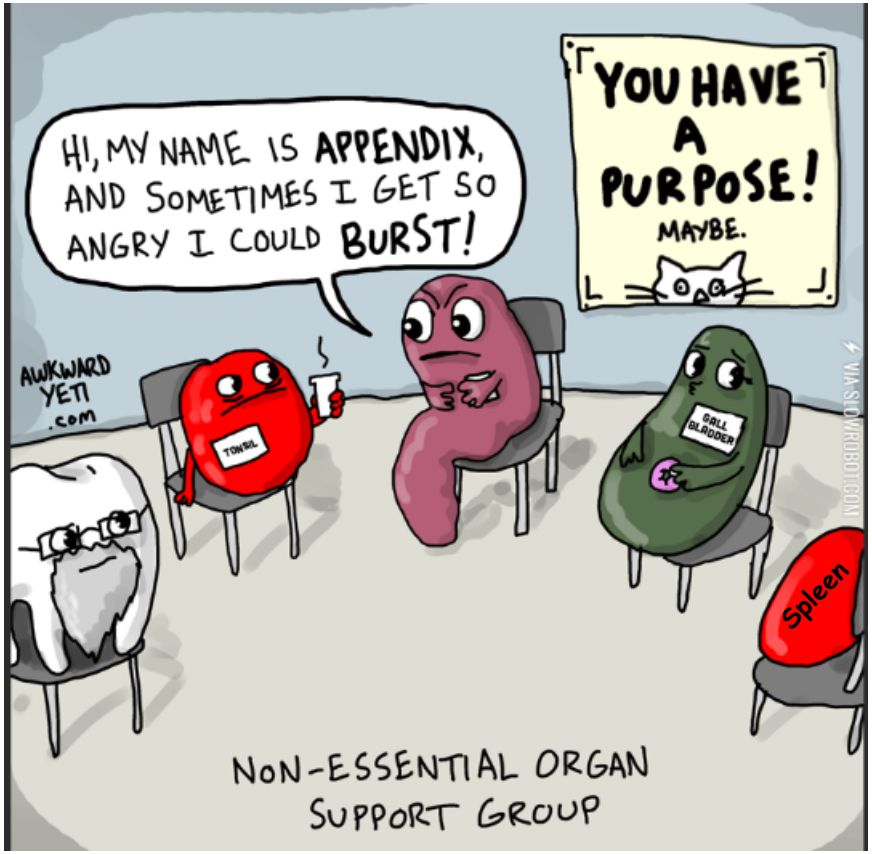
Fred Hutchinson Cancer Center 16th Annual Comprehensive Hematology & Oncology Review: Myeloproliferative Neoplasms



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10/9/25

Disclosures

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- Consulting: Karyopharm, BMS

Objectives

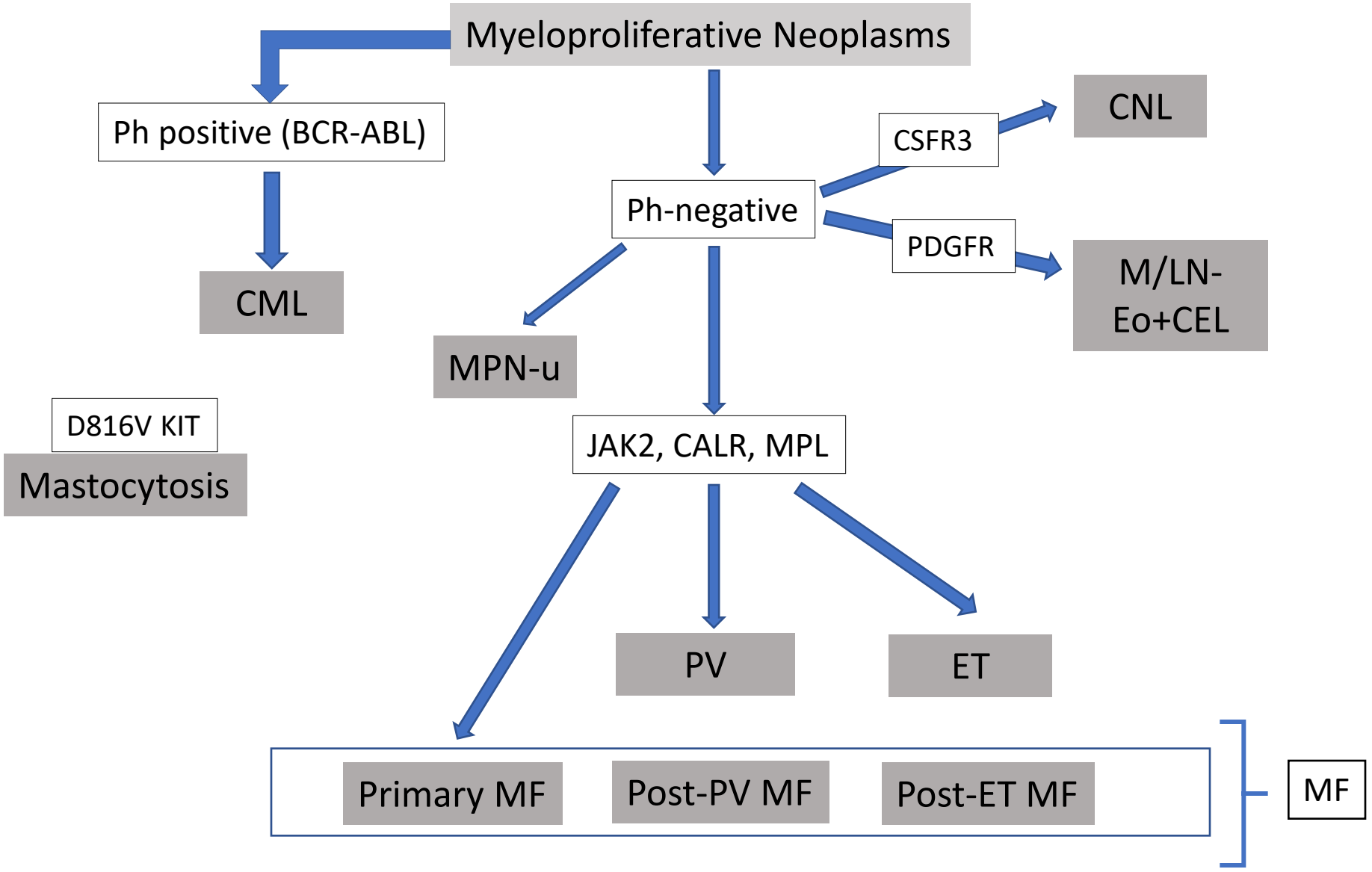
✓Overview MPNs: epidemiology and pathophysiology

✓Presentation, Diagnosis, Risk Stratification, Treatment

Polycythemia vera

Essential thrombocythemia

Myelofibrosis

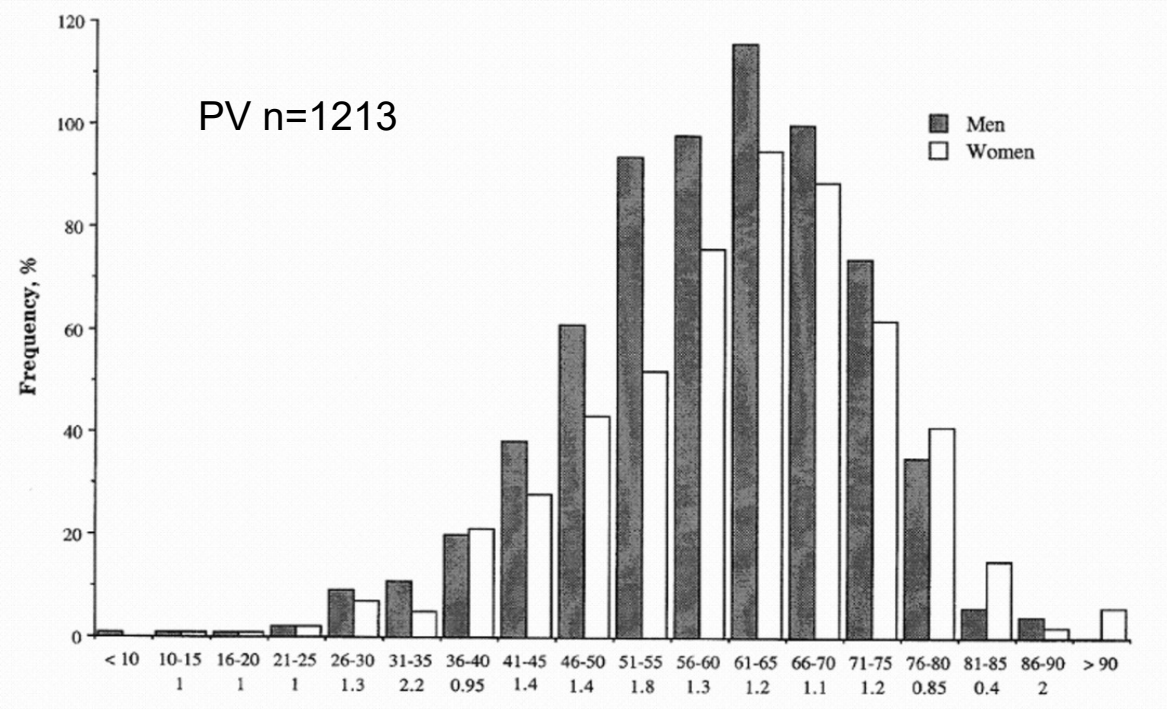


MF=myelofibrosis CNL=Chronic neutrophilic luekemia
PV=polycythemia vera CEL=Chronic Eosinophilic Leukemia
ET=essential thrombocythemia CML=chronic myeloid leukemia

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

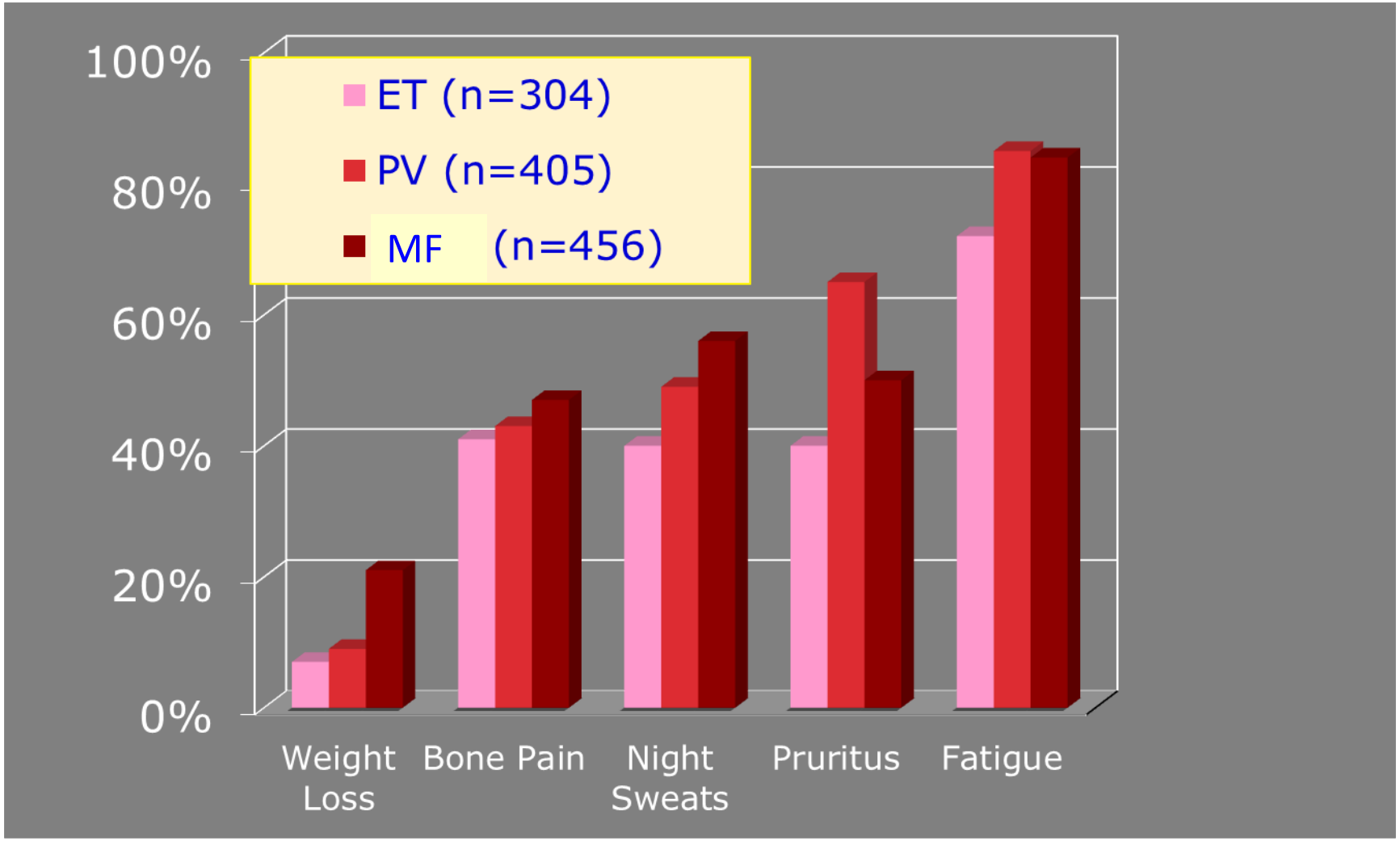
Epidemiology of MPN

- 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



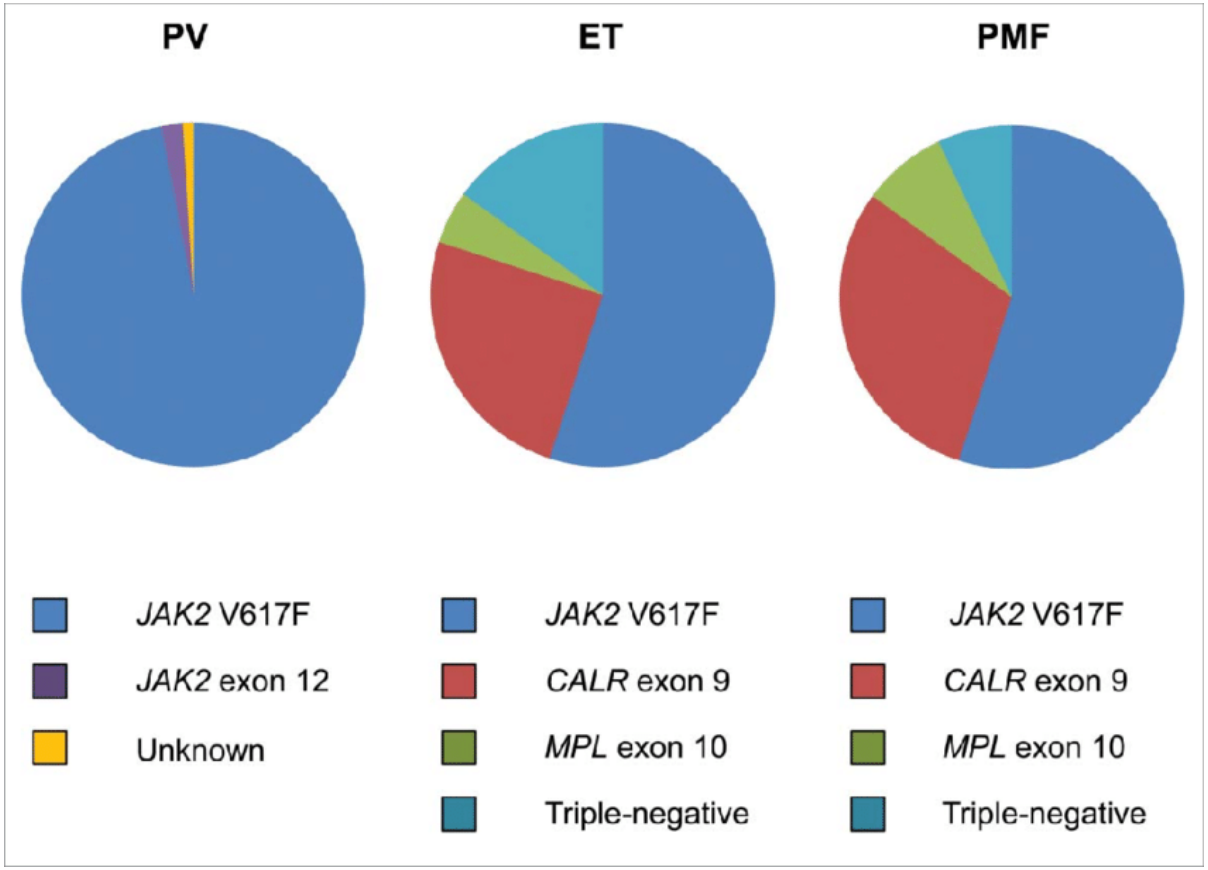
GISP *Ann Intern Med.* 1995;123:656-664

Presenting symptoms of MPN; MF most symptomatic



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

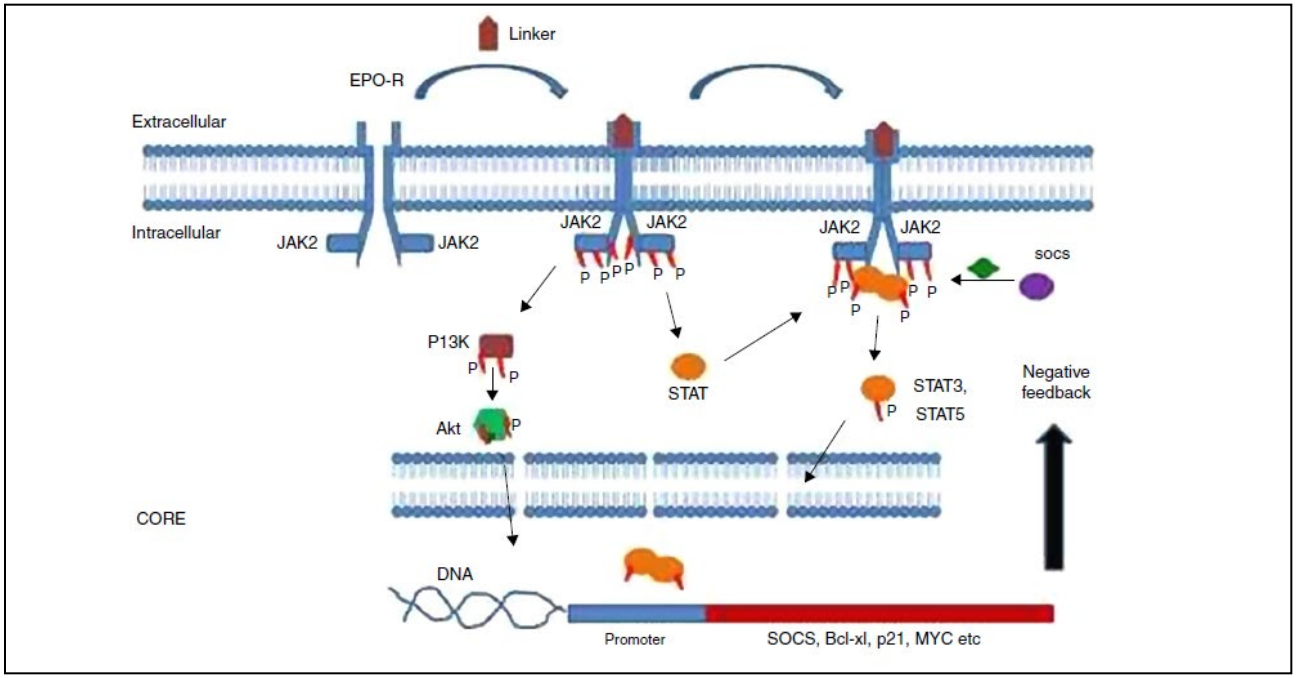
Mutations in MPNs



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.

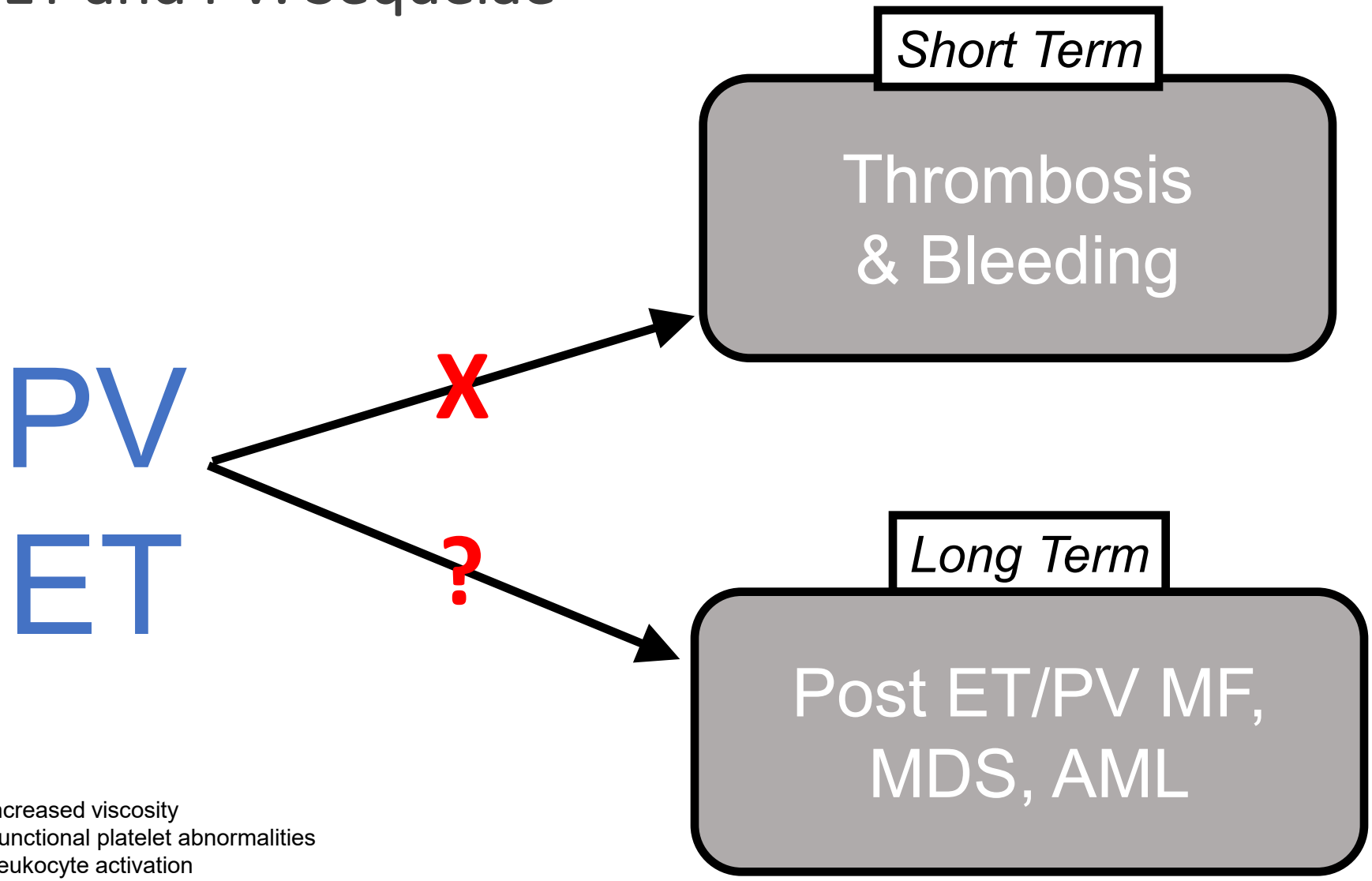
MPN Etiology: Role of *JAK2* Mutation



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

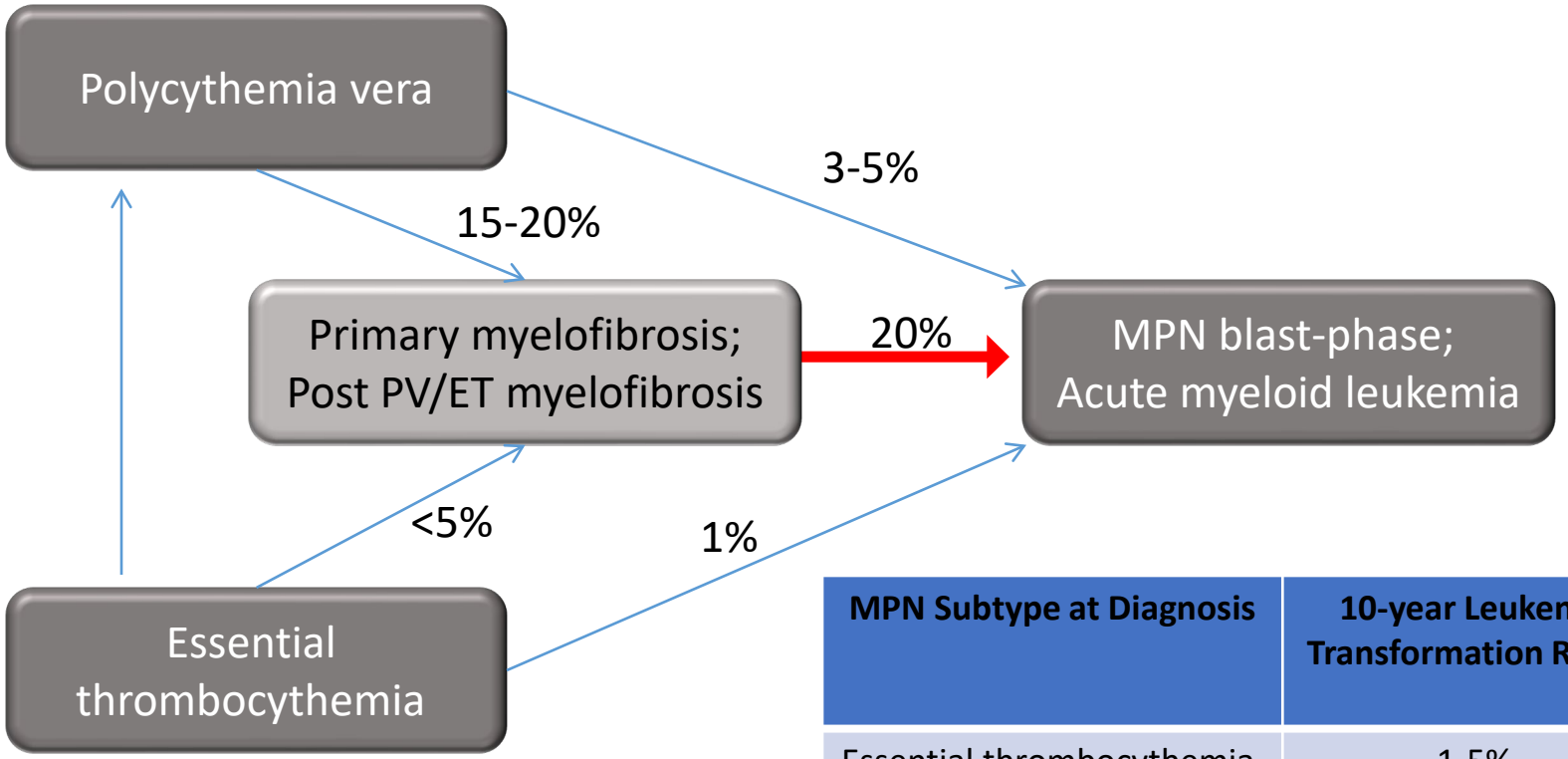
Affects the expression of genes involved in regulation of apoptosis and regulatory proteins and modifies the proliferation rate of hematopoietic stem cells

ET and PV: Sequelae



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

Long term risk MPNs: transformation to MF and AML



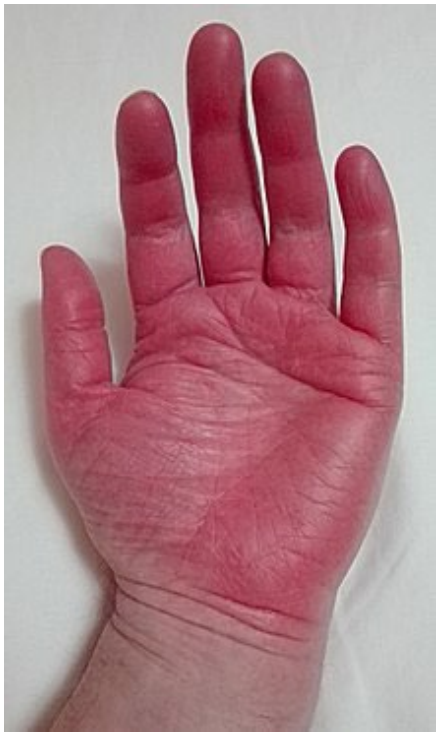
MPN Subtype at Diagnosis	10-year Leukemic Transformation Rate [2]
Essential thrombocythemia	1-5%
Polycythemia vera	3-5%
Primary myelofibrosis	20%

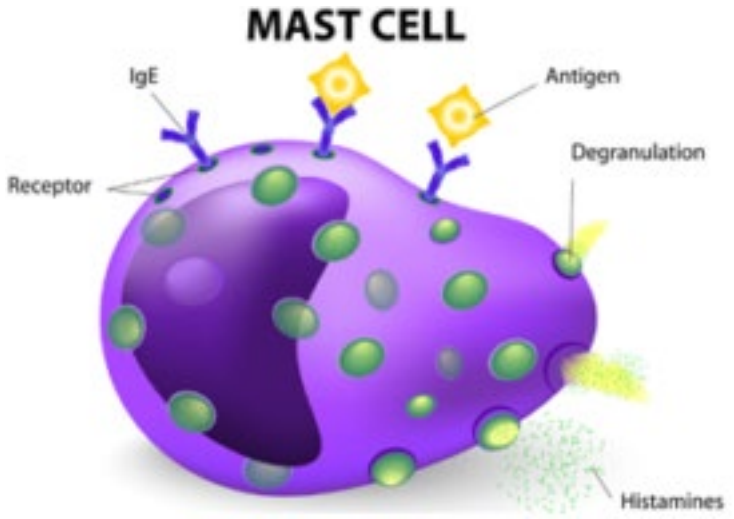
1.Tefferi A. *Am J Hematol*. 2008;83:491-497; 2. Rampal, Mascarenhas. *Curr Opin Hematol.* 2014;21:65-71.

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: white blood count (WBC) 21 K/uL, hemoglobin (Hgb) 18.8 g/dL, hematocrit (HCT) 48, platelets (plts) 490 k/μL
  - Epo level <1
- JAK2 V617F 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 → hydroxyurea→ did not control symptoms → ruxolitinib

Erythromelalgia & aquagenic pruritis, “classic” PV symptoms





- Blood vessels in hands/feet episodically blocked → hyperemia and inflammation
- Severe burning pain (small fiber sensory nerves) and erythema
- Trigged by heat, activity, pressure, stress
- Aquagenic pruritis, classically after hot shower, mediated by mast cells degranulation

Picture from: https://franklincardiovascular.com/do-i-have-mast-cell-activation-syndrome-mcas/

WHO 2022 PV Diagnostic Criteria

Start with CBC, Epo level and JAK2 V617F/BCR-ABL mutations; exclude secondary causes

WHO Criteria: PV

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

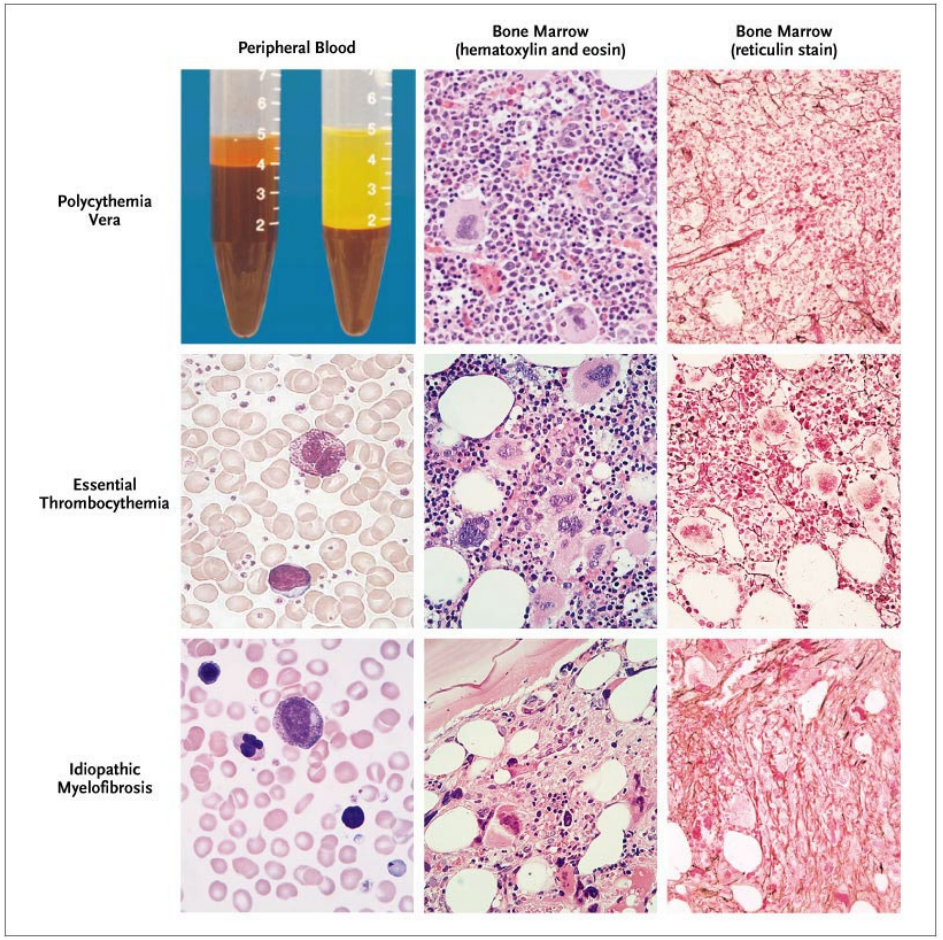
- Hgb > 16.5 g/dL (HCT 49) in men, 16 g/dL HCT (48) in women
- †BM Trilineage Proliferation (panmyelosis)
- *JAK2V617F* or *JAK2* exon 12 mutation

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).



Arber et al. *Blood*. 2016;127(20):2391-2405. Khoury et al. Leukemia 2022; 36: 1703-19.
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

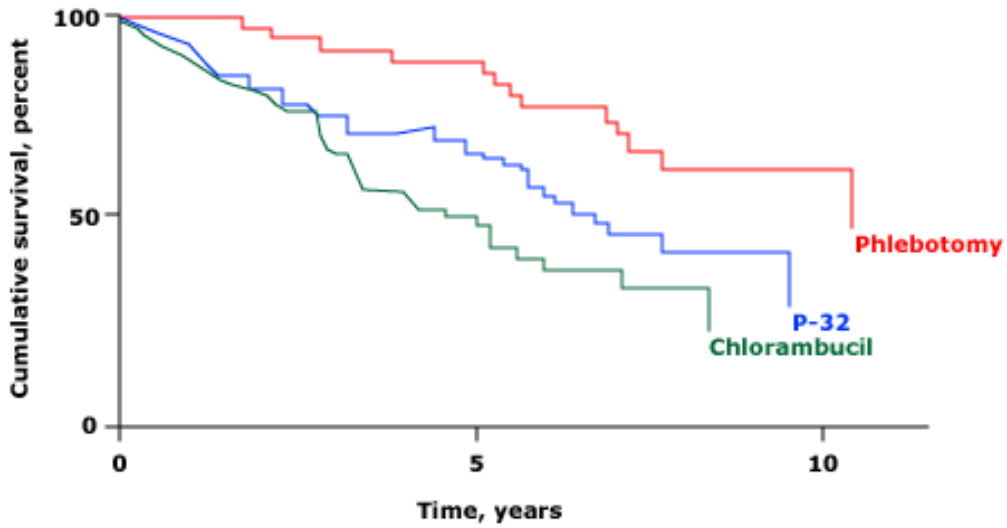
- Phlebotomy to maintain HCT <45%
- Aspirin 81 mg daily
- Cardiovascular risk-factor modification
- Hydroxyurea (HU)
- Interferon: pegylated and ropegylated
- Ruxolitinib
- Chemo X

ALL

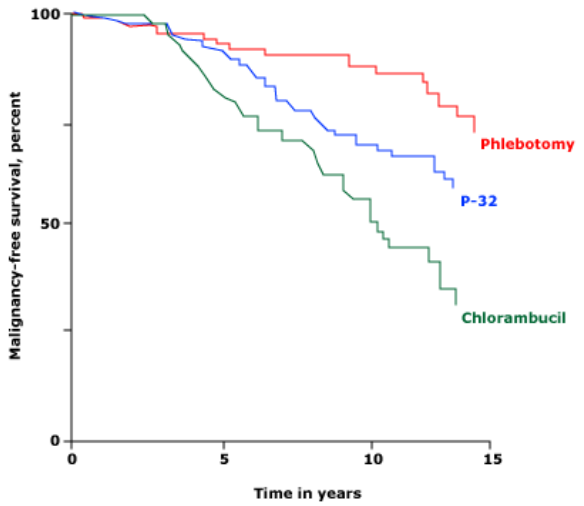
High-risk OR uncontrolled PV symptoms

Initial trials in PV: no more chemo

Lower cumulative survival with chemotherapy in polycythemia vera



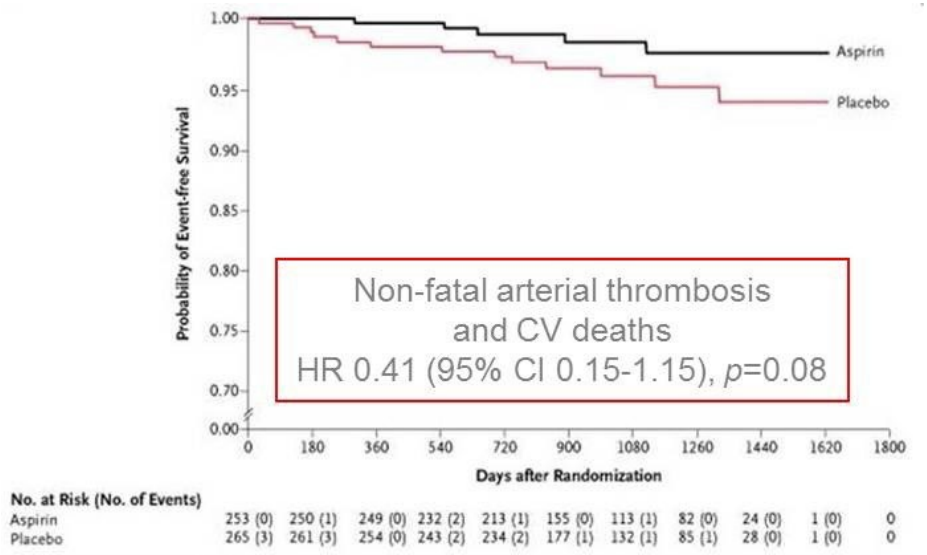
Lower malignancy-free survival with chemotherapy in polycythemia vera



Similarly worse survival with pipobroman

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

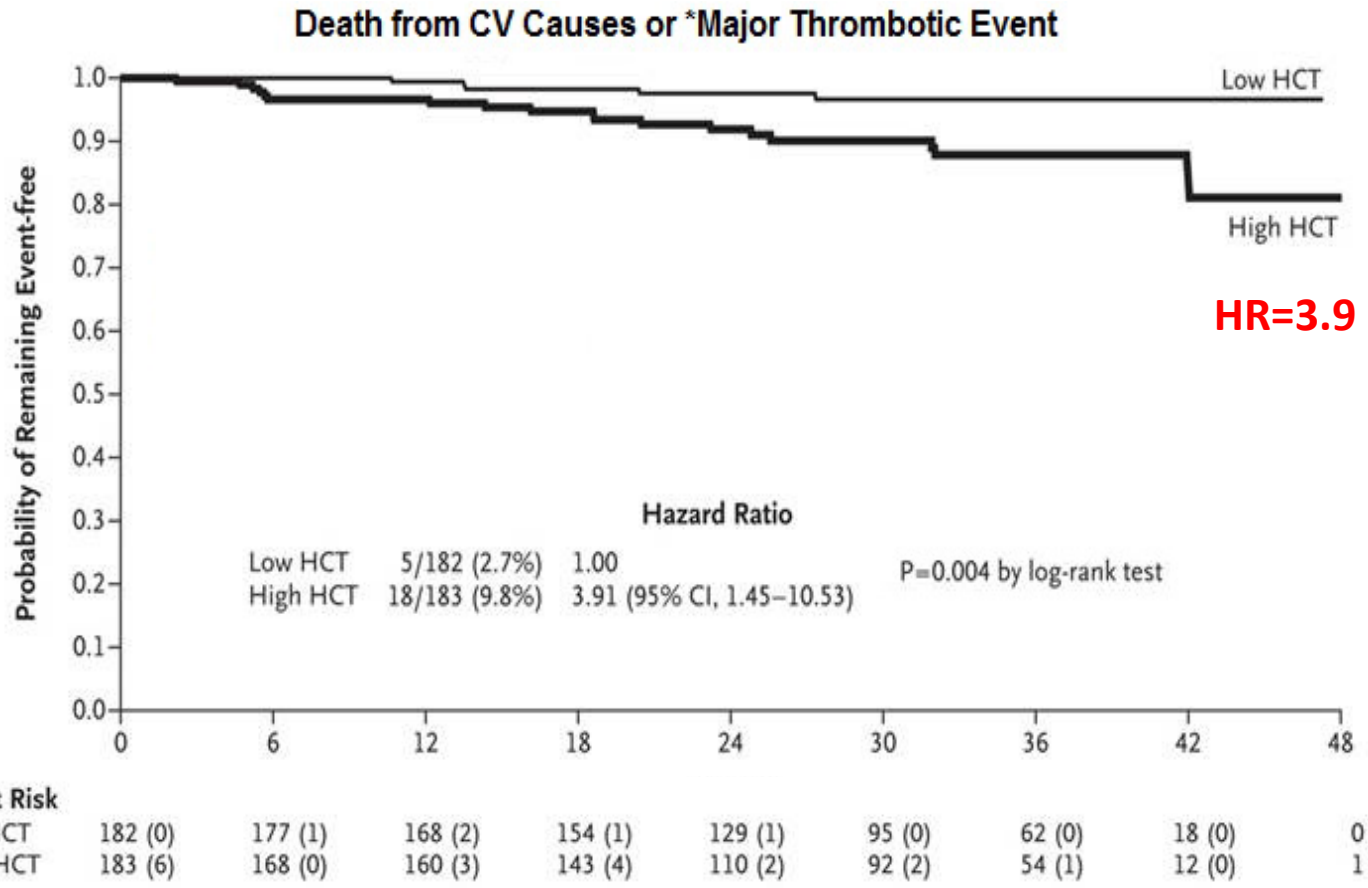
ECLAP TRIAL: RCT ASA vs. Placebo in PV



- 500 PV patients randomized to Aspirin 100 mg daily vs placebo
- Aspirin arm: reduced risk combined endpoint non-fatal arterial and venous thrombosis and 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



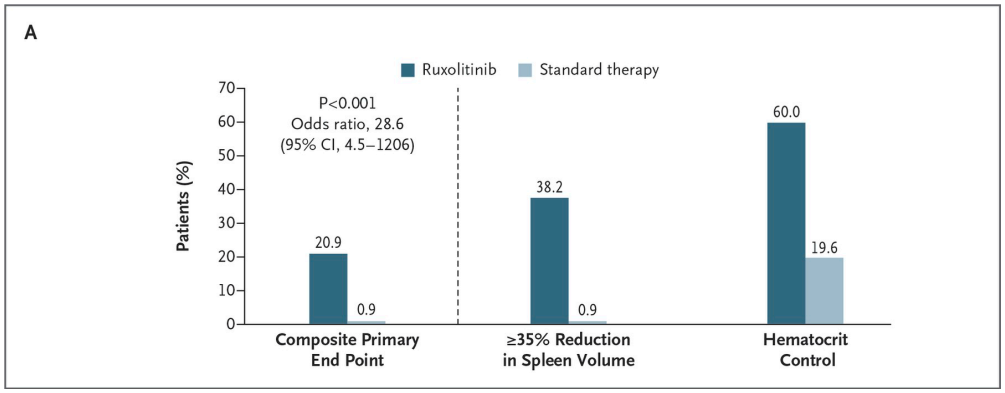
<45%

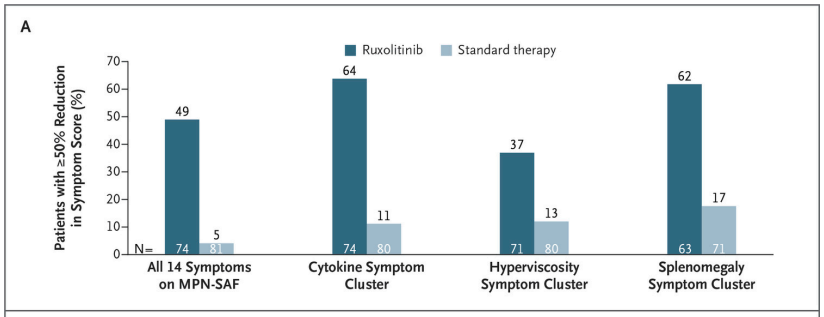
45-50%

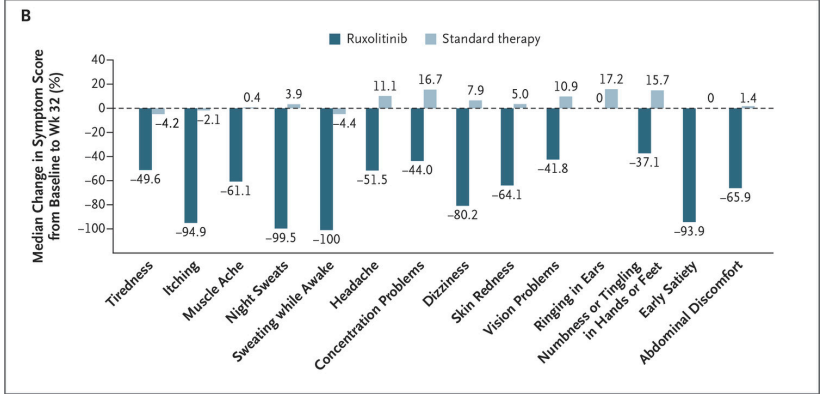
HR=3.9

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

RESPONSE Trial: 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

No thrombotic/transformation outcomes

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

Peginterferon alfa-2a (Pegasys)

- Approved for hepatitis C, used off label for PV/ET
- ORR >80%, 60% of patients CHR, molecular response up to 50%
- AVOID in patients with significant psychiatric history (depression, SI), autoimmune hepatitis, other autoimmune d/o, hepatic decompensation

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

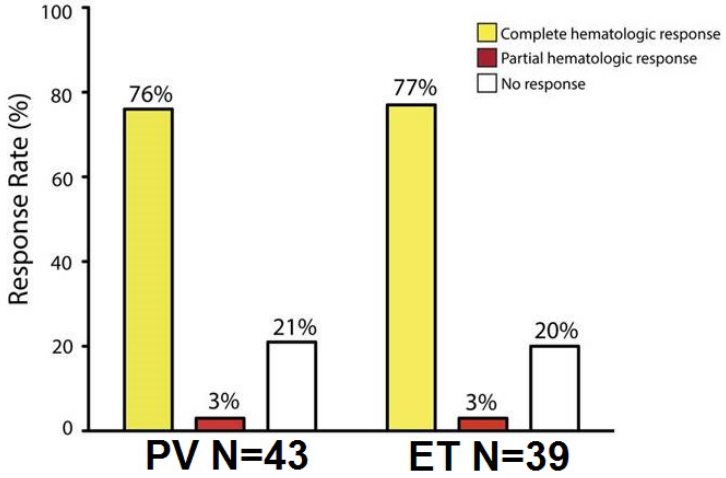
See full prescribing information for complete boxed warning.

- **May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders (5)**

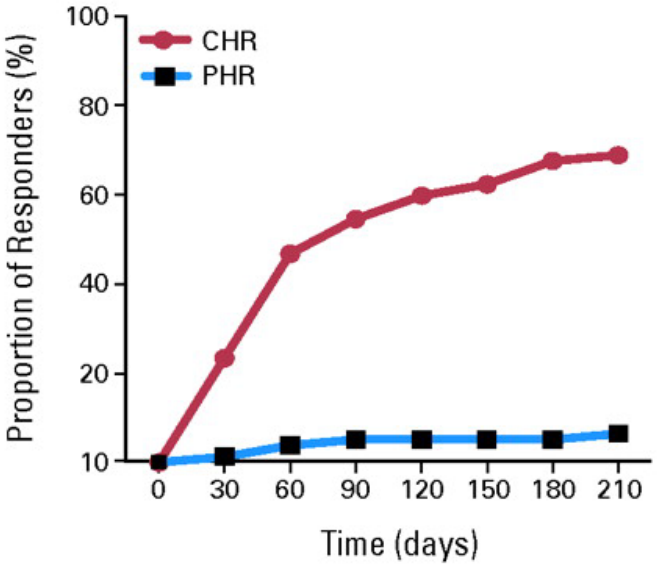
Use with Ribavirin

- **Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients (5.1, 8.1)**

Peginterferon alfa-2a



Hematologic Response



Molecular Response

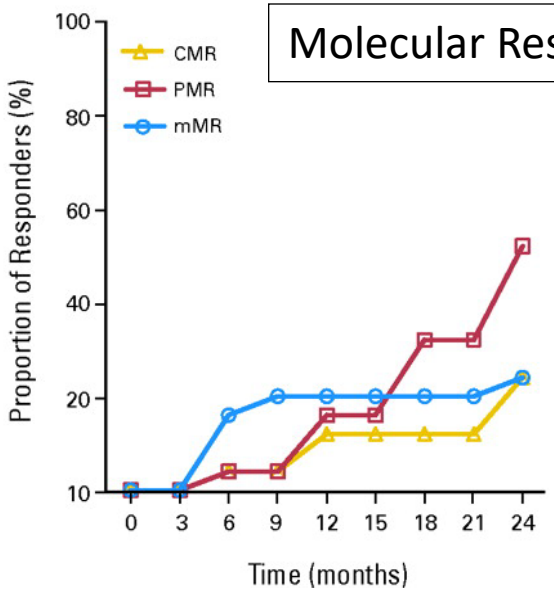


Table 2. Molecular response rates to PEG-IFN-α-2a therapy

*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

Ropeginterferon alfa-2b (BESREMi)

- Next-generation mono-pegylated IFN-α-2b
- Approved in 2021 as BESREMi® for adults with PV
- High tolerability and longer elimination half-life → q 2wks

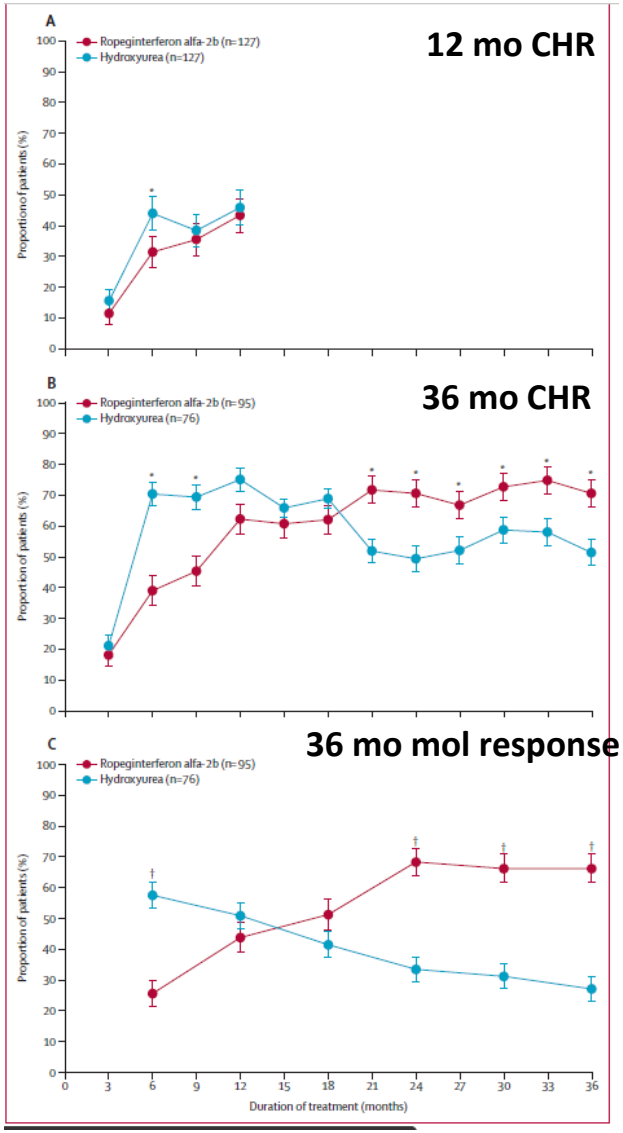
WARNING: RISK OF SERIOUS DISORDERS

See full prescribing information for complete boxed warning.

Risk of Serious Disorders: Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders.

Ropeginterferon alpha-2b: PROUD-PV AND CONTINUATION PV

- Randomized trial of 257 early-stage PV pts (<3 yrs HU) to ropegINF vs. HU (control)
  - Non-inferiority design for CHR and normal spleen size
- PROUD PV: 21% of ropegINF vs 28% HU met primary endpoint [non-inferiority not shown]
- Continuation PV: 71% ropeg vs. 51% HU had hematologic response without spleen criterion (p=0.02)
  - Response to ropegINF increased over time



Gisslinger et al. *Blood* (2015) 126 (15): 1762–1769.
Gisslinger et al. Lancet Haem 2020; 7 (3):e196-208
Kiladjian JJ et al. Leukemia 2022; 36: 1408-1411.

BESREMi side effect profile

Adverse events of special interest

	Ropeginterferon alfa-2b (N=127)	Control (N=127)
Endocrine disorders		
Any adverse event	8 (6%)	2 (2%)
Related to treatment	6 (5%)	0
Psychiatric disorders		
Any adverse event	5 (4%)	6 (5%)
Related to treatment	2 (2%)	1 (1%)
Musculoskeletal and connective tissue disorders		
Any adverse event	2 (2%)	0
Related to treatment	2 (2%)	0
Major cardiovascular and major thromboembolic adverse events		
Any major cardiovascular adverse event	13 (10%); 16 events	8 (6%); 25 events
Major thromboembolic adverse event	4 (3%); 6 events	4 (3%); 4 events
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Any neoplasm	9 (7%); 11 events	10 (8%); 12 events
Leukaemic transformation (acute leukaemia)	0; 0 events	2 (2%); 2 events
Skin cancers related to treatment (basal cell carcinoma and melanoma)	0; 0 events	3 (2%); 3 events

Gisslinger et al. Lancet Haem 2020; 7 (3):e196-208

Interferon side effect profile

	Ropeginterferon alfa-2b (n=127)			Control (n=127)		
	Grade 1–2 *	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	113 (89%)	40 (32%)	3 (2%)	114 (90%)	33 (26%)	1 (1%)
Thrombocytopenia	27 (21%)	3 (2%)	0	36 (28%)	5 (4%)	0
Leucopenia	23 (18%)	3 (2%)	0	28 (22%)	6 (5%)	0
Anaemia	16 (13%)	1 (1%)	0	31 (24%)	2 (2%)	0
Fatigue	17 (13%)	0	0	17 (13%)	1 (1%)	0
γ-glutamyltransferase increased	20 (16%)	9 (7%)	1 (1%)	2 (2%)	2 (2%)	0
Headache	15 (12%)	0	0	16 (13%)	0	0
Diarrhoea	12 (9%)	0	0	14 (11%)	1 (1%)	0
Dizziness	14 (11%)	0	0	10 (8%)	0	0
Alanine aminotransferase increased	16 (13%)	5 (4%)	0	2 (2%)	0	0
Arthralgia	15 (12%)	1 (1%)	0	5 (4%)	0	0
Hypertension	5 (4%)	4 (3%)	0	6 (5%)	5 (4%)	0
Nasopharyngitis	7 (6%)	0	0	13 (10%)	0	0
Nausea	4 (3%)	0	0	15 (12%)	0	0
Aspartate aminotransferase increased	13 (10%)	3 (2%)	0	2 (2%)	0	0
Asthenia	10 (8%)	0	0	6 (5%)	1 (1%)	0
Platelet count decreased	3 (2%)	0	0	12 (9%)	2 (2%)	0
Pain in extremity	10 (8%)	1 (1%)	0	5 (4%)	0	0
Abdominal pain	8 (6%)	0	0	7 (6%)	1 (1%)	0

All adverse events, regardless of causality

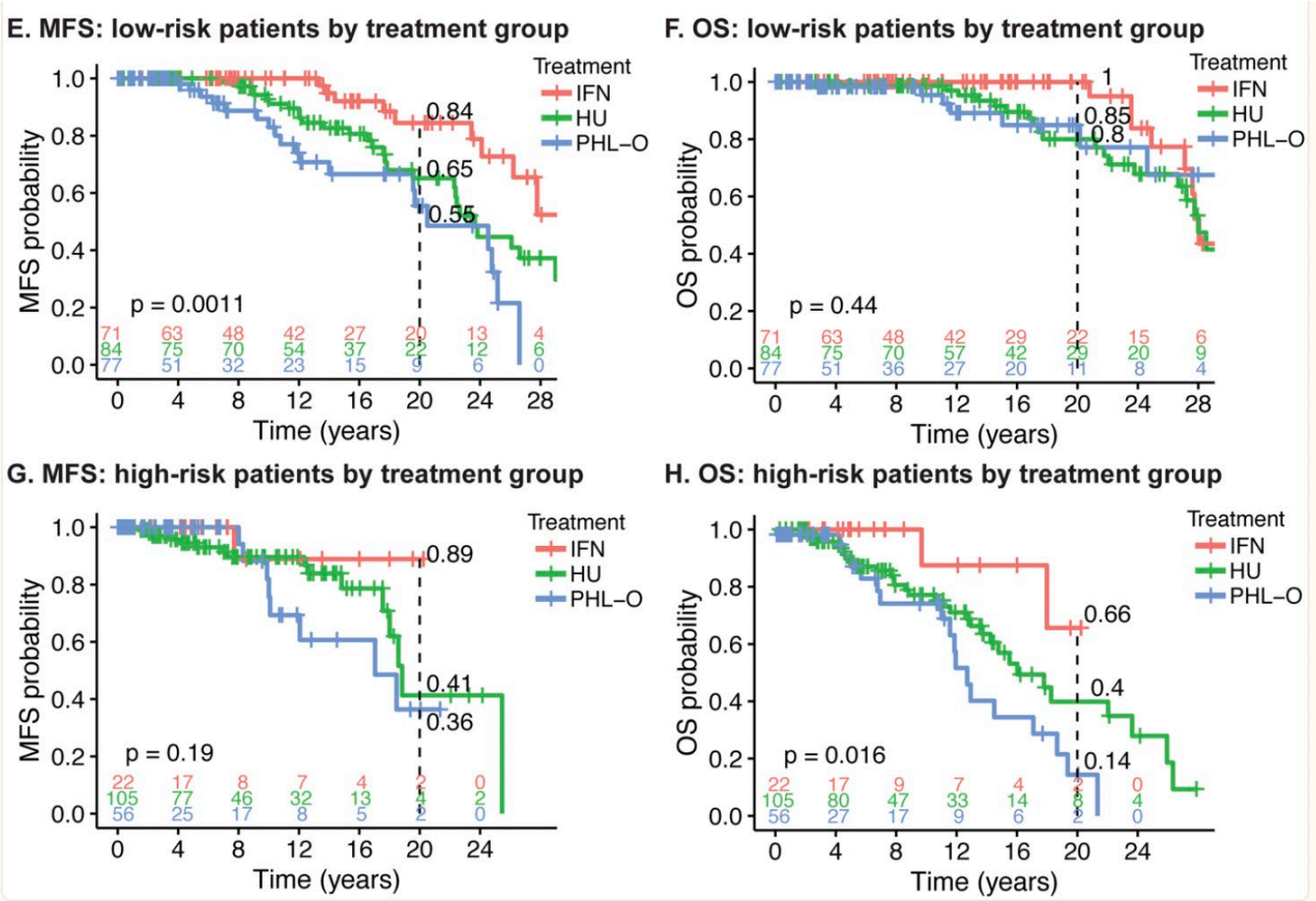
Gisslinger et al. Lancet Haem 2020; 7 (3):e196-208

Do we have data that interferons are disease modifying?

- Limited prospective data
- Randomized clinical trials have more limited follow up than the outcomes of interest (MF & AML transformation, OS) require
  - Crossover on trial
  - Change in therapy after trial
  - Expensive to follow long-term prospectively
- *Clinical endpoints such as hematologic and molecular responses have not been validated as surrogates of MFS or OS*

Disease modification with interferons? Retrospective data

Retrospective study of 470 PV patients, difference baseline ELN Risk



In MV analysis, longer time on rIFNα was associated with a lower risk of myelofibrosis (HR: 0.91, p<0.001) and lower mortality (HR: 0.94, p=0.012)

Ghaith Abu-Zeinah et al. Leukemia. 2021 Mar 2;35(9):2592–2601

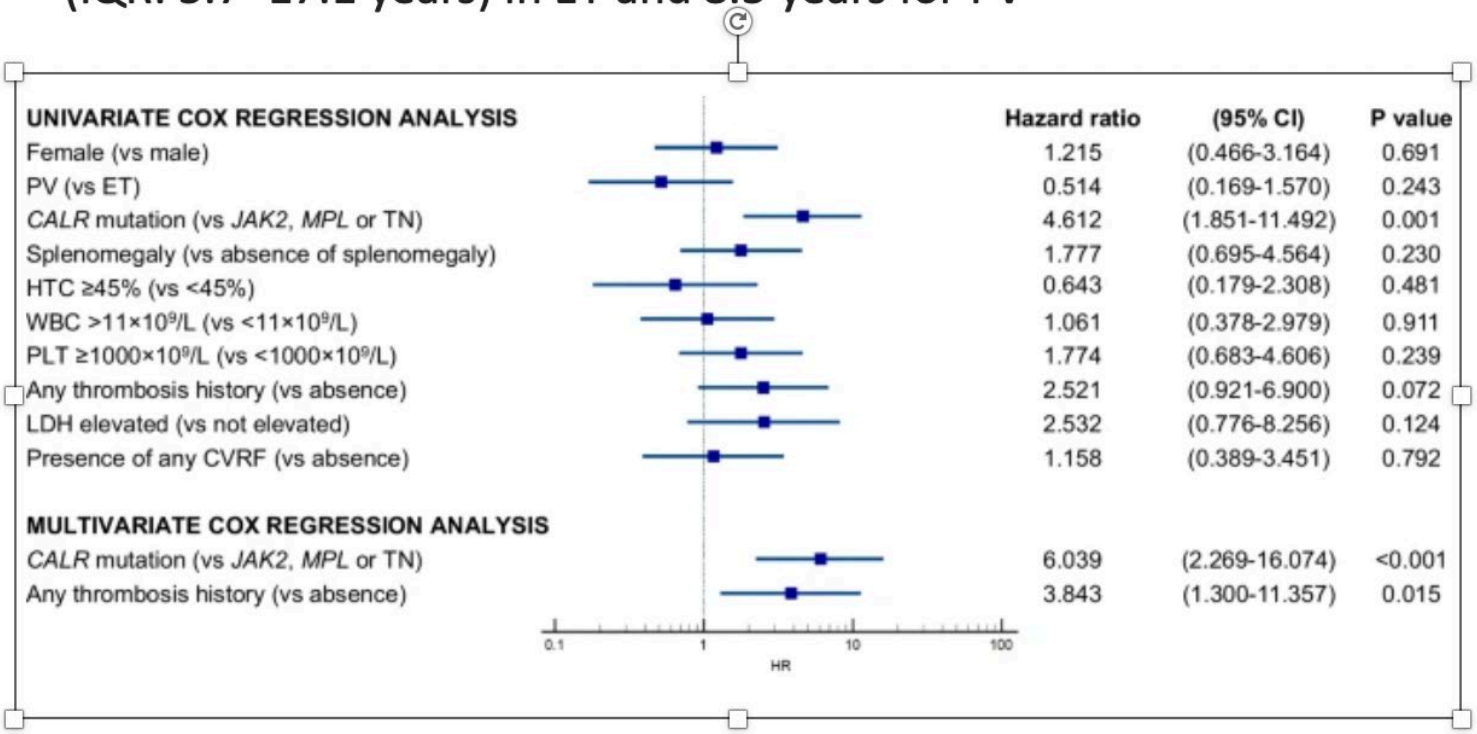
AYA Study evaluating outcomes on different therapy

- Retrospective study of 348 patients (278 ET, 70 PV) dx prior to age 25 (median age 20)
  - For ET: 53% JAK2, 16% CALR, 1% MPL, 30% triple negative; all PV JAK2
  - 68% treated with cytoreduction
- Thrombotic event rate 1.9/100 patient years
- MF transformation 0.7/100 patient years
- Interferon as a first-line treatment significantly improved myelofibrosis-free survival compared to other treatments or no cytoreduction
- Only 1 MDS, no AMLs

Beauverd Y et al. Leukemia 2025; 39: 1135-45.

Evidence for disease modification with interferons

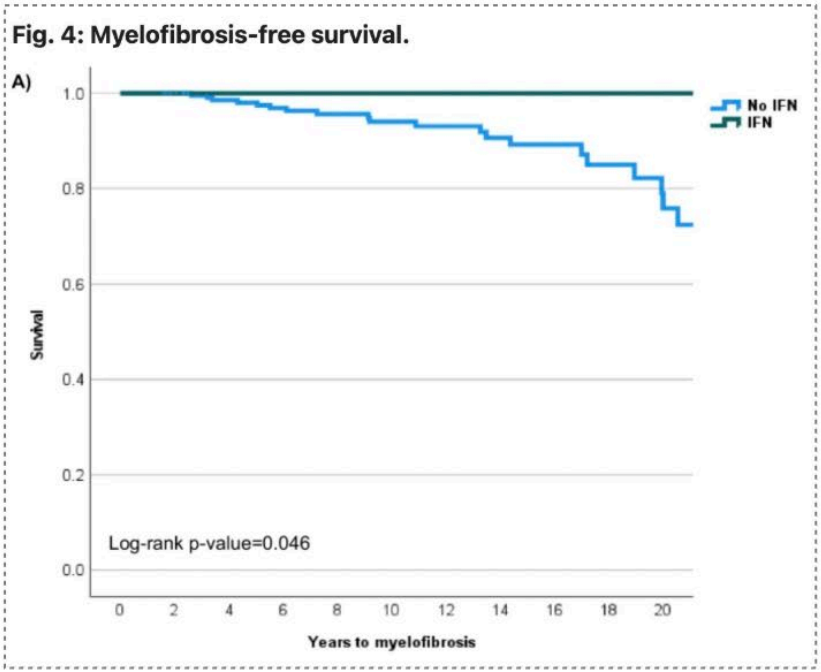
- No significant difference between ET and PV (p = 0.236)
- Median time from diagnosis to sMF progression was 10 years for ET (IQR: 5.7–17.1 years) in ET and 8.5 years for PV

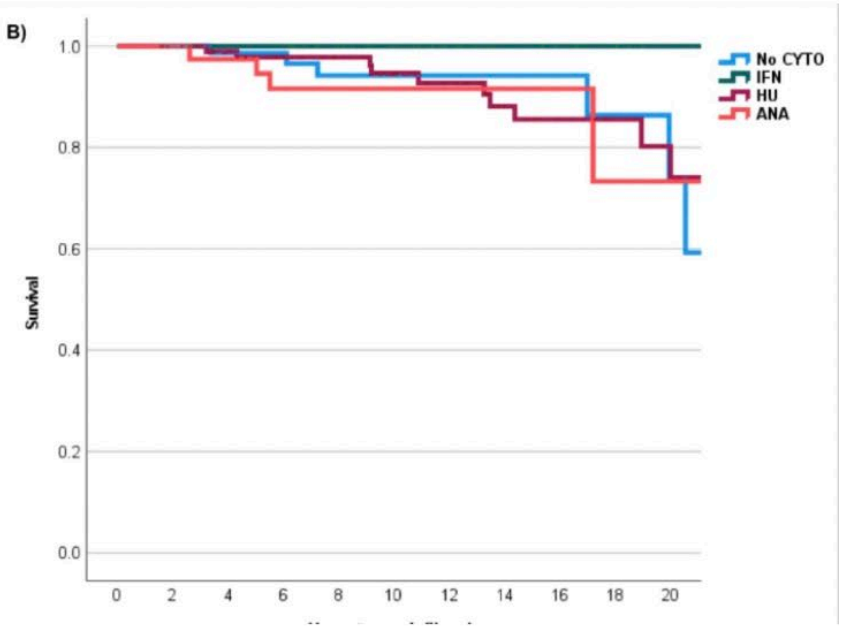


Beauverd Y et al. Leukemia 2025; 39: 1135-45.

Evidence for disease modification with interferons

When comparing IFN with other therapies (HU, ANA or No CYTO), probability of sMF progression was significantly lower in patients treated with IFN ($p = 0.046$)





Beauverd Y et al. Leukemia 2025; 39: 1135-45.

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: 1st Line: Hydroxyurea PegIFN/RopegIFN 2nd Line: Ruxolitinib PegIFN/RopegIFN 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 VW 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 2

- 31 yo F found to have thrombocytosis to 550 k/μL on routine lab check 2010
- BCR-ABL, 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
- Acquired VWF testing negative
- Initiated on Aspirin and PegIFN → plts now 400s, symptoms improved

WHO 2022 ET Diagnostic Criteria

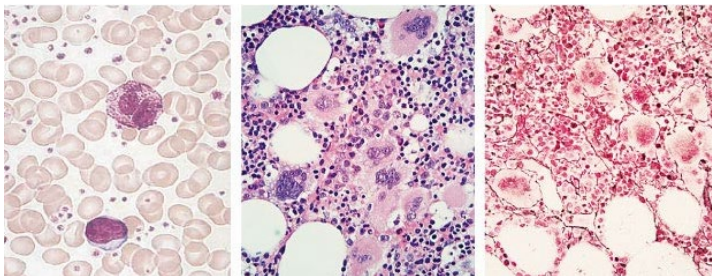
WHO Criteria: ET

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.

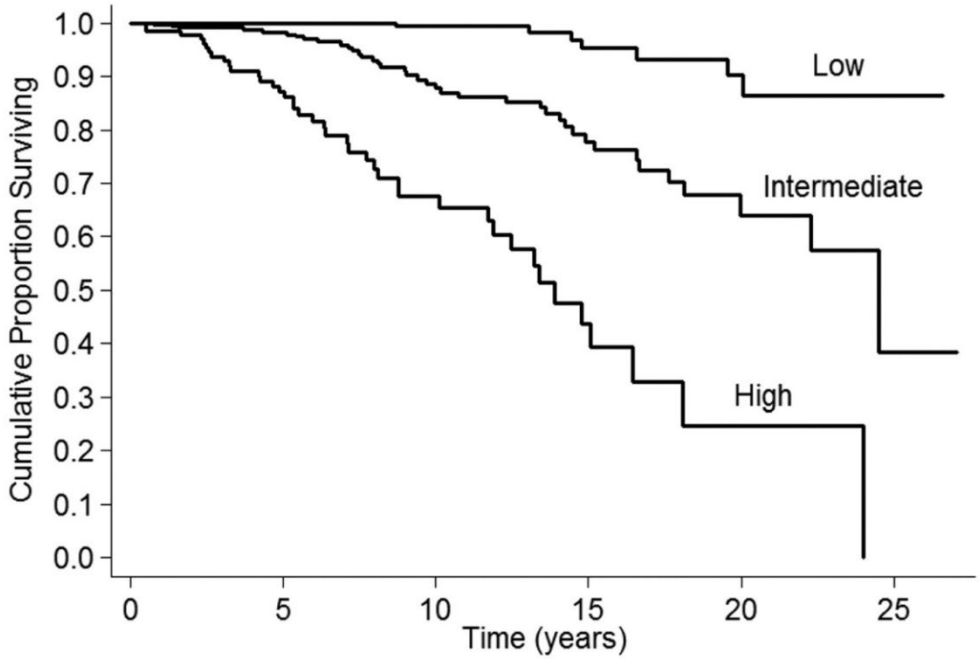
ELN & NCCN Risk Models

Table 2. NCCN and ELN Guidelines for Risk Stratification and Treatment in Patients with Essential Thrombocythemia.*

Guideline	Very Low Risk†	Low Risk†	Intermediate Risk†‡	High Risk
NCCN[33]				
Patient characteristics	Age ≤60 yr, no prior thrombosis, *JAK2* V617F mutation absent	Age ≤60 yr, no prior thrombosis, *JAK2* V617F mutation present	Age >60 yr, no prior thrombosis, *JAK2* V617F mutation absent	Age >60 yr, no prior thrombosis, *JAK2* V617F mutation present
Rate of thrombosis	0.44%/yr, with no cardiovascular risk factors; 1.05%/yr with risk factors	1.59%/yr with no cardiovascular risk factors; 2.57%/yr with risk factors	1.44%/yr with no cardiovascular risk factors; 1.64%/yr with risk factors	2.36%/yr with no cardiovascular risk factors; 4.17%/yr with risk factors
Management of cardiovascular risk factors	Aspirin, 81–100 mg/day for vascular symptoms§	Aspirin, 81–100 mg/day for vascular symptoms§	Aspirin, 81–100 mg/day for vascular symptoms§	Aspirin, 81–100 mg/day for vascular symptoms§
Treatment	Cytoreductive therapy not recommended as initial treatment¶	Cytoreductive therapy not recommended as initial treatment¶	Cytoreductive therapy not recommended as initial treatment¶	First-line therapy with hydroxyurea or interferon alfa-2a or anagrelide, second-line therapy with hydroxyurea, interferon alfa-2a,‖ or anagrelide, or referral to clinical trial
ELN[18]				
Patient characteristics**				
Rate of thrombosis**	—	Score of 0–1, 1.03%/yr	Score of 2, 2.35%/yr	Score ≥3, 3.56%/yr
Management of cardiovascular risk factors	—	Low-dose aspirin for microvascular symptoms§	Low-dose aspirin for microvascular symptoms§	Low-dose aspirin for microvascular symptoms§
Treatment				
First line	—	Cytoreductive therapy not recommended for initial treatment¶	Cytoreductive therapy not recommended for initial treatment¶	First-line therapy, hydroxyurea or interferon alfa-2a
Second line	—	—	—	Cytoreductive therapy with interferon alfa-2a or anagrelide

Tefferi A et al. AM J Hemato 2045. Apr;99(4):697-718.

ET: IPSET Risk Stratification



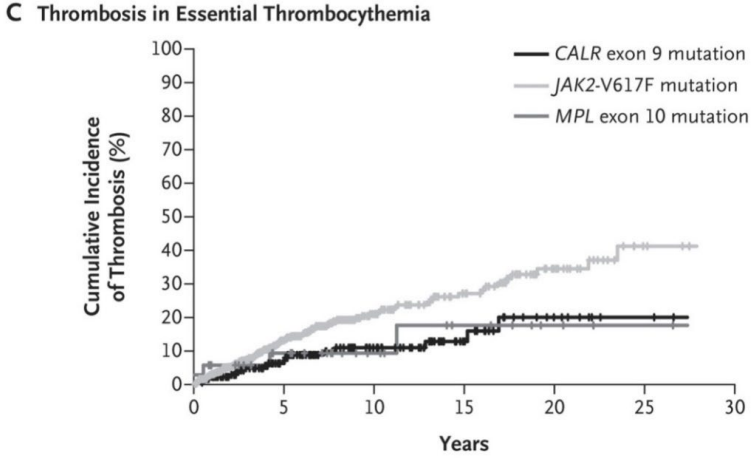
Number at risk						
Low	342	211	123	63	25	3
Intermediate	374	223	109	51	15	2
High	151	84	32	10	2	0

867 patients total

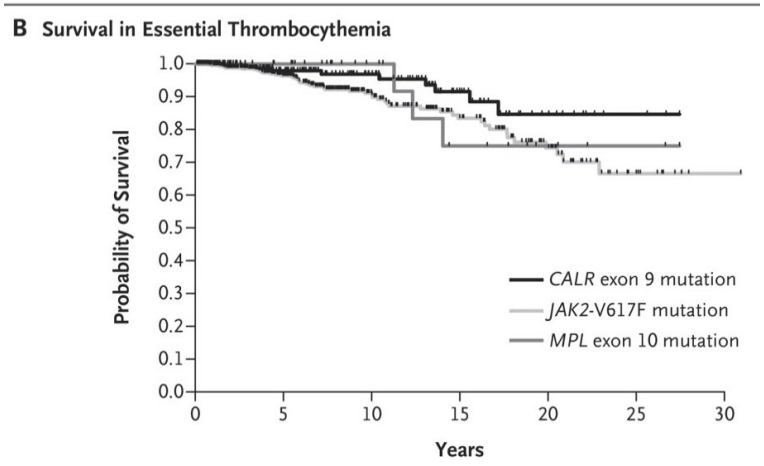
<u>87 patients died</u>
51% thrombosis
10% hemorrhage
17% AML/MDS
22% other cancer

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



No. at Risk							
CALR mutation	186	115	63	27	9	3	0
JAK2 mutation	575	267	116	62	25	5	0
MPL mutation	35	21	13	8	4	2	0



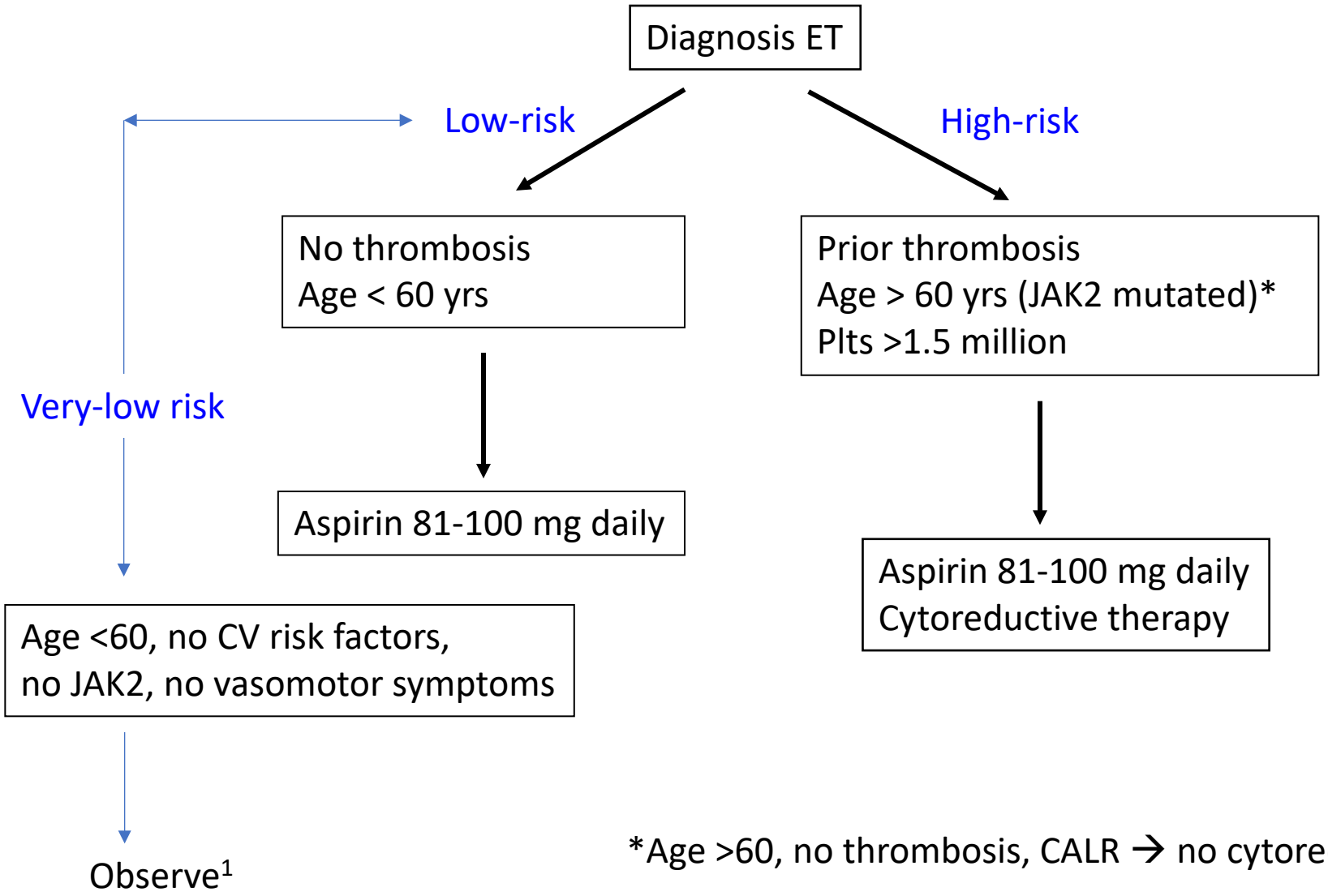
No. at Risk							
CALR mutation	186	122	71	33	11	3	0
JAK2 mutation	576	310	145	83	42	10	1
MPL mutation	35	25	14	8	4	2	0

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

ET: Treatment Options

- Observation
- Aspirin
- Hydroxyurea
- Interferons- pegylated interferon
- Anagrelide
- ~~JAK inhibitors~~

Treatment Recommendations for ET

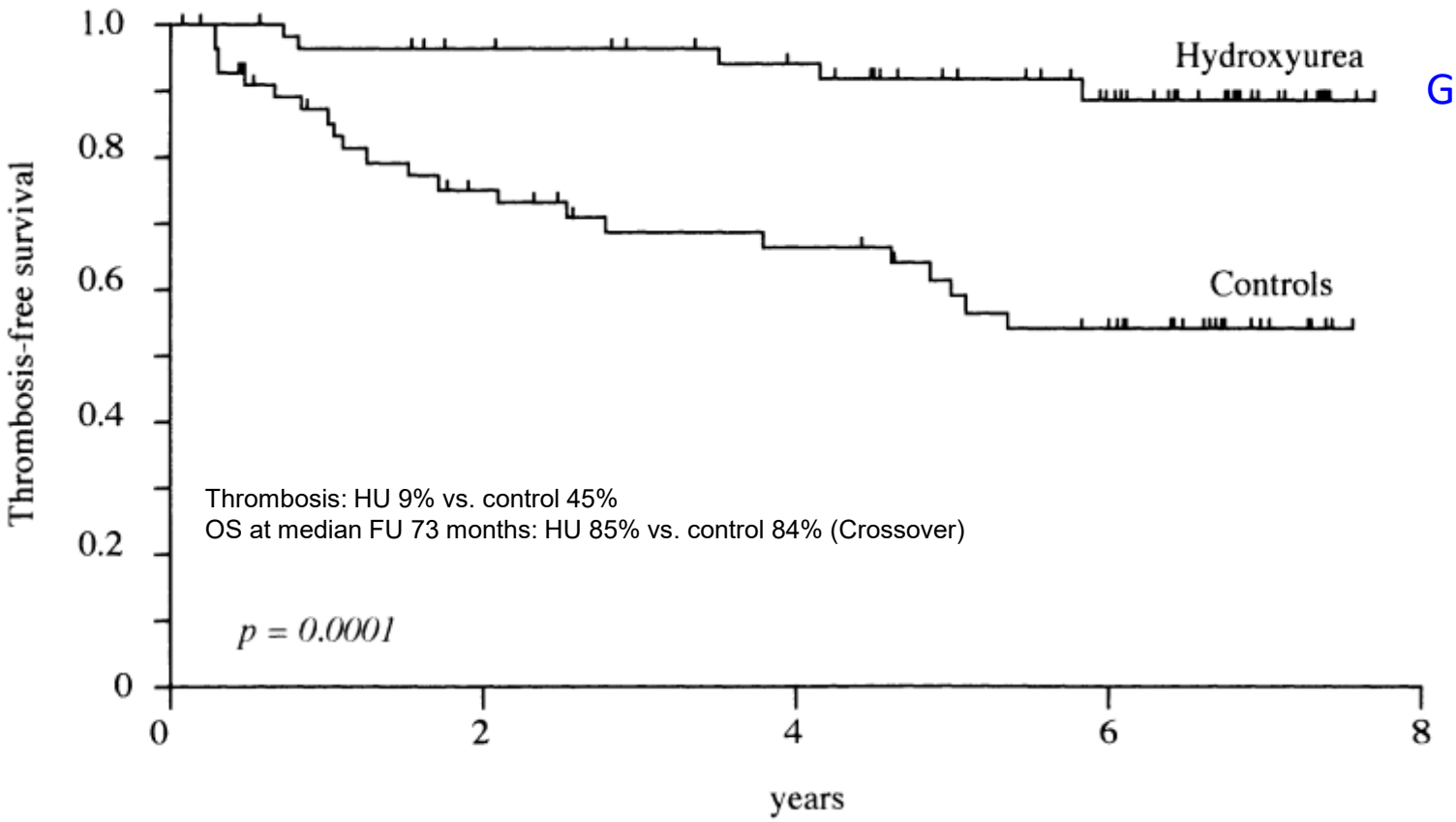


*Age >60, no thrombosis, CALR → no cytoreduction?

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

Hydroxyurea in High-Risk ET: RCT



Goal plt <600K

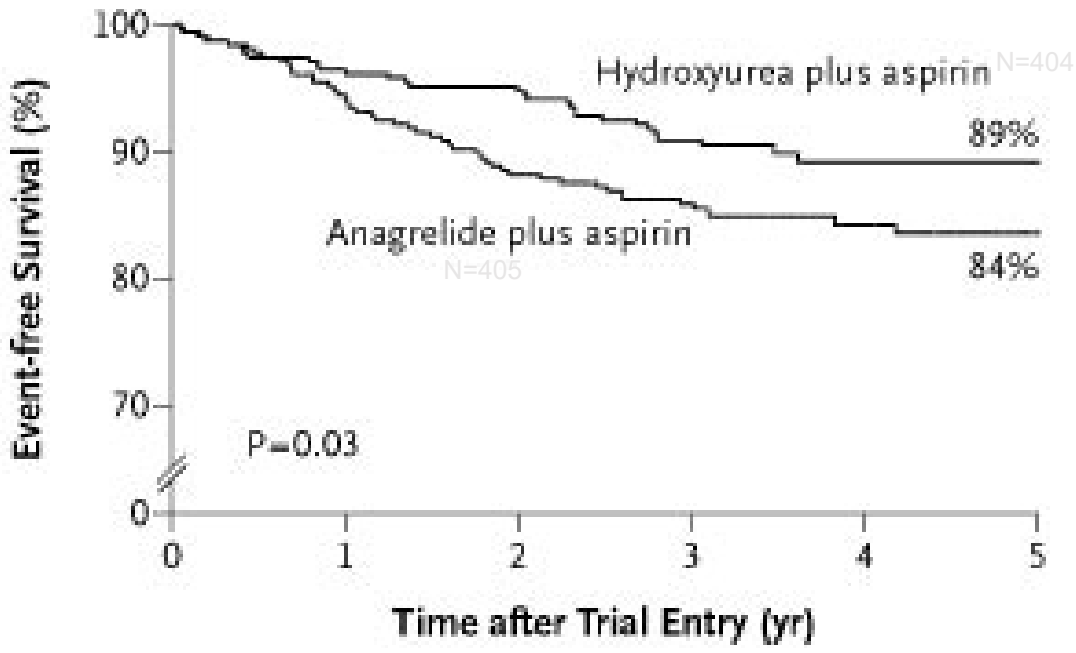
Age > 60 or previous thrombosis and plt ≤ 1.5 million

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

Hydroxyurea vs. Anagrelide (+ASA)

Anagrelide inhibits megakaryocytic differentiation, does cause anemia, does not affect WBC

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



No. at Risk						
Hydroxyurea plus aspirin	404	388	298	204	129	57
Anagrelide plus aspirin	405	379	272	190	119	52

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%, odds ratio 2.9, 95% CI 1.2-6.9)

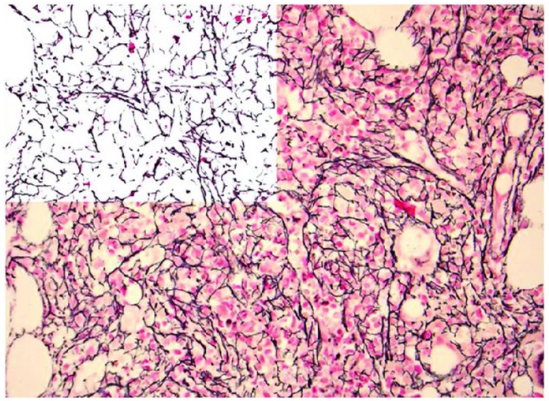
Harrison et al. *N Engl J Med*. 2005;353:33-45. Gisslinger et al. Blood. 2013;121:1720-1728

Case 3

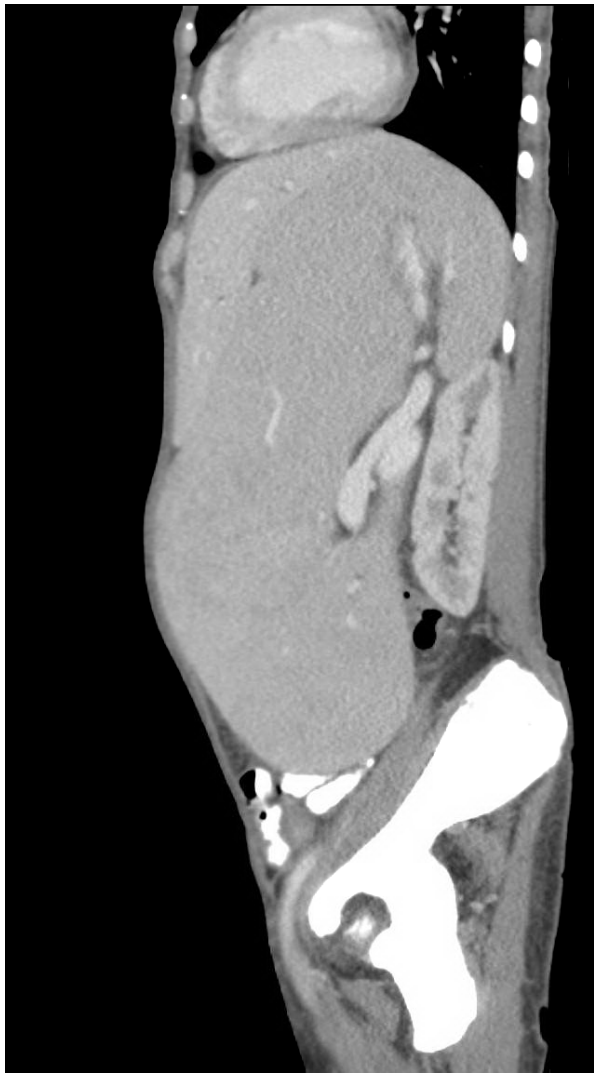
55 yo F with no PMH p/w bilateral leg swelling and DOE. Did not respond to herbal tea/supplements/CBD oil

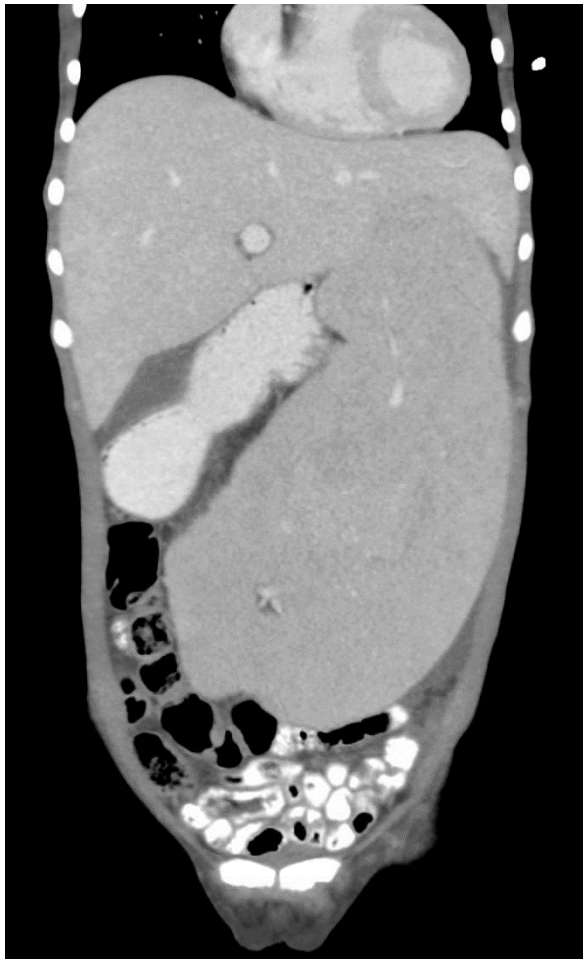
- ROS: 20 lb wt loss/2 months, night sweats
- PE: tachycardia, holosystolic murmur, JVD, LE edema, splenomegaly
- Labs: Hgb 3.4 g/dL, WBC 5.9 K/uL, plts 79 k/μL, anormal BMP
- Normal iron stores, no hemolysis
- Smear: tear drop cells
  - → 13 units of PRBCS
  - Bone marrow biopsy:

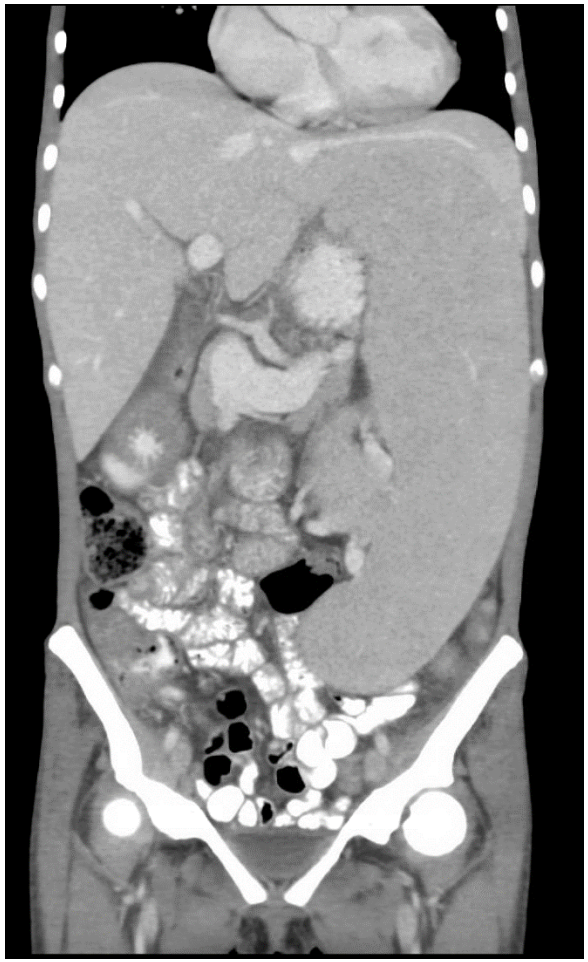
    Hypercellular 90%; Megakaryocytic atypia
    WHO Grade 3/3 fibrosis
    No increased blasts on morphology or flow
    Cytogenetics: 46, XX, del(7)(q11.2q22)[4]/46, XX[2]
    + JAK2 V617F and ASXL1 mutation



CT Abdomen







WHO 2022 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.

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

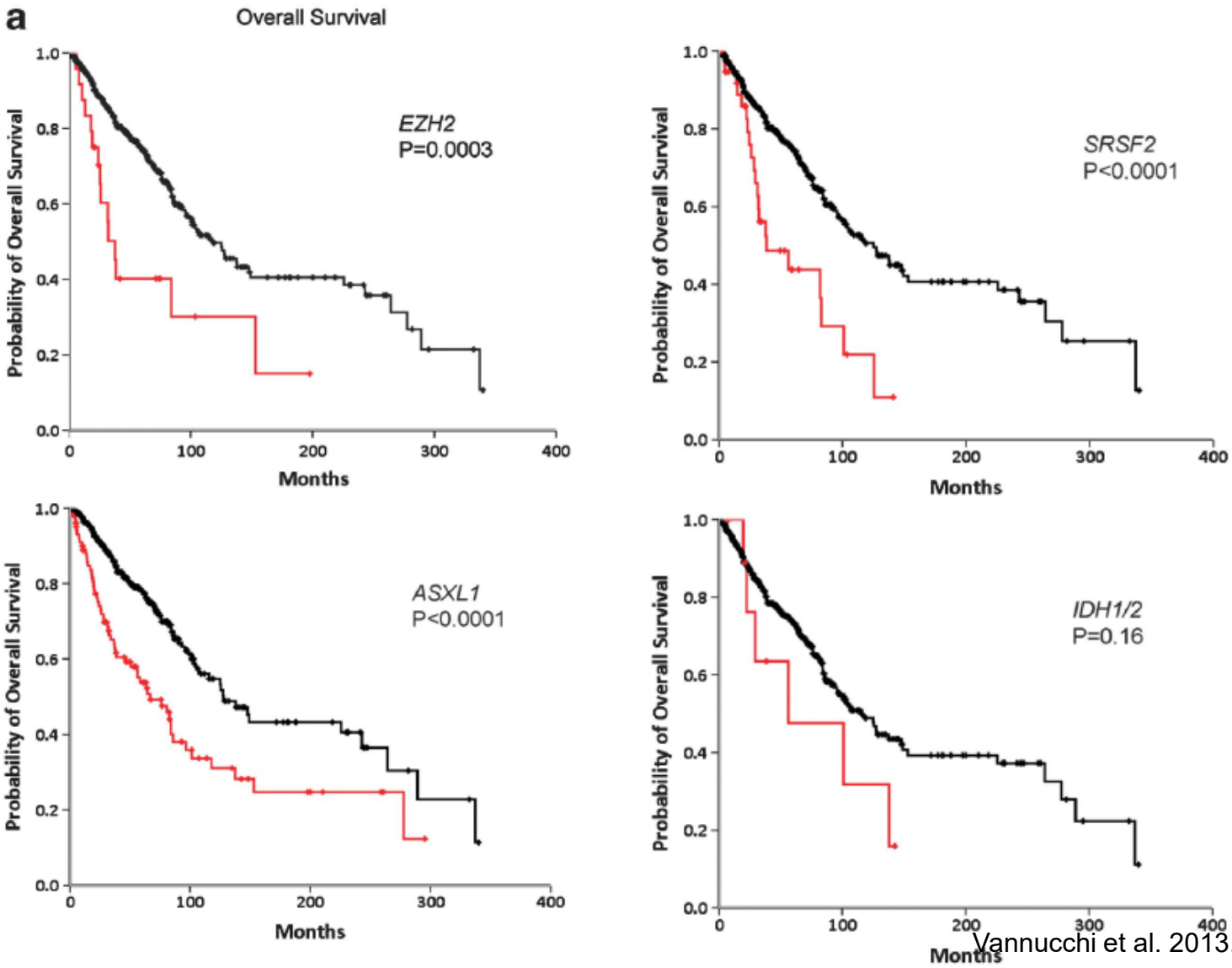
*+8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3) or 11q23 rearrangement ^ any abnormal karyotype other than normal or sole abnormalities in 20q-, 13q-, +9, chromosome 1 translocation/duplication, -Y or sex chromosome abnormality other than –Y

https://pmfscorescalculator.com/

Tefferi A et al. JCO 2018; 36 (17): 1769-1770

Overall Survival by Mutation

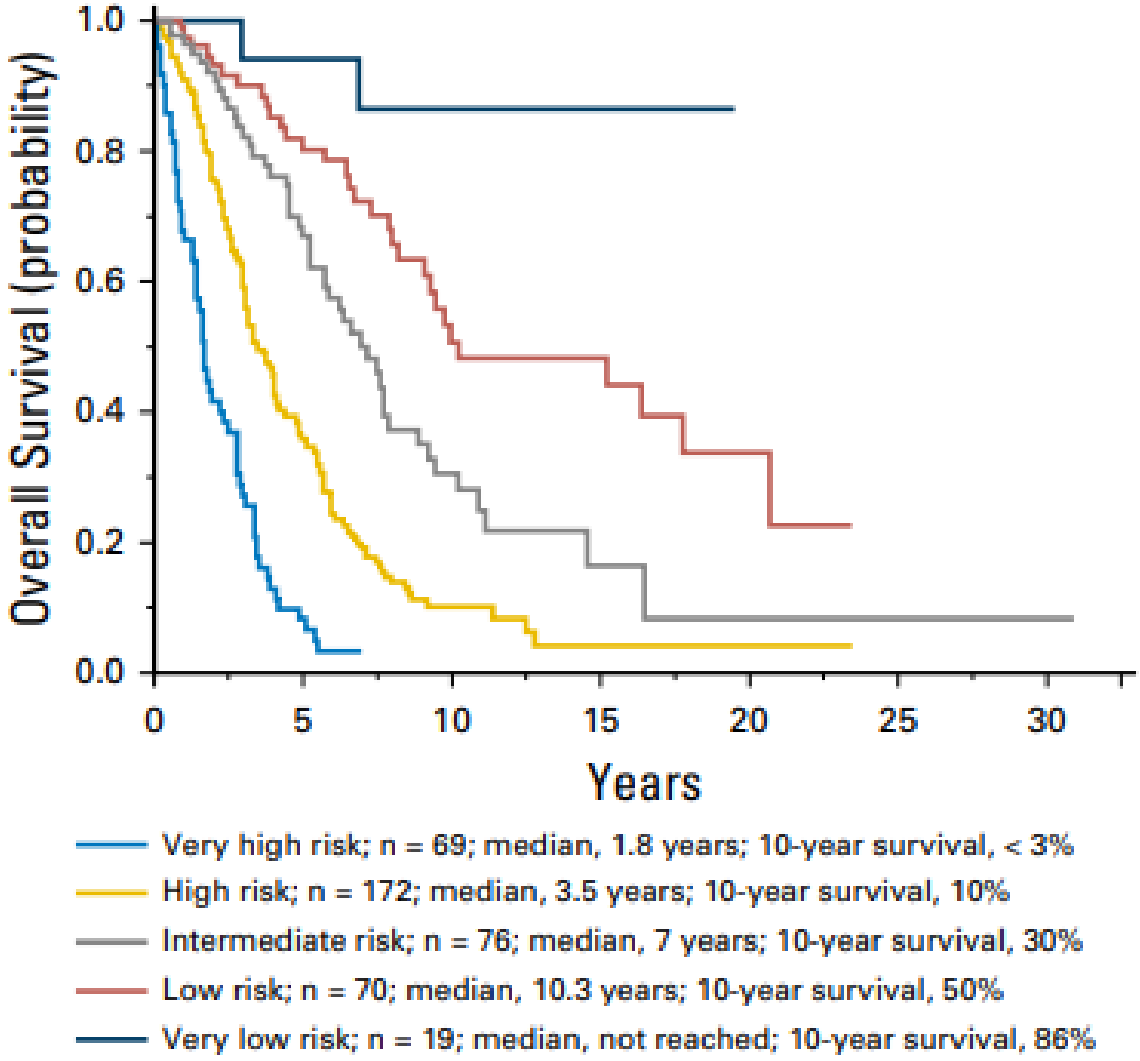
Mutations in “non-driver” genes are found in >50% MF patients



*High risk mutations for MIPSS70+ include ASXL1, EZH2, SRSF2, IDH1/2 and U2AF1

Vannucchi et al. 2013. Leukemia. 27: 1861

Survival by MIPSS70+ score



JCO 2018: 36 (17): 1769-70

MF Treatment Options

- Active surveillance in low-risk disease

OLDER APROACH

- Hydroxyurea for proliferative disease, splenomegaly
- Anemia: ESAs, lenalidomide/prednisone, danazol

NEWER APROACH

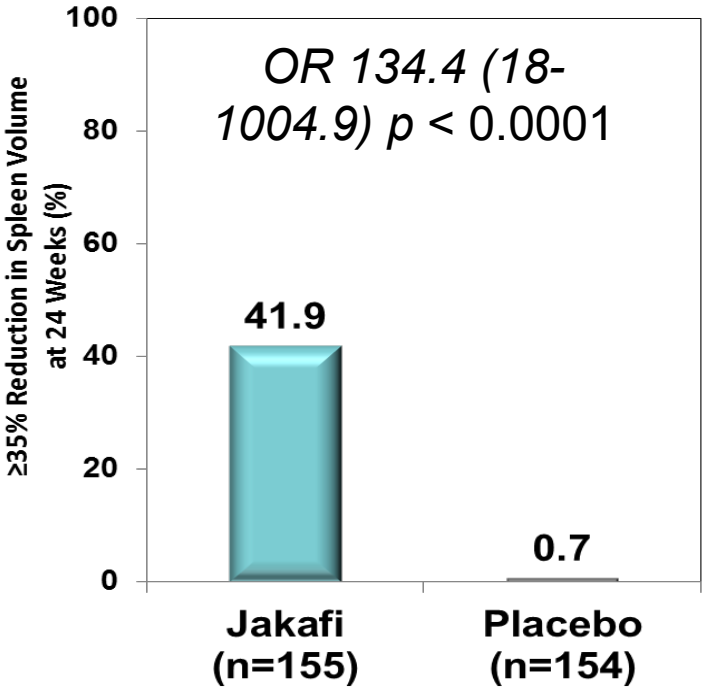
- Ruxolitinib- JAK1/2 inhibitor: int/high-risk MF; best for splenomegaly, constitutional symptoms, pruritic
- Fedratinib- JAK2 inhibitor; int/high-risk MF, plts >50
- Pacritinib- JAK2/IRAK2/FLT3/ACVR1 inhibitor; int/high-risk MF, plts <50
- Momelotinib- JAK1/JAK2/ACVR1 inhibitor: int/high risk MF with anemia
- Allogeneic stem cell transplant for higher risk disease (generally DIPSS int-2 and high-risk)

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

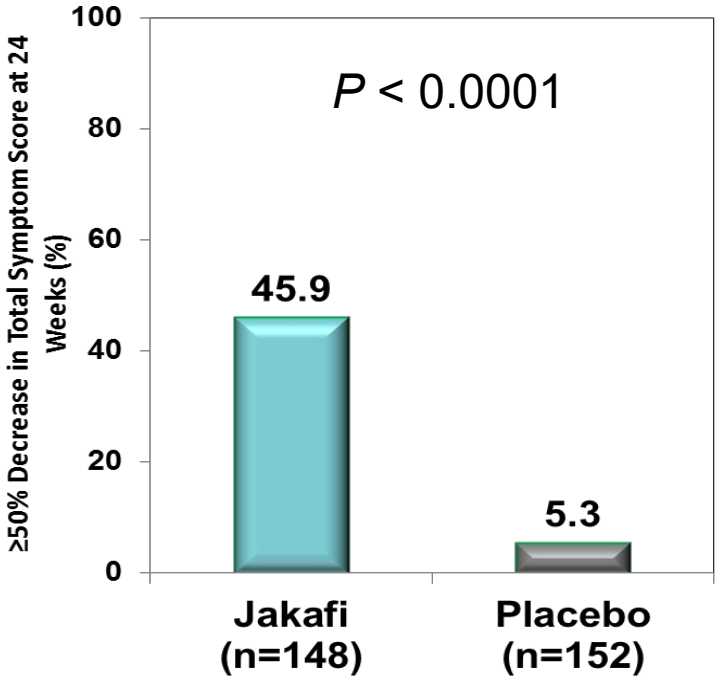
COMFORT-1 : MF patients randomized to ruxolitinib or placebo

Ruxolitinib was associated with significantly decreased spleen volume and improvement in TSS score compared to placebo

Decrease Spleen volume



Improvement MF Symptoms

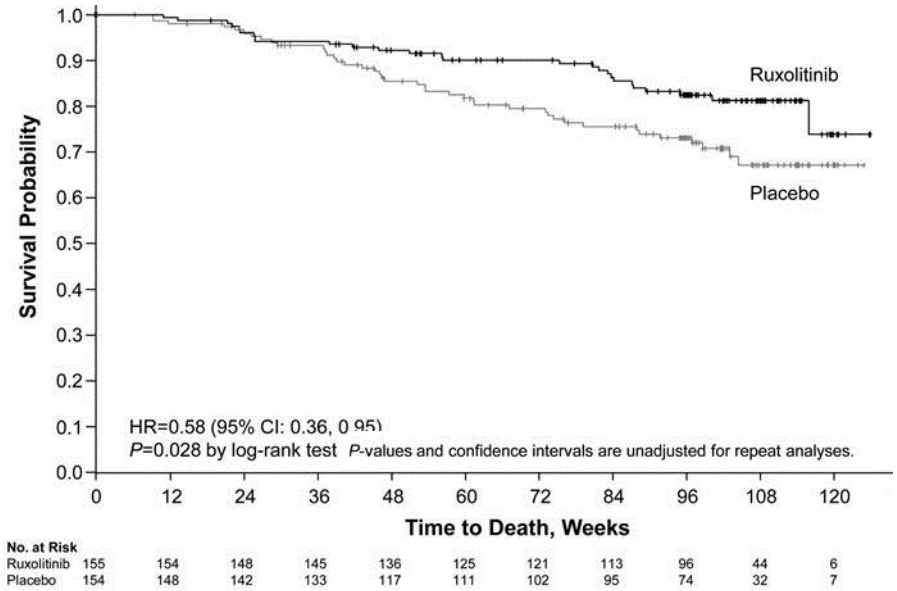


Verstovsek et al. *N Engl J Med.* 2012;366:799-807
Scherber et al. *Blood.* 2011;118:401-408

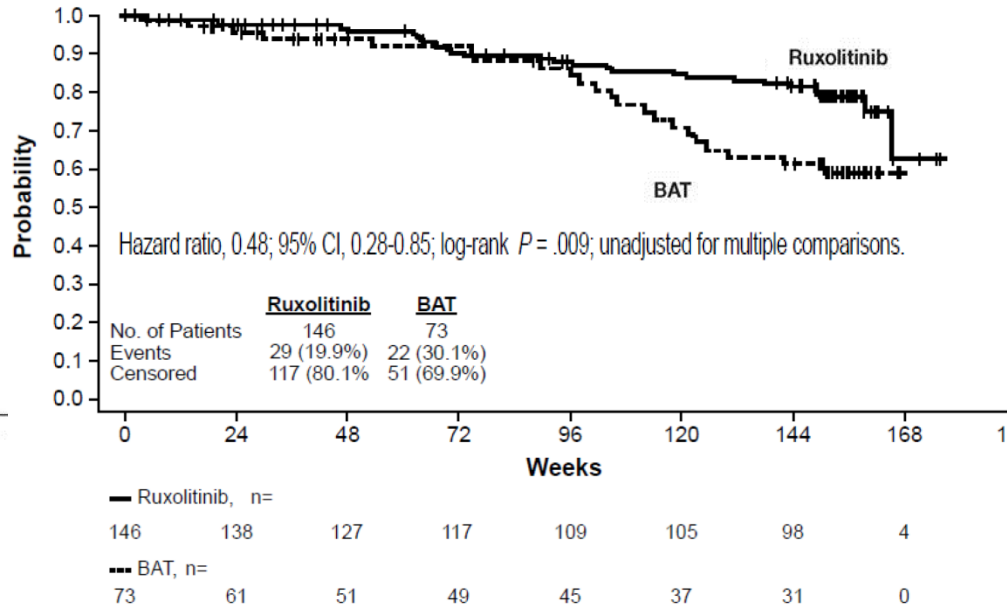
Comfort 2: MF patients randomized to ruxolitinib vs. BAT

Compared to BAT, ruxolitinib as associated with a HR for death at 3 years of 0.48, p=.009

COMFORT 1



COMFORT 2

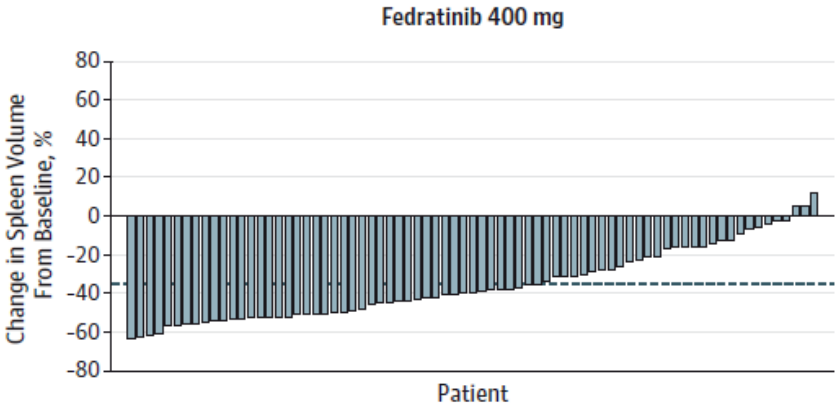


BAT= hydroxyurea or steroids

Harrison et al. NEJM 2012; 366: 787-798. Cervantes et al. Blood 2013; 122: 4047-4053. Harrison et al. Leukemia 2016; 30: 1701-1707.

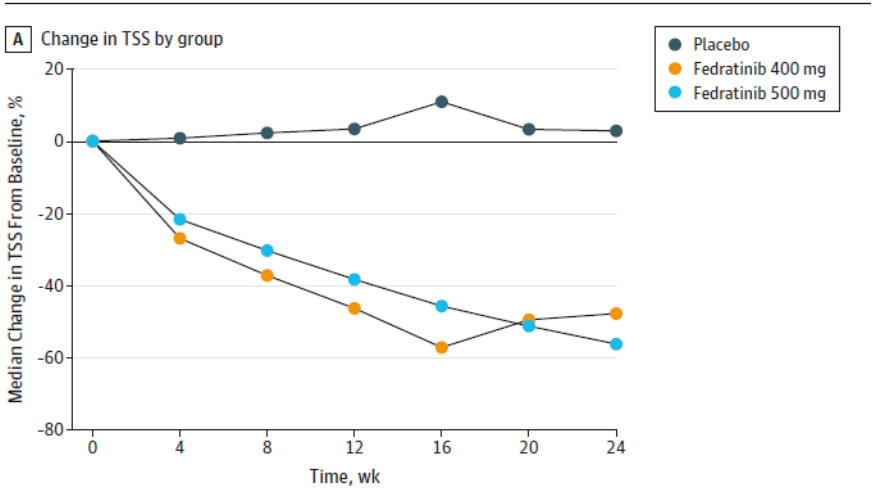
Fedratinib: JAKARTA 1 and 2 Trials

JAK2-selective inhibitor
JAKARTA 1: randomized, placebo controlled, untreated MF
JAKARTA 2: single arm, Rux resistant MF



37% of patients had >35% spleen volume reduction vs. 1% placebo;
med duration 18 months

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



In Rux-resistant patients, open label-trial, 55% spleen response and 26% symptom response.

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

Fedratinib side effects

Adverse Reactions	Fedratinib 400/500 mg (n=96/n=97)		Placebo (n=95)	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Hematologic				
Thrombocytopenia	63/57	17/27	51	9
Anemia	99/98	43/60	91	25
Neutropenia	28/44	8/1		
Nonhematologic				
Diarrhea	66/56	5/		
Vomiting	42/55	3/		
Nausea	64/51	0/		
Constipation	10/18	2/		
Asthenia	9/16	2/		
Abdominal pain	15/12	0/1	16	1
Fatigue	16/10	6/5	10	0
Dyspnea	8/10	0/1	6	2
Weight decrease	4/10	0/0	5	0

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

- FDA placed a clinical hold on fedratinib in 2013 due to 8 patients across studies experiencing neurologic symptoms (Wernicke's encephalopathy)
- After clinical review, hold was lifted with black box warning for encephalopathy
- Check thiamine (B1) levels prior to starting and intermittently in patients with risk factors such as poor nutrition

1. Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651. **2.** Mullally A, et al. *Blood Adv*. 2020;4(8):1792-1800.

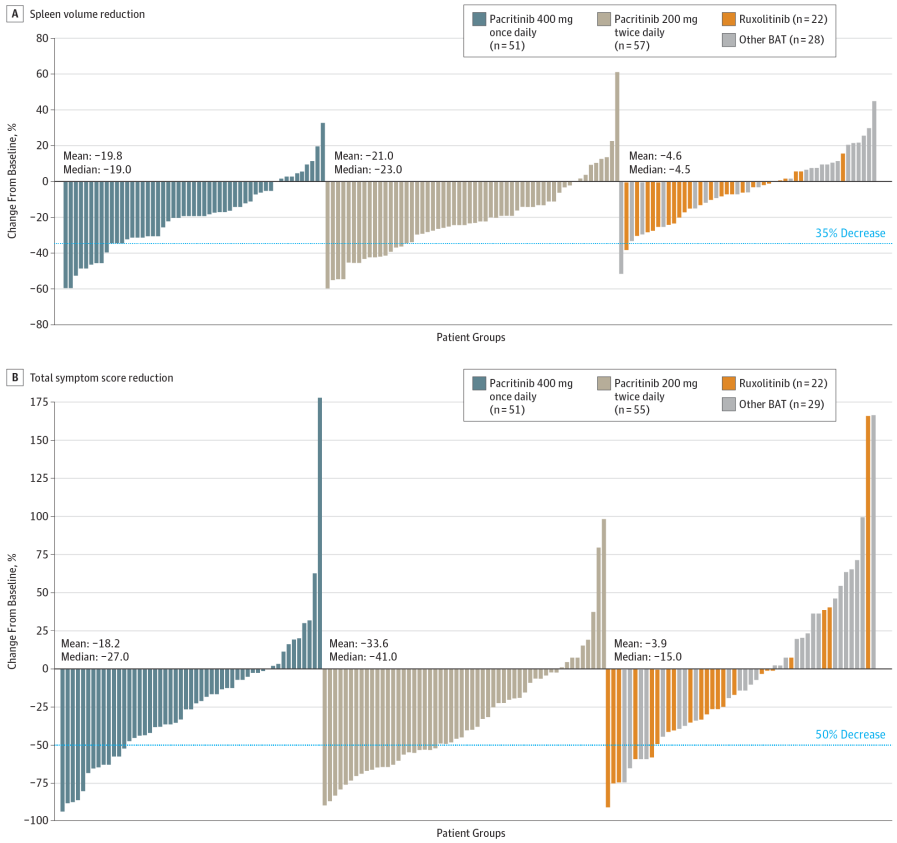
PERSIST STUDIES led to approval of pacritinib for MF

- Pacritinib is a JAK2/FLT3 inhibitor approved for intermediate or high-risk myelofibrosis in patients with a platelet count <50K
- Development put on hold (to gather more data particularly on dosing) in 2016 amid PERSIST-2 over concerns for excess bleeding and CV deaths
- Dose finding studies (PAC203) then found dosing of 200 mg BID to have the most clinical efficacy balanced with safety profile
- Ongoing PACIFICA study: Phase 3 trial pacritinib 200 mg BID vs. physician choice

Mascarenas et al. JAMA Ocology 2018; 4 (5): 652-659; Gerds et al. Blood Adv 202-; 4 (22): 5825-5835

PERSIST-2

- Phase 3, randomized MF patients (prior rux allowed) to pacritinib vs BAT= 45% Rux, 19% HU, 19% observation
- Pacritinib was more effective than BAT for >35% spleen volume reduction: 18% vs 3%
- Greater rate of >50% reduction in total symptom score: 25% vs 14% (NS)
- Clinical improvement in hemoglobin and reduction in transfusion burden were greatest with pacritinib 200 mg twice daily (24% transfusion independent vs 5% BAT)



Mascarenas et al. JAMA Ocology 2018; 4 (5): 652-659;

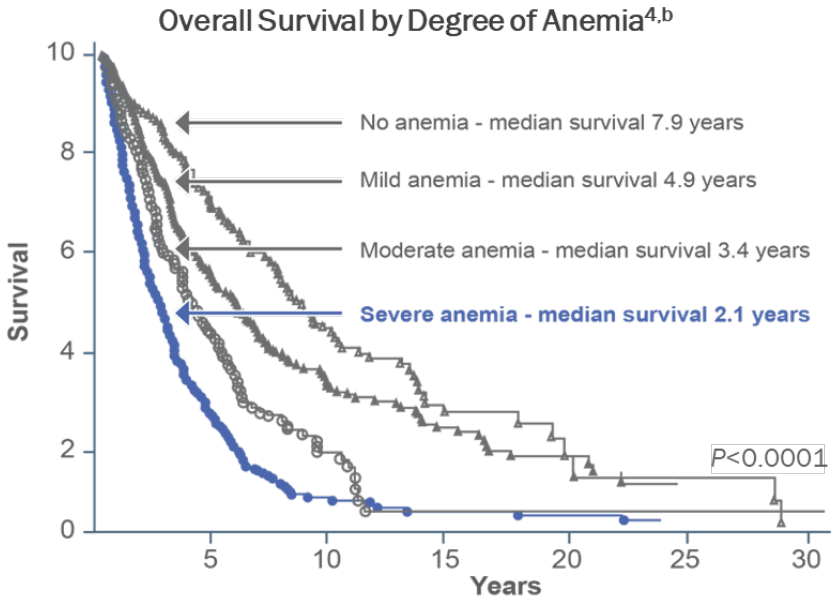
Pacritinib Side effects

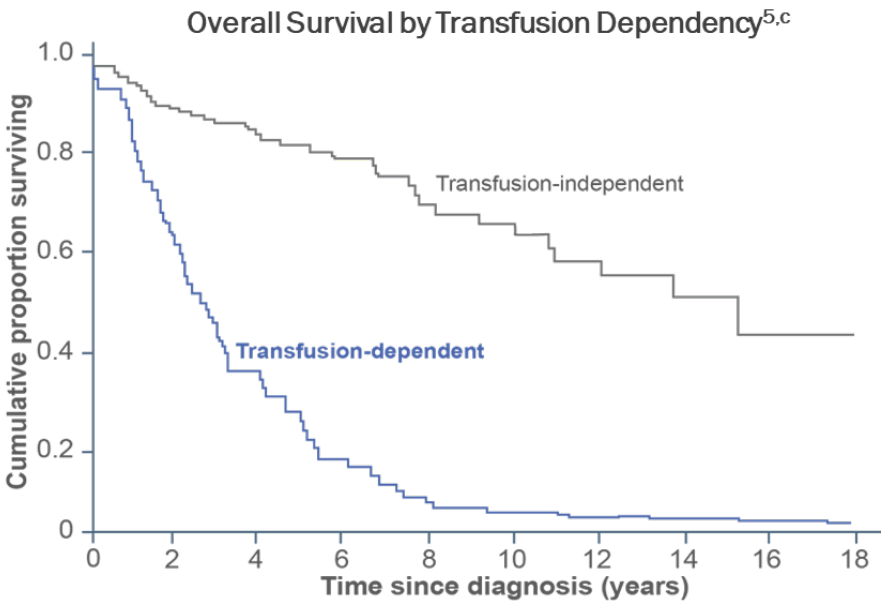
- Gastrointestinal (GI): diarrhea, nausea
  - Early on, typically resolves, supportive care
- Low blood counts- anemia/thrombocytopenia
- Swelling
- Fatigue
- No neurologic symptoms

- Ongoing PACIFICA study: Phase 3 trial pacritinib 200 mg BID vs. physician choice in cytopenic MF

Anemia is an ongoing challenge in MF

- Anemia and RBC transfusion dependance are poor prognostic factors; DIPSS-Plus and MIPSS
- Currently available JAK inhibitors can worsen anemia

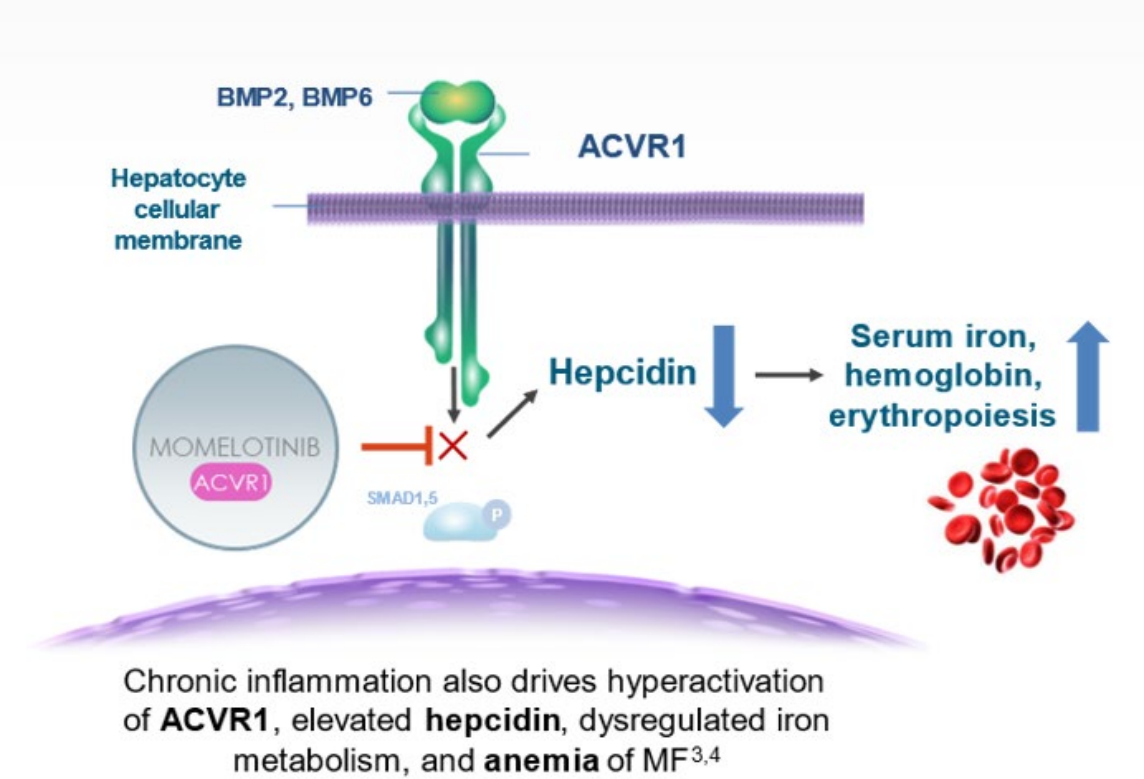




1. Cervantes F, et al. *Blood.* 2009;113(13):2895-2901. 2. Passamonti F, et al. *Blood*. 2010;115(9):1703-1708. 3. Tefferi A, et al. *Mayo Clin Proc*. 2012;87(1):25-33. 4. Nicolosi M, et al. *Leukemia.* 2018;32(5):1254-1258. 5. Elena C, et al. *Haematologica.* 2011;96(1):167-170.

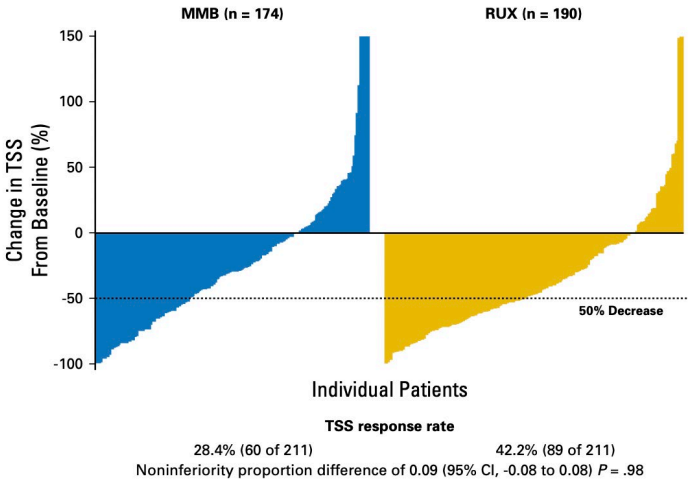
Momelotinib

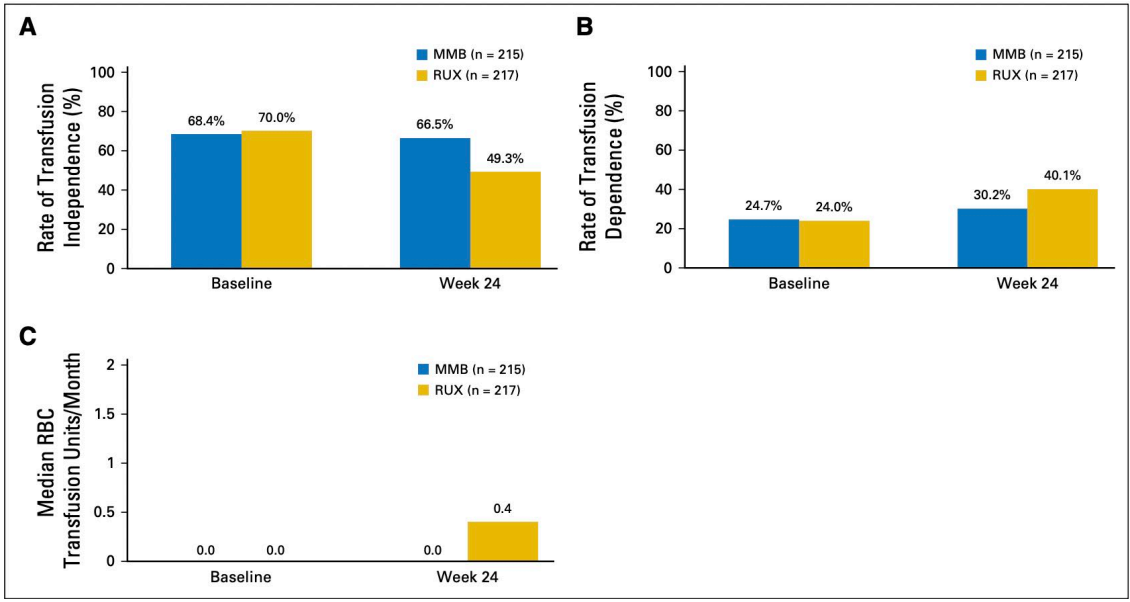
- JAK-STAT signaling drives overproduction of inflammatory cytokines
- Momelotinib inhibits ACVR1 in addition to the JAK-STAT pathway →increase in circulating iron and Hgb and stimulates erythropoiesis
- *Pacritinib, currently approved for MF with plts <50K, also inhibits ACVR1 (and IRAK1)*

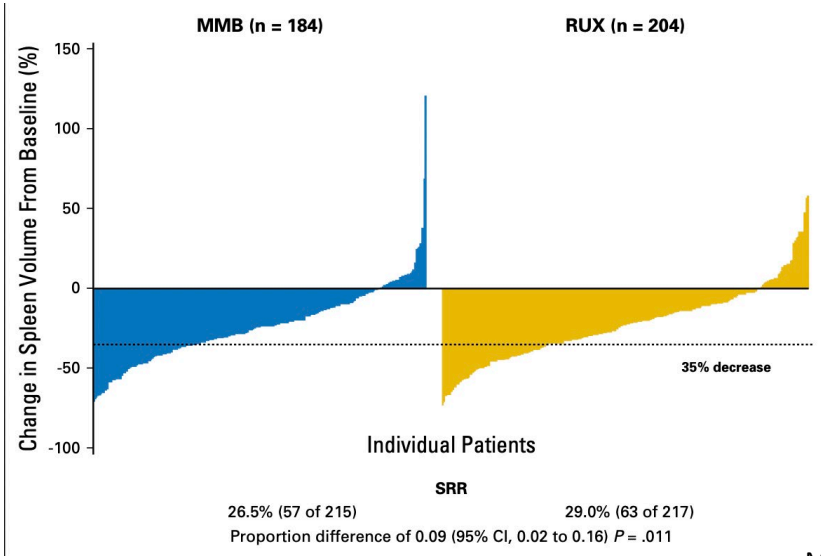


1. Chifotides HT et al. *J Hematol Oncol.* 2022;15(1):7; 2. Verstovsek S et al. *Future Oncol*. 2021;17(12):1449-1458; 3. Asshoff M et al. *Blood.* 2017;129(13):1823-1830; 4. Oh ST et al. *Blood Adv*. 2020;4(18):4282-4291.

Simplify-1 Study: upfront Momelotinib vs. Ruxolitinib



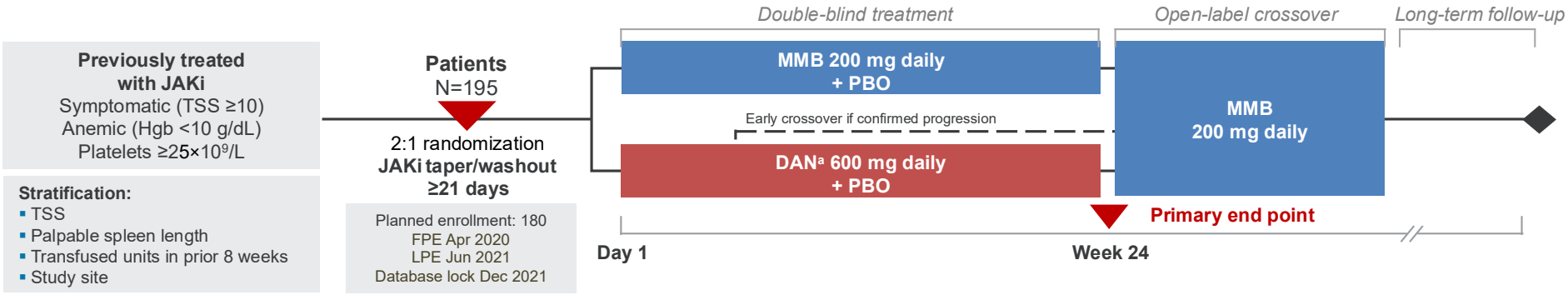




- TI at week 24 : MMB 66.5 % vs. RUX 49.3% (p=.001)
- Transfusion dependent week 24: MMB 30.2% vs. RUX 40.1% (p = .019)
- Rate RBC transfusion through week 24: MMB 0 units/mo vs. RUX 0.4 units/mo (p=.001)
- Week 24 TI response associated with improved OS in MV analysis (HR = 0.311; p < 0.0001)

Mesa R et al. J Clin Oncol 2017; 35:3844-3850. Mesa R et al. Leukemia 2022; 36(9):2261-2268.

Momelotinib vs. Danazol (Momentum phase 3 trial): superior spleen response, symptom benefit, and anemia improvement vs. danazol

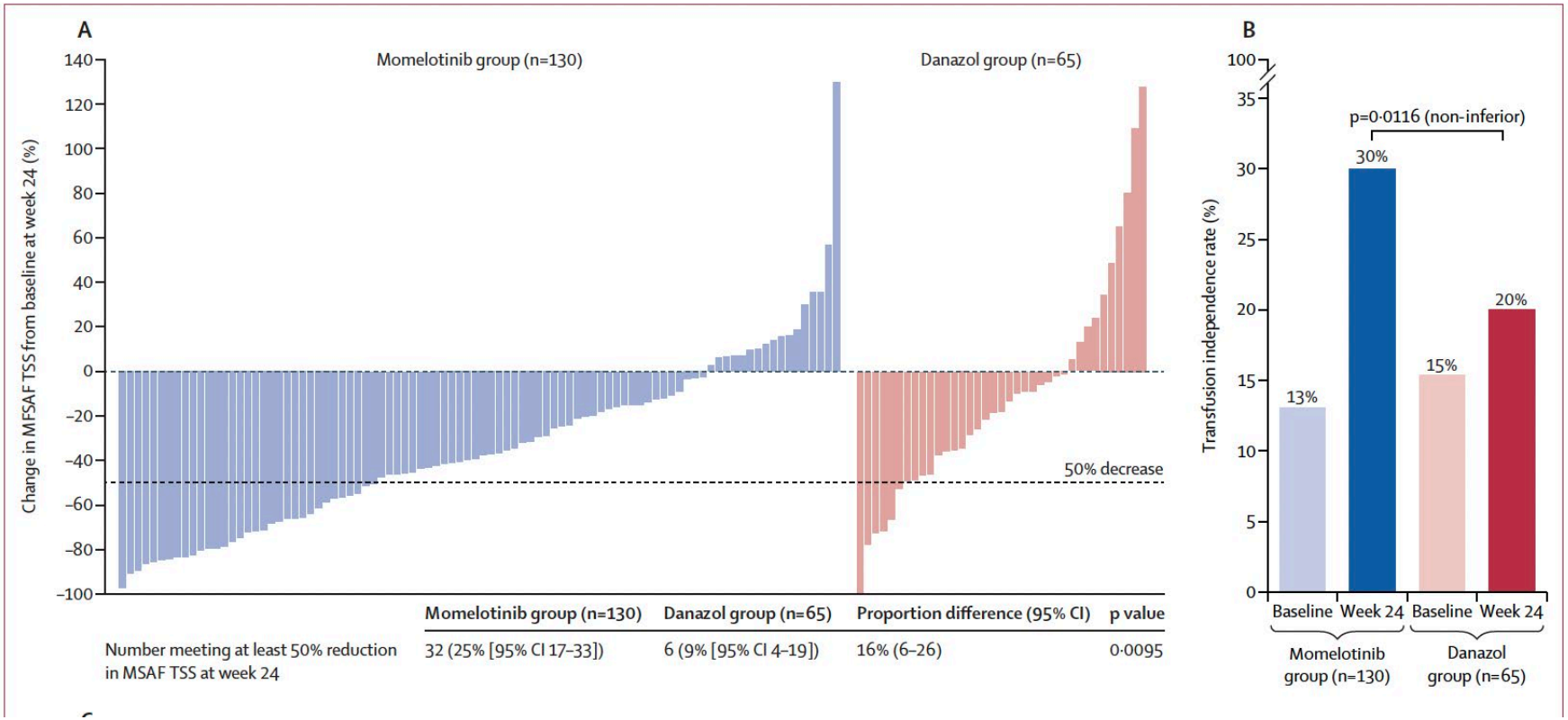


MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

Gerds A et al. *Blood* (2022) 140 (Supplement 1): 1514–1517. Verstovsek S et al. Lancet 2023; 4401: 269-80

Momelotinib: Phase 3 Momentum trial



Also superior for spleen volume reduction 35%: 22% vs 2%

Verstovsek S, et al. *Lancet.* 2023;401(10373):269-280.

Momelotinib side effects

	Momelotinib group (n=130)		Danazol group (n=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological abnormalities (preferred term)				
Diarrhoea	29 (22%)	0	6 (9%)	1 (2%)
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Asthenia	17 (13%)	1 (1%)	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Weight decreased	14 (11%)	0	4 (6%)	0
Blood creatinine increased	10 (8%)	1 (1%)	10 (15%)	2 (3%)
Dyspnoea	10 (8%)	3 (2%)	9 (14%)	1 (2%)
Peripheral oedema	10 (8%)	2 (2%)	9 (14%)	0
Fatigue	8 (6%)	1 (1%)	7 (11%)	2 (3%)
Acute kidney injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)
Haematological abnormalities*				
Anaemia	129 (99%)	79 (61%)	65 (100%)	49 (75%)
Thrombocytopenia	99 (76%)	36 (28%)	40 (62%)	17 (26%)
Neutropenia	38 (29%)	16 (12%)	17 (26%)	6 (9%)

Verstovsek S, et al. *Lancet.* 2023;401(10373):269-280.

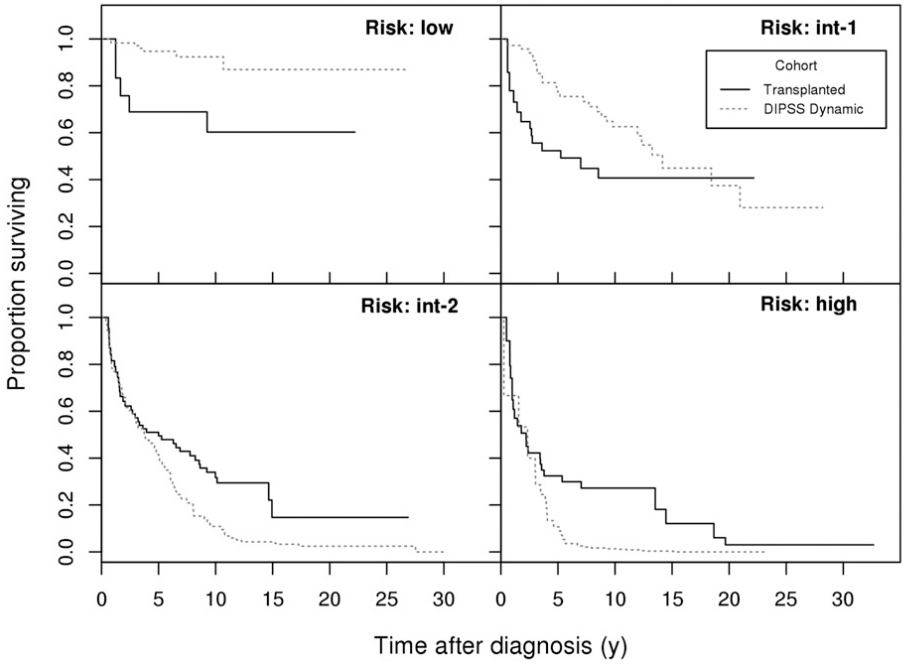
Summary of JAK inhibitors

	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Target	JAK1 and JAK2	JAK2, FLT3	JAK2, FLT3, IRAK1, CSF1R, and ACVR1	JAK1, JAK2, and ACVR1
Indication	Intermediate or high-risk MF	Intermediate or high-risk MF	Intermediate or high-risk MF with platelet count $<50\times10^9/L$	Intermediate or high-risk MF with anemia
Side effects	Cytopenias (anemia, thrombocy topenia), infection, weight gain	Wernicke encephalopathy, GI toxicity	Bleeding, cardiovascular events, GI (diarrhea, nausea)	Cytopenias (anemia, thrombo cytopenia), GI

*Pacritinib is 4x more potent inhibitor of ACV1R1

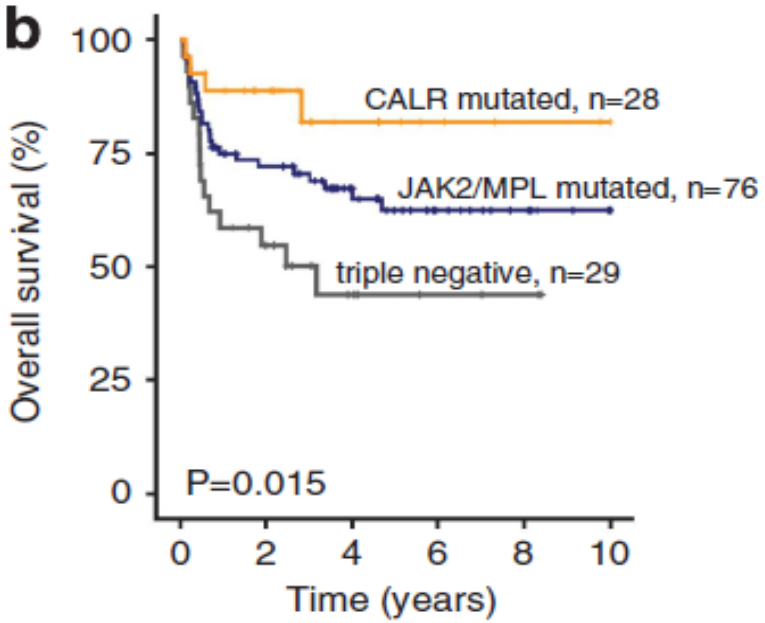
So, Whom and When to Transplant?

- **Disease characteristics:**
  - DIPSS int 1 – some patients (adverse risk mutations, 2+ mutations?, triple negative disease?) will benefit
  - **DIPSS int 2/high –indication for HCT**
  - **MIPSS70 high and very-high risk**
  - Disease progression – HCT only real option
  - Loss of response to JAK inhibitor



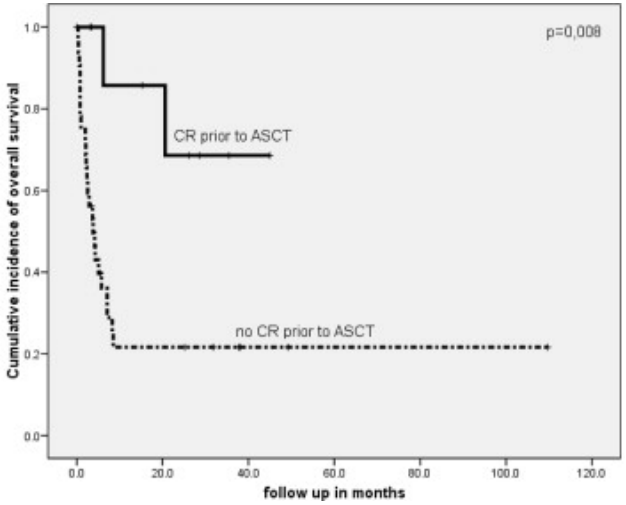
Kroger et al, Blood 2015; 125 (21): 3347-3350

Mutations and transplant outcomes



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

Triple-negative patients do worst



Other risk factors for HCT:

- Comorbidities
- Pulmonary or portal HTN
- Extramedullary hematopoiesis/disease
- Massive splenomegaly (>22 cm)
- Adverse mutations
- Leukemic transformation

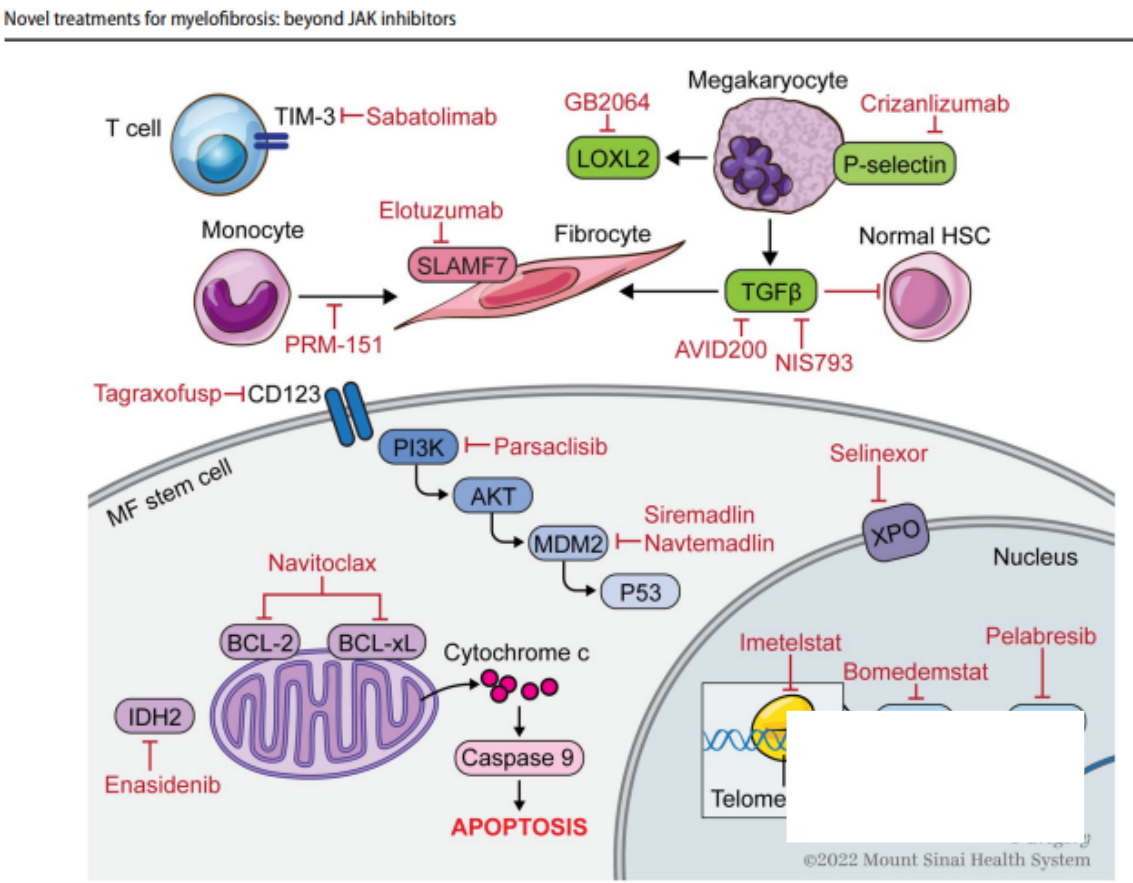
Panagiota V et al, Leukemia 2014; 28:1543-1572

Case 3

- High-risk DIPSS plus score
- No response to Ruxolitinib (low dose due to baseline plts, pacritinib not available at that time)
- 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
- Now >5 years s/p matched, unrelated donor stem cell transplant, doing well

MF: Up and coming therapies

- JAK-inhibitor add ons or single agent
- 111 recruiting trials ct.gov:
  - Navitoclax- ?
  - Pelabresib (BET inhibitor)
  - DISC-0974 (hepcidin Ab)
  - Nuvisertib (PIM1 Kinase)
  - Selinexor/Eltanexor (XPO1 inhibitor)
  - Navtemadlin/ Siremadlin (MDM2 inhibitor)
  - Imetelstat (telomerase inhibitor)
  - BET inhibitors
  - Luspatercept
  - Bomedemstat (LSD1-inhibitor)
  - Interferons
  - CALR vaccine
  - CALR bispecific



Tremblay and Mesa. Int J Hematology 2022; 115: 645-658

Thank You & Questions

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