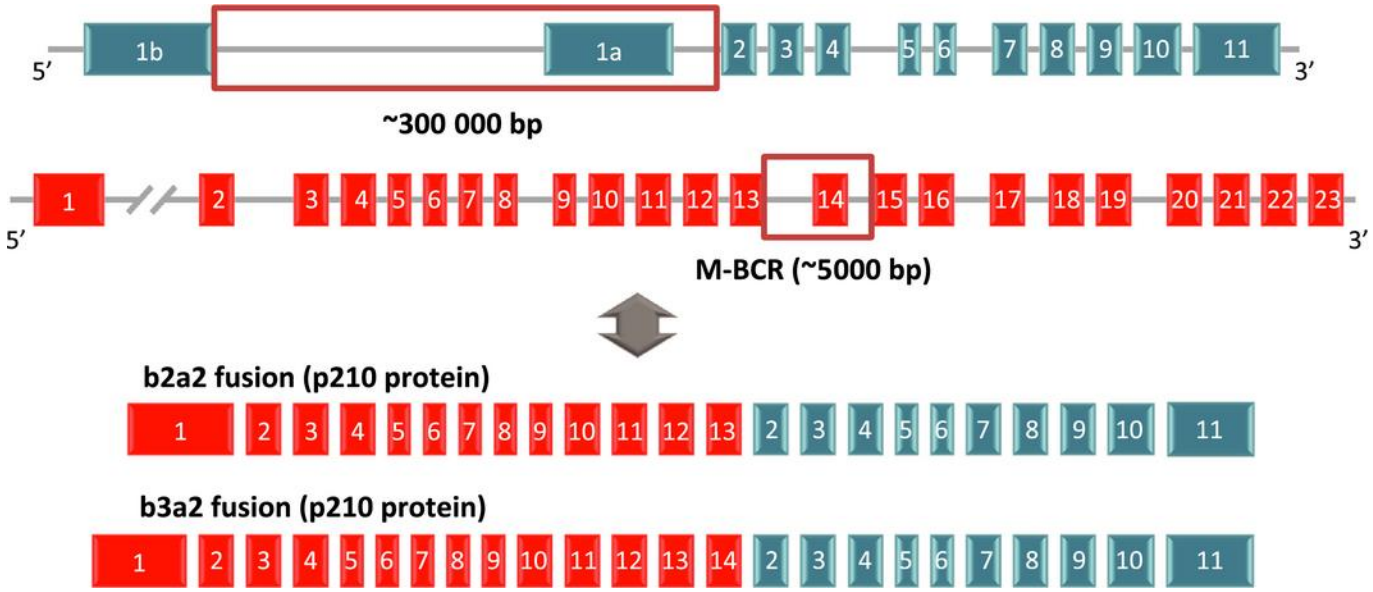
Neves H i wsp.Blood, Vol. 93, Issue 4, 1197-1207, February 15, 1999

Chronic myeloid leukemia

Karyotype analysis, GTG Technique



Localization of genomic breakpoints in the *BCR* and *ABL1* genes. Both *BCR* and *ABL1* display intronic breakpoints dispersed over a wide region, especially in *ABL1*



Soverini, et al. British Journal of Haematology, 7 MAR 2016 DOI: 10.1111/bjh.13966

Clinical features

- 30 percent of patient are asymptomatic at the time of diagnosis
- Symptoms are gradual in onset:

  easy fatigability, malaise, anorexia, abdominal discomfort, weight loss, excessive sweating

  - Less frequent symptoms:

    Night sweats, heat intolerance- mimicking hyperthyroidism, gouty arthitis, symptoms of leukostasis (tinnitus, stupor), splenic infartion (left upper-quadrant and left shoulder pain), urticaria (result of histamine release)

  - Physical signs:

    Pallor, splenomegaly, sternal pain

Laboratory features

- The hemoglobin concentration is decreased
- Nucleated red cells in blood film
- The leukocyte count above 25000/μl (often above 100000/μl), granulocytes at all stages of development
- Hypersegmentated neutrophils
- The basophiles count is increased
- The platelet count is normal or increased
- Neutrophils alkaline phosphatase activity is low or absent (90%)

Laboratory features (2)

- The marrow is hypercellular (granulocytic hyperplasia)
- Reticulin fibrosis
- Hyperuricemia and hyperuricosuria
- Serum vitamin B12-binding proteine and serum vitamin B12 levels are increased
- Pseudohyperkalemia, and spurious hypoxemia and hypoglycemia
- Cytogenetic test- presence of the Ph chromosome
- Molecular test – presence of the BCR-ABL fusion gene

Differential diagnosis

- Polycythemia vera
- Myelofibrosis
- Essential thrombocytemia
- Extreme reactive leukocytosis

CML stages

In chronic phase, fewer than 10% of the cells in the blood and bone marrow are blast cells.

Accelerated phase

In accelerated phase CML, 10% to 19% of the cells in the blood and bone marrow are blast cells.

Blastic phase

In blastic phase CML, 20% or more of the cells in the blood or bone marrow are blast cells. When tiredness, fever, and an enlarged spleen occur during the blastic phase, it is called blast crisis.

Treatment
Prognostic factors

- Sokal score =

  = (11x age + 35x spleen + 89x blasts + 0,4x platelet – 550)/1000

- Euro scale =

  = (0,666x age /0 when age <50, 1 when >/ + 0,0420x spleen + 0,0584x blasts + 0,0413x eosinophils + 0,2039x basophils /0 when basophils <3%, 1 when basophils >3%/ + 1,0956x platelet /0 when platelet <15000G/l, 1 when >/) x 1000

	Sokal	Euro
Low risk	<0,8	<780
Moderate risk	0,8-1,2	781-1479
High risk	>1,2	>1480

EUTOS SCORE

- The new EUTOS score predicts complete cytogenetic remission (CCgR) 18 months after the start of therapy, which is an important predictor for the course of disease. Patients without CCgR at this point of treatment are less likely to achieve one later on and are at a high risk of progressing to blastic and accelerated phase disease
- The strongest predictors for CCgR at 18 months are spleen size and percentage of basophils. Spleen size is measured in cm under the costal margin, basophils as their percent in peripheral blood. Both need to be assessed at baseline. Their relationship to CCgR is expressed by the formula:

  7 * basophils + 4 * spleen size

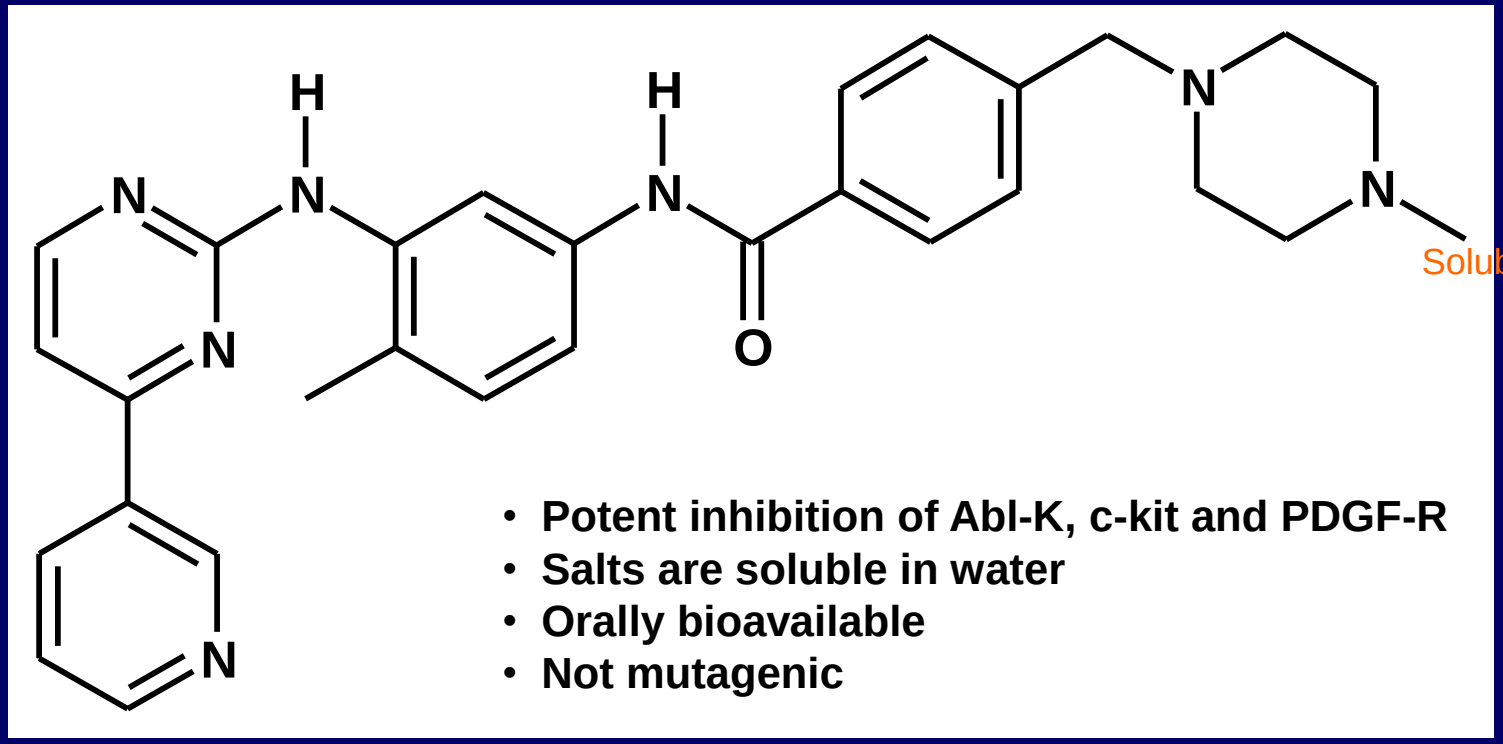
  If the sum is greater than 87, the patient is at high risk of not achieving a CCgR at 18 months, while a sum less than or equal to 87 indicates a low risk

Treatment

- IKT (imatinib, nilotinib, dasatinib, ponatinib)
- Allo- SCT

CGP57148; STI571; imatinib; Glivec

TK inhibitory activity
Stability to hydrolysis

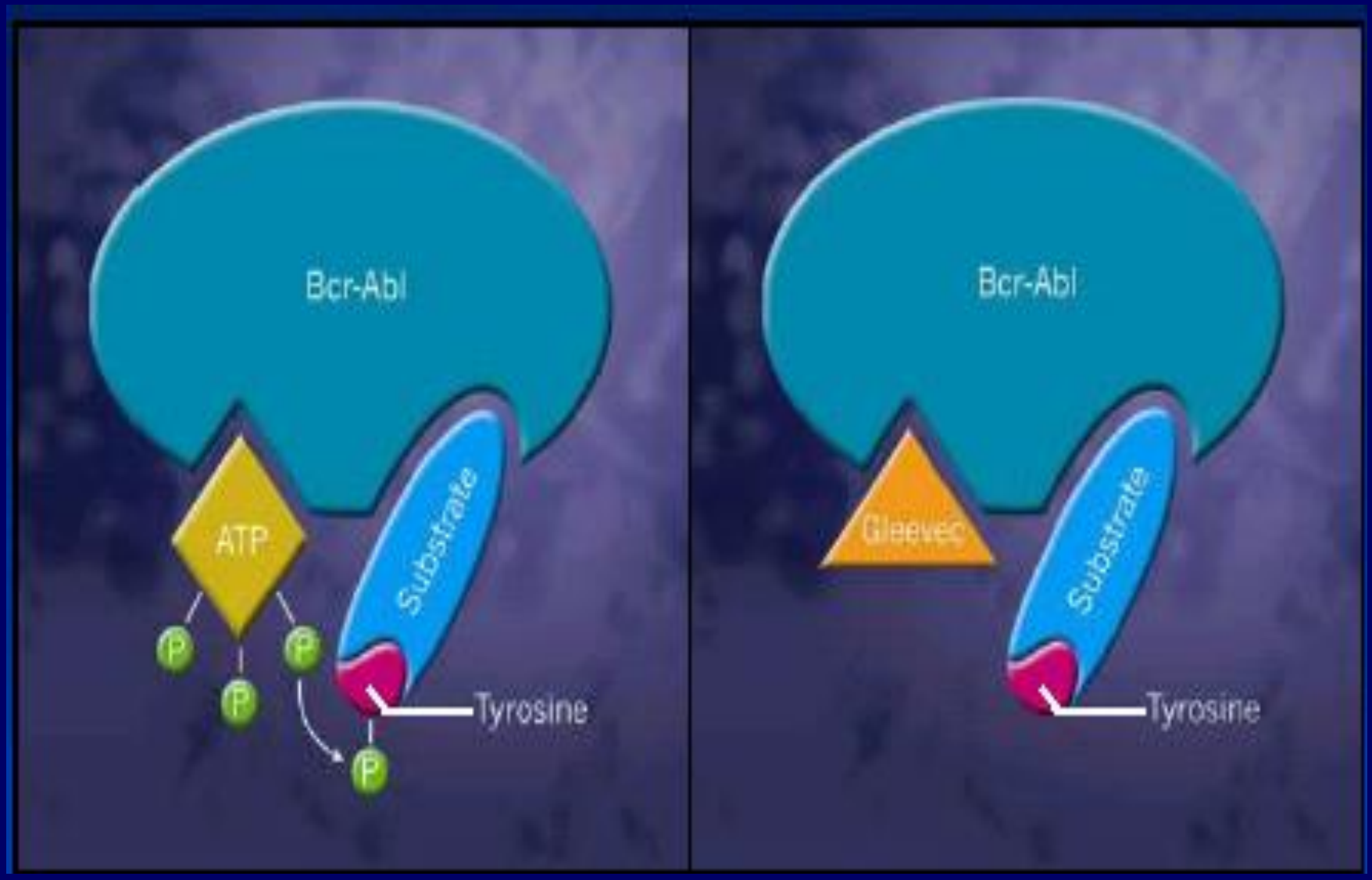


Solubilisation

- **Potent inhibition of Abl-K, c-kit and PDGF-R**
- **Salts are soluble in water**
- **Orally bioavailable**
- **Not mutagenic**

Cellular permeability

1992

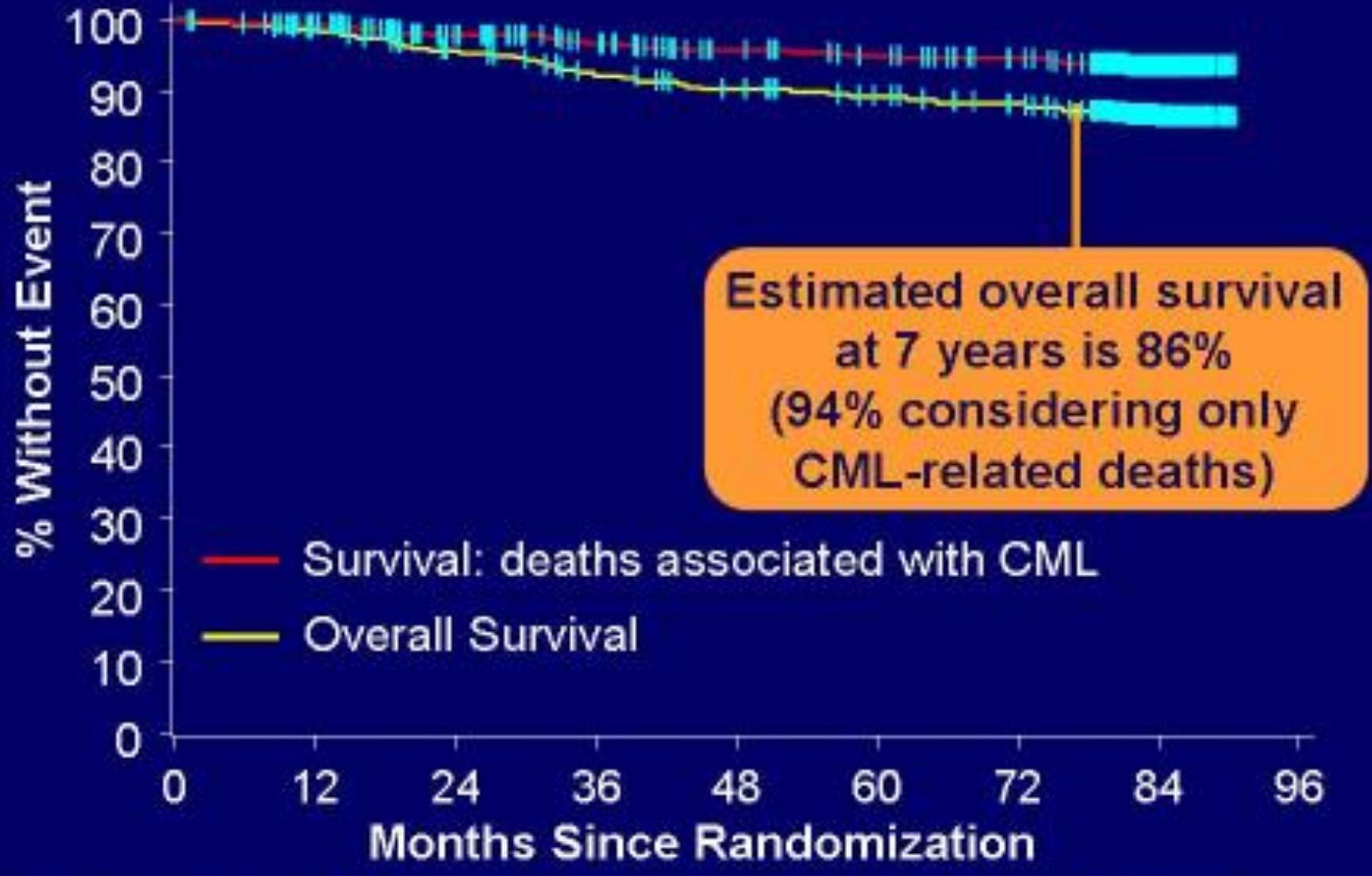

Bcr-Abl
ATP
Substrate
P
P
P
P
Tyrosine
Bcr-Abl
Gleevec
Substrate
Tyrosine

Traetment
Imatinib mesylate (Gleevec)

- Inhibits activity of mutant tyrosine kinase by blocking ATP binding
- Imatinib has less toxicity, is easier to administer, and induces higher hematologic (90 percent vs. 75percent), cytogenetic (40 percent vs. 10 percent) and molecular (7% vs. 2 %) types of remission
- Dose:

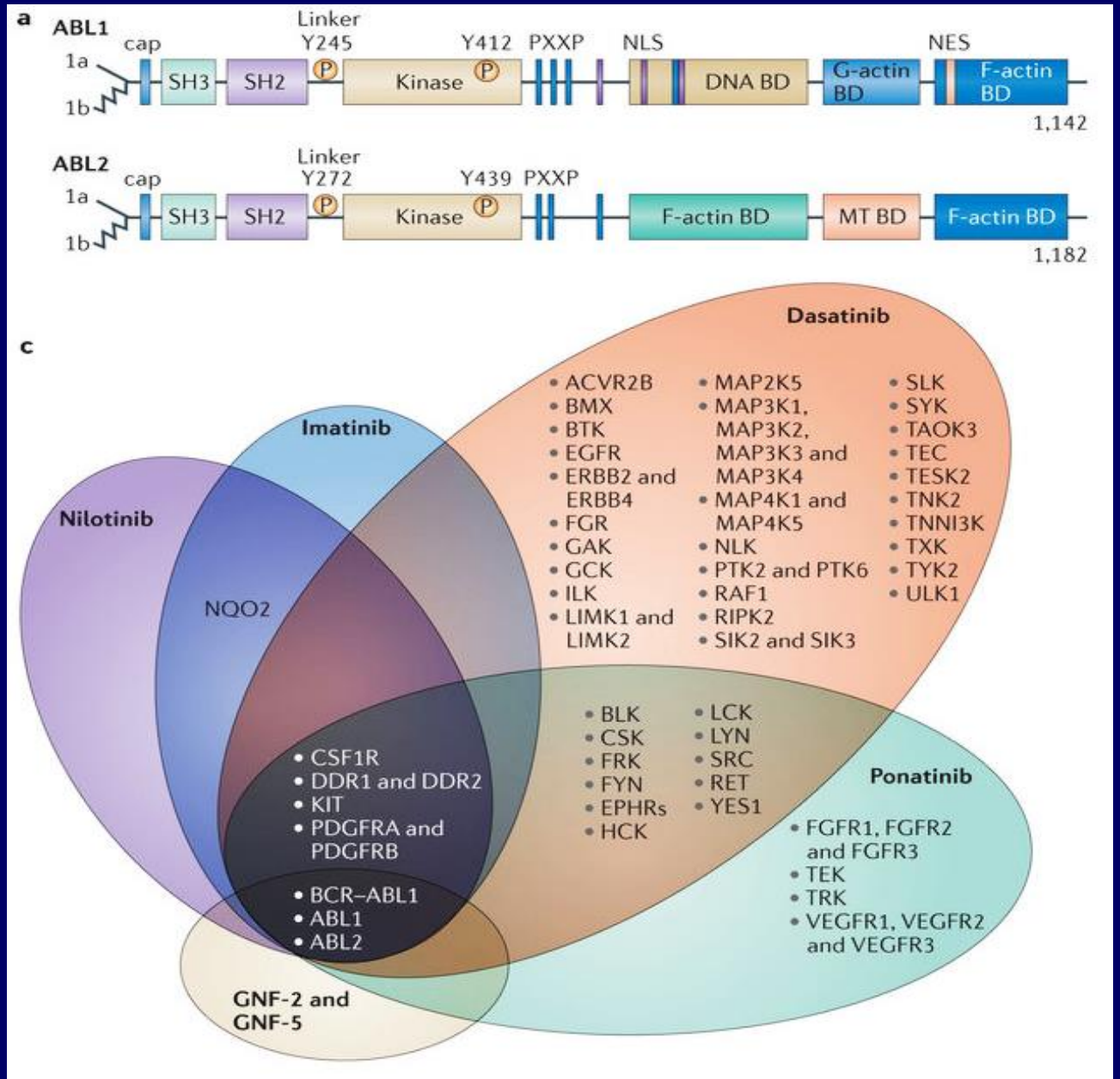
400mg/d orally (chronic phase), 600mg (accelereation phase), 800mg plus chemo (blastic crisis) in two divided doses per day

IRIS: Overall Survival: Imatinib Arm



O'Brien et al. *Blood* (ASH Annual Meeting Abstracts) 2008;112: Abstract 186. Oral presentation.

Modular domain structure of ABL family kinases (a) and molecular targets of different TKI inhibitors (c)



Specificity of selected ABL TKIs:

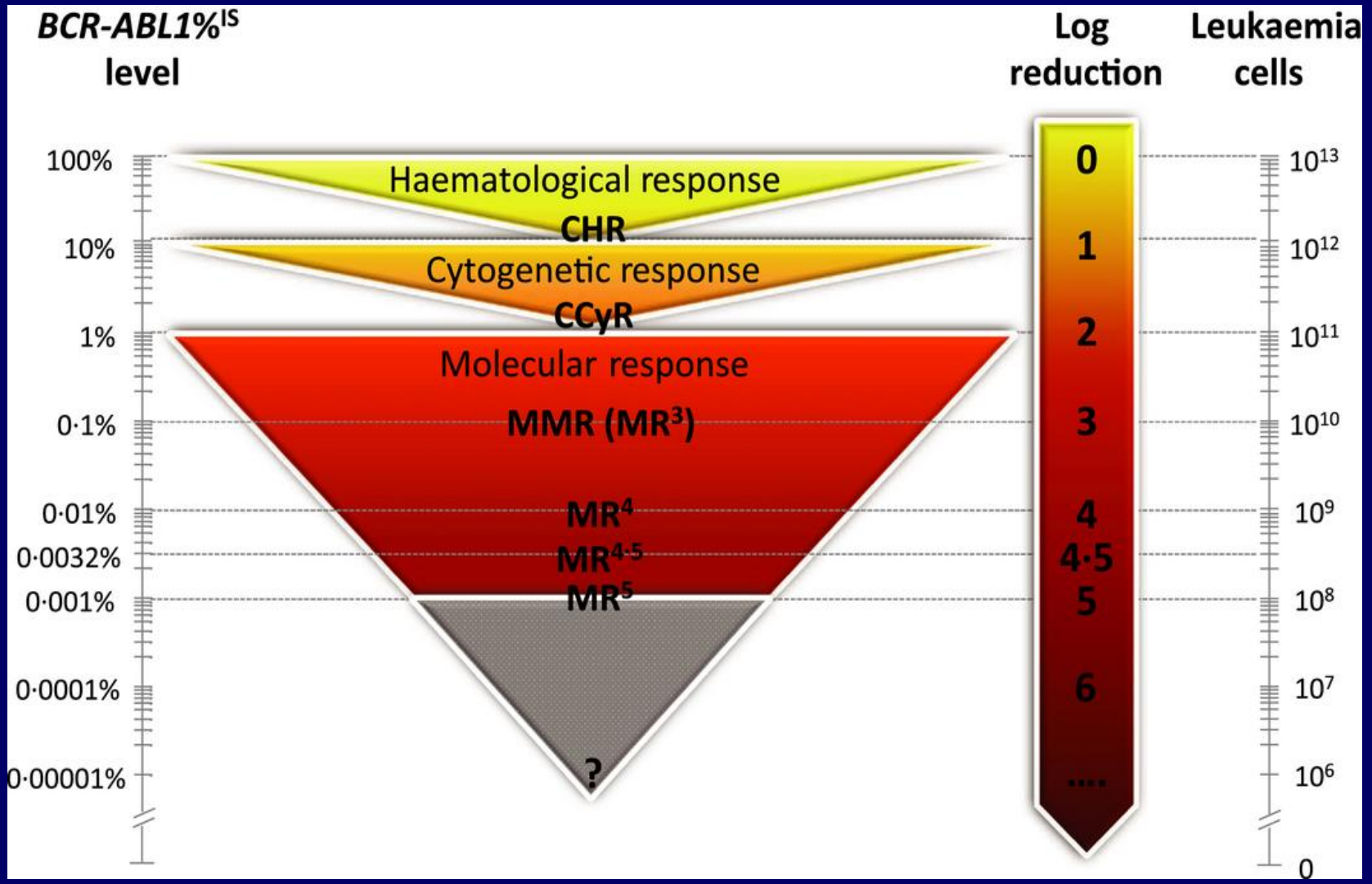
**imatinib (Gleevec, STI571; Novartis),
nilotinib (Tasigna, AMN107; Novartis),
dasatinib (Sprycel, BMS-354825; Bristol-Myers Squibb),
ponatinib (Iclusig, AP24534; Ariad Pharmaceuticals)
and
GNF-2, GNF-5 (allosteric inhibitors in preclinical studies).**

The kinase selectivity profiles for imatinib, nilotinib, and dasatinib were generated based on the binding of cellular kinases to inhibitors immobilized on solid support matrices

Ponatinib-sensitive kinases were identified by in vitro kinase assays; shown are targets with IC50 values of less than 20 nM. Kinases sensitive to GNF-2 and GNF-5 were identified by in vitro kinase assays

Greuber EK, et al. Nature Reviews Cancer 2013;13,559–571

Key levels of molecular response (MR) on the International Scale (IS)



Soverini, et al. British Journal of Haematology, 7 MAR 2016 DOI: 10.1111/bjh.13966

CML - definitions of hematologic, cytogenetic, and molecular response

Response by Type	Definitions
Hematologic	
Complete (CHR)	WBC $< 10 \times 10^9$/L
	Basophils < 5%
	No myelocytes, promyelocytes, myeloblasts in the differential
	Platelet count $< 450 \times 10^9$/L
	Spleen nonpalpable
Cytogenetic*	
Complete (CCgR)	No Ph+ metaphases
Partial (PCgR)	1% to 35% Ph+ metaphases
Minor (mCgR)	36% to 65% Ph+ metaphases
Minimal (minCgR)	66% to 95% Ph+ metaphases
None (noCgR)	> 95% Ph+ metaphases
Molecular†	
Complete (CMolR)	Undetectable *BCR-ABL* mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity $> 10^4$)
Major (MMolR)	Ratio of *BCR-ABL* to *ABL* (or other housekeeping genes) ≤ 0.1% on the international scale

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Timing of Cytogenetic and Molecular Monitoring

At diagnosis	CBA, FISH in case of Ph- (for cryptic or variant translocations), qualitative PCR (transcript type)
During treatment	RQ-PCR every 3 months until MMR has been achieved, then every 3 to 6 months and/or CBA at 3, 6, and 12 months until CCyR has been achieved, then every 12 months. Once CCyR is achieved, FISH on blood cells can be used.
Failure, progression	RQ-PCR, mutational analysis, and CBA. Immunophenotyping in blast phase.
Warning	Molecular and cytogenetic tests more frequently. CBA in case of myelodysplasia or CCA/Ph-

CBA: Chromosome banding analysis of marrow cell metaphases at least 20 metaphases analysed

ESIGN AND REALISATION: WWW.

Baccarani et al, Blood 2013;122:872-884

ELN European LeukemiaNet

UPDATE 2013

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Baccarani et al, Blood 2013;122:872-884

Response definitions for any TKI first line, and 2nd line in case of intolerance, all patients (CP, AP, and BC)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL^{IS} ≤0.1%* (MMR)	BCR-ABL^{IS} 0.1-1%*	BCR-ABL^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

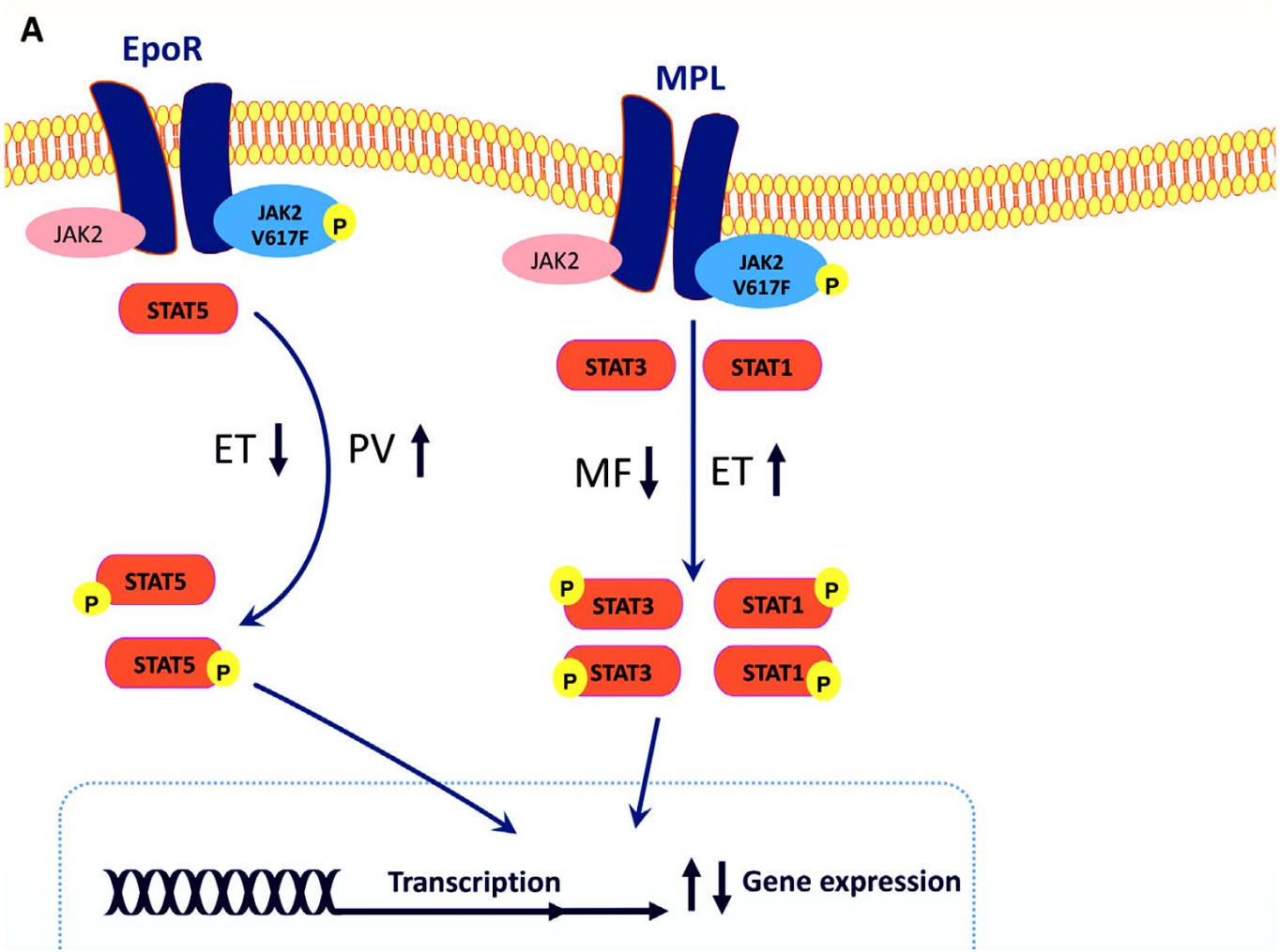
*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

Baccarani et al, Blood 2013;122:872-884

Classical myeloproliferative neoplasms

polycythaemia vera (PV)
essential thrombocythaemia (ET)
primary myelofibrosis (PMF)

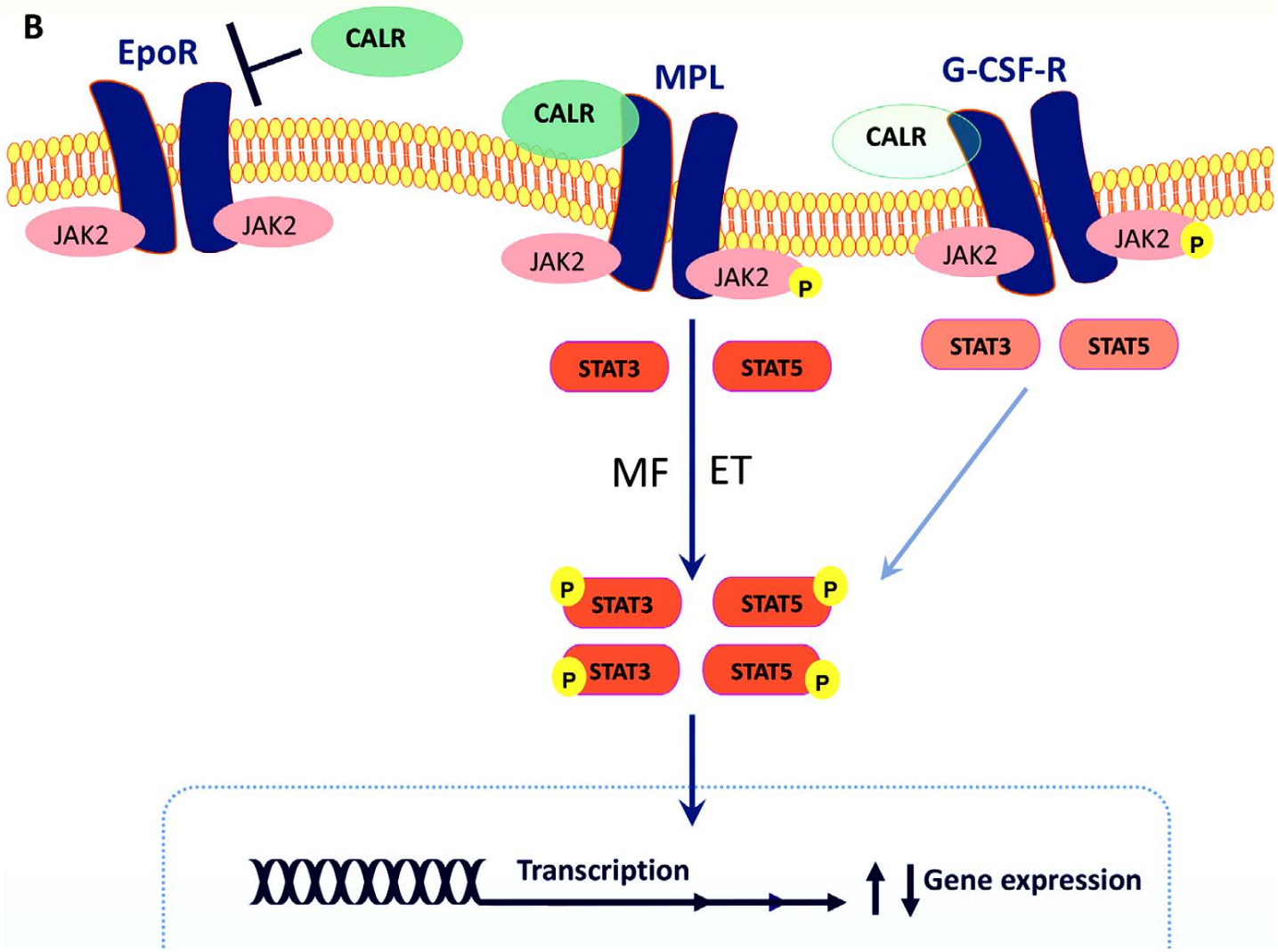
Differential STAT protein activation in myeloproliferative neoplasms



JAK2 V617F, when phosphorylated, activates STAT proteins. In PV, JAK2 V617F binds to EPOR in the cytosol causing an increase in STAT5 activation. In ET, JAK2 V617F binding to MPL causes increased STAT1 and STAT3 but decreased STAT5 activation. In MF reduced activation occurs in STAT3

O'Sullivan J, et al. *Advances in Biological Regulation 2019;71: 55–68*

Differential STAT protein activation in myeloproliferative neoplasms

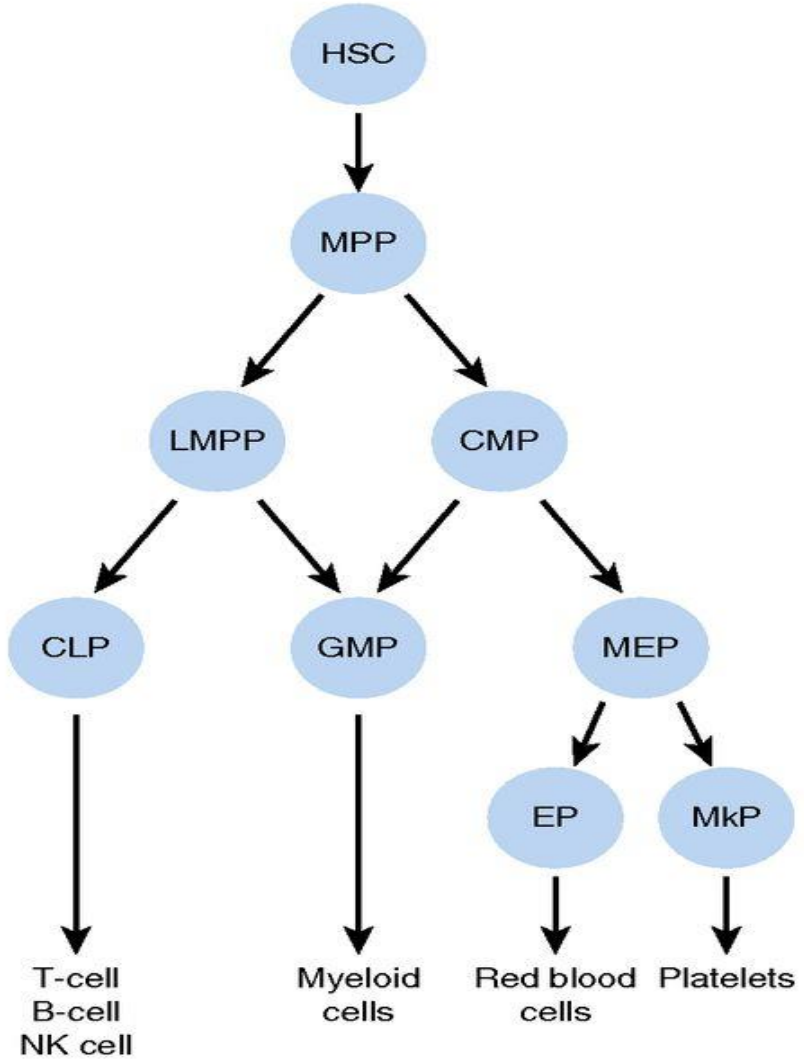


In CALR-mutant MPN, CALR binds directly to MPL, signaling through JAK2 to upregulate STAT3 and STAT5. It binds weakly to G-CSF-R to activate these STAT proteins but does not bind to EPOR explaining only ET and MF phenotypes associated with CALR

O'Sullivan J, et al. *Advances in Biological Regulation 2019;71: 55–68*

Key somatic mutations and growth factor receptors important for MPN development

A



B

Stem and progenitors	HSC	MPP	LMPP/CLP	CMP
Key receptors	MPL	MPL	IL7R FLT3	MPL GMCSFR IL3R GCSFR
Impacting Mutation	JAK2V617F Mutant CALR MPLW515L	JAK2V617F Mutant CALR MPLW515L	None	JAK2V617F Mutant CALR MPLW515L
Progenitors and precursors	GMP	MEP	EP	MkP
Key receptors	GMCSFR IL3R GCSFR	IL3R EPOR MPL	EPOR	MPL
Impacting Mutation	JAK2V617F	JAK2V617F Mutant CALR MPLW515L	JAK2V617F	JAK2V617F Mutant CALR MPLW515L

HSC = hematopoietic stem cell
MPP = multipotent progenitor
LMPP = lymphoid primed multipotent progenitor
CMP = common myeloid progenitor
MEP = megakryocyte erythroid progenitor
GMP = granulocyte macrophage progenitor
MkP = megakaryocyte precursor
EP = erythroid precursor
CLP = common lymphoid progenitor

Mead AJ, et al. Blood 2017 129:1607-1616

Proposed 2016 WHO diagnostic criteria for *BCR-ABL1*-negative myeloproliferative neoplasms

	PV	ET	PMF	
Major criteria				
1	Hemoglobin > 16.5 g/dl (men) > 16 g/dl (women) or hematocrit > 49% (men) > 48% (women) or increased red cell mass (RCM)	Platelet count ≥ 450 × 10^9/l	prePM Megakaryocytic proliferation and atypia[d], without reticulin fibrosis > grade 1,[e] accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation and often decreased erythropoiesis	Overt PMF Megakaryocyte proliferation and atypia[d] accompanied by either reticulin and/or collagen fibrosis (grade 2 or 3)
2	BM with age-adjusted hypercellularity and trilineage myeloproliferation with pleomorphic, mature megakaryocytes (differences in size)	BM with megakaryocyte proliferation with large and mature morphology. No significant left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers	Not meeting WHO criteria for *BCR-ABL1* + CML, PV, ET, MDS or other myeloid neoplasm	Not meeting WHO criteria for *BCR-ABL1* + CML, PV, ET, MDS or other myeloid neoplasm
3	Presence of *JAK2* mutation	Not meeting WHO criteria for *BCR-ABL1* + CML, PV, PMF, MDS or other myeloid neoplasm	Presence of *JAK2*, *CALR or MPL* mutation or in the absence of these mutations, presence of another clonal marker[f] or absence of minor reactive bone marrow reticulin fibrosis[g]	Presence of *JAK2*, *CALR* or *MPL* mutation or in the absence, the presence of another clonal marker[f] or absence of evidence for reactive bone marrow fibrosis[h]
4		Presence of *JAK2*, *CALR* or *MPL* mutation		

	PV	ET	PMF	
Minor criteria				
1	Subnormal serum erythropoietin level	Presence of a clonal marker (e.g. abnormal karyotype) or absence of evidence for reactive thrombocytosis	Presence of one or more of the following[j]: • Anemia not attributed to a comorbid condition • Palpable splenomegaly • Leukocytosis ≥ 11 × 10^9/L • Elevated LDH[j]	Presence of one or more of the following[j]: • Anemia not attributed to a comorbid condition • Palpable splenomegaly • Leukocytosis ≥ 11 × 10^9/L • Elevated LDH[j] • Leukoerythroblastosis[i]

a PV diagnosis requires meeting either all three major criteria or the first two major criteria and one minor criterion
b ET diagnosis requires meeting all four major criteria or first three major criteria and one minor criterion
c prePMF diagnosis requires all three major criteria and at least one minor criterion. Overt PMF diagnosis requires meeting all three major criteria and at least one minor criterion

d Small-to-large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.
e In cases with grade 1 reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (that is, prePMF).
f In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.
g 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.
h Bone marrow fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cel leukemia or other lymphoid neoplasm, metastatic malignancy or toxic (chronic) myelopathies.
i Confirmed in two consequtive determinations
j Degree of abnormality can be borderline or marked and institutional reference range should be used for lactate dehydrogenase level (LDH)

T. Barbui et al. Blood Reviews xxx (2016) xxx–xxx

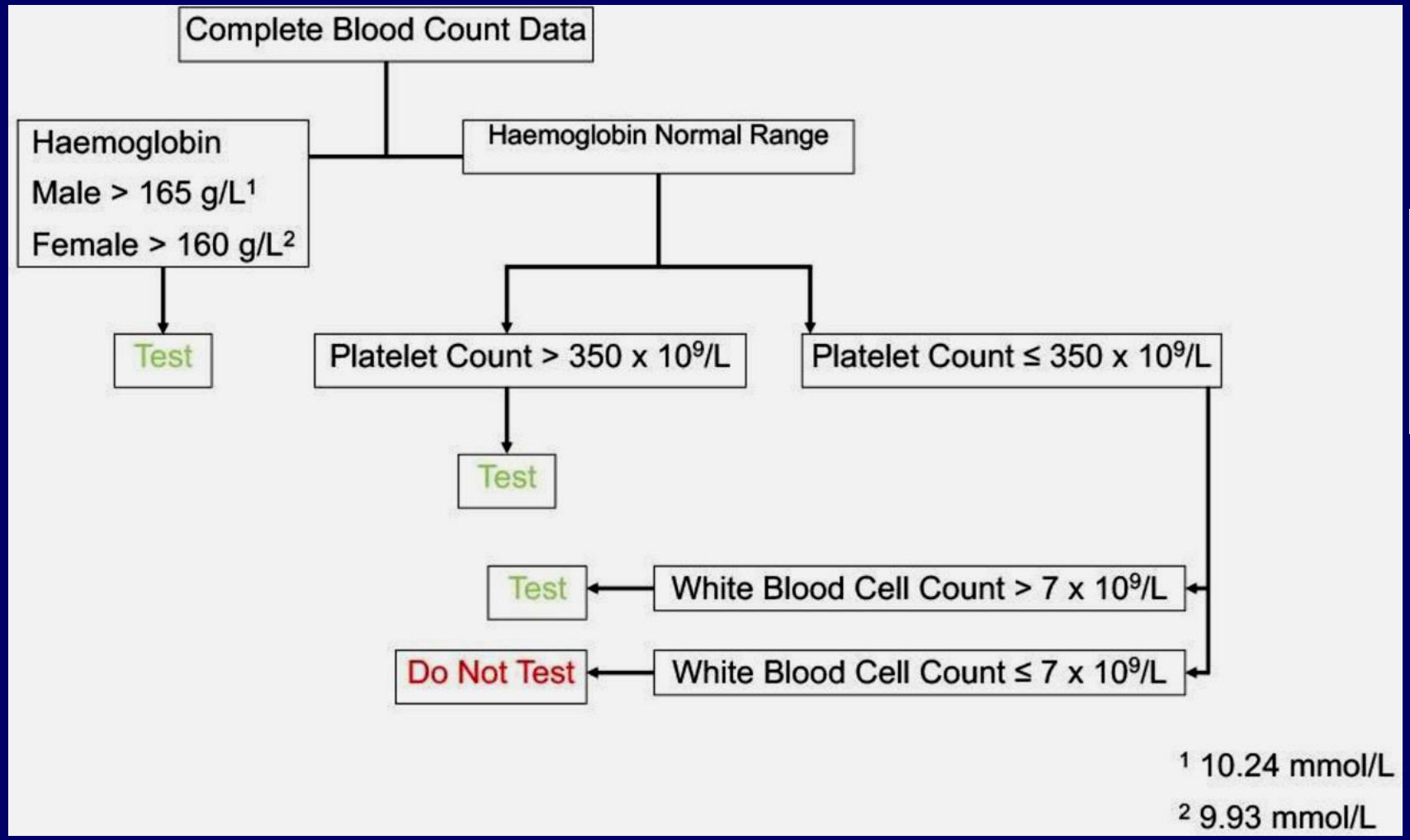
MPN symptoms by subtype

Symptom	ET (n=874)		PV (n=729)		MF (n=486)		Total (n=2089)	
	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;277

JAK2-tree: a simple CBC-based decision rule to guide appropriate JAK2 V617F mutation testing

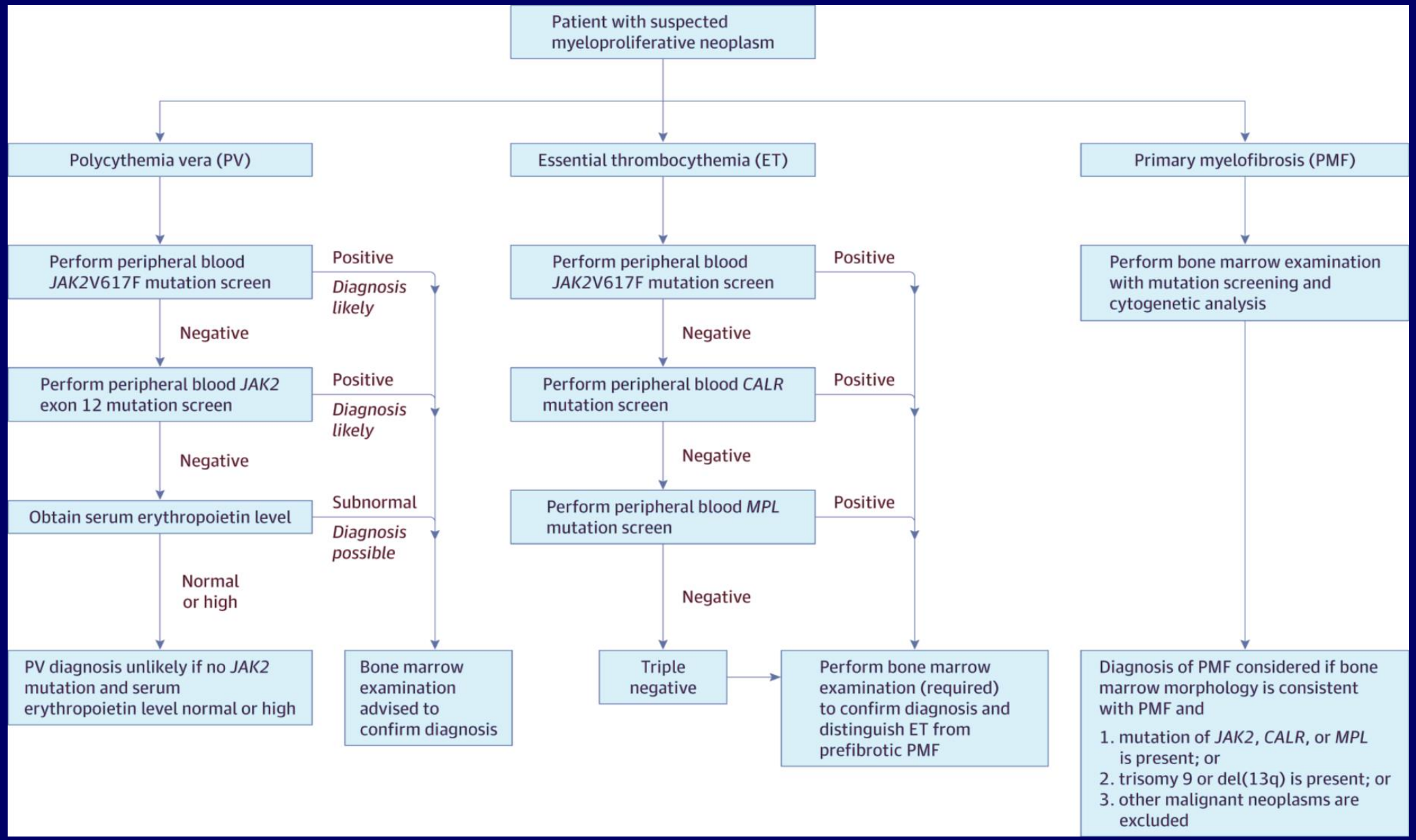


Copenhagen General Population Study JAK2-tree confusion matrix

	JAK2 V617F status (%)	
	Positive	Negative
JAK2-tree algorithm (%)		
Test	62 (0.12%)	28 623 (57%)
Do not test	6 (0.01%)	21 672 (43%)

Mahe E, et al. J Clin Pathol 2019;72:172–176

Practical Algorithm for Diagnosis of Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF)



Tefferi A, et al. JAMA Oncol. 2015;1(1):97-105

POLYCYTHEMIA VERA
treatment

- Phlebotomy
  - initially 450-500 ml phlebotomy every other day until the hematocrit is less than 45% (M), 42% (F)
  - older patients or these with underlying cardiovascular disase should undergo smaller phlebotomies 200-300mL twice weekly

or

100-150mL every day until Ht<45%

  - fluid replacement so that the patients remains isovolemic
- Hydroxycabamide (Hydroxyurea) – 10-30mg/kg bw orally daily

Recommendations for second-line therapy in PV

Current drug options

Interferon-α, *if hydroxyurea resistant / intolerant*

Hydroxyurea, *if Interferon-α resistant / intolerant*

Busulfan, for patients with 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

POLYCYTHEMIA VERA - supportive care

Severe itching (pruritus) — antihistamines, H2-receptor blockers, serotonin reuptake inhibitors, interferon alpha, and in resistant cases, myelosuppression.

Hyperuricemia — allopurinol 300mg/day

Erythromelalgia (a burning pain in the feet or hands accompanied by erythema, pallor or cyanosis) — low-dose aspirin. Erythromelalgia unresponsive to treatment with low-dose aspirin should be treated with myelosuppression

Bleeding — extraneous causes for bleeding (eg, use of high-dose aspirin, antiplatelet agents, anticoagulants) should be stopped. Patients should be evaluated for acquired von Willebrand disease and treated accordingly (vWF ristocetin cofactor activity)

ESSENTIAL THROMBOCYTHEMIA
clinical picture

1. **Thrombotic complications** (intermittent or permanent occlusion of small blood vessels)
   - transient cerebral and ocular ischemic episodes that may progress to infarction
   - peripheral arterial occlusive disease associated with „erythromelalgia”(intermittent, painful errythema and cyanosis of the fingers and toes
2. **Hemorrhagic complications**
   - bleeding after surgery and spontaneus upper gastrointestinal bleeding (the hemorrhagic tendency is worsened if nonsteroidal anti-inflammatory agent are administered)
3. Splenomegaly - 20-50% patients
4. Hepatomegaly - rarely

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

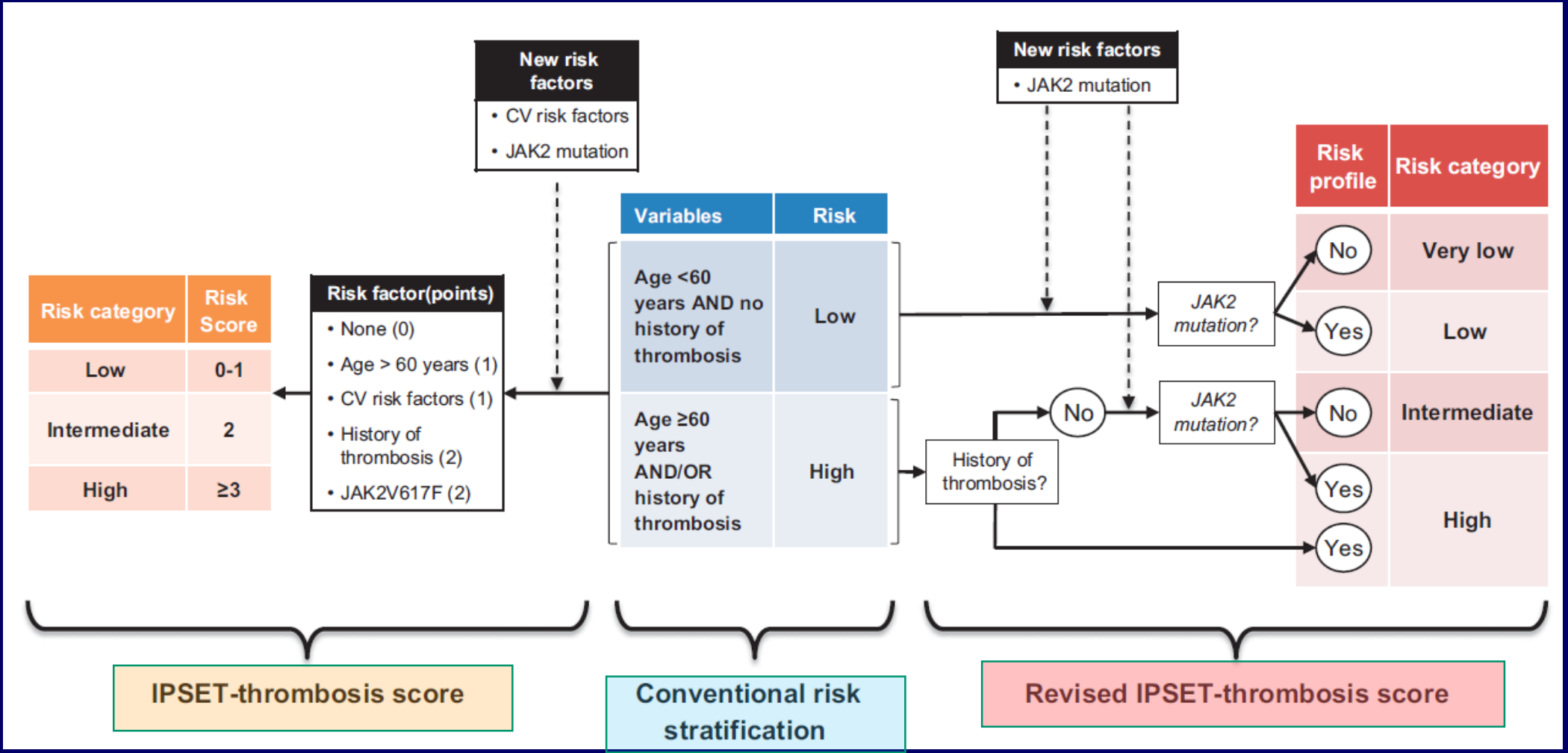
IPSET International Prognostic Score of Thrombosis, *CV* cardiovascular, *% pts/y* percentage of patients per year]

[a]891 patients

[b]1220 patients

Barbui T, A et al. Blood 2012;120:5128–5133

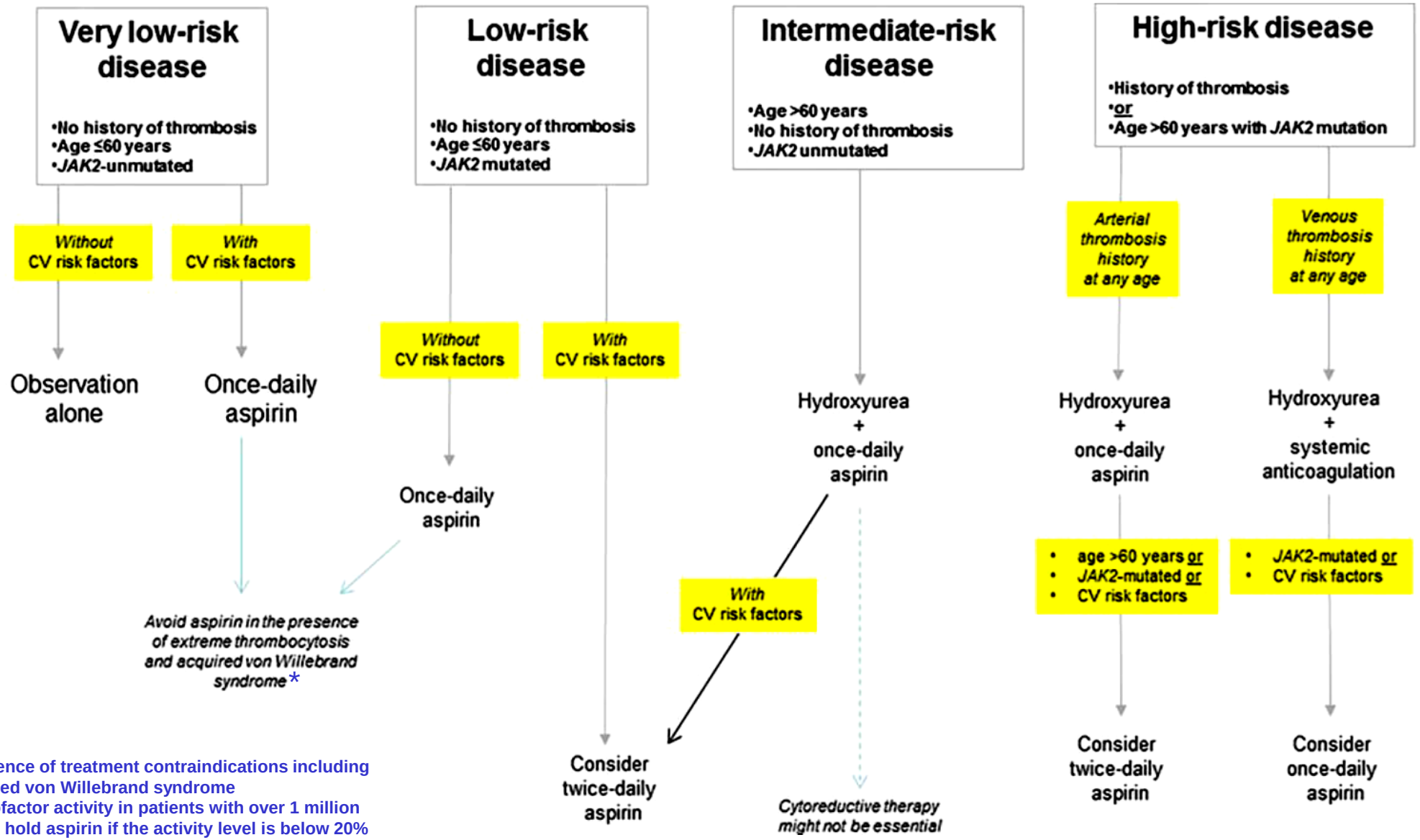
Essential thrombocythaemia thrombotic risk assessement



CV, cardiovascular risk factors, IPSET, International Prognostic Score for Thrombosis in Essential Thrombocythemia

Falchi L, Kantarjian HM, Verstovsek S. Leukemia 2017;Sep;31(9):1845-1854

Contemporary treatment algorithm in essential thrombocythemia (ET)



*Aspirin is used in the absence of treatment contraindications including clinically significant acquired von Willebrand syndrome
→ measure of ristocetin cofactor activity in patients with over 1 million platelets per microliter and hold aspirin if the activity level is below 20%

Tefferi A, et al. Am J Hematol 2017; 92: 95–108
Tefferi A, Barbui T. Am J Hematol. 2015 Apr 14. doi: 10.1002/ajh.24037

Primary myelofibrosis (PMF)

MYELOFIBROSIS

- The incidence of Myelofibrosis is about 0,5/100.000. The median age at diagnosis was approximately 65 years.
- Common complaints: fatigue, weight loss, night sweats, bone pain, abdominal pain, fever
- Physical findings: splenomegaly (often huge), hepatomegaly (in about 50% of patients), symptoms of anaemia and thrombocytopenia

MYELOFIBROSIS
- laboratory findings (1)

- Anemia - Hb<10g/dL in 60% of patients
- Leukocytosis with counts generally below 50 G/L (in about 50%), leukopenia (in about 25% at the time of diagnosis)
- thrombocytosis in 50% at the time of diagnosis, with disease progression thrombocytopenia becomes common
- eosinophilia and basophilia may be present
- retikulocytosis
- LAP score is usually elevaatedd
- Increased level of lactate dehydrogenase
- uric acid level is increased in most patients

PMF prognostic scale

Dynamic IPSS :

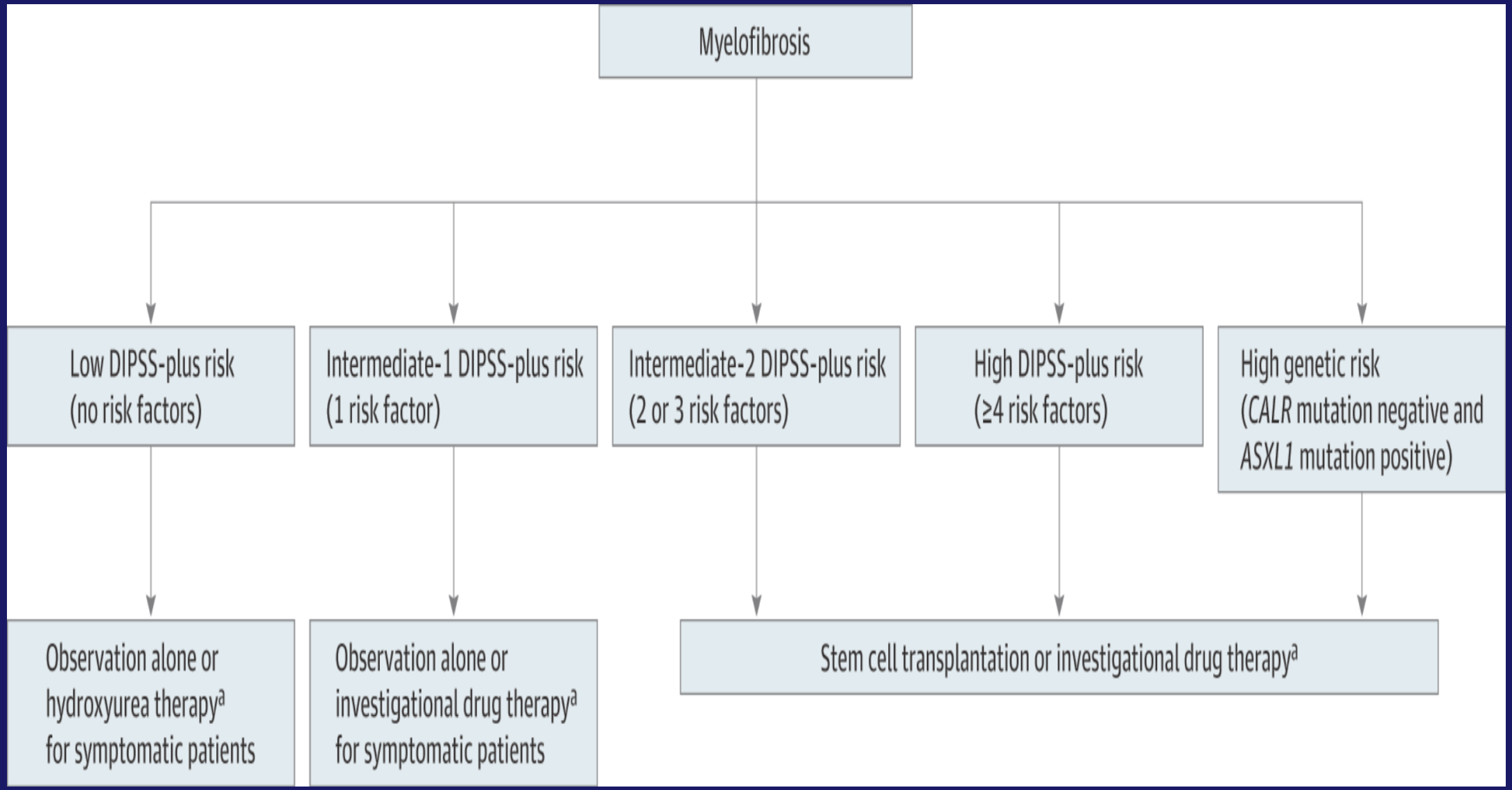
- Age >65 years: 1 point
- Leukocyte count >25,000/microL: 1 point
- Hemoglobin <10 g/dL: 2 points
- Circulating blast cells ≥1 percent: 1 point
- Presence of constitutional symptoms: 1 point

Subjects with zero, one to two, three to four, or 5 to 6 points were considered low, intermediate-1, intermediate-2, or high risk, respectively.

DIPSS Plus — IPSS-independent prognostic factors for survival in PMF:

1. unfavorable karyotype [complex karyotype or sole or two abnormalities that include +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 rearrangements]
2. red cell transfusion need
3. thrombocytopenia

Contemporary Treatment Algorithm for Primary Myelofibrosis



MYELOFIBROSIS - therapy (1)

Drug used for the control of leukocytosis, thrombocytosis:
hydroxyurea

Drugs used for treatment of splenomegaly and constitutional symptoms:
hydroxyurea (HU), ruxolitinib in cases with HU resistance/intolerance

Drugs used for treatment of anemia:
androgen preparations, prednisone, danazol, thalidomide, lenalidomide (in the presence of del(5q)

MYELOFIBROSIS - therapy (2)

- **Allogeneic stem-cell transplantation:** for young patients who have a poor prognosis and have a suitable donor identified
- **Hydroxyurea (HU)**
- **JAK2 inhibitors in case of HU resistance/intolerance**
- **Supportive care:**

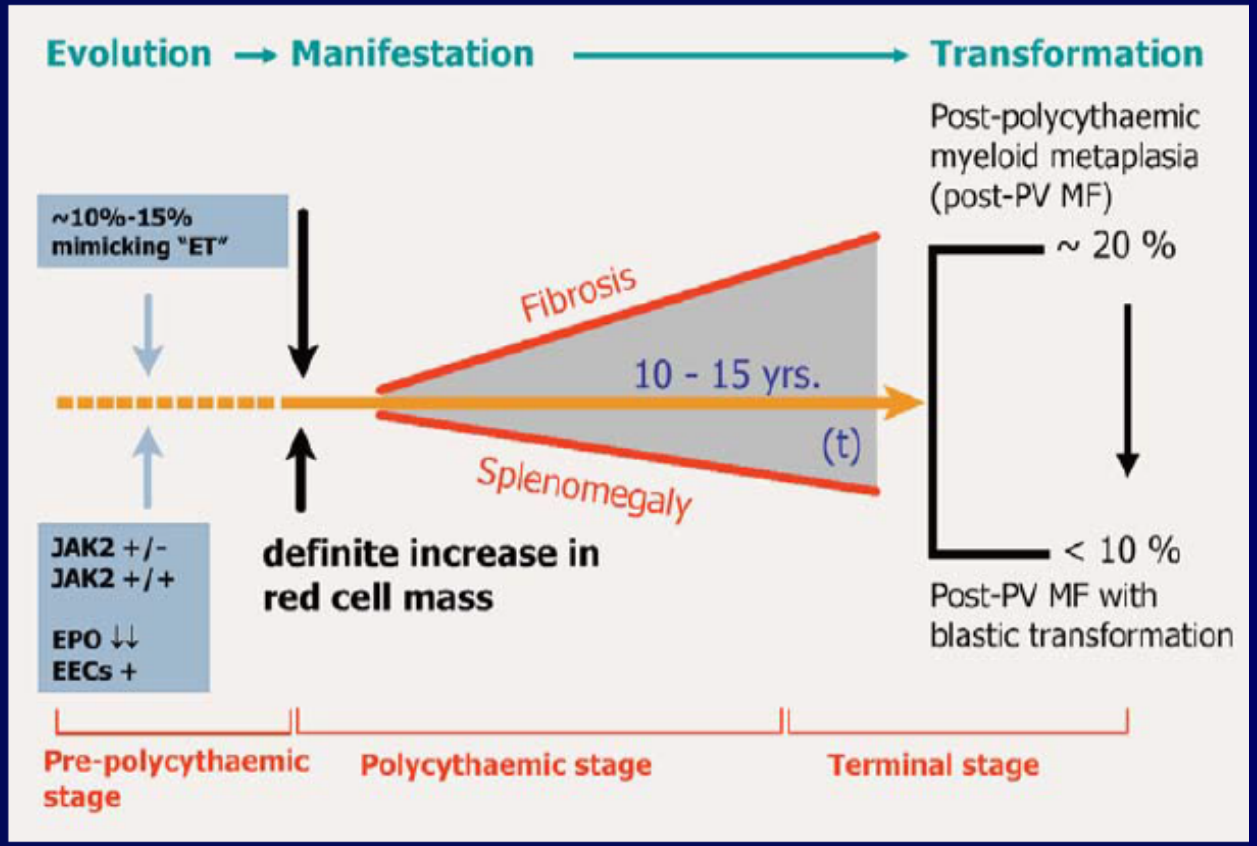
Allopurinol-to prevent hyperuricaemia.

Transfusions of packed red cells for anemia or

platelets for thrombocytopenia with bleeding

PV: a dynamic disease that evolves in stages

- A pre-polycythemic phase characterized by borderline to only mild erythrocytosis
- An overt polycythemic phase, (erythrocytotic phase)
- A post- polycythemic myelofibrotic phase in which cytopenias develop due to ineffective hematopoiesis in association with bone marrow fibrosis and extramedullary hematopoiesis
- Accelerated/Blast phase



Thiele J, Kvasnicka HM, Orazi A et al. WHO 2008

post-PV myelofibrosis

Criteria for post-polycythemia vera myelofibrosis

Required criteria:

1 Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria (see Table II)

2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale) (see footnote for details)

Additional criteria (two are required):

1 Anemia or sustained loss of requirement for phlebotomy in the absence of cytoreductive therapy

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 Development of ≥ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

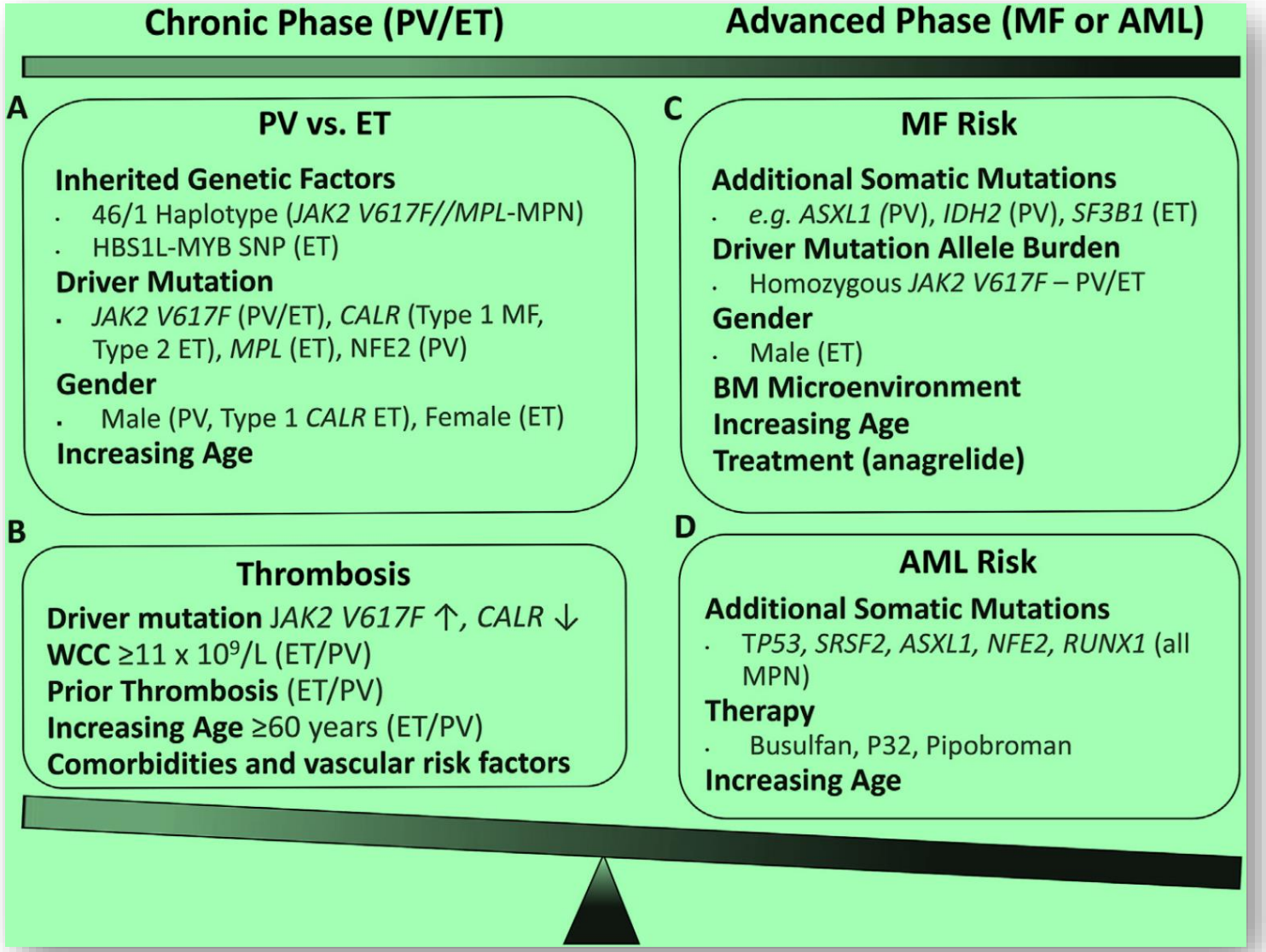
Criteria for post-essential thrombocythemia myelofibrosis

Criteria for post-essential thrombocythemia myelofibrosis	
Required criteria:	
1	Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria (see Table 2)
2	Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale) (see footnote for details)
Additional criteria (two are required):	
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 lactate dehydrogenase
5	Development of ≥ 1 of three constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)

Grade 2–3 according to the European classification:[2] 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). Grade 3–4 according to the standard classification:[3] 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

Tefferi A, et al. Am J Hematol 2017; 92: 95–108

An overview of the principal factors influencing disease heterogeneity in chronic and advanced MPN



A) Risk factors predisposing to development of PV versus (vs.) ET
B) Risk factors predisposing to thrombosis in PV and ET
C) Factors influencing risk of transformation to MF
D) Factors influencing risk of transformation to AML

O'Sullivan J, et al. ***Advances in Biological Regulation 2019;71: 55–68***