Comprehensive Hematology & Oncology Review: MPNs

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Disclosures

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Advisory board: Agios

ABIM & MPNs

Hematology

- MPN- 4.5%:
  - CML
  - PV and secondary erythrocytosis
  - Myelofibrosis
  - ET
  - Mastocytosis
  - CNL

Oncology

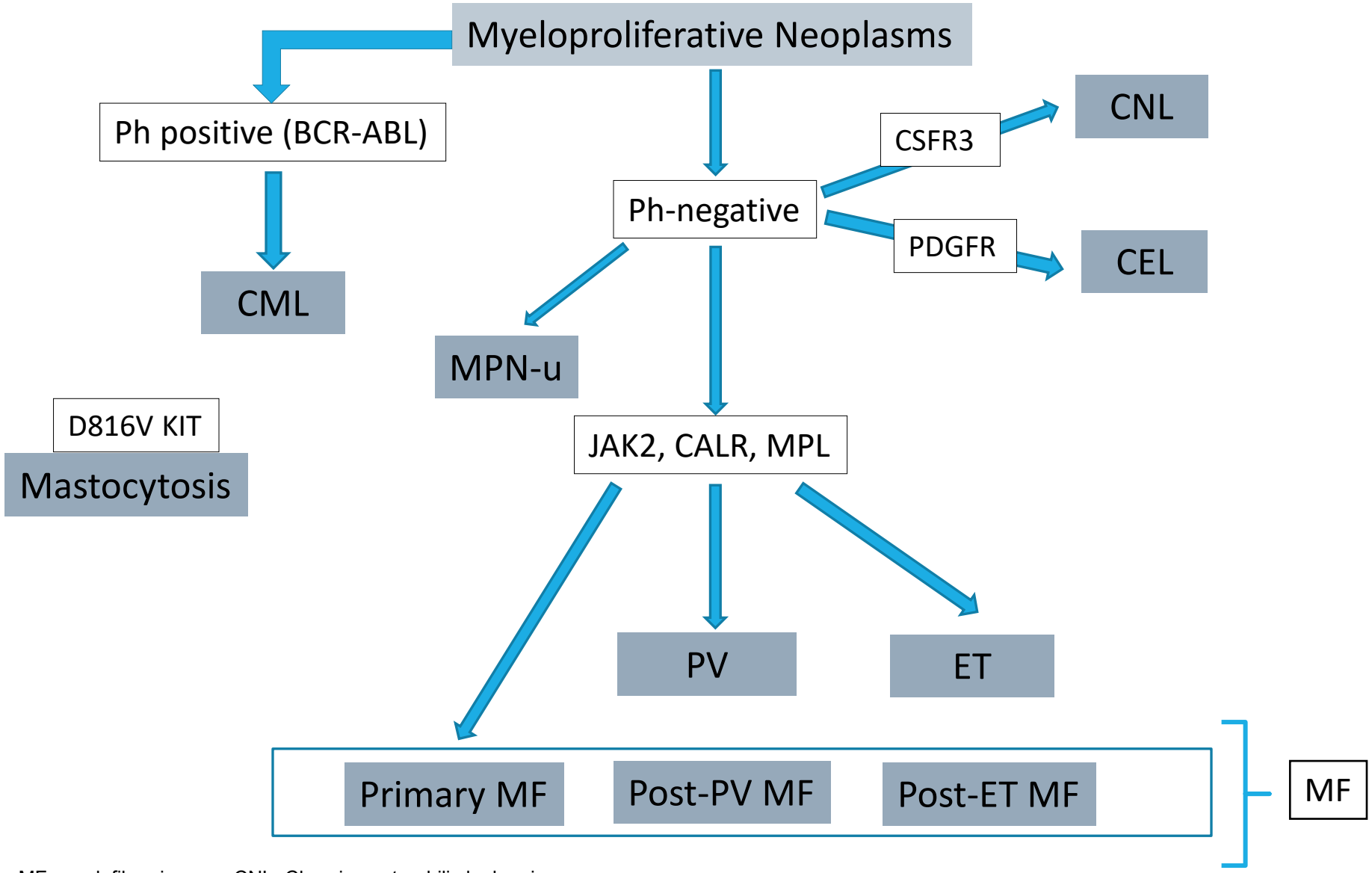
- CML and MPNs: 2%, focus on diagnosis, testing, treatment/care decisions

Objectives

1) Overview MPNs: epidemiology and pathophysiology

2) Presentation, Diagnosis, Risk Stratification, Treatment
   - Polycythemia vera
   - Essential thrombocythemia
   - Myelofibrosis
   - CMML

3) “Pearls” for mastocytosis, chronic neutrophilic leukemia (CNL)

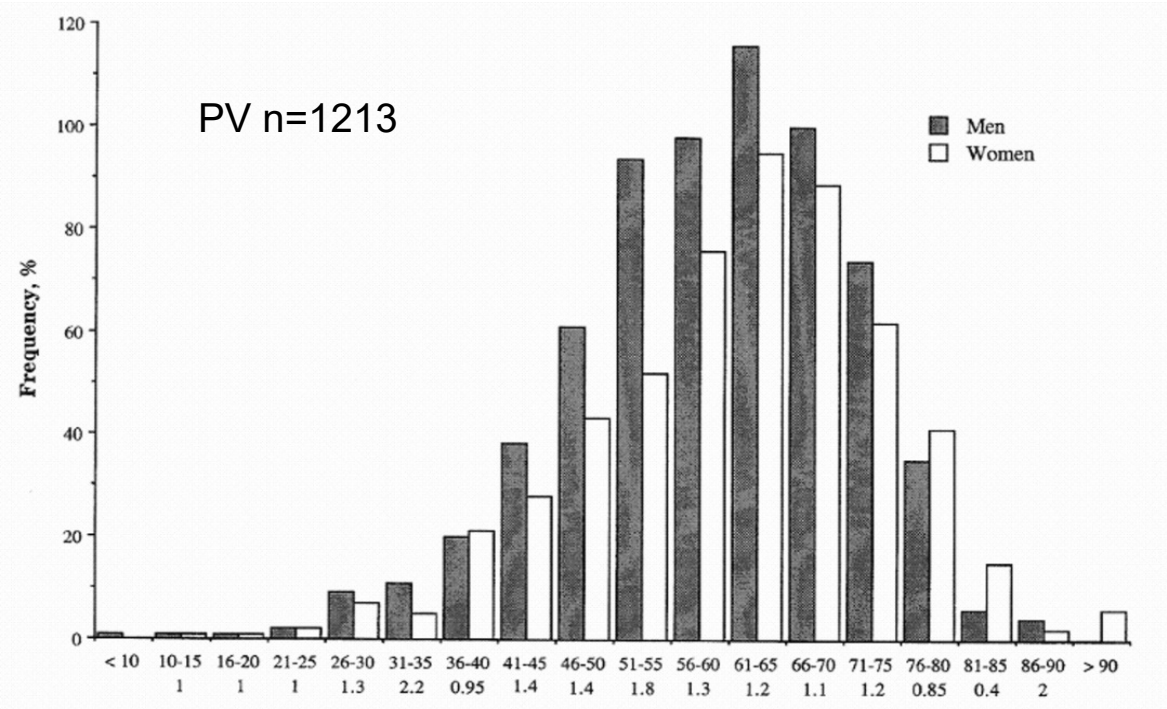


MF=myelofibrosis CNL=Chronic neutrophilic luekemia
PV=polycythemia vera CEL=Chronic Eosinophilic Leukemia
ET=essential thrombocythemia CML=chronic myeloid leukemia

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

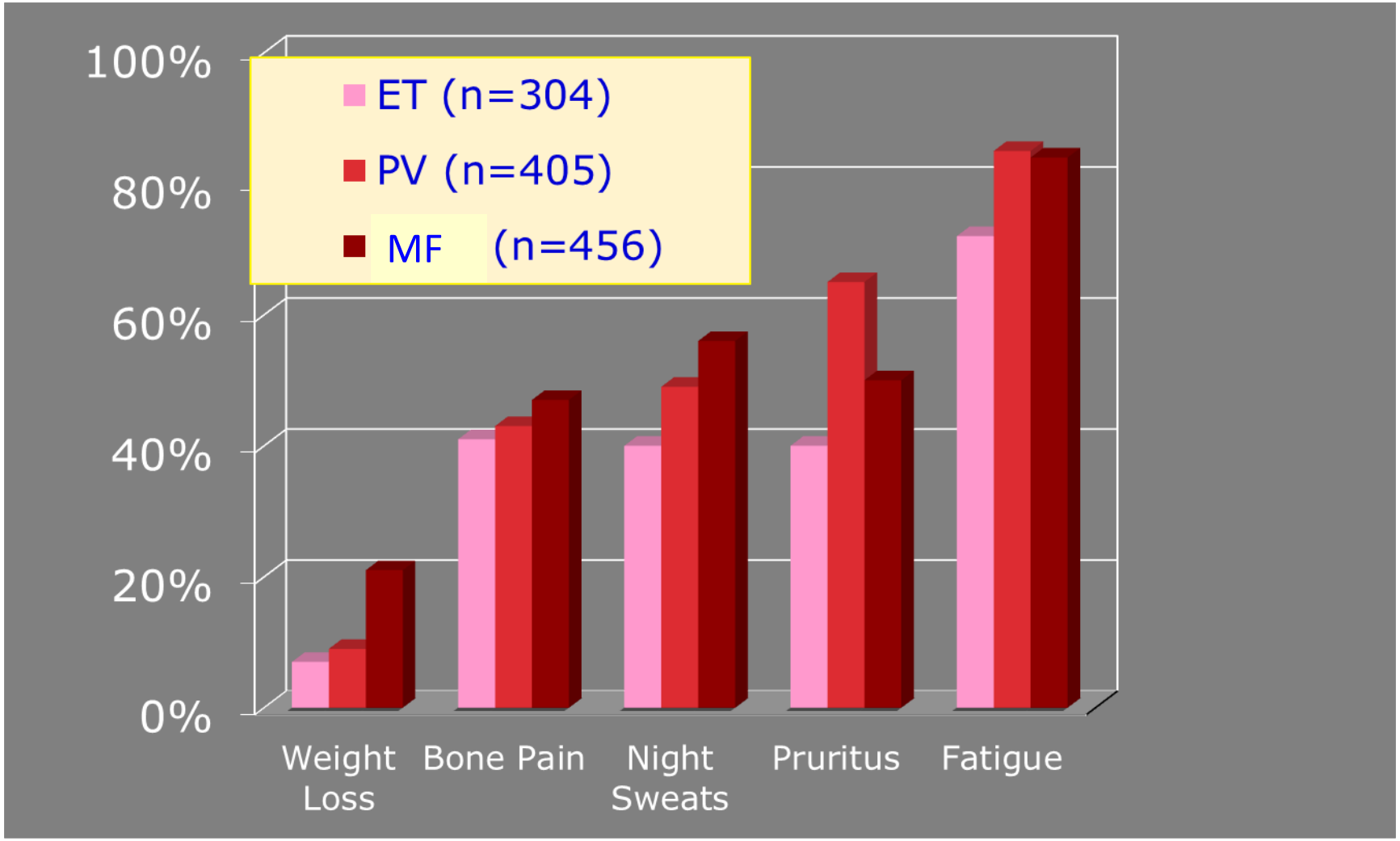
Epidemiology of MPN

- ET: 1.55-2.53/100,000 Median age 72
- PV: 1.9/100,000 Median age 62
- MF: 0.3-1.46/100,000 Median age 67



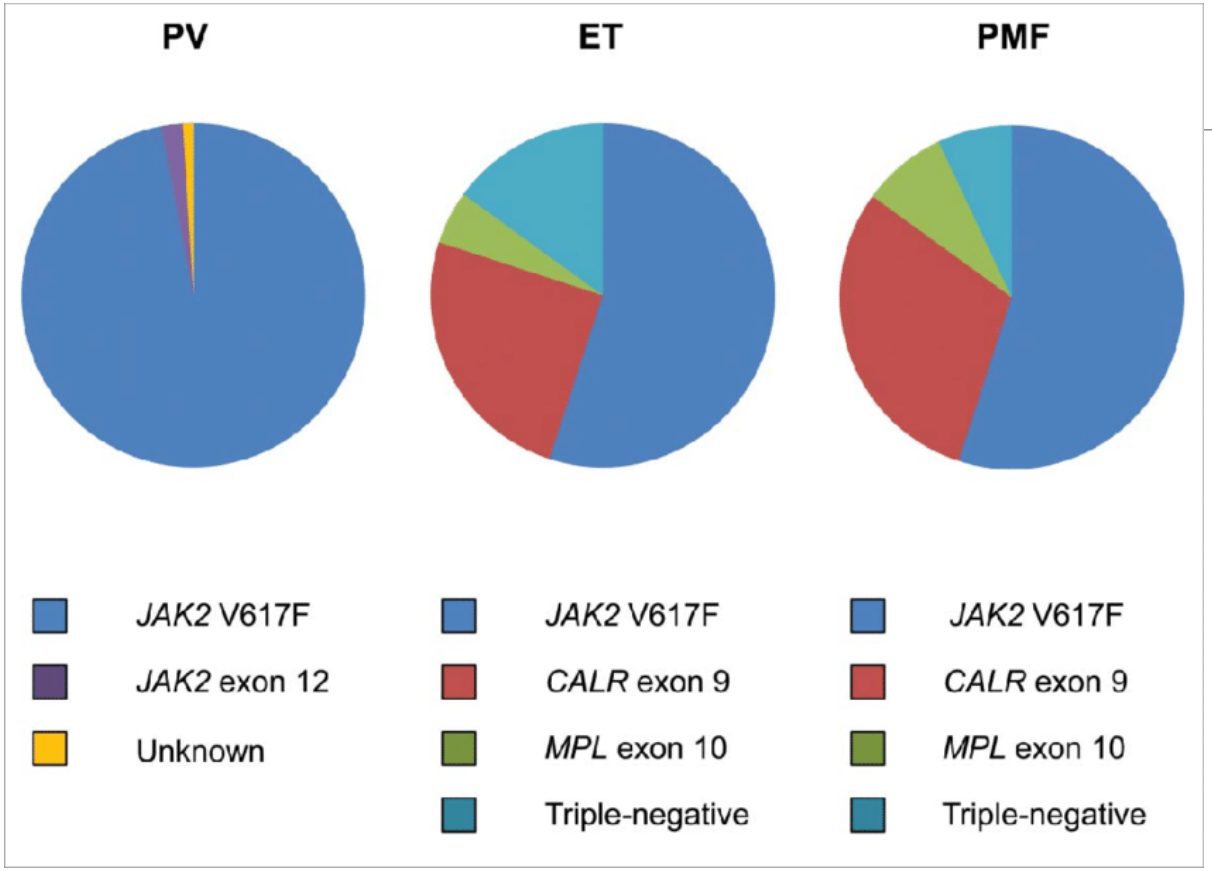
GISP *Ann Intern Med.* 1995;123:656-664

Symptoms in 1179 MPN Patients



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

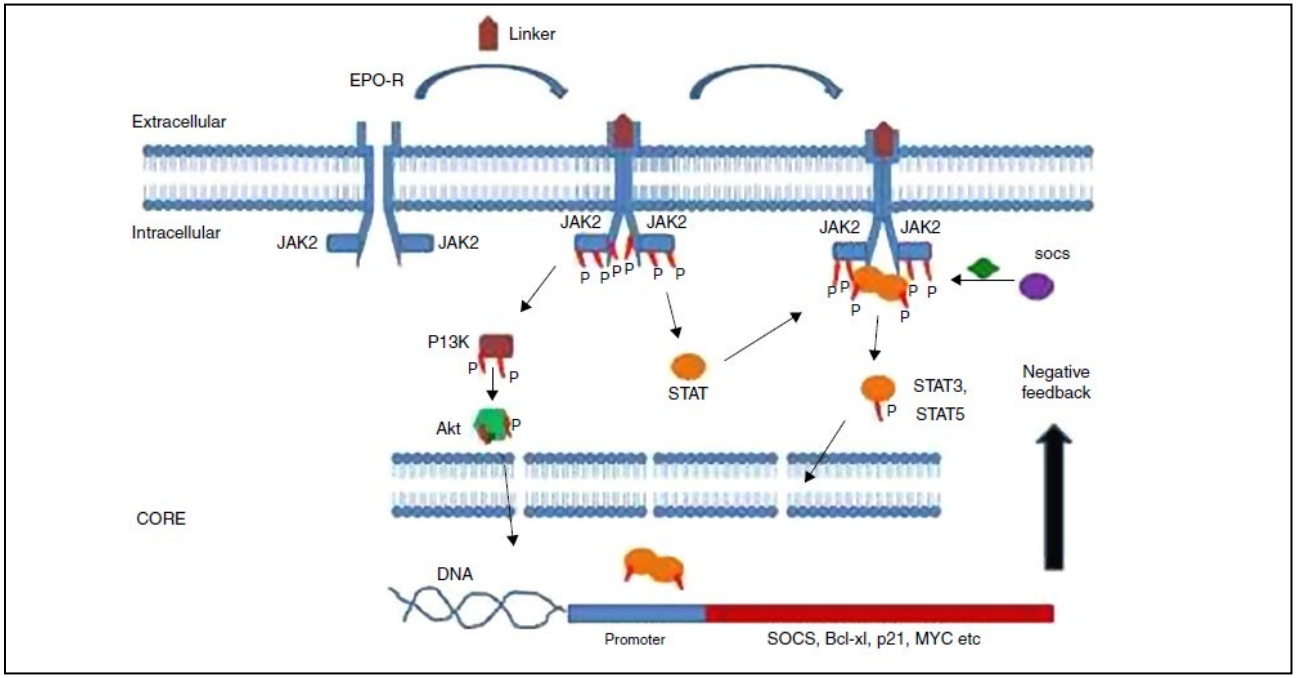
Mutations in MPNs



Disease	Mutation	%Patients
PV	JAK2 V16F JAK2 Exon 12	95-97% 2-4%
ET	JAK2 V16F CALR MPL “triple-neg”	60-65% 20-25% 5% 10-15%
PMF	JAK2 V16F CALR MPL “triple-neg”	60-65% 20-25% 5% 10-15%

Langabeer. JAKSTAT 2016; 5 (2-4): e1248011.

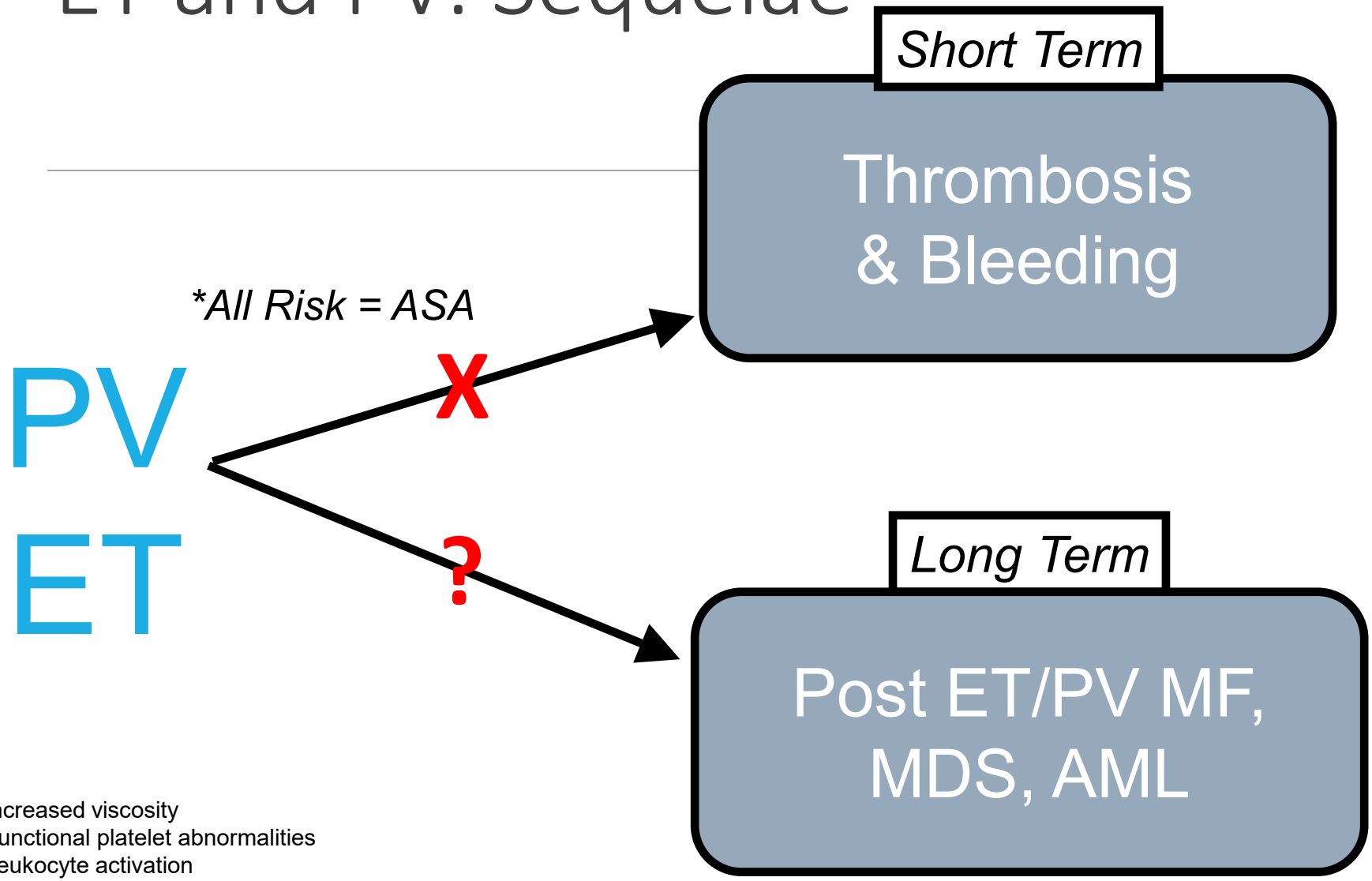
MPN Etiology: Role of *JAK2* Mutation



V617F single point mutation in *JAK2* gene → an altered protein that constitutively activates the JAK/STAT signal transducers and activators of transcription pathways

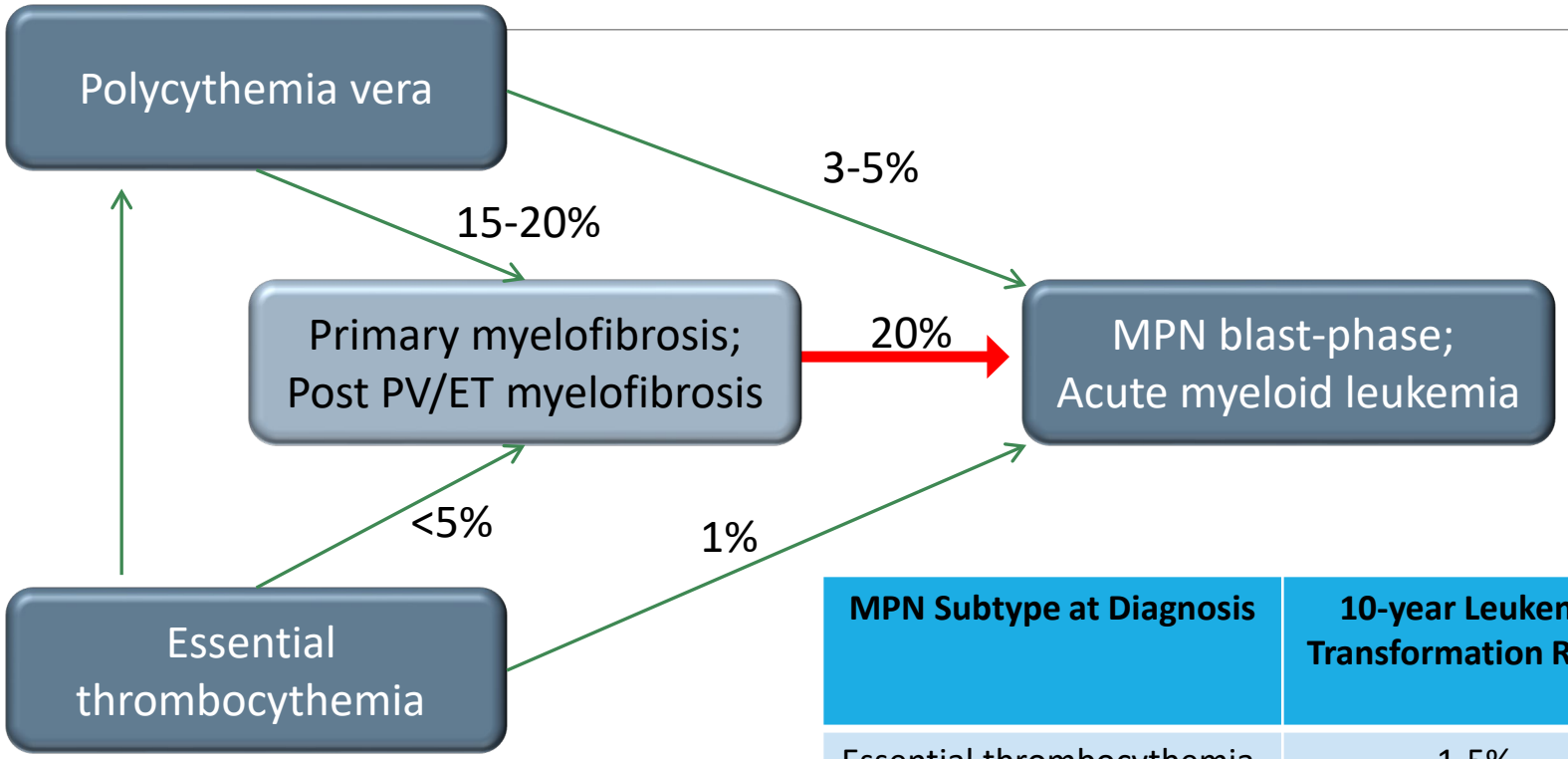
Affects the expression of genes involved in regulation of apoptosis and regulatory proteins and modifies the proliferation rate of hematopoietic stem cells

ET and PV: Sequelae



Increased viscosity
Functional platelet abnormalities
Leukocyte activation
Increased platelets lead to acquired VWD

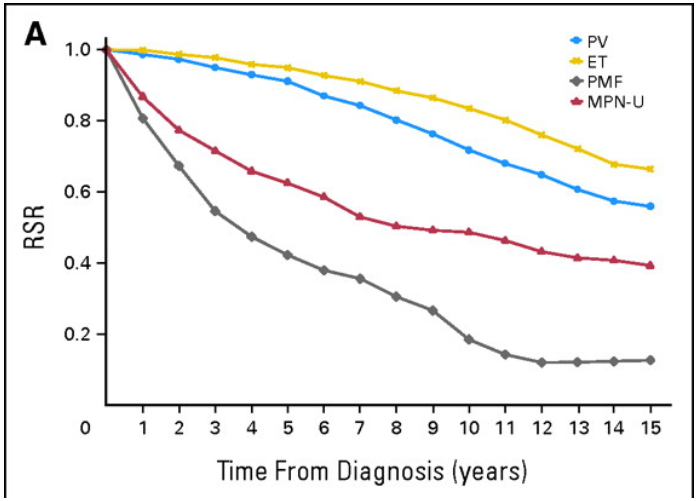
Transformation to MF and AML



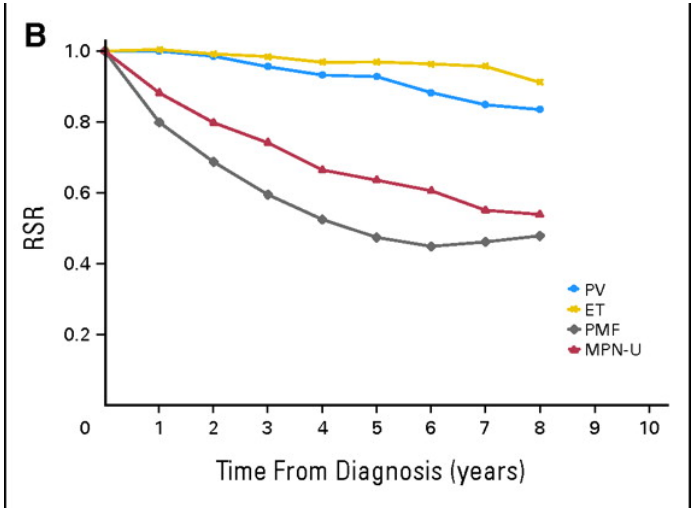
MPN Subtype at Diagnosis	10-year Leukemic Transformation Rate [2]
Essential thrombocythemia	1-5%
Polycythemia vera	3-5%
Primary myelofibrosis	20%

1.Tefferi A. *Am J Hematol*. 2008;83:491-497; 2. Rampal, Mascarenhas. *Curr Opin Hematol.* 2014;21:65-71.

MPN survival improving over time



1993-2008



2001-2008

Malin Hultcrantz et al. JCO 2012;30:2995-3001

Case 1

33 yo M with no PMH, presented with painful/red toes, later developed joint pain and pruritis

Physical: plethoric, no joint abnormalities

CBC: WBC21, Hgb 18.8, HCT 48, plts 490

- Epo level <1

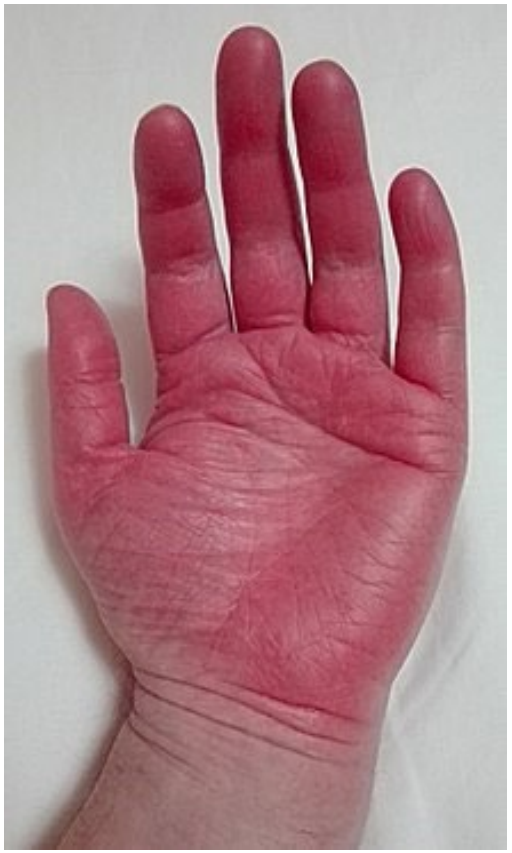
JAK2 VI6F mutation found positive on peripheral blood, BCR-ABL neg

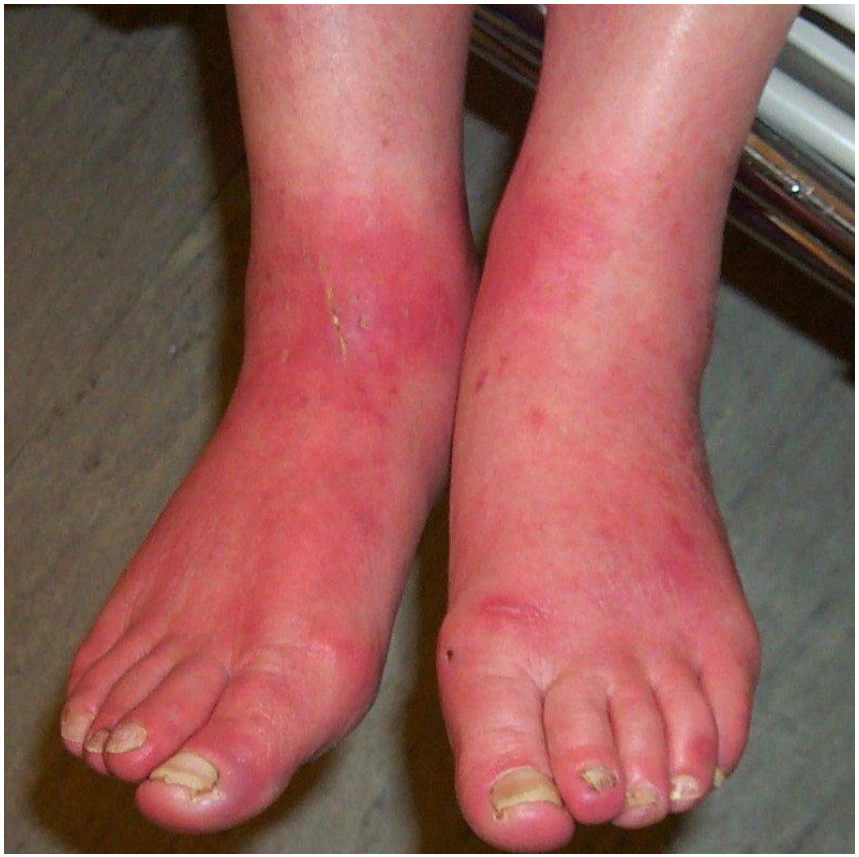
Bone marrow: hypercellular >95%, trilineage hematopoiesis and proliferation, no fibrosis or increased blasts

Diagnosis of PV was made:

- Start Aspirin 81 mg daily
- Started phlebotomy target HCT <45%
- Did not tolerate phlebotomy → hydrea→ did not control symptoms → ruxolitinib

Erythromelalgia





Polycythemia Vera: Presentation

MPN IWG Study presenting signs/symptoms

- Laboratory evaluation:
  - Hemoglobin – median 18.4 g/dL (range 15.1 to 26.5)
  - Hematocrit – median 55% (range 36 to 78%)
  - Leukocyte count – median 10,400/mL (range 3000 to 172,000)
  - Platelet count – median 466,000/mL (range 70 to 2,370,000)
  - Elevated lactate dehydrogenase – 50%
- Hypertension – 46%
- Palpable spleen – 36%
- Pruritus (aquagenic) – 36%
- Vasomotor symptoms (eg, erythromelalgia) – 29%
- Arterial thrombosis – 16%
- Venous thrombosis – 7%
- Major hemorrhage – 4%

Tefferi et al, Leukemia 2013; 27 (9): 1874

Diagnostic Criteria

Start with CBC, Epo level and JAK2 V16F/BCR-ABL mutation; exclude secondary causes

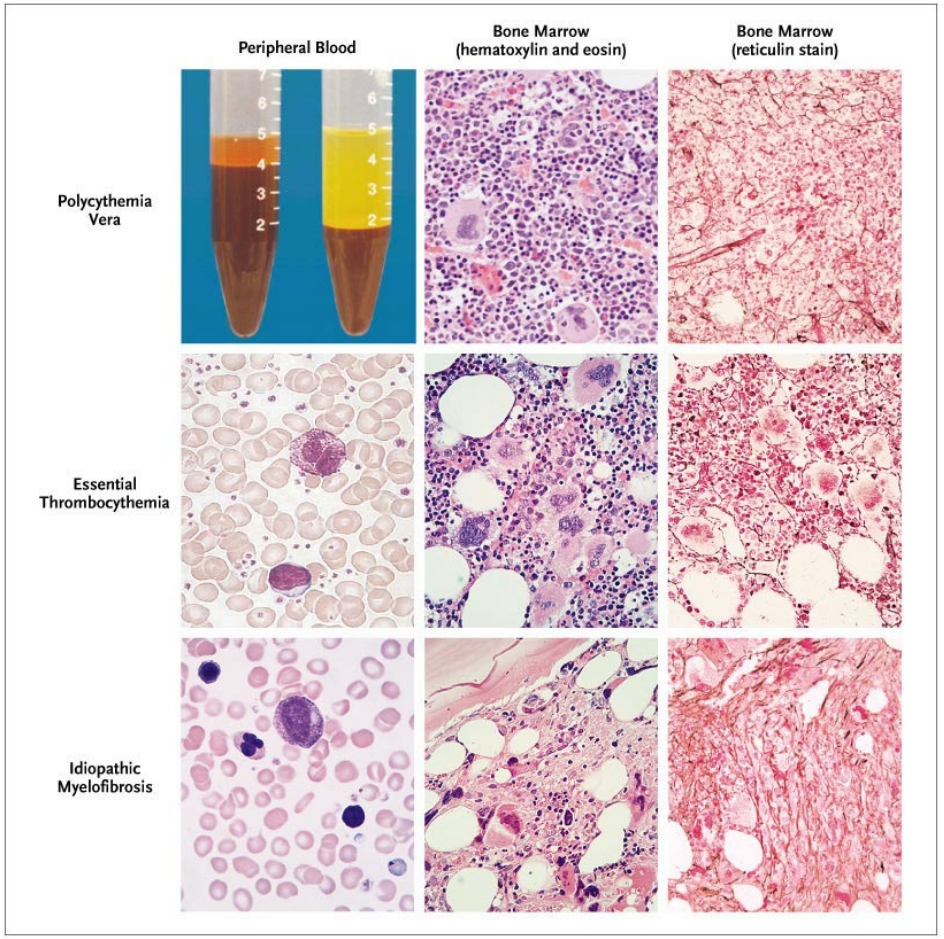
WHO Criteria: PV

Major Criteria (all 3 major or first 2 with minor)

- Hgb > 16.5 g/dL (HCT 49) in men, 16 g/dL HCT (48) in women or increased RCM*
- †BM Trilineage Proliferation (panmyelosis)
- *JAK2V617F* or *JAK2* exon 12 mutation

Minor Criteria

- Low Epo level (<3mU/mL)



†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: Hgb>18.5 g/dL in men (HCT55.5%) or >16.5 g/dL in women (HCT49.5%) if major criterion 3 and the minor criterion are present.

**Initial myelofibrosis (up to 20% of patients) can only be detected by performing a BM biopsy; may predict a more rapid progression to overt myelofibrosis (post-PV MF).

*elevated RCM > 25% above predicted

Arber et al. *Blood*. 2016;127(20):2391-2405.
Campbell P et al. *N Engl J Med.* 2006;355:2452-2466

PV Risk Stratification

LOW RISK:

- Age <60
- No history of thrombosis

HIGH RISK

- Age> 60 OR
- History of thrombosis

[1]Finazzi et al. *Blood.* 2007;109:5104-5111

Principals of Therapy

- Reduce symptoms
- Reduce risk of thrombosis/bleeding
- Reduce splenomegaly

Aspirin
Reduction of blood counts

- Prevent progression of disease to MF/AML

???

- Cure- stem cell transplant

PV: Treatment

Phlebotomy to maintain HCT <45%

Aspirin

Cardiovascular risk-factor modification

Hydroxyurea

Interferon

Ruxolitinib

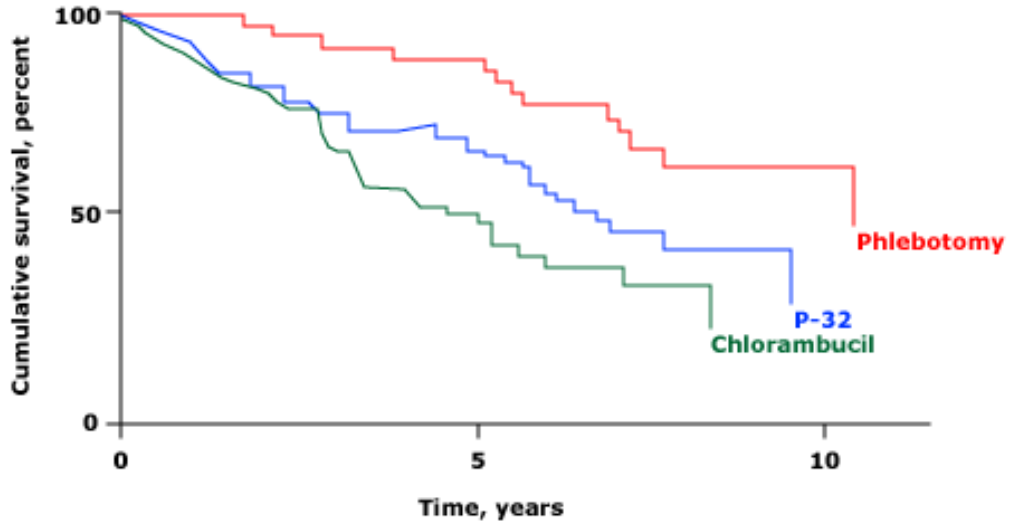
Chemo X

ALL

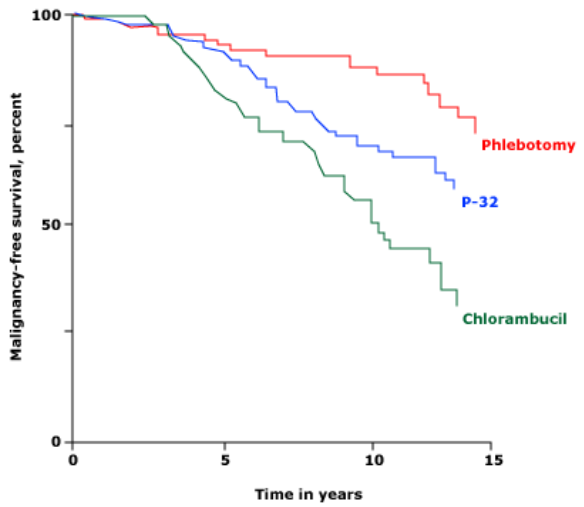
High-risk OR uncontrolled PV symptoms

Initial trials in PV: no more chemo

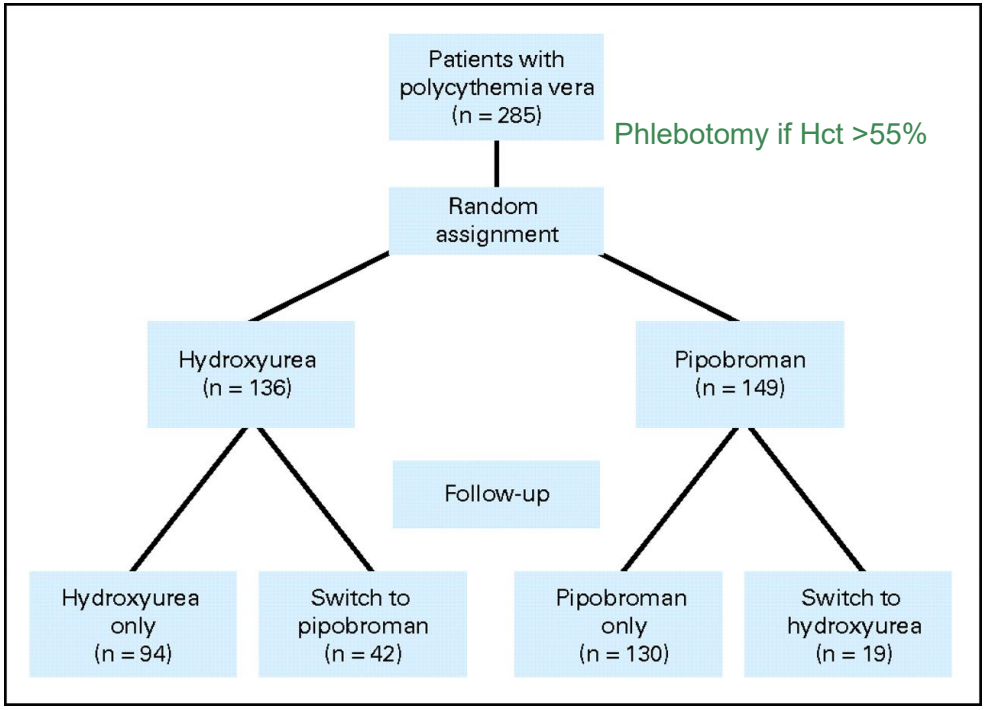
Lower cumulative survival with chemotherapy in polycythemia vera



Lower malignancy-free survival with chemotherapy in polycythemia vera



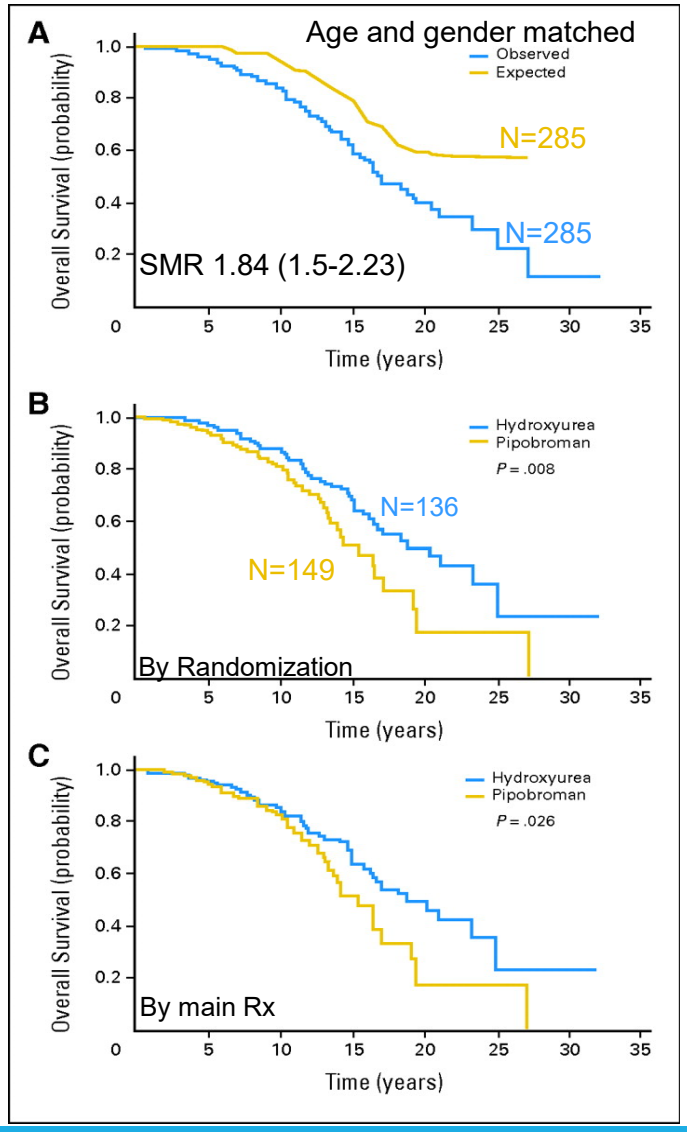
Hydroxyurea vs. Pipobroman (alkylating agent) in PV



Switch to Pi HR 2.06 (95% CI 1.09-3.87, p=0.026)

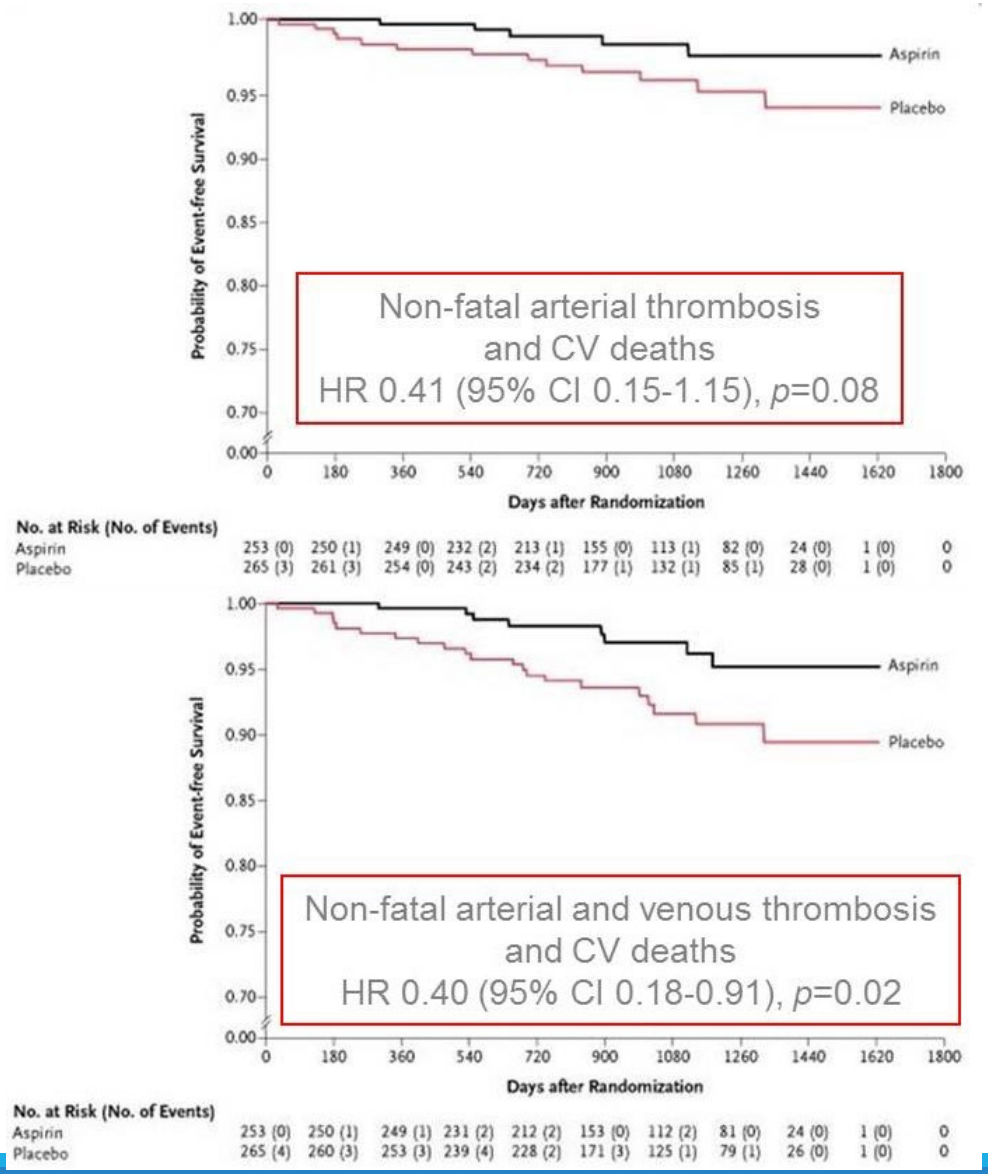
Switch to HU HR 1.37 (95% CI 0.61to 3.08), p=0.45

Cause of death
MDS/AML 54%
Thrombosis 15%



Kiladjian J et al. *J Clin Oncol.* 2011;29:3907-3913
Najean Y et al. *Blood.* 1997;90:3370-3377

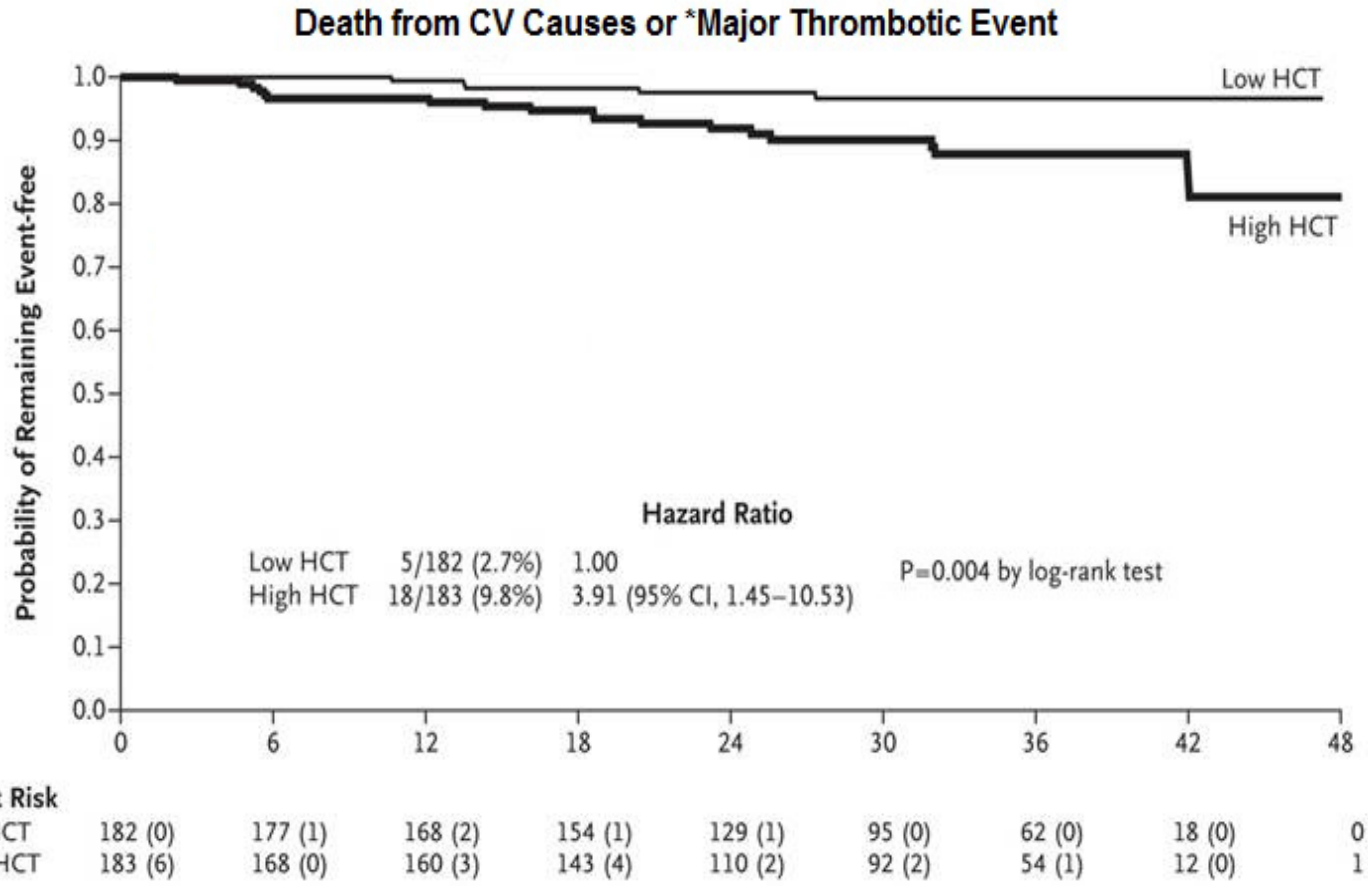
ECLAP TRIAL: RCT ASA vs. Placebo in PV



- 500 PV patients randomized to Aspirin 100 mg daily vs placebo
- Reduced risk combined endpoint non-fatal arterial+venous thrombosis +CV deaths
- No reduction in overall mortality
- No increase incidence bleeding

Landolfi R et al. *N Engl J Med.* 2004;350:114-124.

Target HCT in PV: CYTO-PV Trial

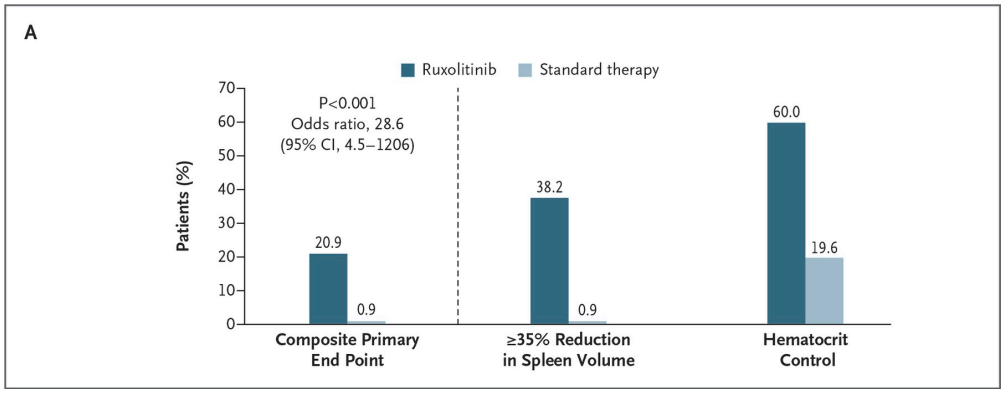


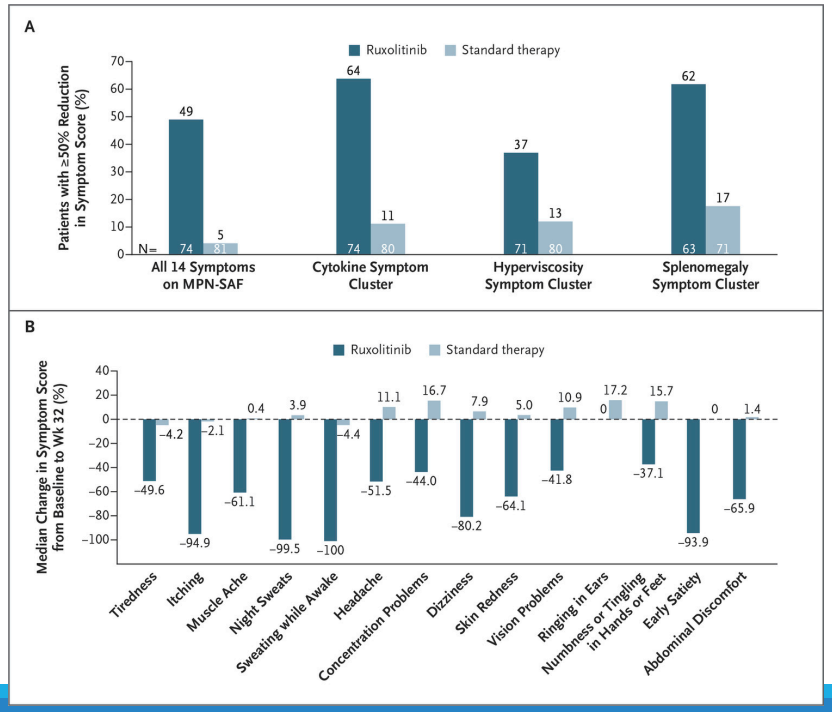
<45%

45-50%

Marchioli R., et al. *Thrombosis* 2011;2011:794240
Marchioli R., et al. *N Engl J Med* 2013;368:22-33

RESPONSE: Ruxolitinib vs BAT in PV





Open label, 222 patients with PV
Resistant (46%) or intolerant to HU (54%)

Randomly assigned to:

Ruxolitinib (110)

BAT (112): 59% HU, INF 12%, pipobroman 2%, no med 15%

Primary endpoint HCT control (wk 32) and >35% reduction spleen volume

Symptoms evaluated by MPN-SAF TSS

Vannucchi et al. NEJM 2015; 372 (5): 426-35.
Verstovsek et al. Haematologica 2016; 101 (7): 821.

Thrombosis Risk-Adapted Management of PV

Category	Characteristics	Treatment
Low-risk	Age <60 AND No thrombosis	Phlebotomy : goal HCT <45 Aspirin 81 mg daily Address CV risk factors
High-risk	Age ≥ 60 OR Thrombosis history	All of the above AND Cytoreductive Therapy: 1) 1st Line: Hydrea PegIFN 1) 2nd Line: Ruxolitinib PegIFN Busulfan (age >70)

Indications for cytoreduction in low-risk pts may include:

- Poor tolerance of phlebotomy
- Progressive leukocytosis
  - Platelets > 1500 x 10^9/L (risk of bleeding)
  - Severe disease-related symptoms

**Pts with plts >1 million should be tested for acquired VWD prior to initiation of Aspirin

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

Case #1.5

40 yo M with presenting with fatigue, pruritus and burning after showers and sexual activity

On exam: ruddy, plethoric, obese

CBC: white count of 8, hemoglobin of 18.5, plts 455

History:

- Non-smoker
- Lives in Seattle area
- No history of lung disease
- Not on diuretics
- Girlfriend says he snores and “stops breathing” all night long
- Self-injects testosterone x 4 years
- Epo level is 18

Primary vs secondary polcythemia

Polycythemia vera: EPO independent

Secondary polycythemia: EPO dependent

- Appropriate Epo production:
  - High altitude
  - COPD
  - OSA/obesity
  - Smoking
  - Diuretics
  - Carbon monoxide poisoning (chronic)
  - ***Anabolic steroids, testosterone, blood doping***
- Inappropriate Epo production:
  - Tumors: RCC, HCC, uterine leiomyoma
  - Renal ischemia
  - Hereditary defects in Epo/associated proteins/high-affinity oxygen Hgb (familial polycythemia)

Distinguish these by history and Epo level

Case 2

31 yo F found to have thrombocytosis to 550k on routine lab check 2010

JAK2, MPL negative; +CALR

Bone marrow: normocellular, trilineage hematopoeisis, atypical megakaryocytic proliferation, no increased blasts, no fibrosis, normal cytogenetics

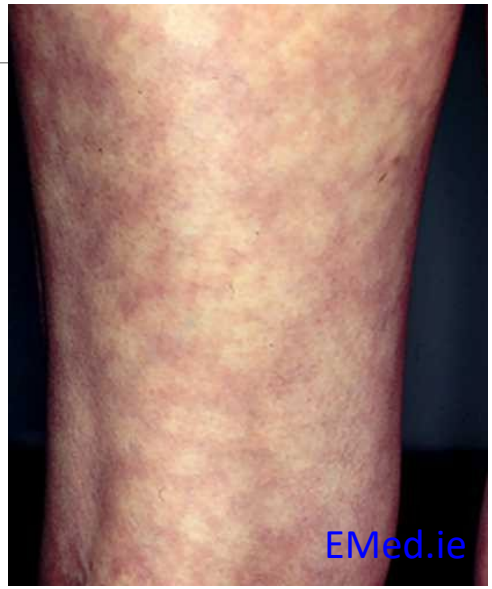
Monitored for 10 years, plts decreased in 2 pregnancies

2018 – plts rose to 1.85 million, developed headaches, fatigue, chest tightness, heavy menstrual bleeding

VWF testing negative

Initiated on Aspirin and PegIFN → plts now 500K, symptoms improved

Essential Thrombocythemia (ET)



- Asymptomatic ~50%
- Vasomotor symptoms – 13-40%
  - Headache
  - Lightheadedness
  - Syncope
  - Atypical chest pain
  - Acral paresthesia
  - Livedo reticularis
  - Erythromelalgia (burning pain of the hands or feet with erythema and warmth)
  - Transient visual disturbances (eg, amaurosis fugax, scintillating scotomata, ophthalmic migraine)
- Splenomegaly – 35%
- Thrombosis – 9-20% (fetal loss 11%)
- Hemorrhage – 3-37%

Wolanskyu AP et al. Br J Haematology 2005; 131 (2): 208.

Diagnostic Criteria

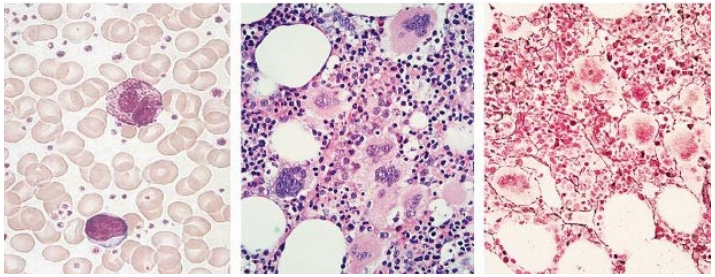
WHO Criteria: ET

Major Criteria (all 4 major or first 3 with minor)

- Plt Count ≥ 450 x 10^9/L sustained
- BM bx: megakaryocyte proliferation with increased # of enlarged mature megakaryocytes. No significant increase in granulo/erythropoiesis
- Not meeting WHO criteria for : PV¥, MF†, CML‡, MDS∫
- *JAK2V617F, CALR, or MPL mutation*

Minor Criteria (all 3 major or first 2 with minor)

- Presence of a clonal maker or no evidence of reactive thrombosis§



¥ failure of Fe to increase Hgb in setting of a low ferritin
† absence of relevant reticulin or collagen fibrosis, leukoerythroblastosis, or abnml meg morphology (n/c ratio, hyperchromatic, bulbous, irregularly folded nuclei, and clustering)
‡ absence of BCR-ABL1.
∫ absence of erythroid and granulocytic dysplasia
§ the presence of a condition associated with reactive thrombocytosis (Fe def, infection, inflammation, met cancer, connective tissue disease, lymphoproliferative d/o) does not exclude possibility of ET

Arber et al. *Blood*. 2016;127(20):2391-2405.
Campbell P et al. *N Engl J Med*. 2006;355:2452-2466

ET Prognostic Models

IPSET

Risk factors	Scores 0	1	2
Age, y	< 60		≥ 60
WBC count, × 10^9/L	< 11	≥ 11	
History of thrombosis	No	Yes	

Low risk implies a sum of scores equal to 0; intermediate risk, a sum of scores equal to 1-2; and high risk, a sum of scores equal to 3-4.

ET indicates essential thrombocythemia; and WBC, white blood cell count.

Risk	% Pts	Median OS
Low (0)	48%	NR
Intermediate (1-2)	47%	24.5 years
High-risk (3-4)	5%	13.8 years

IPSET-Thrombosis

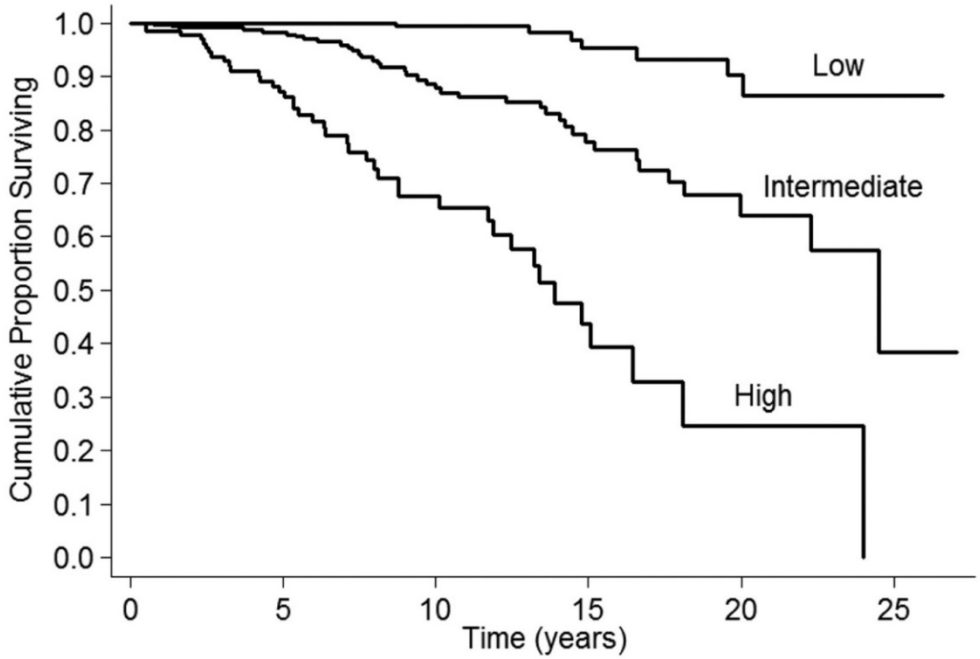
Risk factor	HR	Score
Age > 60 y	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
*JAK2*V617F	2.04	2

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

Risk	%/year thrombosis
Low (0-1)	1%
Intermediate (2)	2.4%
High-risk (>2)	3.6%

Passamonti F et al. Blood 2012; 120 (6): 1197-1201; Barbui T et al, Blood 2012; 120 (26): 5128-33.

IPSET Risk Stratification



Number at risk						
Low	342	211	123	63	25	3
Intermediate	374	223	109	51	15	2
High	151	84	32	10	2	0

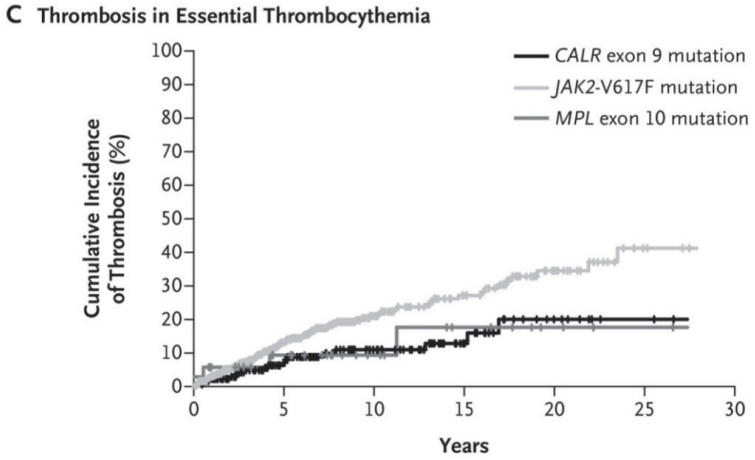
867 patients total

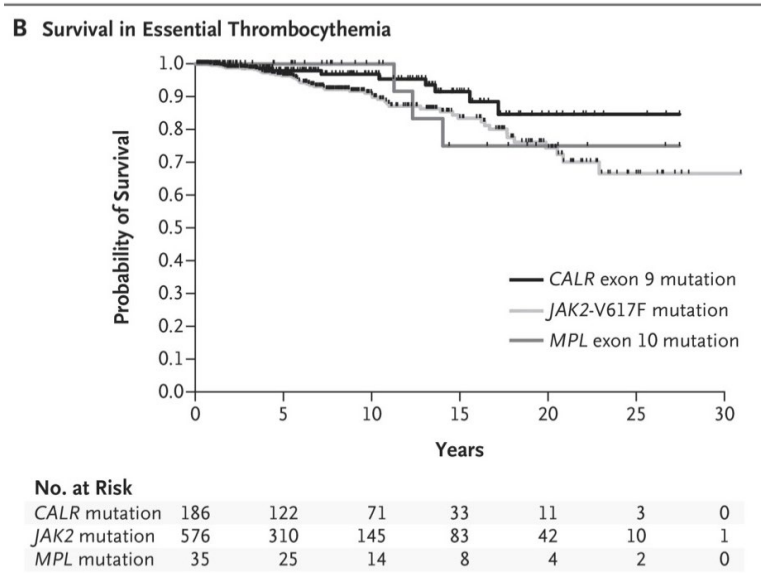
<u>87 patients died</u>
51% thrombosis
10% hemorrhage
17% AML/MDS
22% other cancer

Passamonti et al. *Blood* 2012;120:1197-1201
Barbui et al. Blood 2012;120:5128-5133

Impact of Mutations on prognosis

JAK2 associated with higher thrombotic risk than CALR



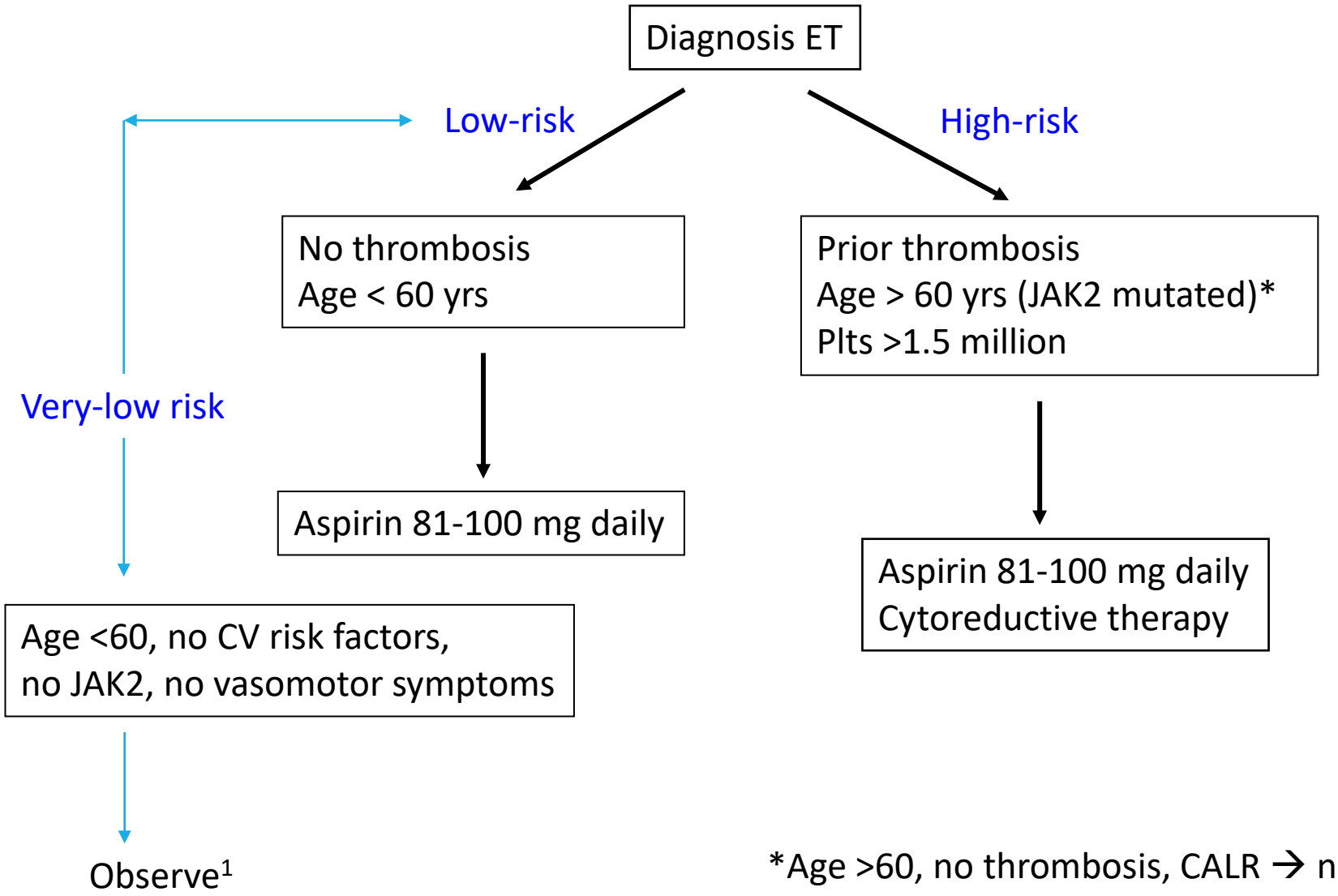


Klampfl T et al. *N Engl J Med* 2013;369:2379-2390

ET: Treatment Options

- Observation
- Aspirin
- Hydroxyurea
- Interferon
- Anagrelide
- ~~Ruxolitinib~~

Treatment Recs for ET

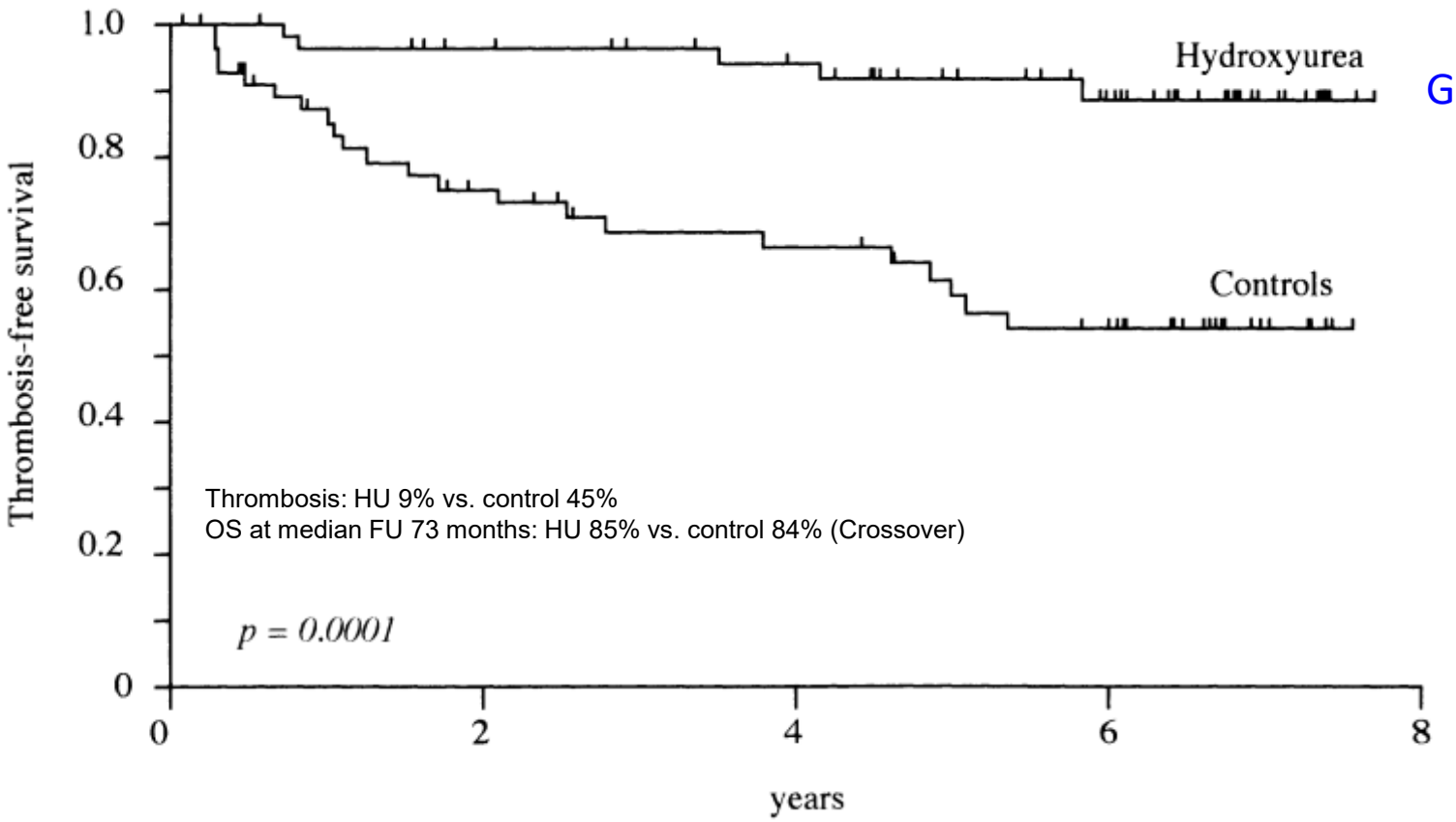


*Age >60, no thrombosis, CALR → no HU?

1 Ruggeri M et al. Br J Haematology. 1998l 103 (3): 772.

Beer et al. *Blood*. 2011;117:1472-1482
Alvaraz-Larrán et al. *Blood*. 2010;116:1205-1210

Hydrea in High-Risk ET: RCT

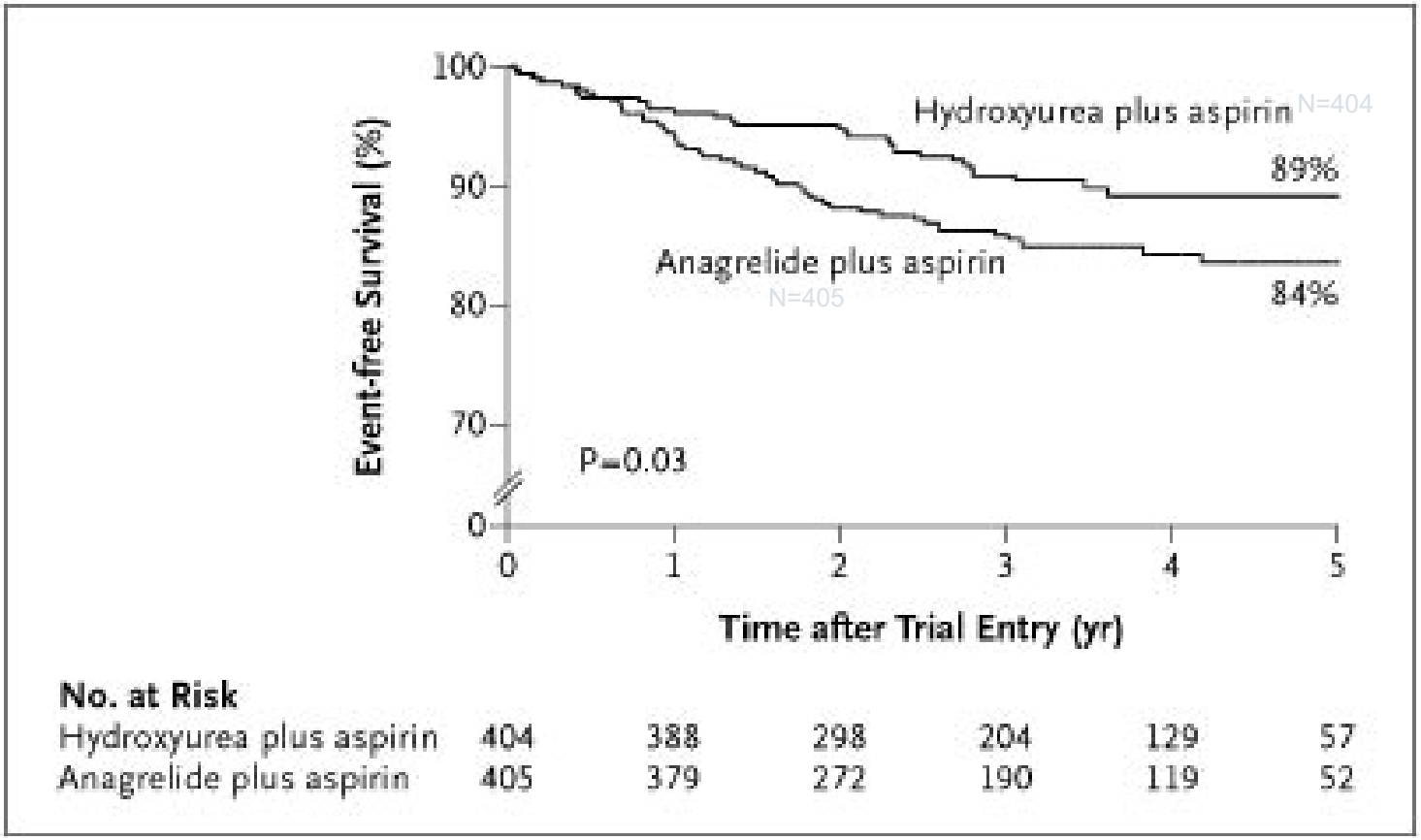


Goal plt <600K

Age > 60 or previous thrombosis and plt ≤ 1.5 million

Cortelazzo et al. *N Engl J Med.* 1995;332:1132
Finazzi et al. *Br J Haematol.* 2000;110:577-583

Hydrea vs. Anagrelide (+ASA)

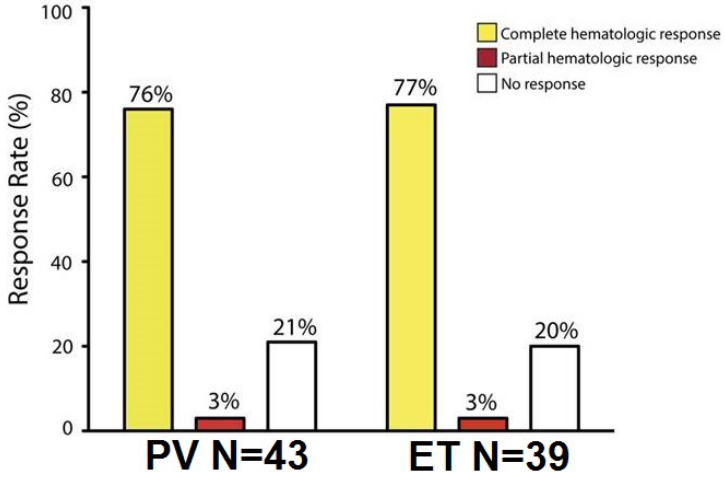


Composite endpoint: arterial and venous thrombosis, hemorrhage, death from vascular causes

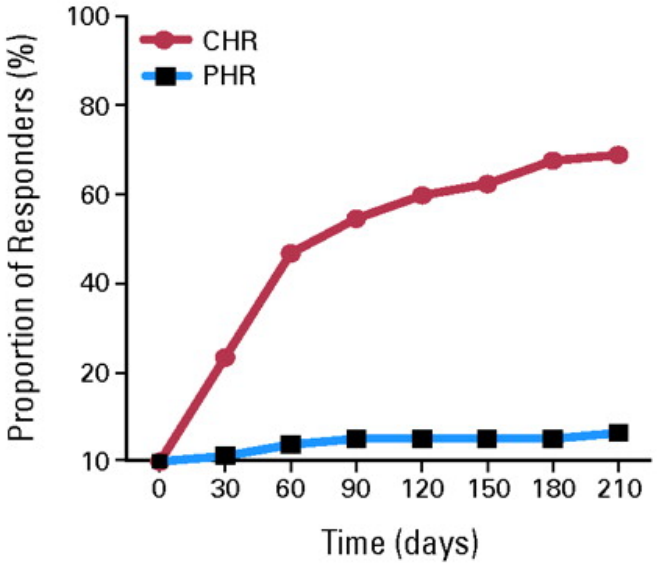
Anagrelide-treated patients had a significantly greater increase in bone marrow reticulin and a higher rate of transformation into myelofibrosis at five years (7 versus 2 percent, odds ratio 2.9, 95% CI 1.2-6.9)

Harrison et al. *N Engl J Med*. 2005;353:33-45
Gisslinger et al. Blood. 2013;121:1720-1728

PEG-IFN-α-2a



Hematologic Response



Molecular Response

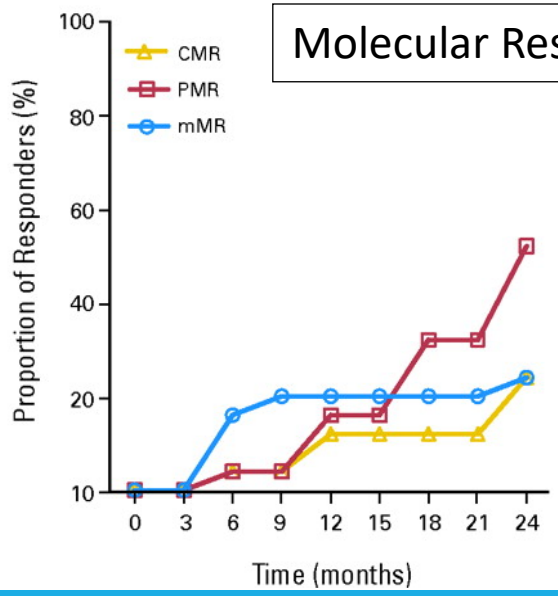


Table 2. Molecular response rates to PEG-IFN-α-2a therapy

*JAK2*V617F allele burden	PV (n = 40) number (%)	ET (n = 18) number (%)
CMR (undetectable)	7 (18)	3 (17)
PMR (>50% decrease)	14 (35)	6 (33)
mMR (20%-49% decrease)	3 (8)	3 (17)
No response	16 (40)	6 (33)

*Gowin et al. *Haematologica* 2012;97:1570-1573

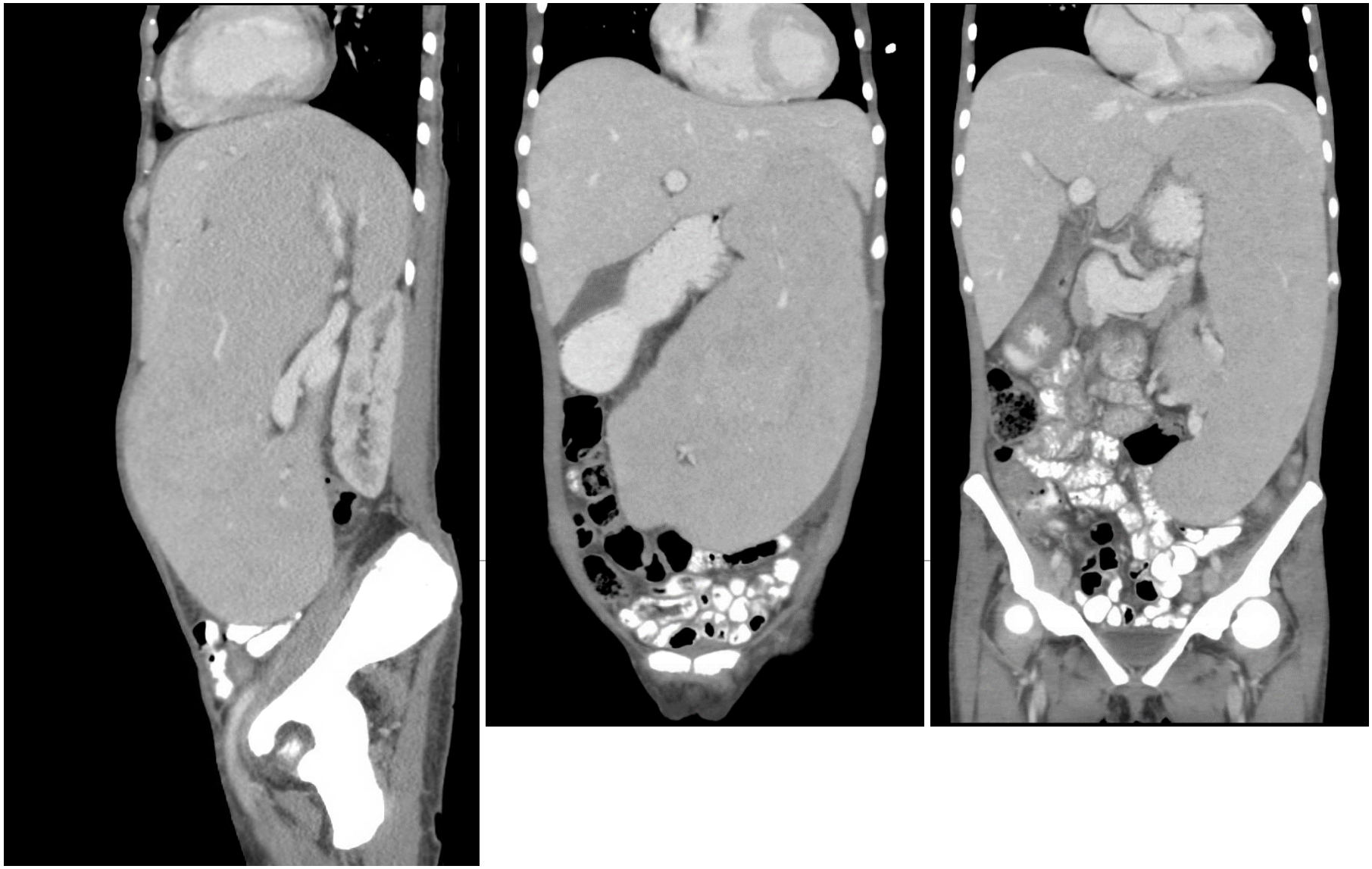
Quintás-Cardama et al. *J Clin Oncol*. 2009;27:5418-5424
Quintás-Cardama et al. *Blood*. 2013;122:893-901

Case 3

55 yo F with no PMH p/w bilateral leg swelling and DOE. Did not respond to herbal tea/supplements/CBD oil

- ROS: 20 lb wt loss/2 months, night sweats
- PE: tachycardia, holosystolic murmur, JVD, LE edema, splenomegaly
- Labs: Hgb 3.4, WBC 5.9, plts 79, normal BMP, ferritin 487, iron sat 38%, B12 548, folate >24, LDH 584, INR 1, Hapto 64, normal BR, smear: tear drop cells
  - → 13 units of PRBCS
  - CT Abdomen
  - Bone marrow biopsy

CT Abdomen



Bone marrow biopsy

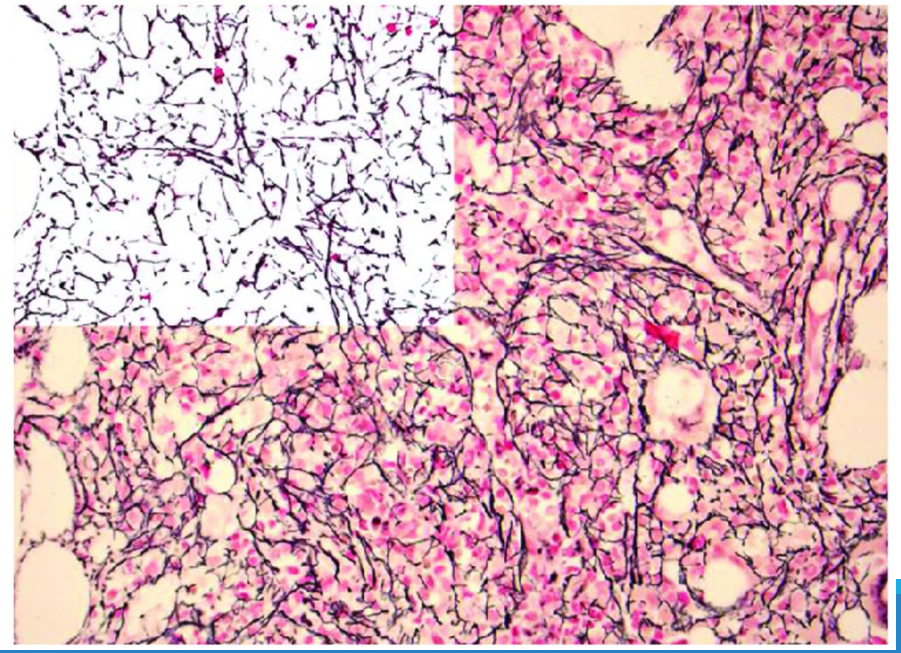
Hypercellular 90%; Megakaryocytic atypia

WHO Grade 3/3 fibrosis

No increased blasts on morphology or flow

Cytogenetics: 46, XX, del(7)(q11.2q22)[4]/46, XX[2]

+ JAK2 V617F and ASXL1 mutation



MF Diagnostic Criteria

WHO Criteria: Primary MF

Major criteria *(all 3 major + 1 minor)*

- Megakaryocyte proliferation and atypia with reticulin or collagen fibrosis grade 2 or 3
- Does not meet WHO criteria for other myeloid disorders (ET, PV, CML, MDS)
- Clonal marker (*JAK2*, *MPL*, *CALR*), presence of another clonal marker, or absence of reactive fibrosis §

Minor criteria *(2 consecutive determinations)*

- Increase in serum LDH >ULN
- Palpable splenomegaly
- Leukocytosis (≥11x10^9/L)
- Anemia
- Leukoerythroblastosis

§ 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] Arber, et al. *Blood*. 2016;127(20):2391-2405
[2]Barosi G, et al. *Leukemia*. 2008;22(2):437-438.

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]

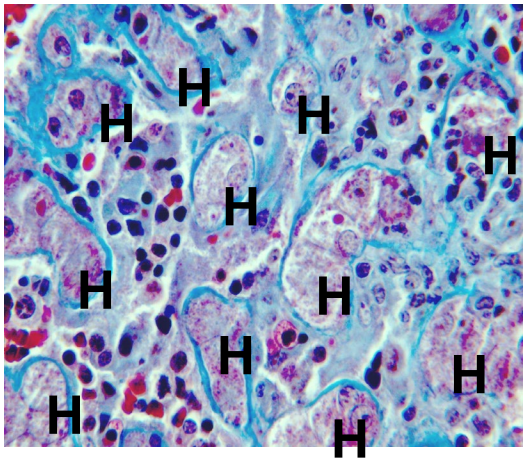
- Abdominal pain/discomfort, early satiety

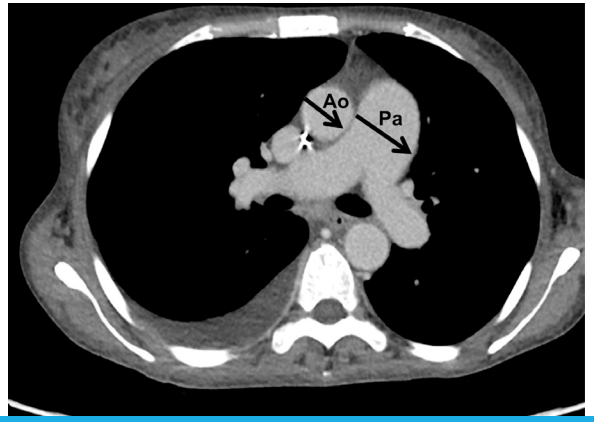
Other MF symptoms that can be present include[3]

- Pruritus- 50%
- Night sweats – 56%
- Bone pain – 47%

Extramedullary features:

- Sinusoidal hepatic fibrosis
- Extramedullary hematopoiesis (collage deposition blue)
- Pulmonary and portal HTN





Pictures courtesy of G.McDonald and R Salit

[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.

PMF - Risk Classification

Age > 65 years (1)

Constitutional symptoms (1)

Hgb < 10 /L (2)

WBC > 25,000 (1)

PB blasts ≥ 1% (1)

Abnormal chromosomes*

Plts <100,000

Transfusion dependence

Absence of CALR

High-risk mutations^

Marrow fibrosis ≥ grade 2

HMR genes: ASXL1, EZH2, SRSF2, IDH 1/2, U2AF1

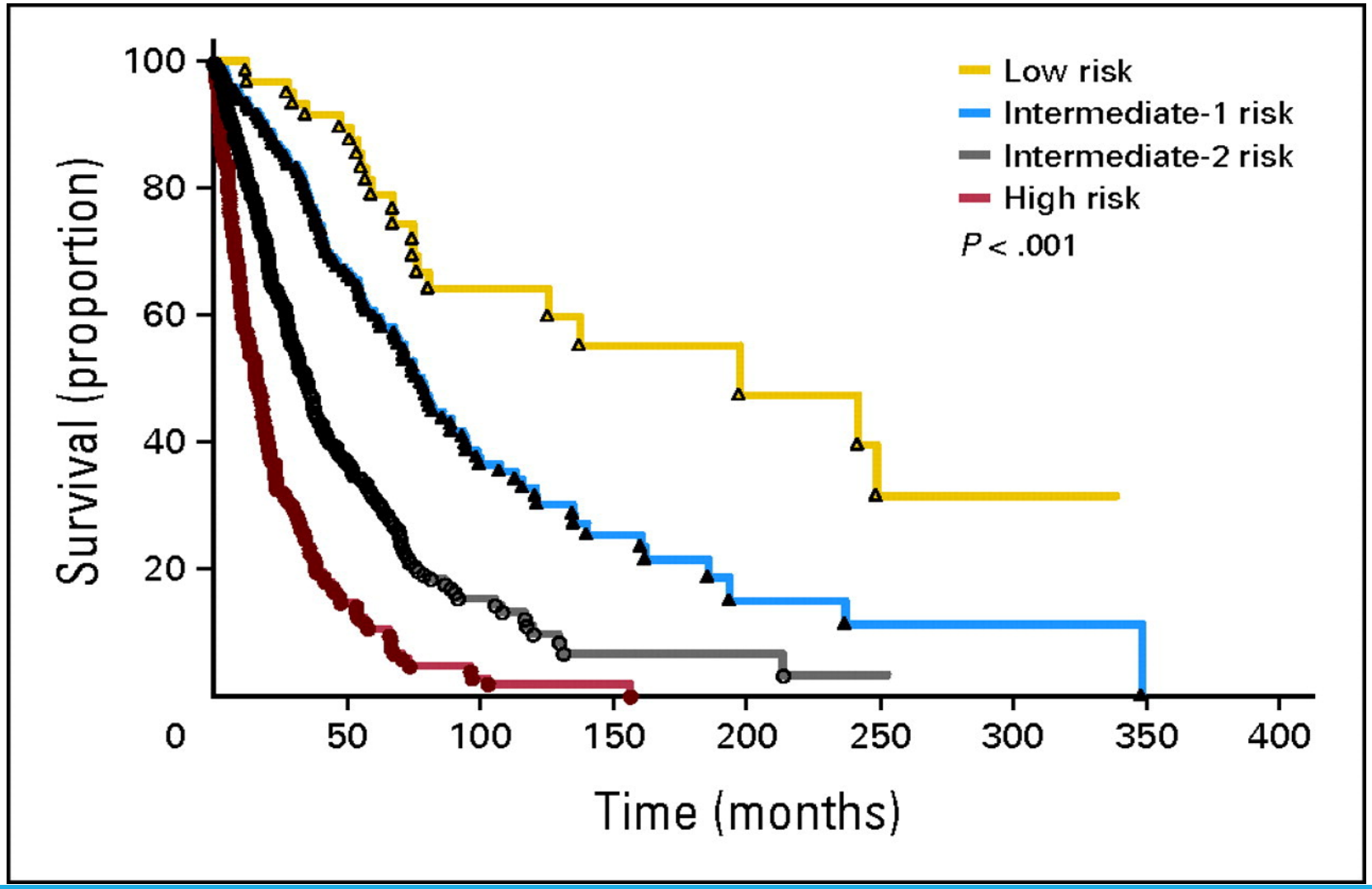
DIPSS

DIPSS-plus

MIPSS70-plus

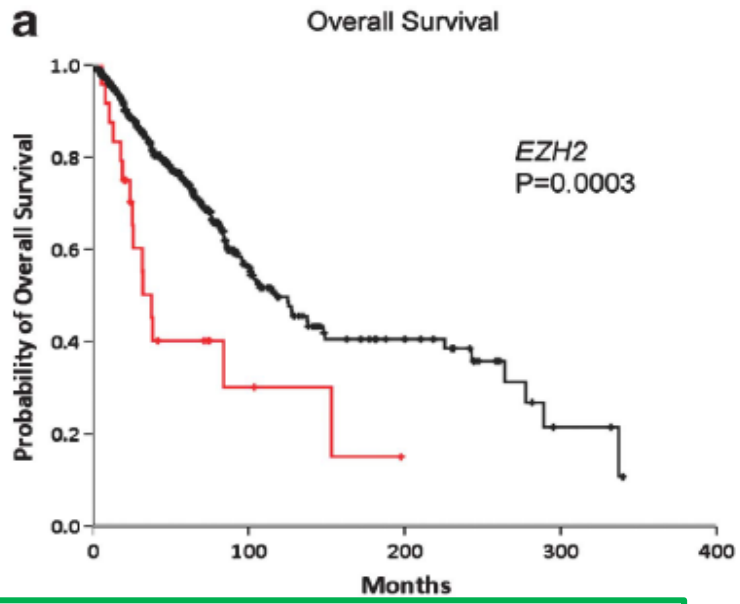
*+8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3) or 11q23 rearrangement ^ any abnormal karyotype other than normal or sole abnormalities in 20q-, 13q-, +9, chromosome 1 translocation/duplication, -Y or sex chromosome abnormality other than –Y

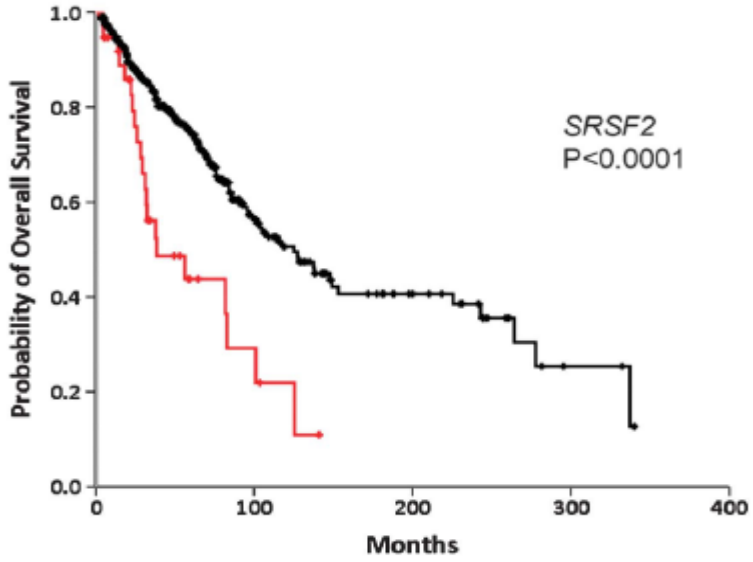
DIPSS-plus and Survival

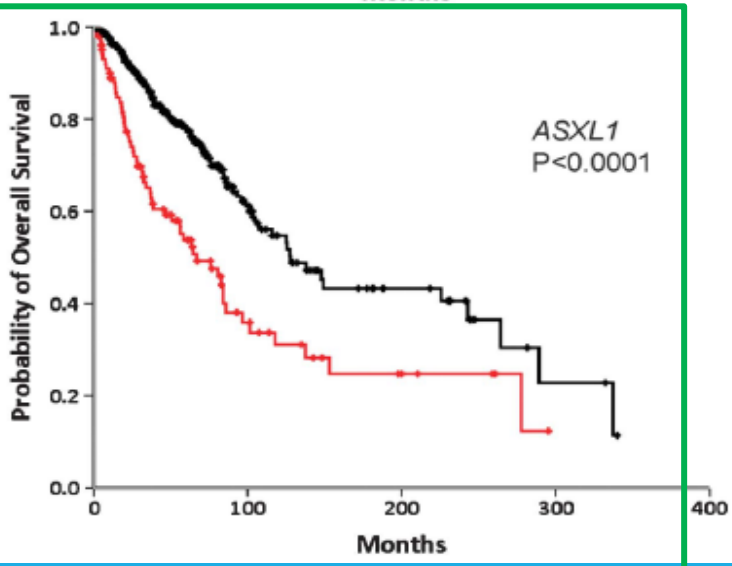


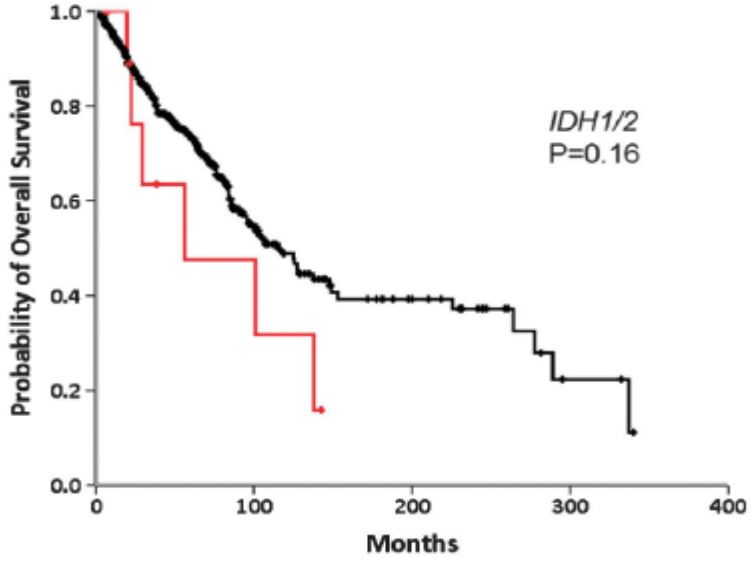
N. Gangat et al, JCO 29: 392, 2010

Overall Survival by Mutation









WT

Mut

Vannucchi et al. 2013. Leukemia. 27: 1861

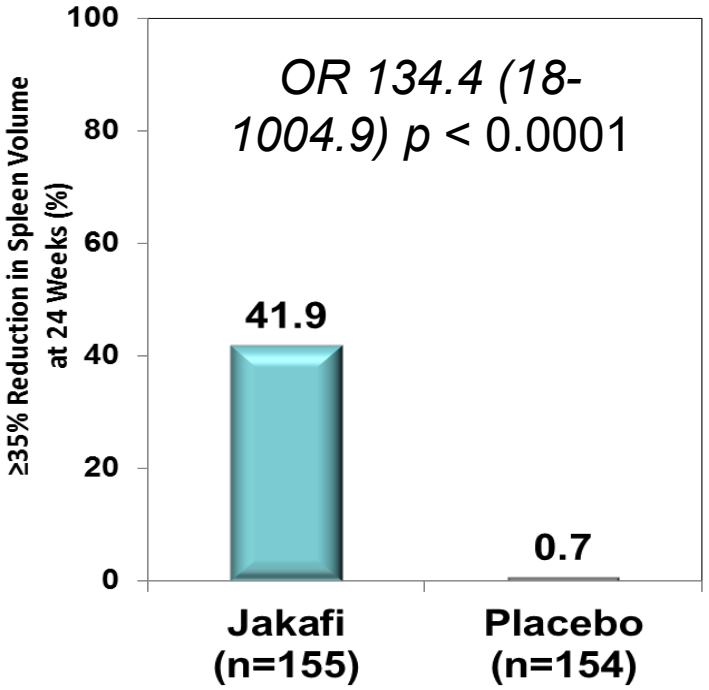
Treatment Options

- Active surveillance in low-risk disease
- Hydrea for proliferative disease, splenomegaly
- Anemia: Lenalidomide/prednisone, danazol
- Newest options:
  - Ruxolitinib (Jakafi) – JAK1/2 inhibitor: best for splenomegaly, constitutional symptoms, pruritis
  - Fedratinib (Inrebic) – JAK2 inhibitor; 2019 for int-2/high-risk MF, plts >50
- Allogeneic stem cell transplant for higher risk disease (generally DIPSS int-2 and high-risk)

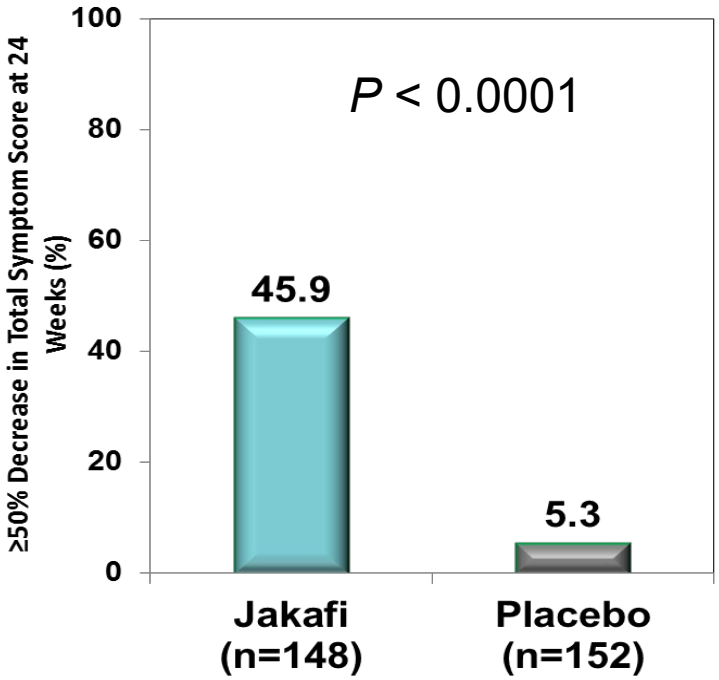
Kroger et al. Blood 2015; 125 (21): 3347-3350

COMFORT-1 : MF patients randomized to Ruxolitinib or placebo

DECREASE SPLEEN VOLUME



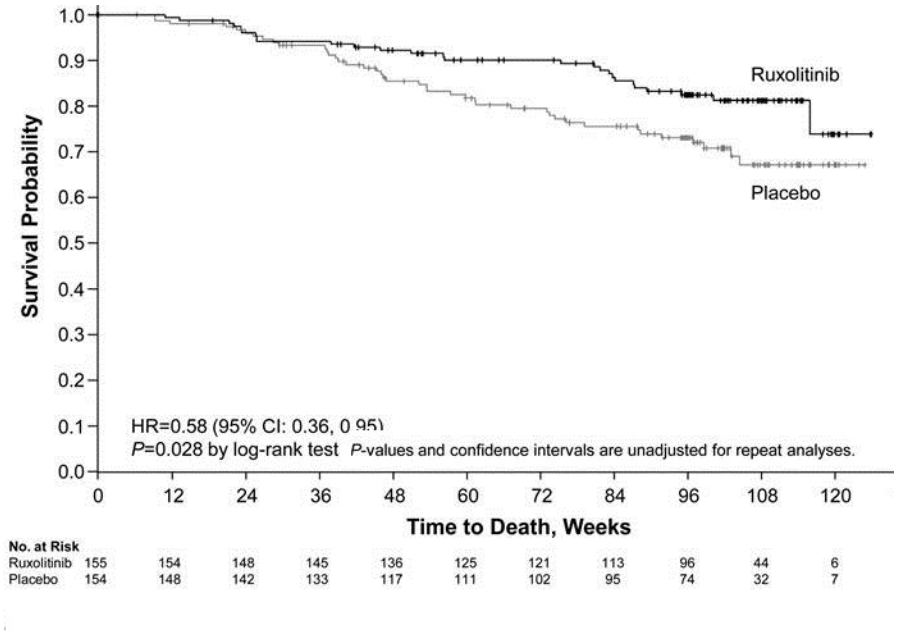
IMPROVEMENT MF SYMPTOMS



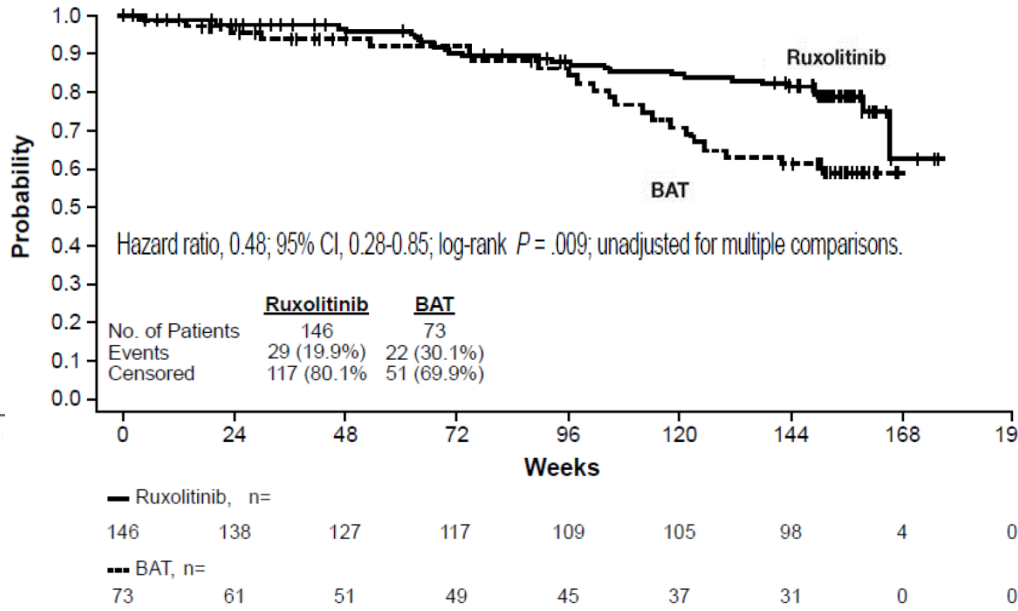
Verstovsek et al. *N Engl J Med.* 2012;366:799-807
Scherber et al. *Blood.* 2011;118:401-408

Comfort 2: MF patients randomized to Ruxolitinib vs. BAT

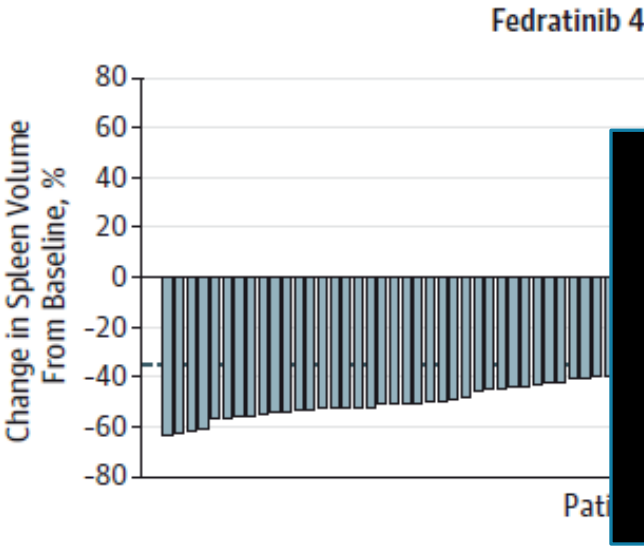
COMFORT 1



COMFORT 2



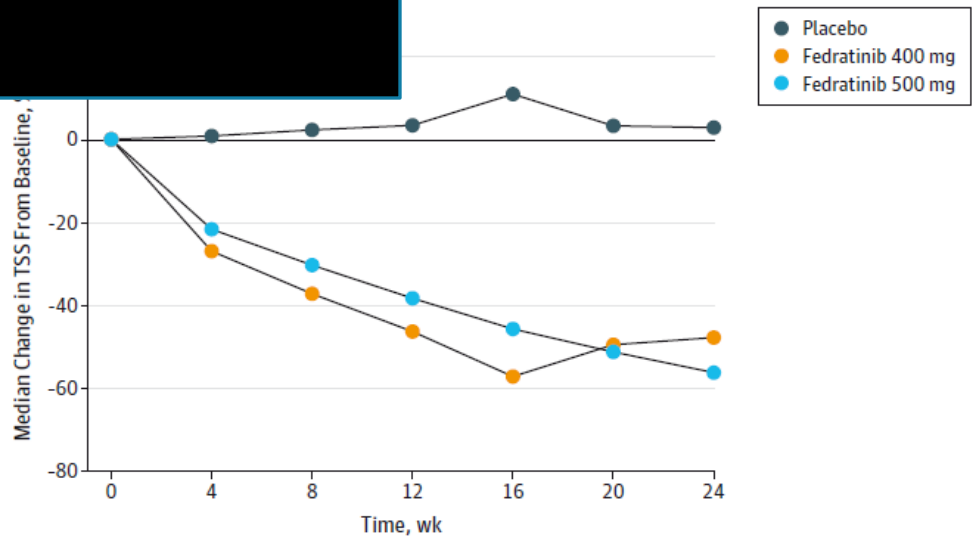
Fedratinib: JAKARTA Trials



37% >35% spleen volume reduction vs. 1% placebo; med duration 18 mo

BLACK BOX WARNING:
WERNICKE ENCEPHALOPATHY:
CHECK THIAMINE level (B1)
PRIOR TO STARTING THERAPY

40%: > 50% reduction in MF-TSS vs. 9% placebo

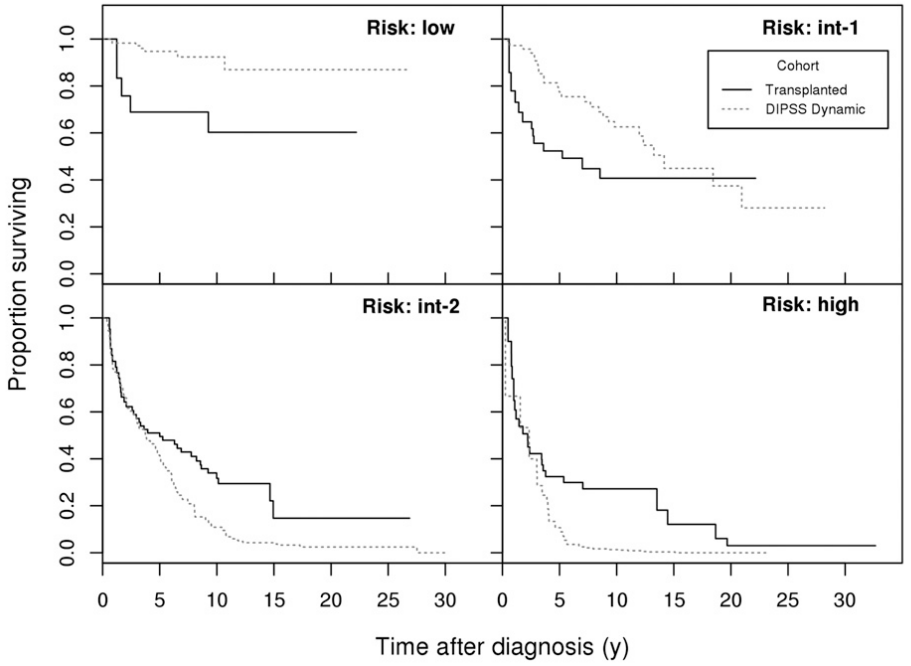


Pardanani A. et al. JAMA Oncology 2015; 1 (5): 643-651.
Harrison C et al. Lancet Haematology 2017; 4: e317-24

So, Whom and When to Transplant?

Disease characteristics:

- DIPSS int 1 – some patients (adverse risk mutations, 2+ mutations?, triple negative disease?) will benefit
- DIPSS int 2/high –indication for HCT
- Disease progression – HCT only real option
- Loss of response to JAK inhibitor



Kroger et al, Blood 2015; 125 (21): 3347-3350

Risk Factors for transplant

Comorbidities

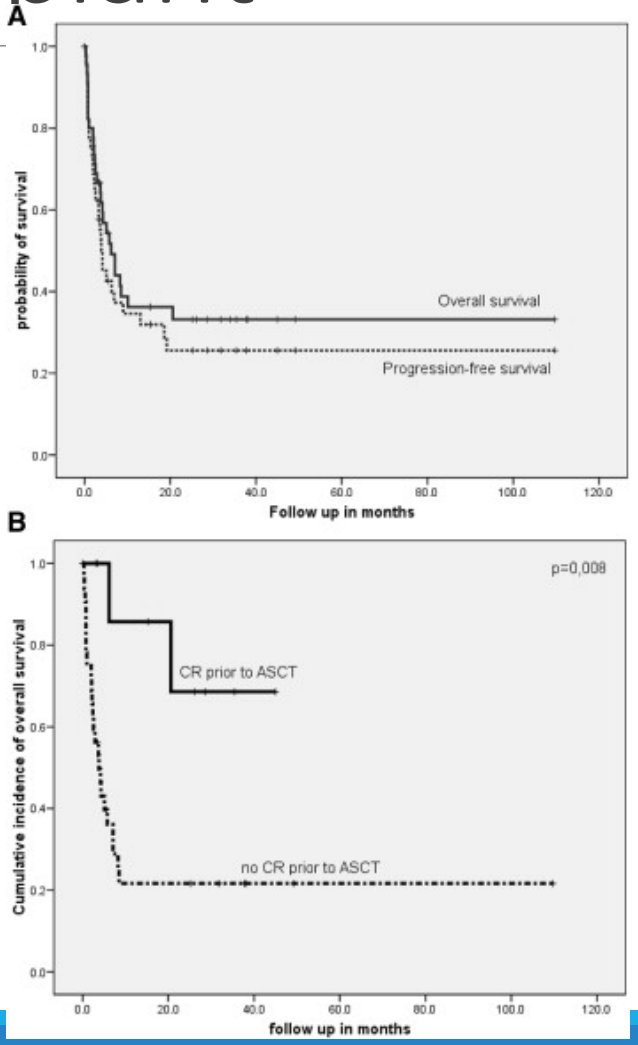
Pulmonary or portal HTN

Extramedullary hematopoiesis/disease

Massive splenomegaly (>22 cm)

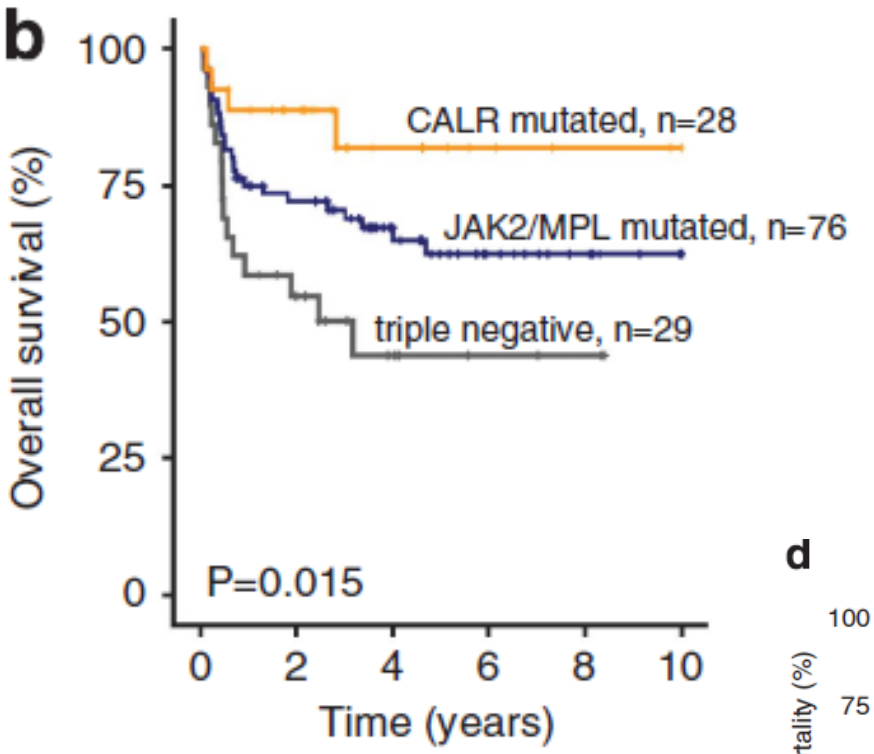
Adverse mutations

Leukemic transformation



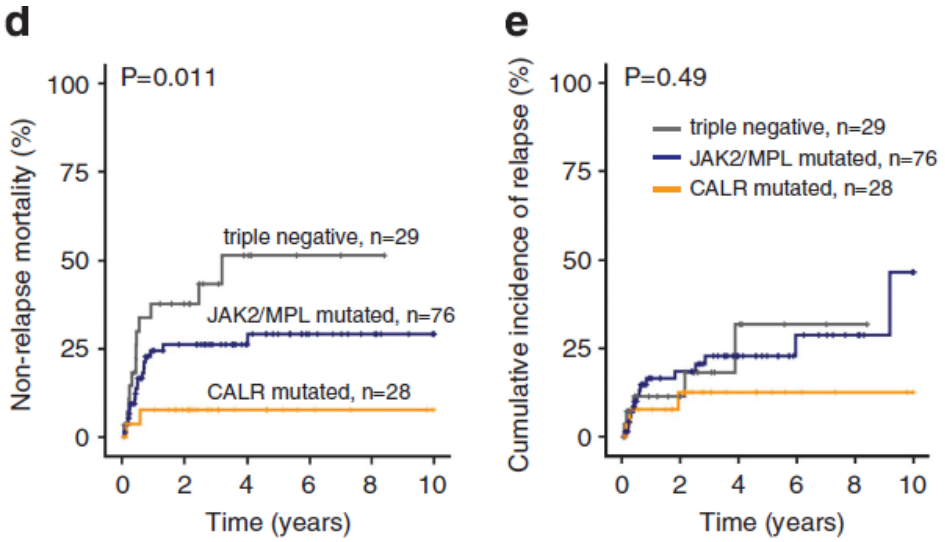
Alchalby H et al. Biology of Blood and Marrow Transplant 2014; 20 (2): 279-81.

Mutations and transplant outcome



CALR mutated patients have prolonged OS after HCT, both due to decreased relapse and non-relapse mortality

Triple-negative patients do worst



Case 3

High-risk DIPSS plus score

No response to Ruxolitinib (low dose due to baseline plts)

Referred to transplant, still with massive splenomegaly up to 27 cm, cachexia at 38 kg (BMI 15)

Patient had splenectomy given size and severe malnutrition, tolerated it well

Now >1 year s/p matched, unrelated donor stem cell transplant, doing well

MPN-accelerated/blast phase

MPN-AP (10-19% blasts) and MPN-BP (≥20% blasts) difficult to treat

- ~15% PV, 3-5% ET, 20% MF will progress to AML

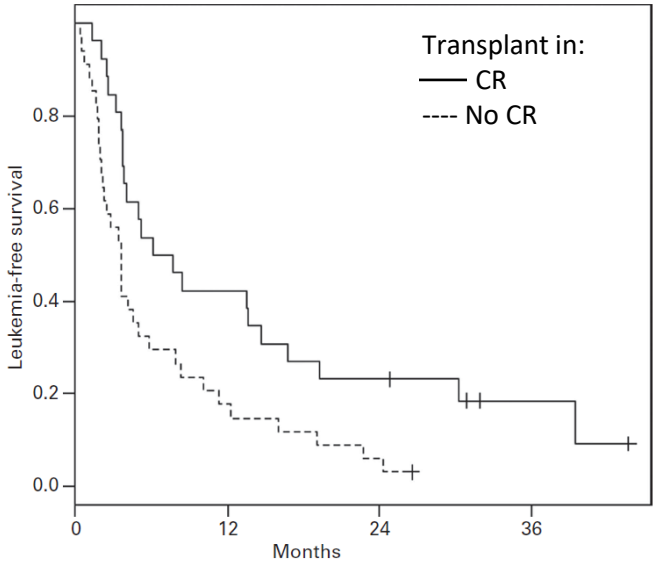
Sequelae of their chronic underlying MPN (eg splenomegaly, fibrosis) often complicate their treatment

Prognosis in absence HCT 3-6 months

Treatment options:

- Hypomethylating therapy (HMA)
- AML-induction type therapy
- Early clinical experience with HMA+ruxolitinib

Myeloproliferative neoplasms in blast phase
X Cahu *et al*



Tefferi et al. Leukemia 2018; 32(5): 1200-1210; Tam et al., Blood 2008; 112 (5): 1628-1637; Alchalby et al, Biol Blood Marrow Transplant 201420(2): 279-281; Cahu Bone Marrow Transplant 2014;49 (6): Bose et al. Leukemia 2020; epub; Assi et al. AJH 2017; 93: 277-285; Rampal et al. Blood Advances 2018; 2(24): 3572-3580.

Mastocytosis

No longer considered an MPN in WHO 2016

Cutaneous mastocytosis- limited to skin

Systemic mastocytosis (SM) involves extracutaneous organs

- >70% adults have D816V KIT mutations
- Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)

Skin, GI, neuropsychiatric, anaphylaxis, episodic mediator release:

- episodes of vasodilation, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue, and headache

+ KIT mutations: Midostaurin FDA approved for aggressive SM or SM-AHN

- NO KIT mutations: Imatinib approved for aggressive SM

Chronic Neutrophilic Leukemia (CNL)

WHO Criteria: CNL

1) PB WBC >25 x10^9/L
2) Hypercellular BM
3) Not meeting WHO criteria for CML, PV, ET, PMF
4) No PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2
5) Presence of CSF3R T6181 or other activating CSF3R mutation
   OR if no CSF3R mutation: persistent neutrophilia >3 months, no cause of reactive neutrophilia, splenomegaly, or clonality of myeloid cells by cytogenetic or molecular studies

Mature granulocytic proliferative in blood and marrow, hepatosplenomegaly
Short survival (<2 years)
Treatment (?): hydroxyurea, ruxolitinib, interferon, cladribine, TKI- dasatanib, transplant

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

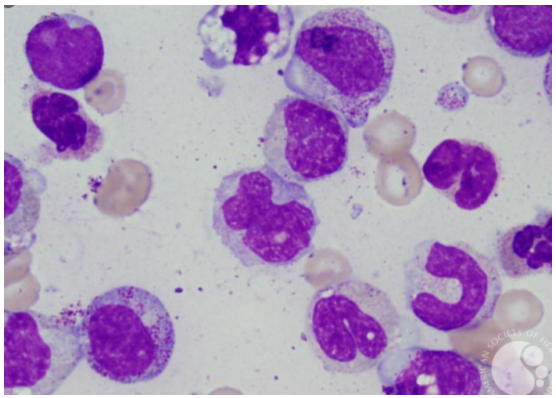
The challenge of CMML

MDS/MPN overlap syndrome WHO 2016

Few CMML-specific studies

"MDS-CMML" WBC <13
- Ineffective hematopoiesis
- Cytopenias- mostly anemia, less thrombocytopenia
- Dysplasia

"MPN- CMML" wbc >13
- Leukocytosis
- Constitutional symptoms
- Splenomegaly
- Extramedullary disease
- Autoimmune/inflammatory disease



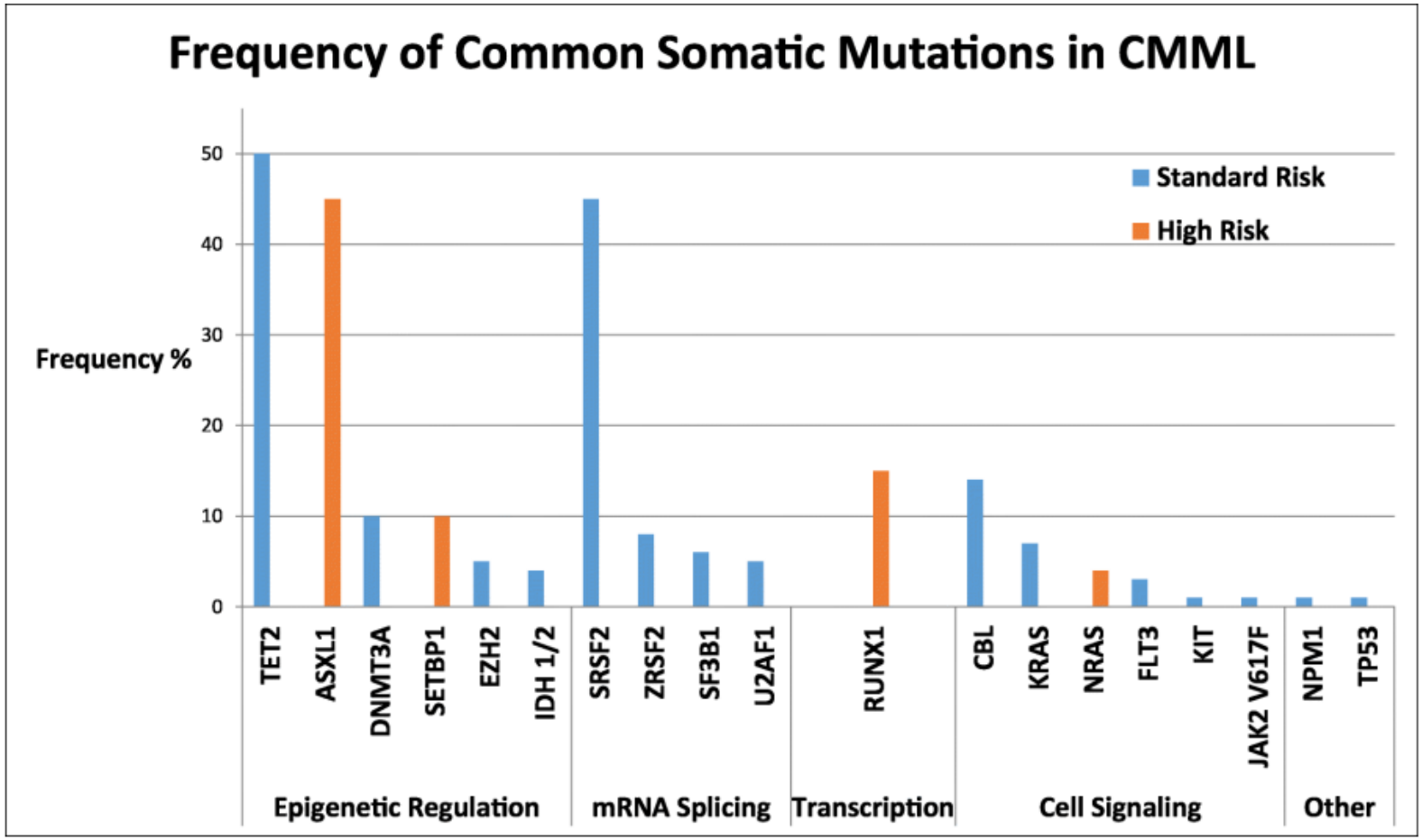
WHO Criteria: CMML[1]

1) Persistent (>3 months) PB monocytosis ≥ $1x10^9$/L, with monocytes accounting for ≥ 10% of the WBC count
2) Not meeting WHO criteria CML, PMF, PV, ET*
3) No evidence of PDGFRA, PDGFRB, FGFR1, PCM1-JAK2
4) <20% blasts/blast equivalents in blood and marrow
5) Dysplasia in ≥1 myeloid lineages, unless:
    1) There is a clonal cytogenetic/molecular abnormality §
    2) Monocytosis persisted >3 months
    3) Reactive causes excluded

CMML-0: <5% marrow blasts
CMML-1: 5-9% marrow blasts
CMML-2: 10-19% marrow blasts
>20% =AML arising from CMML

Arber et al. *Blood*. 2016;127(20):2391-2405; Elena C et al, Blood 2016; 128 (10): 1408-17).

Common mutations CMML



Solary and Itzykson, Blood 130, 2017; Salit MDS/MPN Foundation

CMML Risk stratification

Multiple risk models for CMML with various factors:

- Cytopenias, WBC, blast %, transfusion, cytogenetics, age
- These have recently been upgraded to include mutational information

Mayo molecular model: AMC ≥ 10K, circulating immature cells, Hgb <10, plts <100, ASXL1

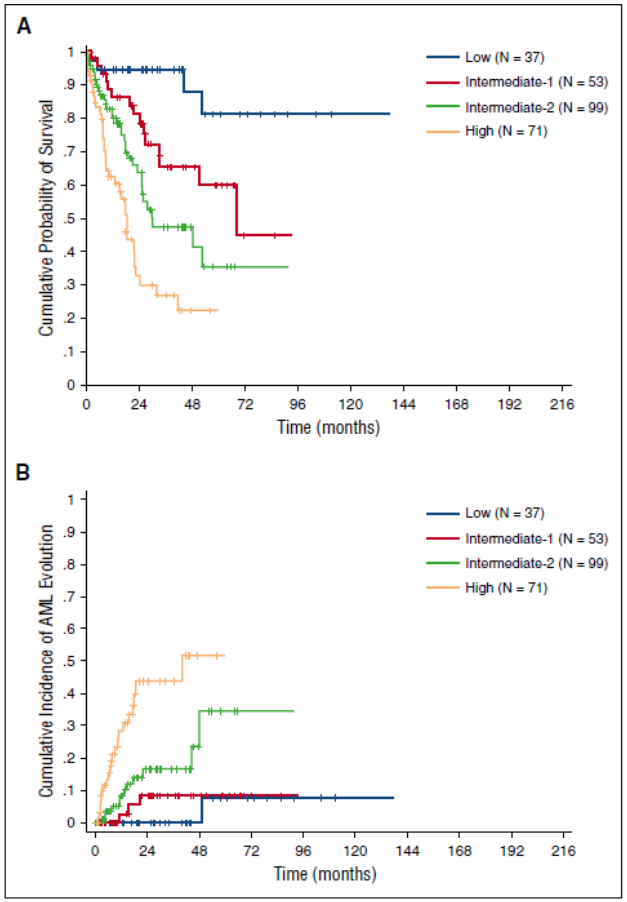
GFM Score: age >65, WBC ≥15K, Hgb <10, plt <100, ASXL1

CPSS-Mol: WBC ≥ 13K, BM blasts ≥ 5%, RBC transfusion dependence, cytogenetic risk group, ASXL1, NRAS, SETBP1, RUNX1 (2 pts)

MD Anderson Score: 8 features including PS, no molecular

Elena at al. Blood 2016; 128(10): 1408-1417)

CPSS-Mol



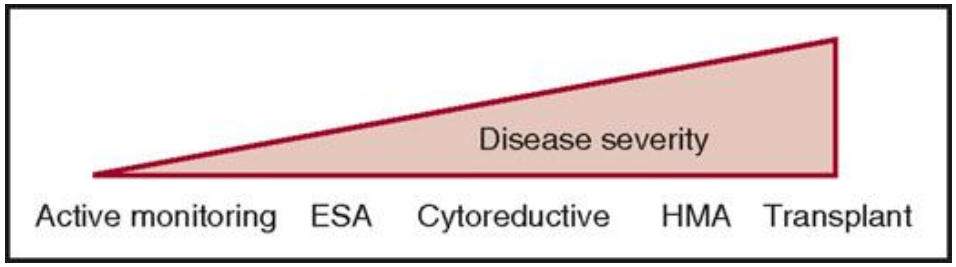
Factor	Points
Clinical features	
WBC ≥13,000	1
BM blasts ≥5%	1
RBC transfusion dependence	1
Genetic Risk Group	
Low: normal or isolated –Y	0
Int: other	1
High: trisomy 8, complex (≥3), chrom 7	2
Mutation risk	
ASXL1, NRAS, SETBP1	1
RUNX1	2

Risk Group	Median OS	CIL at 48 mo
Low	Not reached	0
Intermediate-1	64 months	3%
Intermediate-2	37 months	21%
High	18 months	38%

Elena at al. Blood 2016; 128(10): 1408-1417)

CMML- Treatment Options

Strategies from MDS and MPNs



Indications for treatment

- Systemic symptoms
- Organ involvement
- Alterations in blood counts
- High-risk disease

Lower-risk patients

- Active surveillance
- ESA for anemia
- Hydroxyurea for leukocytosis/splenomegaly/extramedullary disease

Higher-risk patients (+/- young)

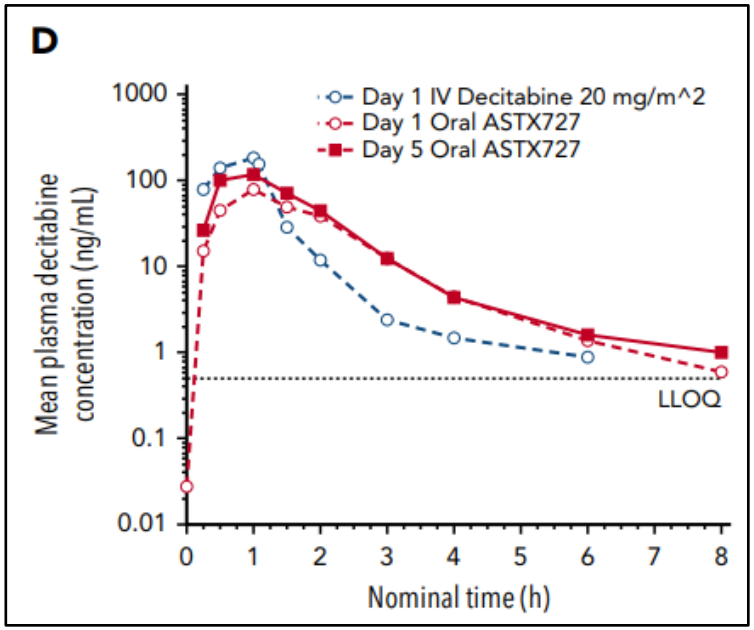
- Hypomethylating agents
  - ORR ~30-60%
  - CR ~15%
  - OS 12-37 months
- Multi-agent induction chemotherapy
- Allogeneic stem cell transplant – only curative approach

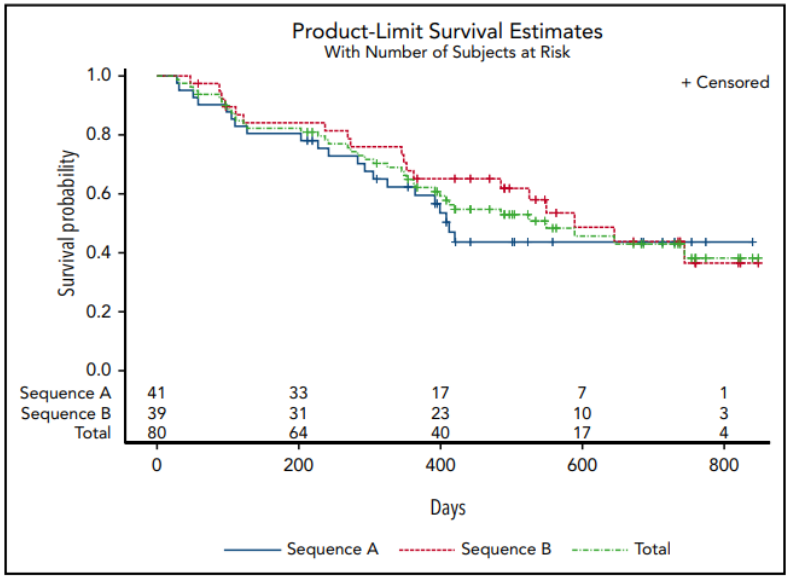
Patnaik and Tefferi, Am J Hematol, 206; Ades, Leuk Res 2013; Fianchi et al, Leuk Lymphoma 2013; Solary and Itzykson, Blood 130, 2017)

Inqovi (decitabine+cedazuridine) for CMML

Oral therapy taken days 1-5 q28 day cycle

Approved for: MDS and CMML-1/2





A= oral first B = IV first

Garcia-Manero et al. Blood 2020; 6: 674-683