Myeloproliferative disorders : are a group of diseases in which the bone marrow produces too many red blood cells, white blood cells, or platelets

- Clonal haematopoeitic disorders
- Proliferation of one of myeloid lineages
  - Granulocytic
  - Erythroid
  - Megakaryocytic
- Relatively normal maturation

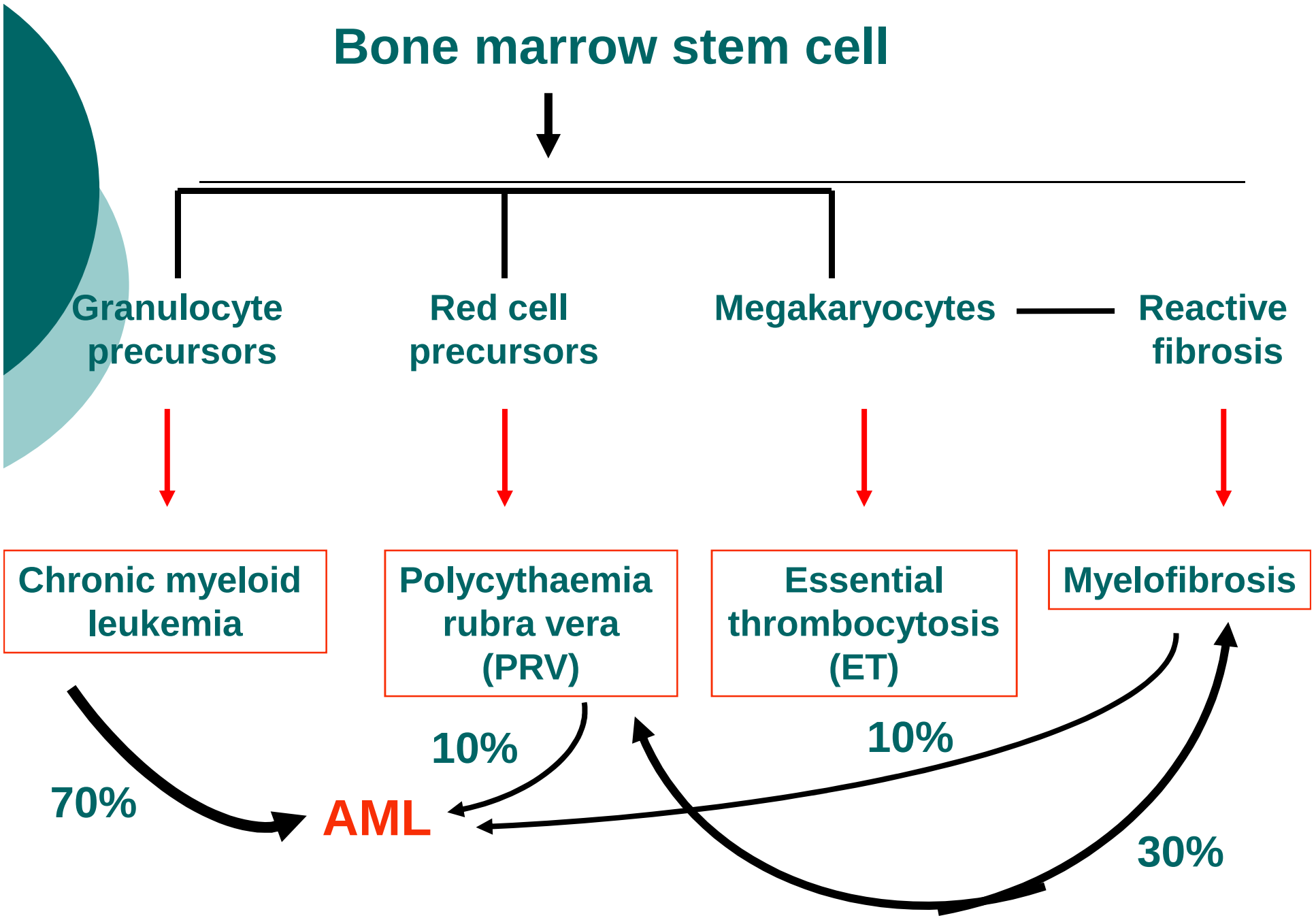
Myeloproliferative disorders

WHO Classification of CMPD

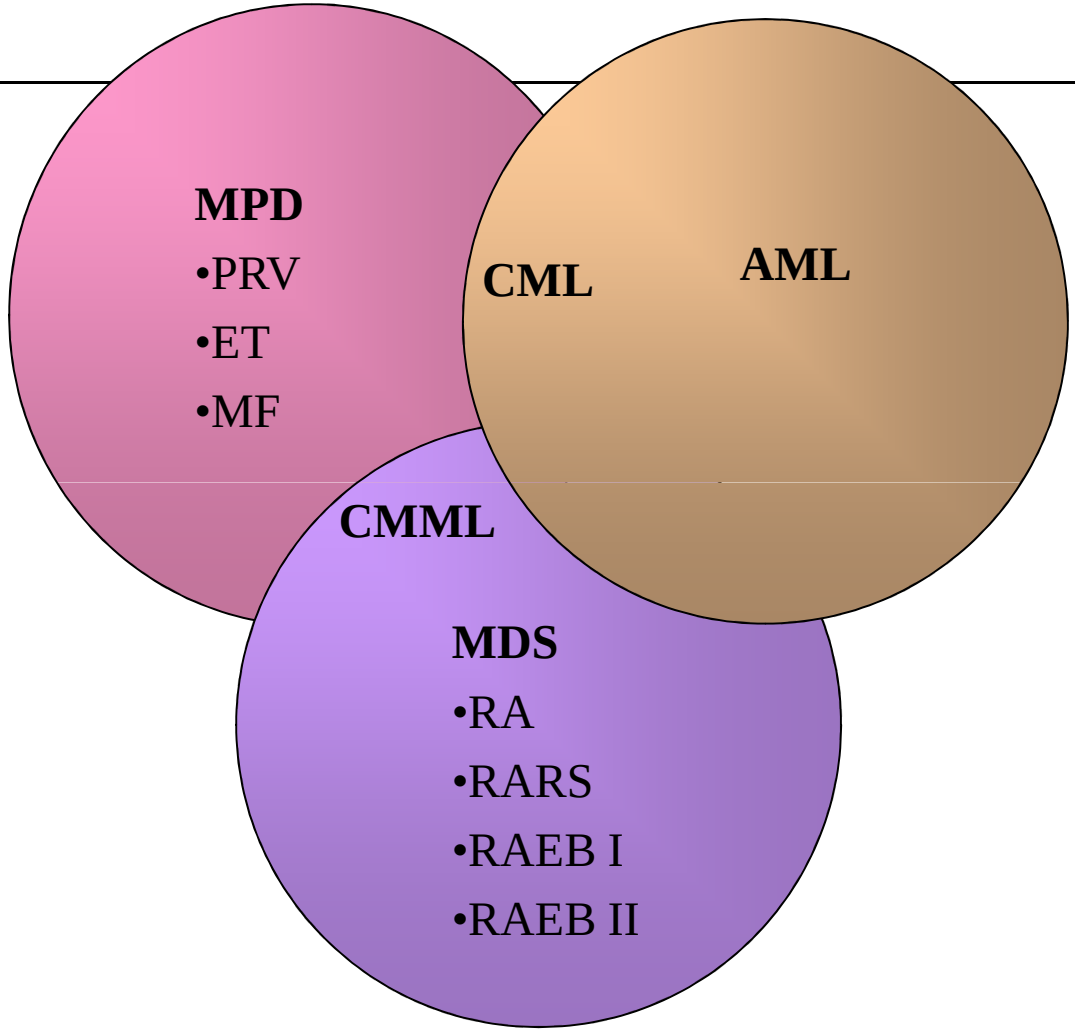
- Ch Myeloid leukemia
- **Ch Neutrophillic leukemia**
- **Ch Eosinophillic leukemia / Hyper Eo Synd**
- Polycythemia Vera
- Essential Thrombocythemia
- Myelofibrosis
- **CMPD unclassifiable**

Myeloproliferative disorders (neoplasias)

- **Polycythemia Vera (JAK2 V617F in 95%)**
- **Ch Myeloid leukemia (*BCR-ABL positive)***
- **Essential Thrombocythemia (JAK2 V617F in 50%, Calreticulin 9 mutation in almost 100%)**
- **Myelofibrosis (JAK2 V617F in 50%)**
- Specific clincopathologic criteria for diagnosis and distinct
- diseases, have common features
  - Increased number of one or more myeloid cells
  - Hepatosplenomegaly
  - Hypercatabolism
  - Clonal marrow hyperplasia without dysplasia
  - Predisposition to evolve AML and fibrosis in the course


Bone marrow stem cell
Granulocyte precursors
Red cell precursors
Megakaryocytes
Reactive fibrosis
Chronic myeloid leukemia
Polycythaemia rubra vera (PRV)
Essential thrombocytosis (ET)
Myelofibrosis
70%
10%
10%
30%
AML

Myeloproliferative disorders



POLYCYTHEMIA VERA

- **Chronic, clonal myeloproliferative disorder characterized by an absolute increase in number of RBCs**
- **a single nucleotide JAK2 somatic mutation (JAK2V617F mutation) in the majority of PV patients**
- **2-3 / 100000**
- **Median age at presentation: 55-60**
- **M/F: 0.8:1.2**

PVR is probable

WBC	15.1	Giga/L	H	4.0-10.0
x Neutrofil sejt	77.5	%	H	53.0-75.0
x Limfocita	11.1	%	L	25.0-40.0
x Monocita	2.8	%		2.0-10.0
x Eozinofil	7.2	%	H	0.0-7.0
x Bazofil	1.4	%	H	0.0-1.0
x vvt szám	7.42	Tera/L	H	4.10-5.10
x Hemoglobin	162	g/L	H	123-153
x Hematokrit	0.53	L/L	H	0.35-0.45
x MCV	71.2	fL	L	80.0-96.0
x MCH	21.8	pg	L	28.0-33.0
x MCHC	306	g/L	L	320-360
x RDW	18.8	%	H	11.6-14.8
x Thrcyta	530	Giga/L	H	150-400
x MPV	8.5	fL		6.5-12.0
x Retikulocyta****	16	%o		5-20
x Reticuloc. abs.	116.2	Giga/L	H	30.0-100.0

PVR is probable

A2 Normal O2 sat and low EPO

A3 Palpable spleen

A4 No BCR-ABL fusion

B1 Thrombocytosis >400 x 109/L

B2 Neutrophilia >10 x 109/L

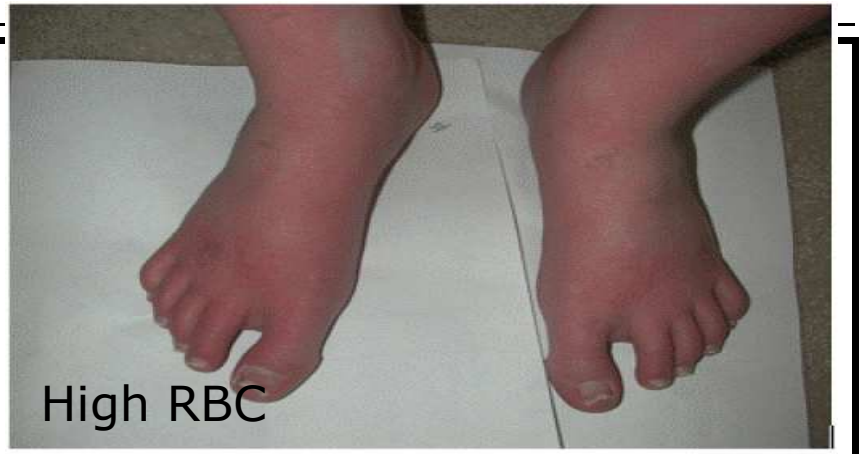
Clinical features

- **Plethora**
- **Splenomegaly**
- **Generalized pruritus (after bathing)**
- **Unusual thrombosis (e.g., Budd-Chiari syndrome) and Haemorrhage**
- **Erythromelalgia (acral dysesthesia and erythema)**
- **Vasomotor**
  - **Headache**
  - **Lightheadedness**
  - **Syncope**
  - **Transient visual disturbances (eg, amaurosis fujax, scintillating scotomata, ocular migraine)**

PVR symptomes and pathogenesis 1

Headache, dizziness, lethargy, blurred vision, loss of concentration, numbness, tingling	Increased cerebral blood viscosity
Weight loss, night sweats, hyperuricaemia and gout	Hypermetabolic state
Bleeding tendency	Abnormal platelet function
Pruritus after bath	Increased histamine?

PVR symptomes and pathogenesis 2

Reddis-purple face, nose, fingers, blood-shotted eyes, deep-raspberry-red mucous membrane	 High RBC
Splenic pain	splenomegaly
Cerebrovascular and peripherial vascular disease, AMI, DVT	Increased whole blood viscosity

Comorbidities / consequences

- **Hypertension**
- **Gout**
- **Leukaemic transformation**
- **Myelofibrosis**

Differential diagnosis of Polycythemia

- **True / Absolute**
  - **Primary Polycythemia**
  - **Secondary Polycythemia**
    - **Epo dependent**
      - **Hypoxia dependent**
      - **Hypoxia independent**
    - **Epo independent**
- **Apparent / Relative**
  - **Reduction in plasma volume**

Causes of secondary polycythemia

- ERYTHROPOIETIN (EPO)-MEDIATED
  - Hypoxia-Driven
    - Chronic lung disease
    - Right-to-left cardiopulmonary vascular shunts
    - High-altitude habitat
    - Chronic carbon monoxide exposure (e.g., smoking)
    - Hypoventilation syndromes including sleep apnea
    - Renal artery stenosis or an equivalent renal pathology
  - Hypoxia-Independent (Pathologic EPO Production)
    - Malignant tumors
      - Hepatocellular carcinoma
      - Renal cell cancer
      - Cerebellar hemangioblastoma
    - Nonmalignant conditions
      - Uterine leiomyomas
      - Renal cysts
      - Postrenal transplantation
      - Adrenal tumors
- EPO RECEPTOR–MEDIATED
  - Activating mutation of the erythropoietin receptor
- DRUG-ASSOCIATED
  - EPO Doping
  - Treatment with Androgen Preparations

Diagnostic algorythm

- Hgb, RBC > normal
- O2 saturation: normal
- EPO determination: low
- JAK2 mutation: present
- Abdominal US: splenomegaly present and no renal cyst, etc
- -----If not characteristic, consider secondary polycythemia
- (encounter smoking habit, alcohol consumption, iron overoad, exsiccosis)

Treatment

- **The mainstay of therapy in PV remains phlebotomy to keep the hematocrit below 45 percent in men and 42 percent in women**
- **Aspirin (75-100 mg/d) if no CI**
- **JAK2 Inhibitor Jakavi (ruxolitinib)**
- **hydroxyurea in high-risk pts for thrombosis (age over 70, prior thrombosis, platelet count >1,500,000/microL, presence of cardiovascular risk factors)**
- **IFNa (3x3 IU / wk) in pregnancy, refractory pruritus**
- **Anagrelide (0.5 mg qds/d) is used mainly to manage thrombocytosis in patients refractory to other treatments.**
- **Allopurinol**

Epidemiology of CML

- Incidence 1-1.5/100,000 population
- Male predominance
- **Median age range at presentation: 45 to 55 years, Incidence increases with age.12% - 30% of patients are >60 years old**

Presentation:

Anorexia and weight loss

Symptoms of anaemia

Splenomegaly (moderate)

Insidious onset

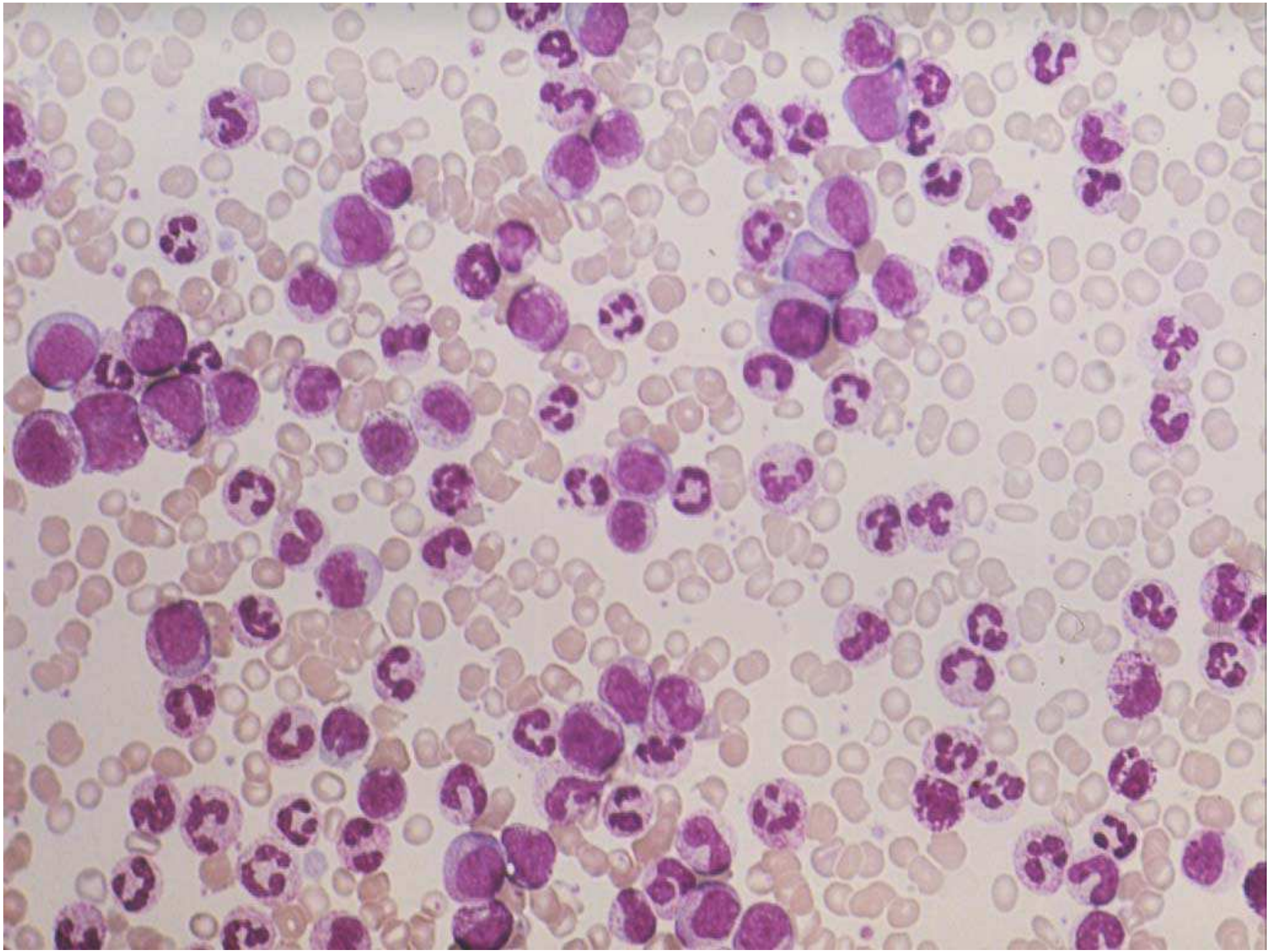
At presentation

50% diagnosed by routine laboratory tests

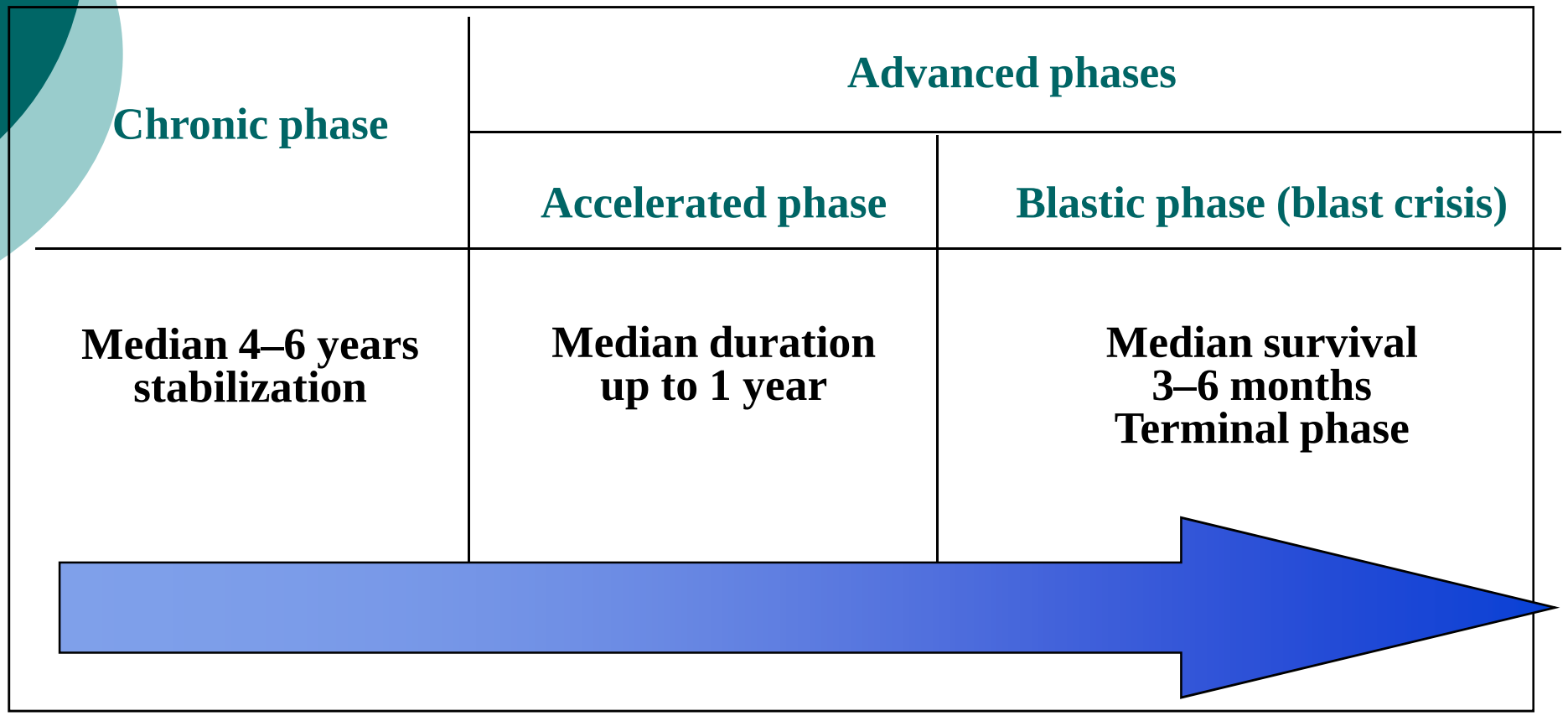
:Pt . maybe asymptomatic (incidental findig)

In 85% diagnosed during chronic phase

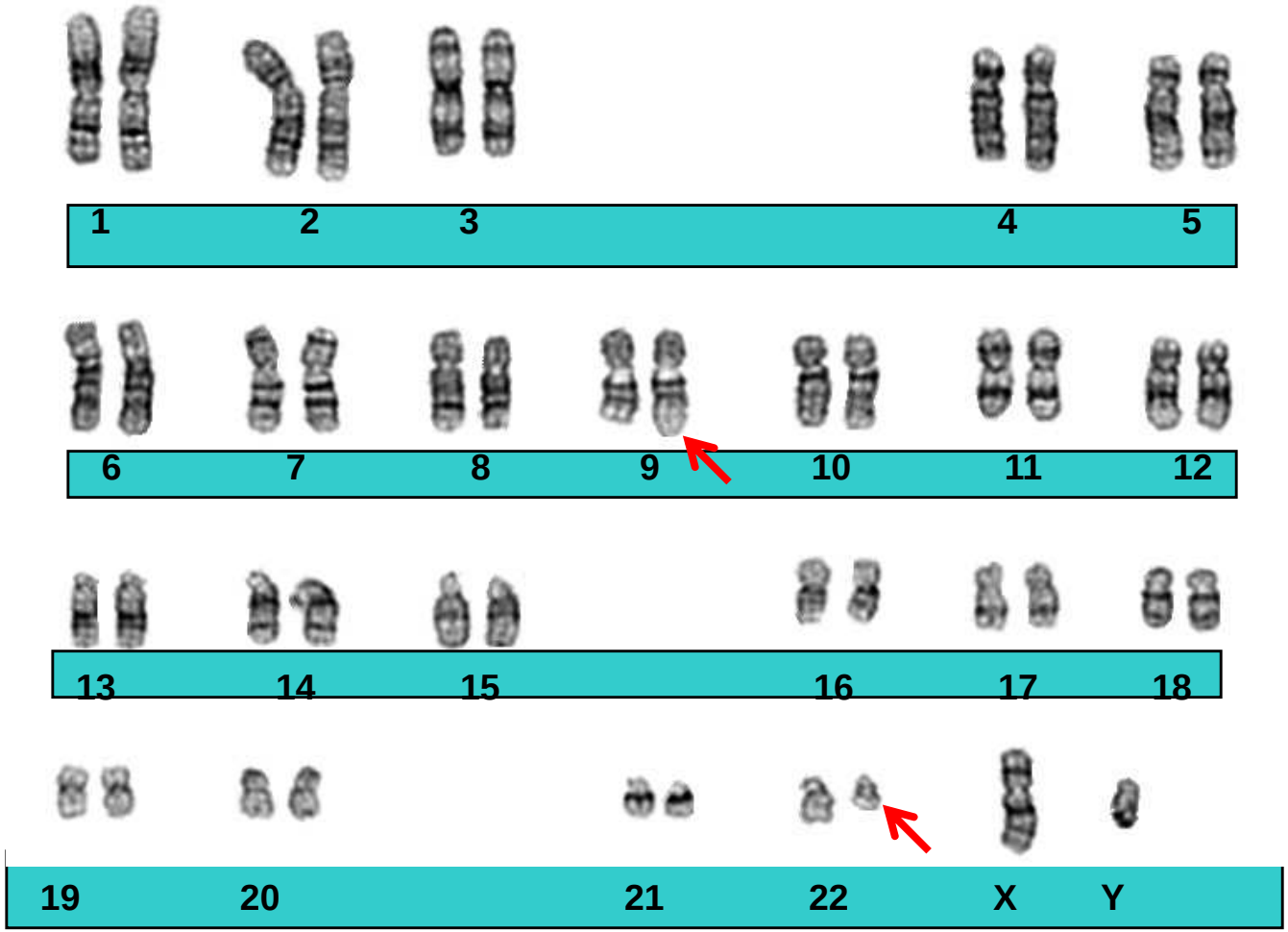
WBC	90.51	10'9/L	H	4.0-10.0		F
x Neutrofil sejt	--	%				F
x Limfocita	--	%				F
x Monocita	--	%				F
x Eozinofil	--	%				F
x Bazofil	--	%				F
x vvs szám	2.78	10'12/L	L	4.10-5.10		F
x Hemoglobin	87	g/L	L	123-153		F
x HCT	0.26	L/L	L	0.35-0.45		F
x MCV	93	fL		80-96		F
x MCH	31	pg/sejt		28-33		F
x MCHC	339	g/L		330-360		F
x RDW	16.9	%		12.0-18.0		F
x Trombocita	798	10'9/L	H	180-400		



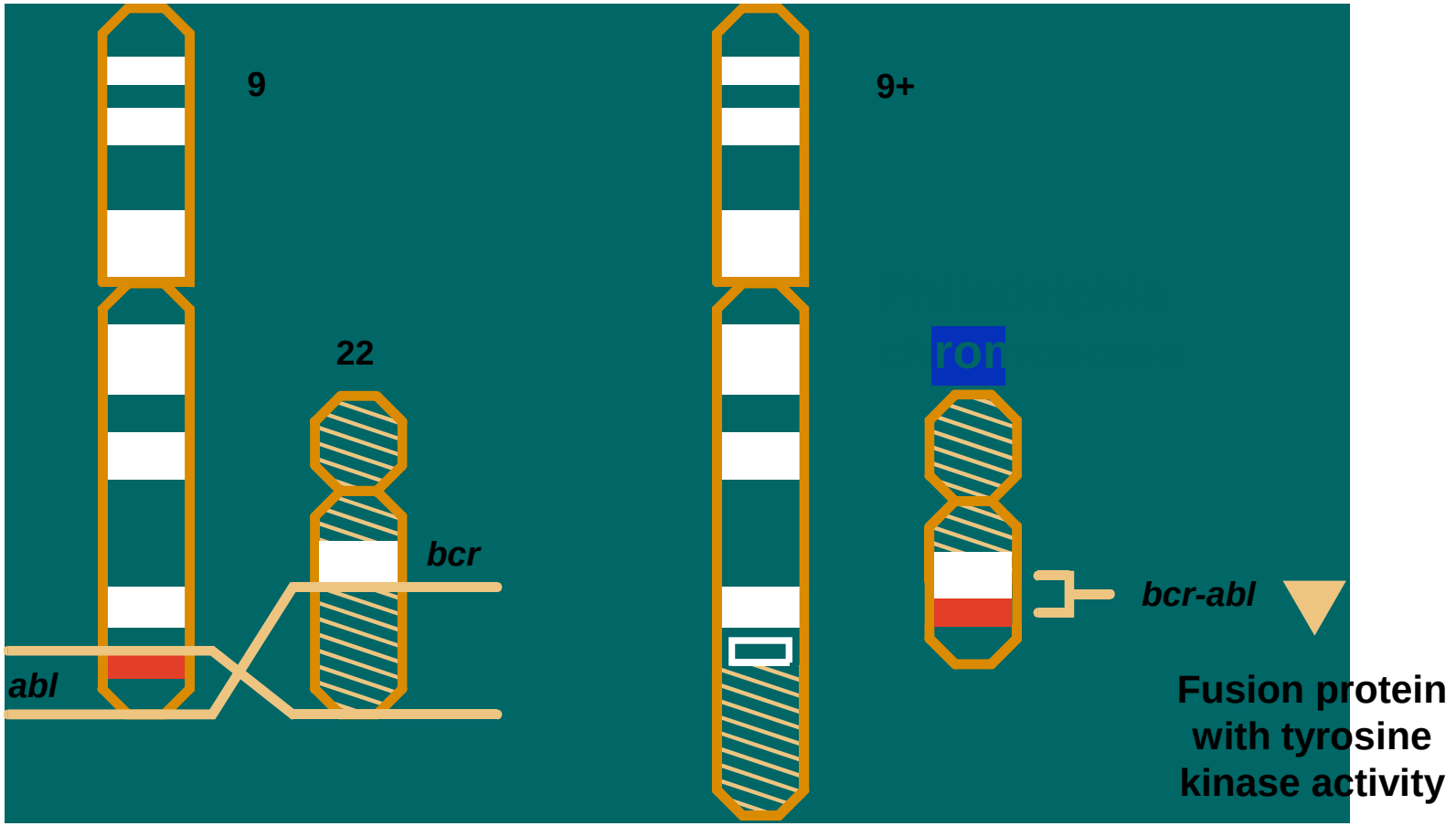
Clinical Course: Phases of CML



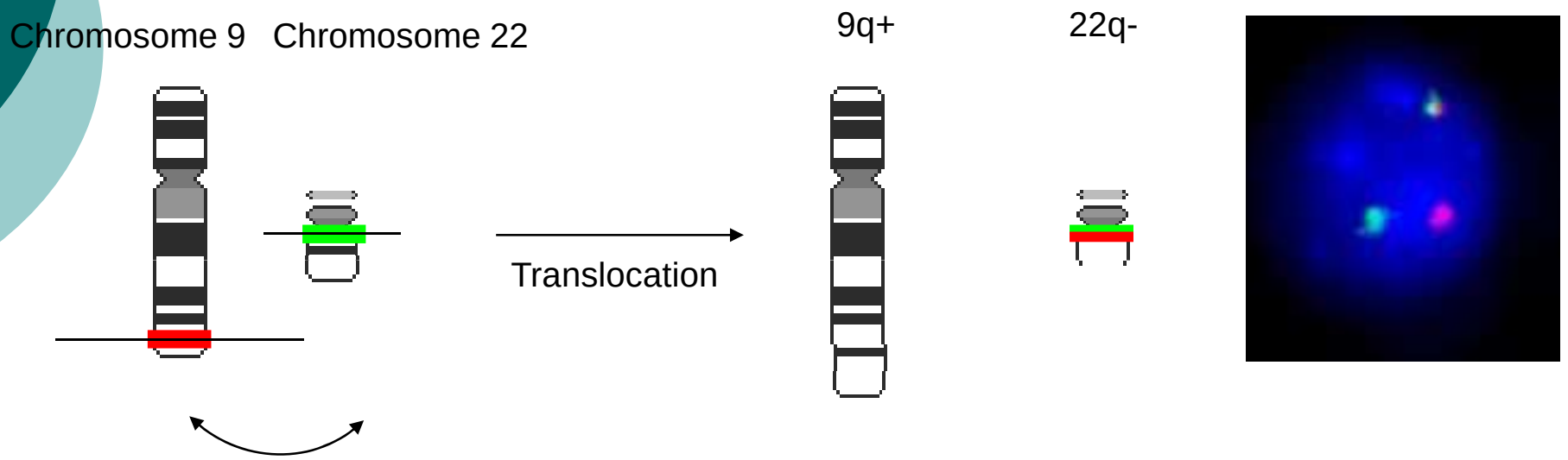
Philadelphia Chromosome



The Philadelphia Chromosome: t(9;22) Translocation

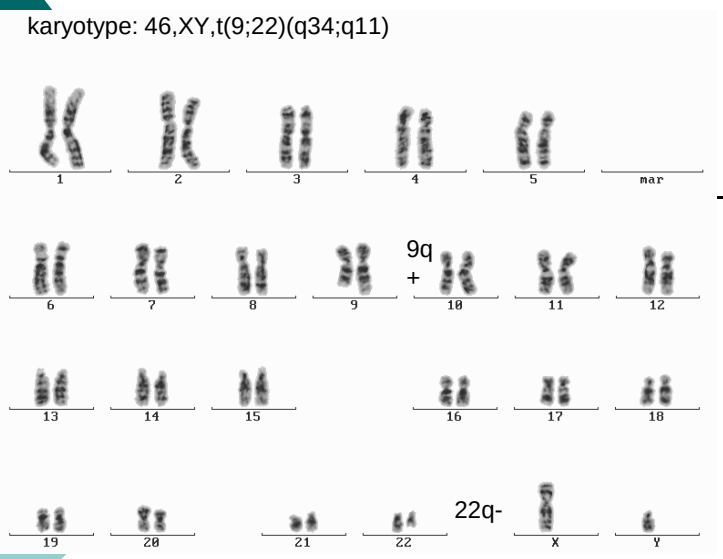


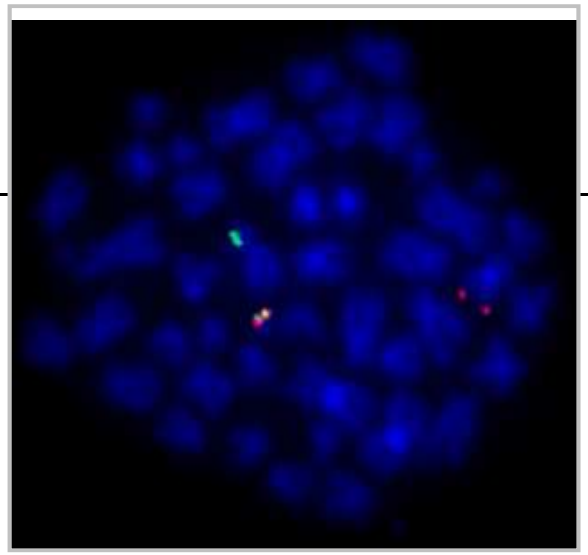
t(9;22)(q34;q11) with 9q+ deletion

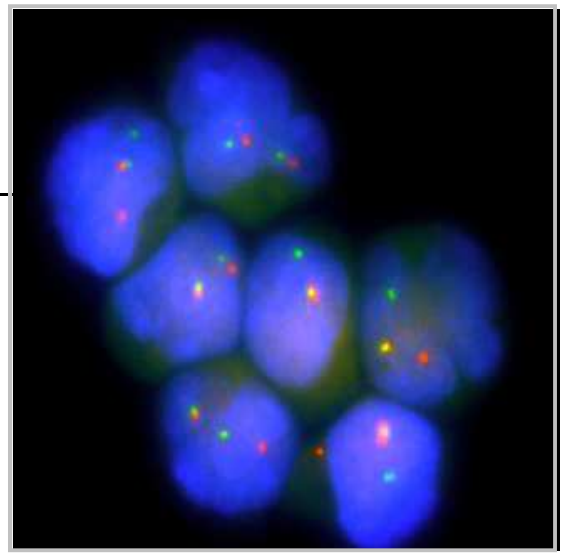


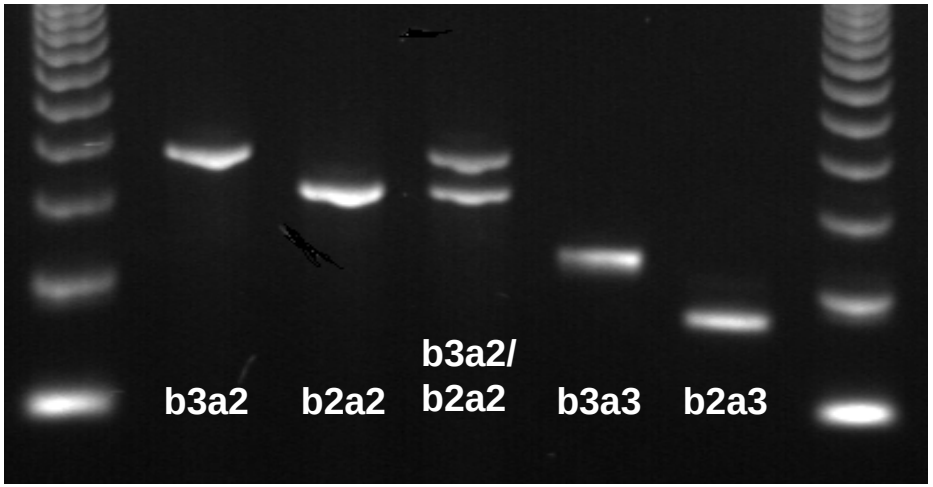
nuc ish 9q34(ABLx2),22q11(BCRx2)(ABLconBCRx1)

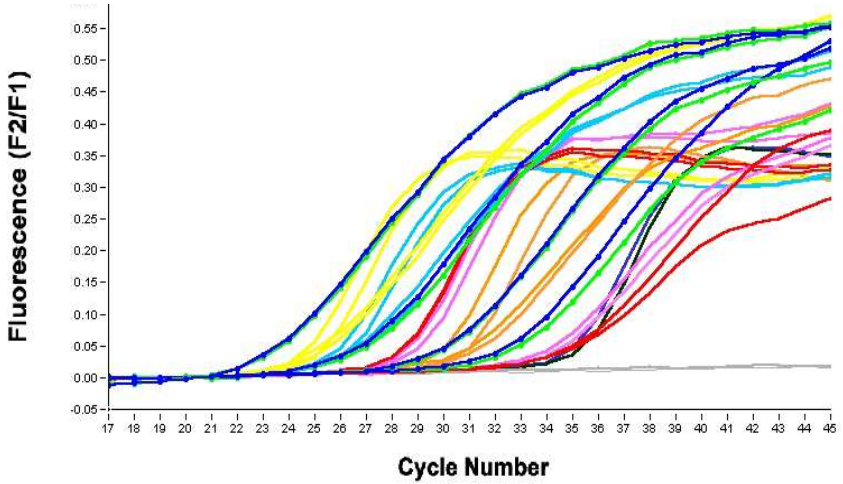
C. Schoch, München


karyotype: 46,XY,t(9;22)(q34;q11)
1
2
3
4
5
mar
6
7
8
9
9q
+
10
11
12
13
14
15
16
17
18
19
20
21
22
22q-
X
Y

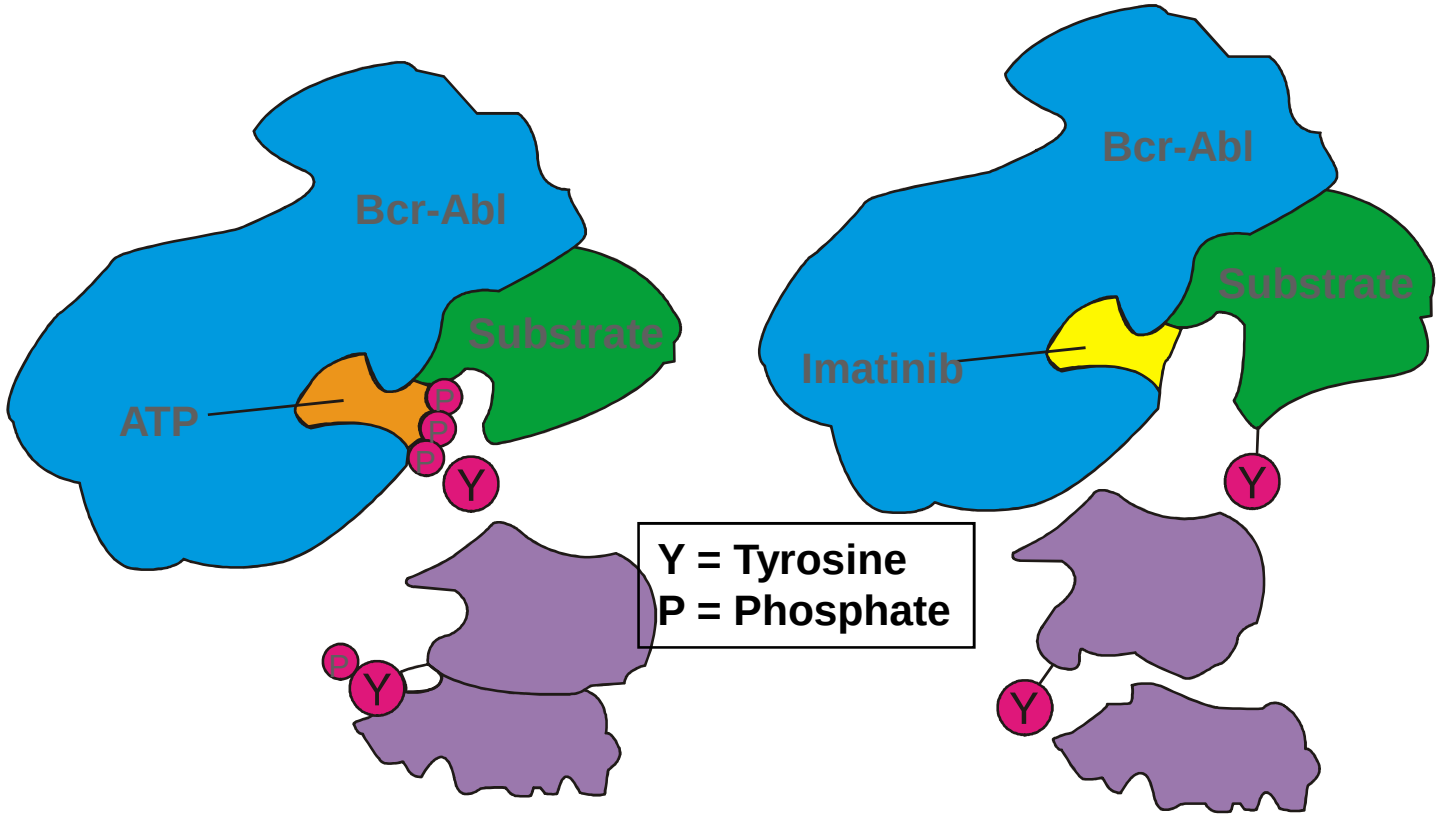





b3a2
b2a2
b3a2/
b2a2
b3a3
b2a3


Fluorescence (F2/F1)
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Cycle Number

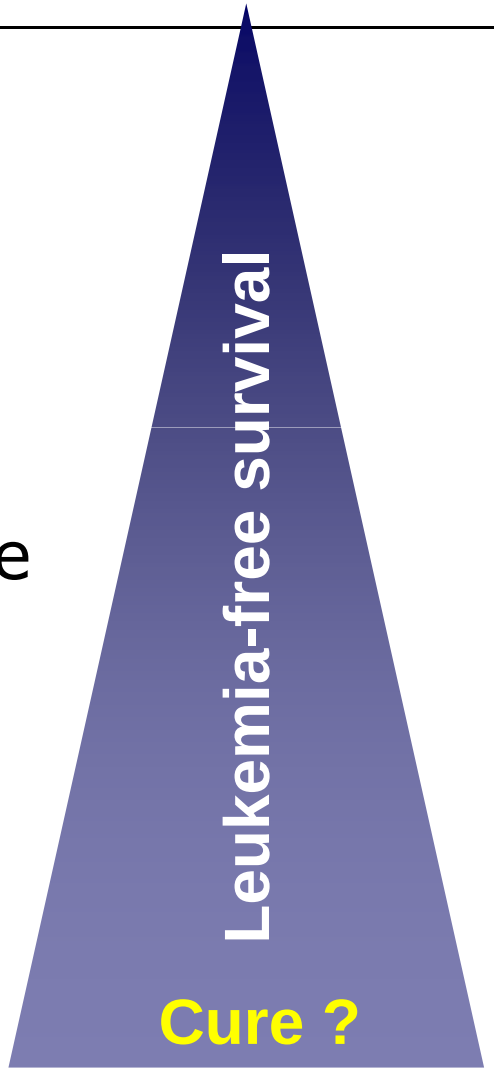
Mechanism of Action of Imatinib



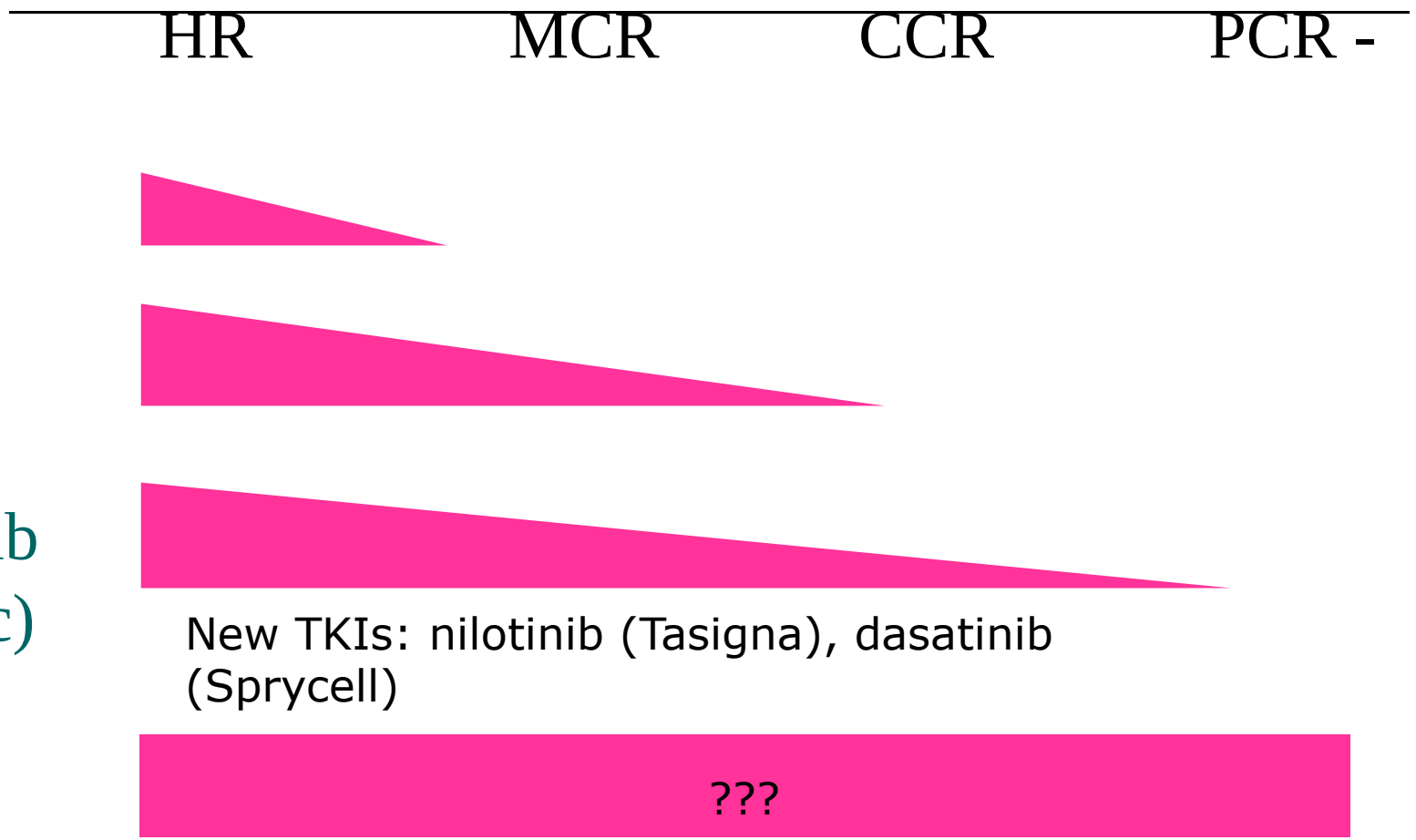
Goldman JM. *Lancet*. 2000;355:1031-1032.

Goals of CML Therapy

- Hematologic response
- Cytogenetic response
  Complete cytogenetic response
- Molecular response
  Undetectable *BCR-ABL*



Evolution of treatment goals



Essential Thrombocythaemia (ET)

- **Clonal MPD**
- **Persistent elevation of Plt>600 x109/l**
- **2.5 cases/100000**
- **M:F 2:1**
- **Median age at diagnosis: 60, however 20% cases <40yrs**

Investigations

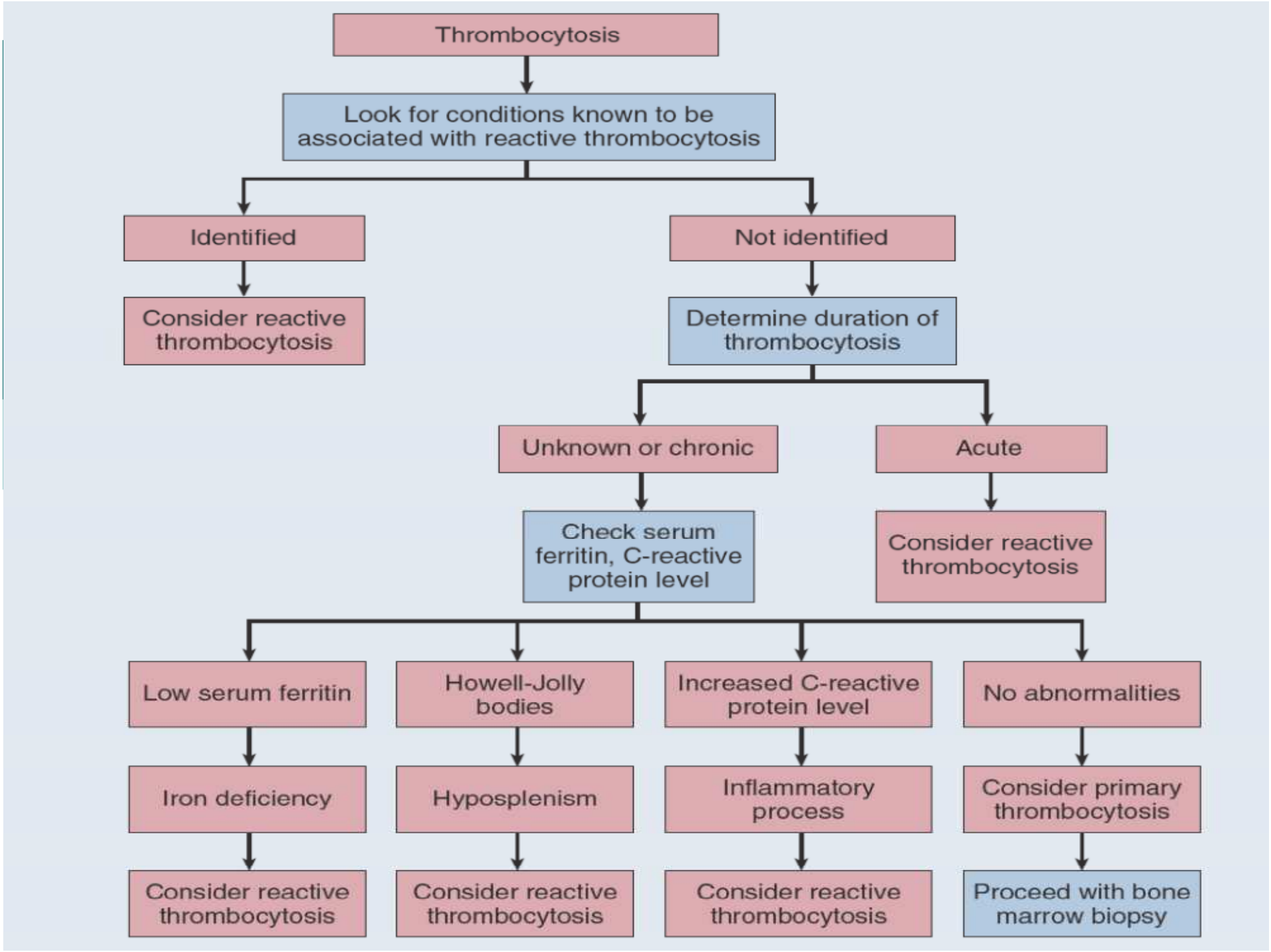
Az ETT kizárásos diagnózis

CONDITION	ADULTS	PLATELET COUNT OF 1 MILLION/μL OR ABOVE	CHILDREN
Infection	22%	31%	31%
Rebound thrombocytosis	19%	3%	15%
Tissue damage (surgery)	18%	14%	15%
Chronic inflammation	13%	9%	4%
Malignancy	6%	14%	2%
Renal disorders	5%	NS	4%
Hemolytic anemia	4%	NS	19%
Postsplenectomy	2%	19%	1%
Blood loss	NS	6%	NS
Primary thrombocythemia	3%	14%	0%

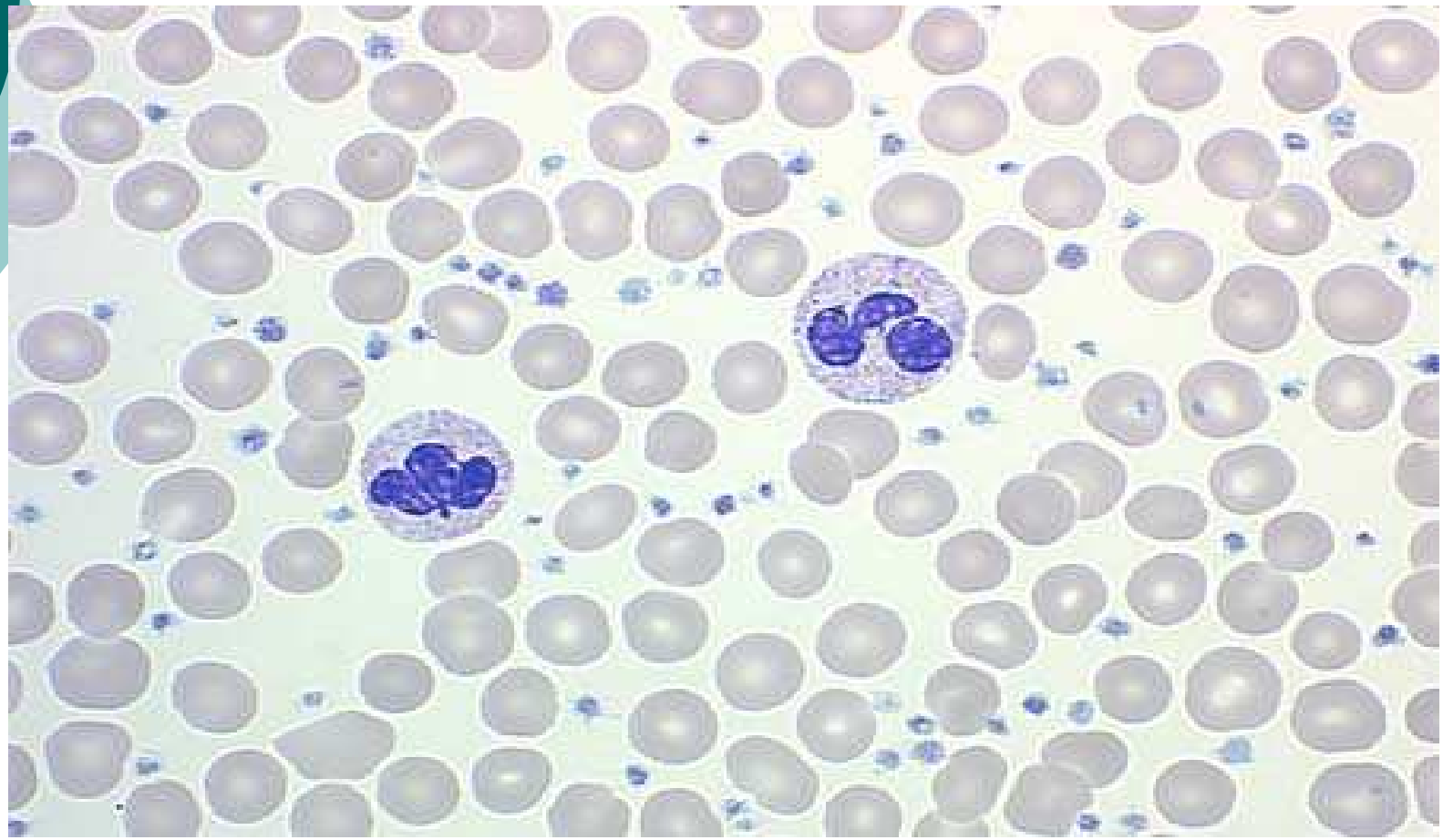
NS = not specified.

Diagnostic criteria for ET

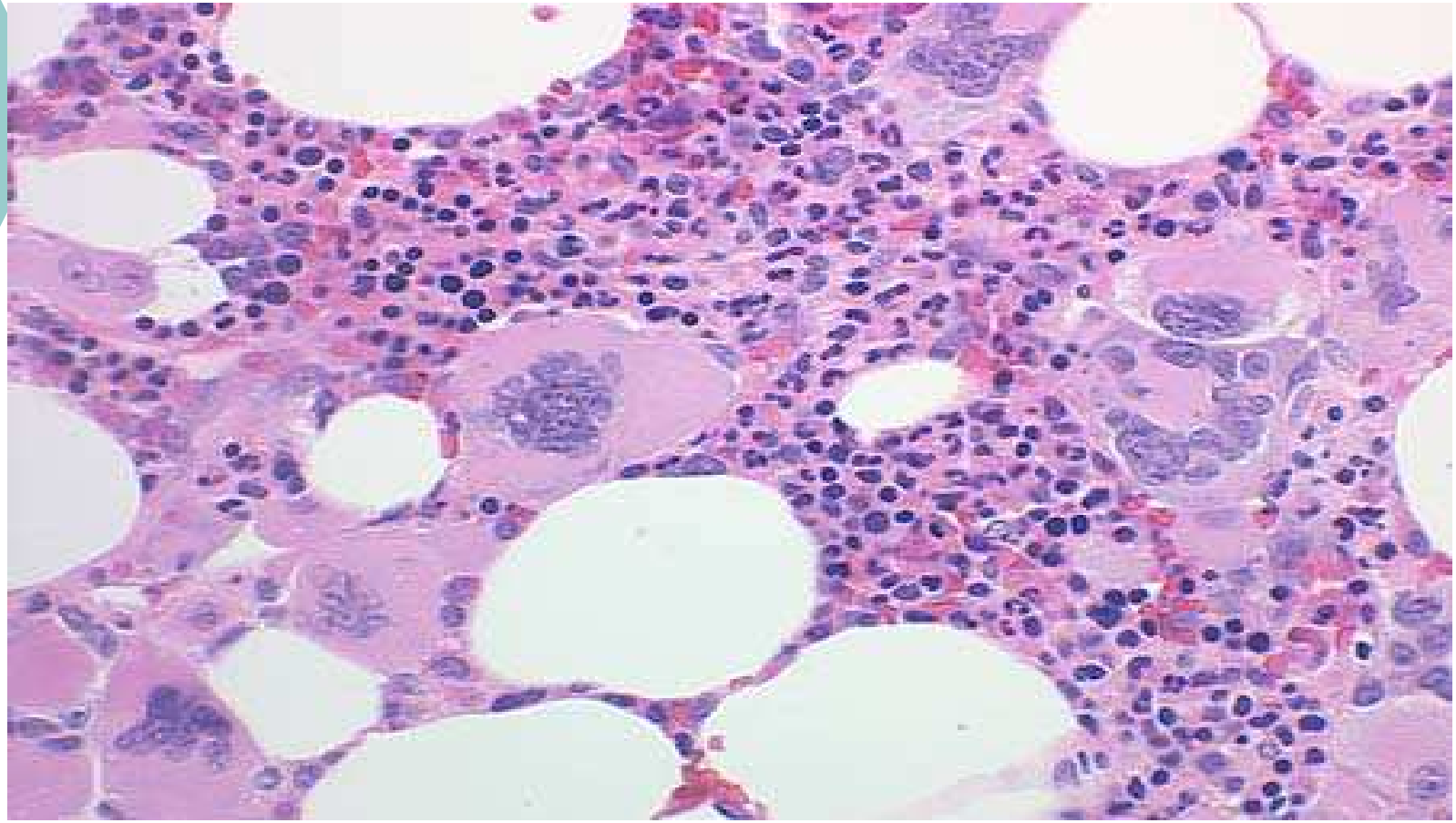
- **Platelet count >600 x 109/L for at least 2 months**
- **No cause for reactive thrombocytosis**
- **Normal red blood cell (RBC) mass or a HCT <0.48**
- **Absence of the Philadelphia chromosome**
- **JAK2 mutation is present in 50% of all ETT cases and those who are JAK2wt Calreticulin mutation on exon 9 is present in almost 100%**
- **Megakaryocytic hyperplasia on bone marrow biopsy, but No evidence of myelofibrosis**
- **No evidence of 5q-/RARS-T MDS**


Thrombocytosis
Look for conditions known to be associated with reactive thrombocytosis
Identified
Consider reactive thrombocytosis
Not identified
Determine duration of thrombocytosis
Unknown or chronic
Check serum ferritin, C-reactive protein level
Acute
Consider reactive thrombocytosis
Low serum ferritin
Iron deficiency
Consider reactive thrombocytosis
Howell-Jolly bodies
Hyposplenism
Consider reactive thrombocytosis
Increased C-reactive protein level
Inflammatory process
Consider reactive thrombocytosis
No abnormalities
Consider primary thrombocytosis
Proceed with bone marrow biopsy

ETT



ETT



A terápia indikációjánál a thrombosis rizikóra figyelemmel

Risk category	Low risk*	High risk†	Intermediate risk‡ +Cardiovascular risk factors +Extreme thrombocytosis
Cytoreductive therapy	No	Yes	No Sometimes
Aspirin therapy	Optional	Yes	Yes No

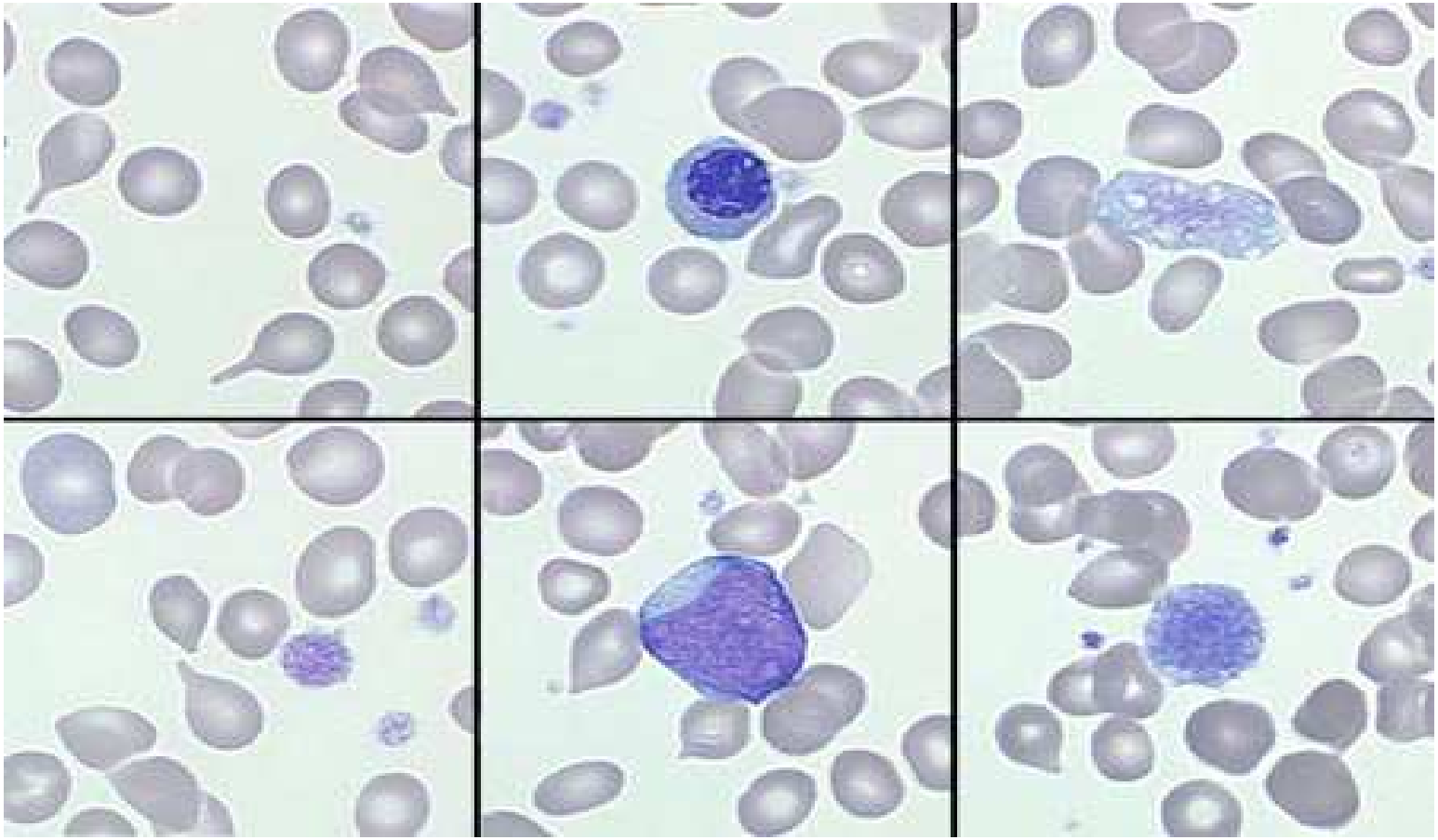
*Age <60 years *and* no history of thrombosis, extreme thrombocytosis (platelet count ≥1,500,000/μL), or cardiovascular risk factors (smoking, hyperlipidemia).

†Age ≥60 years *or* a history of thrombosis.

‡Neither low risk nor high risk.

Thromboreductin (Anagrelid)

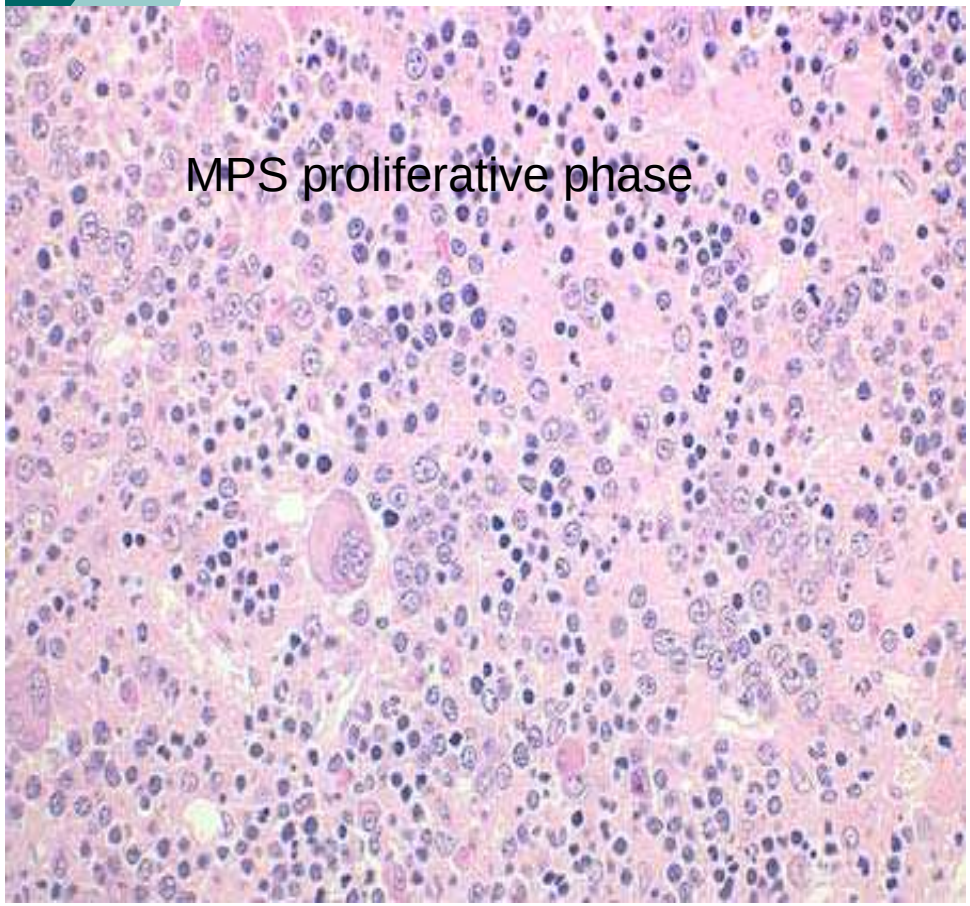
Blood smear signs in MPS

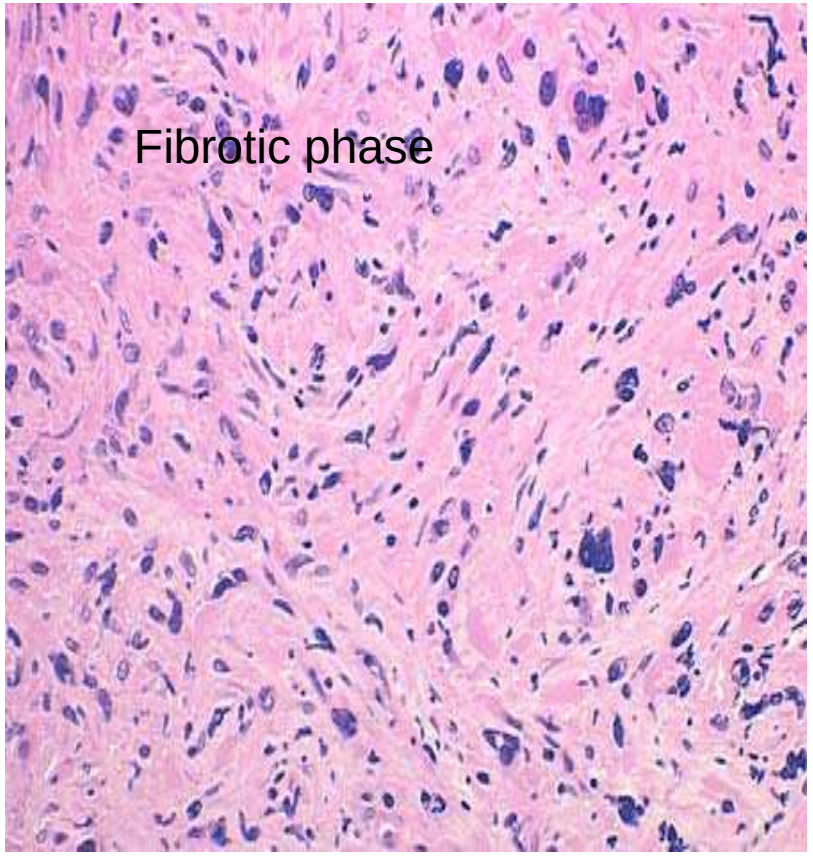


Myelofibrosis

- Myelofibrosis is rare: < 2 of 100,000; age of 50- 70
- *Myelofibrosis is a disorder in which fibrous tissue replaces the blood-producing cells in the bone marrow*
- Consequently, red blood cell production decreases, anemia develops, becoming progressively more severe.
- As myelofibrosis progresses, the number of white blood cells may increase or decrease, and the number of platelets typically decreases.
- weakness, fatigue, weight loss, and a general feeling of illness (malaise).
- Fever and night sweats may occur.
- The liver and spleen often enlarge as they try to take over some of the job of making blood cells. Enlargement of these organs may cause pain in the abdomen and may lead to portal hypertension and bleeding from esophageal varices.
- JAK2 mutation is present in 60% of all cases

myelofibrosis





Therapy for MF

- Jakavi (ruxolitinib) TKI
- Midostaurin in study
- Supportive care
- BMT

Rare forms of MPN

- HES
- CEL

>1500/ul eo for more than 3mos

Disclosing secondary forms, like worm infestation, allergic diseases, Churg – Strauss syndrome, paraneoplasia

Diangosis: detection of FIP1L1-PDGFR α / ß ; gene rearrengement

Therapy: Imatinib in low dose.

MDS/MPS

- WHO classification „ the blue book”
- CMML
- JCMML
- MDS/MPS unclassifiable

CMML