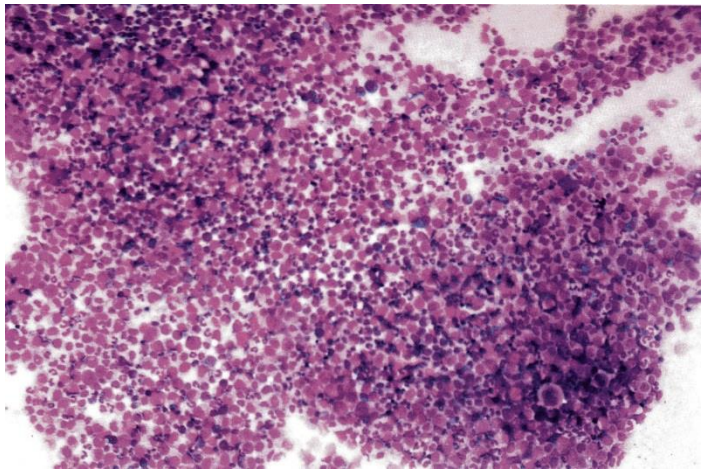


Neoplasie mieloproliferative croniche

The 2016 revision to the World Health Organization Classification of Myeloid Neoplasms and acute leukemias

1. Myeloproliferative neoplasms
2. Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
3. Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
4. Myelodysplastic syndromes (MDS)
5. Blastic plasmacytoid dendritic cell neoplasm
6. Acute leukemias of ambiguous lineage
7. Acute myeloid leukemia (AML) and related neoplasms
8. B-lymphoblastic leukemia/lymphoma
9. T-lymphoblastic leukemia/lymphoma

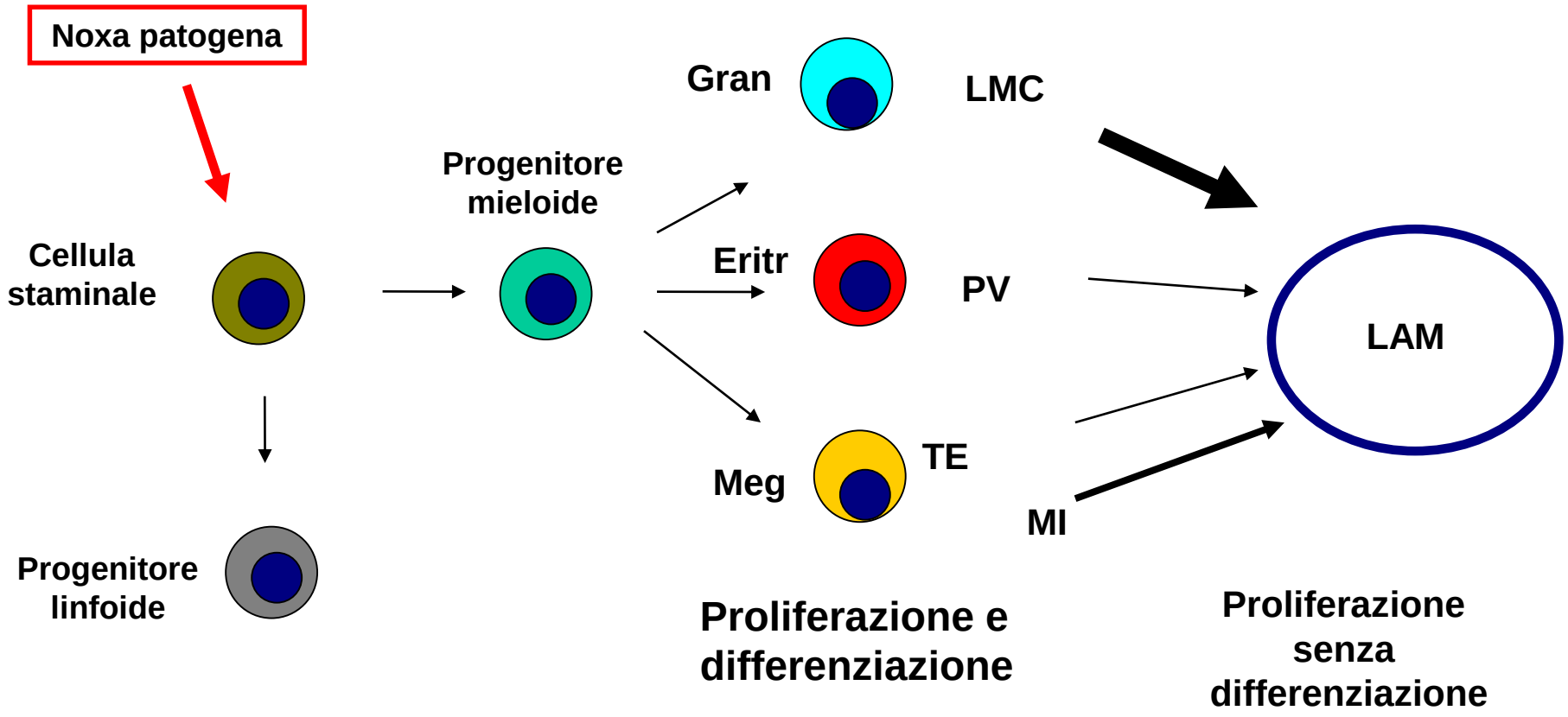
Arber DA et al. Blood. 2016; 127(20):2391-2405

The 2016 revision to the WHO classification of myeloid neoplasms and acute leukemia

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis

Arber DA et al. Blood. 2016; 127(20):2391-2405

SMP: definizione



Varietà di disordini clonali acquisiti della cellula staminale pluripotente, contrassegnati dalla proliferazione clonale di uno o più progenitori emopoietici nel midollo ed in sedi extramidollari

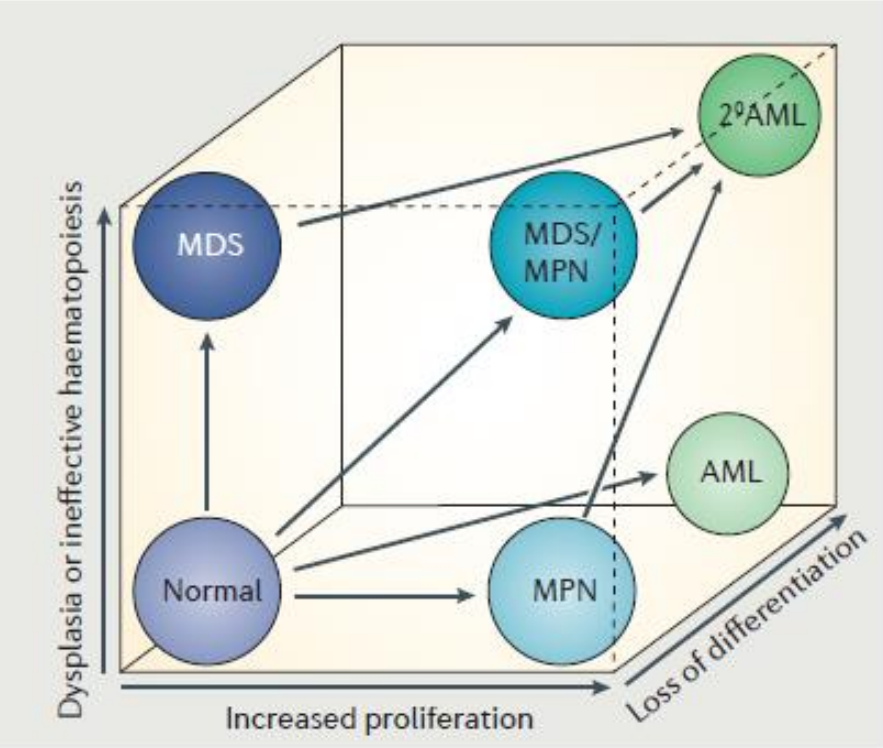
Differentiation and proliferation

	MDS	AML	MPD
Differentiation	Impaired	Impaired	Normal ← ←
Proliferation/survival	Impaired → →	Preserved	Increased

Arrows indicate where a second hit could result in progression to AML.

Nimer SD. Blood 2008;111:4841.

Normal myelopoiesis and myeloid malignancies



- **Myeloproliferative neoplasms (MPN) are characterized by excess proliferation in one or more of the myeloid lineages and frequently by extramedullary haematopoiesis. Blood cell morphology is normal and differentiation is maintained.**

- **Myelodysplastic syndromes (MDS) exhibit decreased numbers of cells in the blood, whereas their bone marrow is frequently hypercellular (ineffective haematopoiesis).**

- **Acute myeloid leukaemia (AML) is characterized by differentiation arrest and accumulation of primitive undifferentiated myeloid cells (myeloblasts)**

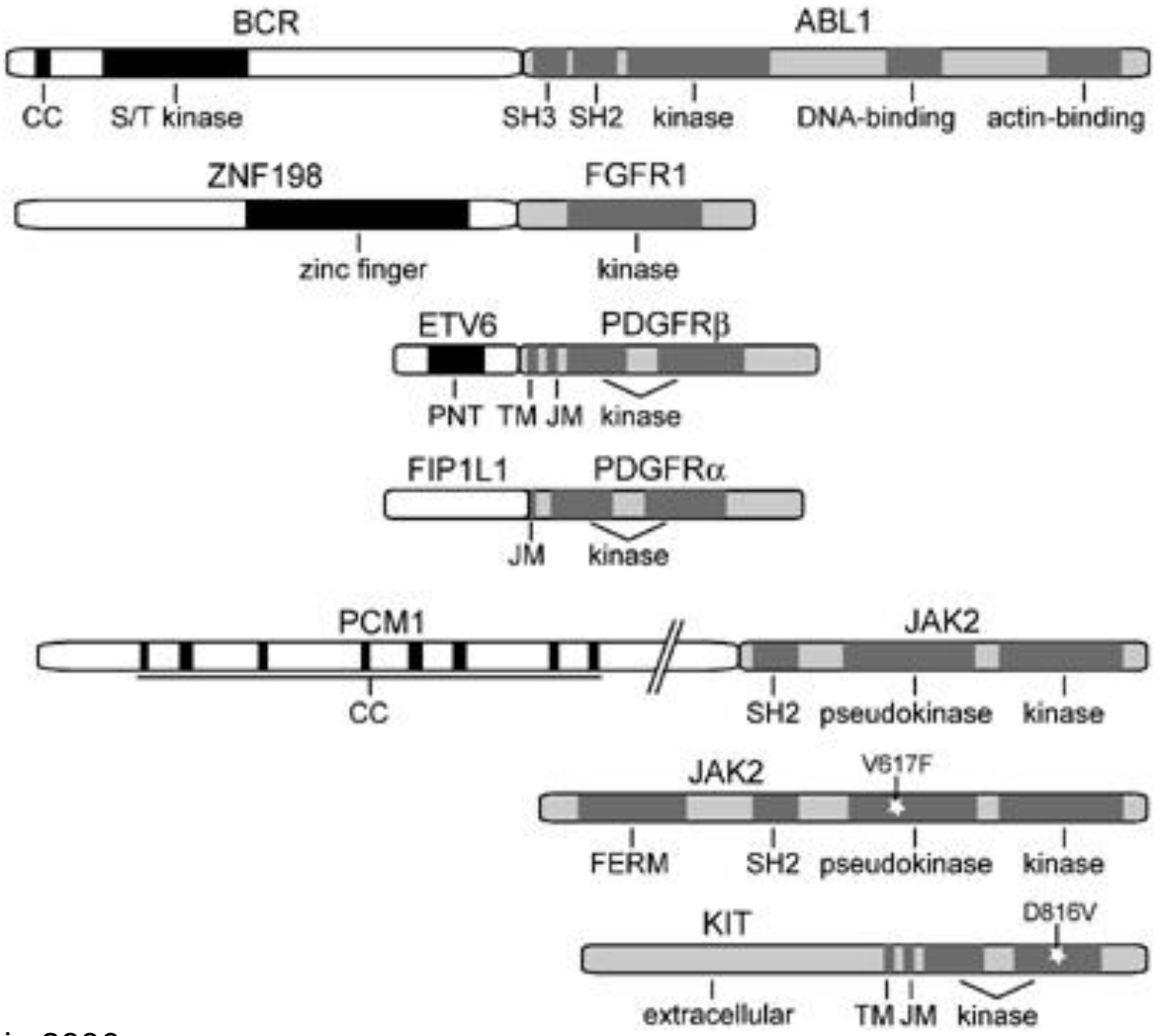
- **MDS/MPN display a combination of the features of MDS and MPN with dysplasia and excess production of blood cells in at least one of the myeloid lineages.**

Deininger MWN et al. Nature Review Cancer. 2017;17:425

Tyrosine kinase genes in MPN

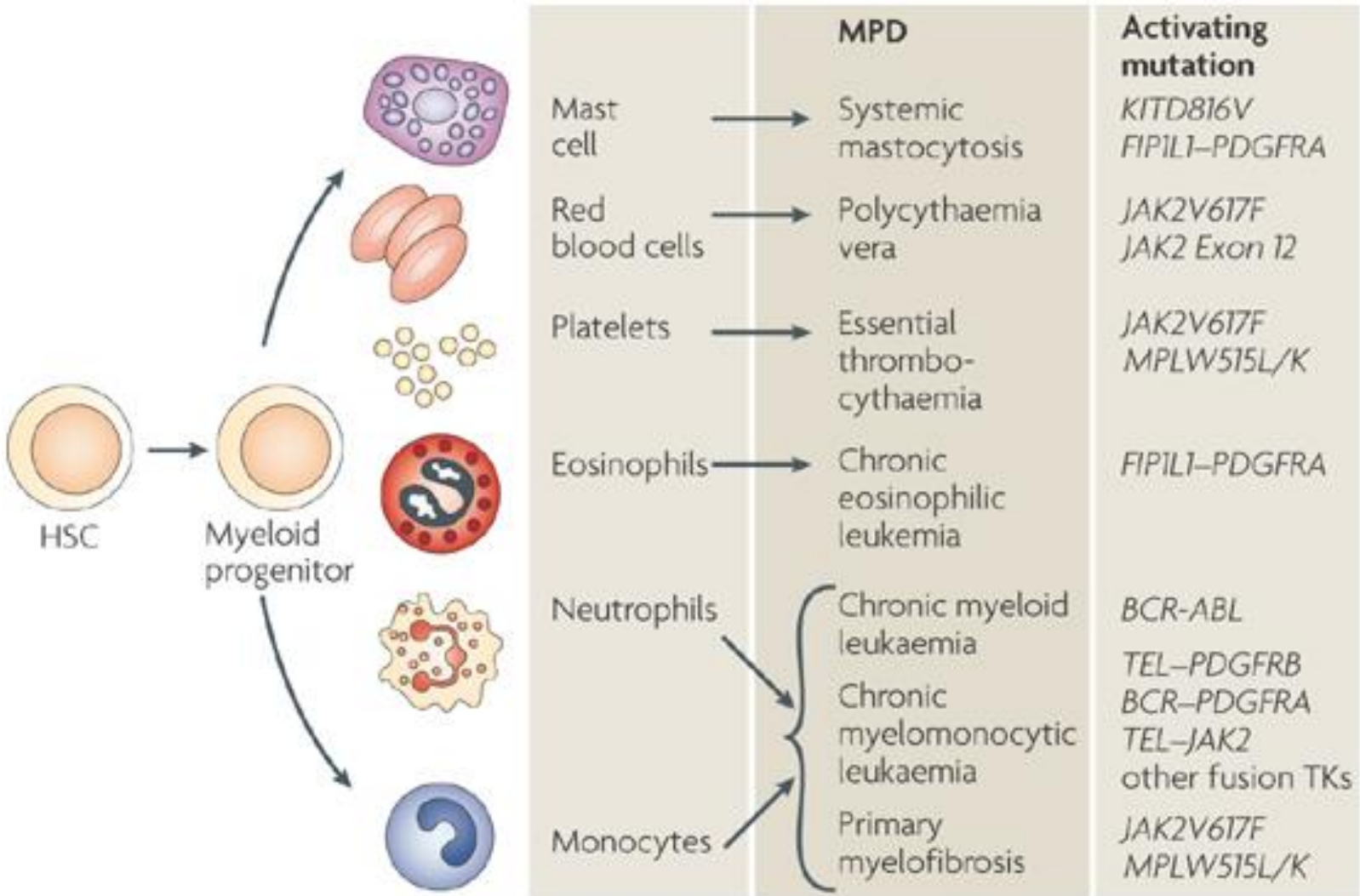
- **9q34: ABL1**
  - t(9;22)(q34;q11): BCR-ABL1 CML
- **5q33: PDGFRB**
  - t(5:12)(q33;p13): ETV6-PDGFRB CMML with eosinophilia
- **8p11: FGFR1**
  - t(8;13)(p11;q12): 8p11 CMPD
- **4q12: PDGFRA**
  - del4q12: FIP1L1-PDGFRA: HES
- **4q12: KIT**
  - KIT (D816V): systemic mastocytosis
- **9p24: JAK2**
  - JAK2(V617F): PV, ET, IM

Tyrosine kinase involved in the pathogenesis of CMPD



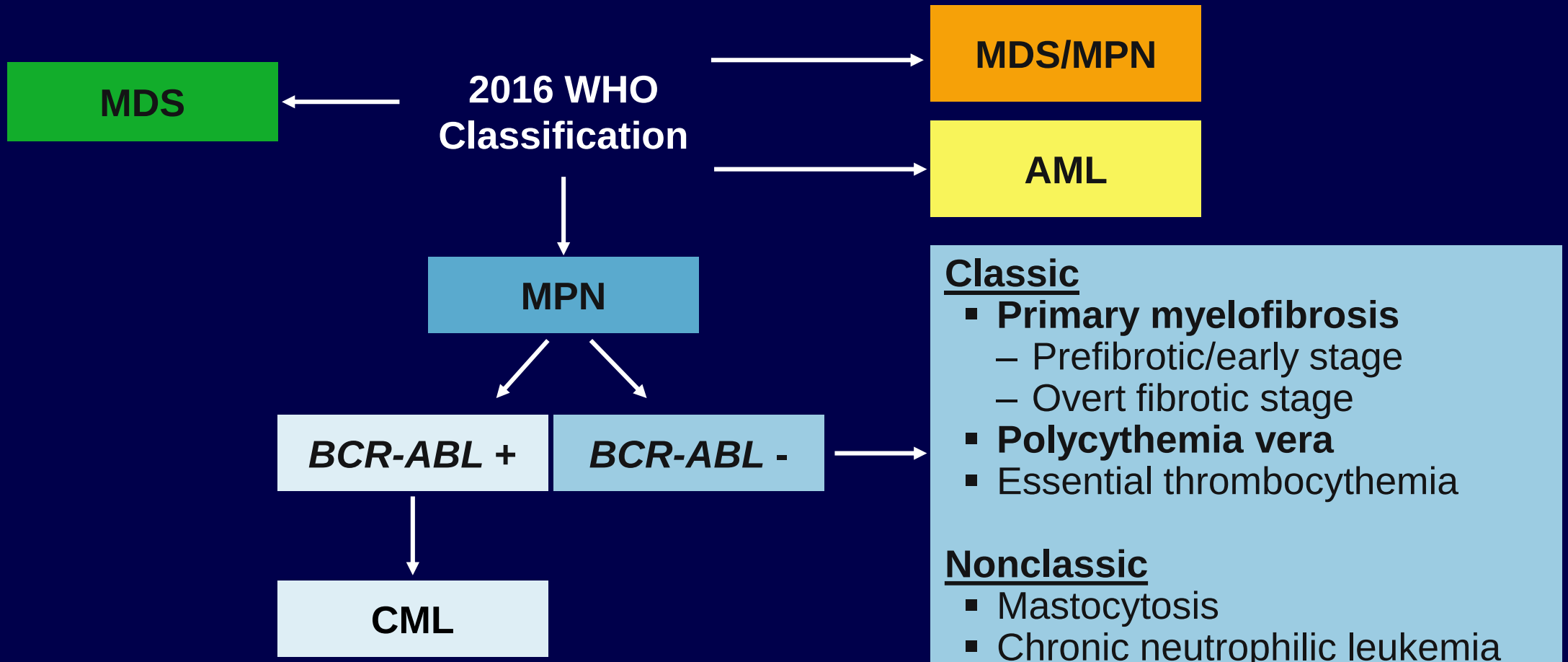
Keersmaecker Leukemia 2006

Classification and molecular pathogenesis of the MPD



Levine RL et al. Nat Rev Cancer. 2007;7:673-83

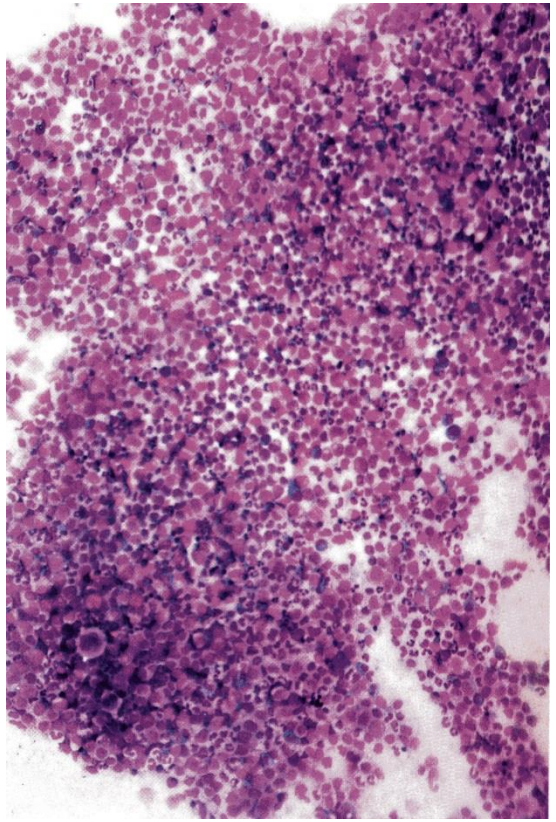
Myeloid Malignancies

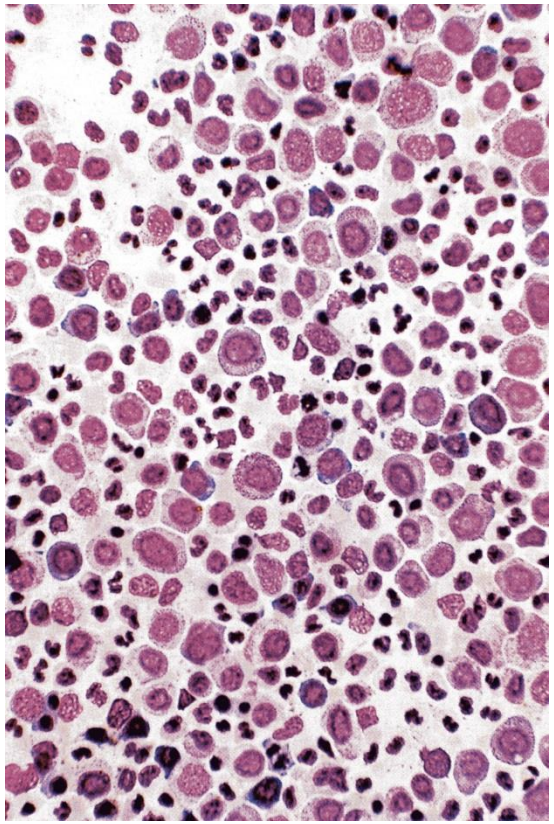


Arber DA, et al. Blood. 2016;127:2391-2405.

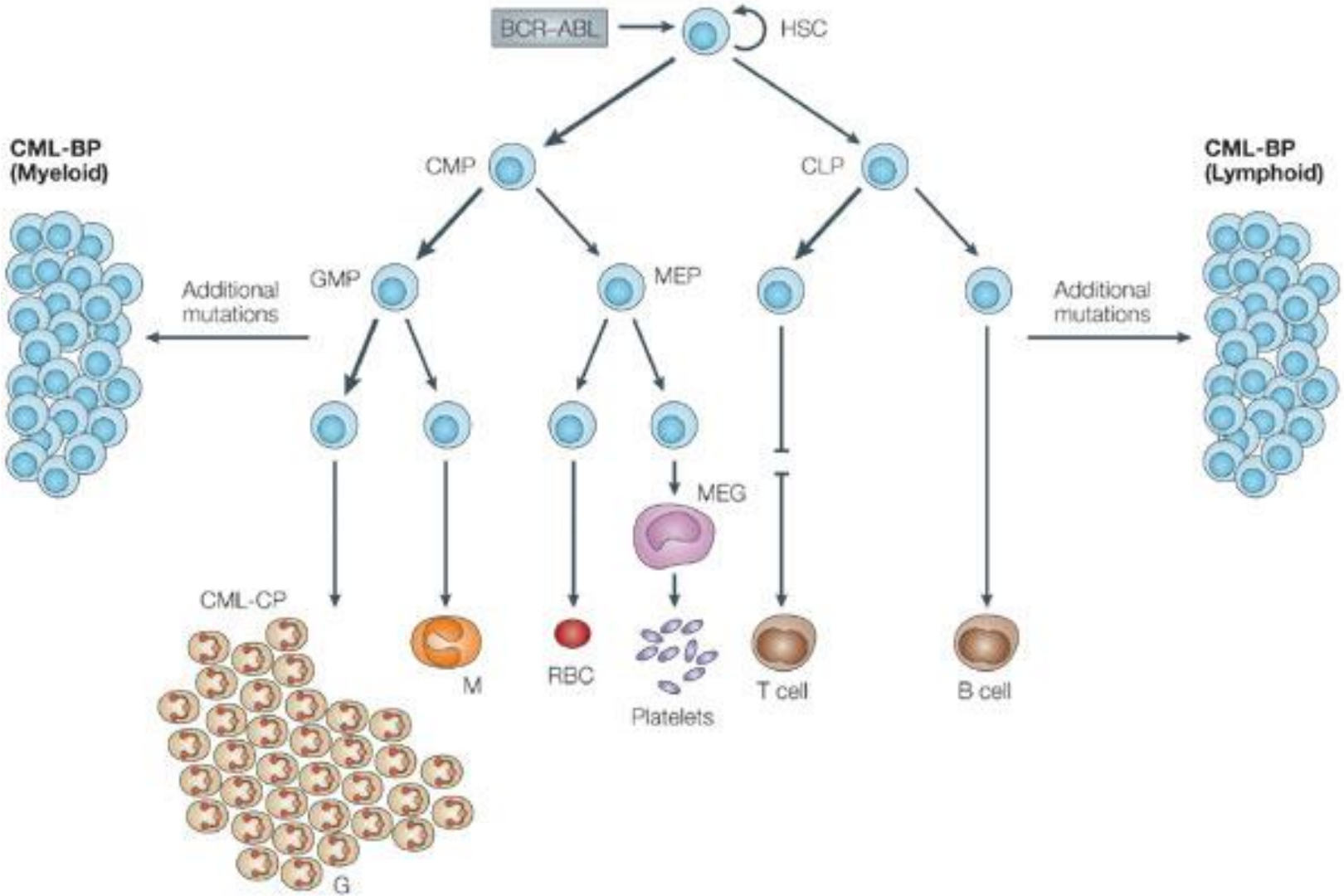
Slide credit: clinicaloptions.com

LEUCEMIA MIELOIDE CRONICA





The development of CML



Nature Reviews | Cancer

Milestones in the history of CML

1960: Abnormal chromosome 22 (Philadelphia chromosome) identified and associated with CML

1973: Translocation 9;22 defined

1983: Molecular studies of fusion abnormality of breakpoint cluster gene (bcr) with cellular abl gene (c-abl)

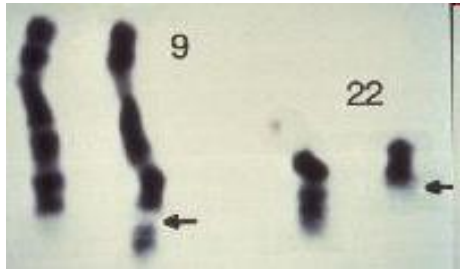
1984: Fusion cytoplasmic protein BCR-ABL found to alter cell proliferation, adhesion and survival

1984: Constitutive abnormal BCR-ABL tyrosine kinase activity defined

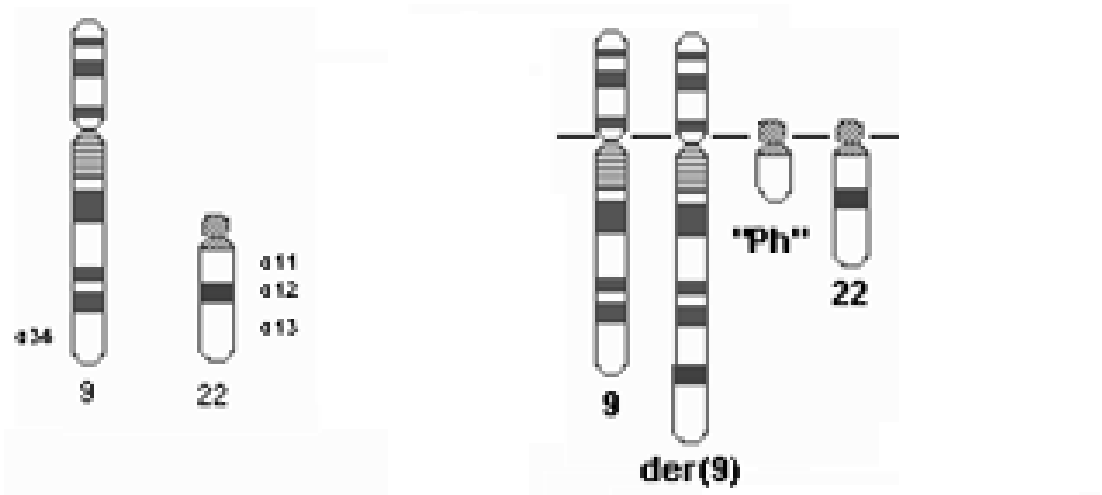
1988: Development of synthetic pharmacologic inhibitors that target tyrosine kinases

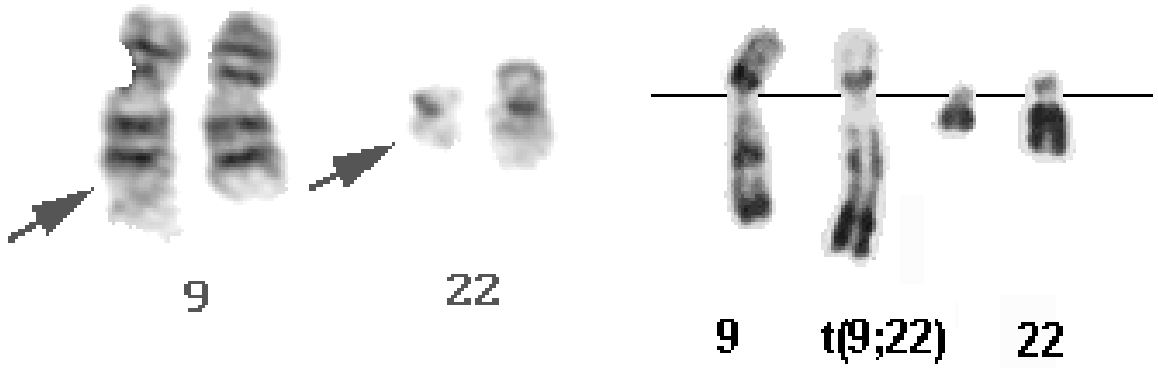
1998: Phase I clinical trials using STI-571 initiated

2001: STI571 is approved for treatment of CML that is refractory to IFN-therapy

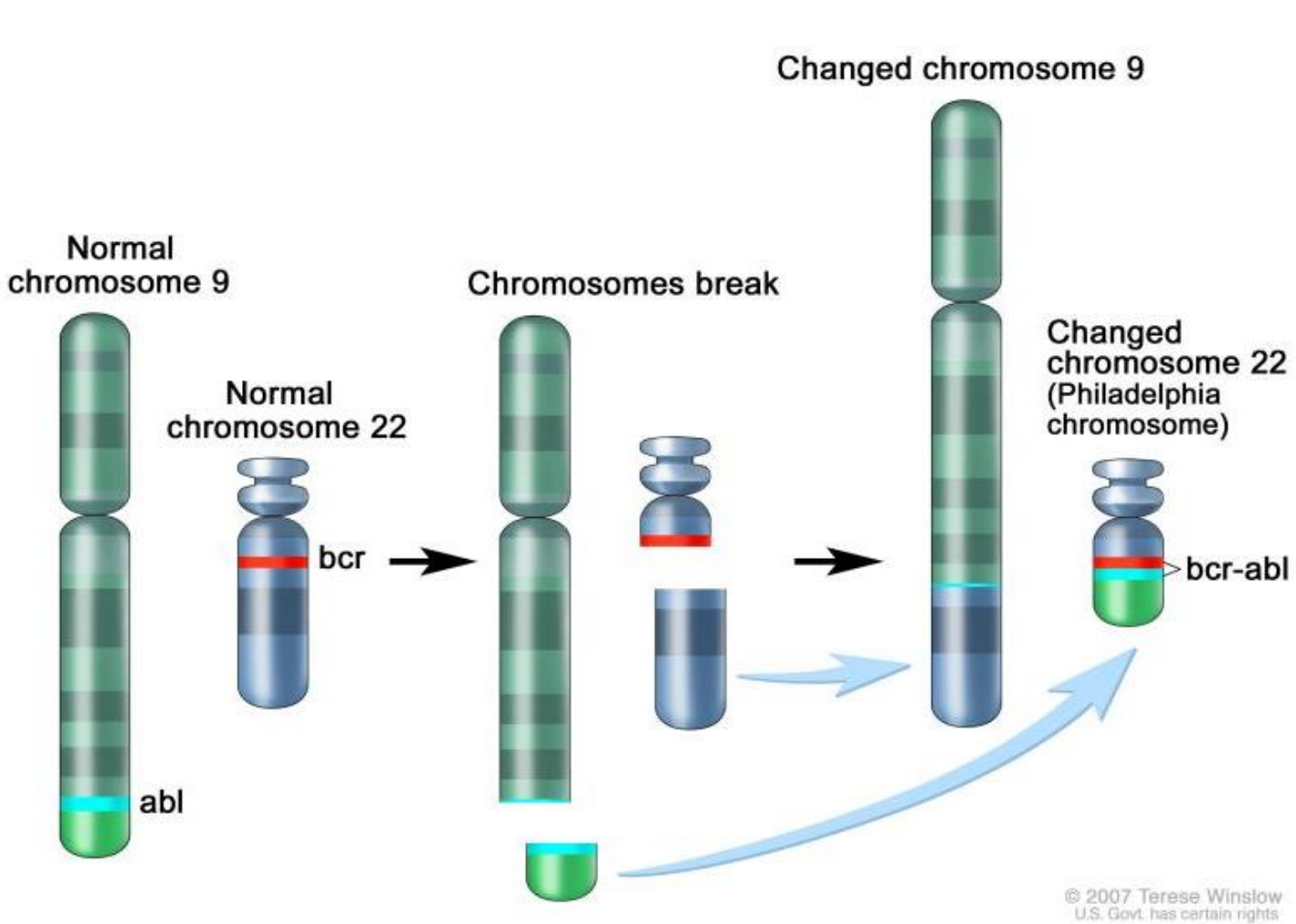


t(9;22)

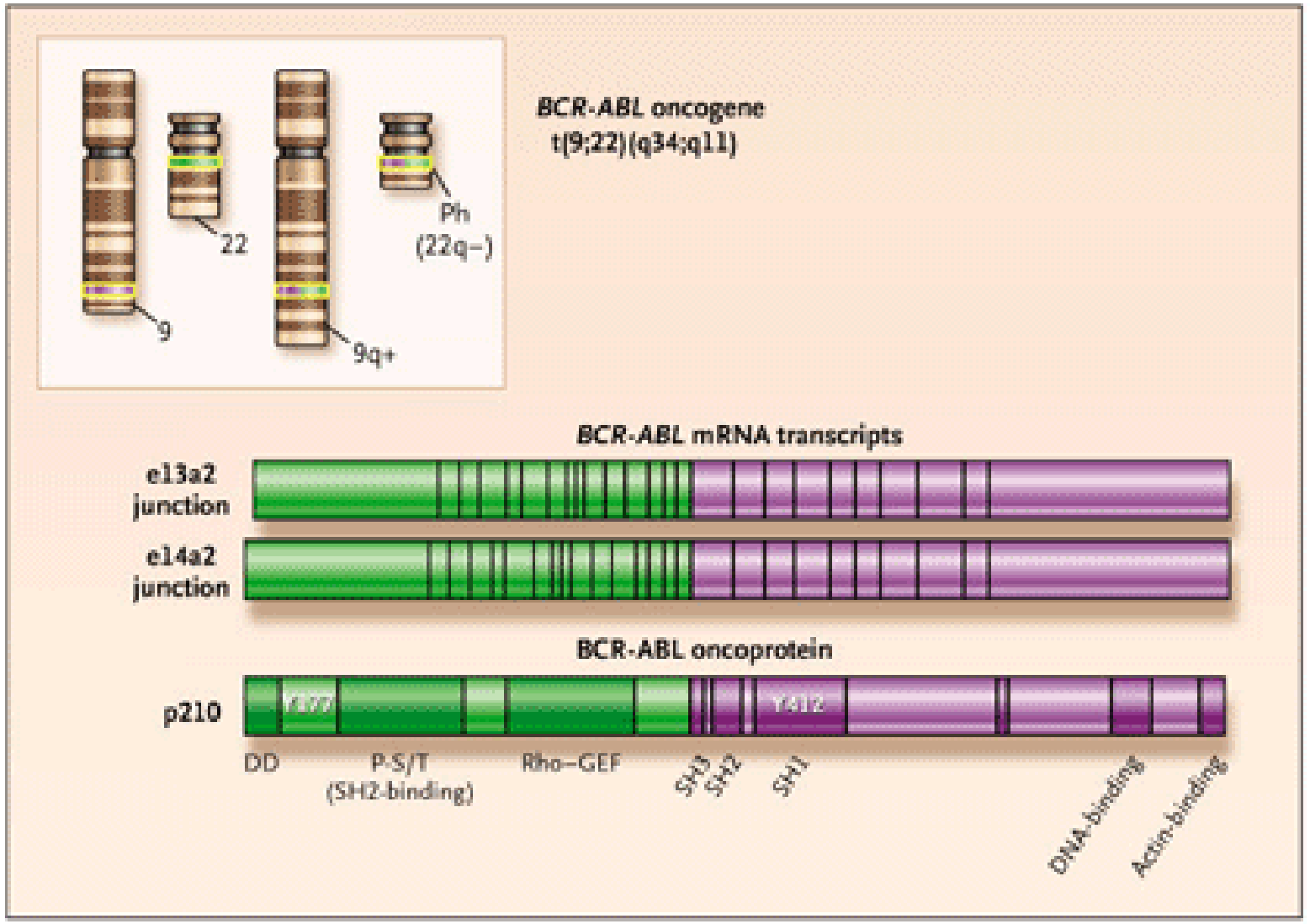




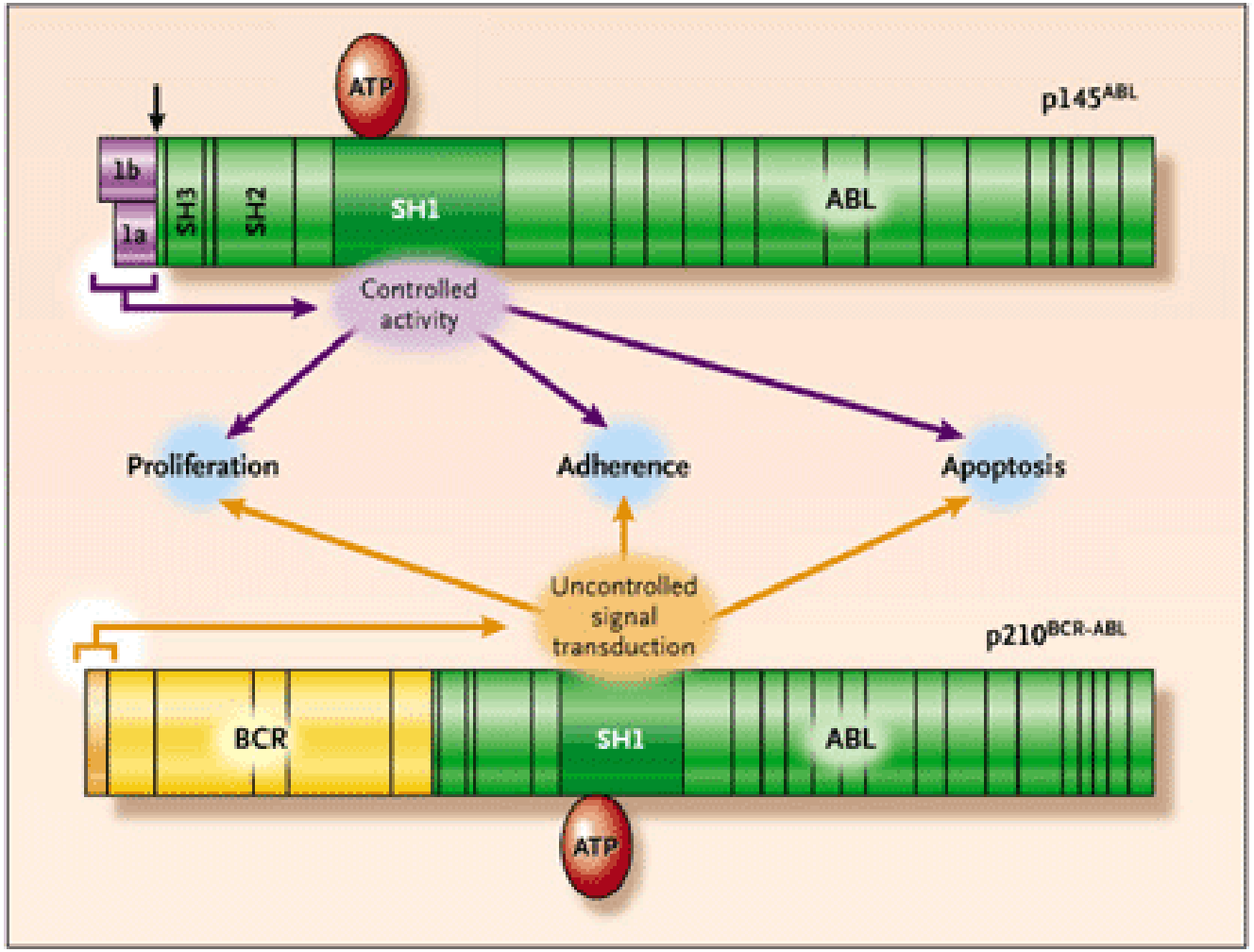
Schematic diagram of the translocation that creates the Philadelphia chromosome.



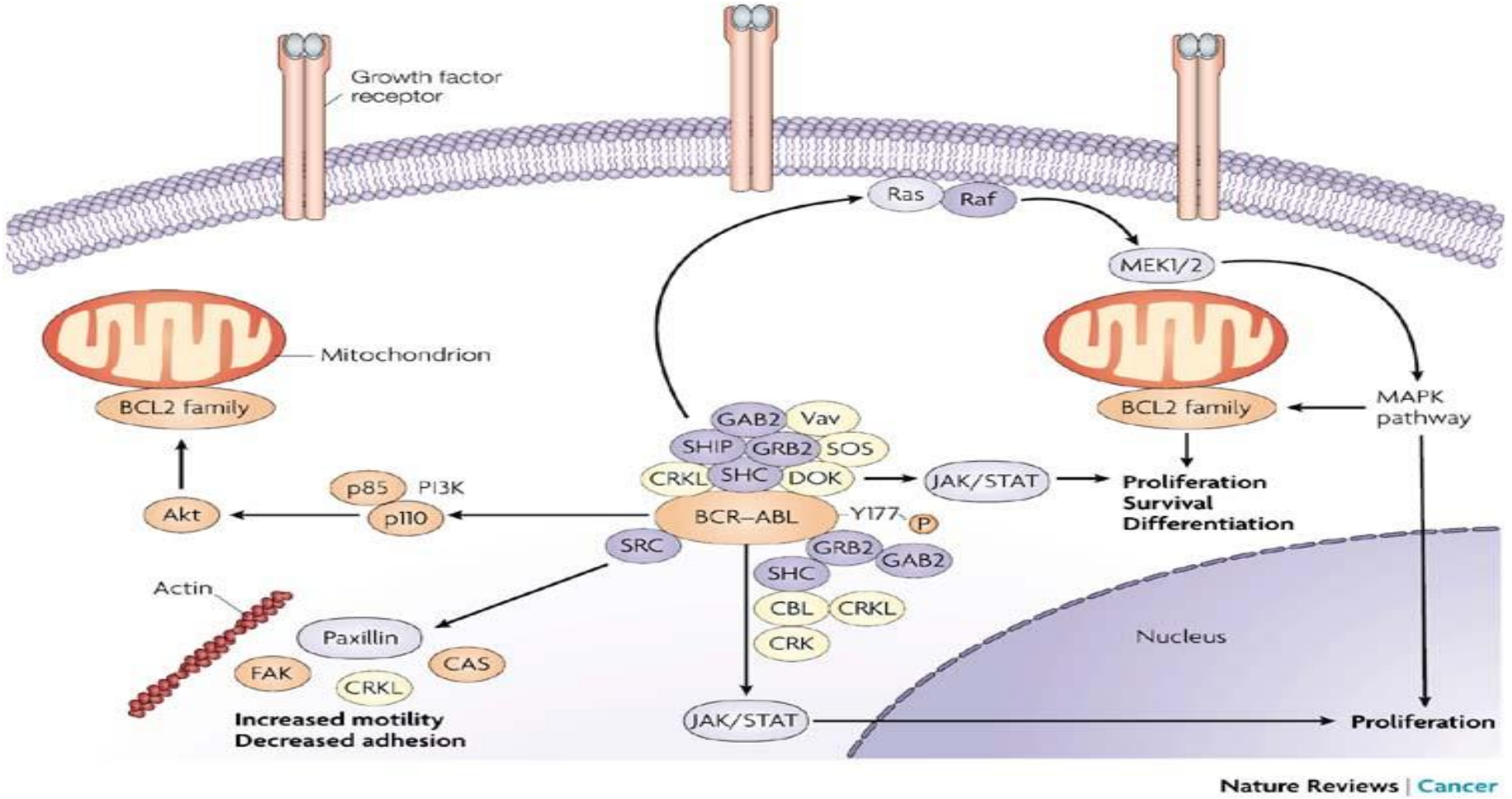
The t(9;22) translocation and ts products



Deregulation by BCR-ABL of proliferation, adherence, and apoptosis

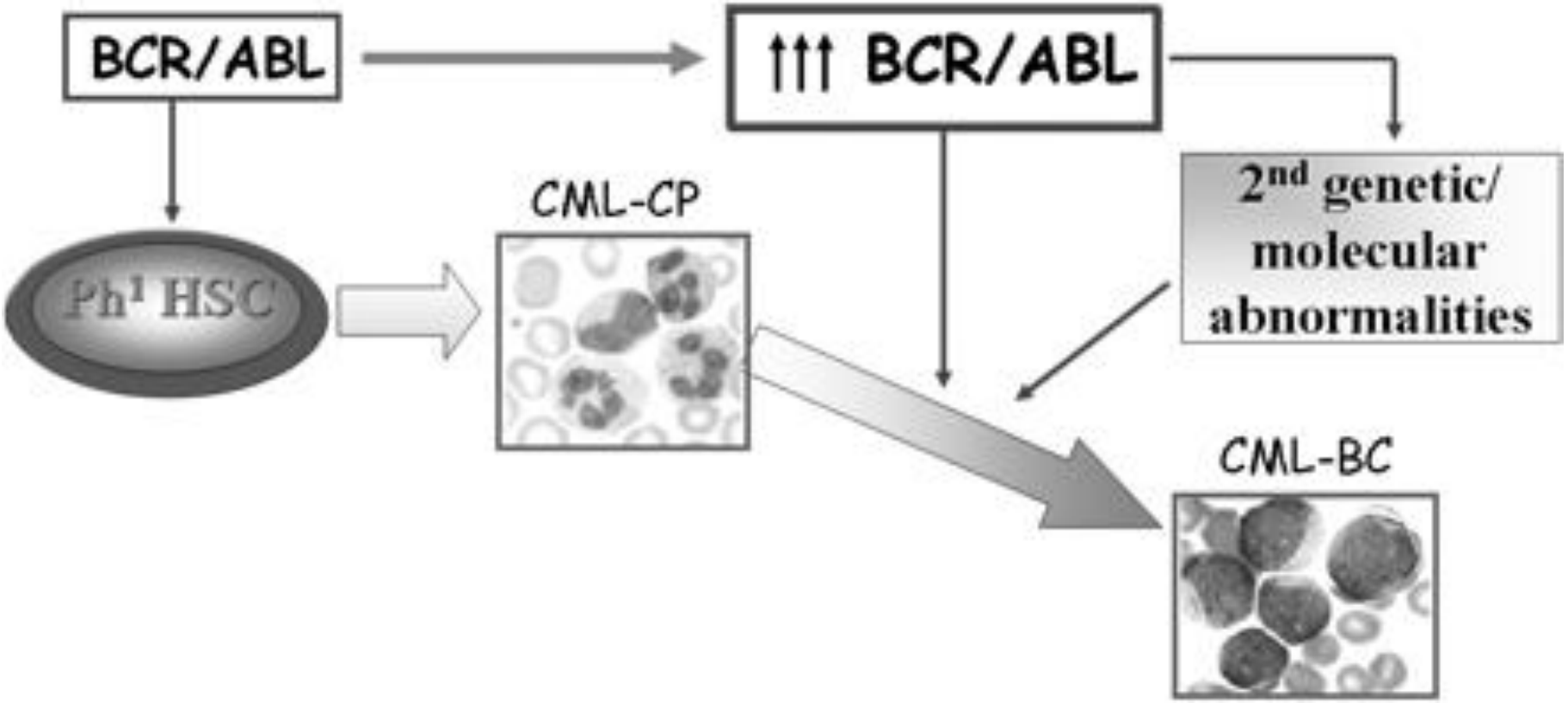


Main BCR/ABL-activated pathways regulating proliferation and survival of hematopoietic cells



Weisberg E et al. Nature Reviews Cancer 7:345-356;2007.

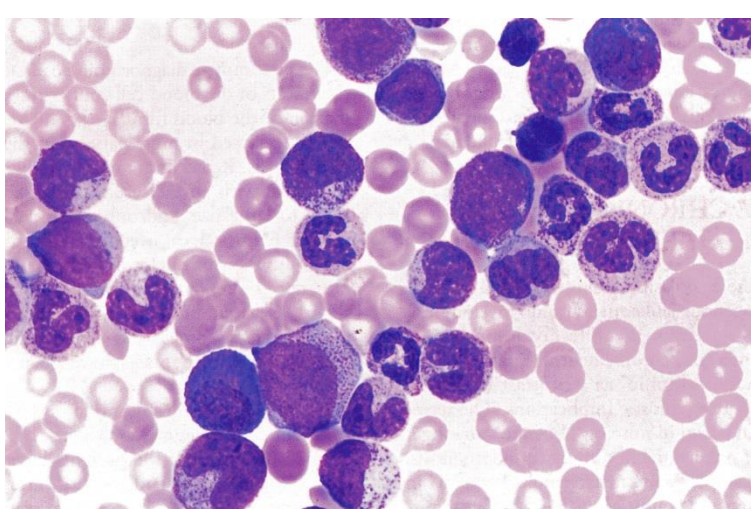
Possible mechanisms of CML disease progression

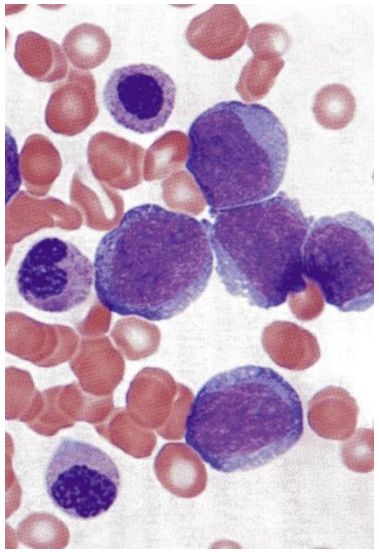


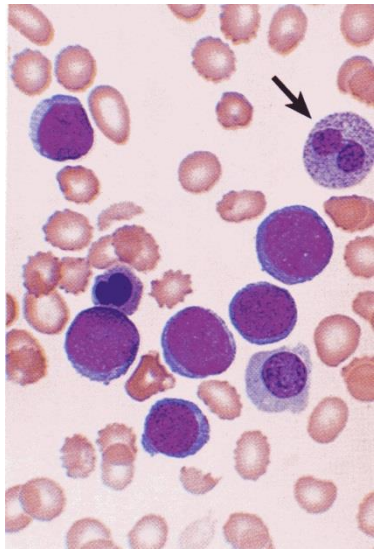
LMC: epidemiologia

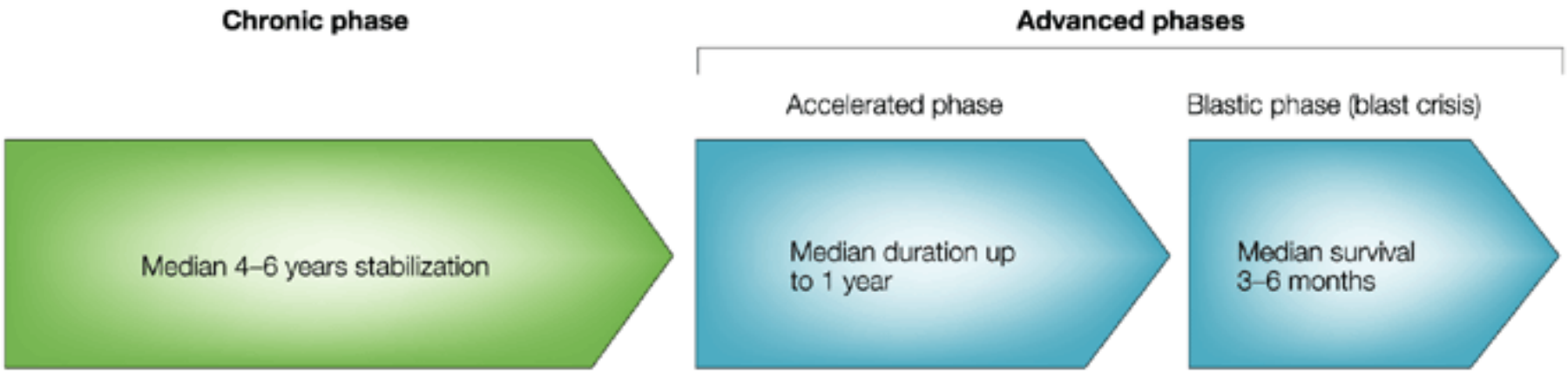
- Rappresenta il 15-20% di tutte le leucemie
- Incidenza 1-1,5 casi/100.000 individui anno
- M>F
- Età mediana: 50 anni

Clinical course of CML









Nature Reviews | Drug Discovery

Panel 1: Presenting symptoms and signs of chronic myeloid leukaemia

Frequent

- Fatigue
- Night sweats
- Malaise and weight loss
- Left upper quadrant pain, discomfort, satiety
- Splenomegaly

Less frequent

- Priapism
- Retinal haemorrhages
- Thrombosis, bleeding, or both
- Bone pain*
- Hepatomegaly
- Lymphadenopathy*
- Skin infiltration*
- Extramedullary mass (chloroma)*

*Should raise suspicions of presentation with advanced phase disease.

LMC: clinica

Asintomatica in un terzo dei casi

- Leucocitosi di diversa entità
- Splenomegalia

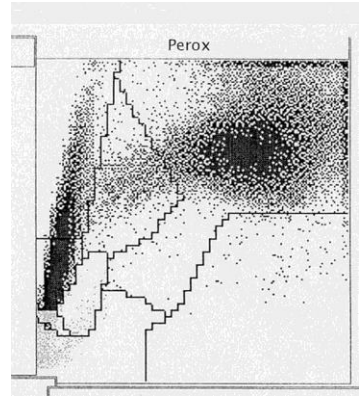
- **Fase accelerata/blastica:**
  - come leucemia

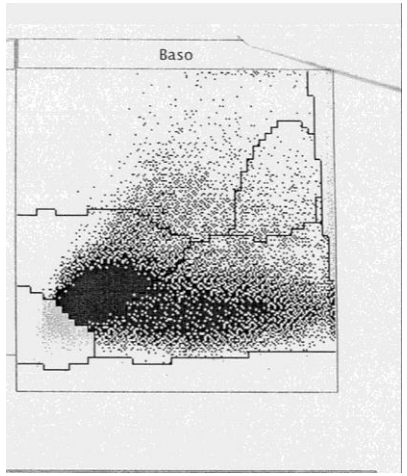
Apperley JF. Lancet 2015; 385: 1447–59

TEST	RISULT	PAT	NORMALI	UNITA'
WBC		107.0	(5.2 - 12.4)	x10.e3 /uL
RBC		3.71	(4.2 - 6.1)	x10.e6 /uL
HGB		11.7	(12 - 18)	g/dL
HCT		34.1	(37 - 50)	%
MCV	91.9		(80 - 99)	fL
MCH		31.5	(27 - 31)	pg
MCHC	34.3		(33 - 37)	g/dL
CHCM	34.0		(33 - 37)	g/dL
RDW		15.4	(11.5 - 14.5)	%
HDW	3.10		(2.2 - 3.2)	g/dL
PLT	177		(130 - 400)	x10.e3 /uL
MPV	8.1		(7.2 - 11.1)	fL
			(40 - 74)	%
			(19 - 48)	%
			(3.4 - 9)	%
			(0 - 7)	%
			(0 - 1.5)	%
			(0 - 4)	%
			(1.9 - 8)	x10.e3 /uL
			(0.9 - 5.2)	x10.e3 /uL
			(0.16 - 1)	x10.e3 /uL
			(0 - 0.8)	x10.e3 /uL
			(0 - 0.2)	x10.e3 /uL
			(0 - 0.4)	x10.e3 /uL
LI	2.42		(1.90 - 3)	
MPXI	9.5		(-10 - 10)	
WBCPEROX	106.2			
WBC BASO	107.0			

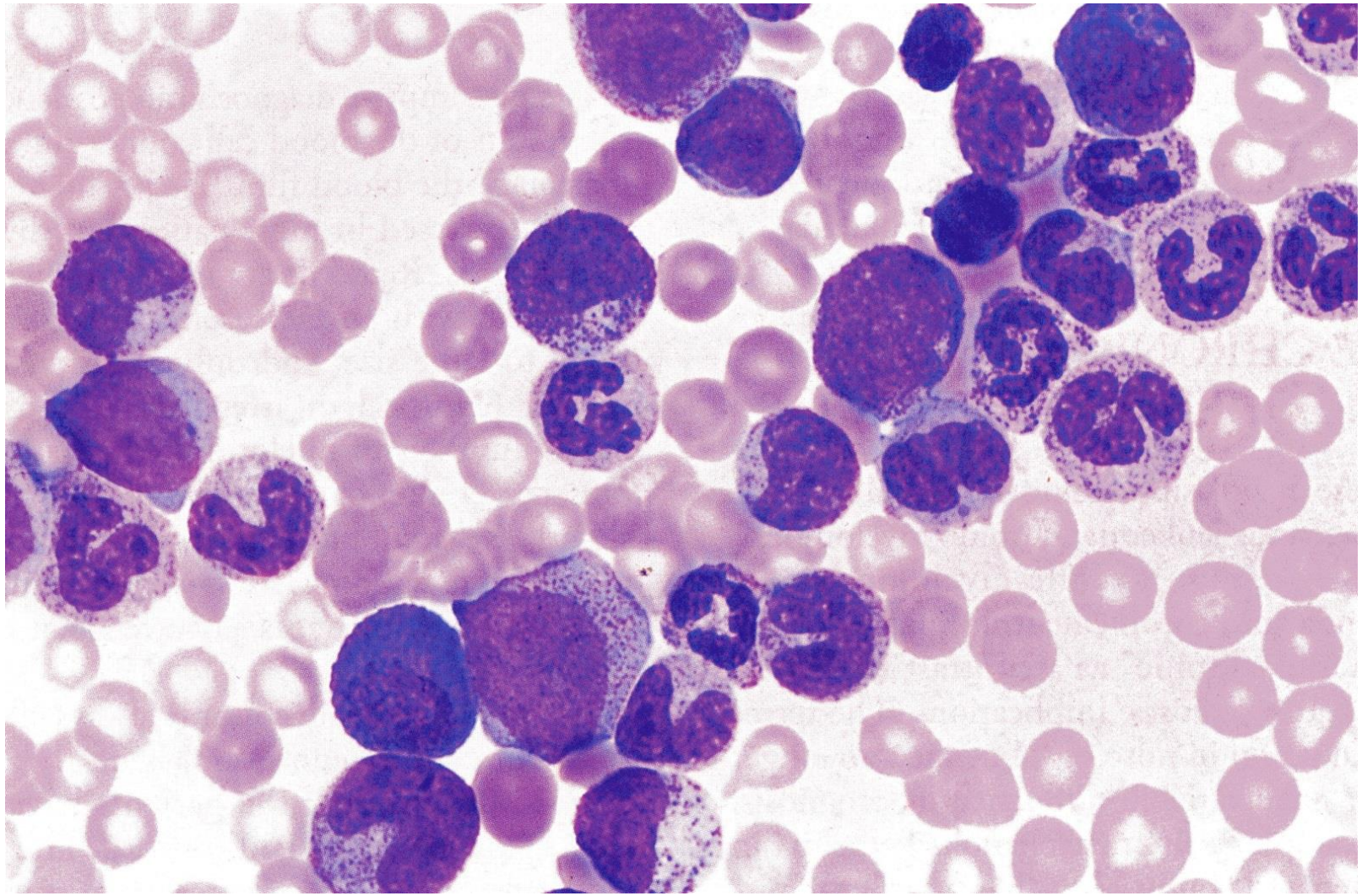
Formula al microscopio ottico
Neutrofili 66%
Promielociti 5%
Mielociti 6%
Metamielociti 6%
Blasti 1%
Linfociti 4%
Monociti 8%
Eosinofili 1%
Basofili 3%

IG	+++
LS	+
ATYP	++
BLASTS	++



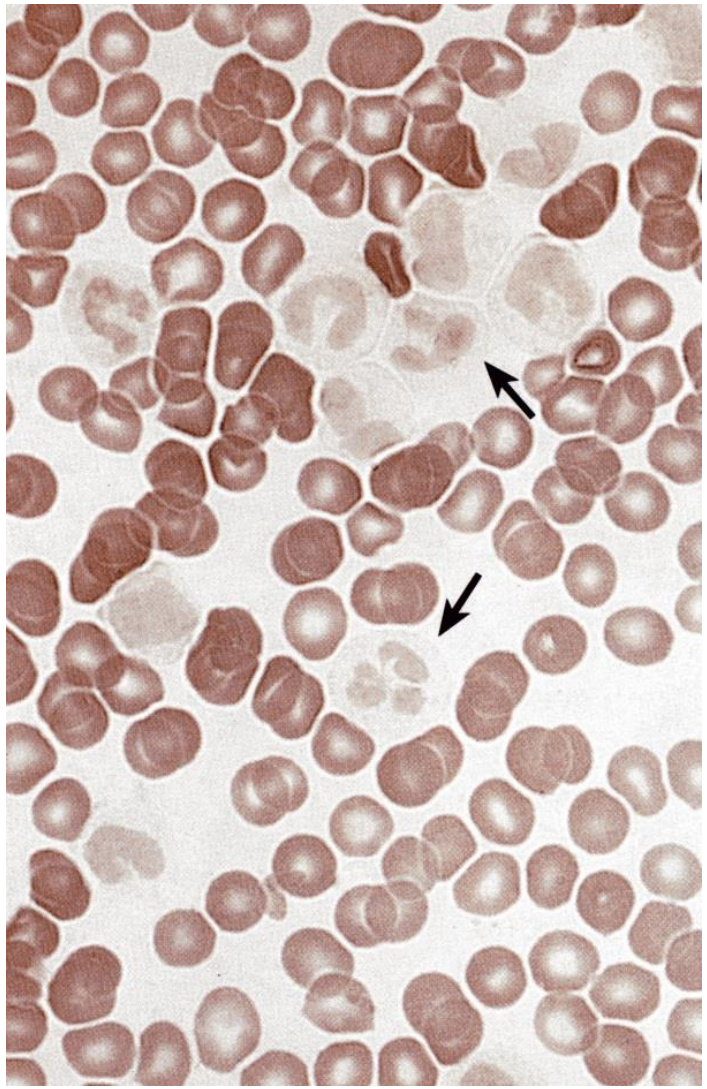


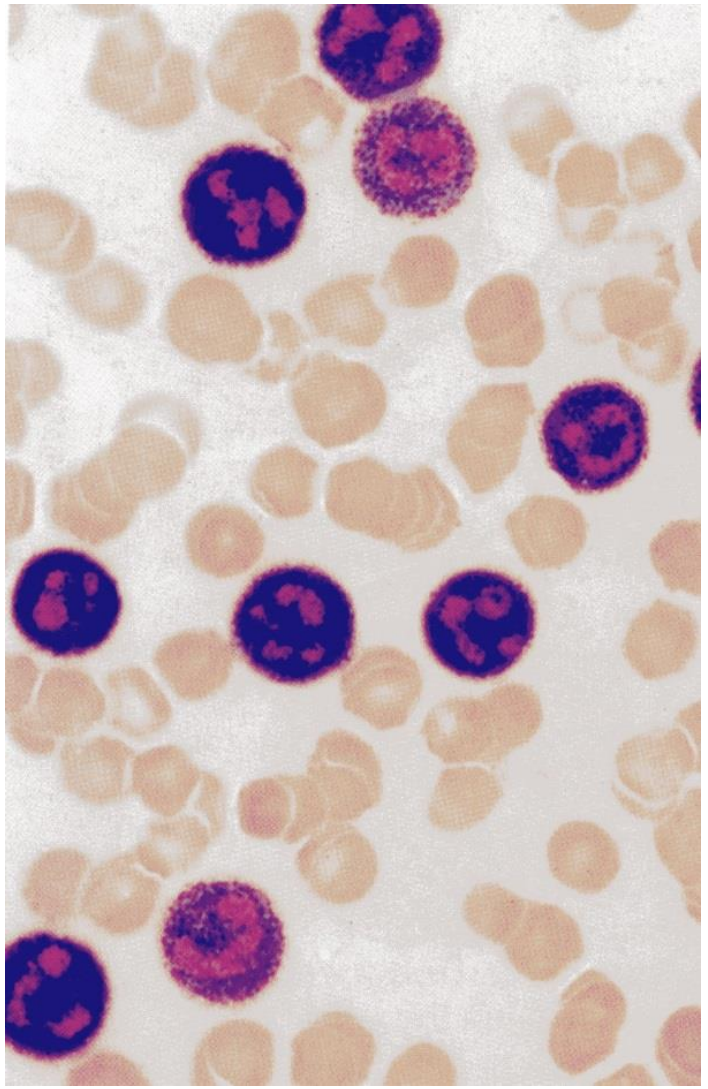
LEUCEMIA MIELOIDE CRONICA: fase cronica



CML: fosfatasi alcalina leucocitaria

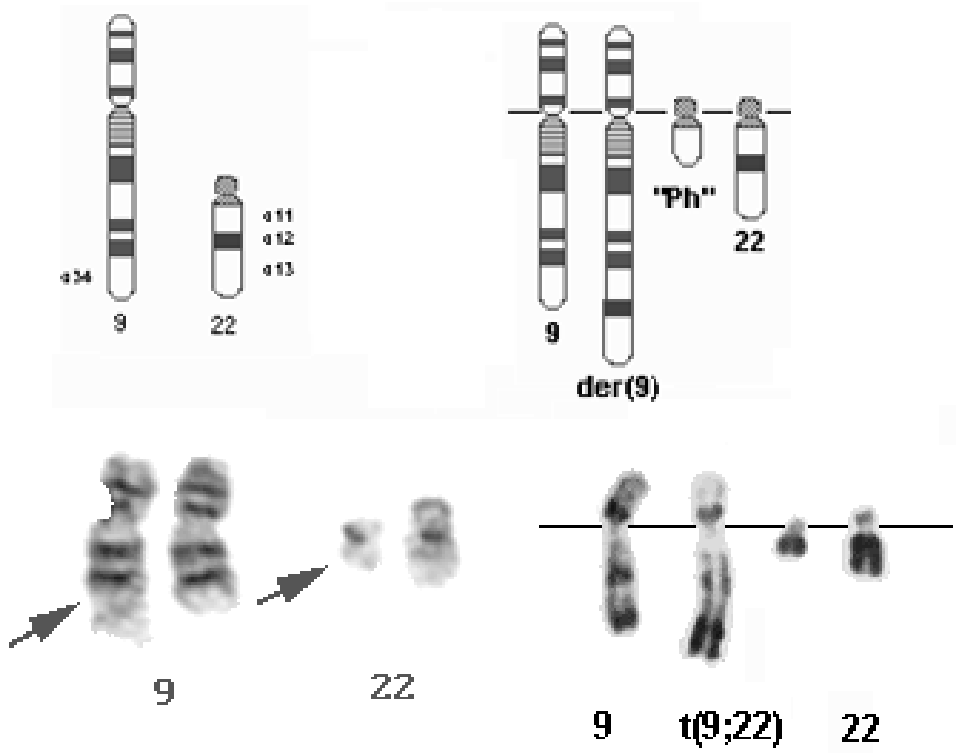
Leucemia mieloide cronica





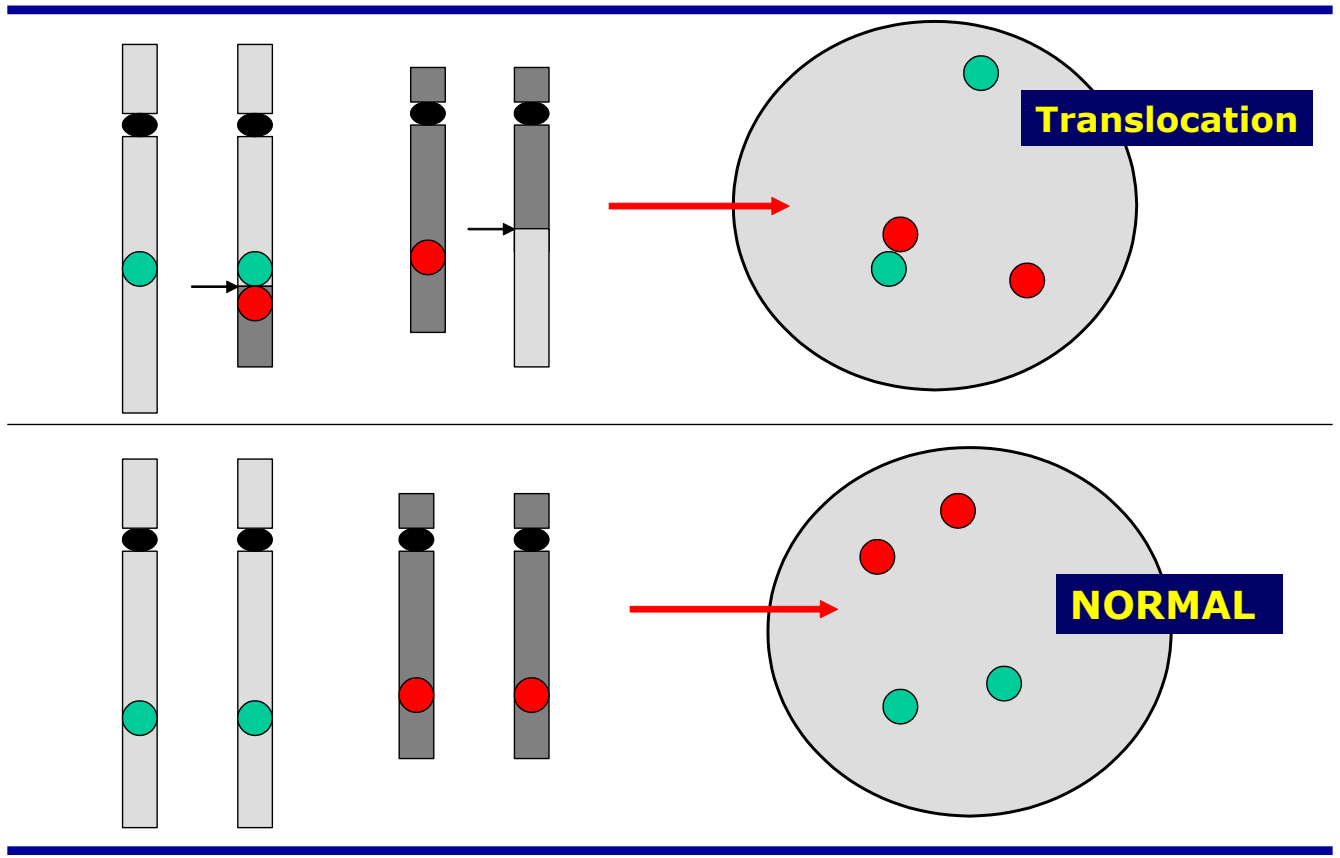
Policitemia vera

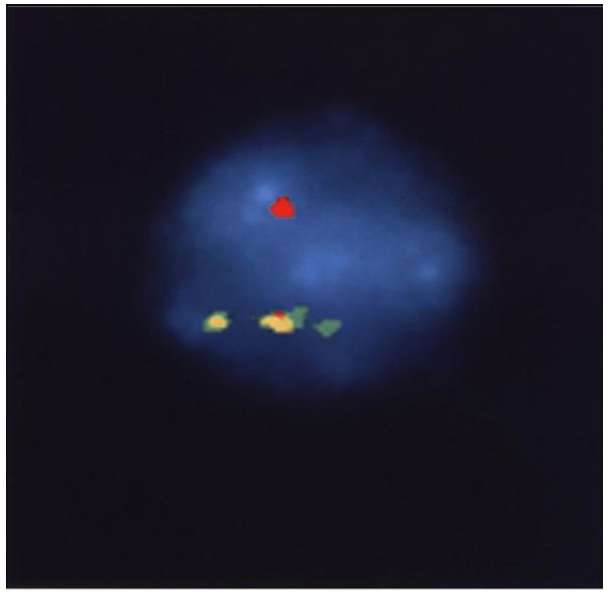
t(9;22): citogenetica

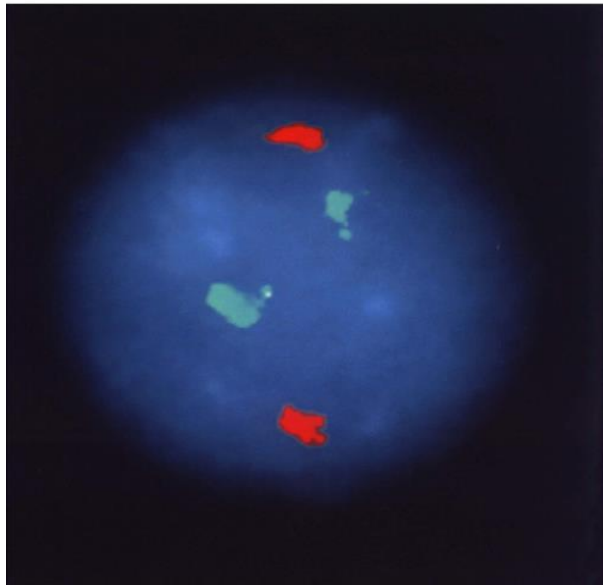


DUAL COLOUR FISH TO DETECT CHROMOSOME TRANSLOCATIONS

Fusion gene detection







Mandatory diagnostic tests for CML

1. **Blood count with blood film differential.**
   - This will typically show a so-called left shift of the myeloid series with the presence of rare blasts, promyelocytes, myelocytes and metamyelocytes, basophils, and eosinophils.
   - these must be accurately quantified as the results contribute to accurate identification of disease stage and prognostic scoring systems.

2. **Bone marrow aspirate with differential**
   - to include percentages of blasts, promyelocytes, myelocytes, eosinophils, and basophils.

3. **Cytogenetics and karyotyping by G banding:**
   - **FISH is not sufficient at diagnosis** as it is unable to identify chromosomal abnormalities in addition to the t(9;22) translocation

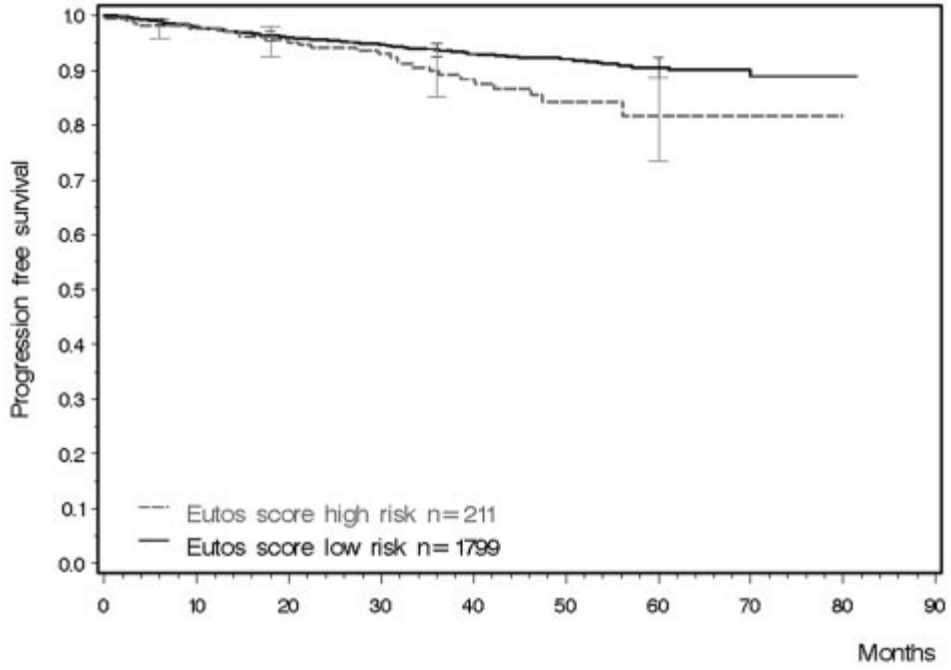
4. **Reverse transcriptase PCR for BCR-ABL1 mRNA transcripts.**

Apperley JF. Lancet 2015; 385: 1447–59

Calculation of relative risk

Study	Calculation	Risk definition by calculation
Sokal et al. 1984[7]	Exp 0.0116 × (age − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)^2 − 0.563] + 0.0887 × (blast cells − 2.10)	Low risk: <0.8 Intermediate risk: 0.8-1.2 High risk: >1.2
Euro Hasford et al. 1998[8]	0.666 when age ≥50 y + (0.042 × spleen) + 1.0956 when platelet count >1500 × 10^9L + (0.0584 × blast cells) + 0.20399 when basophils >3% + (0.0413 × eosinophils) × 100	Low risk: ≤780 Intermediate risk: 781-1480 High risk: >1480
EUTOS Hasford et al. 2011[9]	Spleen × 4 + basophils × 7	Low risk: ≤87 High risk: >87

Age is given in years. Spleen is given in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are given in percent of peripheral blood differential. All values must be collected before any treatment. To calculate Sokal and Euro risk score, go to http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html. To calculate EUTOS risk score, go to http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html.

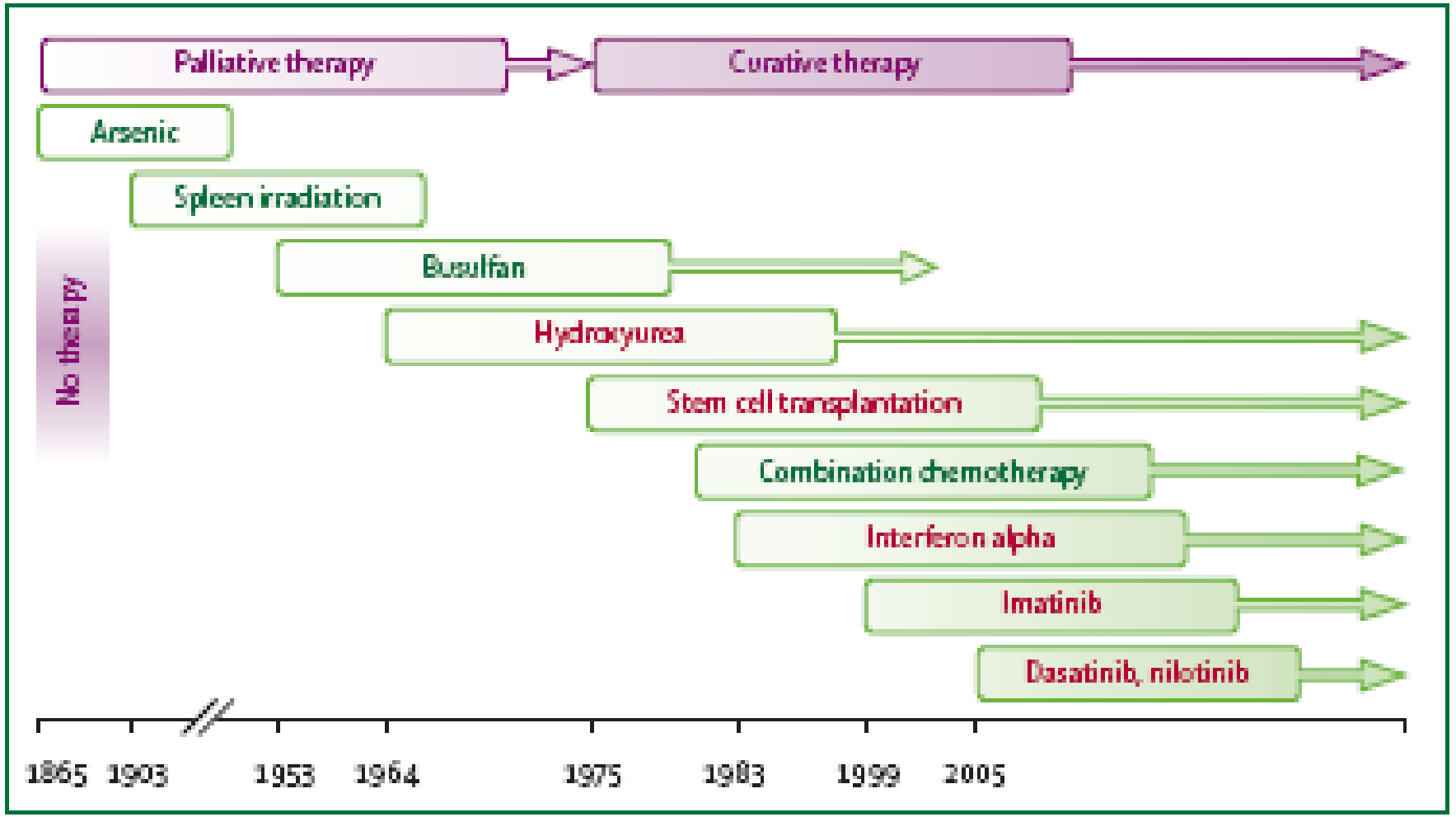


Baccarani et al. Blood. 2013;122(6):872-884)

PFS calculated for 2010 pts with follow-up (*P* .0069).

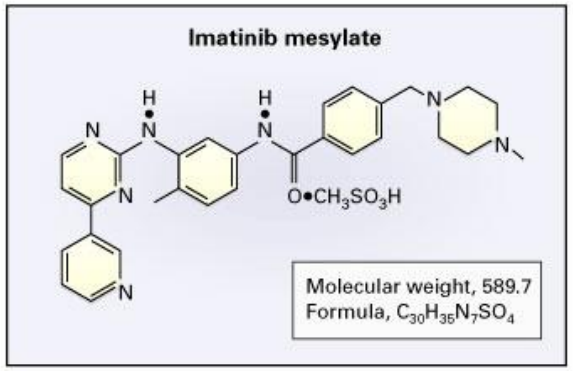
Hasford et al *Blood*. 2011;118(3):686-692)

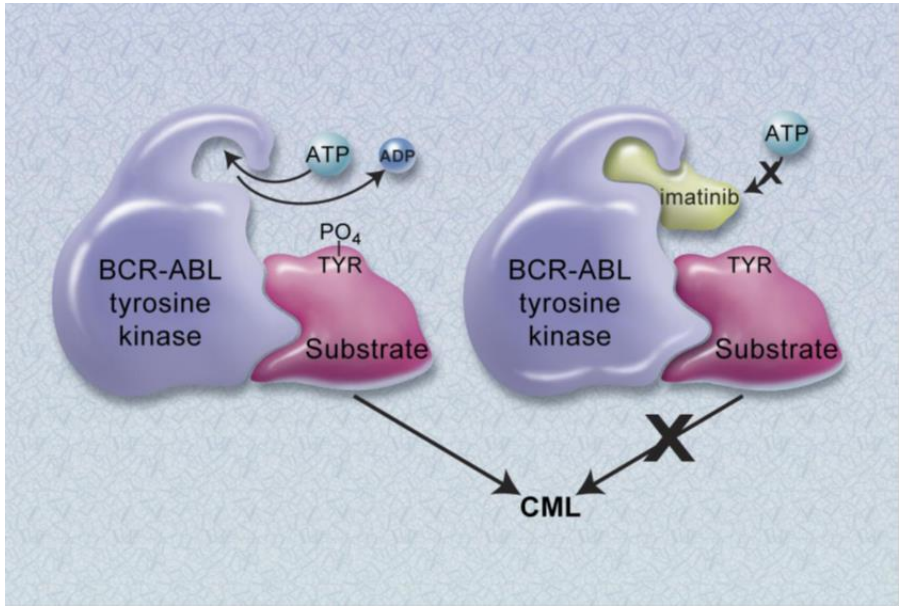
Development of treatments for CML



Lancet 2007; 370: 342–50

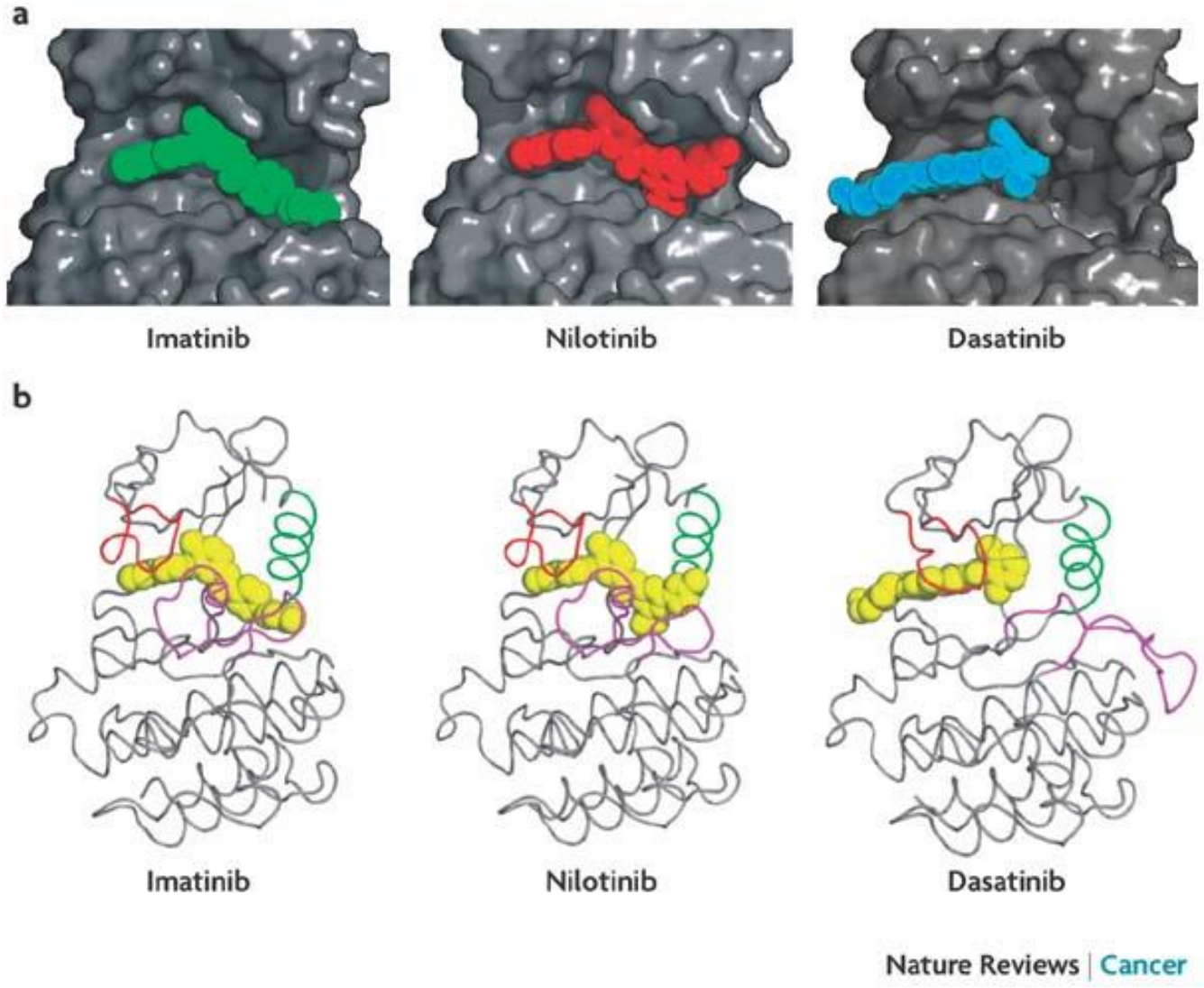
Imatinib Mesylate





Druker BJ. Blood. 2008;112:4808-4817)

Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant CML



Tyrosine Kinase Inhibitors Available for Chronic Myeloid Leukemia

Agent	Indications for use	Dosing	Key toxicities	Comment
Imatinib	CP—newly diagnosed CP, AP, BP—after interferon therapy	CP—400 mg once daily (up to 800 mg) AP, BP—600 mg once daily (up to 800 mg)	Peripheral edema, myalgias, nausea	First TKI approved for CML, has the longest duration of follow up
Nilotinib	CP—newly diagnosed CP, AP—patients with resistance or intolerance to prior therapy	CP (newly diagnosed) — 300 mg twice daily CP (prior therapy), AP—400 mg twice daily	QT prolongation, pancreatitis, hyperglycemia, hepatotoxicity, vascular events	Superior to imatinib in a randomized study for newly diagnosed patients
Dasatinib	CP—newly diagnosed CP, AP, BP—patients with imatinib resistance or intolerance	CP—100 mg once daily AP, BP—140 mg once daily	Pleural effusions, hematologic, pulmonary hypertension, hemorrhage	Superior to imatinib in a randomized study for newly diagnosed patients
Bosutinib	CP, AP, BP—patients with resistance or intolerance to prior therapy	500 mg once daily	Diarrhea, hematologic, hepatotoxicity	In a randomized study versus imatinib, failed to meet the primary endpoint (though was not worse)
Ponatinib	CP, AP, BP—patients with T315I mutation CP, AP, BP—patients in which no other TKI is indicated	45 mg once daily	Hypertension, arterial and venous thrombotic events, heart failure, pancreatitis, hepatotoxicity	Only available TKI active against T315 mutations

Jabbour AJH 2016

	Imatinib		Dasatinib		Nilotinib		Bosutinib		Ponatinib	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Fatigue	++++	+	+++	+	++++	-	NR	NR	++++	++
Rash	++++	++	+++	+	++++	-	++++	++	++++	++
Headache	+++	-	++++	-	++++	-	++++	++	++++	++
Myalgia and arthralgia	+++++	-	++++	-	NR	NR	++	-	++++	++
Bone pain	+++	++	NR	NR	NR	NR	++	-	NR	NR
Diarrhoea	++++	++	++++	+	+++	+	+++++	++++	NR	NR
Nausea	++++	-	++++	-	+++	+	++++	++	++++	+
Vomiting	+++	-	+++	-	++	-	++++	++	NR	NR
Abdominal pain	++	-	NR	NR	NR	NR	++++	++	++++	+++
Pancreatitis	+	+	NR	NR	++	++	NR	NR	+++	+++
Bleeding events (GI, CNS)	+	+	++	++	++	+	NR	NR	NR	NR
Oedema	++++	++	++++	++	+++	-	+++	++	NR	NR
Pleural effusion	++	+	++++	++	++	+	NR	NR	NR	NR
PAH	NR	NR	+	+	NR	NR	NR	NR	NR	NR
QT prolongation	+	NK	++	NK	++	NK	NR	NR	NR	NR
Hypertension	NR	NR	NR	NR	NR	NR	NR	NR	+++	++
PAOD	-	-	NR	NR	++	++	NR	NR	++++	++++
Elevated lipase	++++	+++	NG	-	++++	+++	++++	+++	++++	++++
Elevated ALT	++++	++	NG	+	+++++	+++	+++++	++++	++++	++
Low phosphate	+++++	++++	NG	+++	++++	+++	++++	++	NR	NR
Raised glucose	-	-	-	-	++++	+++	-	-	NR	NR
Anaemia	+++++	+++	+++++	++++	++++	++	+++++	+++	+++	+++
Neutropenia	+++++	++++	+++++	++++	++++	+++	++++	++++	++++	++++
Thrombocytopenia	+++++	++++	+++++	++++	++++	+++	++++++	++++	++++	++++
Abn platelet function	+++++	NK	+++++	NK	-	-	++++	NK	NR	NR
LGL expansion	NR	NR	++++	NK	NR	NR	NR	NR	NR	NR

Data derived from studies of first line use with the exception of ponatinib (so far used only as second or subsequent line) and rare events such as PAH, PAOD, and abnormal platelet function.[72,78,79,82,83,86,92,93] +=<1% of patients. ++=1–5%. +++=5–10%. ++++=10–50%. +++++=50–100% =specifically reported as absent. NR=not reported. GI=gastrointestinal. PAH=pulmonary arterial hypertension. NK=effect of side-effect not known. PAOD=peripheral arterial occlusive disease. NG=data not given. ALT=alanine transaminase. Abn=abnormal. LGL=large granular lymphocytes.

Table 4: **Most frequently reported side-effects of tyrosine-kinase inhibitors**

Apperley JF. Lancet 2015; 385: 1447–59

Chronic phase treatment recommendations for first, second, and subsequent lines of treatment

First line
Imatinib or nilotinib or dasatinib
HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
Second line, intolerance to the first TKI
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)
Second line, failure of imatinib first line
Dasatinib or nilotinib or bosutinib or ponatinib
HLA type patients and siblings
Second line, failure of nilotinib first line
Dasatinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Second line, failure of dasatinib first line
Nilotinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Third line, failure of and/or intolerance to 2 TKIs
Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T315I mutation
Ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT

In first line, the choice is among 3 TKIs that are currently approved and available, but are not always reimbursable, worldwide. The approved doses are 400 mg once daily for imatinib, 300 mg twice daily for nilotinib, and 100 mg once daily for dasatinib. Higher doses of all 3 drugs were tested, and a superiority of a higher dose was reported only in 1 study of imatinib.[31] There are no recognized and solid criteria that can be recommended for making the choice. Provisional clinical criteria can be the characteristics of the disease (high risk, CCA/Ph+) on one hand, and the relationship between the patient (comorbidities) and the safety profile of the drugs on the other hand. In second line, a change of drug is preferred to an increase of imatinib dose.[5,42-50] To make the switch from one TKI to another, there are things that must always be taken into account: the presence and type of a mutation (see Table 4), the side effects and the toxicity of the previous TKI, and different comorbidities that can be of concern with different TKIs. The definition of intolerance may sometimes be objective and based on evidence, but sometimes is subjective and open to criticism. Experience and common sense suggest that a patient who is intolerant to 1 TKI can easily respond to other TKIs, whereas a patient in whom 1 TKI has failed, and who is intolerant to another TKI, is at considerable risk of subsequent treatment failure. Recommendations for alloSCT are based on the results from HLA-identical siblings or HLA-matched unrelated donors, myeloablative and RIC, T-cell replete or T-cell depleted. They do not include cord blood or haplotype-matched donors, or experimental conditioning regimens. The EBMT risk score[125] is still of value, although insufficient numbers of patients have been transplanted in recent years and after TKI therapy to allow a robust reanalysis.

Baccarani et al. Blood. 2013;122(6):872-884)

Box 2 | Concise recommendations for first and subsequent lines of treatment in CML

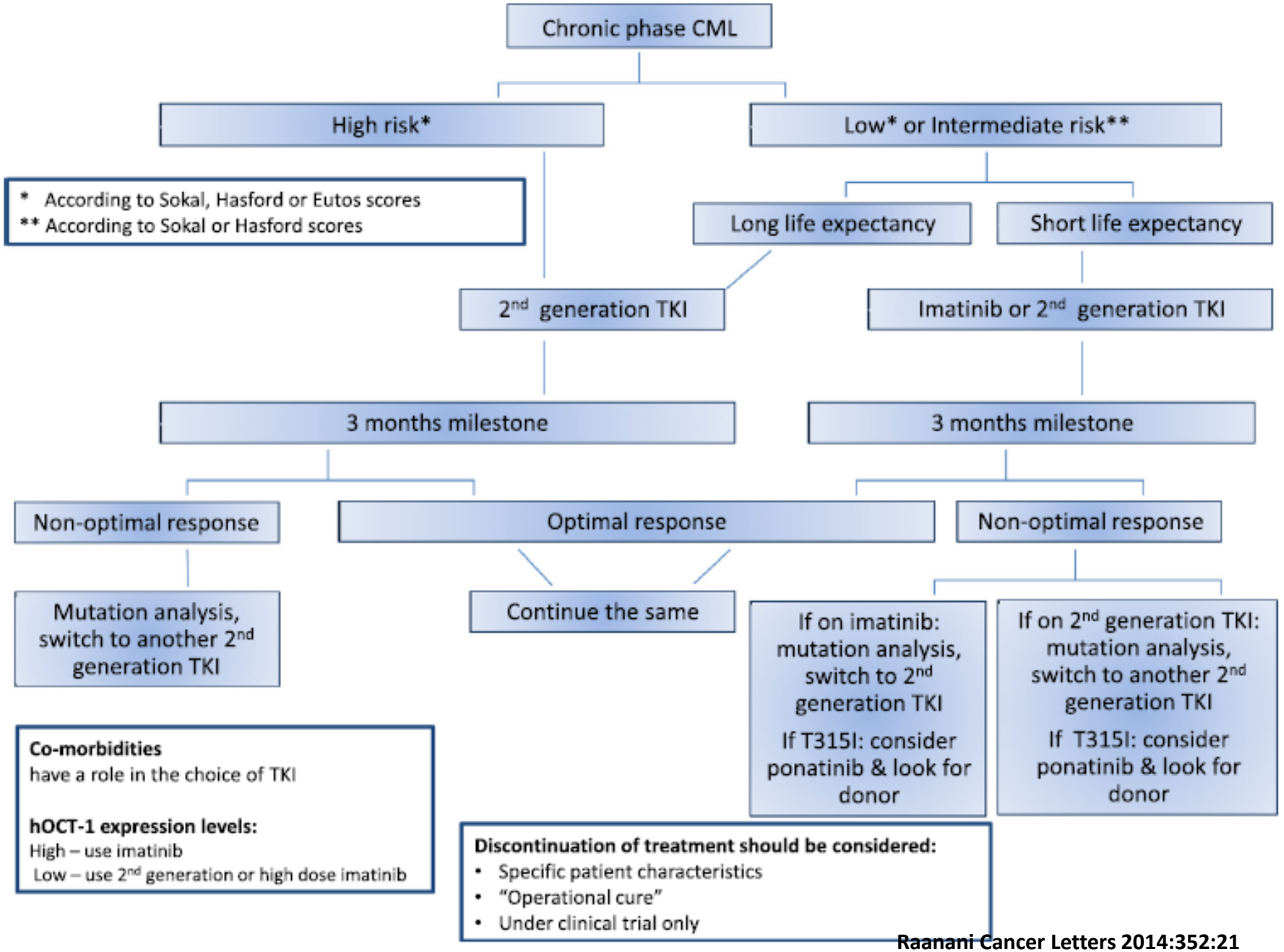
Frontline treatment

- No selective approach is recommended because overall survival rates are similar for patients with chronic-phase CML, independent of the tyrosine kinase inhibitor (TKI) used in the first line[10]
- Early molecular response (EMR) failure rate is higher with imatinib than with second-generation TKIs[2,3]: after EMR failure, either event-free survival (EFS) and overall survival rates are significantly worse compared with patients achieving an EMR
- Patients failing EMR have a significantly lower probability of reaching a deep molecular response[2,3,78]
- Imatinib has a more favourable safety profile than nilotinib and dasatinib; thus, accurate risk–benefit assessment is essential[60]
- Second-generation TKIs might be preferable as frontline treatment in patients with a high risk of progression to advanced phase, and when treatment-free remission is the selected end point[2,3]
- Patients with newly diagnosed, accelerated-phase CML should be treated similarly to patients with chronic-phase high-risk CML, whereas patients with newly-diagnosed, blast-phase CML should be treated with TKIs and/or chemotherapy followed by allogeneic stem-cell transplantation[10]

Second and following lines

- Intolerance and resistance to frontline imatinib encompasses a heterogeneous array of conditions with different PFS and overall survival outcomes. Failure and intolerance to frontline second-generation TKIs are also troublesome conditions, for which less evidence is available
- The timely implementation (by strict adherence to guidelines) of second-line treatments is pivotal for treatment success[10,79]
- In patients who have not responded to imatinib therapy, and in the absence of safety concerns or *BCR–ABL1* mutations, second-generation TKIs lead to favourable long-term results[108,113,116,118]
- Indirect evidence favours the efficacy of ponatinib over other TKIs; ponatinib should be the first option in situations of lack of sensitivity to previous second-generation TKI treatment. In addition, ponatinib is the treatment of choice in patients harbouring the T315I mutation in *BCR–ABL1* (REF. 32)
- Allogeneic stem-cell transplantation should be considered for patients who do not respond to treatment with two or more TKIs, and for patients with accelerated-phase disease who progress despite TKI treatment[10]
- The risk–benefit balance is a mainstay of the treatment decision, with cardiovascular safety being a priority. The availability of five different TKIs drugs with well-known safety profiles should help overcome the issue of intolerance to previous TKIs[60]

Rosti et al. Nature Reviews Clinical Oncology 2017



Raanani Cancer Letters 2014:352:21

Risposta ematologica, citogenetica e molecolare

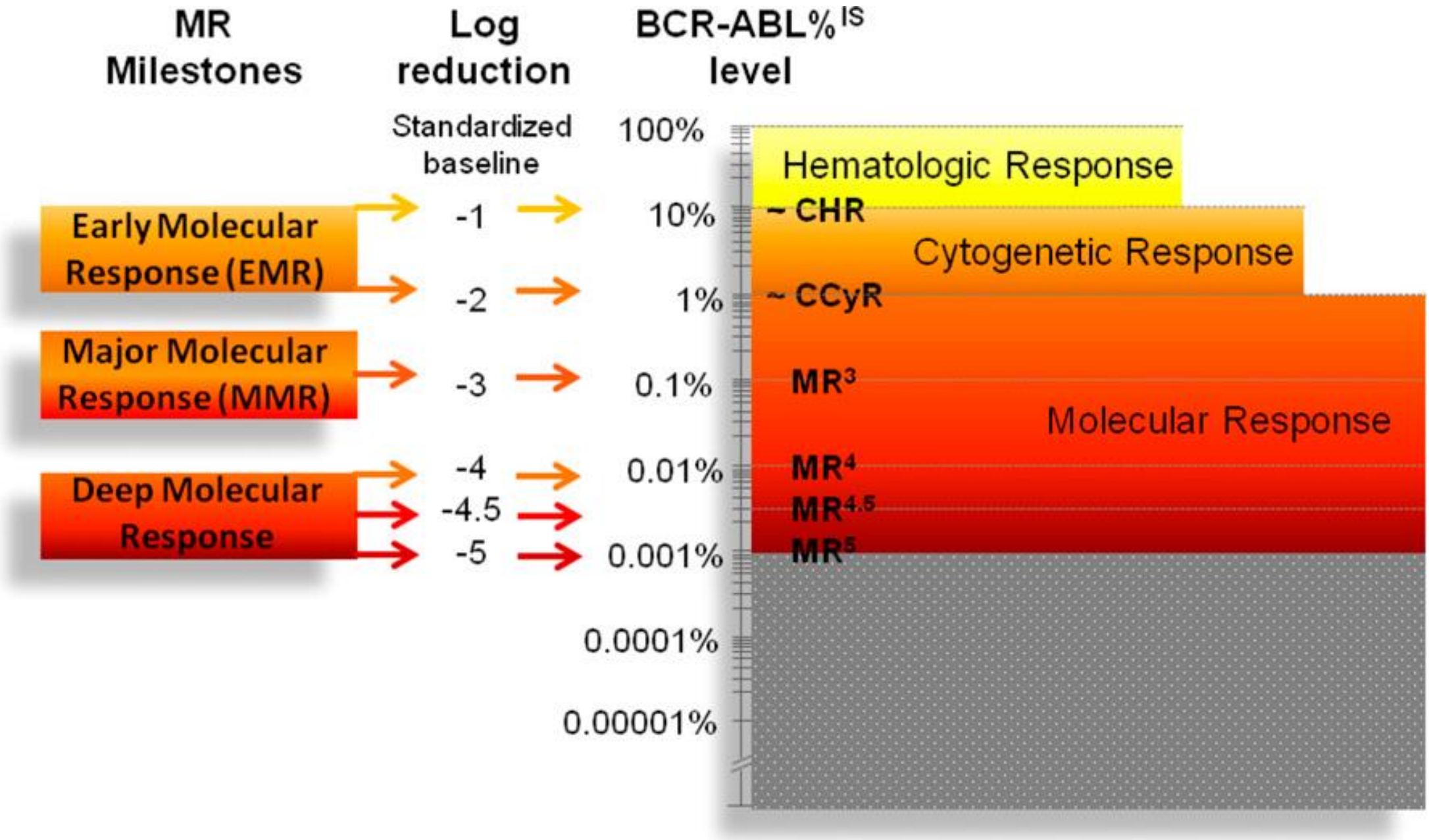
Risposta ematologica completa:
- WBC < 10 x 10^9/L
- Piastrine < 450 x 10^9/L
- Conta differenziale normale
- Milza non palpabile

Risposta citogenetica	metafasi Ph+ (almeno 20)
Minore	35-90 %
Parziale	1-34 %
Completa	0 %

Risposta molecolare:
- Early molecular response (EMR): BCR–ABL1 ≤10% at 3 months
- Major molecular response (MMR): BCR–ABL1 ≤0.1% and, at least, 10,000 copies of ABL1 transcript
- Deep molecular response: detectable disease with BCR–ABL1 ≤0.01%, or undetectable disease with 10,000–31,999 ABL1 transcript copies (MR4); or by detectable disease with BCR–ABL1 ≤0.0032%, or undetectable disease with at least 32,000 ABL1 transcript copies (MR4.5)

Monitoraggio

Ematologico: ogni 2 settimane fino alla risposta completa, poi ogni 3 mesi
Citogenetico: ogni 6 mesi fino alla risposta citogenetica completa, poi ogni 12 mesi
Molecolare: ogni 3 mesi; analisi mutazionale in caso di non risposta o risposta subottimale o aumento del trascritto



Soverini et al. The Oncologist 2016

Definition of the response to TKIs as first-line treatment

	Optimal	Warning	Failure
Baseline	NA	High risk Or CCA/Ph+, major route	NA
3 mo	BCR-ABL1 ≤10% and/or Ph+ ≤35%	BCR-ABL1 >10% and/or Ph+ 36-95%	Non-CHR and/or Ph+ >95%
6 mo	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1-10% and/or Ph+ 1-35%	BCR-ABL1 >10% and/or Ph+ >35%
12 mo	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1-1%	BCR-ABL1 >1% and/or Ph+ >0
Then, and at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7, or 7q–)	Loss of CHR Loss of CCyR Confirmed loss of MMR* Mutations CCA/Ph+

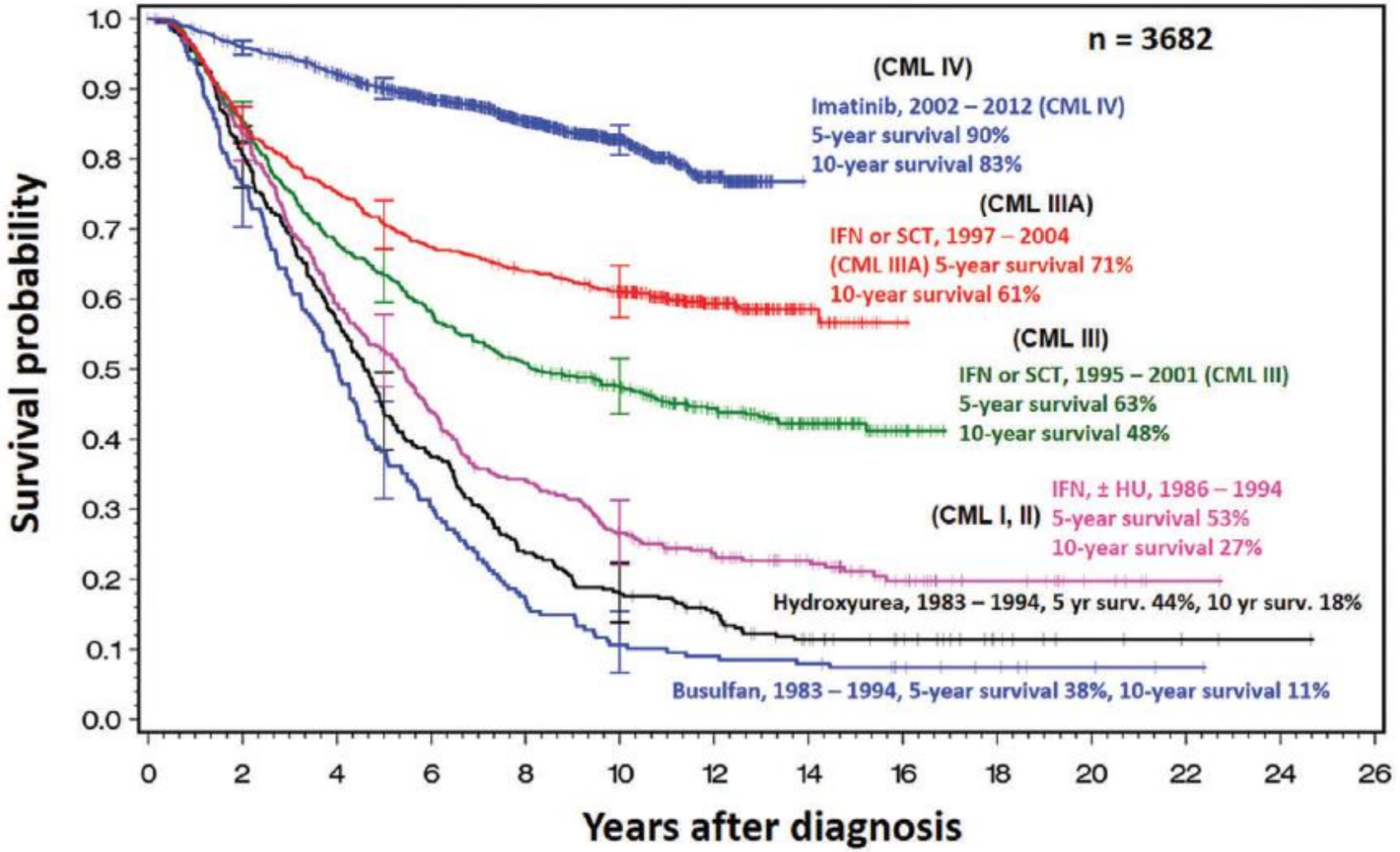
The definitions are the same for patients in CP, AP, and BP and apply also to second-line treatment, when first-line treatment was changed for intolerance. The response can be assessed with either a molecular or a cytogenetic test, but both are recommended whenever possible. Cutoff values have been used to define the boundaries between optimal and warning, and between warning and failures. Because cutoff values are subjected to fluctuations, in case of cytogenetic or molecular data close to the indicated values, a repetition of the tests is recommended. After 12 months, if an MMR is achieved, the response can be assessed by real quantitative polymerase chain reaction (RQ-PCR) every 3 to 6 months, and cytogenetics is required only in case of failure or if standardized molecular testing is not available. Note that MMR ($MR^{3.0}$ or better) is optimal for survival but that a deeper response is likely to be required for a successful discontinuation of treatment.

NA, not applicable; MMR, BCR-ABL1 ≤0.1% = $MR^{3.0}$ or better; CCA/Ph+, clonal chromosome abnormalities in Ph+ cells; CCA/Ph–, clonal chromosome abnormalities in Ph– cells.

*In 2 consecutive tests, of which one with a BCR-ABL1 transcripts level ≥1%.

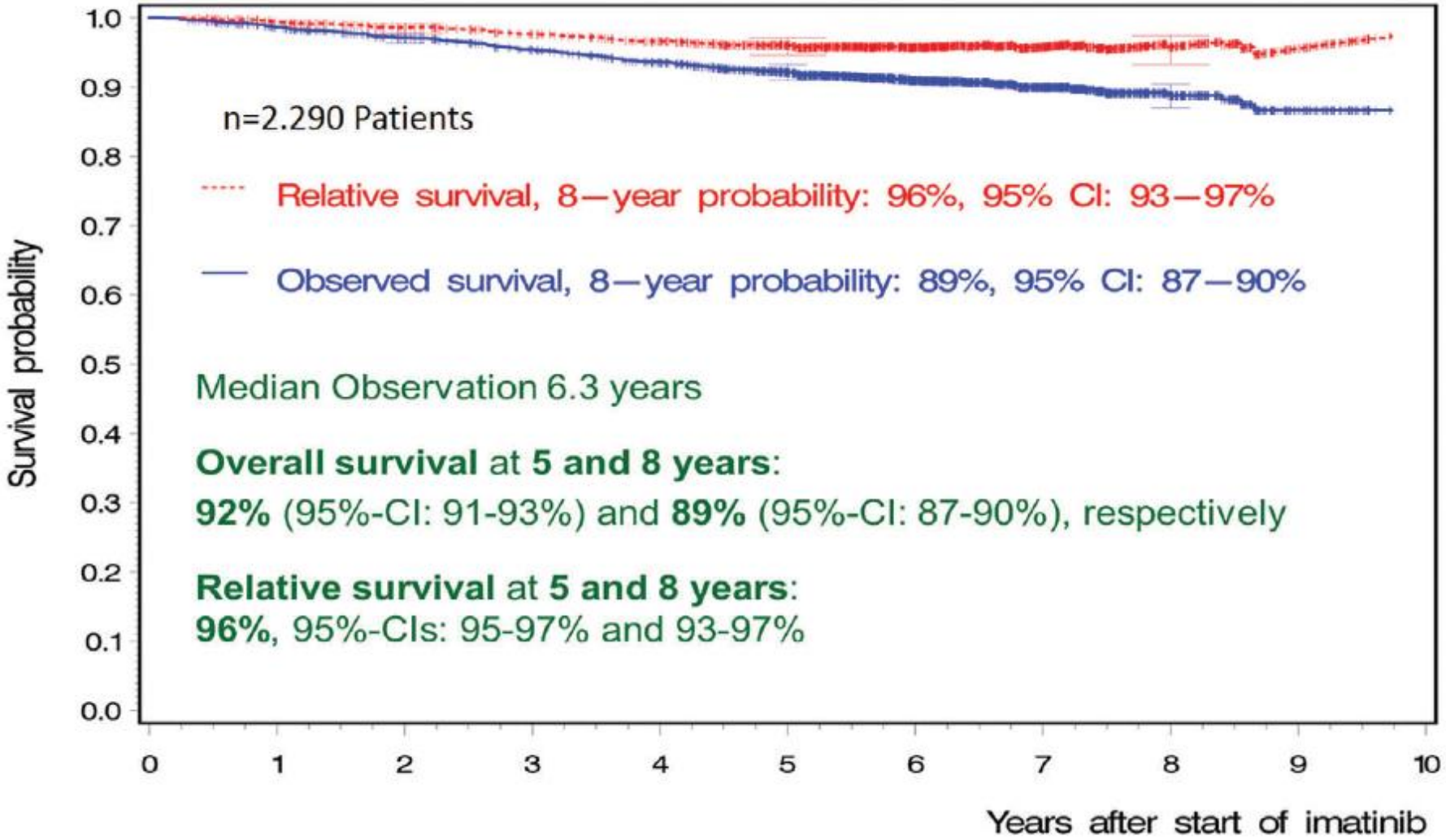
Baccarani et al. Blood. 2013;122(6):872-884

Survival with CML in five consecutive randomized studies of the German CML Study Group since 1983; update 2016.



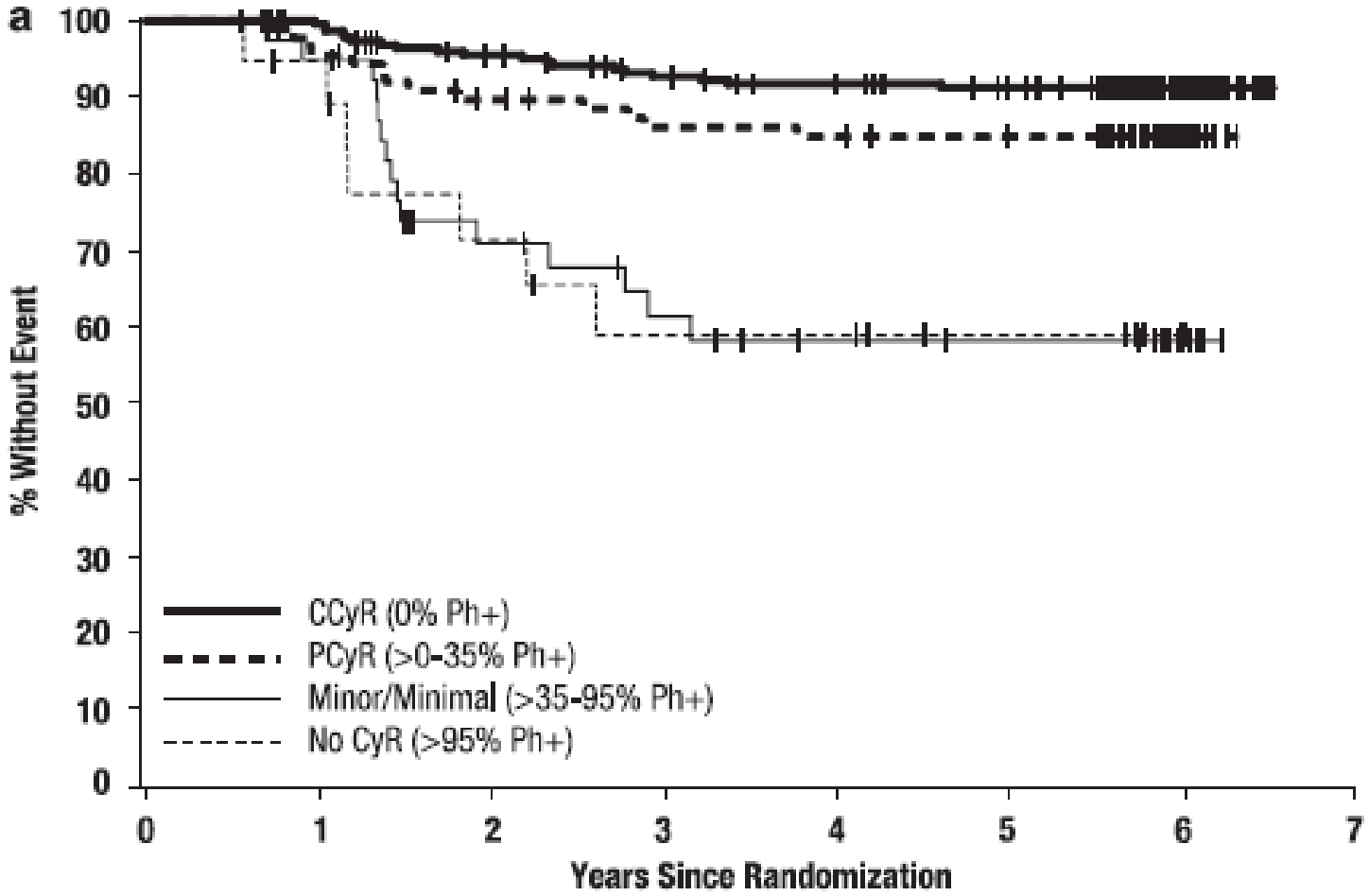
Rüdiger Hehlmann. Haematologica. 2016;101:657-9

Relative and overall survival of 2290 CML patients from the EUTOS Study for CML treated with imatinib



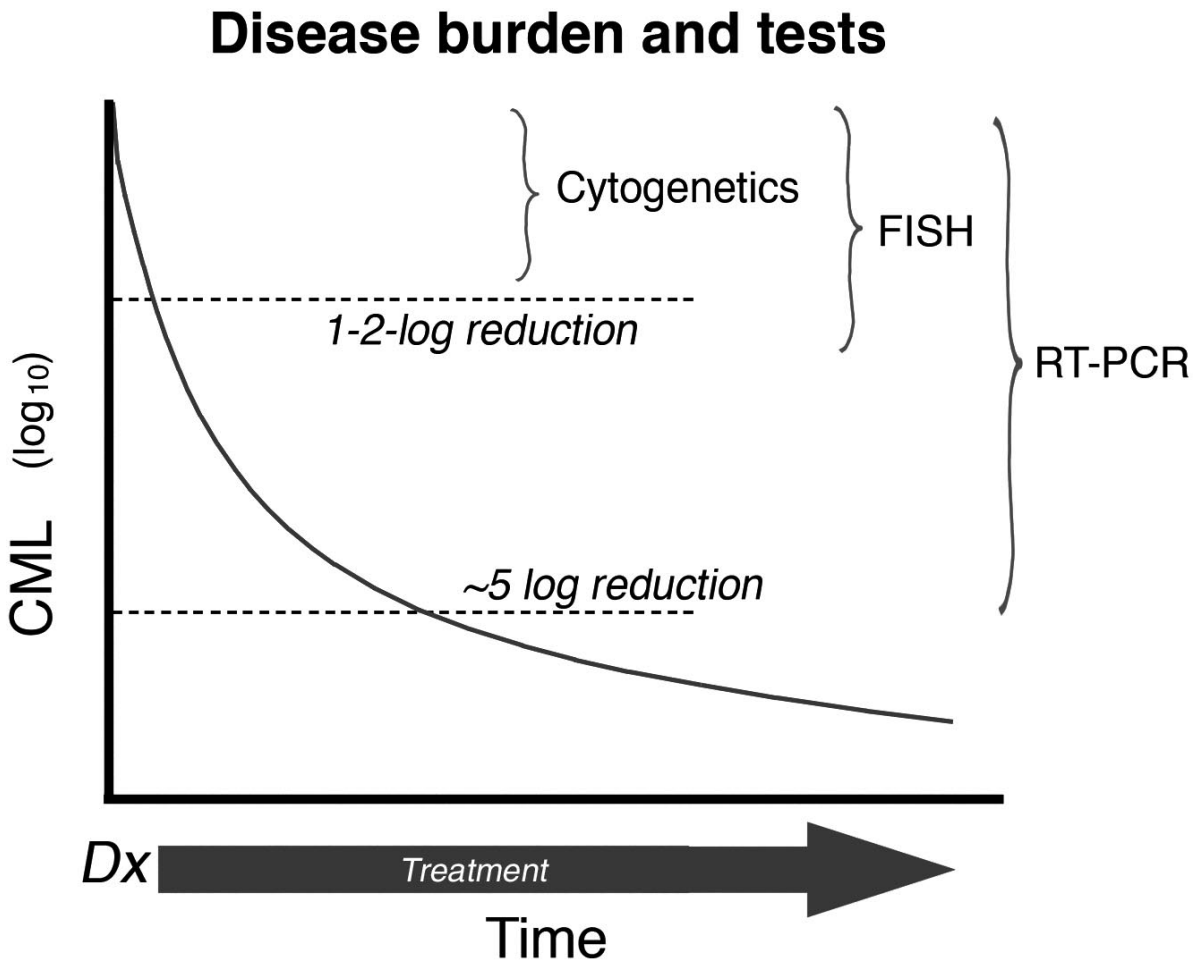
Rüdiger Hehlmann. Haematologica. 2016;101:657-9

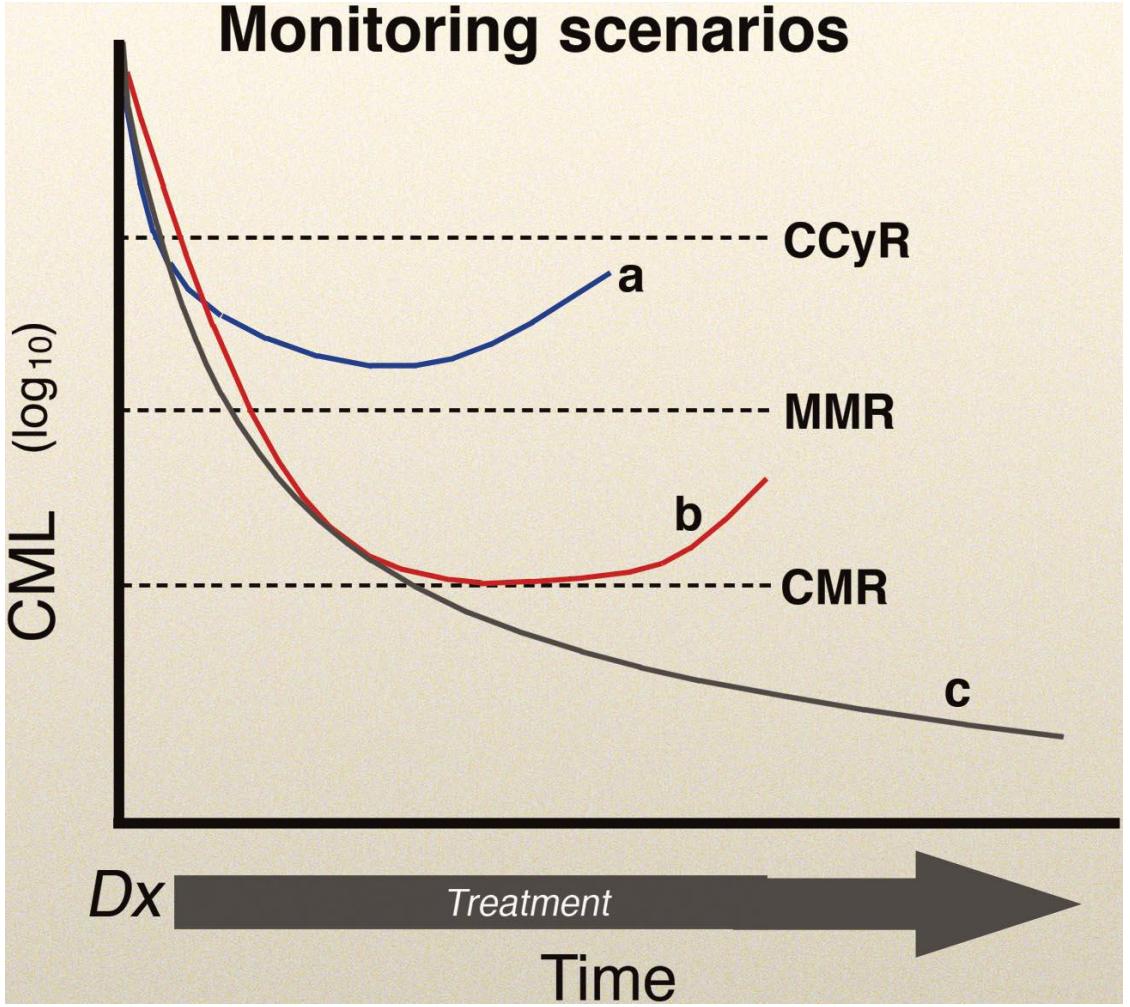
Event-free survival by level of cytogenetic response at 6 months after the initiation of imatinib treatment.



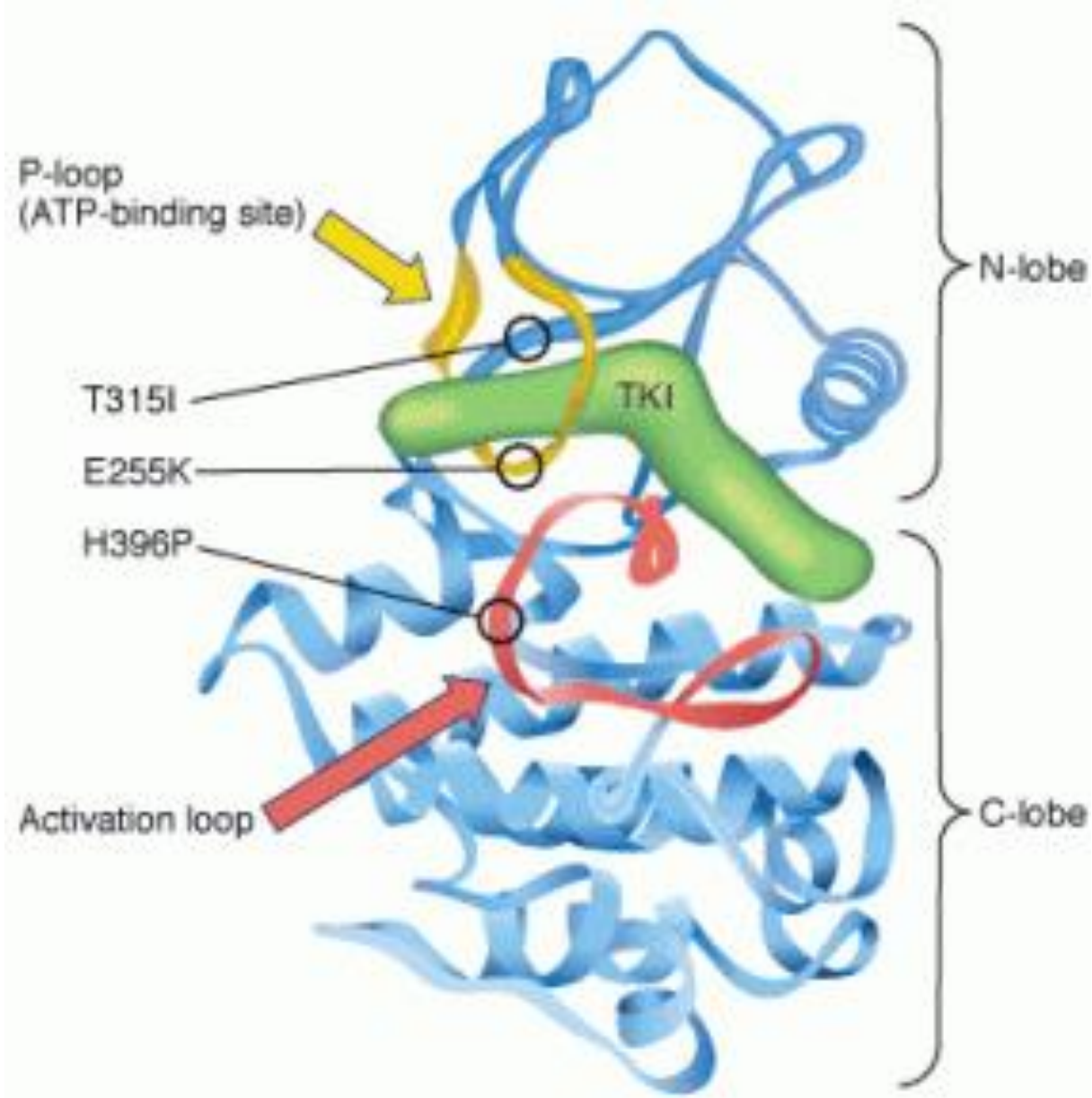
Hochhau et al. Leukemia (2009) 23, 1054–1061;

Disease burden and tests.





Blood. 2009;114:3376-3381


P-loop
(ATP-binding site)
T315I
E255K
H396P
Activation loop
TKI
N-lobe
C-lobe

In vitro sensitivity of unmutated BCR-ABL1 and of some more frequent BCR-ABL1 kinase domain mutants to imatinib, nilotinib, dasatinib, bosutinib, and ponatinib

BCR-ABL1	Imatinib IC_{50}, range (nM)	Nilotinib IC_{50}, range (nM)	Dasatinib IC_{50}, range (nM)	Bosutinib IC_{50} (nM)	Ponatinib IC_{50} (nM)
Unmutated	260-678	<10-25	0.8-1.8	41.6	0.5
M244V*	1600-3100	38-39	1.3	147.4	2.2
L248V	1866-10 000	49.5-919	9.4	NA	NA
G250E*	1350 to >20 000	48-219	1.8-8.1	179.2	4.1
Q252H	734-3120	16-70	3.4-5.6	33.7	2.2
Y253F	>6400-8953	182-725	6.3-11	40	2.8
Y253H*	>6400-17 700	450-1300	1.3-10	NA	6.2
E255K*	3174-12 100	118-566	5.6-13	394	14
E255V	6111-8953	430-725	6.3-11	230.1	36
D276G	1147	35.3	2.6	25	NA
E279K	1872	36.5-75	3	39.7	NA
V299L	540-814	23.7	15.8-18	1086	NA
F311L	480-1300	23	1.3	NA	NA
T315I*	>6400 to >20 000	697 to >10 000	137 to >1000	1890	11
T315A	125	N.A.	760	NA	1.6
F317L*	810-7500	39.2-91	7.4-18	100.7	1.1
F317V	500	350	NA	NA	10
M351T*	880-4900	7.8-38	1.1-1.6	29.1	1.5
F359V*	1400-1825	91-175	2.2-2.7	38.6	10
V379I	1000-1,630	51	0.8	NA	NA
L384M*	674-2800	39-41.2	4	19.5	NA
L387M	1000-1100	49	2	NA	NA
H396R*	1750-5400	41-55	1.3-3	33.7	NA
H396P	850-4300	41-43	0.6-2	18.1	1.1
F486S	2728-9100	32.8-87	5.6	96.1	NA
Plasma drug concentration					
Cmin	2062 ± 1334	1923 ± 1233	5.5 ± 1.4	268 (30-1533)	64.3 ± 29.2
Cmax	4402 ± 1272	2329 ± 772	133 ± 73.9	392 (80-1858)	145.4 ± 72.6

The half maximal inhibitory concentration (IC_{50}) shown here is universally regarded as a measure of the degree of sensitivity of a *BCR-ABL1* mutant to a given TKI and is experimentally determined by quantifying the TKI concentration required to reduce by 50% viability of a Ba/F3 mouse lymphoblastoid cell line engineered to express that mutant form of *BCR-ABL1*. The table lists all of the *BCR-ABL1* mutants for which the IC_{50} values of at least 2 TKIs are available. For imatinib, dasatinib, and nilotinib, ranges of IC_{50} values were provided when differences in IC_{50} values reported by different studies were observed (reviewed in Baccarani et al[5]). For bosutinib and ponatinib, IC_{50} values come from a single study each.[68,71] Plasma drug concentration is also given in nM. Values of plasma drug concentration are mean ± standard deviation for imatinib (400 mg once daily), nilotinib (300 mg twice daily), dasatinib (100 mg once daily), and ponatinib (45 mg once daily), and median (range) for bosutinib (500 mg once daily).[34,50,72-75]

NA, not available.

*Representative of the 10 most frequent mutations.[56,59]

Baccarani et al. Blood. 2013;122(6):872-884)

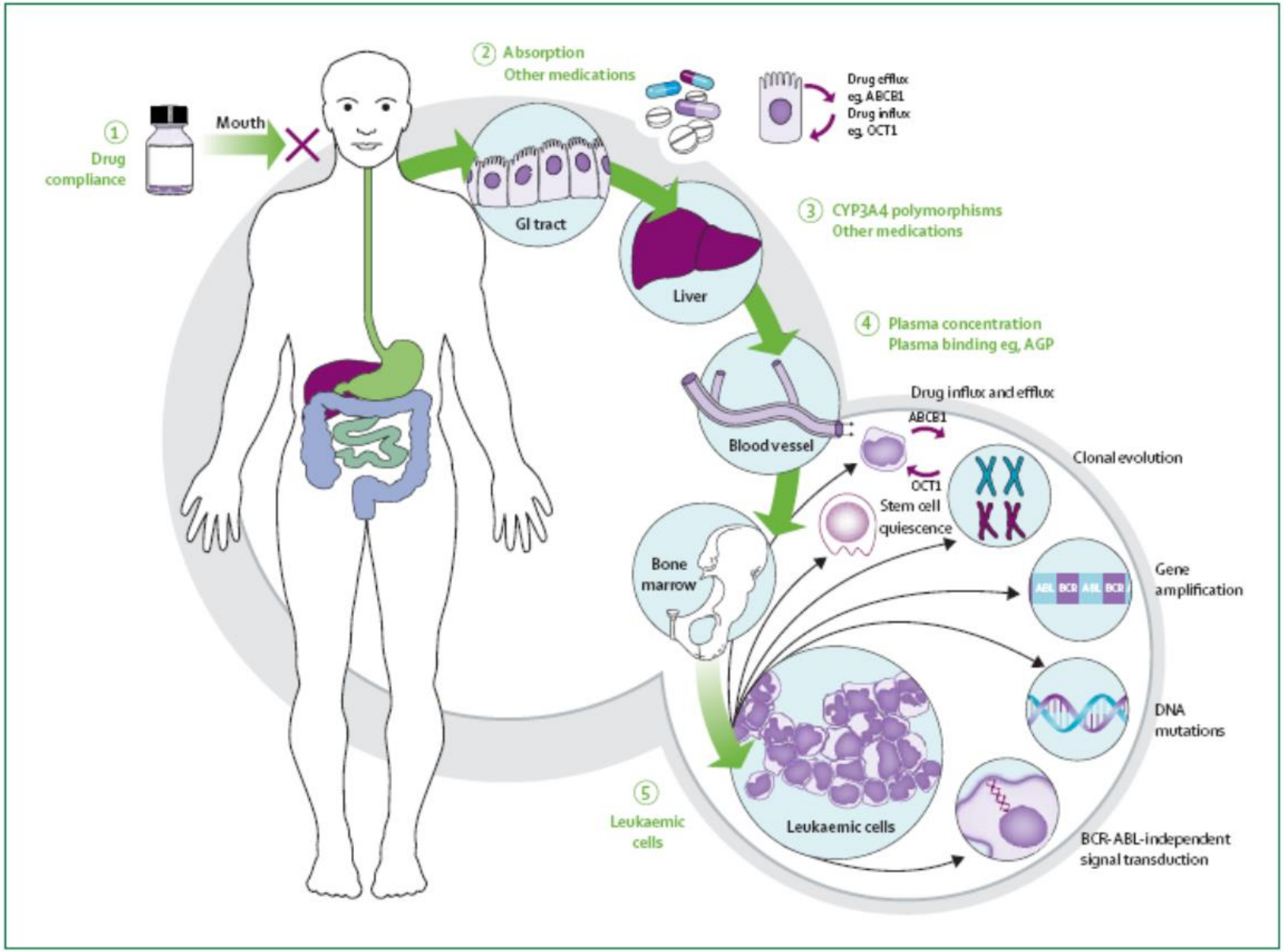


Figure 2: **Mechanisms of imatinib resistance**
ABCB1=ATP-binding competitor B1. OCT1=organic cation transporter 1. CYP3A4=cytochrome P450 isoenzyme 4A. AGP=alpha-1 acid glycoprotein.

Apperley JL Lancet Oncology 2007, 8, 1018

Definitions of the response to second-line therapy in case of failure of imatinib

	Optimal	Warning	Failure
Baseline	NA	No CHR or loss of CHR on imatinib or lack of CyR to first-line TKI or high risk	NA
3 mo	BCR-ABL1 ≤10% and/or Ph+ < 65%	BCR-ABL1 >10% and/or Ph+ 65-95%	No CHR or Ph+ >95% or new mutations
6 mo	BCR-ABL1 ≤10% and/or Ph+ < 35%	Ph+ 35-65%	BCR-ABL1 >10% and/or Ph+ >65% and/or new mutations
12 mo	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1-10% and/or Ph+ 1-35%	BCR-ABL1 >10% and/or Ph+ >35% and/or new mutations
Then, and at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7 or 7q–) or BCR-ABL1 >0.1%	Loss of CHR or loss of CCyR or PCyR New mutations Confirmed loss of MMR* CCA/Ph+

These definitions are mainly based on data reported for nilotinib and dasatinib,5,42-46,69,77,104-109 but can be used provisionally also for bosutinib and ponatinib, until more data are available. These definitions cannot apply to the evaluation of the response to third-line treatment.

NA, not applicable; MMR, BCR-ABL1 ≤0.1% = MR3.0 or better; CCA/Ph+, clonal chromosome abnormalities in Ph+ cells; CCA/Ph–, clonal chromosome abnormalities in Ph– cells.

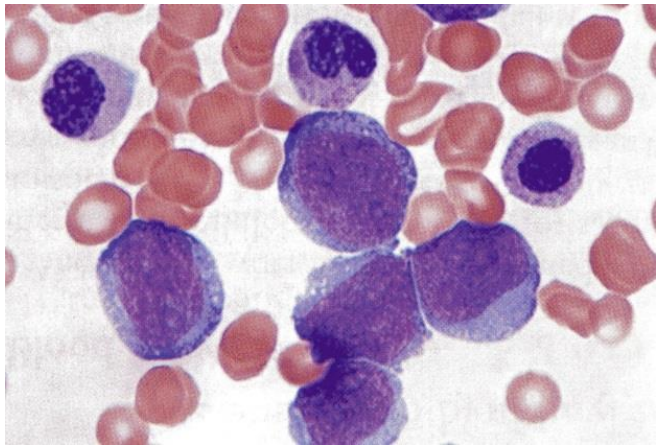
*In 2 consecutive tests, of which one with a BCR-ABL transcripts level ≥1%.

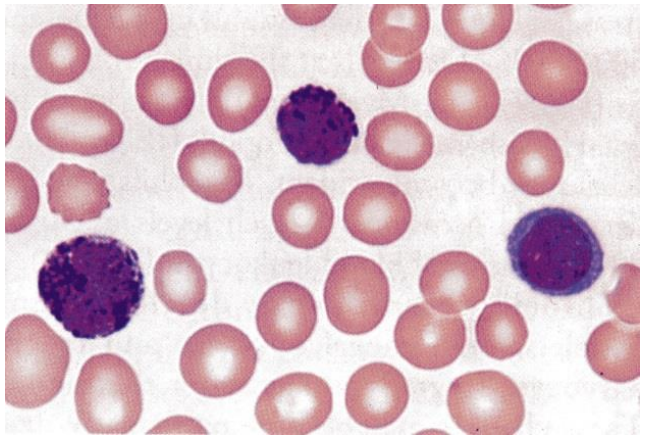
Baccarani et al. Blood. 2013;122(6):872-884)

CML, accelerated phase criteria

Arber DA et al. Blood. 2016; 127(20):2391-2405

Any 1 or more of the following hematologic/cytogenetic criteria or response-to-TKI criteria:	
• Persistent or increasing WBC (>10 × 10^9/L), unresponsive to therapy	**"Provisional" response-to-TKI criteria**
• Persistent or increasing splenomegaly, unresponsive to therapy	• Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response* to the first TKI) or
• Persistent thrombocytosis (>1000 × 10^9/L), unresponsive to therapy	• Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs or
• Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy	• Occurrence of 2 or more mutations in *BCR-ABL1* during TKI therapy
• 20% or more basophils in the PB	
• 10%-19% blasts† in the PB and/or BM	
• Additional clonal chromosomal abnormalities in Ph^+ cells at diagnosis that include "major route" abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2	
• Any new clonal chromosomal abnormality in Ph^+ cells that occurs during therapy	

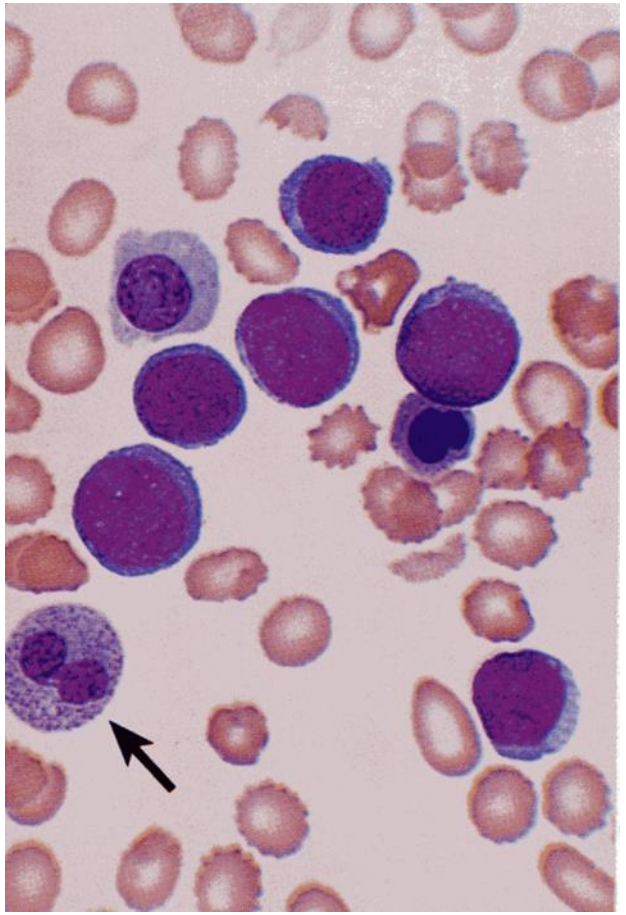




Criteria for blast phases of CML

	WHO criteria[5]	European Leukaemia Net criteria[6]
Accelerated phase		
Blasts in peripheral blood or bone marrow	10–19%	15–29% or blasts plus promyelocytes in peripheral blood or bone marrow ≥30% with blasts <30%
Basophils in peripheral blood	≥20%	≥20%
Platelets	<100 × 10^9/L not attributable to treatment, or platelets >1000 × 10^9/L uncontrolled on treatment	<100 × 10^9/L not attributable to treatment
Additional chromosomal abnormalities	Occurring on treatment	Occurring on treatment
White cell count and spleen size	Increasing and uncontrolled on treatment	..
Blast crisis		
Blasts in peripheral blood or bone marrow	≥20%	≥30%
Blast proliferation	Extramedullary, except spleen	Extramedullary, except spleen
Large foci of blasts	Bone marrow or spleen	..

Table 1: **Definitions of accelerated phase and blast crisis according to present classification systems**



Apperley JF. Lancet 2015; 385: 1447–59

Treatment strategy recommendations for CML in AP or BP

AP and BP in newly diagnosed, TKI-naïve patients	Imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily Stem cell donor search. Then, alloSCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response. Chemotherapy may be required before alloSCT, to control the disease.
AP and BP as a progression from CP in TKI-pretreated patients	Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients. Chemotherapy is frequently required to make patients eligible for alloSCT.

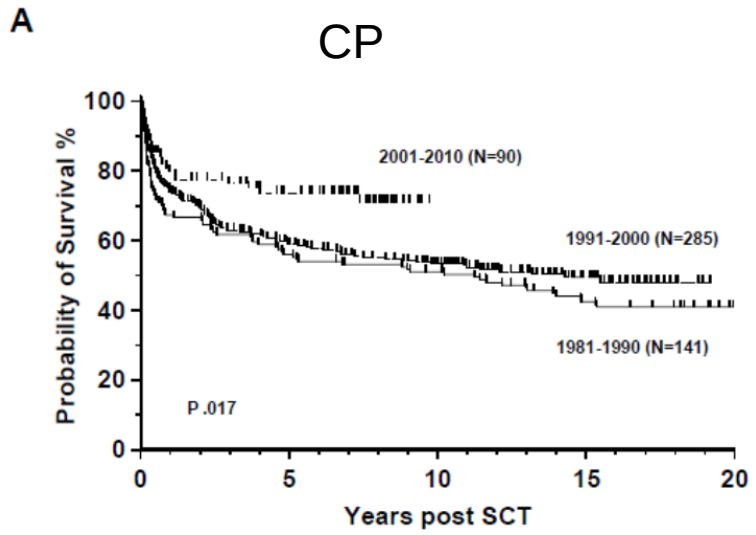
In treatment-naïve patients, AP is believed to be close to high-risk CP, so that TKIs have priority. In patients who progress to AP or BP during TKI therapy, the response to any subsequent treatment is poorer, and less durable, so that alloSCT is recommended for all patients who are eligible for the procedure. However, in these patients, not only TKIs but also cytotoxic chemotherapy may be necessary to reinsert some degree of remission to permit alloSCT. In case of uncontrolled, resistant BP, alloSCT is not recommended. All recommendations for alloSCT imply that the patient is eligible for that procedure. Note that nilotinib was tested, but not approved, for the treatment of BP.[119,121,122]

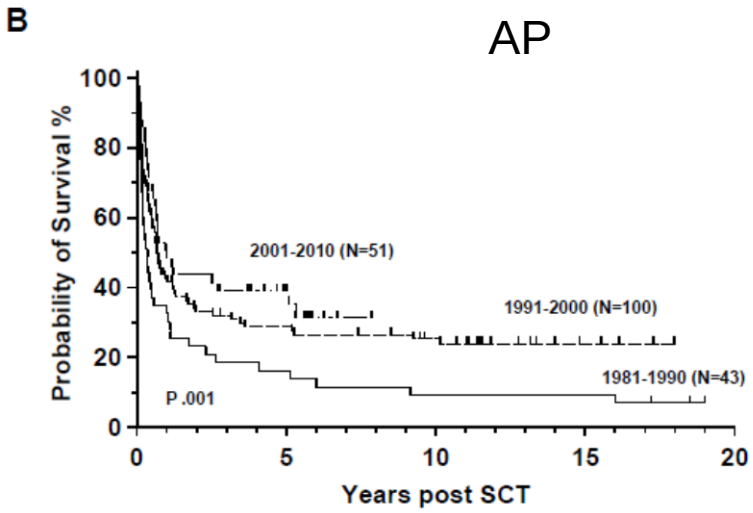
Baccarani et al. Blood. 2013;122(6):872-884)

Indication for allo-SCT in CML

CML phase	Clinical situation	TKI and chemotherapy management	HLA typing and donor search	Immediate allo-SCT referral
CP	First failure of imatinib, high risk	Second-line TKI	Yes	No
	First failure of nilotinib or dasatinib	Second-line TKI	Yes	Yes
	Failure to 2 TKIs	Third-line TKI	Yes	Yes
	T315I mutation	Ponatinib or omacetaxine	Yes	Yes
AP	TKI naïve	TKI ± chemotherapy	Yes	Yes
	TKI naïve, without optimal response	Second-line TKI ± chemotherapy	Yes	Yes
	TKI pretreated	Second-line TKI ± chemotherapy	Yes	Yes
BP	TKI naïve or pretreated	Induction chemotherapy, TKI	Yes	Yes

Barrett Blood. 2015;125(21):3230-3235)





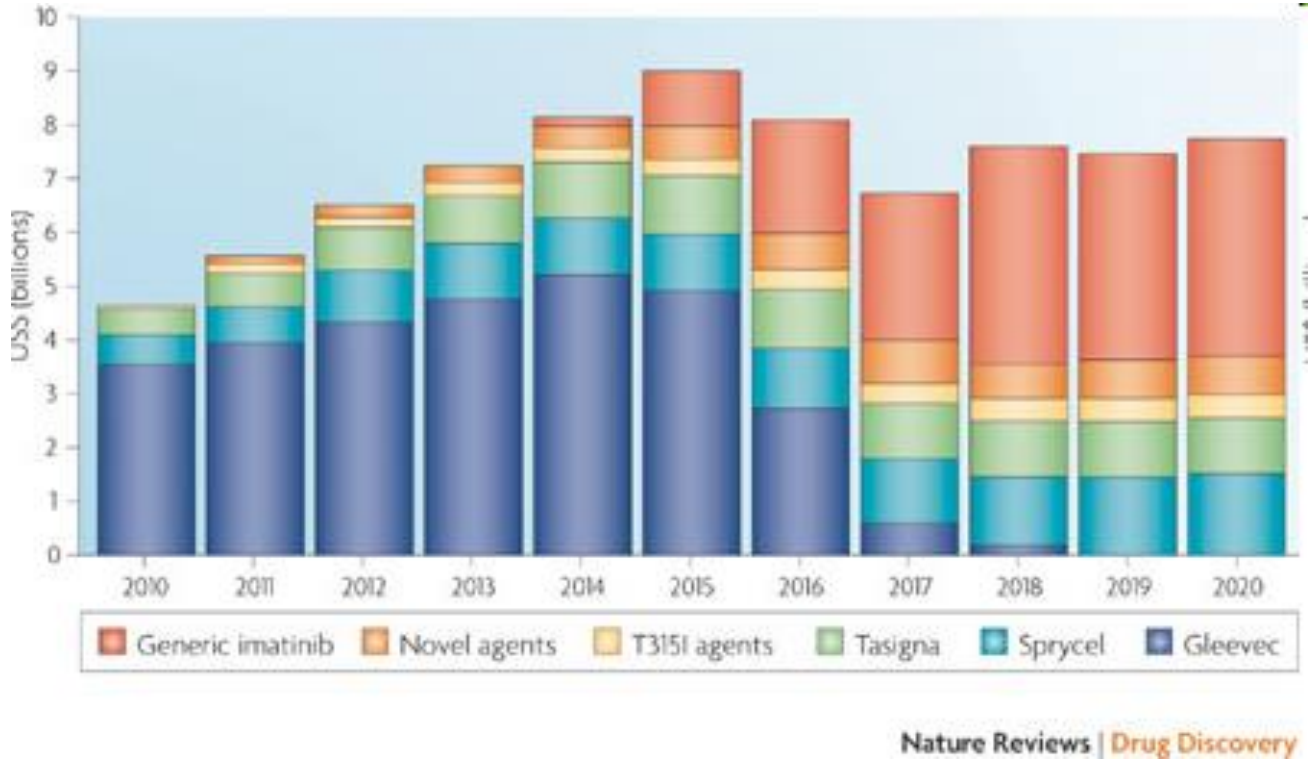
	Score*
Age (years)	
<20	0
20–40	1
>40	2
Disease phase	
Chronic phase	0
Acceleration, second of subsequent chronic phase	1
Blast crisis	2
Stem cell source	
HLA-matched sibling	0
Volunteer unrelated donor or mismatched family member	1
Donor-recipient sex combinations	
Male to male	0
Male to female	0
Female to female	0
Female to male	1
Time from diagnosis to transplant	
<12 months	0
>12 months	1

Taken from Gratwohl/European Group for Blood and Marrow Transplantation score.[30] *Total score will be in the range 0–7.

Table 3: **Factors affecting transplant outcome in chronic myeloid leukaemia**

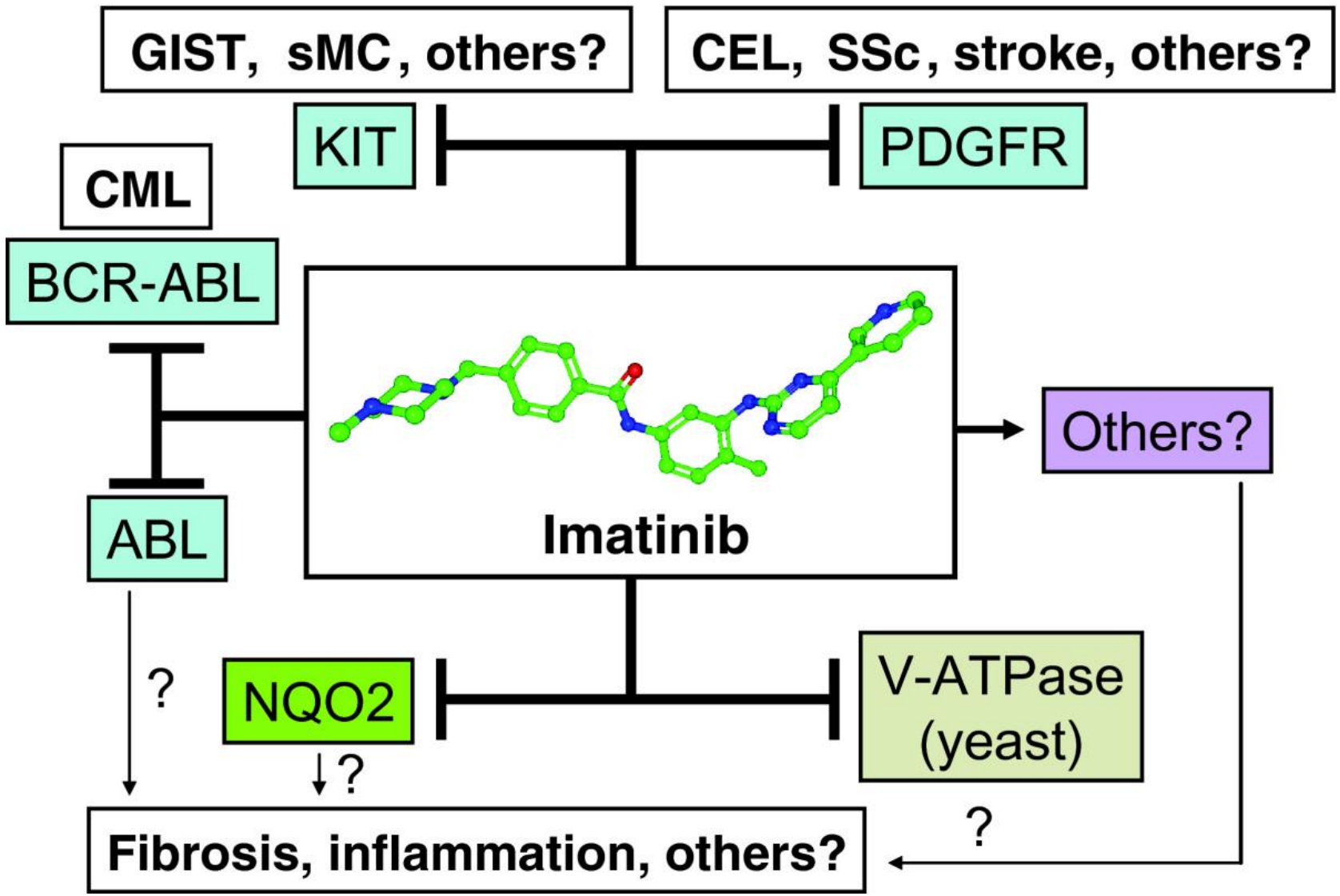
Apperley JF. Lancet 2015; 385: 1447–59

Shifting market composition for CML agents 2010–2020



Data are for the major pharmaceutical markets (US, France, Germany, Italy, Spain, UK and Japan). The established long-term safety and efficacy of imatinib (Gleevec; Novartis) will make it difficult for dasatinib (Sprycel; Bristol–Myers Squibb) and nilotinib (Tasigna; Novartis) to increase their penetration of the first-line treatment setting. Both agents will also experience competition from novel agents pushing in to the second-line territory they now occupy. Novel agents and T315I-targeted therapies will grow important market niches. Source: Wilson HTM Research.

Shane Storey Nature Reviews Drug Discovery 8, 447-448 (June 2009)


GIST, sMC, others?
CEL, SSc, stroke, others?
KIT
PDGFR
CML
BCR-ABL
ABL
Imatinib
Others?
?
NQO2
↓?
V-ATPase
(yeast)
?
Fibrosis, inflammation, others?

Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia

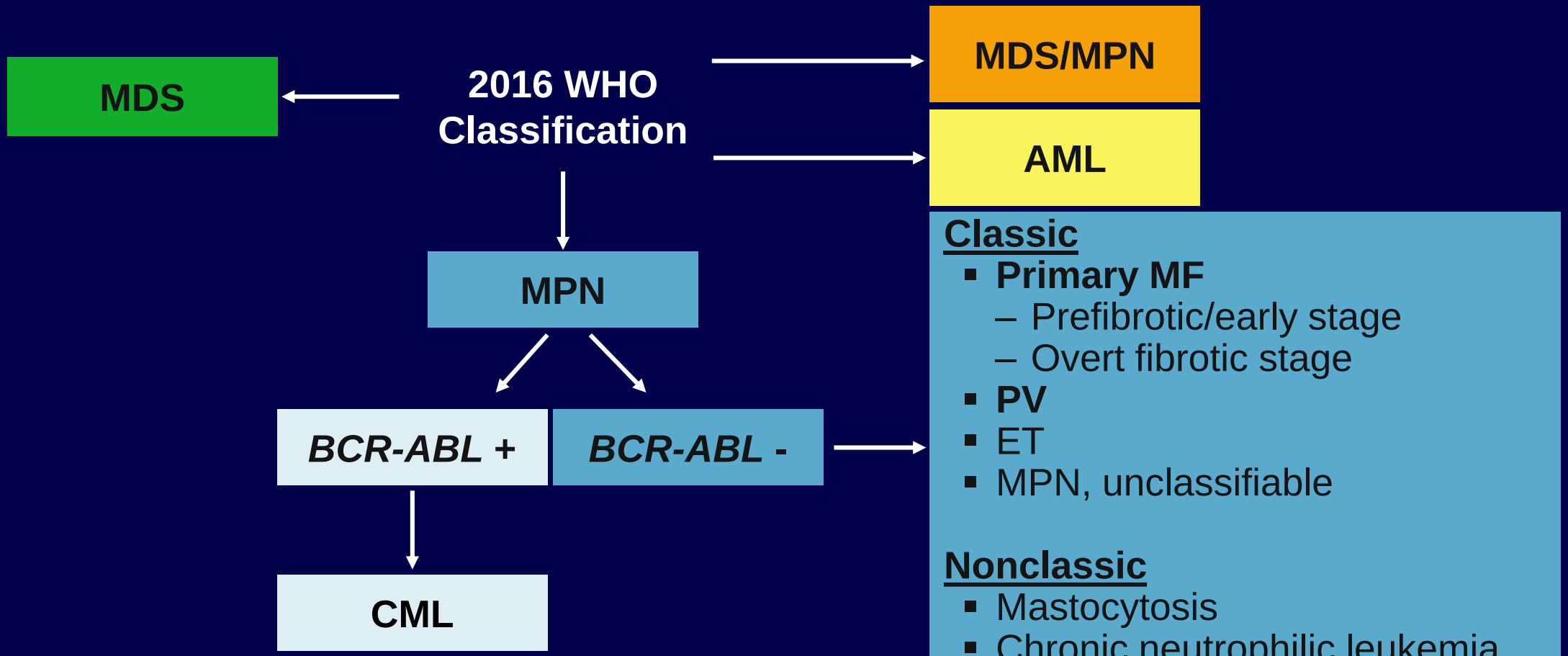
Table 10. Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia

Disease	Presentation	Genetics	Treatment
PDGFRA	Eosinophilia ↑Serum tryptase ↑Marrow mast cells	Cryptic deletion at 4q12 *FIP1L1-PDGFRA*, at least 66 other partners	Respond to TKI
PDGFRB	Eosinophilia Monocytosis mimicking CMML	t(5;12)(q32;p13.2) *ETV6-PDGFRB*, at least 25 other partners	Respond to TKI
FGFR1	Eosinophilia Often presents with T-ALL or AML	Translocations of 8p11.2 *FGFR1*-various partners	Poor prognosis; do not respond to TKI
PCM1-JAK2	Eosinophilia Rarely presents with T-LBL or B-ALL Bone marrow shows left-shifted erythroid predominance and lymphoid aggregates	t(8;9)(p22;p24.1) *PCM1-JAK2*	May respond to JAK2 inhibitors

↑, Increased.

Arber DA et al. Blood. 2016; 127(20):2391-2405

Myeloid Malignancies

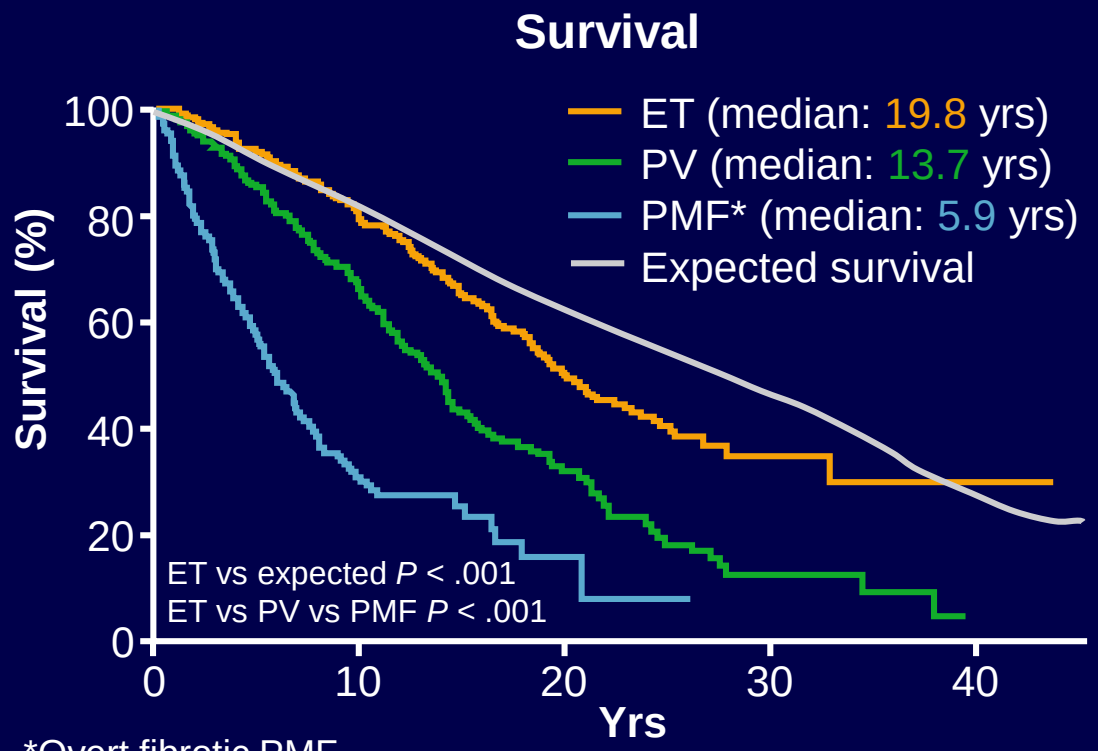


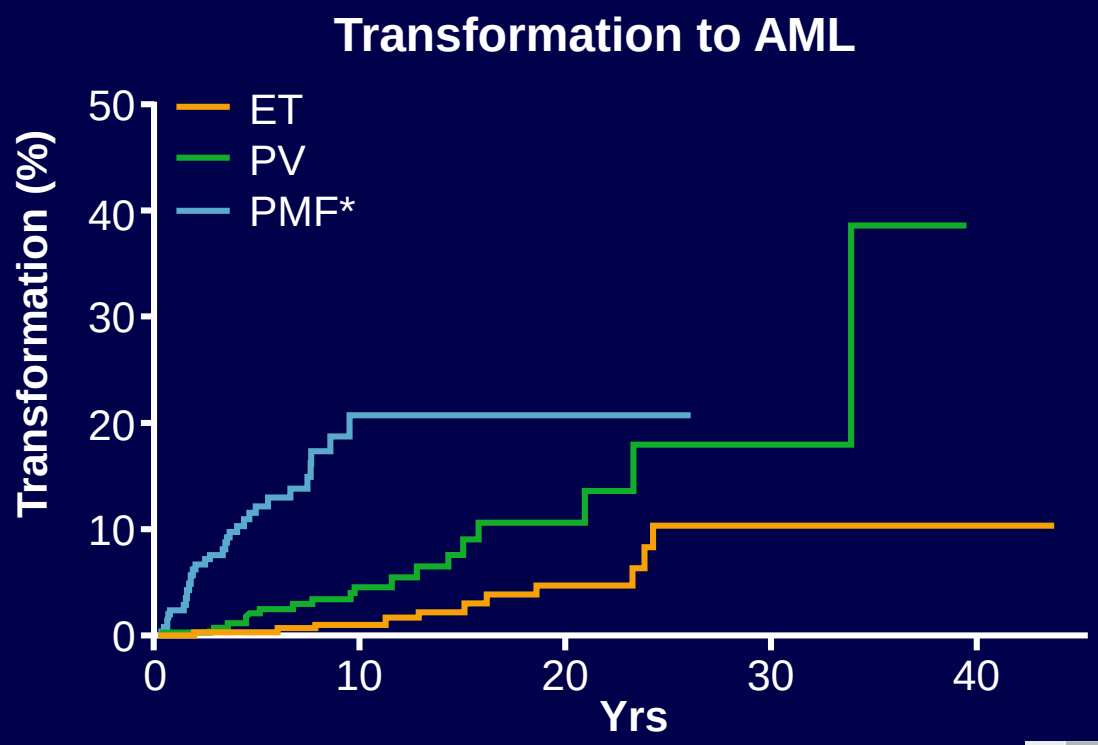
Arber DA, et al. Blood. 2016;127:2391-2405.

Slide credit: clinicaloptions.com

Survival and Disease Progression in Pts With PV, MF, or ET

- Although similarities exist in the molecular signature and presentation of PV, MF, and ET, it is important to distinguish among these conditions as prognosis and management can differ
- Assessment of survival and progression in pts with PV, MF, or ET at Mayo Clinic (N = 826)



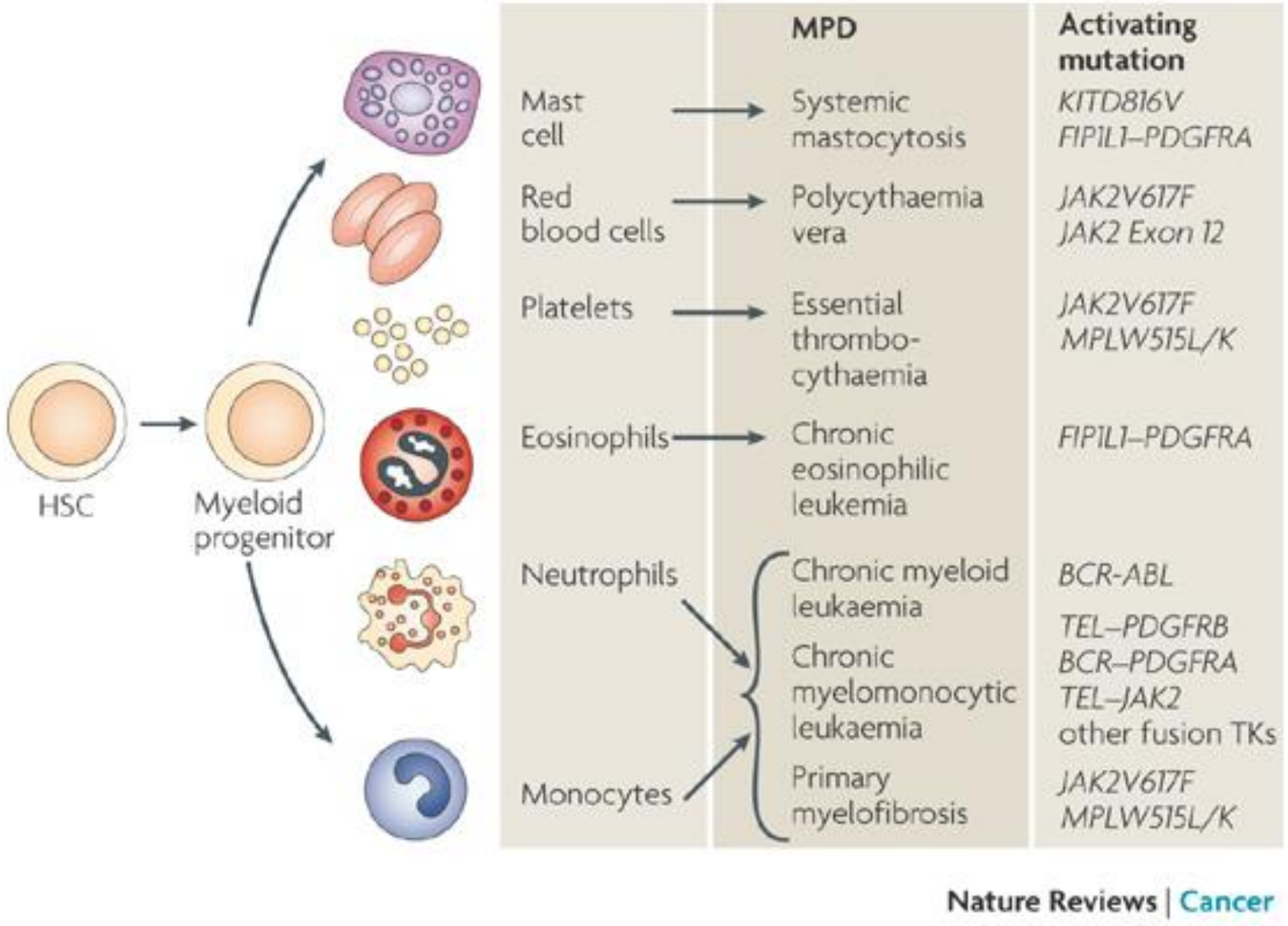


*Overt fibrotic PMF.

Tefferi A, et al. Blood. 2014;124:2507-2513.

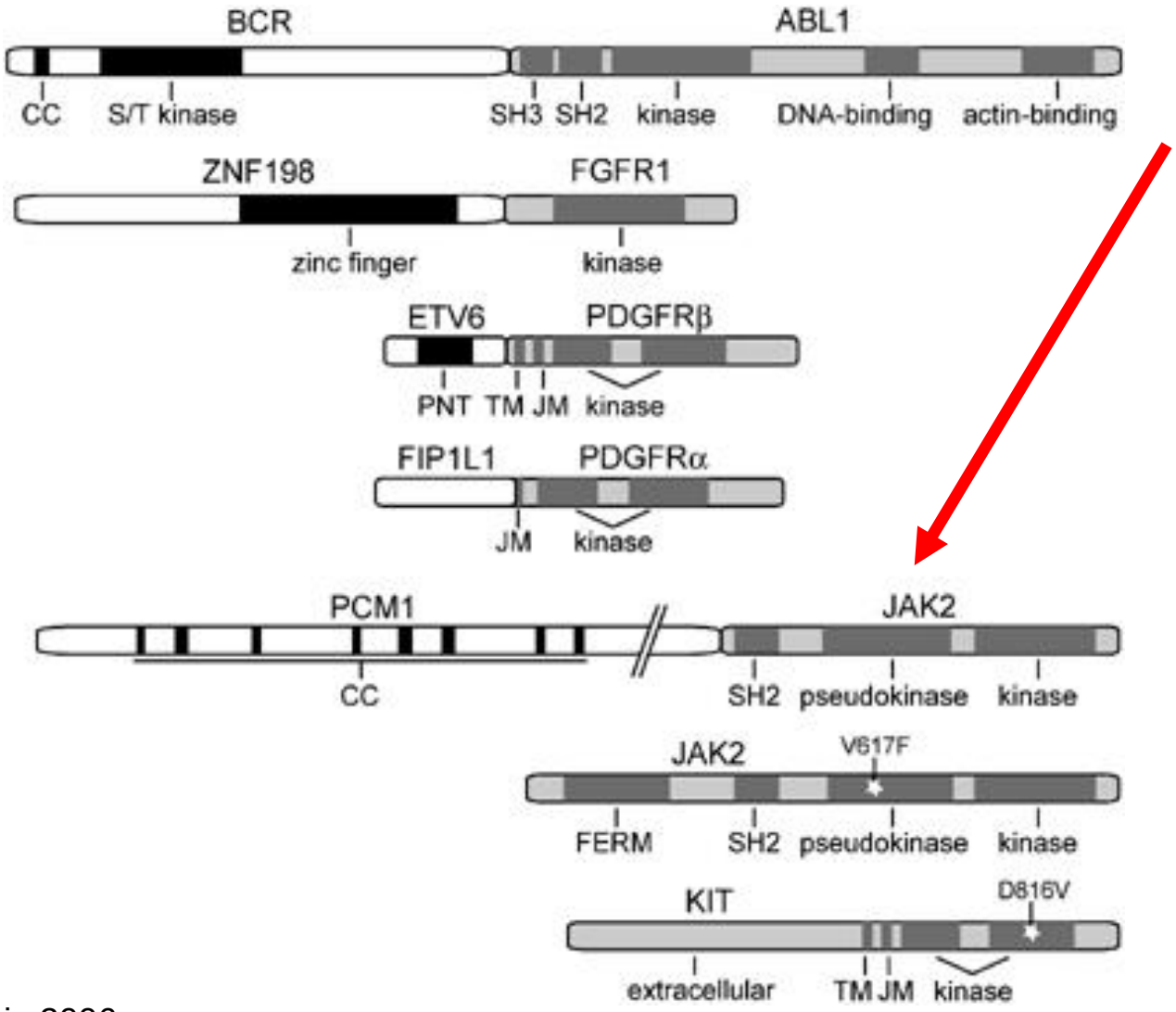
Slide credit: clinicaloptions.com

Classification and molecular pathogenesis of the MPD



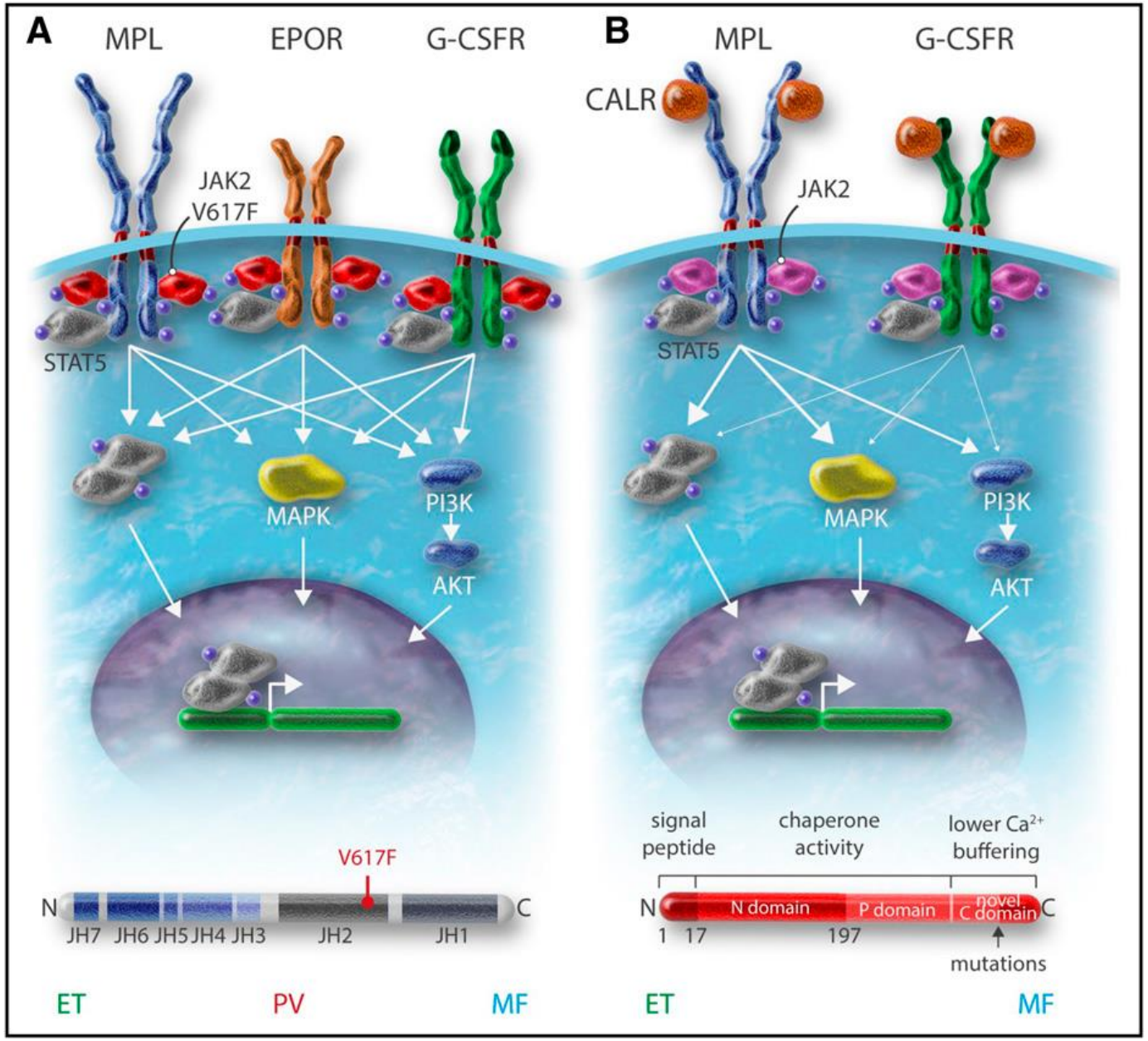
Levine RL et al. Nat Rev Cancer. 2007;7:673-83

Tyrosine kinase involved in the pathogenesis of CMPD



Keersmaecker Leukemia 2006

Role of cytokine receptors in the oncogenic properties of JAK2V617F and CALR mutants.



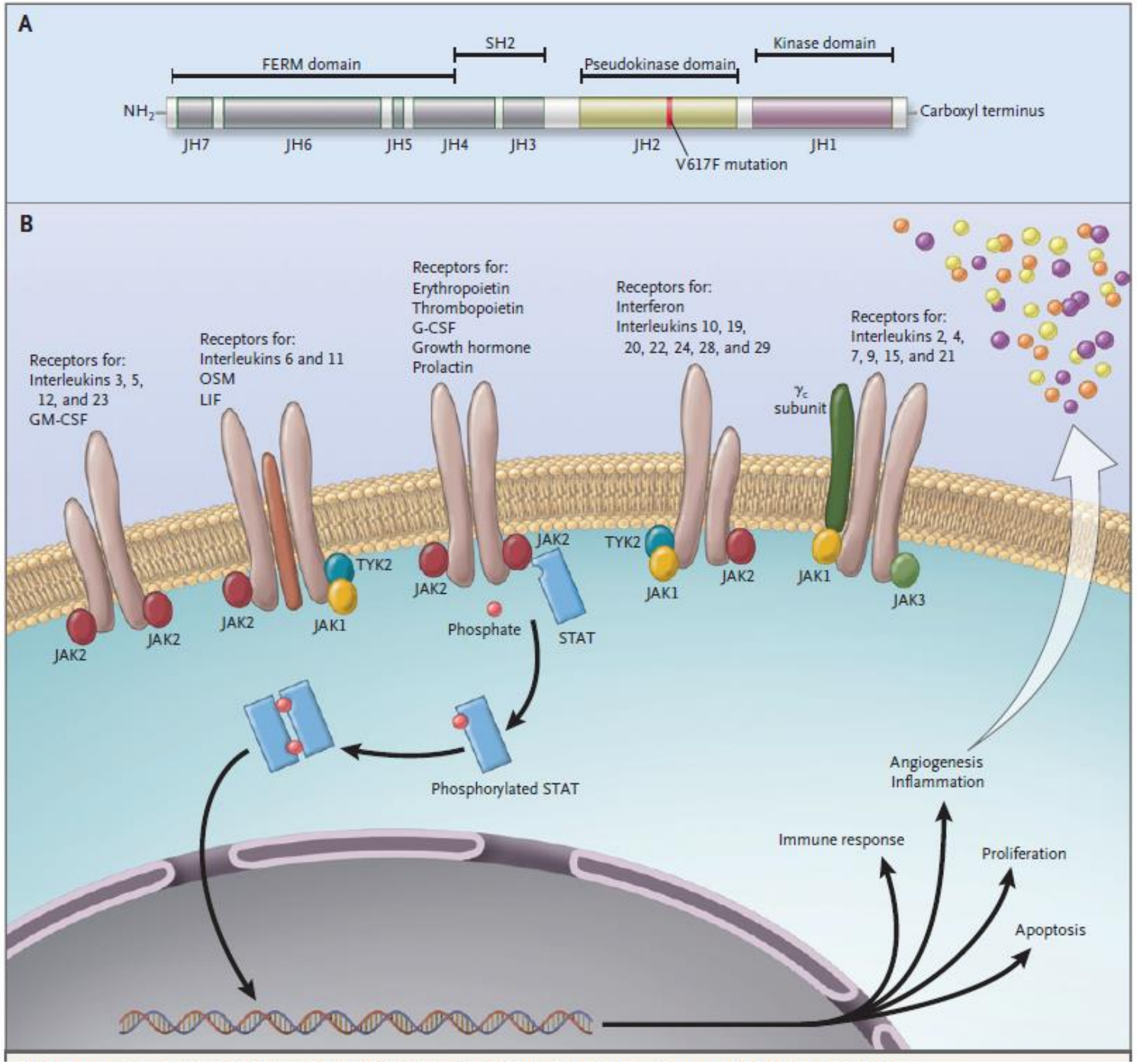
(A) JAK2V617F activates signaling through the 3 main homodimeric receptors EPOR, MPL, and G-CSFR, which are involved in erythrocytosis, thrombocytosis, and neutrophilia, respectively.

(B) The CALR mutants mainly activate MPL and at a low level the G-CSFR but not the EPOR, explaining the thrombocytosis associated with these mutants

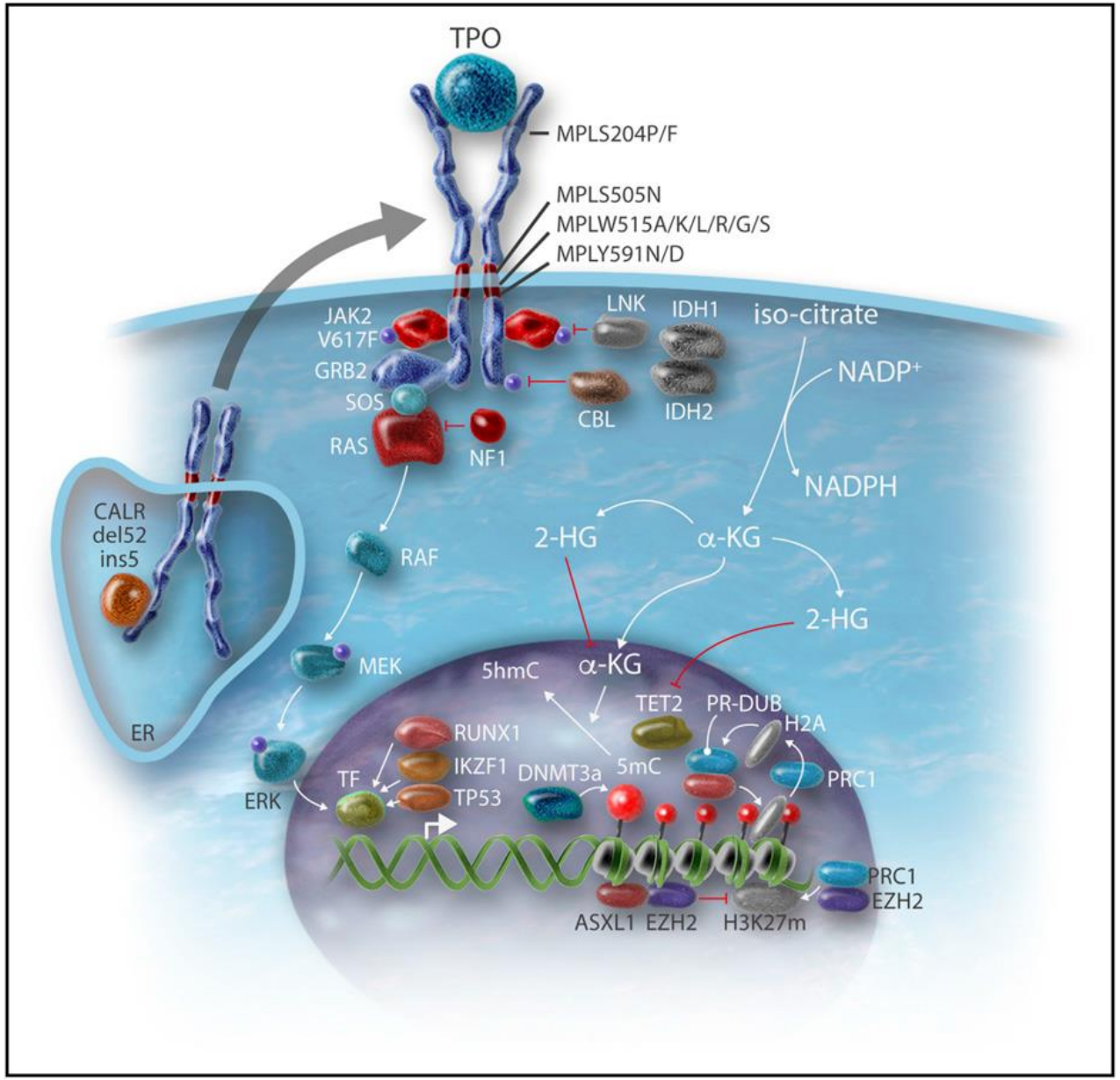
Vainchenker W. Blood. 2017;129(6):667-679

JAK2 V617F

Vannucchi AM. NEJM, 2010;3623:1180



Genes involved in epigenetic regulation and leukemic transformation.



The mechanisms by which the genes involved in the epigenetic regulation lead to modifications in gene regulation are detailed.
Some genes involved in leukemic transformation (N-Ras pathway and transcription factors such as p53, RUNX1) are also described.
MEK, MAPK/ERK-kinase; RAF, rapidly accelerated fibrosarcoma; SOS, Son of Sevenless; TF, transcription factor.

Vainchenker W. Blood. 2017;129(6):667-679

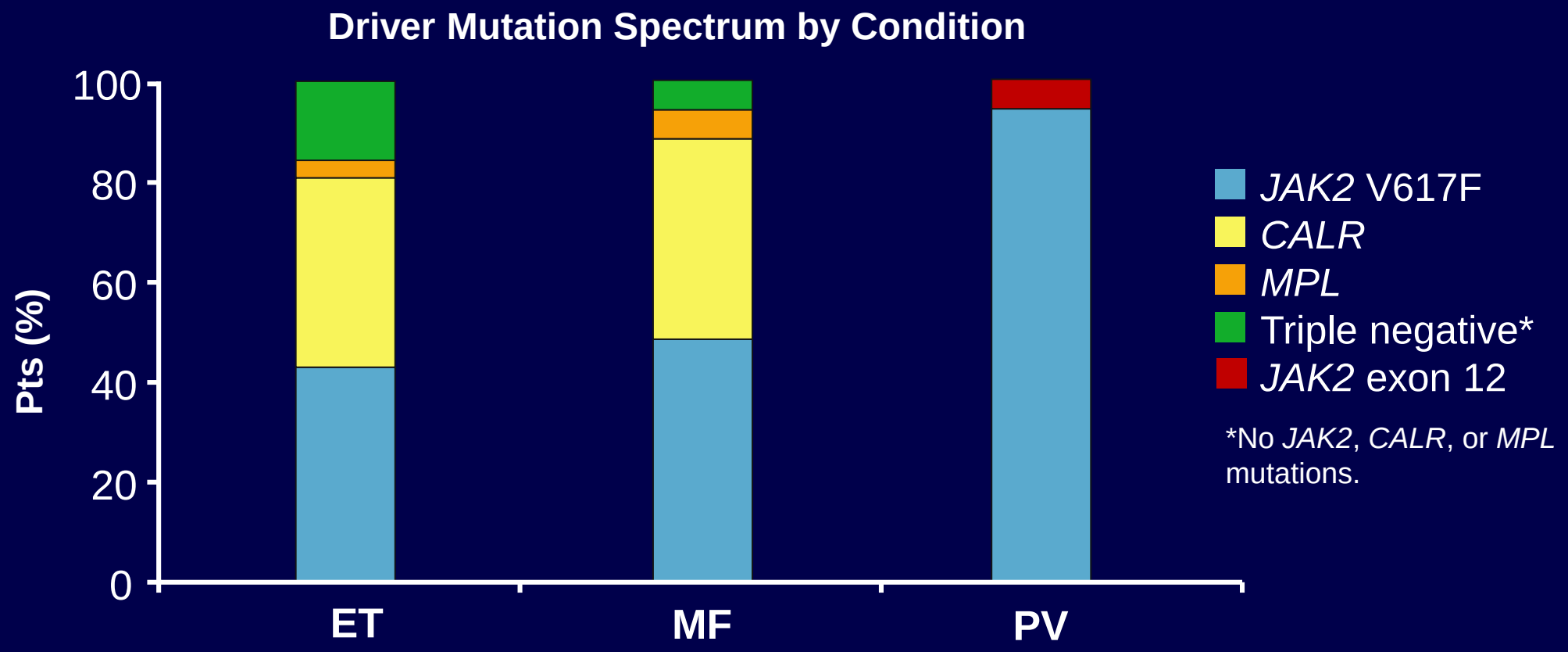
Commonly mutated genes in the myeloproliferative neoplasms

Gene	Chromosome location	Mutation location	Frequency (%)		
			PV	ET	PMF
JAK2	9p24	exon 14	97	50–60	55–60
JAK2	9p24	exon 12	1–2	rare	rare
MPL	1p34	exon 10	rare	3–5	5–10
CALR	19p13	exon 9	rare	20–30	25–35
TET2	4q24	all coding regions	10–20	5	10–20
IDH1/IDH2	2q33/15q26	exons 4	rare	rare	5
DNMT3A	2p23	exons 7–23	5–10	1–5	5–10
ASXL1	20q11	exon 13	2–5	2–5	15–30
EZH2	7q35-q36	all coding regions	1–3	rare	5–10
CBL	11q23	exons 8–9	rare	rare	5–10
SH2B3	12q24	exon 2	rare	rare	rare
SF3B1	2q33	exons 12–16	rare	rare	5–10
SRSF2	17q25	exon 1	rare	rare	10–15
U2AF1	21q22	exons 2–7	rare	rare	5–15

PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis

Langabeer et al EJH 2015:95;270–279

Phenotype Driver Mutations Activating the JAK-STAT Pathway in MPNs



- A very small percentage of PV pts may have *LNK* or *CALR* driver mutations
- Nondriver mutations most frequently occurring in MPNs: *TET2, ASXL1, DNMT3A*

Grinfeld J, et al. Haematologica. 2017;102:7-17.

Slide credit: clinicaloptions.com

2016 Revised WHO Diagnostic Criteria for Myeloproliferative Neoplasms

Arber et al. Blood 2016;127:2391

		Polycythemia Vera (PV)		Essential Thrombocythemia (ET)		Primary Myelofibrosis (PMF) (overt)	Primary Myelofibrosis (prefibrotic) (prePMF)
Major criteria	1	Hemoglobin (Hgb) >16.5 g/dL (men) >16 g/dL (women) or Hematocrit >49% (men) >48% (women) or ↑ red cell mass >25% above mean	1	Platelet count ≥450 x 10^9/L	1	Megakaryocyte proliferation and atypia*** and ≥ grade 2 reticulin/collagen fibrosis ***megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering	Megakaryocyte proliferation and atypia*** and ≤ grade 1 reticulin/collagen fibrosis, Increased cellularity, granulocytic proliferation and decreased erythropoiesis
	2	Bone marrow (BM) tri-lineage myeloproliferation with pleomorphic mature megakaryocytes*	2	BM megakaryocyte proliferation with large and mature morphology and hyper-lobulated nuclei. Reticulin fibrosis grade should be ≤1	2	Not meeting WHO criteria for other myeloid neoplasm	Not meeting WHO criteria for other myeloid neoplasm
	3	Presence of *JAK2* mutation	3	Not meeting WHO criteria for other myeloid neoplasms	3	Presence of *JAK2*, *CALR* or *MPL* mutation or presence of another clonal marker or absence of evidence for reactive bone marrow fibrosis	Presence of *JAK2*, *CALR* or *MPL* mutation or presence of another clonal marker or absence of evidence for reactive bone marrow fibrosis
			4	Presence of *JAK2*, *CALR* or *MPL* mutation			
Minor criteria		1. Subnormal serum erythropoietin level		1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis	1	1. Anemia not otherwise attributed 2. Leukocytosis ≥11 x 10^9/L 3. Palpable splenomegaly 4. Increased lactate dehydrogenase (LDH), above upper normal limit 5. Leukoerythroblastosis	1. Anemia not otherwise attributed 2. Leukocytosis ≥11 x 10^9/L 3. Palpable splenomegaly 4. Increased lactate dehydrogenase (LDH), above upper normal limit

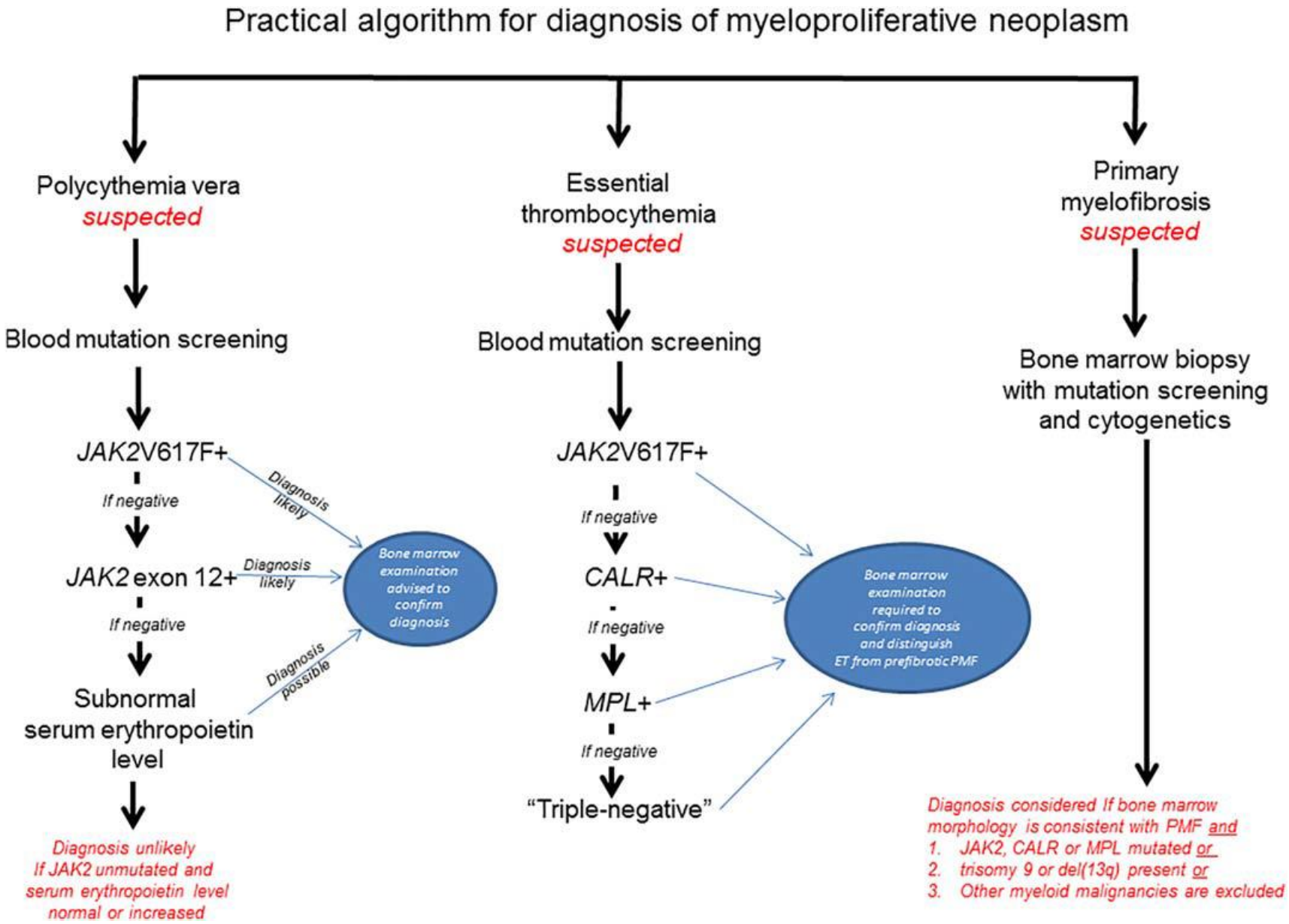
PV diagnosis requires meeting all three major criteria or the first two major criteria and one minor criterion.
*BM biopsy may not be not required if Hb >16.5 g/dL in men or 16.5 in women (Hct >55.5 in men and 49.5 in women)

ET diagnosis requires meeting all 4 major criteria or first three major criteria and one minor criterion

PMF diagnosis requires meeting all 3 major criteria and at least one minor criterion

prePMF diagnosis requires meeting all 3 major criteria and at least one minor criterion

Tefferi & Barbui AJH 2016



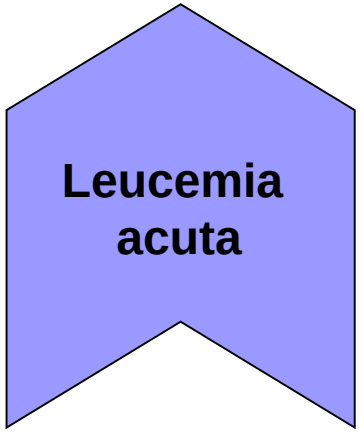
Tefferi & Barbui Am. J. Hematol. 92:95–108, 2016.

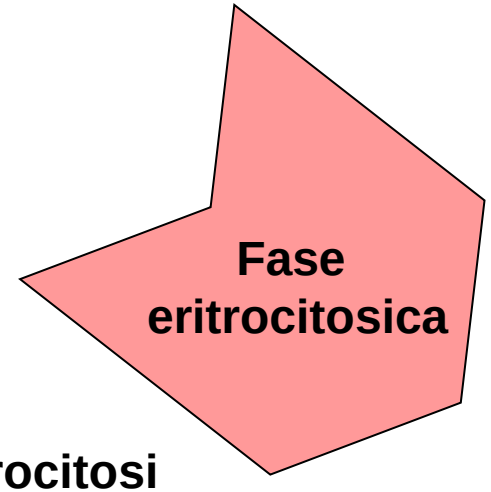
Policitemia Vera (PV)

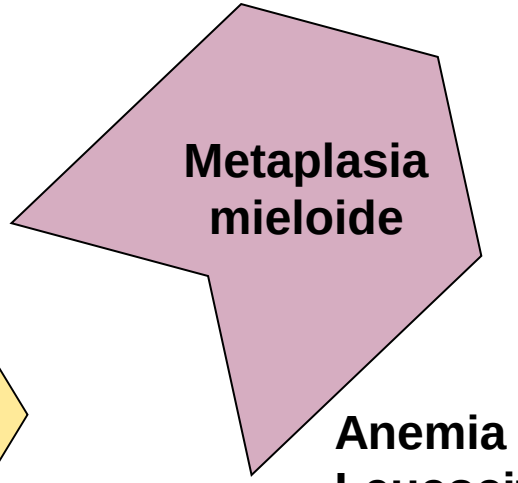
- **Definizione**
  - Malattia neoplastica derivata dall'espansione clonale della cellula staminale trasformata e caratterizzata soprattutto da incremento della massa eritrocitaria.

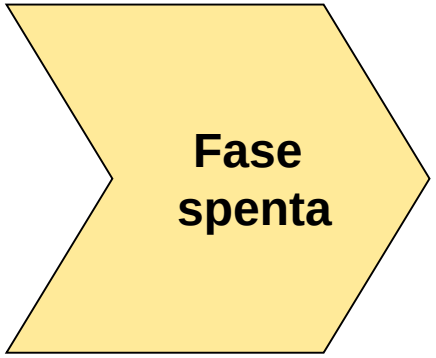
- **Epidemiologia**
  - Incidenza in Europa: 8-10 casi/1,000,000 per anno (2 in Giappone, 13 in Australia)

PV: decorso









Eritrocitosi
Leucocitosi
Piastrinosi
Splenomegalia
Trombosi
Emorragie
Prurito

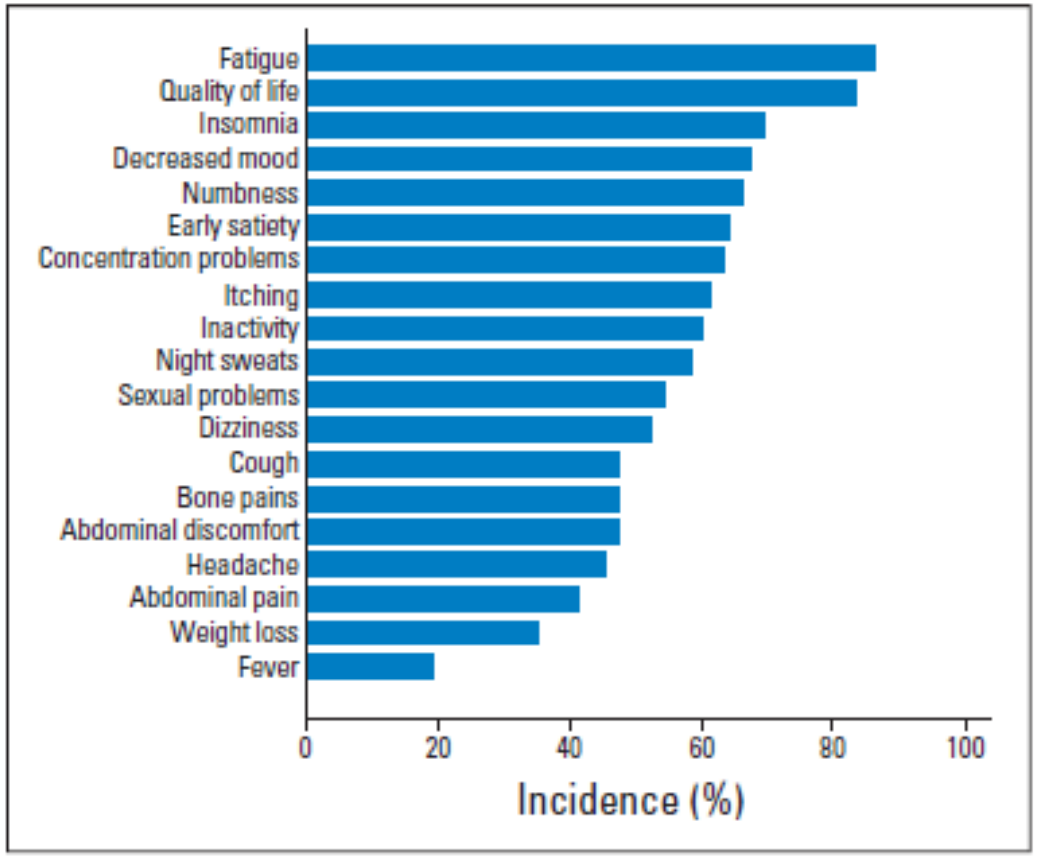
Parametri ematologici stabili
Nessuna terapia

Anemia
Leucocitosi
Piastrinosi o piastrinopenia
Splenomegalia
Febbre
Calo ponderale

PV: clinica

- **Età media 60 anni,**
- **M/F 2:1**

- **Esordio**
  - **Asintomatico**
  - **Sintomatico**
    - **Cefalea, acufeni, vertigini, disturbi visivi, (scotomi, diplopia) da iperviscosità ematica**
    - **Episodi vascolari (trombotici e/o emorragici) di diversa gravità (40% dei casi causa di morte)**
    - **Prurito**
    - **Ipertensione**
    - **rubeosi**



Stein et al, JCO 2015

2008 WHO DIAGNOSTIC CRITERIA FOR PV

A1	**Hgb >18.5 g/dl (men) or >16.5 g/dl (women) or Hgb or Hct > 99th percentile of reference range for age, sex or altitude of residence or** **Hgb >17 g/dl (men), or > 15 g/dl (women) if associated with a sustained increase of >= 2g/dl from baseline that cannot be attributed to correction of iron deficiency or** **Elevated red cell mass > 25% above mean normal predicted value**
A2	**Presence of *JAK2*617V>F or similar mutation**
B1	**BM trilineage myeloproliferation**
B2	**Subnormal serum EPO levels**
B3	**Endogenous erythroid colony formation in vitro**

A1 + A2 + 1 minor criterion or A1 and 2 minor criteria

Tefferi A & Vardiman JW, Leukemia 2008; 22: 14.

Evolution of WHO PV Diagnostic Criteria

2008 WHO[1]	2016 WHO[2]
Requirement for diagnosis	
▪ 2 major and 1 minor criteria OR 1 major and 2 minor criteria	▪ All 3 major criteria OR first 2 major criteria and the minor criterion
Major criteria	
1. Hb > 18.5 g/dL (Men); > 16.5 g/dL (Female) *2.* *JAK2* V617F mutation or similar (*JAK2* exon 12)	1. Hb > 16.5 g/dL or Hct > 49% (men); or Hb > 16.0 g/dL or Hct > 48% (women); or increased red cell mass 2. BM biopsy showing hypercellularity, trilineage growth (panmyelosis) with erythroid, granulocytic, and pleomorphic, mature megakaryocytic proliferation *3.* *JAK2* V617F or *JAK2* exon 12 mutation
Minor criteria	
1. Subnormal serum EPO level 2. BM trilineage proliferation 3. Endogenous erythroid colony growth	1. Subnormal serum EPO level

1. Thiele J, et al. Curr Hematol Malig Rep. 2009;4:33-40. 2. Arber DA, et al. Blood. 2016;127:2391-2405. Slide credit: clinicaloptions.com

Familial polycythemia (rare)

- **High Epo levels**
  - Low P50: increased affinity of hemoglobin for oxygen
    - High-O2-affinity hemoglobin variants
    - 2,3-bisphosphoglycerate (2,3-BPG) deficiency
    - Methemoglobinemia
  - Normal P50: defects in oxygen sensing
    - Homozygous Chuvash *VHL* mutation
    - Other *VHL* mutations
- **Low or normal Epo levels**
  - *Epo-R* mutations: primary familial and congenital polycythemias

Table II. Germline mutations causing MPN-like disorders.

Gene	Disease	Inheritance	Representative references
Hereditary erythrocytosis			
EPOR	ECYT1: Primary familial and congenital polycythaemia (PFCP)	AD	de la Chapelle *et al* (1993)
VHL	ECYT2: von Hippel-Lindau disease	AR	Ang *et al* (2002)
			Pastore *et al* (2003)
			Percy *et al* (2003)
			Perrotta *et al* (2006)
EGLN1 (*PHD2*)	ECYT3	AD	Percy *et al* (2006)
			Percy *et al* (2007)
EPAS1 (*HIF2α*)	ECYT4	AD	Percy *et al* (2008)
HBB	High oxygen affinity variants	AD	Rumi *et al* (2009)
BPGM	2,3 DPG deficiency	AR-AD	Max-Audit *et al* (1980)
Hereditary thrombocytosis			
THPO	THCYT1	AD	Wiestner *et al* (1998)
			Kondo *et al* (1998)
			Ghilardi and Skoda (1999)
			Ghilardi *et al* (1999)
			Liu *et al* (2008)
MPL	THCYT2 (*MPL* S505N)	AD	Ding *et al* (2004)
			Teofili *et al* (2007)
	MPL Baltimore (*MPL* K39N)	Functional SNP*	Moliterno *et al* (2004)
	MPL P106L	Functional SNP*	El-Harith *et al* (2009)

AD, autosomal dominant; AR, autosomal recessive; ECYT, familial erythrocytosis; MPN, myeloproliferative neoplasm; SNP, single nucleotide polymorphism; THCYT, thrombocythaemia.

*Mild thrombocytosis in heterozygous individuals, severe thrombocytosis in homozygous individuals.

Rumi & Cazzola BJH 2017

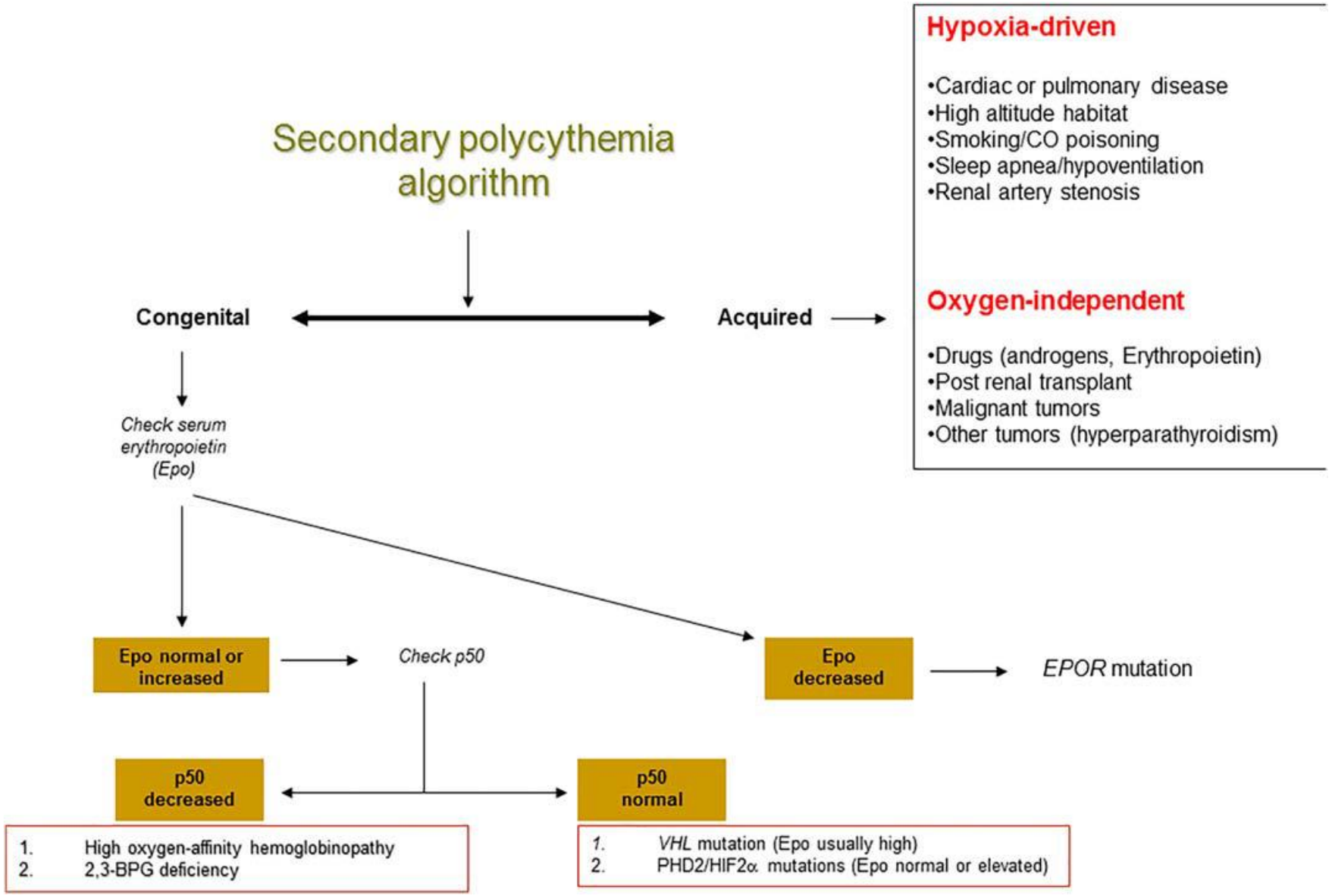
Secondary polycythemia

- **Physiologically inappropriate EPO increase**
  - **Tumors:**
    - renal cell carcinoma,
    - Wilms tumor,
    - hepatoma,
    - uterine fibroma,
    - cerebellar hemangioma,
    - atrial myxoma
  - **Benign renal disease:**
    - polycystic kidney disease,
    - hydronephrosis,
    - renal artery stenosis (rare)
  - **Postrenal transplantation erythrocytosis**
  - **Endocrine disorders:**
    - pheochromocytoma,
    - primary aldosteronism,
    - Bartter syndrome,
    - Cushing syndrome
  - **Erythropoiesis-stimulating hormones**
    - Epo, androgens

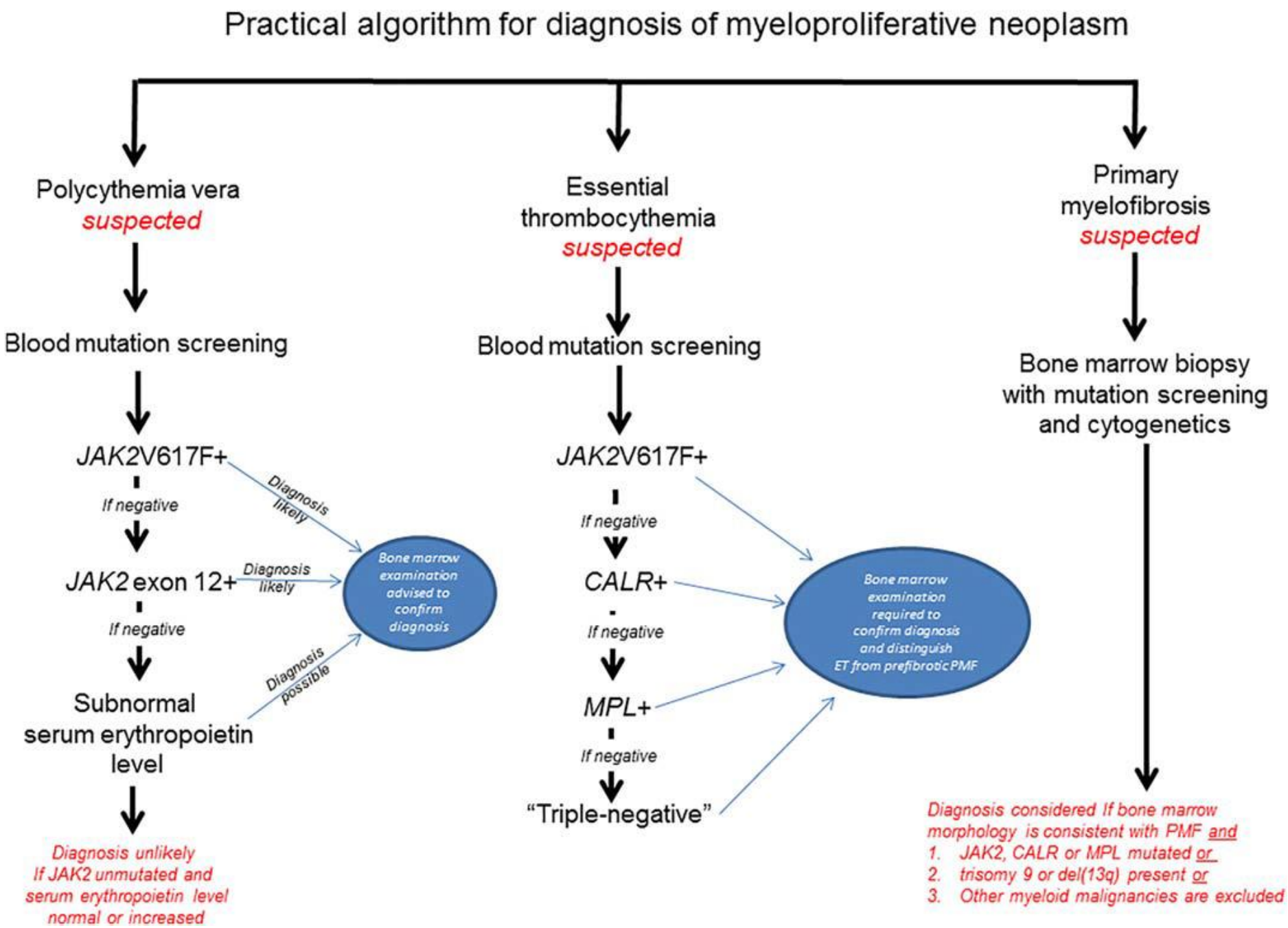
Secondary polycythemia

- **Physiologically appropriate EPO increase: response to hypoxia**
  - **Reduced PaO2**:
    - chronic lung disease,
    - pickwickian (obesity-hypoventilation) syndrome,
    - sleep apnea,
    - high altitude,
    - cyanotic heart disease
  - **Normal PaO2**:
    - smokers' and CO-induced polycythemia

diagnostic algorithm for secondary erythrocytosis



Tefferi & Barbui Am. J. Hematol. 92:95–108, 2016.



Tefferi & Barbui Am. J. Hematol. 92:95–108, 2016.

Table 1. Risk Factors Associated With Increased Morbidity and Mortality in Patients With Polycythemia Vera

Risk Factors
For thrombosis
Age > 60 years
Previous history of thrombosis
Leukocytosis[39-42]*
Increased *JAK2 V617F* allele burden[6,43-45]*
High-risk gene expression profile[46]*
For transformation to myelofibrosis or secondary acute myeloid leukemia
Older age[47]
Longer disease duration[48]
Leukocytosis[41]
Exposure to phosphorus-32, pipobroman, or chlorambucil[7,48]
Risk factor associated with decreased survival
Older age[7]
Leukocytosis[7]
History of venous thrombosis[7]
Abnormal karyotype[7]

*Emerging or controversial risk factor.

Stein et al, JCO 2015

Thrombosis Risk-Adapted Management of PV

Category	Characteristics	Treatment
Low risk	Age ≤ 60 yrs AND no history of thrombosis	▪ Therapeutic phlebotomy (goal Hct < 45%) ▪ ASA 81 mg daily ▪ Address CV modifiable risk factors
High risk	Age > 60 yrs OR history of thrombosis	▪ All the above, AND ▪ Cytoreductive therapy ▪ First line ▪ Hydroxyurea ▪ IFN-α ▪ Busulfan* ▪ Second line ▪ Ruxolitinib ▪ IFN-α

*For pts > 70 yrs of age.

- Indications for cytoreduction in low-risk pts with:
  - Frequent phlebotomy requirement
  - Progressive leukocytosis
  - Platelets > 1500 x 10^9/L (risk of bleeding)
  - Severe disease-related symptoms

Barbui T, et al. J Clin Oncol. 2011;29:761-770. Tefferi A, et al. Am J Hematol. 2015;90:162-173.

Recommendations for Second-line PV Therapy

Pt Characteristics	Options
Inadequate response or intolerance to HU	Ruxolitinib, IFN-α[1,2]
Inadequate response or intolerance to IFN-α	HU[1]
Short life expectancy	Busulfan, pipobroman, or ^{32}P[1]

1. Barbui T, et al. J Clin Oncol. 2011;29:761-770.
2. Ruxolitinib [package insert].

Slide credit: clinicaloptions.com

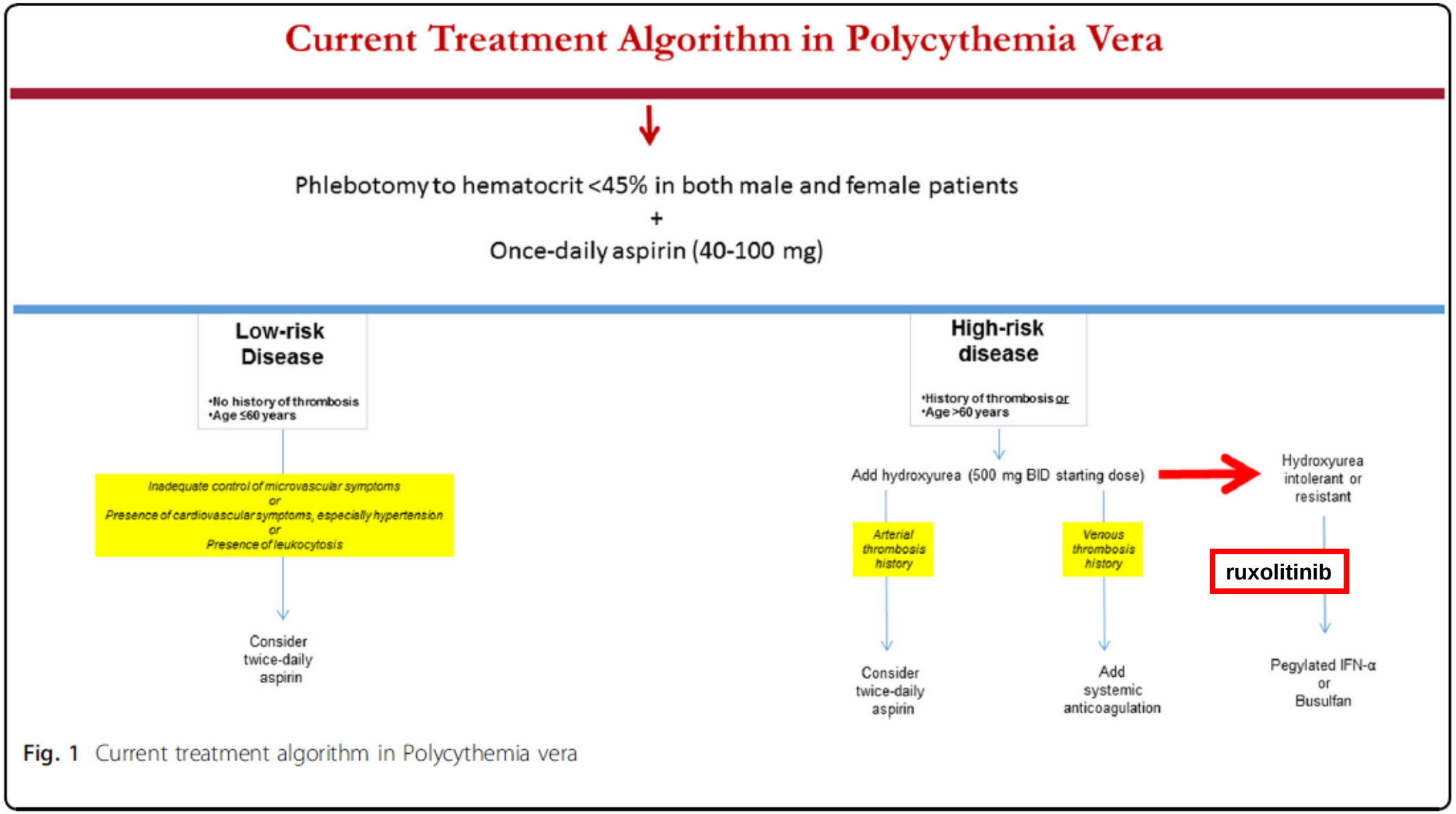


Fig. 1 Current treatment algorithm in Polycythemia vera

CV risk factors: Hypertension, hypercolesterolemia, diabetes, smoking, congestive heart failure

Tefferi et al. Blood Cancer Journal (2018) 8:3.

Treatment of PV

- Low-risk PV patients
  - phlebotomy (grade A; Hct < 45%) and low-dose aspirin (grade A)
- Intermediate and high-risk patients
  - HU + phlebotomy and aspirin (grade A).
  - Alpha-interferon in younger subjects and women of childbearing age (grade C).
- New treatments:
  - JAK2 inhibitors: ruxolitinib

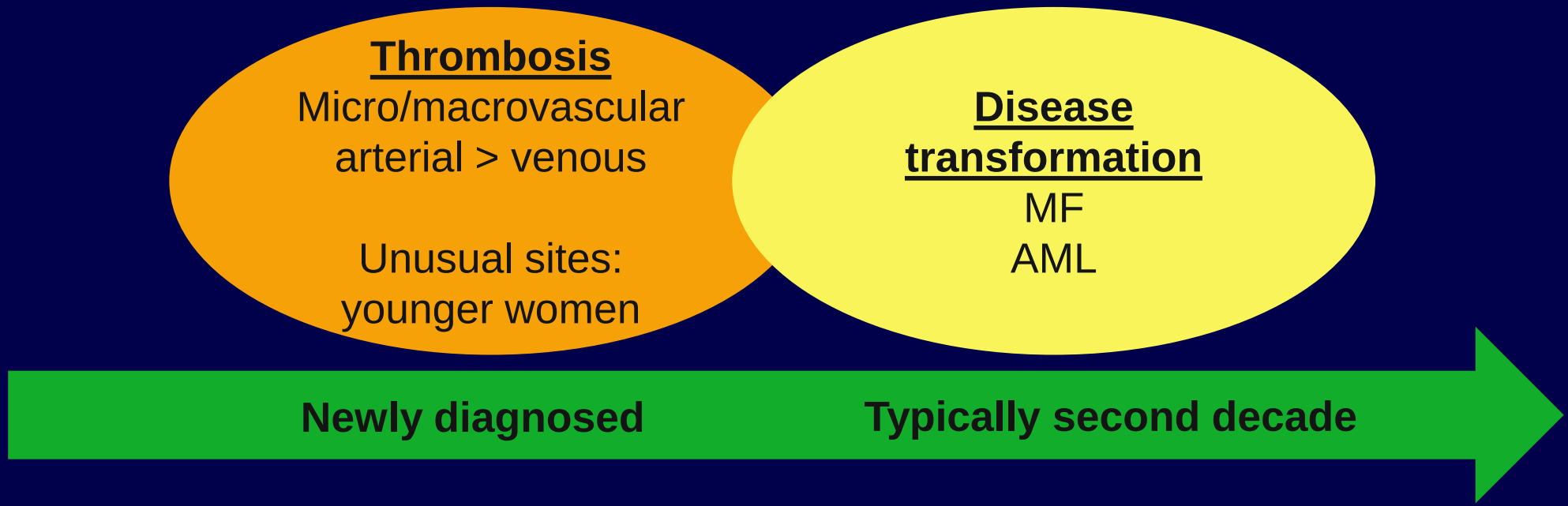
Clinical Complications of PV

Symptoms (*Independent of Risk*)

Cytokine: fatigue, pruritus, constitutional symptoms, bone pain

Vascular: headache, dizziness, numbness, decreased concentration, low mood, sexual issues

Disease evolution: splenomegaly, constitutional symptoms



Mesa RA, et al. Cancer. 2007;109:68-76. Scherber R, et al. Blood. 2011;118:401-408. Geyer HL, et al. Blood. 2014;124:3529-3537. Stein BL, et al. Ann Hematol. 2014;93: 1965-1976. Stein BL, et al. Leuk Lymphoma. 2013;54:1989-1995.

Slide credit: clinicaloptions.com

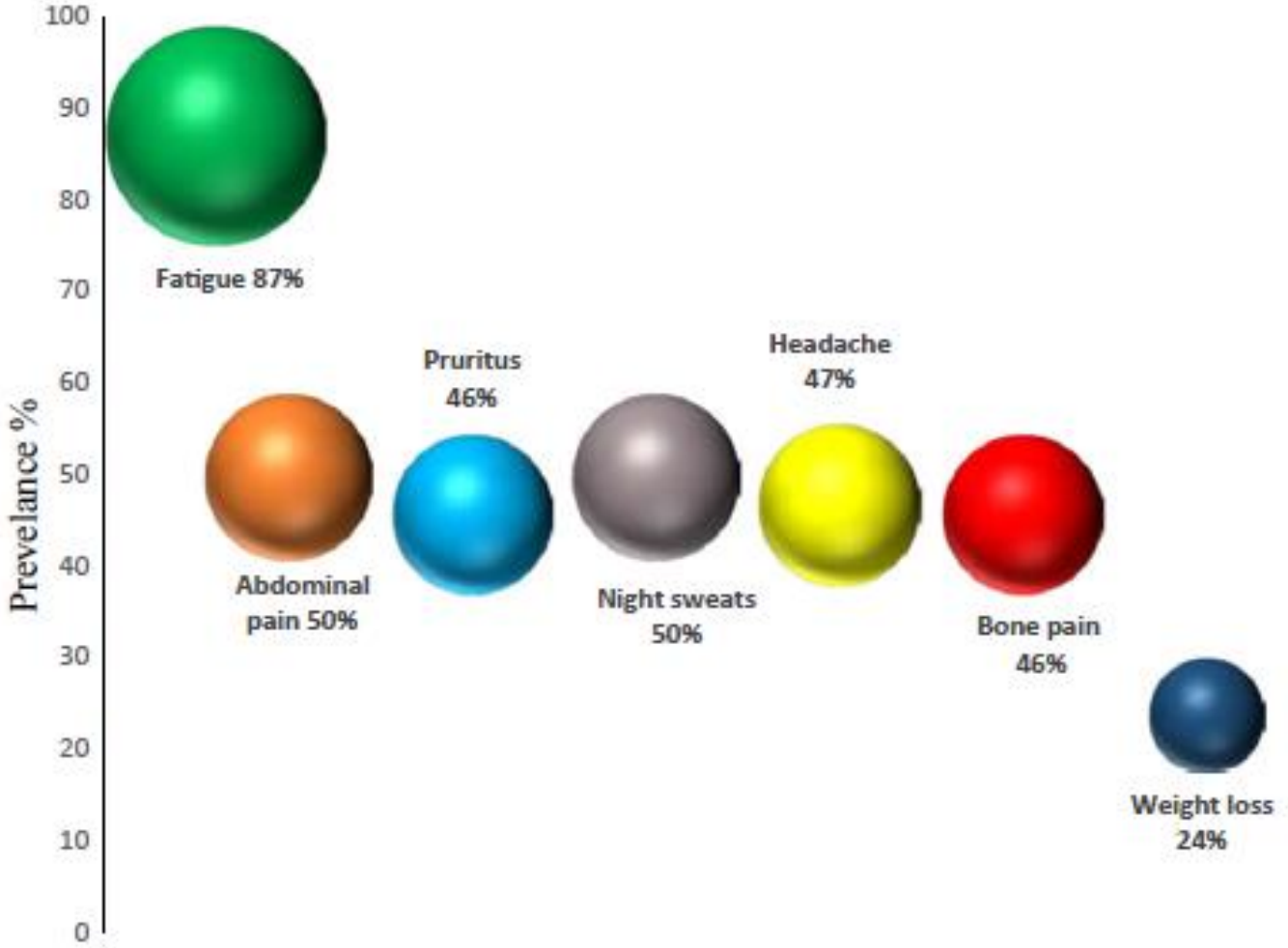
Trombocitemia essenziale TE

- **Definizione**
  - Disordine clonale mieloproliferativo cronico caratterizzato da trombocitosi (pst > 450.000 μL) con iperplasia megacariocitaria nel midollo.
- **Incidenza**
  - 1-2.5 casi 100.000 individui anno

TE: clinica

- Età: media 50 anni (range 40-70)
- M=F
- Esordio
  - Asintomatico
  - Manifestazioni trombotiche arteriose e venose (1/3 dei casi)
    - Distretti mesenterico, renale, portale, plenico
  - Manifestazioni emorragiche cutanee e mucose
    - Ematemesi e melena
    - S. di von Willebrand acquisita (Plt > 1.000.000 μL)
  - Manifestazioni neurologiche
    - Cefalea, parestesie, instabilità microcircolo piedi e emani (eritromelalgia), eritema e dolore urente alle estremità
    - Aborti in gravidanza
  - Splenomegalia

Prevalence of constitutional symptoms reported by ET patients



Aliman t al, BJH 2015:171:306

2008 WHO diagnostic criteria for ET

A1	**Sustained platelet count > 450 x 109/L**
A2	**Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid proliferation.**
A3	**Not meeting WHO criteria for PV, PMF, CML, MDS or other myeloid neoplasm**
A4	**Demonstration of *JAK2*617V>F or other clonal marker, or no evidence for reactive thrombocytosis‖**

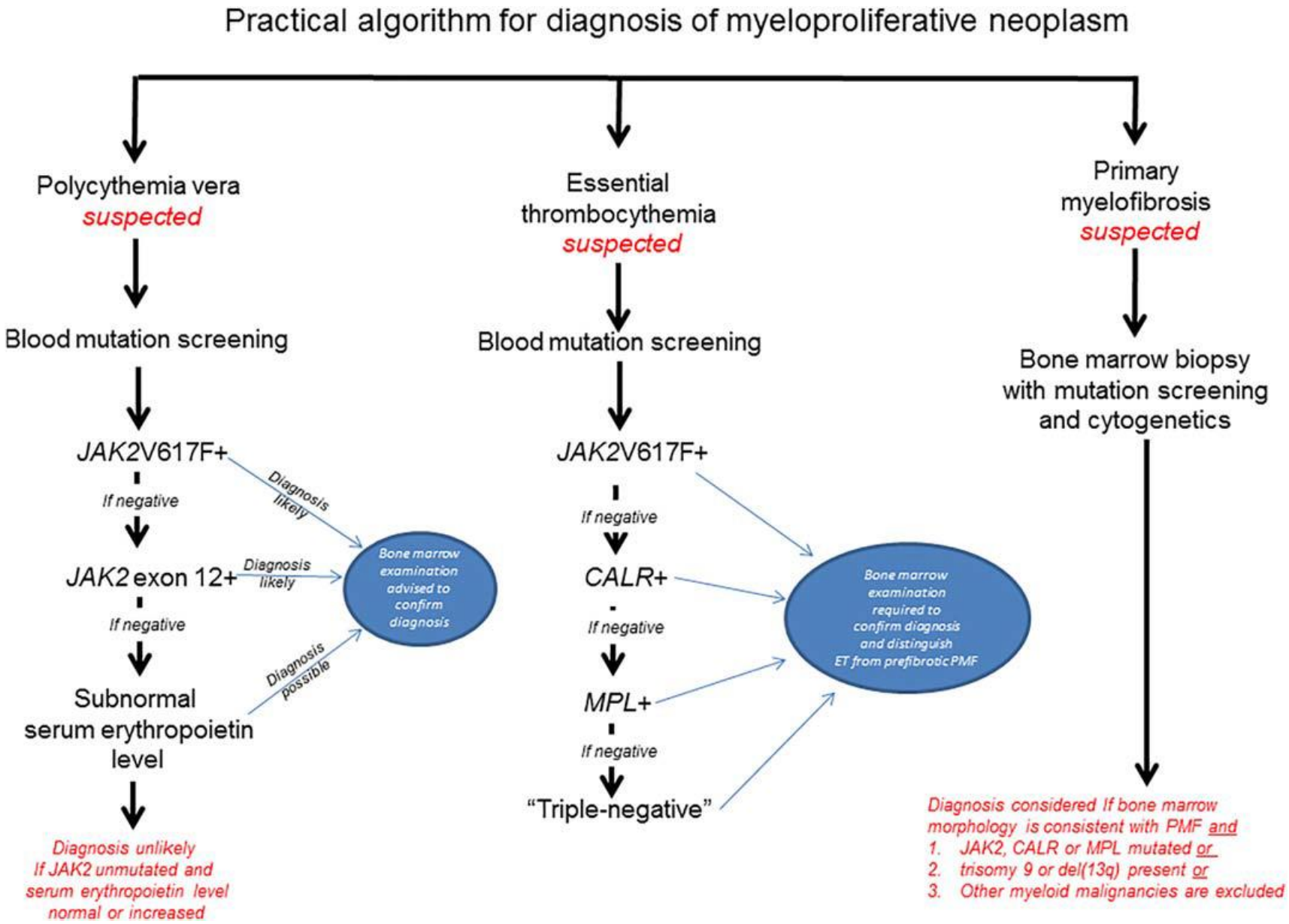
Diagnosis of ET requires all 4 major criteria

Tefferi A & Vardiman JW, Leukemia 2008; 22: 14.

2016 WHO criteria for ET

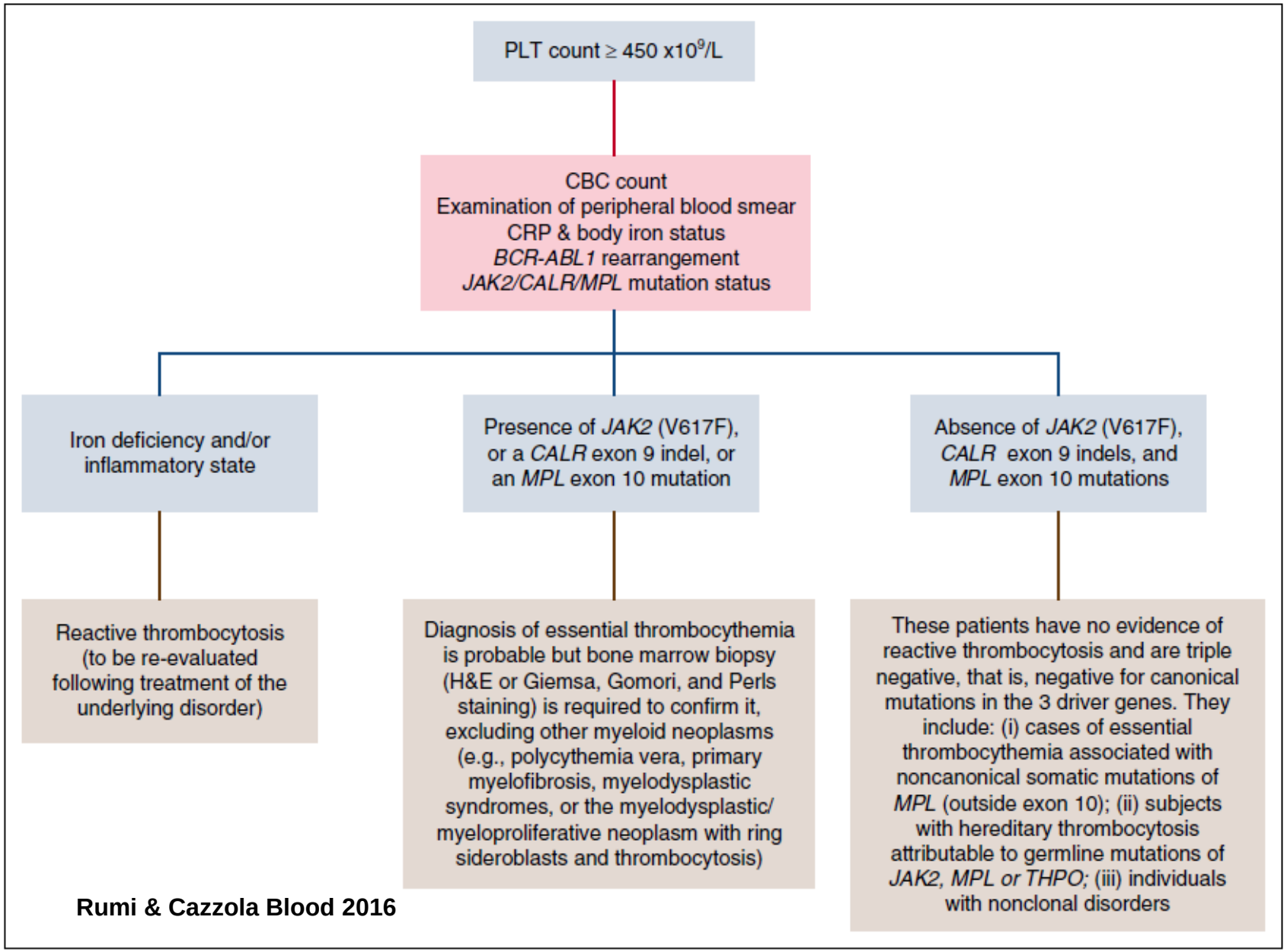
WHO ET criteria
Major criteria
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis 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

Arber DA et al. Blood. 2016; 127(20):2391-2405



Tefferi & Barbui Am. J. Hematol. 92:95–108, 2016.

approach to the differential diagnosis of thrombocytosis.



Rumi & Cazzola Blood 2016

Familial thrombocytosis

- **Familial thrombocytosis (rare)**
  - High *Tpo* levels:
    - *Tpo* gene mutations
  - Activating mutation of *c-Mpl (Tpo-R)*
  - Others

Differential Diagnosis of Thrombocytosis

Reactive Causes

- Iron deficiency anemia
- Post-surgery
- Splenectomy
- Infection
- Inflammation
- Connective tissue disease
- Metastatic cancer
- Lymphoproliferative disorders

Other Myeloid Disorders

- PV
- Primary MF
- Chronic myeloid leukemia
- MDS with deletion of 5q
- Refractory anemia with ring sideroblasts and thrombocytosis

Bleeker JS, et al. Thrombosis. 2011;2011:536062.

Slide credit: clinicaloptions.com

Secondary thrombocytosis

- **Secondary thrombocytosis**
  - **Transient processes**
    - Acute blood loss
    - Recovery ("rebound") from thrombocytopenia
    - Acute infection or inflammation
    - Response to exercise
    - Drug reactions
  - **Sustained processes**
    - Iron deficiency
    - Hemolytic anemia
    - Asplenic state (eg, after splenectomy)
    - Chronic inflammatory or infectious diseases
    - Cancer

Criteria for evaluating the thrombotic risk of ET (IPSET

Risk factor	HR	Score
Age > 60 years	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
JAK2V617F	2.04	2

Low risk implies a score = 0–1; intermediate risk, score = 2; and high risk, score ≥ 3

CV risk factors: Hypertension, hypercolesterolemia, diabetes, smoking, congestive heart failure

Barbui et al. Leukemia. 2018;32:1057-1069.

Current Treatment Algorithm in Essential Thrombocythemia

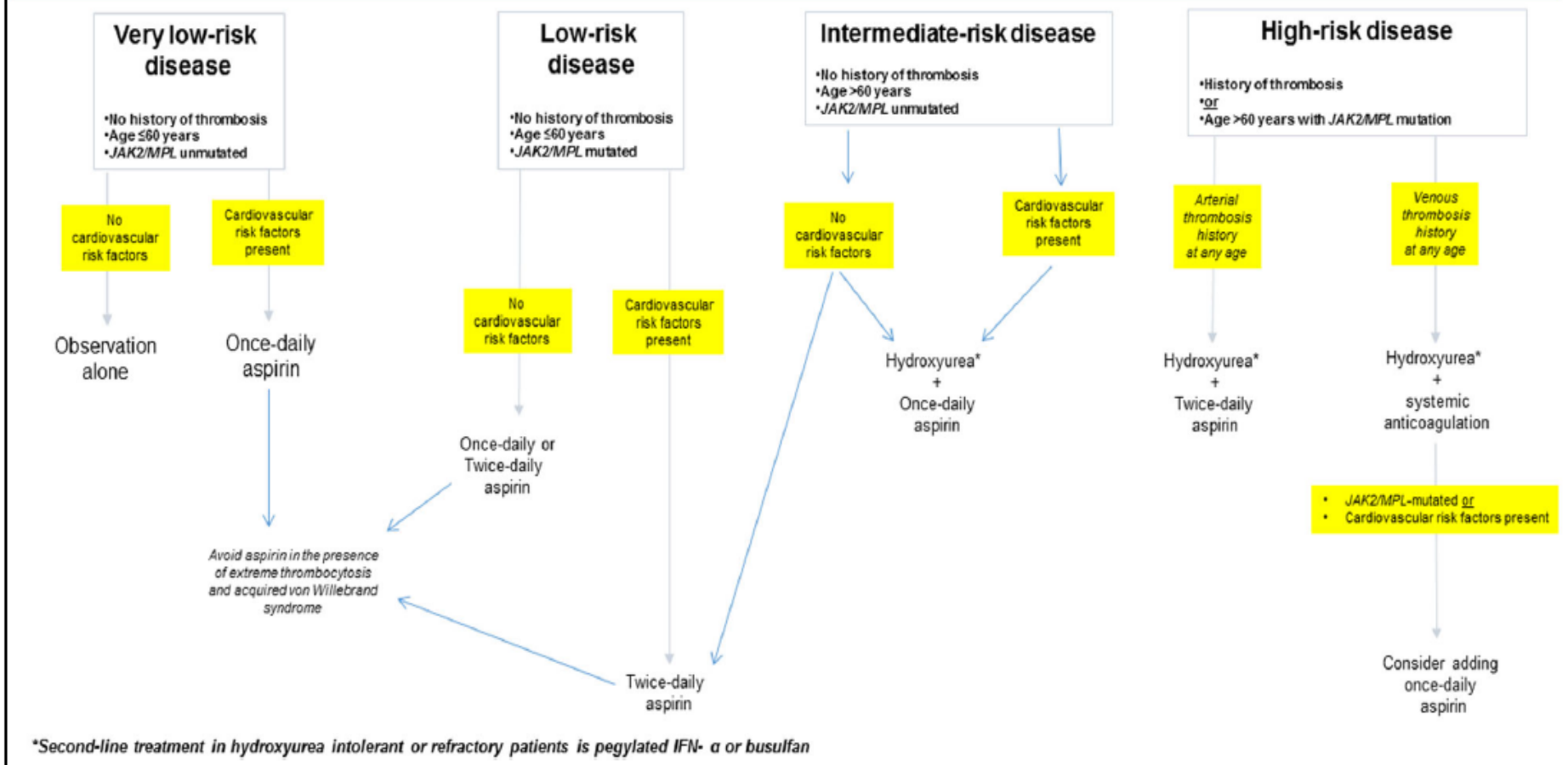


Fig. 1 Current treatment algorithm in essential thrombocythemia Second-line treatment in hydroxyurea intolerant or refractory patients in pegylated IFN-α or busulfan

CV risk factors: Hypertension, hypercolesterolemia, diabetes, smoking, congestive heart failure

Tefferi et al. Blood Cancer Journal (2018) 8:2

Risk-stratified approach to the management of ET

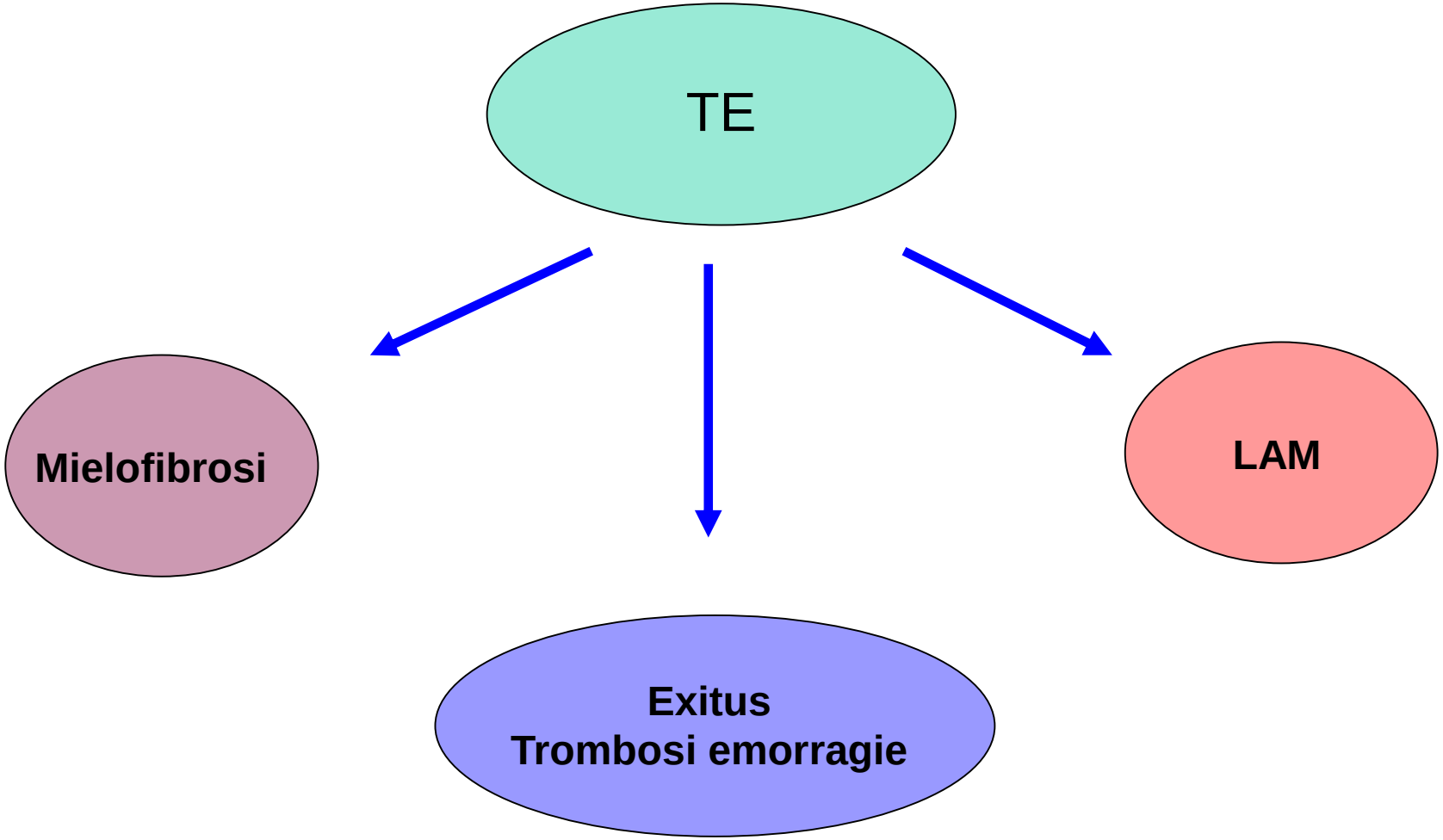
1. **Manage reversible risk factors for vascular disease (smoking, diabetes, hypercholesterolaemia, etc.)**

2. **Low-dose ASA, except in pts with history of haemorrhage or acquired von Willebrand's disease.**

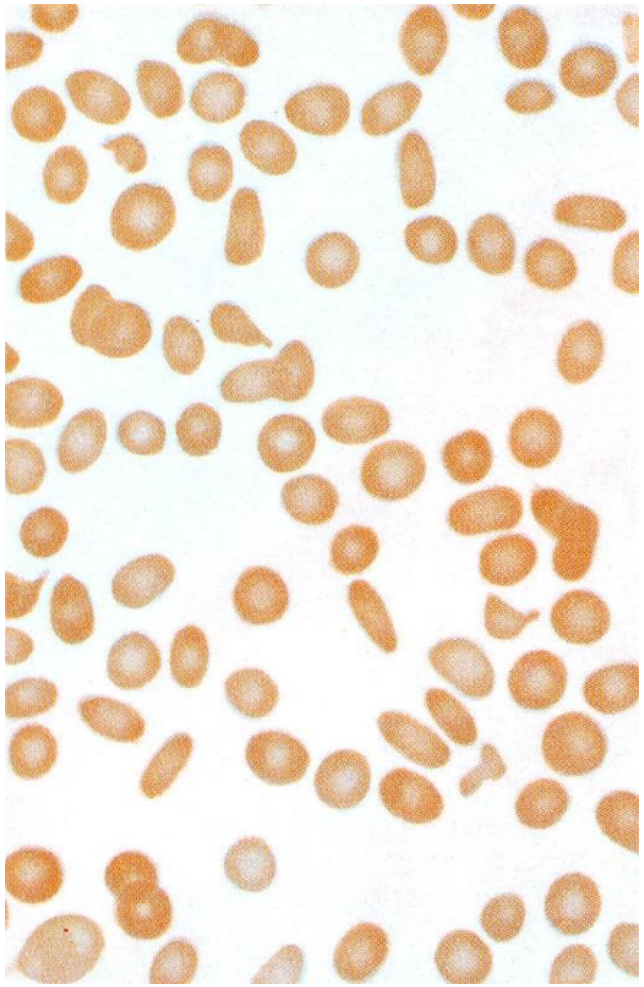
3. **Stratify treatment according to thrombotic risk:**
    i. **High-risk pts**
        i. **HU and low-dose ASA**
    ii. **Intermediate-risk pts**
        i. **low-dose ASA ± HU**
    iii. **Low-risk patients**
        i. **low-dose ASA**

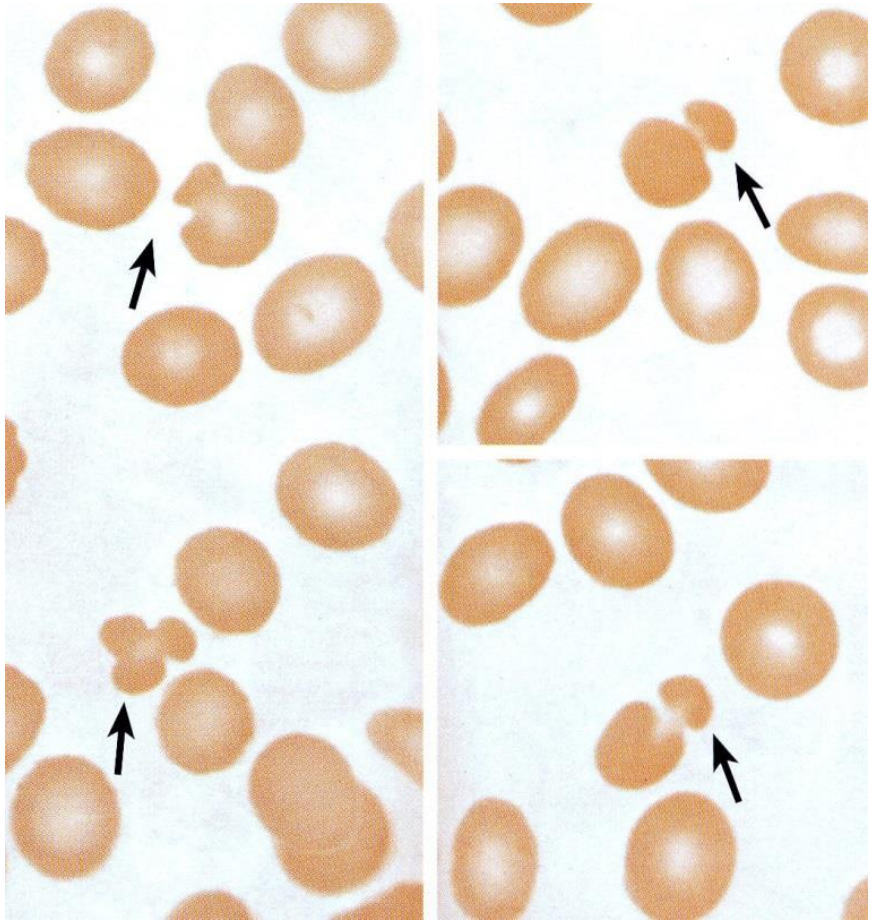
4. **For patients refractory to or intolerant of HU; non-leukaemogenic treatment (IFN-α or anagrelide).**

TE: evoluzione



Idiopathic myelofibrosis





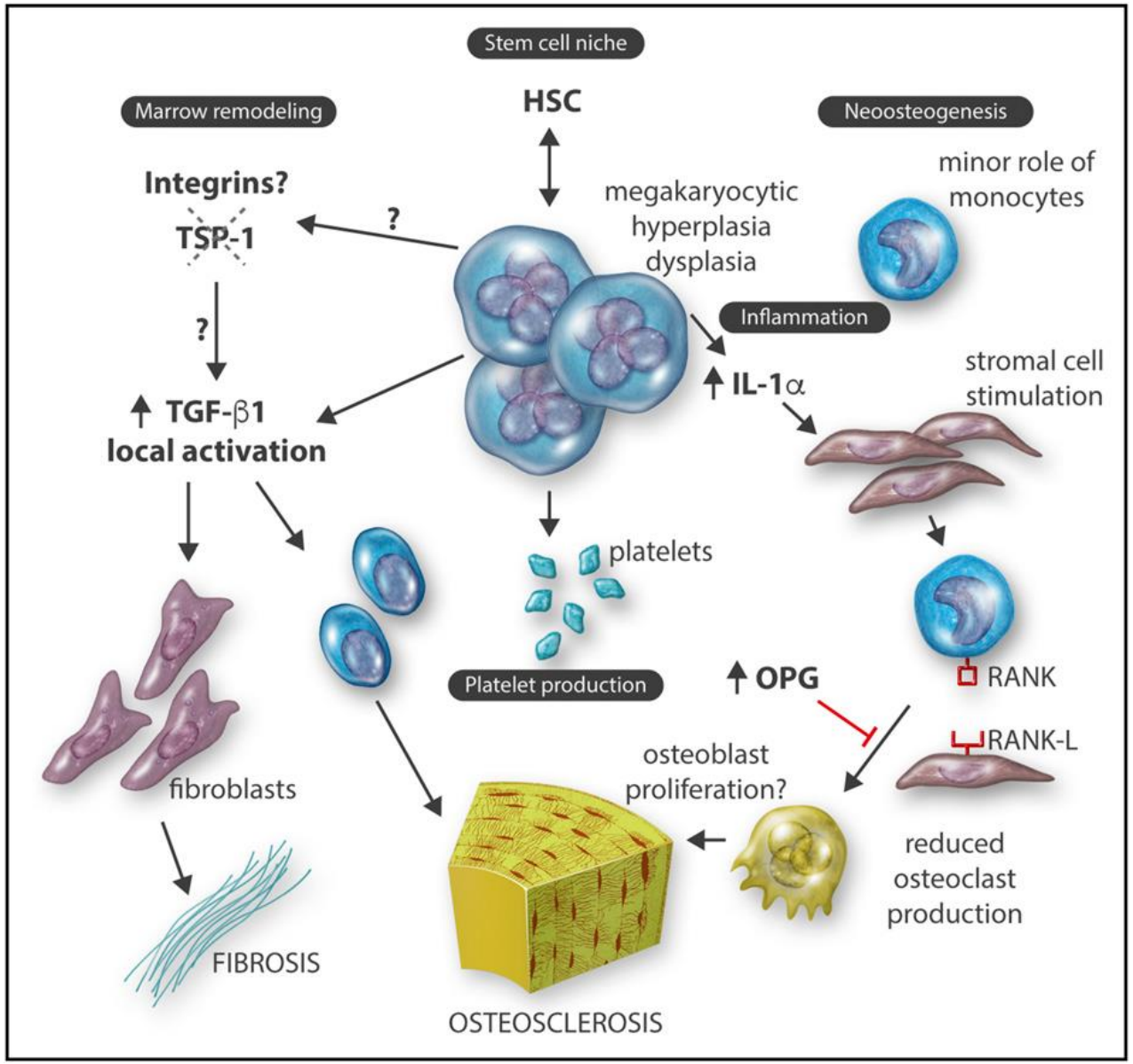
definition

- **Chronic myeloproliferative disorder characterised by:**
  - **Anemia**
  - **Splenomegaly**
  - **Immature granulocytes, erythroblasts, teardrop-shaped red cells and an increase in CD34+ cells in the blood**
  - **Marrow fibrosis**
  - **Osteosclerosis**
  - **Fibrohematopoietic tumors that can occur in virtually any tissue**

epidemiology

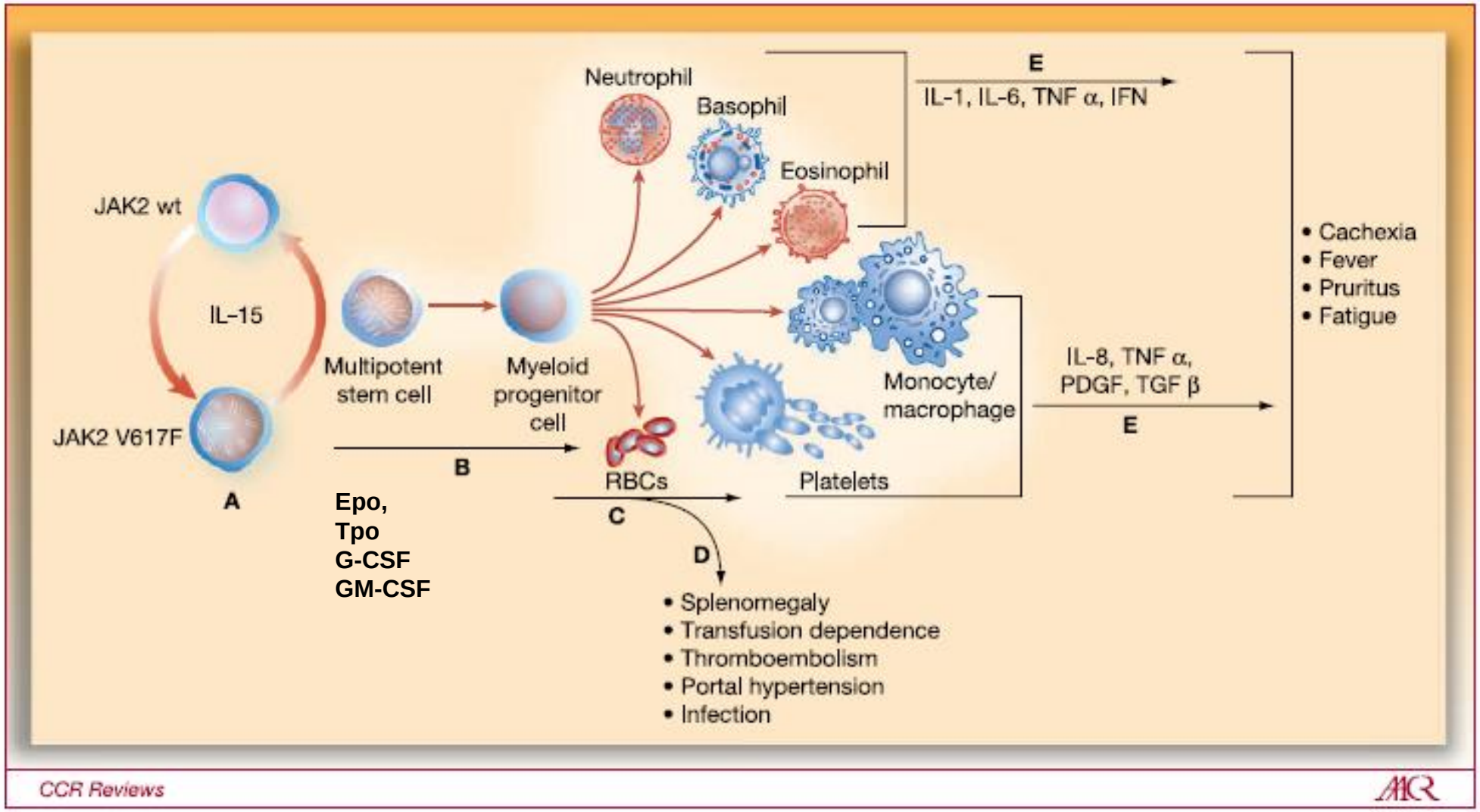
- **Incidence in western countries**
  - 0.4-0.7 new cases per 100.000 person/year
- **Median age at presentation 65 years**
  - 22% of patients are aged 55 years or less
- **Secondary complication** of polycythemia vera and essential thrombocythemia (rate 10-20% after 15-20 years of follow-up)
- 10-20% of patients have **leukemic transformation** in the first 10 years

MKs play a central role in MI pathogenesis.



Vainchenker W. Blood. 2017;129(6):667-679

Role of JAK2 signaling in the pathogenesis of splenomegaly, clinical manifestations, and constitutional symptoms in myelofibrosis.



Srdan Verstovse.k Clin Cancer Res; 16(7) April 1, 2010

2008 WHO diagnostic criteria for primary MF

A1	**Megakaryocyte proliferation and atypia* accompanied by either reticulin and/or collagen fibrosis, or** **In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).**
A2	**Not meeting WHO criteria for PV, CML, MDS, or other myeloid neoplasm**
A3	**Demonstration of *JAK2*617V>F or other clonal marker, no evidence ofreactive marrow fibrosis**
B1	**Leukoerythroblastosis**
B2	**Increase in serum lactate dehydrogenase level**
B3	**Anemia**
B4	**Palpable splenomegaly**

Diagnosis of PMF requires meeting all 3 major criteria and 2 minor criteria

Tefferi A & Vardiman JW, Leukemia 2008; 22: 14.

WHO Diagnostic Criteria: Primary Prefibrotic MF

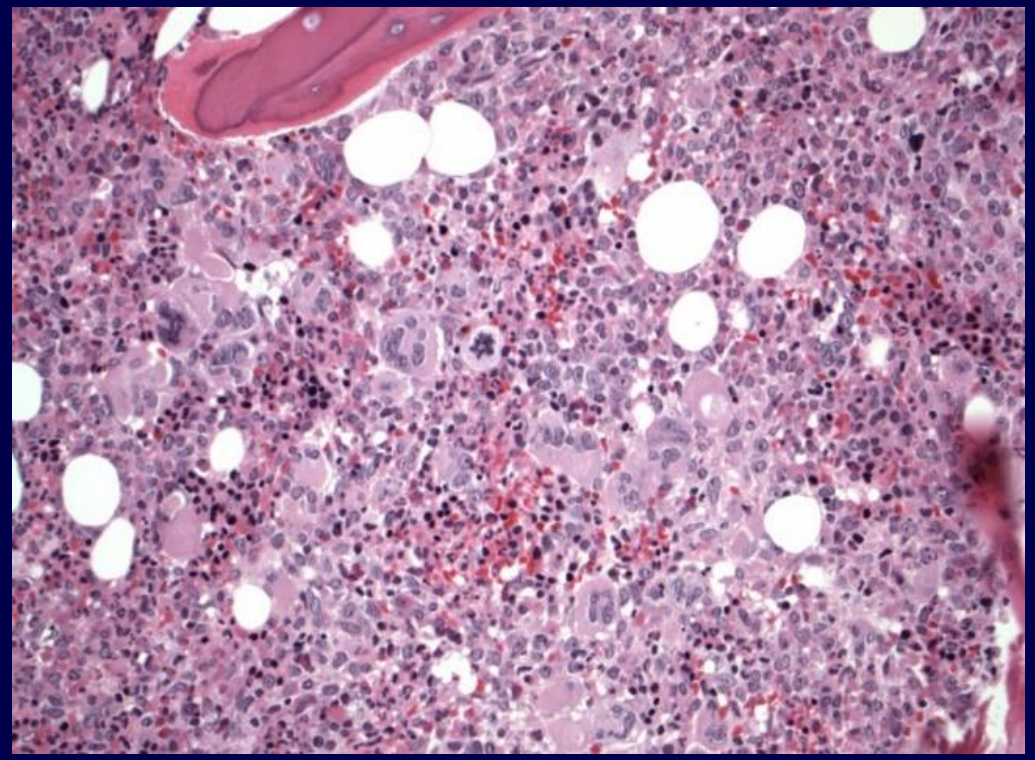
Primary Prefibrotic MF Diagnosis	
Requirement for diagnosis	
▪ All 3 major criteria AND ≥ 1 minor criteria	
Major criteria	
1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1**	
2. JAK2, CALR, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF	
3. Not meeting WHO criteria for other myeloid malignancies	
Minor criteria	
1. Anemia not attributed to a comorbid condition	3. Palpable splenomegaly
2. Leukocytosis ≥ 11 x 10^9/L	4. LDH increased above ULN

*eg, *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1.*

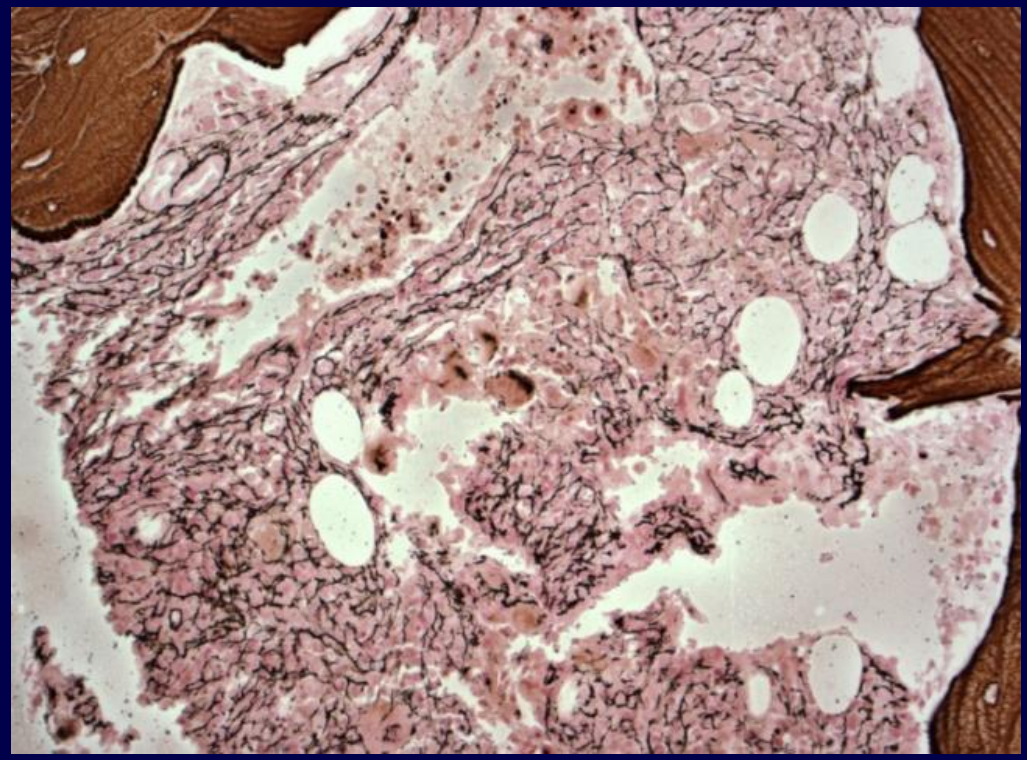
Arber DA, et al. Blood. 2016;127:2391-2405.

Slide credit: clinicaloptions.com

Primary MF



Clustering, atypical megakaryocytes



Bone marrow reticulin fibrosis

Faculty communication.

Slide credit: clinicaloptions.com

Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
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 focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Arber DA et al. Blood. 2016; 127(20):2391-2405

Essential Thrombocythemia vs Prefibrotic MF: Diagnosis

Parameter	ET	Prefibrotic MF
Blood counts	Sustained thrombocytosis ($\geq 450 \times 10^9$/L)	Sustained thrombocytosis plus ≥ 1 of: **anemia, leukocytosis > 11 x 10^9/L, palpable splenomegaly, or ↑ LDH**
Bone marrow	**↑ enlarged, mature megakaryocytes with hyperlobulated nuclei**	**Atypical megakaryocyte proliferation with no reticulin fibrosis > grade 1; ↑ BM cellularity, granulocytic proliferation, and often ↓ erythropoiesis**
Mutations	*JAK2, CALR, MPL* (~ 90%) or another clonal marker	*JAK2, CALR, MPL* (~ 90%) or another clonal marker
Overt MF at 15 yrs, %	**9.3**	**16.9**
Cumulative AML at 15 yrs, %	**2.1**	**11.7**
15-yr survival, %	**80**	**59**

Barbui T, et al. J Clin Oncol. 2011;29:3179-3184. Arber DA, et al. Blood. 2016;127:2391-2405.

Differential Diagnosis of Thrombocytosis

Reactive Causes

- Iron deficiency anemia
- Post-surgery
- Splenectomy
- Infection
- Inflammation
- Connective tissue disease
- Metastatic cancer
- Lymphoproliferative disorders

Other Myeloid Disorders

- PV
- Primary MF
- Chronic myeloid leukemia
- MDS with deletion of 5q
- Refractory anemia with ring sideroblasts and thrombocytosis

Bleeker JS, et al. Thrombosis. 2011;2011:536062.

Slide credit: clinicaloptions.com

WHO Diagnostic Criteria: Primary Overt MF

Primary Overt MF Diagnosis	
Requirement for diagnosis	
▪ All 3 major criteria AND ≥ 1 minor criteria	
Major criteria	
1. Megakaryocytic proliferation and atypia **with reticulin and/or collagen fibrosis grade 2/3**	
2. JAK2, CALR, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF	
3. Not meeting WHO criteria for other myeloid malignancies	
Minor criteria	
1. Anemia not attributed to a comorbid condition	3. Palpable splenomegaly
2. Leukocytosis ≥ 11 x 10^9/L	4. LDH increased above ULN
	5. Leukoerythroblastosis

*eg, *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1.*

Arber DA, et al. Blood. 2016;127:2391-2405.

Post-ET vs Post-PV Myelofibrosis

Parameter	Post-ET MF	Post-PV MF
Clinical features	2 of the following: ▪ ≥ 1 constitutional symptom ▪ Increasing splenomegaly (> 5 cm, or newly palpable) ▪ Anemia and Hb decline ≥ 2 g/dL ▪ Increased LDH ▪ Leucoerythroblastic blood smear	2 of the following: ▪ ≥ 1 constitutional symptom ▪ Increasing splenomegaly (≥ 5 cm, or newly palpable) ▪ Anemia or loss of phlebotomy/ cytoreductive requirement ▪ Leucoerythroblastic blood smear
Bone marrow fibrosis	Grade 2/3 on a 0-3 scale	
Prognosis	Is the prognosis different than that of primary MF?	

Note: documentation of prior diagnosis of ET or PV (WHO criteria) required.

Barosi G, et al. Leukemia. 2008;22:437-438.

If Diagnostic Criteria for MF Not Met, What Are Other Causes of Fibrosis?

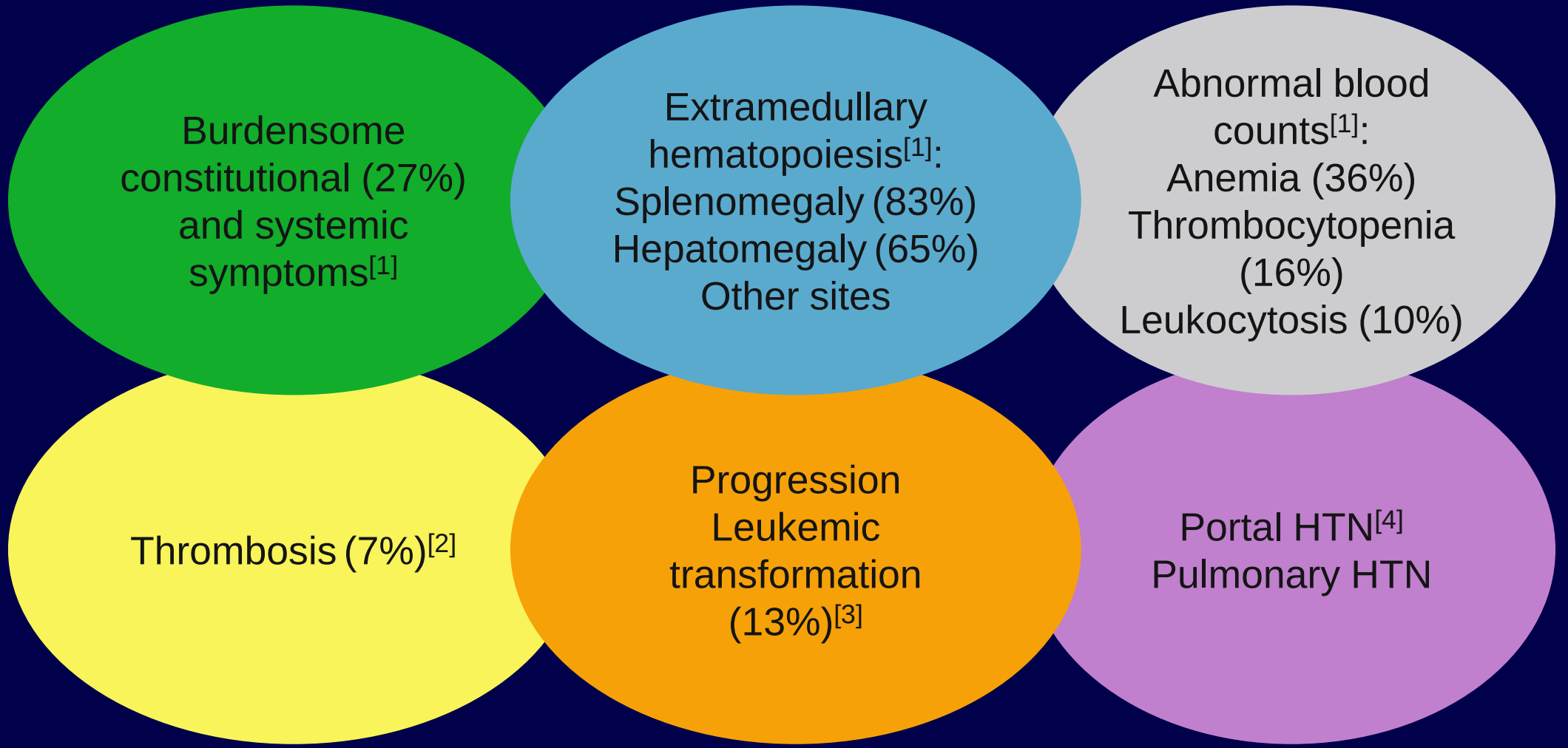
- Autoimmune MF
- Acute panmyelosis
- MDS with fibrosis
- Hodgkin and non-Hodgkin lymphoma
- Hairy cell leukemia
- Bone marrow metastases
- Secondary hyperparathyroidism
- HIV, tuberculosis
- Medication induced (TPO agonists)

Kuter DJ, et al. Br J Haematol. 2007;139:351-362.

presentation

- Heterogeneous presentation
  - Asymptomatic patients
  - Symptomatic patients
    - Splenomegaly
    - Anemia
    - Constitutional symptoms

Clinical Complications of MF

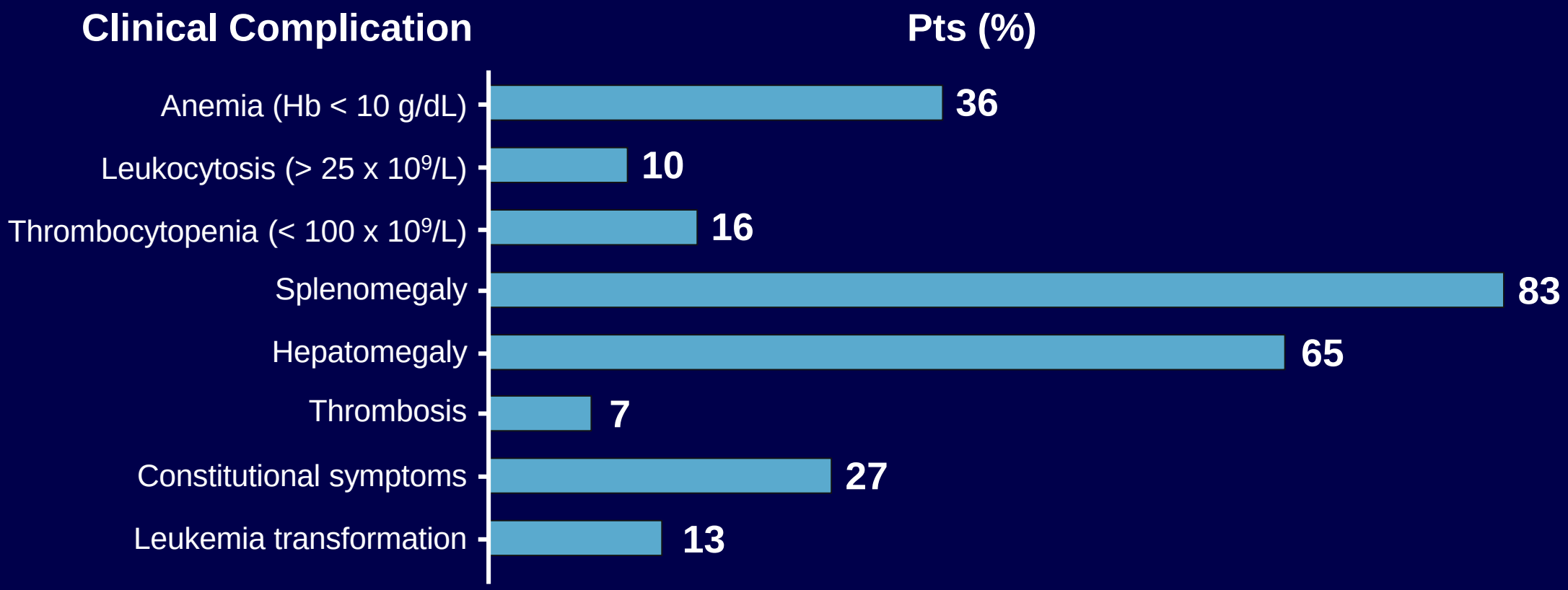


1. Passamonti F, et al. Blood. 2010;115:1703-1708. 2. Barbui T, et al. Blood. 2010;115:778-782.
3. Passamonti F, et al. Blood. 2010;116:2857-2858. 4. Mesa RA. Blood. 2009;113:5394-5400.

Hematologic features

- Leukopenia
- Leukocytosis
  - (leukoerythroblastosis)
- Thrombocytopenia
- Thrombocytosis
- Anemia
  - (dacriocytes)
- Increased LDH

Main Clinical Complications in MF



Passamonti F, et al. Blood. 2010;115:1703-1708. Barbui T, et al. Blood. 2010;115:778-782. Passamonti F, et al. Blood. 2010;116:2857-2858.

Slide credit: clinicaloptions.com

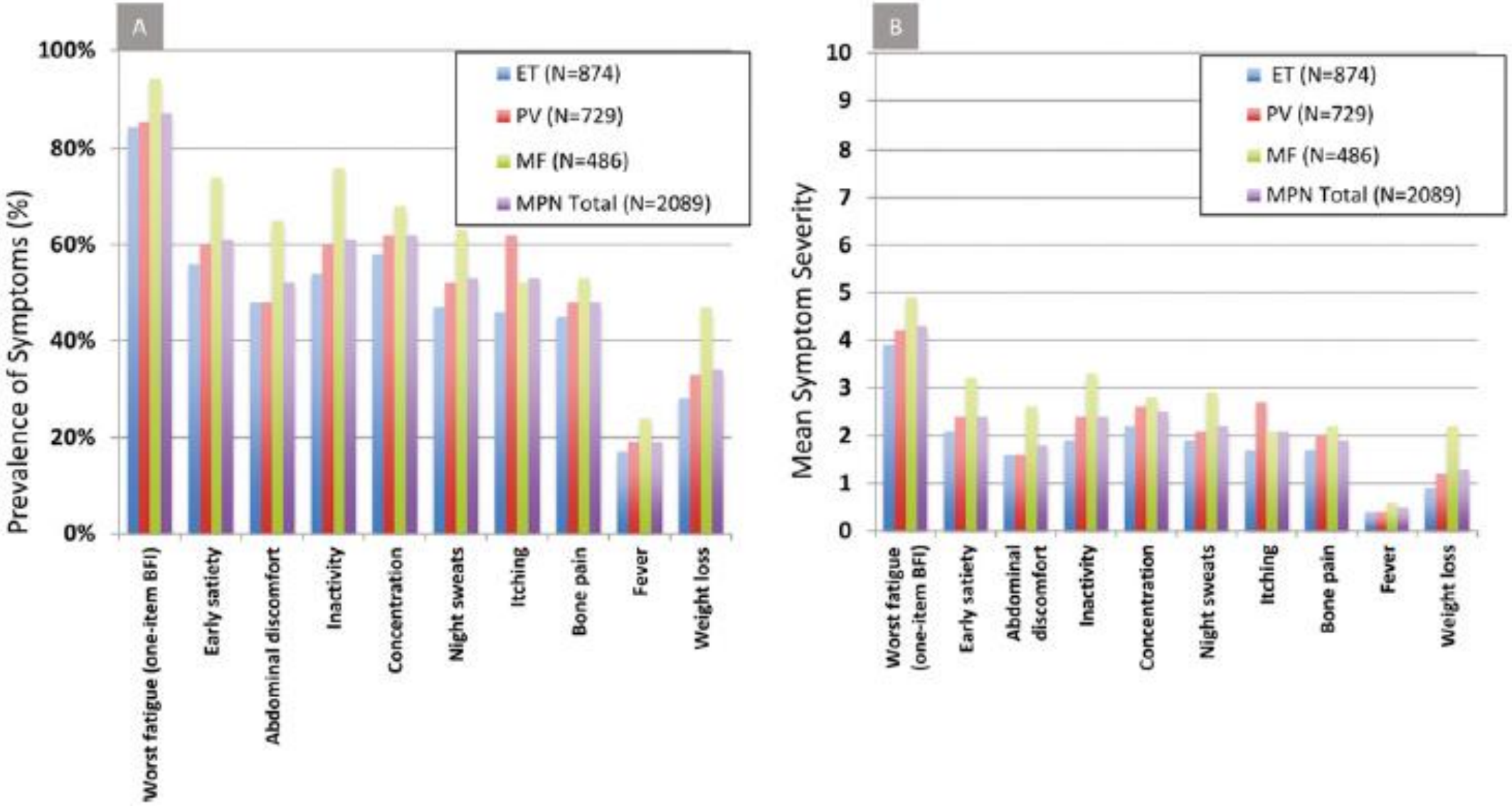
MPN symptoms by subtype.

	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 Blood. 2014;124(24):3529-3537)

MPN symptom severity (A) and prevalence (B) by subtype.



Geyer Blood. 2014;124(24):3529-3537)

Prognosis

- Median survival: 3.5-5 years
  - Wide variability
- Adverse prognostic factors
  - Constitutional symptoms
  - Hb < 10 g/dL
  - WBC count < 4 or > 30 x 10^9/L
  - Blood blasts > 1%
  - cytogenetics
  - Type of mutation

International Prognostic Scoring System: Risk Classification of MF at Presentation

- Risk factors
  - Older than 65 yrs of age
  - Constitutional symptoms
  - Hb < 10 g/dL
  - WBC count > 25 x 10^9/L
  - Peripheral blood blasts ≥ 1%

No. Risk Factors	Risk Group	Median Survival, Yrs
0	Low	11.3
1	Intermediate-1	7.9
2	Intermediate-2	4.0
≥ 3	High	2.3

Cervantes F, et al. Blood. 2009;113:2895-2901.

IPSS and DinamicIPSS(plus) prognostic scoring systems

Risk factors	Point value		IPSS			DIPSS		
	IPSS	DIPSS	Risk group	Risk score	Median survival	Risk group	Risk score	Median survival
Age >65	1	1	Low	0	11.3 years	Low	0	Not reached
Constitutional symptoms[a]	1	1	Intermediate-1	1	7.9 years	Intermediate-1	1 to 2	14.2 years
Hb <10 g/dL	1	2	Intermediate-2	2	4 years	Intermediate-2	3 to 4	4 years
WBC count >25 $\times$ 10^9/L	1	1	High	$\geq$ 3	2.3 years	High	$\geq$ 5	1.5 years
Blood blasts $\geq$ 1%	1	1						

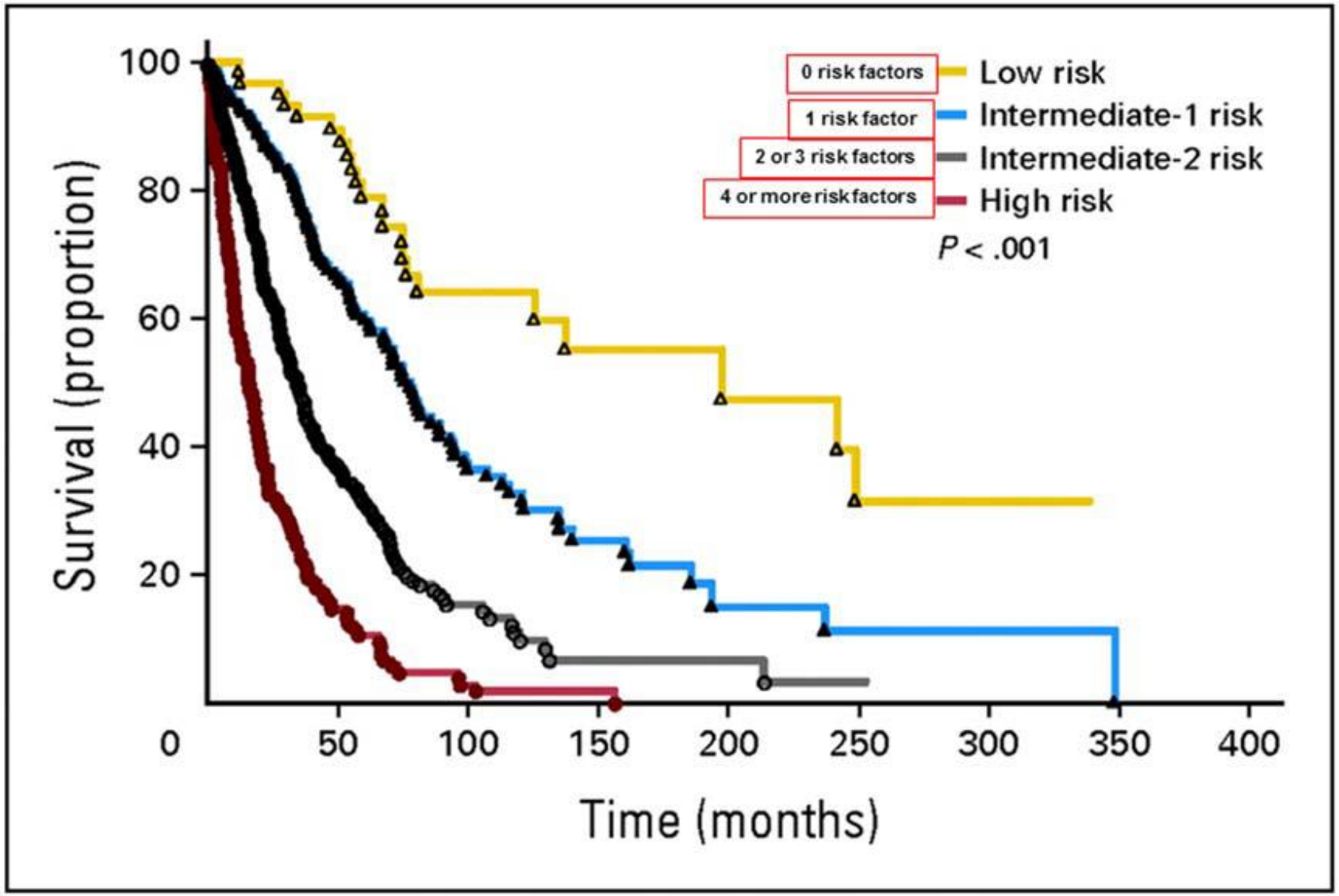
[a] Constitutional symptoms defined as weight loss >10% of the baseline value in the year preceding PMF diagnosis and/or unexplained fever or excessive sweats persisting for more than 1 month.

Risk factors	Points	DIPSS plus		
		Risk group	Risk score	Median survival
DIPSS intermediate-1	1	Low risk	0	15.4 years
DIPSS intermediate-2	2	Intermediate-1	1	6.5 years
High risk	3	Intermediate-2	2 to 3	2.9 years
Unfavorable karyotype[a]	1	High	4 to 6	1.3 years
Platelets <100 $\times$ 10^9/L	1			
RBC transfusion dependent	1			

[a] Unfavorable karyotype = complex karyotype or single or two abnormalities that include +8, −7/7q-, i(17q), −5/5q, 12p-, inv(3) or 11q23 rearrangement.

Survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System (DIPSS-plus) that employs eight variables:

Age >65 yrs; Hgb <10 g/dL; RBC transfusion-dependent; platelets <100 x 10(9)/L; WBC > 25 x 10(9)/L; ≥1% circulating blasts; constitutional symptoms; karyotype.



Median
15.4 years
6.5 years
2.9 years
1.3 years

Gangat N et al. JCO 2011;29:392-397

Prognostic Impact of Driver and High Molecular Risk Nondriver Mutations in Primary MF

- Analysis of association between driver mutations and survival in pts with primary MF (N = 617)[1]

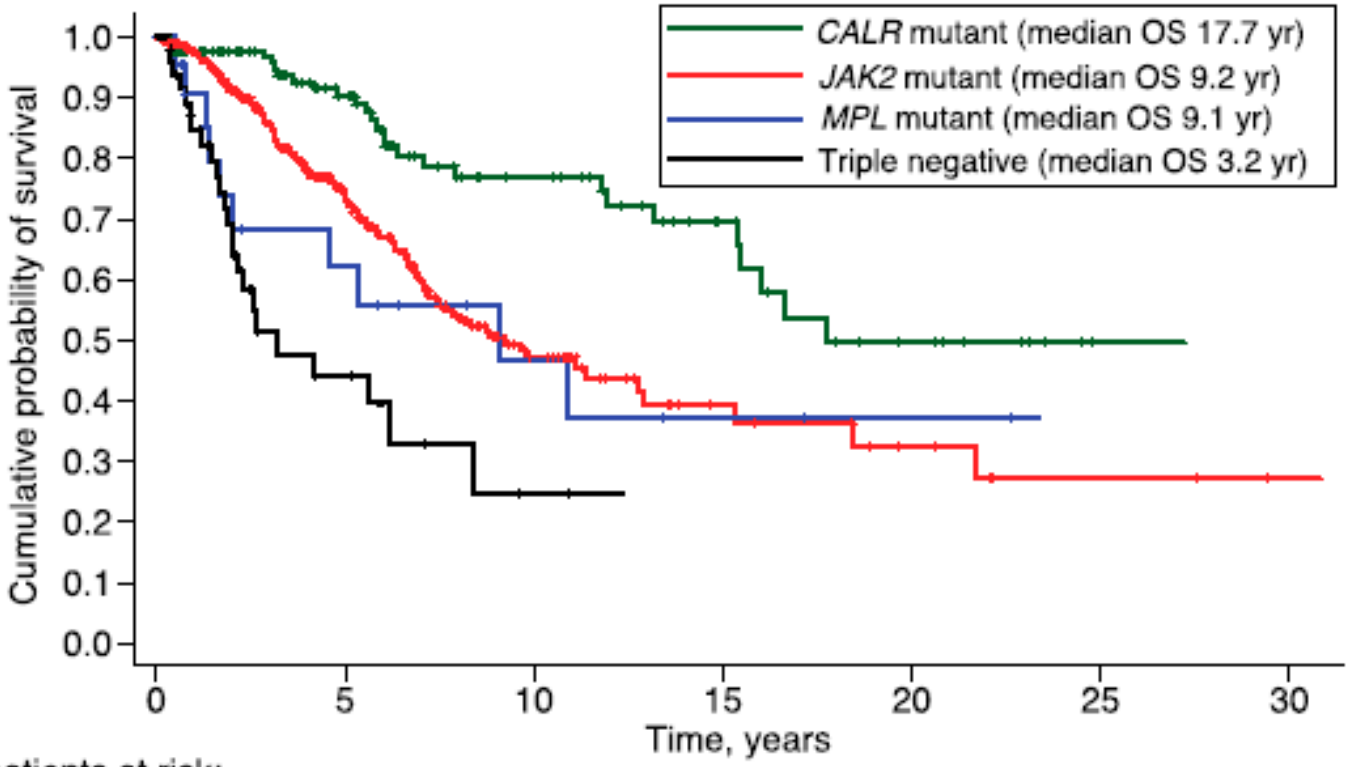
Driver Mutation	Pts, %	Median OS, Yrs
CALR mutated	22.7	17.7
JAK2 mutated	64.7	9.2
MPL mutated	4.0	9.1
Triple negative	8.6	3.2

- Analysis of association between set of nondriver mutations (*IDH*, *EZH2*, *ASXL1*, *SRSF2)* and survival in pts with PMF (N = 797)[2]
  - Presence of mutations predicted decreased survival; ≥ 2 mutations predicted worst survival

1. Rumi E, et al. Blood. 2014;124:1062-1069. 2. Guglielmelli P, et al. Leukemia. 2014;28:1804-1810.

Slide credit: clinicaloptions.com

Survival in MI



No. of patients at risk:

CALR mutant	140	72	37	19	9	1
JAK2 mutant	396	135	39	13	7	3
MPL mutant	25	10	5	3	2	0
Triple negative	53	11	2	0	0	0

Rumi et al, Blood. 2014;124(7):1062-1069)

treatments

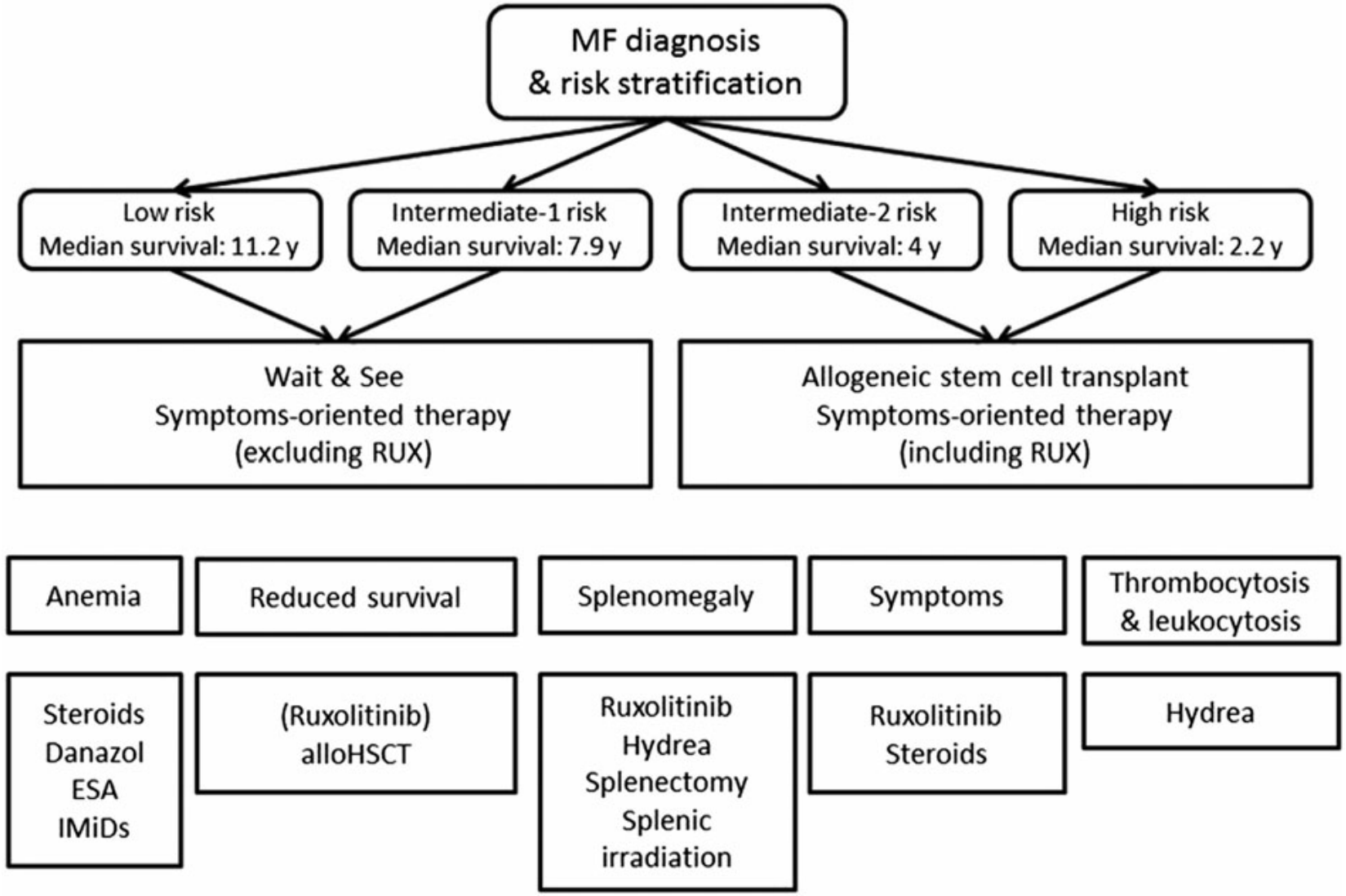
- Treatment options:
  - Supportive treatments (EPO)
  - Hydrossycarbamide
  - Steroids
  - JAK2 inhibitors (ruxolitinib)
  - Immunomodulating drugs (Imids)
  - Splenectomy
  - Radiotherapy
  - Allo-BMT
  - Telomerase inhibitors

MF Treatment Is Based on Risk and MF-Related Symptoms/Signs

Low Risk	Minimally symptomatic → observation or interferon Many symptoms → ruxolitinib
Intermediate-1 Risk	Ruxolitinib or anemia treatment and/or allogeneic HSCT
Intermediate-2 Risk	Allogeneic HSCT or ruxolitinib and/or anemia treatment
High Risk	Allogeneic HSCT or ruxolitinib and/or anemia treatment

Mesa RA. Leuk Lymphoma. 2013;54:242-251.
Geyer HL, et al. Hematology Am Soc Hematol Educ Program. 2014;2014:277-286.

Prognostic and therapeutic treatment algorithm in primary and secondary myelofibrosis



RUX, ruxolitinib; ESA, erythropoiesis stimulating agents;
HSCT, hemopoietic stem cells transplant; IMiDs, immunomodulating drugs.

Palandri et al. Hematol Oncol 2016

Allogeneic HSCT: Why We Prognosticate

- Consider HSCT in younger, higher-risk pts whose survival is expected to be < 5 yrs

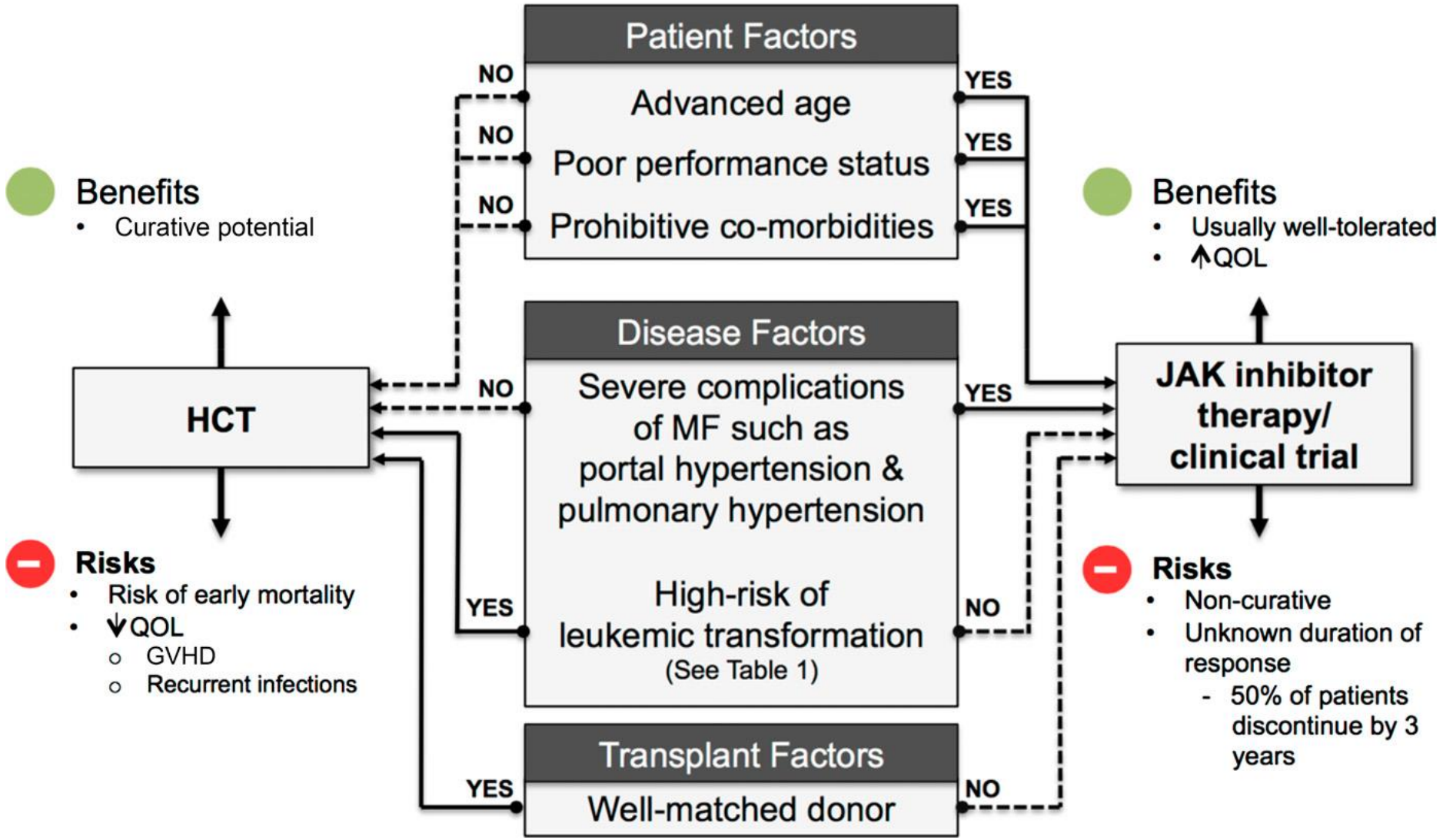
Risk Group[1]	Median Survival, Yrs
Low	11.3
Intermediate-1	7.9
Intermediate-2	4.0
High	2.3

- Very few MF pts undergo HSCT
  - Traditionally limited to pts younger than 60 yrs of age and those with HLA-identical sibling match; now possible up to age 75
  - High transplant-related mortality and morbidity associated with transplantation due to acute and chronic graft vs host disease[2]
    - 1-yr nonrelapse mortality rate: 12% (completely matched donors) to 38% (mismatched)
    - 5-yr survival rate: 56% (matched sibling donors) to 34% (partially matched/mismatched)

1. Cervantes F, et al. Blood. 2009;113:2895-2901.
2. Kröger NM, et al. Leukemia. 2015;29:2126-2133.

Slide credit: clinicaloptions.com

Selection of upfront therapy for patients with MF: HCT vs nontransplant therapies



Devlin & Gupta. ASH 2016

Clinical and molecular risk stratification and risk-adapted therapy in primary myelofibrosis

		Molecular risk		
		High risk Presence of adverse mutations (e.g. *ASXL1*, *SRSF2*), and absence of type 1/like *CALR* mutation	**Intermediate risk** Not classifiable as high or low risk	**Low risk** Presence of type 1/like CALR mutation and absence of adverse mutations (e.g. *ASXL1*, *SRSF2*)
DIPSS-plus risk	**High**	Stem cell transplant or Investigational drug therapy	Stem cell transplant or Investigational drug therapy	Stem cell transplant or Investigational drug therapy
	Intermediate-2	Stem cell transplant or Investigational drug therapy	Stem cell transplant or Investigational drug therapy	Investigational drug therapy
	Intermediate-1	Stem cell transplant or Investigational drug therapy	Observation or Investigational drug therapy	Observation
	Low	Stem cell transplant or Investigational drug therapy	Observation	Observation

Tefferi AJH 2016

Needs-Oriented Therapy for MF

Clinical Issue	Treatments	
Anemia	▪ ESAs ▪ Corticosteroids ▪ Danazol	▪ Thalidomide, lenalidomide (IMIDs)
Symptomatic splenomegaly	▪ Ruxolitinib ▪ Hydroxyurea	▪ Cladribine, IMIDs ▪ Splenectomy
Constitutional symptoms/QoL	▪ Ruxolitinib ▪ Corticosteroids	
Extramedullary hematopoiesis	▪ Radiation therapy	
Hyperproliferative (early) disease	▪ Interferon	
Risk of thrombosis	▪ Low-dose aspirin	
Accelerated/blastic phase	▪ Hypomethylating agents	
Improved survival	▪ Allogeneic HSCT ▪ Ruxolitinib	

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