MYELOPROLIFERATIVE NEOPLASMS

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September 12, 2017
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Objectives

- Discuss an approach to increased cell counts
- Discuss clinical and laboratory diagnosis of myeloproliferative neoplasms
- Overview of treatment options and potential complications of disease and therapy

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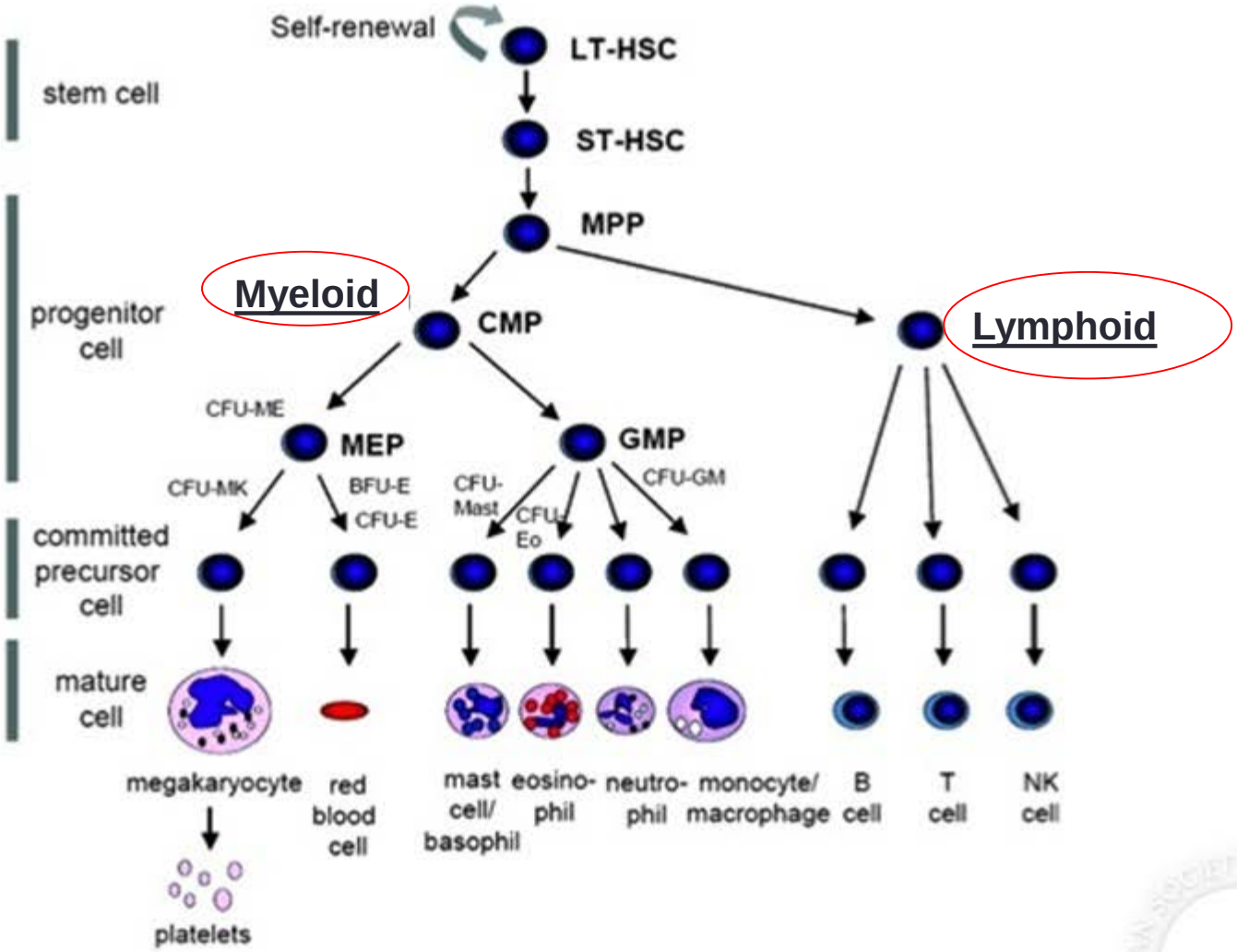
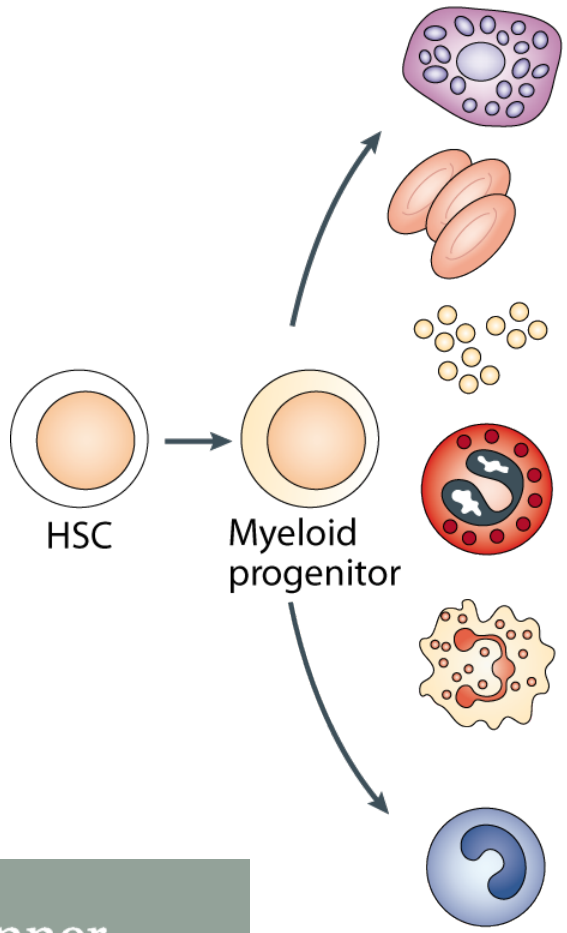
Figure 12-3 Classical hierarchal map of hematopoietic development



Cantor, A. B. et al. ASH-SAP 2010;2010:331-372

Myeloproliferative Disorders



		MPD	Activating mutation
Mast cell	→	Systemic mastocytosis	KITD816V FIP1L1-PDGFRA
Red blood cells	→	Polycythemia vera	
Platelets	→	Essential thrombocytosis	
Eosinophils	→	Chronic eosinophilic leukemia	FIP1L1-PDGFRA
Neutrophils	→	Chronic myeloid leukemia	BCR-ABL
	→	Chronic myelomonocytic leukemia	TEL-PDGFRB BCR-PDGFRA TEL-JAK2 other fusion TKs
Monocytes	→	Primary myelofibrosis	CALR MPL

Nature Reviews | Cancer

Marrow Production and Peripheral Blood Half-Life

	Output/day	Blood Count	Lifespan
RBC	**200 x 10^9**	**~ 5 x 10^6/μL**	**120 days**
WBC	**10 x 10^9**	**~ 3 x 10^3/μL (neutrophils)**	**< 1/2 day**
Plts	**400 x 10^9**	**~ 200 x 10^3/μL**	**10 days**

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Leukocytosis

- A word to discourage from clinical use
  - Be more specific!
- For diagnosing MPNs – focus on Absolute counts, not %

- Specific type of cell will help build your differential
  - Neutrophilia: leukemoid reaction/reactive, CML, myelofibrosis
  - Lymphocytosis: CLL, MBL, pertussis,
  - Monocytosis: CMML, TB/fungal,
  - Eosinophilia : allergy/atopy, parasites, adrenal insufficiency, CEL
  - Basophilia: CML
  - Peripheral Blasts: Acute leukemia, high-grade MDS

Case 1 - Presentation

- 32yo resident presents with sore throat and fever
- Cervical adenopathy is present on exam

- CBC: 35>45%<455k

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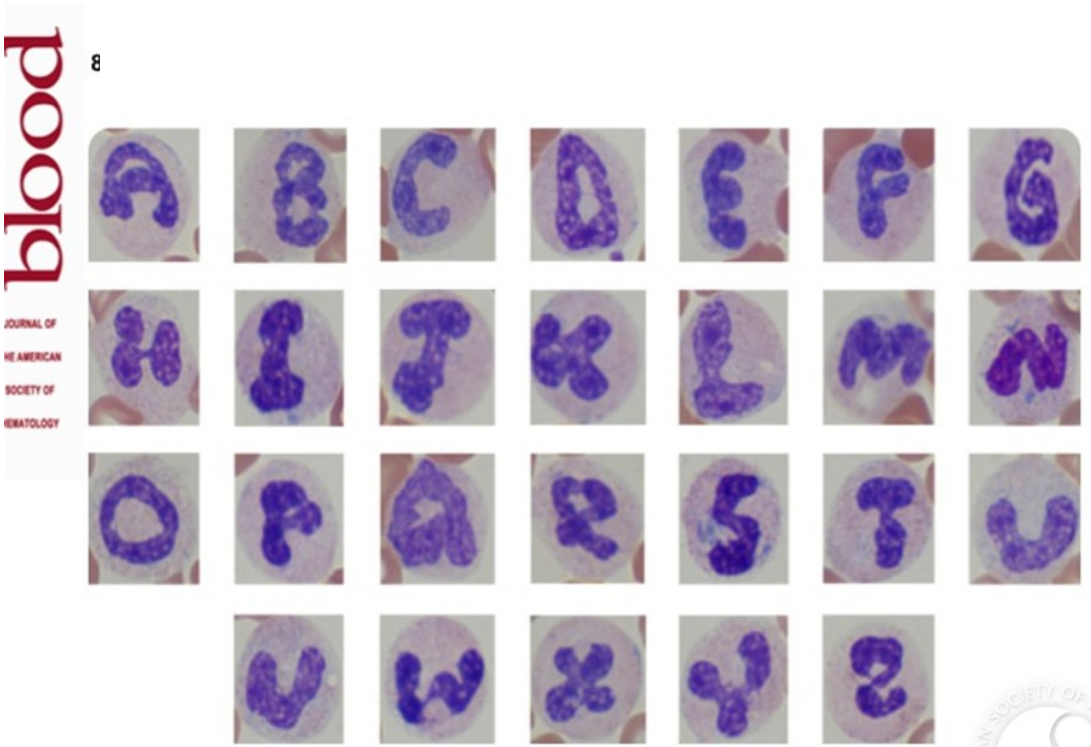
Case 1 - Differential

- 86% Neutrophils
- 12% Immature Granulocytes
- 2% Lymphocytes

- Rapid strep test is positive
- He improves with a course of antibiotics



Morgan A S , and Yang D T Blood 2013;121:3546-3546

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Origin of MPN

MF: Dr. Gustav Heuck 1879 Two cases of leukemia with peculiar blood and bone marrow findings, respectively

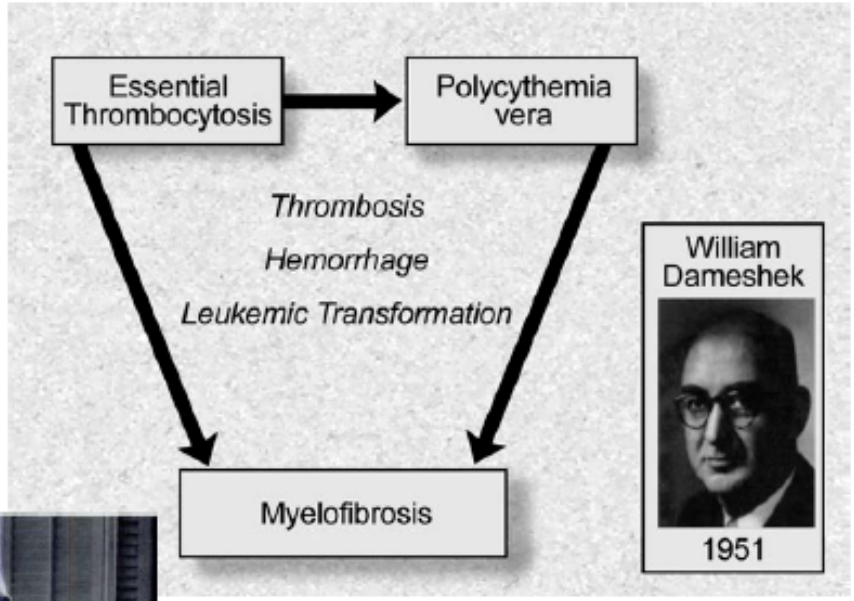
PV: Dr. Louis Henri Vaquez 1892 On a special form of cyanosis accompanied by excessive and persistent erythrocytosis Dr. Osler coins "Vaquez's disease" in 1903 chronic cyanosis with polycythemia and enlarged spleen

ET: Drs. Emil Epstein and Alfred Goedel 1934 Hemorrhagic thrombocythemia with a cascular, sclerotic spleen

TABLE 1.—*The Myeloproliferative Disorders*

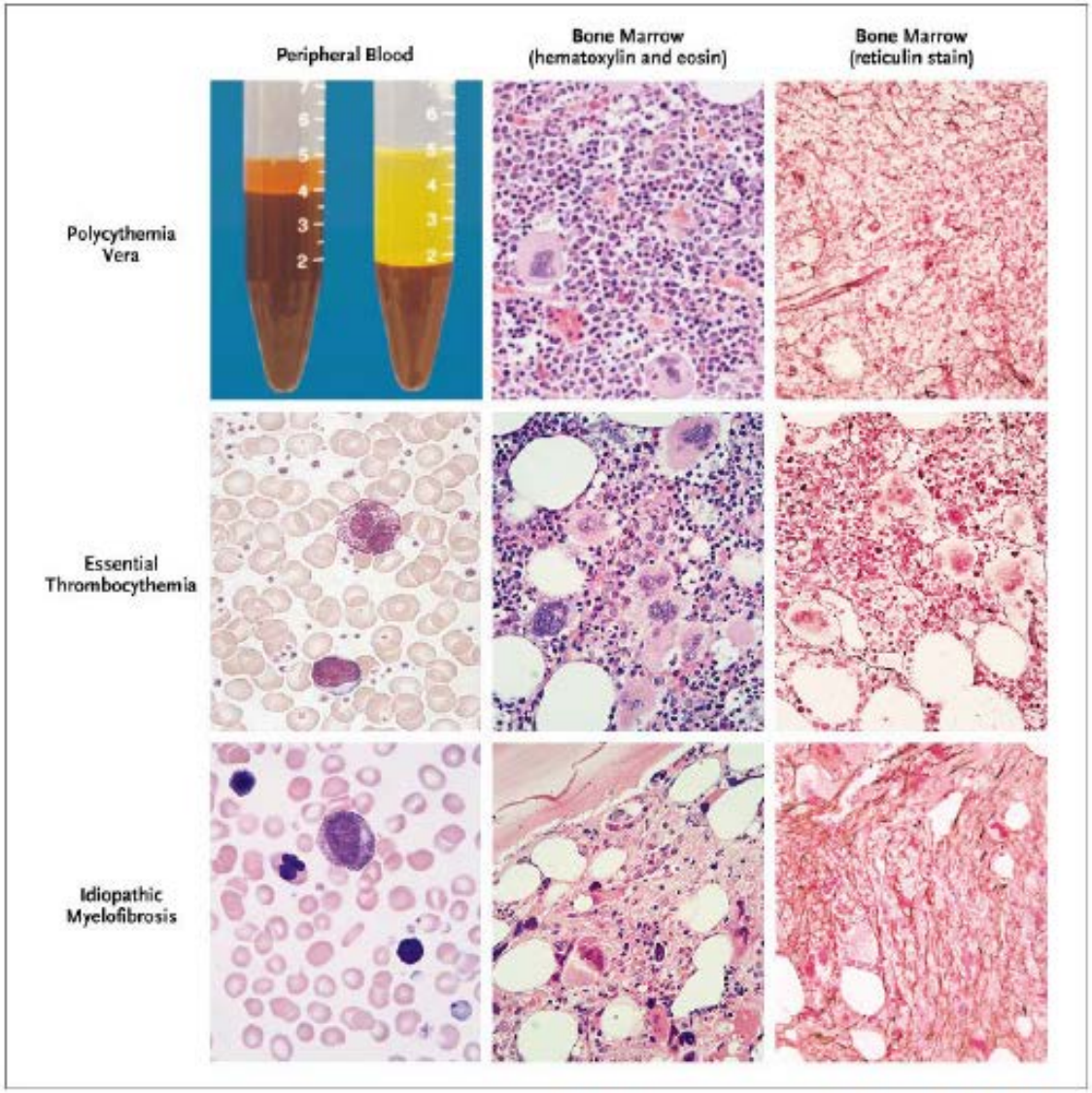
Syndromes	Myelostimulatory Factor(s) → Bone marrow: Erythroblasts	Granulocytes	Megakaryocytes	Fibroblasts	Potential bone marrow: Myeloid metaplasia of spleen and liver
Chronic Granulocytic Leukemia	±	+++	+ to +++	+	++
Polycythemia Vera	+++	++	++ to +++	+ to +++	+ to +++
Idiopathic or Agnogenic Myeloid Metaplasia of Spleen	±	±	+++	+ to +++	+++
Megakaryocytic Leukemia	±	±	+++	+	+ to +++
Erythroleukemia (including diGuglielmo syndrome)	+++	+	±	±	+ to +++

Degrees of Proliferation: + slight, ++ moderate, +++ marked



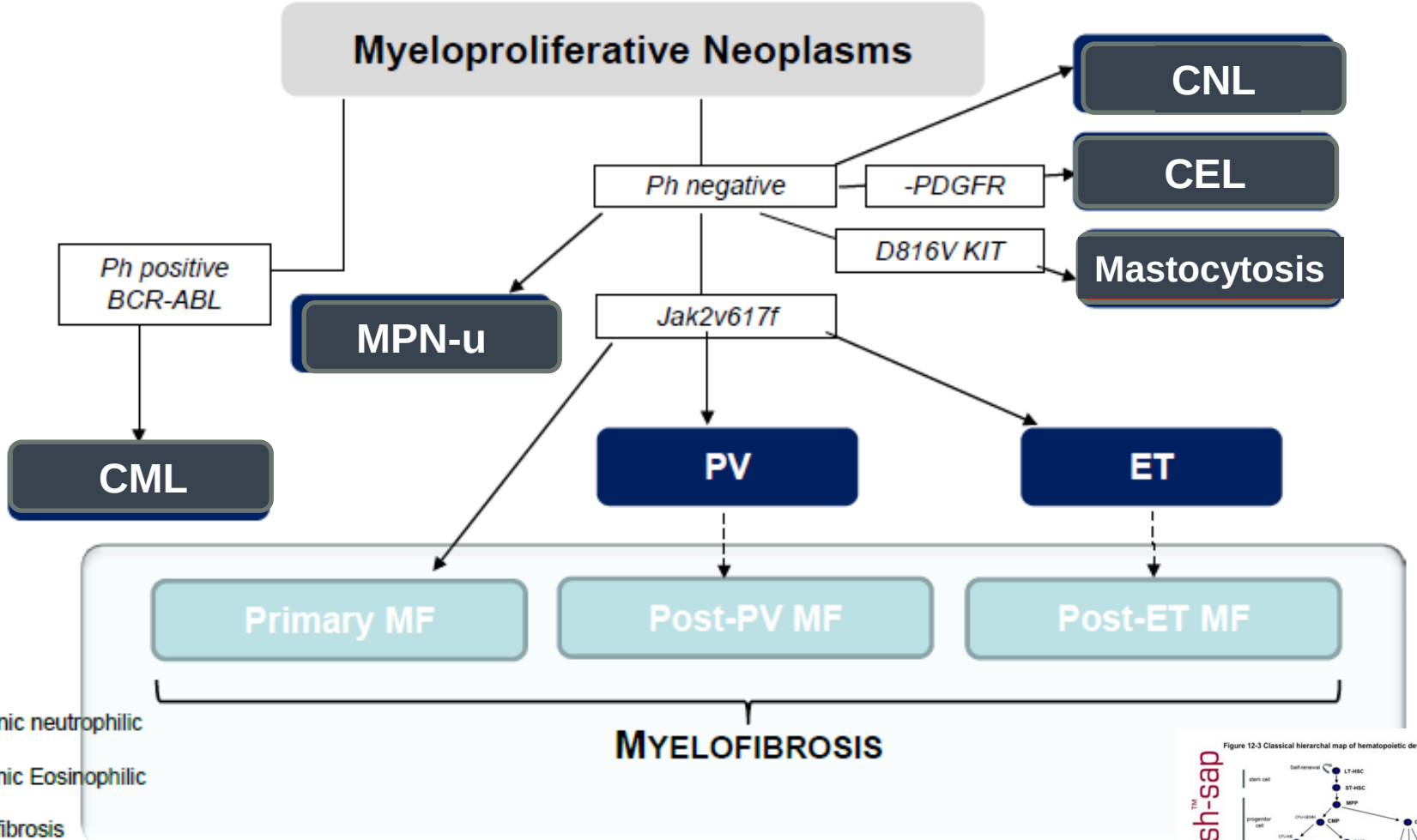
Dameshek et al. *Blood* 1951;6:372-375
Levine and Gilliland *Blood* 2008;112:2190-2198

Lab Features of PV, ET, and MF

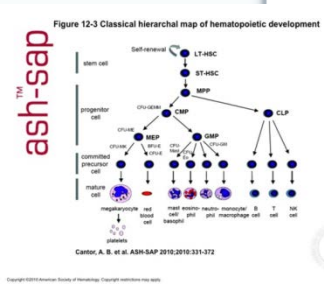


Campbell P and Green A. *N Engl J Med* 2006;355:2452-2466

Making a Molecular Diagnosis

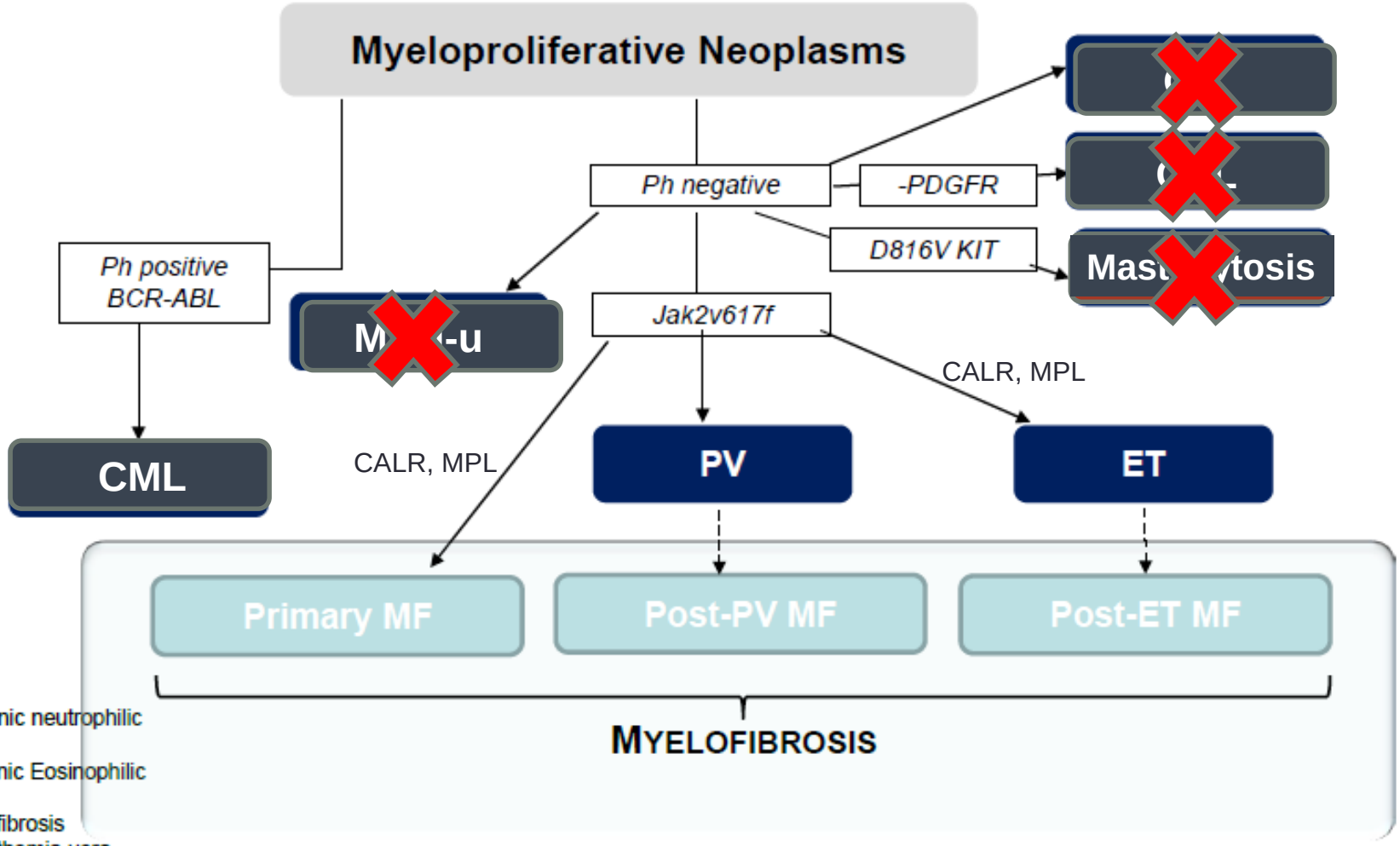


CNL=Chronic neutrophilic luekemia
CEL=Chronic Eosinophilic Leukemia
MF=myelofibrosis
PV=polycythemia vera
ET=essential thrombocythemia
CML=chronic myeloid leukemia



Tefferi A, Vardiman JW. *Leukemia*. 2008;22:14-22; Vardiman JW, et al. *Blood*. 2009;114(5):937-951 Mesa RA. *Blood*. 2009;113(22):5394-5400; Tam CS, et al. *J Clin Oncol*. 2009;27:5587-5593.

Making a Molecular Diagnosis



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Klampfl NEJM 2013

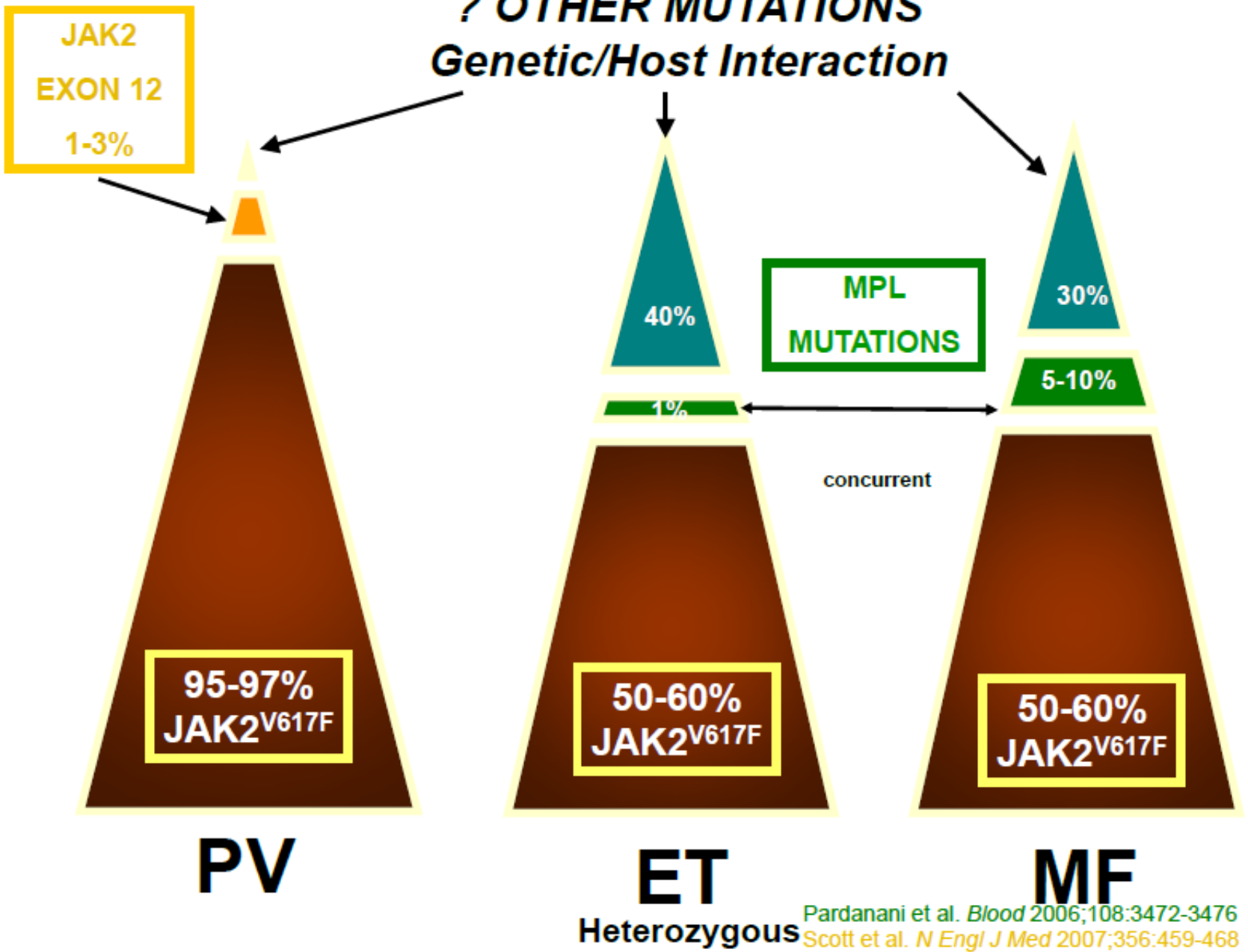
Jak 2 Testing in MPN

Reference	Assay	Source*	PV %(N)	ET %(N)	MMM %(N)	Controls
Baxter et al.#	AS-PCR	PB & BM	97% (73)	57% (51)	50% (16)	0% (90)
Levine et al.#$	PCR	PB	74% (164)	32% (115)	35% (46)	0% (270)
James et al.#	PCR	PB & BM	89% (45)	43% (21)	43% (7)	0% (45)
Kralovics et al.#$^	PCR	PB	65% (128)	23% (93)	57% (23)	0% (82)
Zhao et al.	PCR	PB	83% (24)	N/A	N/A	0% (12)
Teffera et al.	PCR	PB	95% (38)	55% (22)	30% (10)	0% (30)
Jones et al.	AS-PCR	PB	81% (72)	41% (59)	43% (35)	0% (160)

* purified granulocytes

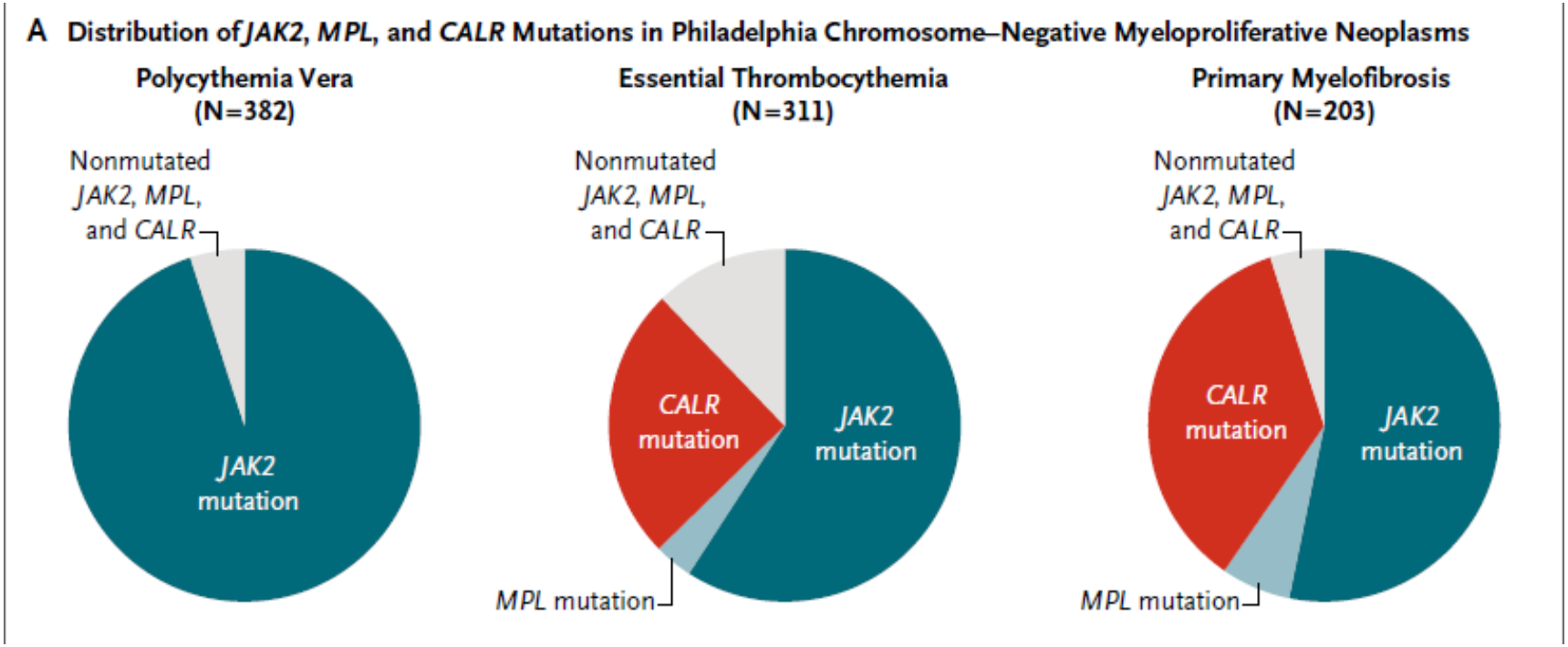
#T-Lymphocytes, $Buccal mucosal cells, and ^hair follicles were negative

Baxter et al *Lancet* 2005. 365:1054
Levine et al *Cancer Cell* 2005. 7:387.
James et al. *Nature* 2005. 434: 1144



Pardanani et al. *Blood* 2006;108:3472-3476
Scott et al. *N Engl J Med* 2007;356:459-468
Kralovics et al. N Engl J Med 2005;352:1779-1790

Calreticulin as the ‘other mutation’



Klampfl NEJM 2013

WHO 2016 Diagnostic Criteria

PV

(Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion)

Major criteria	
Criterion 1 (clinical)	
Hb, or	>16.5 g/dL in men, >16.0 g/dL in women
Hematocrit, or	>49% in men, >48% in women
Red cell mass	Increased 25% above mean normal predicted value
Criterion 2 (morphologic)	
BM morphology*	Hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature MKs (differences in size)
Criterion 3 (genetic)	
JAK2V617F, or	Presence
JAK2 exon 12 mutation	Presence
Minor criterion	
Serum Epo level	Subnormal

ET

(Diagnosis of ET requires meeting all 4 major criteria, or the first 3 major criteria and the minor criterion)

Major criteria	
Criterion 1 (clinical)	
Platelet count	$>450 \times 10^9$/L
Criterion 2 (morphologic)	
BM morphology	Proliferation mainly of the MK lineage with increased numbers of enlarged, mature MKs with hyperlobulated nuclei. No significant increase or left-shift in neutrophil granulopoiesis or erythropoiesis, and very rarely minor (grade 1) increase in reticulin fibers
Criterion 3 (clinical)	
WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS, or other myeloid neoplasms	Not meeting
Criterion 4 (genetic)	
JAK2, *CALR*, or *MPL* mutation	Presence
Minor criterion	
Clonal marker, or	Presence
Reactive thrombocytosis	Absence

WHO 2016 Diagnostic Criteria

PV

(Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion)

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JAK2V617F, or	Presence
JAK2 exon 12 mutation	Presence
Minor criterion	
Serum Epo level	Subnormal

So what do you need?

- CBC
- Marrow
- Mutation testing
- Good history

ET

(Diagnosis of ET requires meeting all 4 major criteria, or the first 3 major criteria and the minor criterion)

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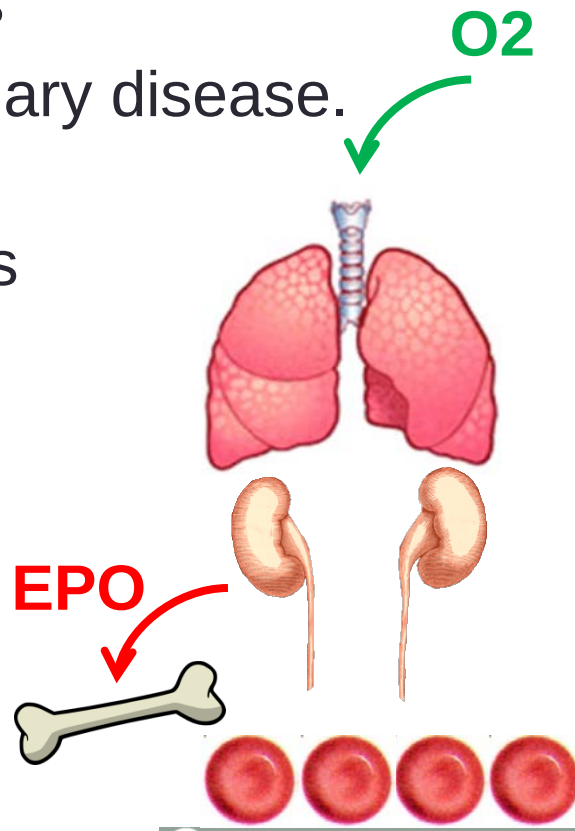
Minor criterion	
Clonal marker, or	Presence
Reactive thrombocytosis	Absence

Case 2 - Presentation

- 65yo woman is referred for ‘abnormal labs’
- Nonsmoker, no OSA, no history of pulmonary disease. She does not live at altitude.
- She reports pruritis but no other symptoms
- O2 saturation 98% RA
- Hb = 19
- WBC 9 Plt 400k

Next Tests?



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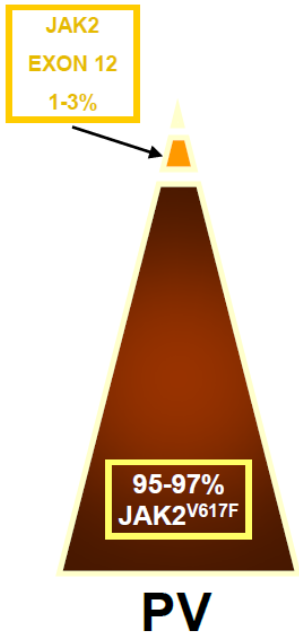
Case 2 – Diagnostics: Polycythemia Vera

- EPO = 5 (2-18)
- JAK2 V617F mutation positive

- (Potential causes of secondary polycythemia include altitude, lung disease/hypoxia, renal cell carcinoma and hepatocellular carcinoma as well as testosterone/anabolic steroid use or exogenous EPO)



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Case 2 – Treatment: Back to the Future

- Goal Hct is <45% (better than <50% in randomized trial by Marchioli et al. *NEJM* 2013 368:22)
  - Phlebotomy
  - Hydroxyurea
- ASA

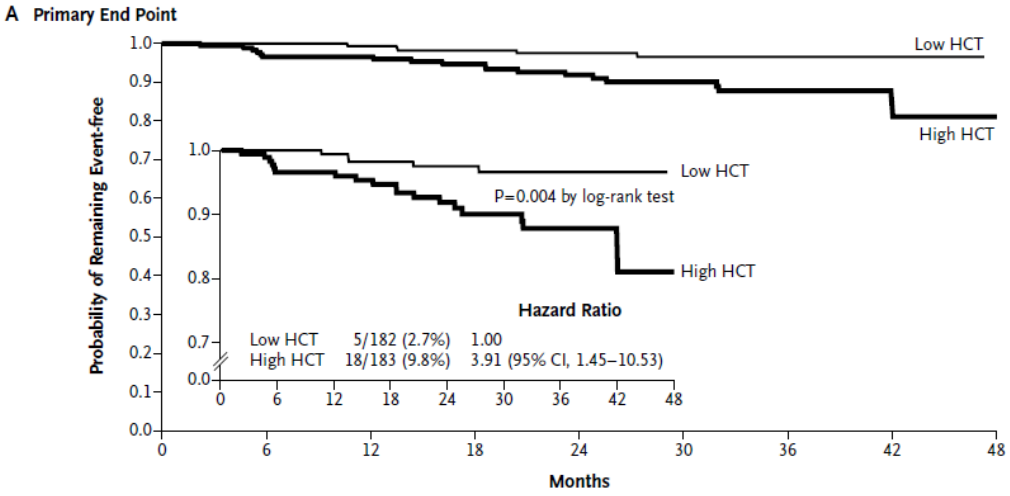
Ancient Greek Painting

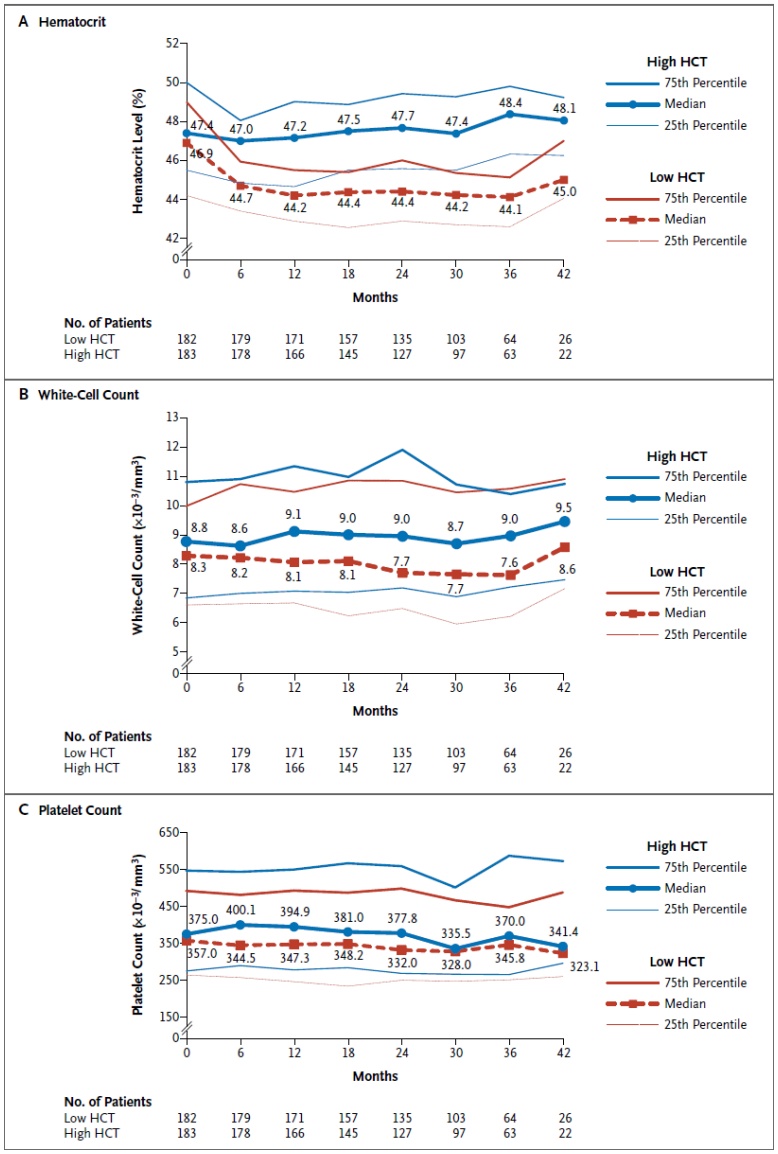
Photograph from the Burns Archive 1860

Patients with PV cannot donate blood, but patients with hemochromatosis can

CYTO-PV Study: 45% vs 50%

- 365 patients, randomized
- Primary end point
  - death from cardiovascular causes or thrombotic events
- HU or phlebotomy allowed

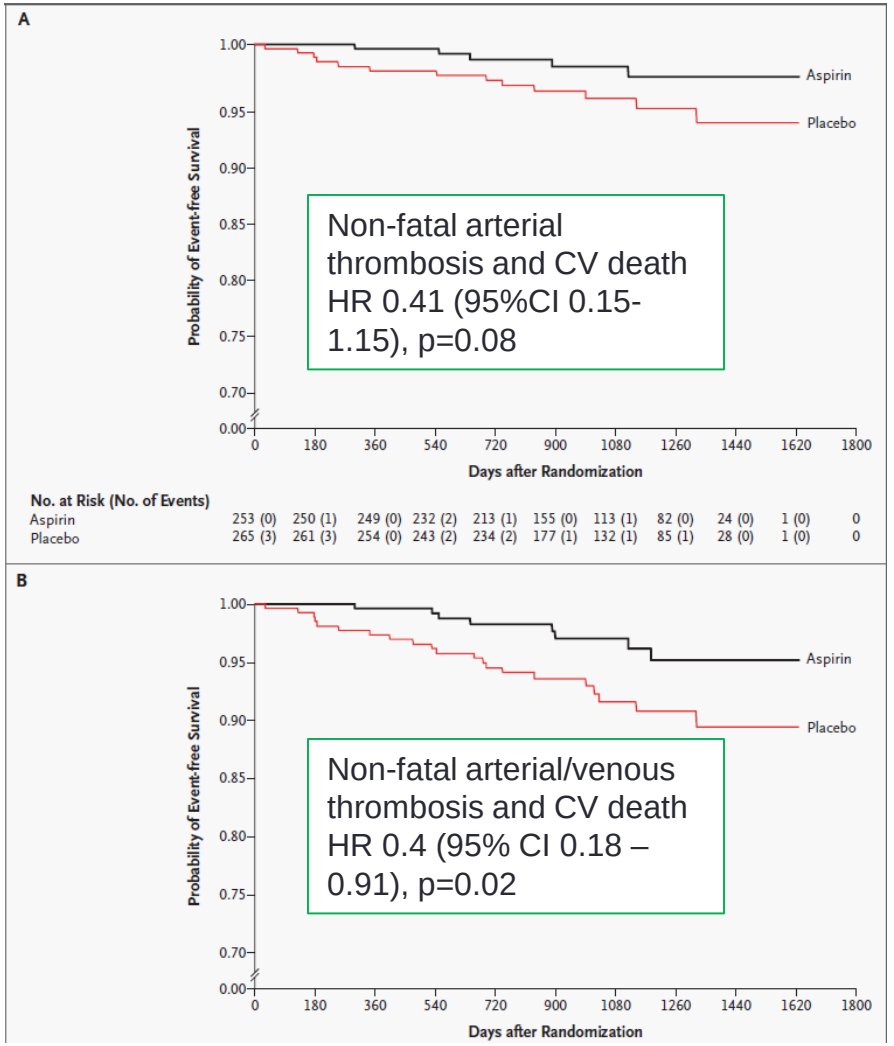




Marchioli et al. *NEJM* 2013 368:22

ECLAP: ASA vs Placebo in PV

- Efficacy and Safety of Low Dose Aspirin in PV
  - Multicenter European Study
- 518 patients, randomized
- Mean follow up 3 years
- More smokers in ASA arm
- Other tx as needed
  - Cytoreduction (HU)
  - Phlebotomy
- No difference in overall mortality
- NS reduction in major thrombosis
- Major bleeding not different



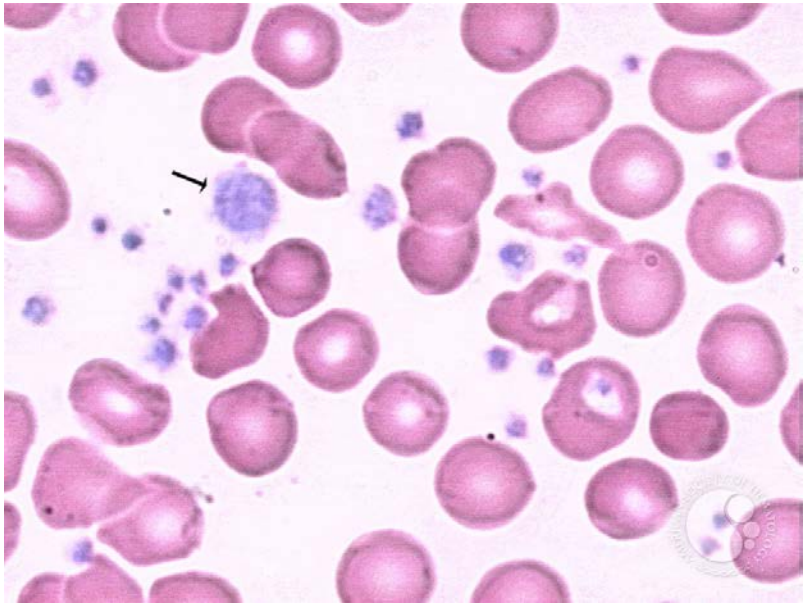
Landolfi et al. NEJM 2004. 350:114

Case 3 - Presentation

- 55yo man presents with fatigue, and abnormal labs prior to upcoming hernia surgery.
- He has no active infections. Exam reveals no major findings and his hernia is easily reducible without associated erythema or tenderness.

- CBC: 27>45%<750
- N65%, L25%, M8%, E2%

Next Tests?

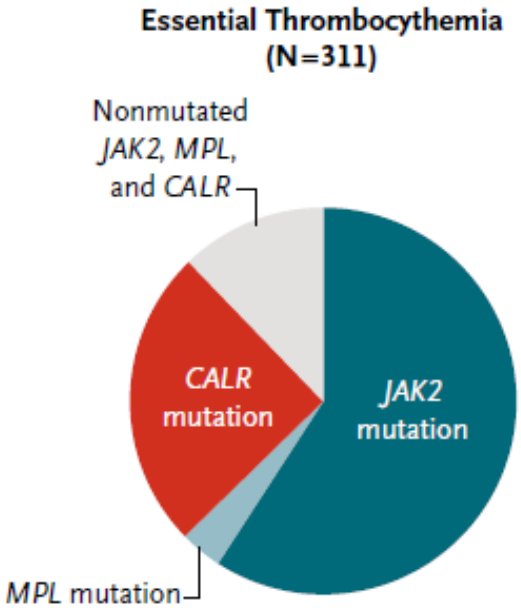


Peter Maslak

Case 3 - Diagnostics

- JAK2 V617F mutation negative
- BCR/ABL negative
- CALR positive
- Bone Marrow - increased megakarycytes, some are increased in size but not abnormal. No increase in fibrosis.

- Diagnosis of Essential Thrombocythemia



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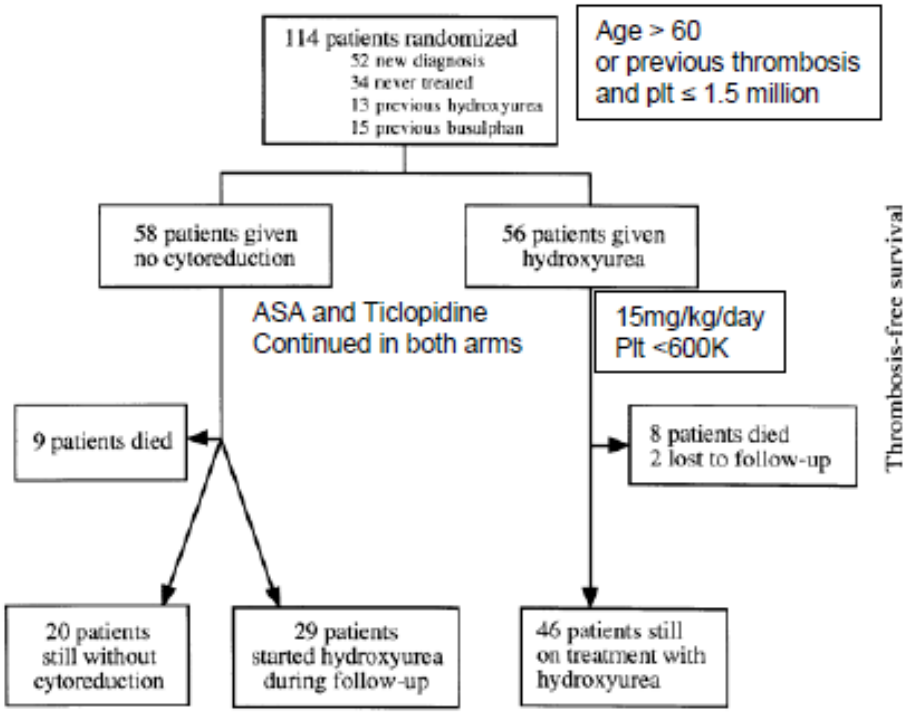
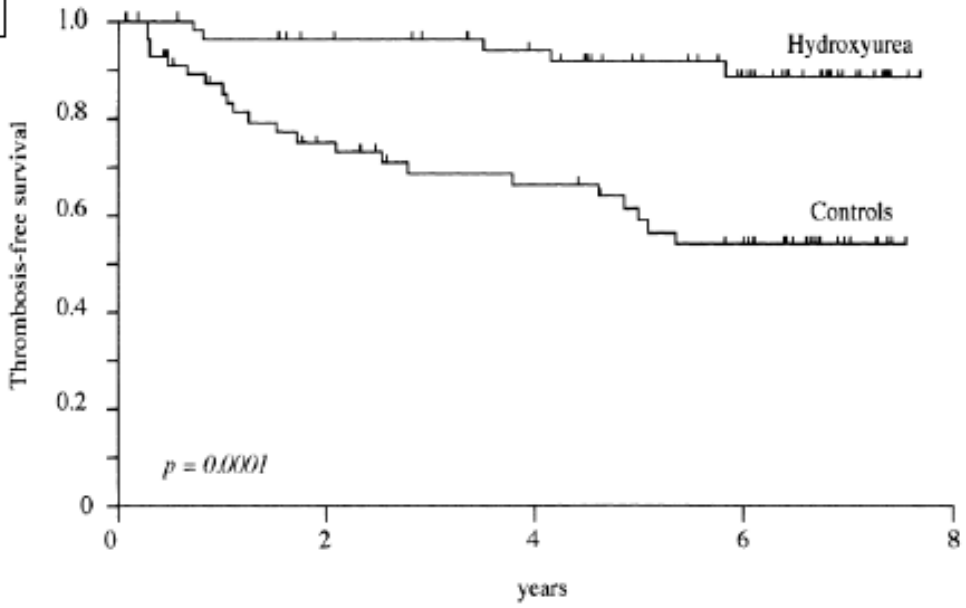
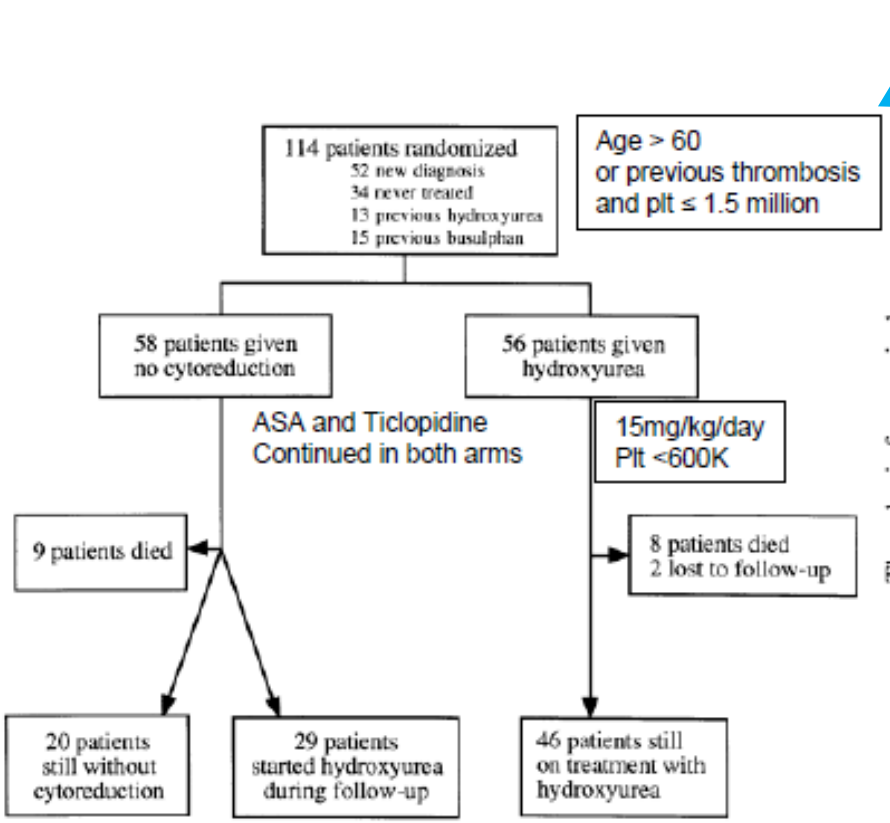
HU in High-Risk ET

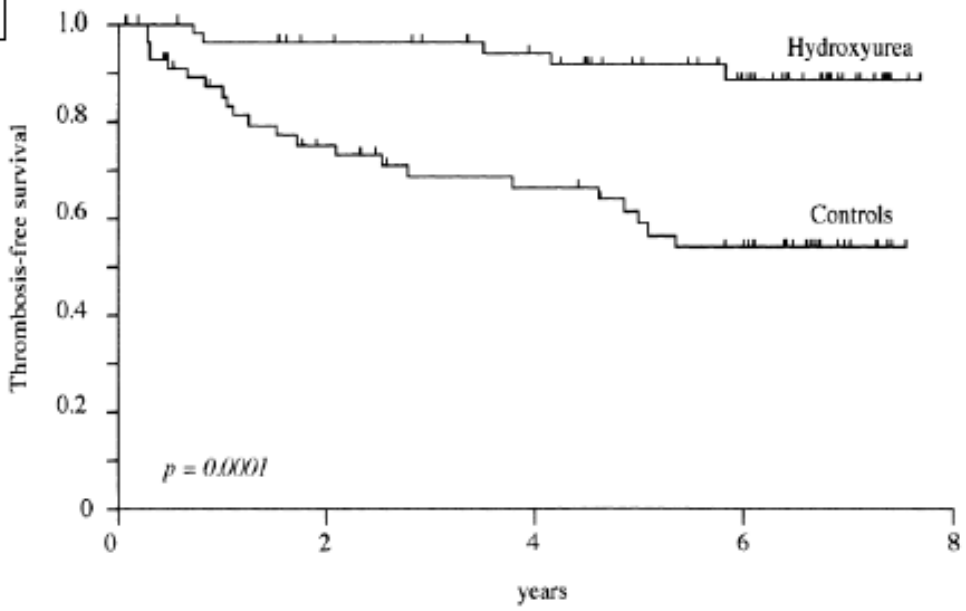




Cortelazzo et al. *N Engl J Med* 1995;332:1132
Finazzi et al. *Br J Haematol* 2000;110:577

HU in High-Risk ET





Cortelazzo et al. *N Engl J Med* 1995;332:1132
Finazzi et al. *Br J Haematol* 2000;110:577

Who gets treated with ET (and who just phones home)?

	Age <60yo	Age >60yo
No prior Thrombosis	NO CYTOREDUCTION	Cytoreduce
Prior Thrombosis*	Cytoreduce	Cytoreduce

Barbui, JCO. 2011;29: 761.

* Includes CVA, TIA, AMI, Arterial thrombus, or VTE

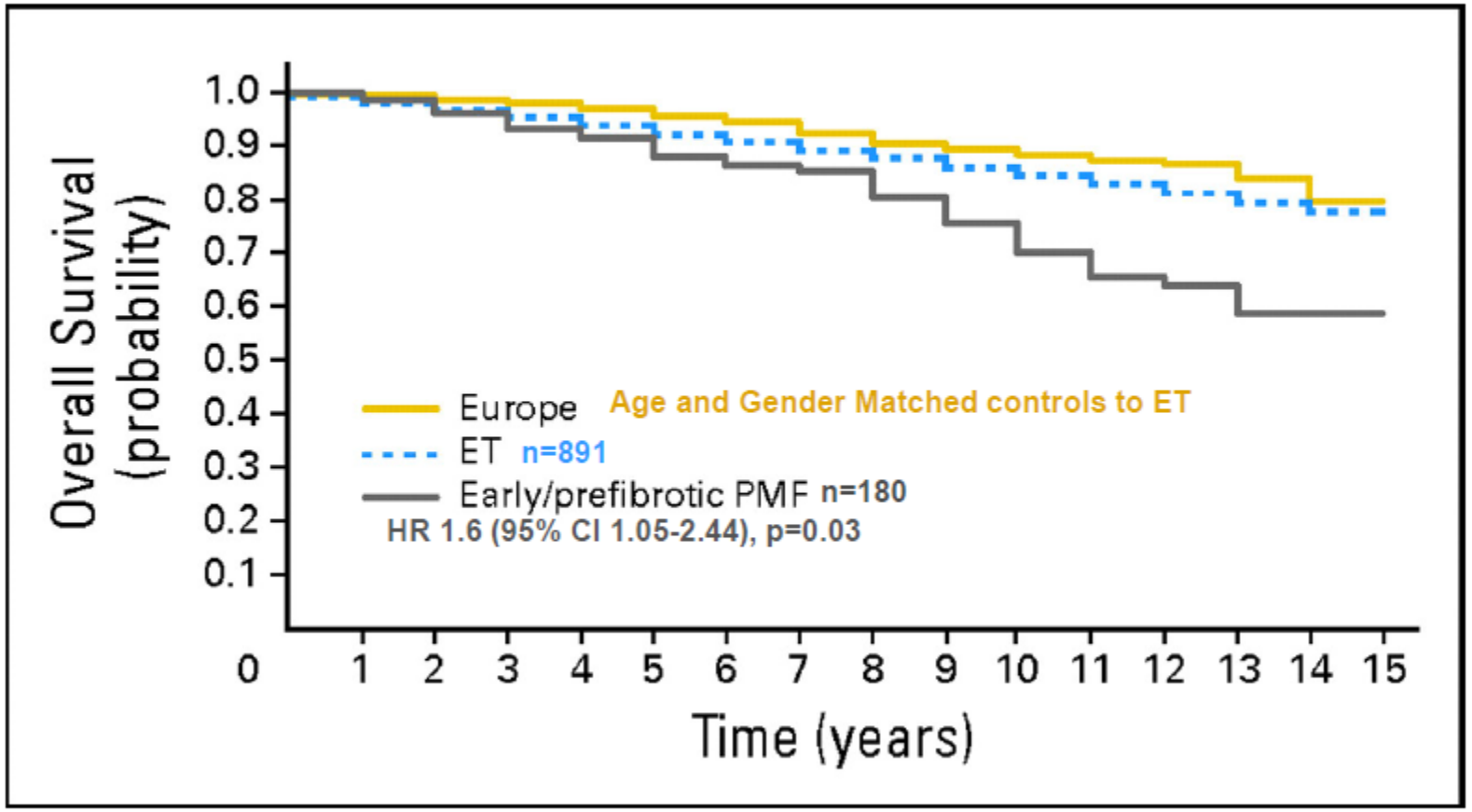
Table 2. Significant risk factors for thrombosis in 891 patients with WHO-defined ET and associated prognostic scores

Risk factor	HR	Score
Age > 60 y	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
*JAK2*V617F	2.04	2

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

Barbui, Blood 2012. 120:5128

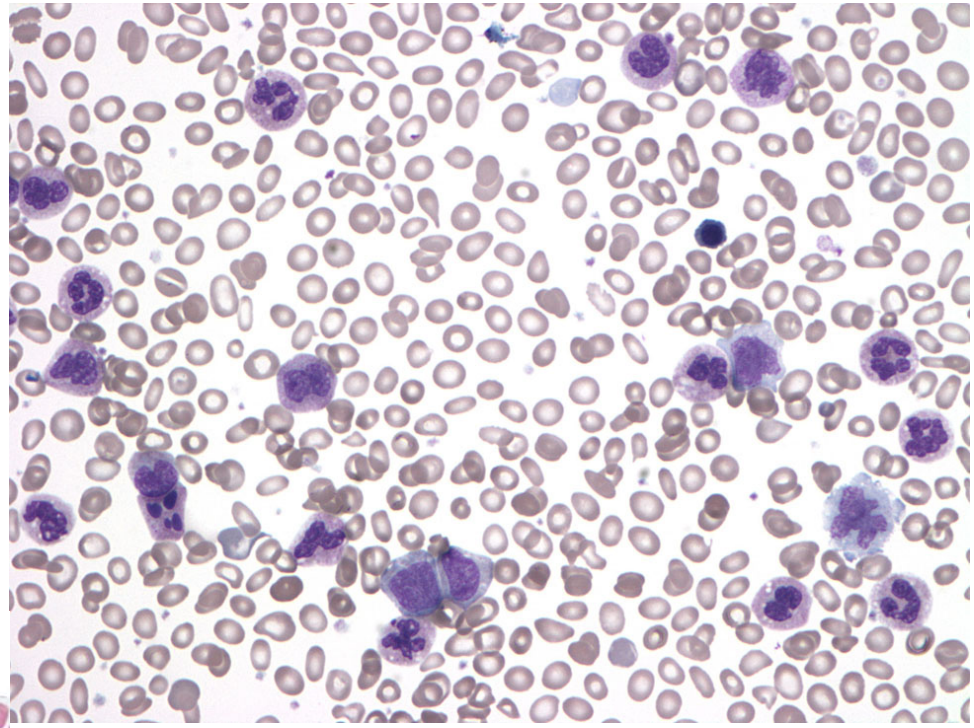
ET vs. MF vs. Control

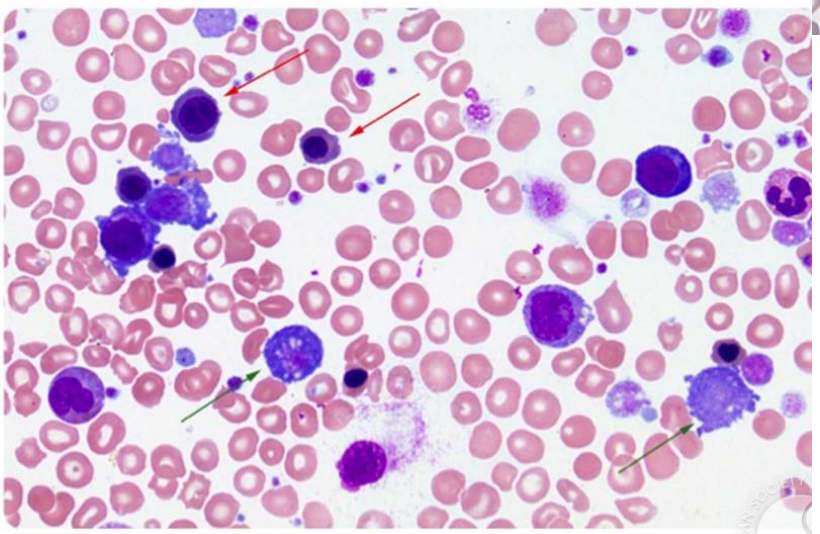


Barbui T et al. *J Clin Oncol*. 2011;29:3179-3184

Case 4 - Presentation

- 62yo woman presents with LUQ abdominal pain, early satiety and weight loss x 3 months
- Examination reveals splenomegaly 8cm below the costal margin
- Next Test?





Sanford D , and Hsia C Blood 2013;122:4163

Diagnostic Criteria

(Diagnosis of pre-PMF requires meeting all 3 major criteria, and at least 1 minor criterion)

Major criteria	
Criterion 1 (morphologic)	
BM morphology	Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
Criterion 2 (clinical)	
WHO criteria for BCR-ABL1 + CML, PV, ET, MDS, or other myeloid neoplasms	Not meeting
Criterion 3 (genetic)	
JAK2, *CALR* or *MPL* mutation, or	Presence
Clonal marker,† or	Presence
Reactive BM reticulin fibrosis‡	Absence
Minor criteria	
Anemia not attributed to a comorbid condition	Presence
Leukocyte count	$\geq 11 \times 10^9$/L
Spleen size	Palpable
Serum LDH	Increased to above upper normal limit of institutional reference range

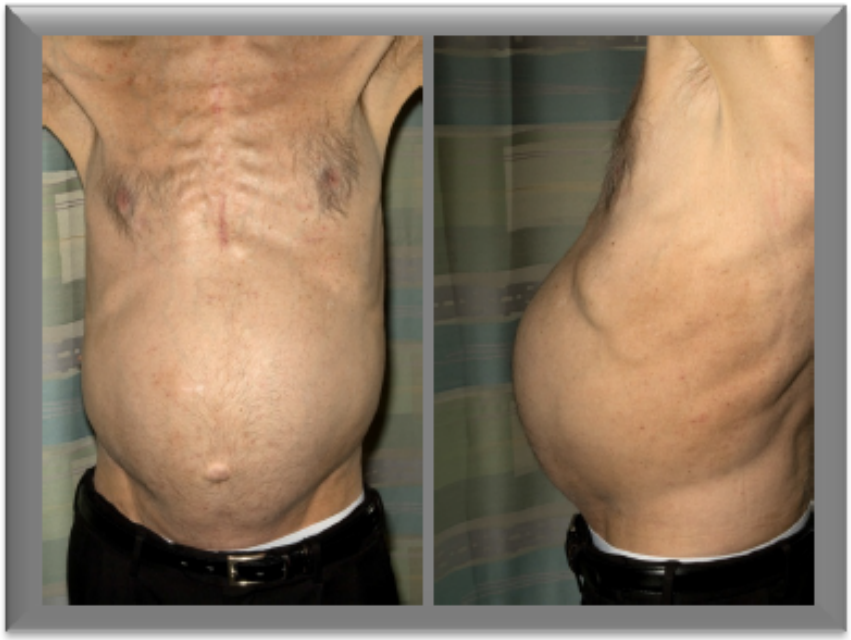
MF

(Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion)

Major criteria	
Criterion 1 (morphologic)	
BM morphology	Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
Criterion 2 (morphologic)	
WHO criteria for ET, PV, BCR-ABL1 + CML, MDS, or other myeloid neoplasms	Not meeting
Criterion 3 (genetic)	
JAK2, *CALR*, or *MPL* mutation, or	Presence
Clonal marker,† or	Presence
Reactive BM reticulin fibrosis‡	Absence
Minor criteria	
Anemia not attributed to a comorbid condition	Presence
Leukocyte count	$\geq 11 \times 10^9$/L
Spleen size	Palpable
Serum LDH	Increased to above upper normal limit of institutional reference range
Leukoerythroblastosis	Presence

MF Disease Features

- 85% or more of MF patients present with palpable splenomegaly at the time of diagnosis[1]
- 60% to 80% of MF patients report spleen-related symptoms[2]
  - e.g., abdominal pain / discomfort, early satiety
- Other MF symptoms that can be present include[3]
  - Pruritus
  - Night sweats
  - Bone pain

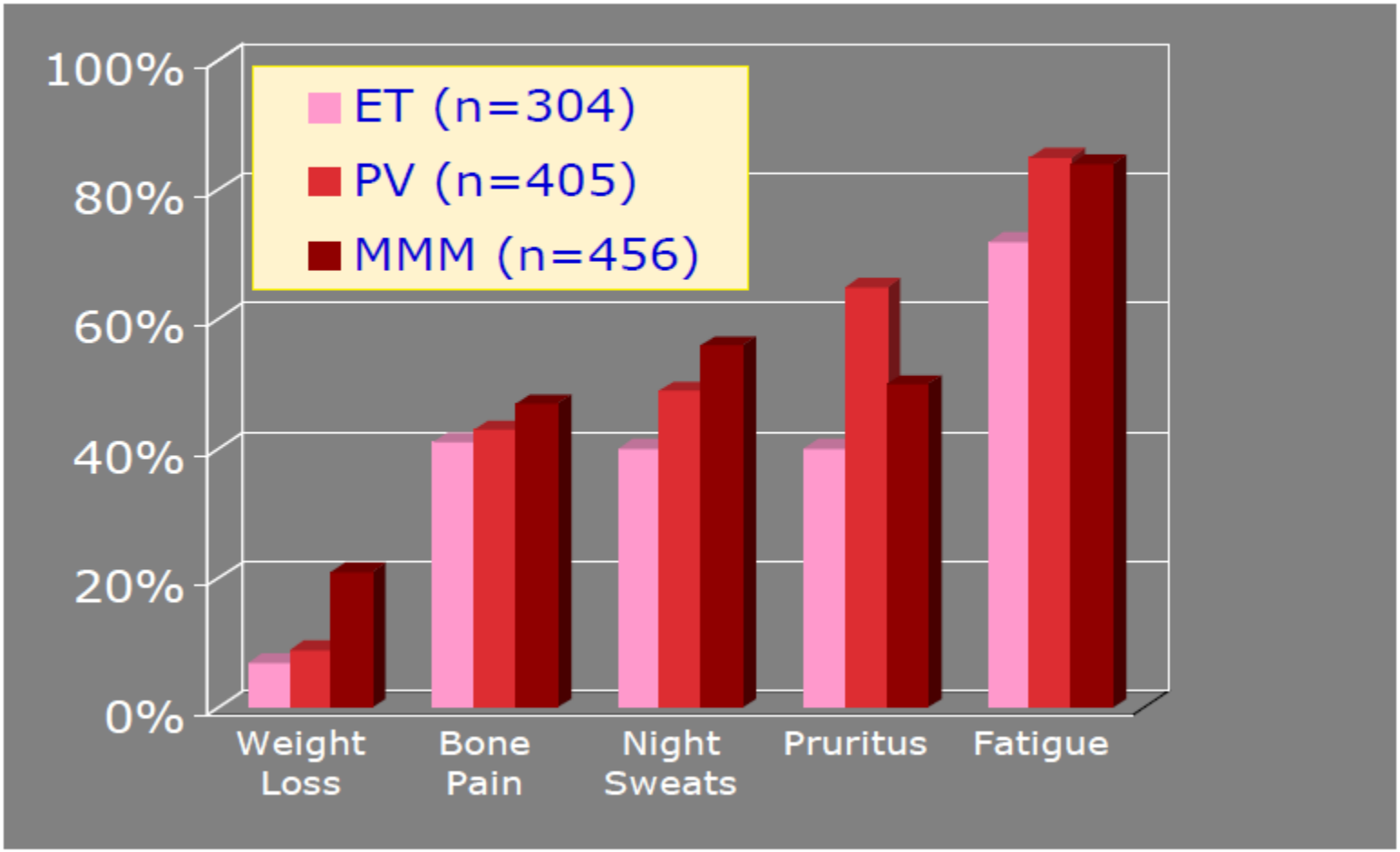


Splenomegaly in MF Patient

Image courtesy of
MD Anderson Cancer Center

[1]Barosi G. *J Clin Oncol*. 1999;17:2954-2970.
[2]Scherber RM, et al. *Blood*. 2011;118(2):401-408.
[3]Mesa RA, et al. *Leuk Res*. 2009;33:1199-1203.

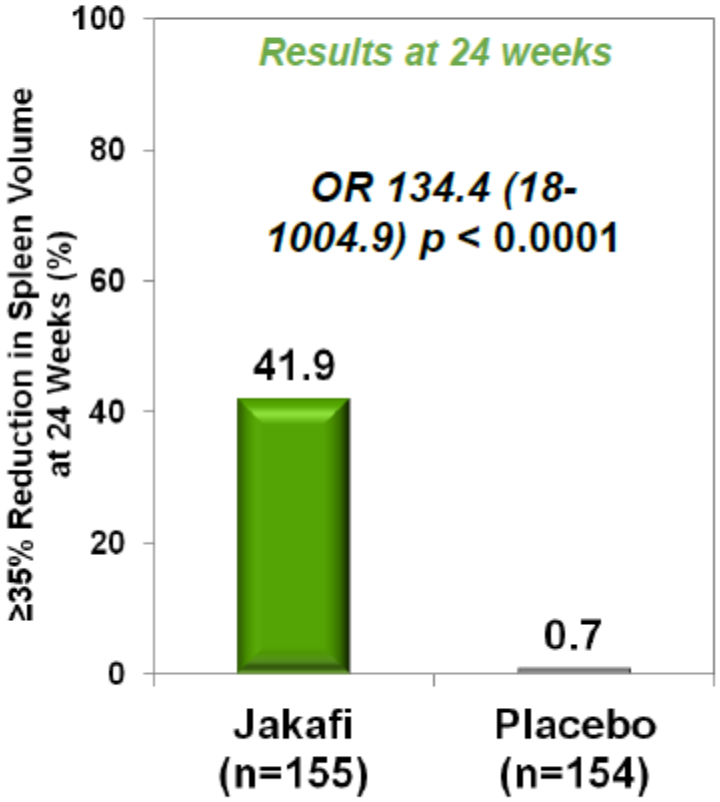
Symptoms in 1179 MPN Patients

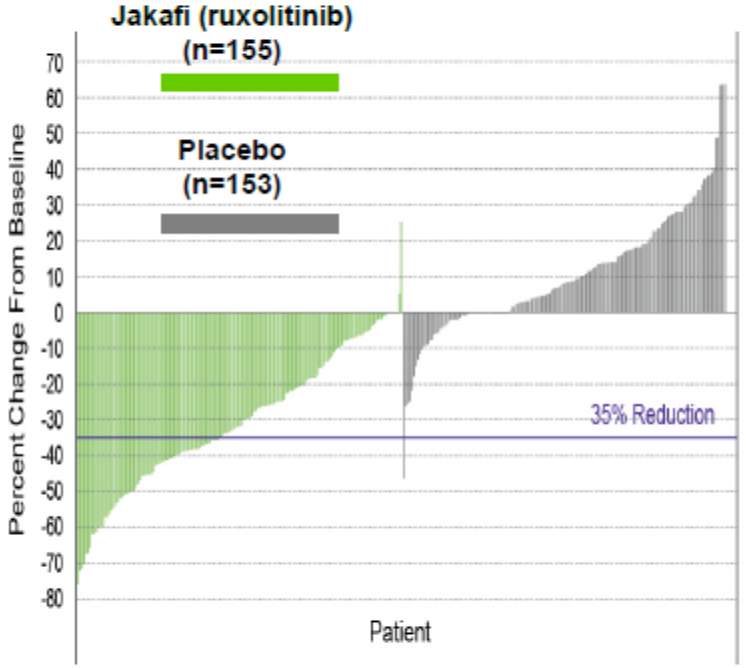


Mesa et. al. *Cancer* 2007;109:68-76

COMFORT-I: Spleen Volume Reduction

Jakafi (ruxolitinib) provided significant improvement in spleen volume

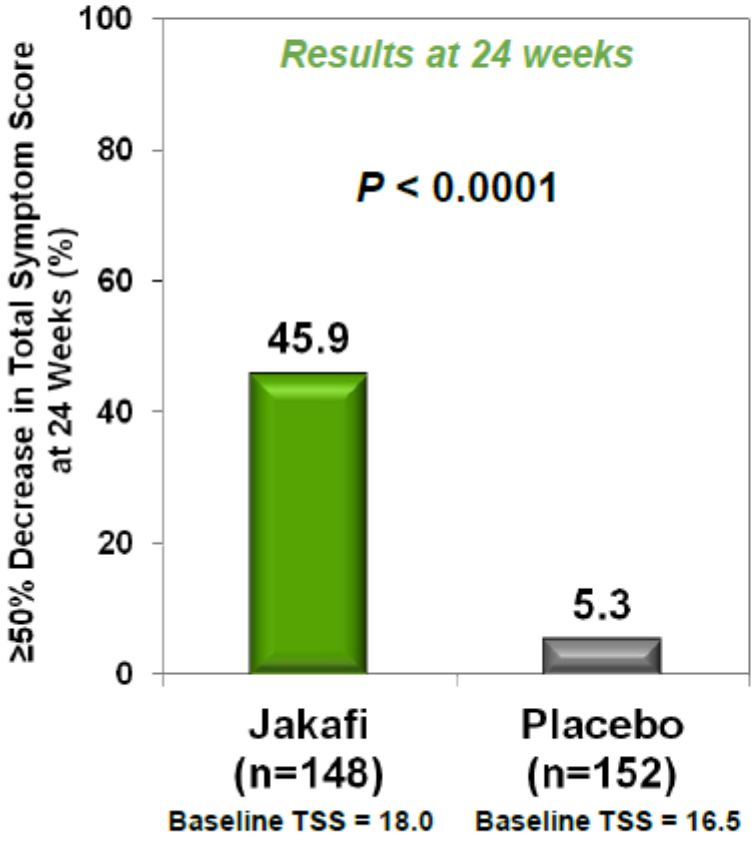




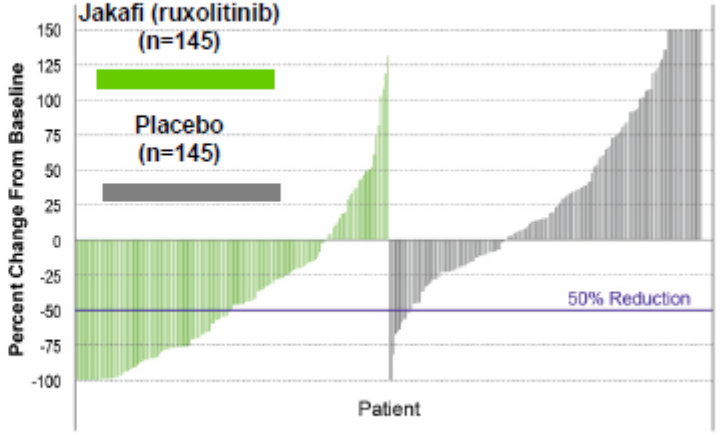
Verstovsek et al. *N Engl J Med* 2012;366:799-807

COMFORT-I: Symptom Improvement

Significant improvement in MF symptoms (MFSAF v2.0)

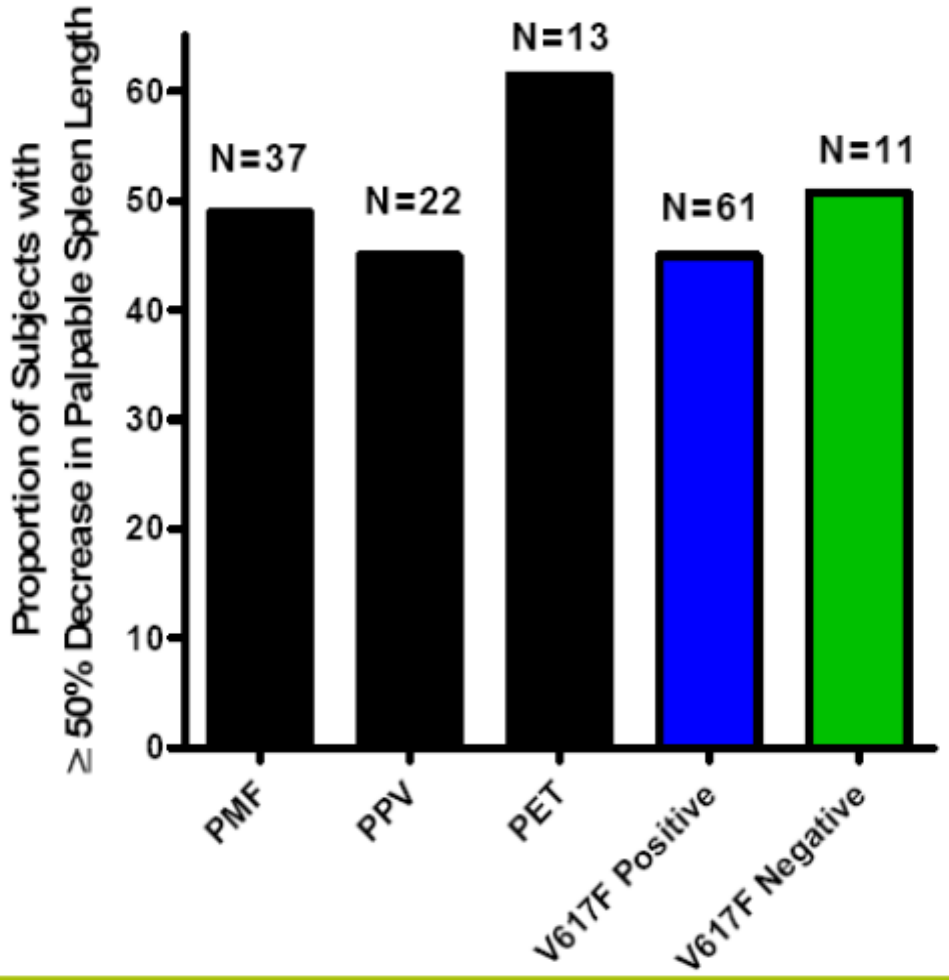


- Jakafi (ruxolitinib) provided significant improvement in total MF symptoms
  - Median time to response: <4 weeks
- Total symptom score (TSS) includes
  - Abdominal discomfort
  - Pain under the left ribs
  - Night sweats
  - Itching
  - Bone/muscle pain
  - Early satiety
- Symptom scores ranged from 0 (absent) to 10 (worst imaginable) and were added to create the daily TSS (maximum of 60)

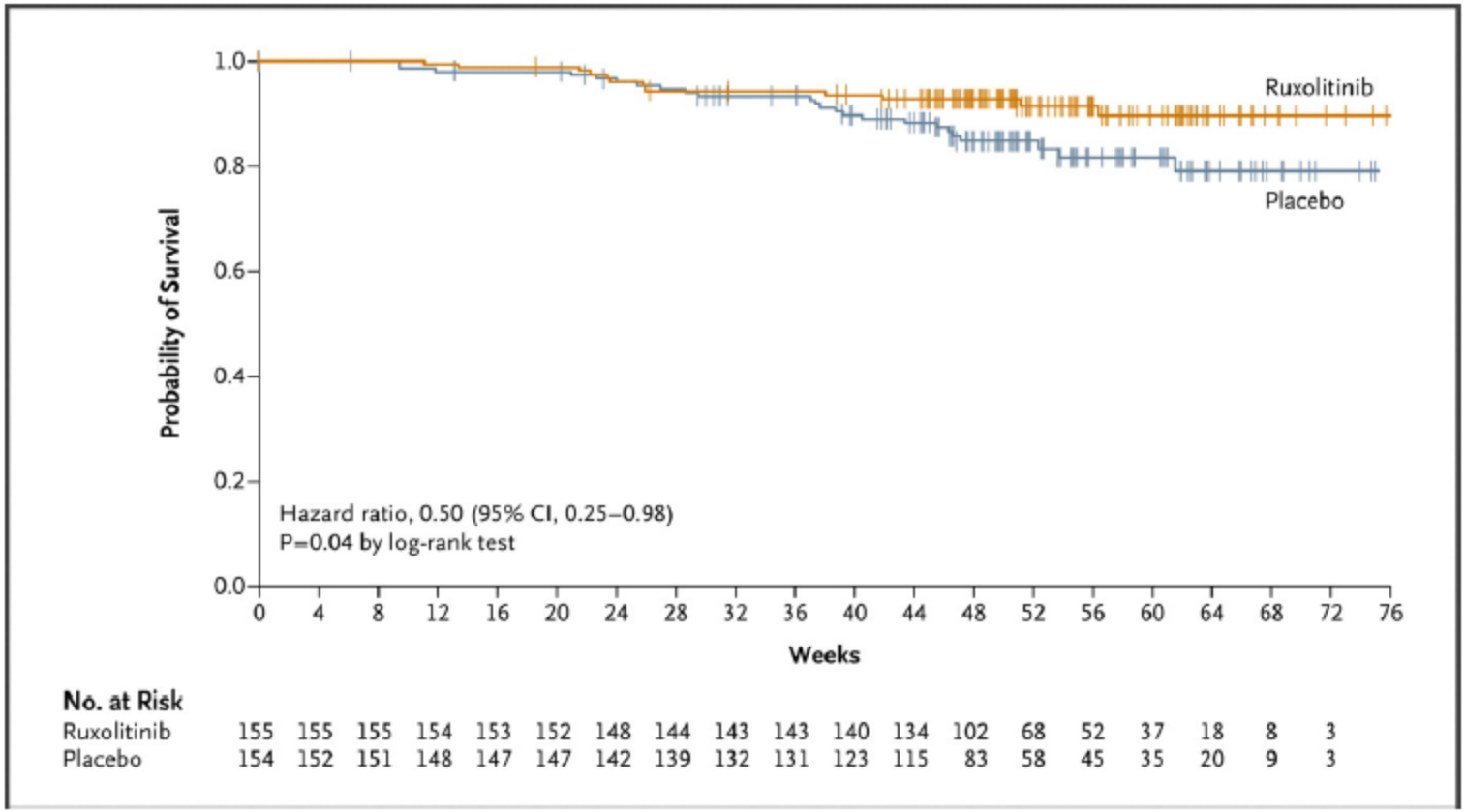


Verstovsek et al. *N Engl J Med* 2012;366:799-807
Scherber et al. *Blood* 2011;118:401-408

Spleen Size Reduction Is Independent Of JAK Mutation Status Or Disease Subtype



Overall Survival in COMFORT I

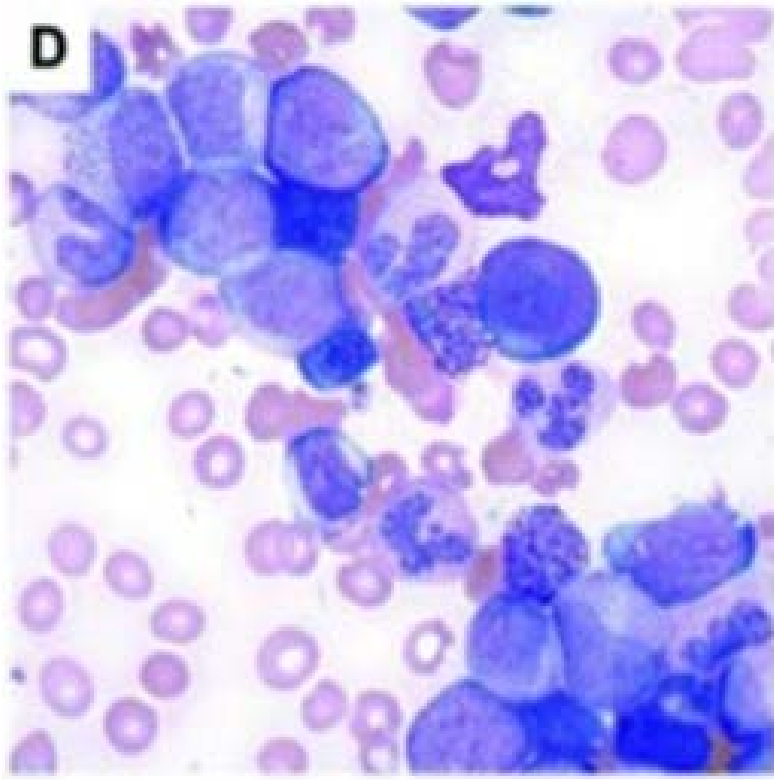


Verstovsek S et al. *N Engl J Med* 2012;366:799-807.

56yo admitted with abdominal pain and leukocytosis

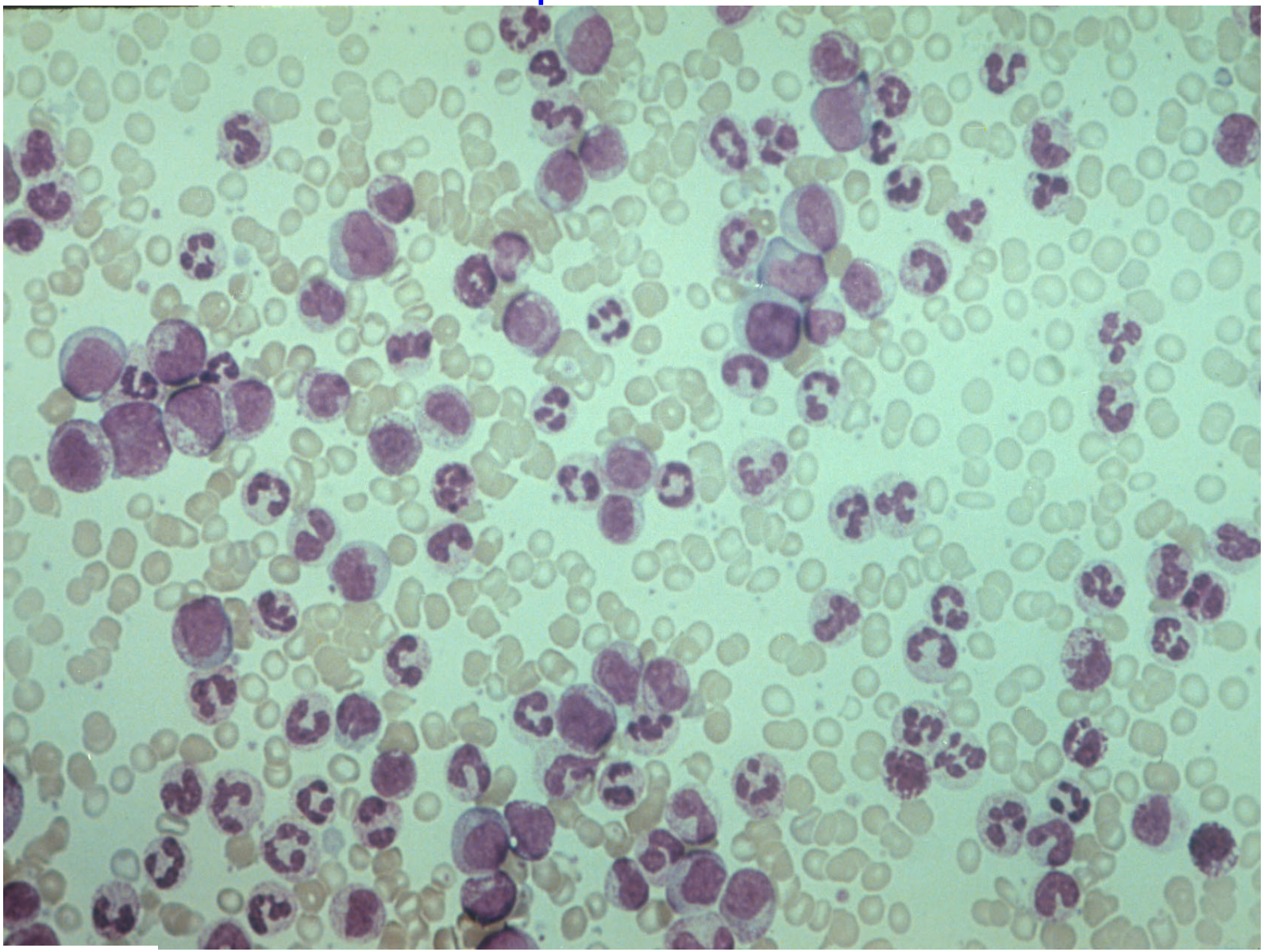
- 3 months of gradually increasing abdominal pain, L>R
- Temp 100.8 HR 110
- Abdomen TTP in the LUQ, spleen palpable 8cm below the costal margin

What is the most likely diagnosis?



George T I Hematology 2012;2012:475-484

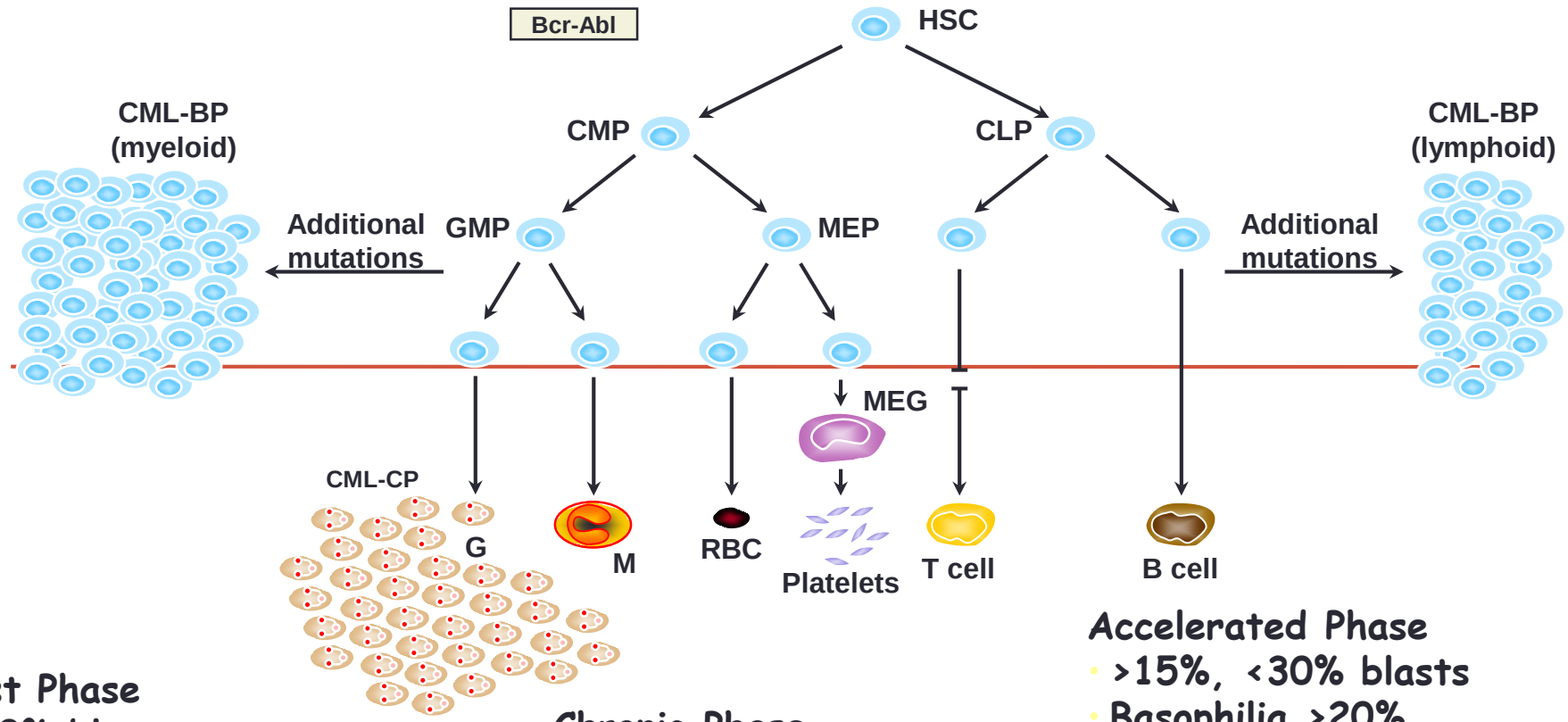
Peripheral blood smear



CML clinical features

- **~4500 new US cases per year**
- **Median age at presentation 53 years**
- **60% men**
- **Disease is clinically divided into three phases**
  - **Chronic phase**
  - **Accelerated phase**
  - **Blast crisis (lymphoid (ALL) or myeloid (AML))**

Progression of CML



Blast Phase
- >30% blasts
- ~2/3 of patients have myeloid blast crisis
- ~1/3 have lymphoid blast crisis
- Very poor prognosis

Chronic Phase
- Myeloid hyperplasia
- <15% blasts
- Natural history of disease progression, 3-5 years untreated

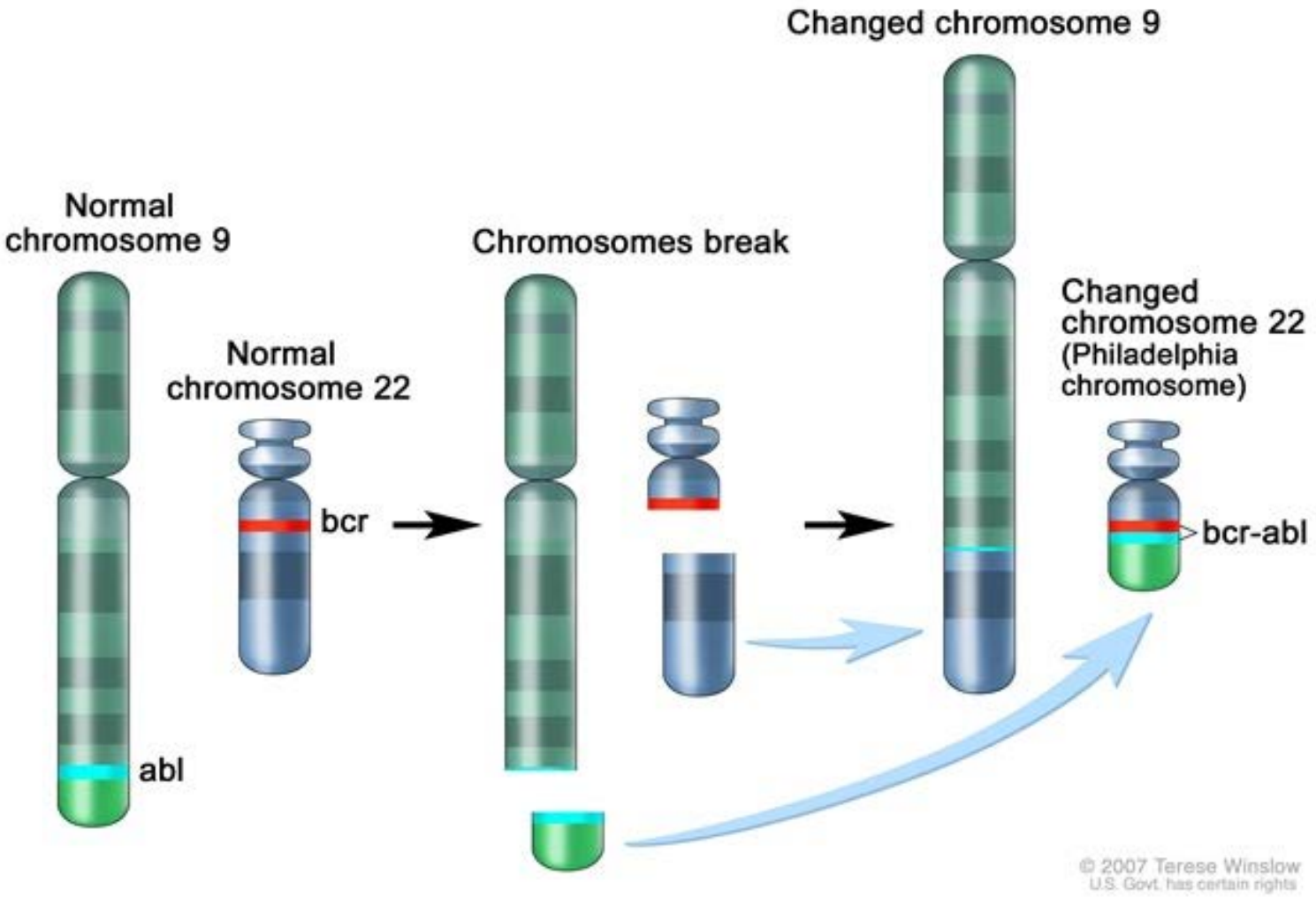
Accelerated Phase
- >15%, <30% blasts
- Basophilia >20%
- New cytogenetic abnormalities in 50% to 80% of patients
- Plt <100k

Clinical Course: Phases of CML

Chronic phase	Advanced phases	
	Accelerated phase	Blastic phase (blast crisis)
Median 4–6 years stabilization	Median duration up to 1 year	Median survival 3–6 months

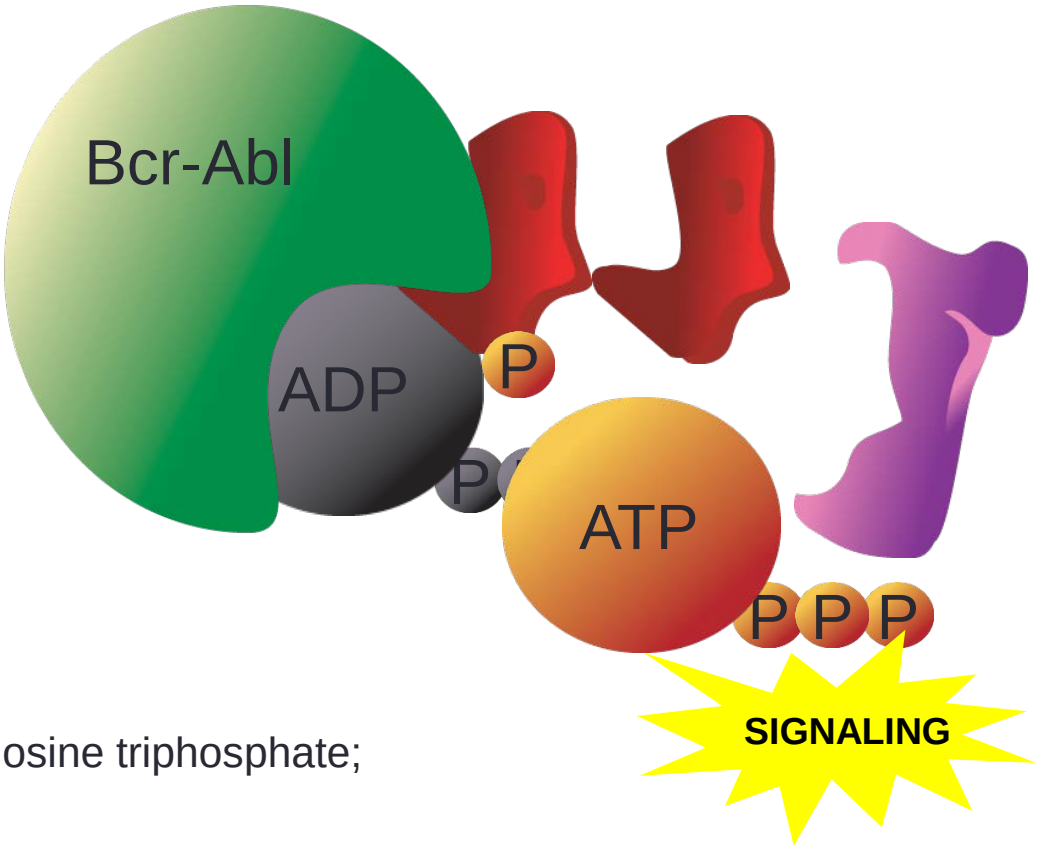
**loss of p53; trisomy 8; second Ph; PAX5 deletion; others*

CML BCR/ABL1 fusion gene, the result of a genomic rearrangement



Normal Bcr-Abl Signaling*

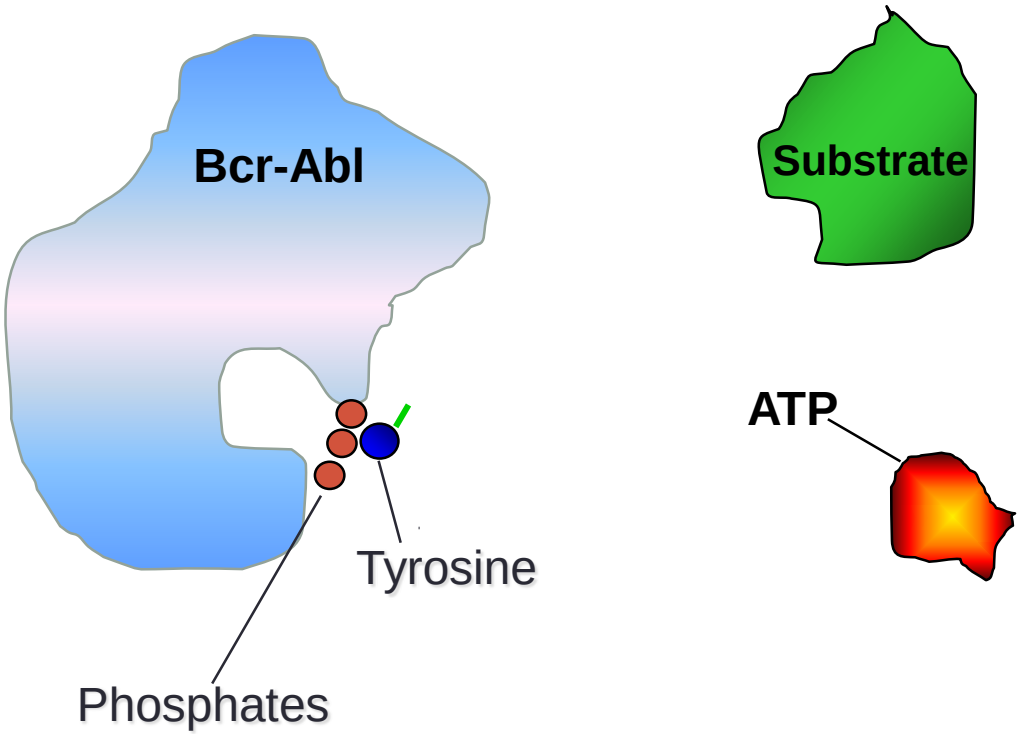
- The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival



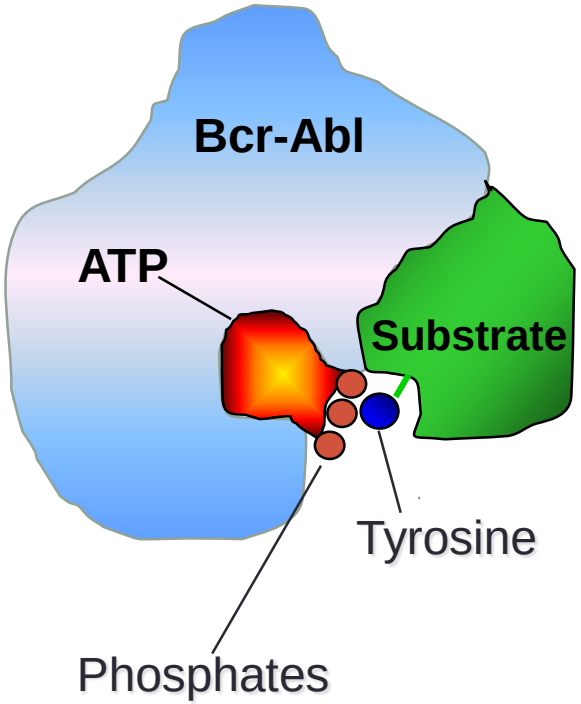
ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Savage and Antman. *N Engl J Med.* 2002;346:683
Scheijen and Griffin. *Oncogene.* 2002;21:3314.

Mechanism of Activation of Bcr-Abl



Mechanism of Activation of Bcr-Abl



Signal transduction cascade
uncontrolled activity

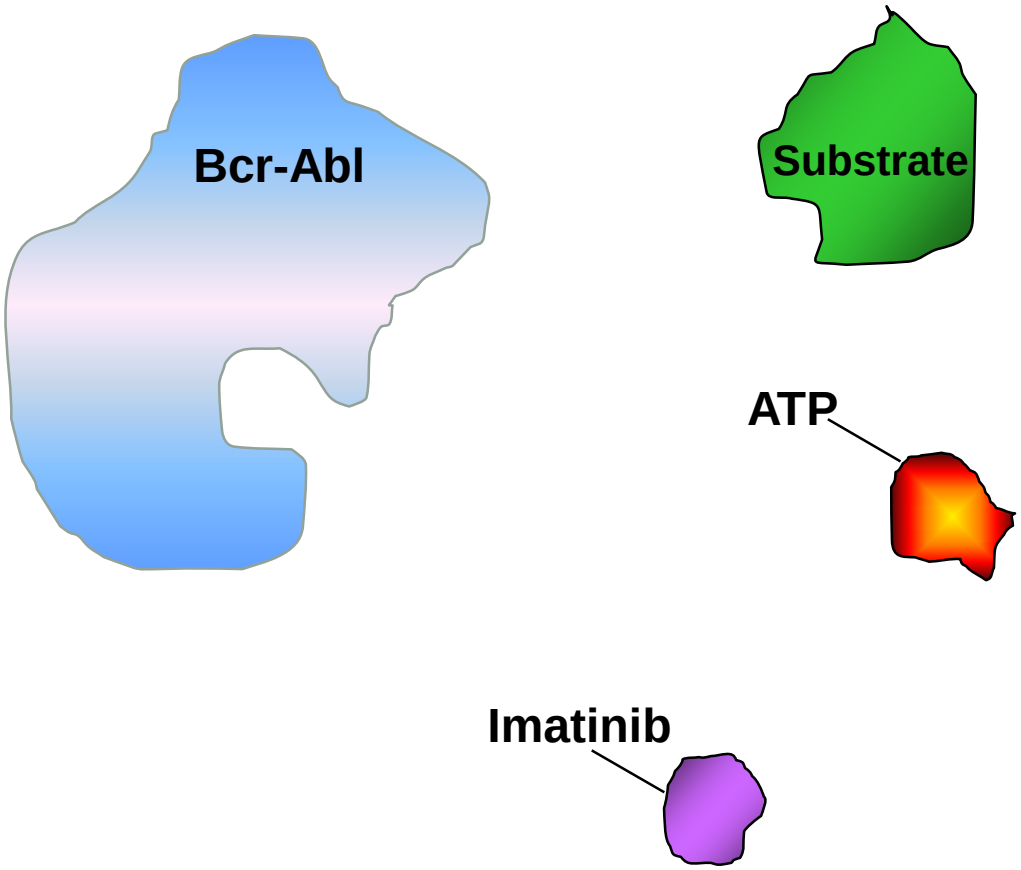
Proliferation

Survival

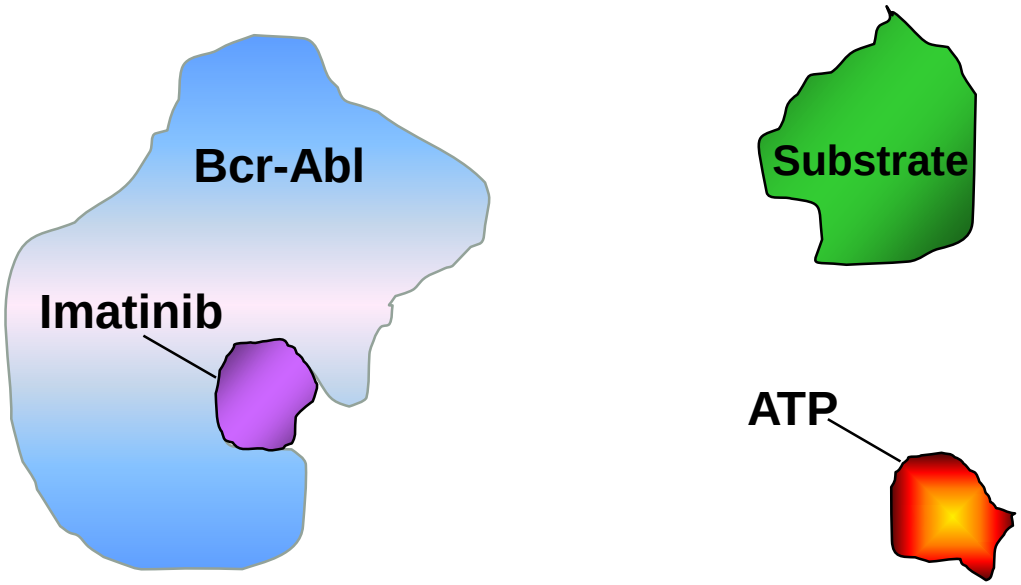
Adherence

Genetic Instability

Mechanism of Action of Imatinib

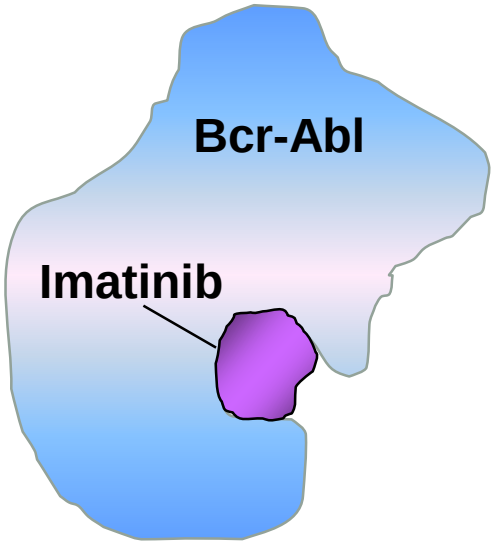


Mechanism of Action of Imatinib



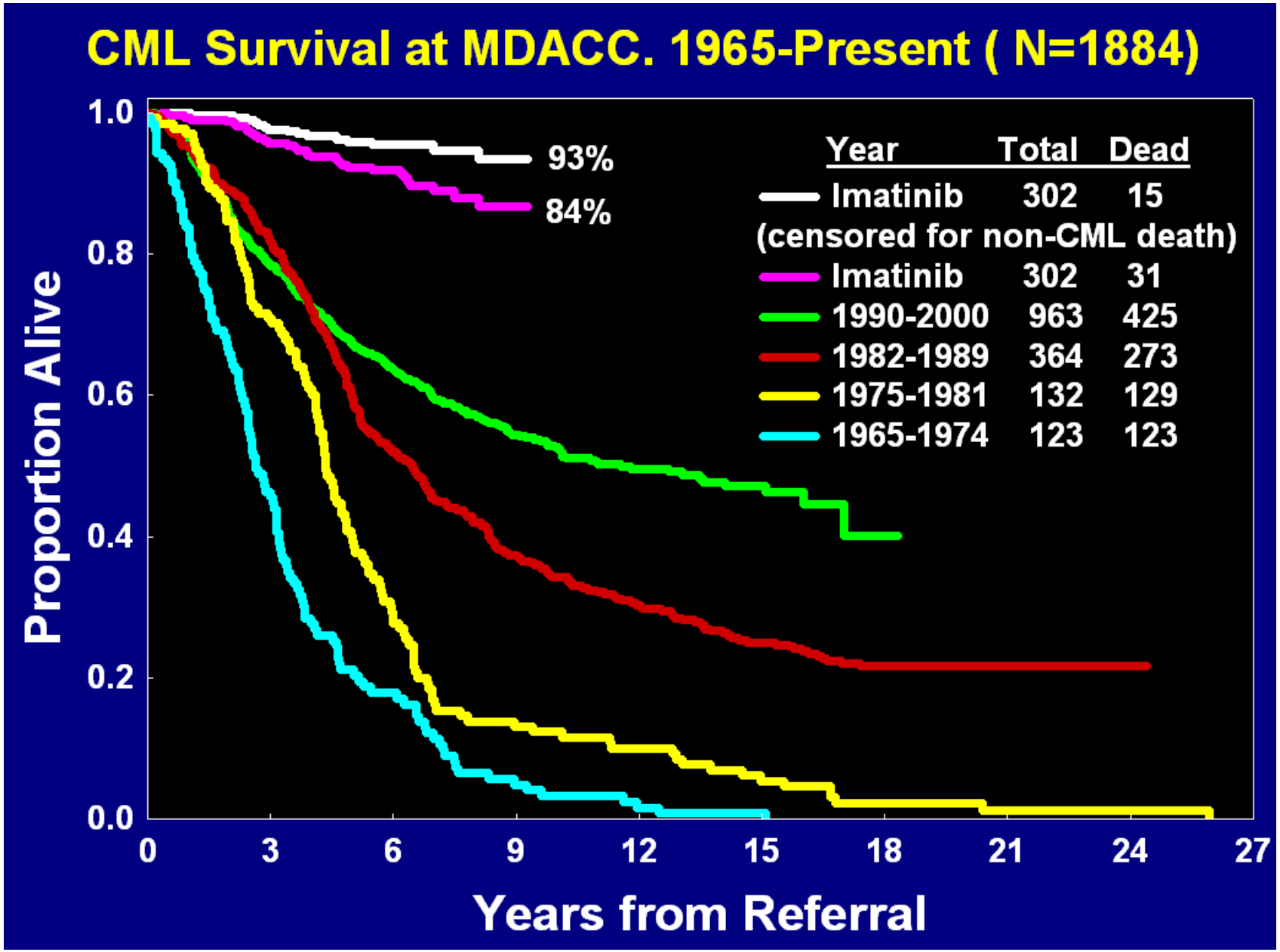
Adapted from Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086

Mechanism of Action of Imatinib



Adapted from Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086

Imatinib has dramatically improved survival



Next Generations of TKIs

- Dasatinb – improved responses compared to imatinib (DASISION, Kantarjian *NEJM* 2010 362(24): 2260)
- Nilotinib – improved responses compared to imatinib (ENESTnd, Saglio *NEJM* 2010 362(24)2251)
- Ponatinib – effective against T315I mutations
- Bosutinib

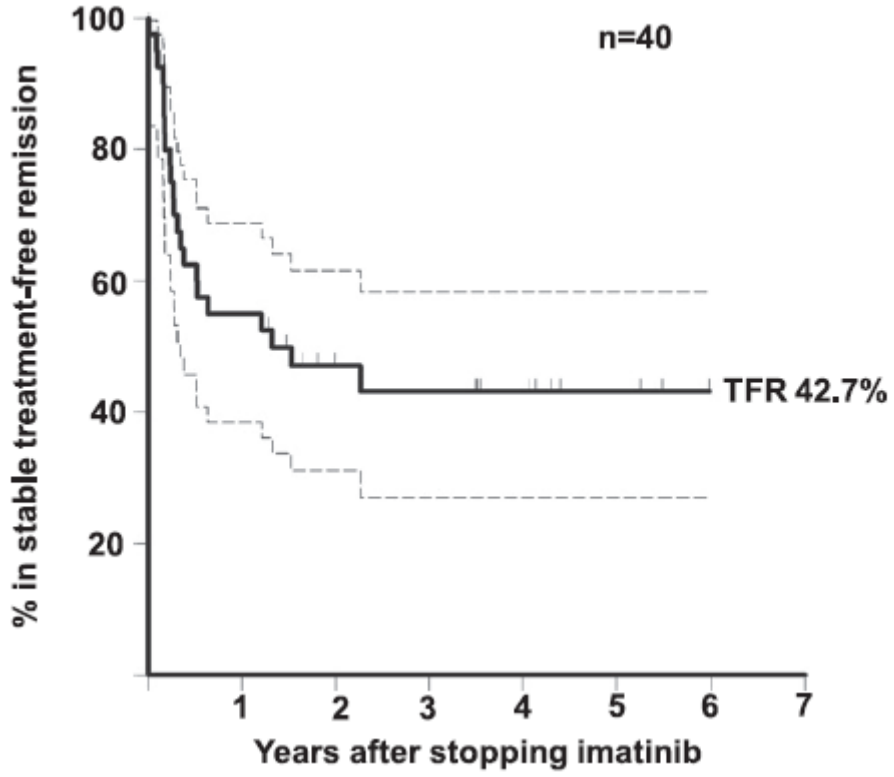
Side effects of TKIs

- Common side effects: edema, myalgias (rhabdo), cytopenias, LFTs, CYP450

- Dasatinb – pleural effusions
- Nilotinib – diarrhea, pancreatitis
- Ponatinib- cardiovascular events
- Bosutinib

Can you stop medication?

- Ross et al. Blood 2013.
- In selected patients – yes, but follow very closely



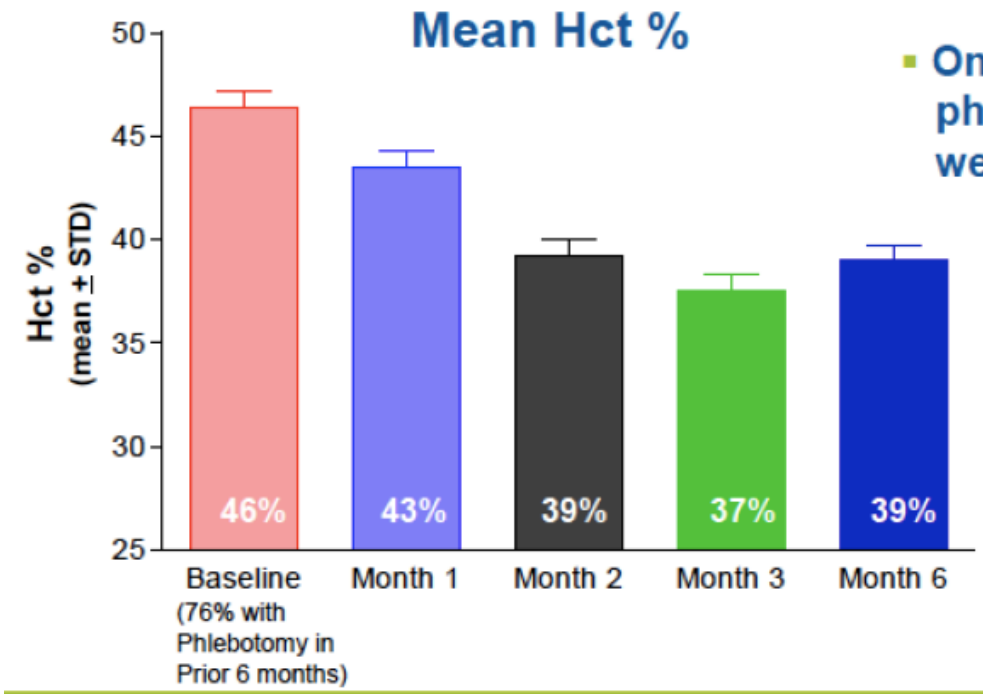
Questions?


"...AND YOU CANNOT CHANGE A THING, AS YOU ARE COMPLETELY CONTROLLED BY YOUR GENES."

Treating a Molecular Disease

PV Results: Hct % (n=34)

- Normalization of Hct % Achieved in the Absence of Phlebotomy



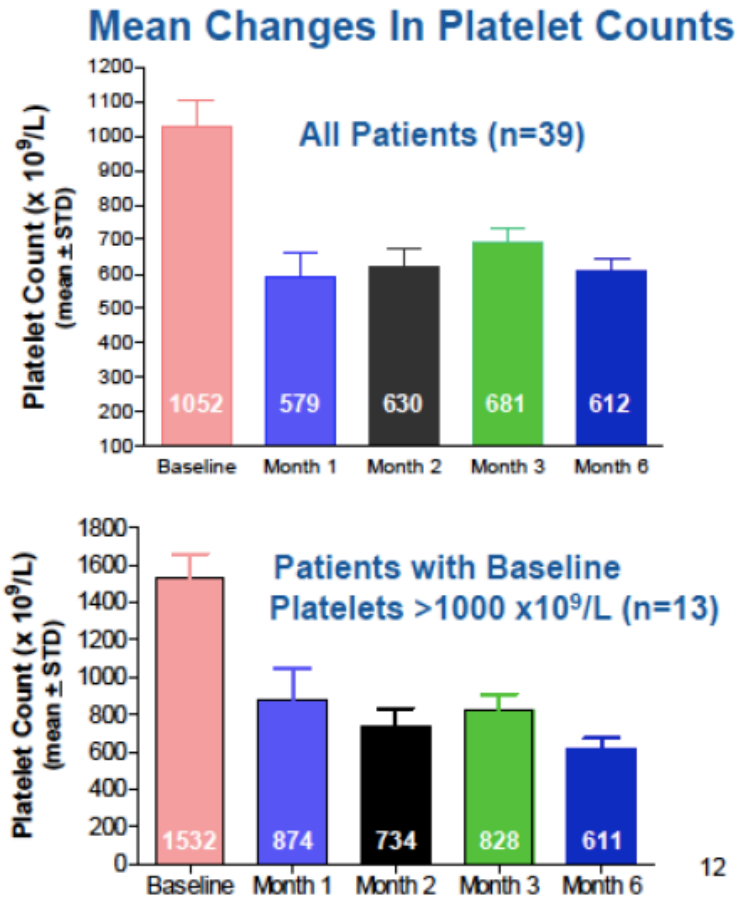
- Only 2 subjects required phlebotomy in the first 2 weeks, none since

Ruxolitinib (Jakafi) is a JAK2 inhibitor

Ruxolitinib (JAK2 inhibitor)

ET Results: Platelets

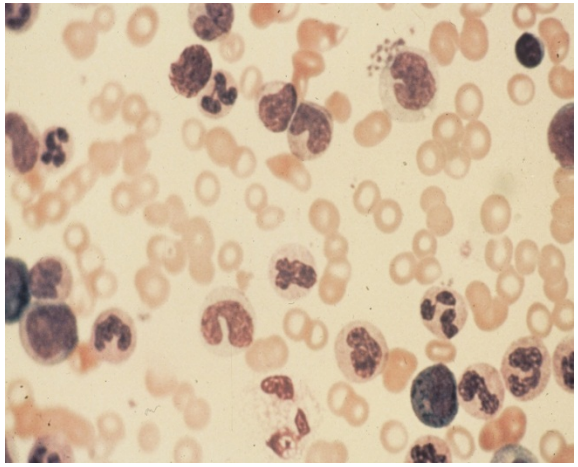
- **Rapid and Sustained Reduction in Platelets**
- Baseline median platelets of 884 decreased to 558 after 6 months
- At baseline, 13 patients (33%) had platelets > 1000 x10^9/L
  - Baseline median platelets of 1443 decreased to 553 after 6 months



Myeloid Malignancies

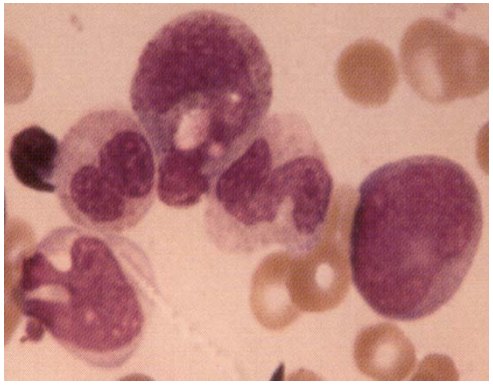
Myeloproliferative neoplasms

- enhanced proliferation/survival
- normal differentiation
- high white blood cell count
- may progress to AML



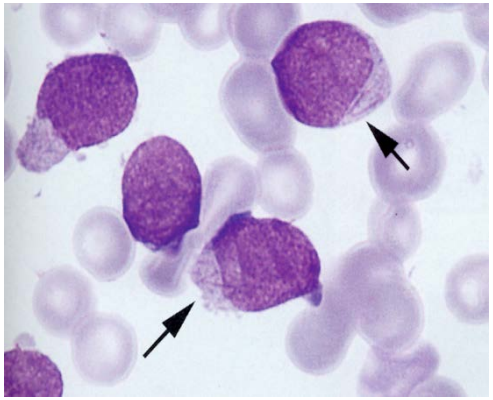
Myelodysplastic syndrome

- impaired differentiation
- low blood cell counts
- may progress to AML

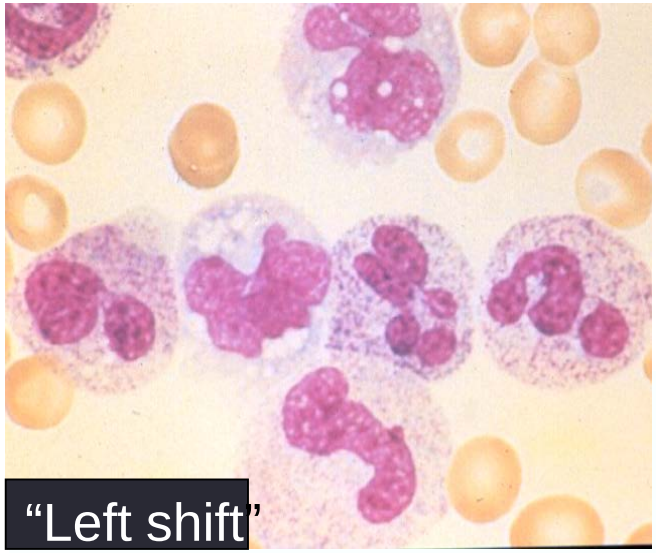


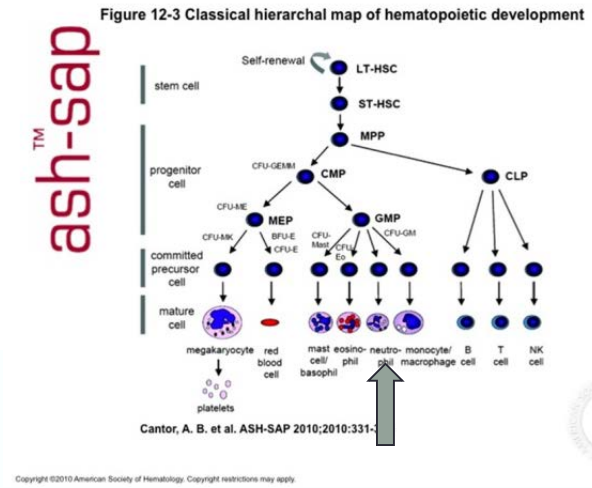
Acute myeloid leukemia (AML)

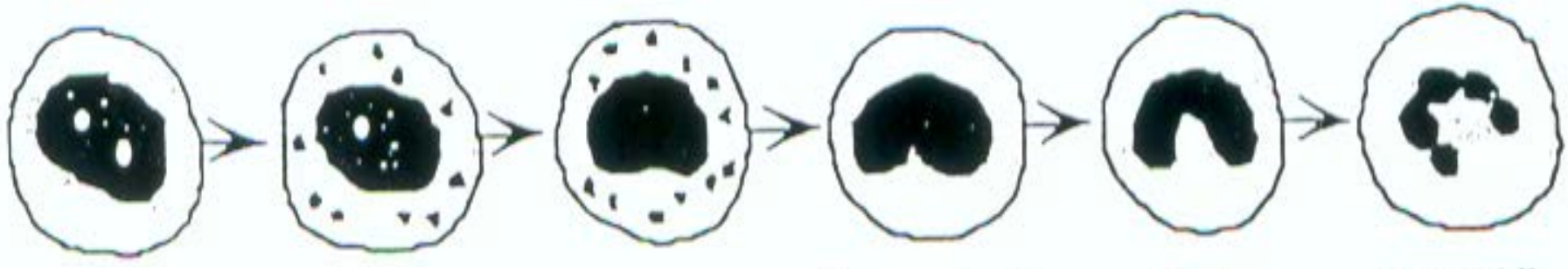
- enhanced proliferation and survival
- impaired differentiation
- limitless self-renewal



Myeloid Precursors







Myeloblast Promyelocyte Myelocyte Metamyelocyte Band Neutrophil

"Left Shift"

Case 5 - Presentation

- 35yo female presents with abdominal pain and jaundice
- She has no history of liver disease, heavy EtOH intake, or thrombosis.
- Exam reveals ascites and RUQ pain, icteric sclerae

Case 5 - Presentation

- 35yo female presents with abdominal pain and jaundice
- She has no history of liver disease, heavy EtOH intake, or thrombosis. No recent surgery, immobility, trauma, or plane flights.
- Exam reveals ascites and RUQ pain, icteric sclerae

- T Bili = 12
- RUQ ultrasound with doppler reveals portal vein thrombosis.

Additional tests to consider

- Mesenteric/portal vein thrombosis without risk factor (cirrhosis):
  - JAK2 V617F mutation (~32% of all splanchnic vein thromboses associated with this mutation) (Dentali, Blood 2009, 113:5617)
    - ***about half of these patients will have abnormal blood counts at time of clot
  - Flow cytometry to evaluate for PNH (paroxysmal nocturnal hemoglobinuria via CD59, GPI deficient clone) (*rare*)
    - Most of these patients will have intermittent 'hematuria'/hemolysis
    - May also present with cerebral thromboses
    - May also have cytopenias (aplastic anemia, MDS assoc)

MF Diagnostic Criteria

WHO Criteria[1]: Primary MF

Major criteria *(all required)*

- Megakaryocyte proliferation and atypia
  - Reticulin or collagen fibrosis
- Does not meet criteria for other myeloid disorders (e.g., PV[¥], CML[‡], MDS[∫])
- Clonal marker (e.g., *MPL*W515K/L, *JAK2*V617F) or no evidence for secondary marrow fibrosis[§]

Minor criteria *(must meet 2)*

- Increase in serum LDH
- Palpable splenomegaly
- Leukoerythroblastosis
- Anemia

¥ failure of Fe to to increase Hgb in setting of a low ferritin
‡ absence of BCR-ABL1.
∫ absence of erythroid and granulocytic dysplasia
§ infection, autoimmune, chronic inflammatory, hairy cell leukemia or other lymphoid neoplasm, met malignancy, or toxic chronic myelopathies

IWG Criteria[2]: Post-ET MF & Post-PV MF

Major criteria *(all required)*

- Previous diagnosis of ET or PV
- Grade 2-3 bone marrow fibrosis (on 0-3 scale) or Grade 3-4 bone marrow fibrosis (on 0-4 scale)

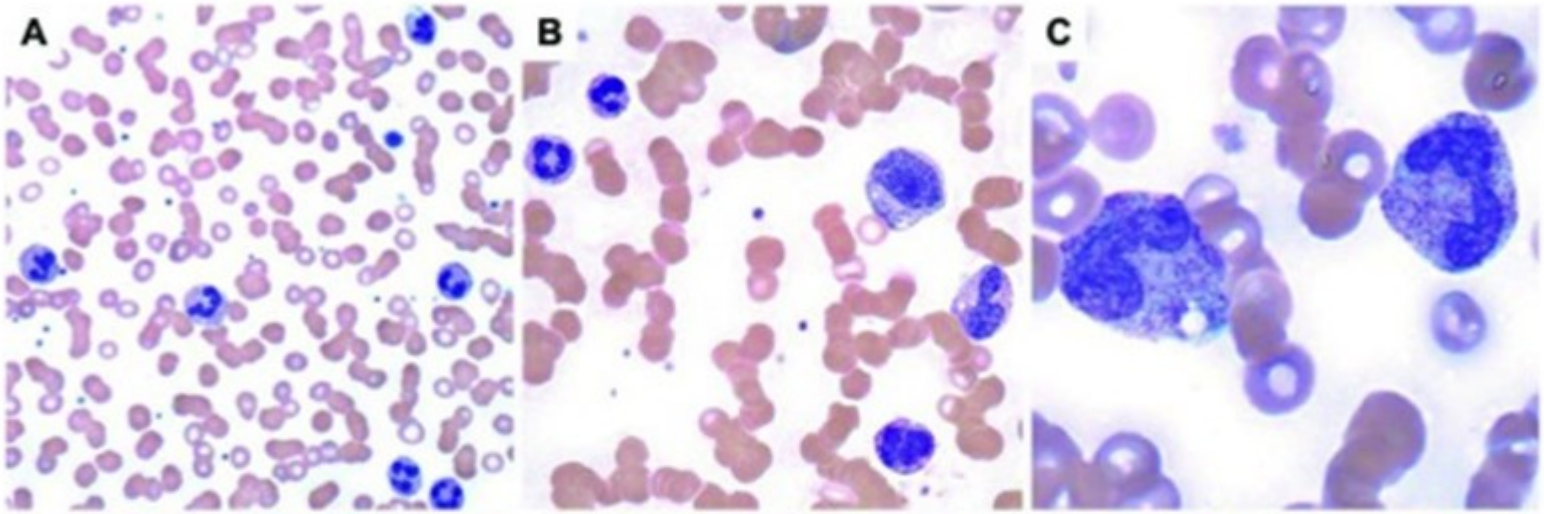
Minor criteria *(must meet 2)*

- ≥5 cm increase in palpable splenomegaly or new splenomegaly
- Leukoerythroblastosis
- One or more constitutional symptoms
- Increase in serum LDH (Post-ET MF only)
- Anemia with a Hgb ≥2 mg/mL decrease from baseline (Post-ET MF only)
- Anemia or sustained loss of requirement for either cytoreductive treatment or phlebotomy (Post-PV MF only)

[1]Vardiman JW, et al. *Blood*. 2009;114(5):937-951.
[2]Barosi G, et al. *Leukemia*. 2008;22(2):437-438.

56yo man admitted with abdominal pain and leukocytosis

- 4 days of abdominal pain and diarrhea
- Recently discharged from the hospital
- Temp 100.8 HR 110
- Abdomen diffusely tender to palpation



George T I Hematology 2012;2012:475-484

What is the most likely diagnosis?