

Myeloproliferative Neoplasms

Evaluation, Diagnosis, Prognostication, and Emerging Therapies

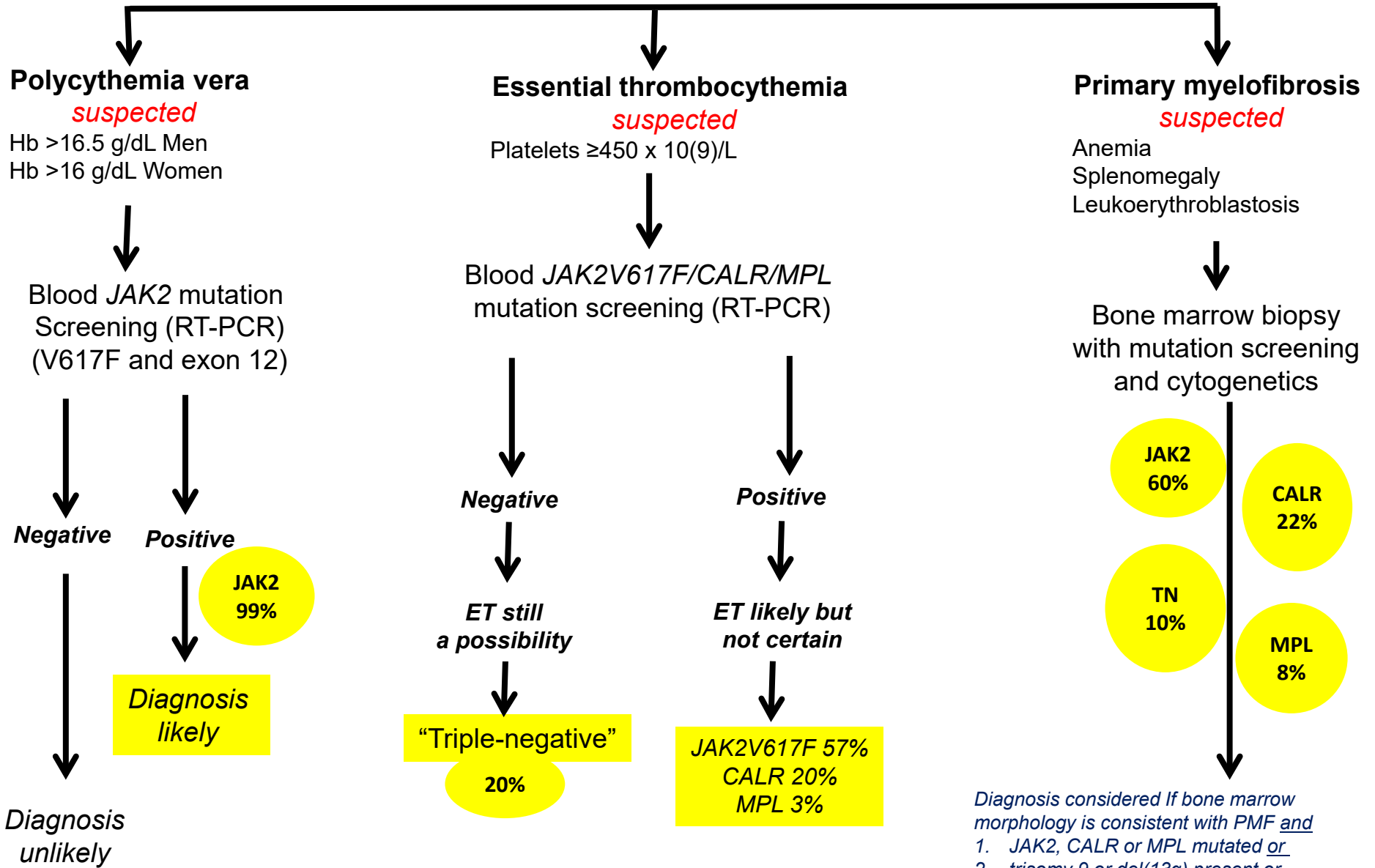
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I have nothing to declare

International Consensus Classification

Arber et al. Blood 2022;140:1200



Triple-A (AAA) survival model for essential thrombocythemia

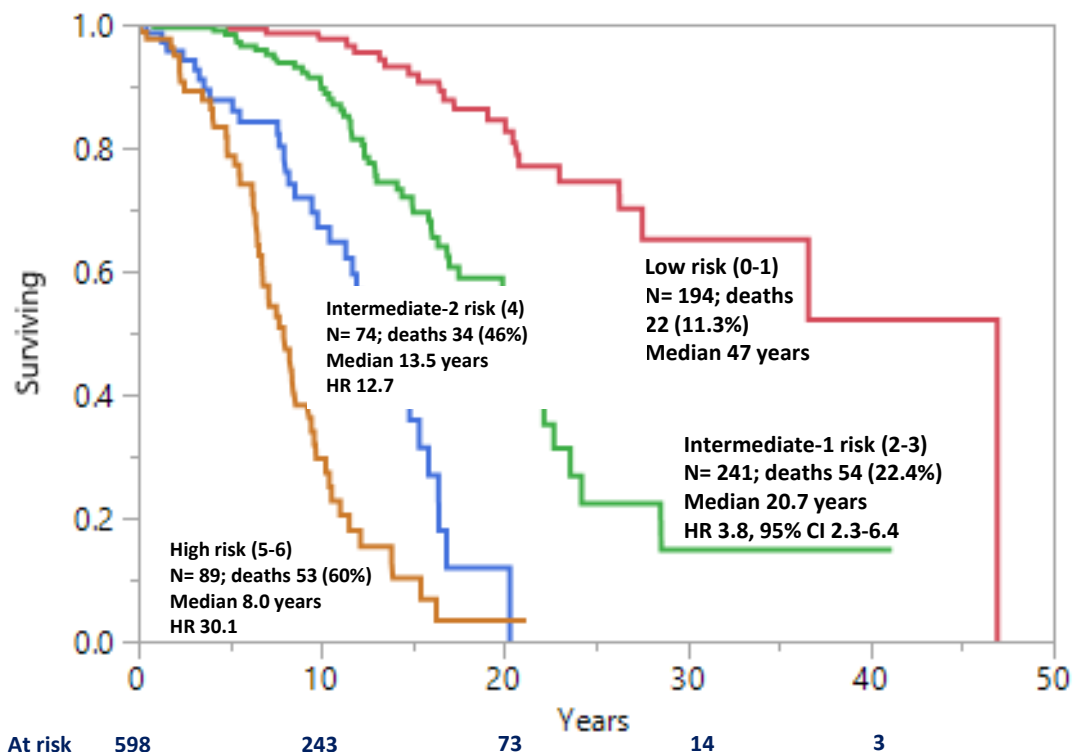
Overall survival data among 598 Mayo Clinic patients with essential thrombocythemia
Stratified by Age, Absolute neutrophil and Absolute lymphocyte count (AAA) risk model
Median follow-up 8.4 years

Age >70 years = 4 points

Age 50-70 years = 2 points

Absolute lymphocyte count $<1.7 \times 10^9/L = 1$ point

Absolute neutrophil count $\geq 8 \times 10^9/L = 1$ point

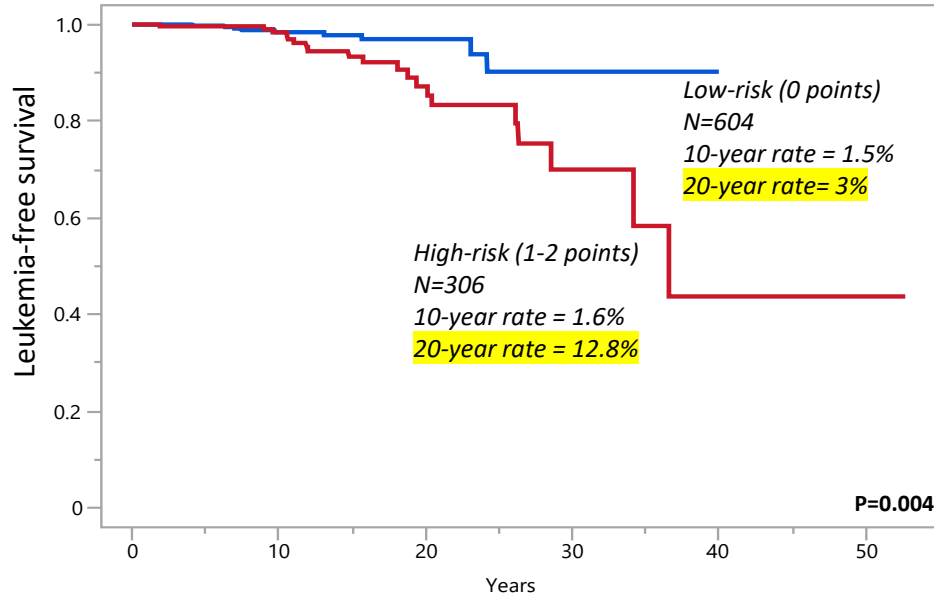


Abnormal karyotype and high-risk mutations (*TP53*, *SF3B1*, *SRSF2*, *U2AF1*)
carried additional prognostic relevance

Leukemic transformation risk model in essential thrombocythemia

"N" scorable based on availability of information on risk variables = 910

Abnormal karyotype: HR 3.1 (1.1-9.3) - 1 point
Platelet count $\geq 1,000 \times 10^9/l$: HR 2.3 (1.0-5.2) - 1 point



Prognostic impact of platelet count $\geq 1,000 \times 10^9/l$

JAK2 p=0.0002

CALR p=0.85

MPL p=0.50

TN p=1.0

Prognostic impact of abnormal karyotype

JAK2 p=0.17

CALR p=0.03

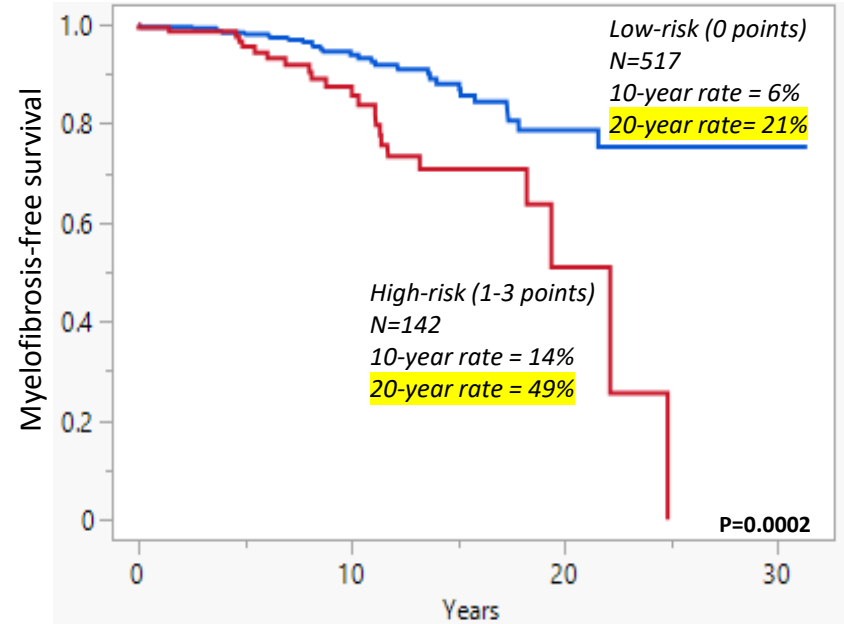
MPL p=1.0

TN p=1.0

Fibrotic progression risk model in essential thrombocythemia

"N" scorable based on availability of information on risk variables = 659

MPL mutation: HR 3.9 (1.8-8.4) - 2 points
Absolute neutrophil count $\geq 8 \times 10^9/l$: HR 2.3 (1.2-4.3) - 1 point



Prognostic impact of ANC $\geq 8 \times 10^9/l$

JAK2 p=0.03

CALR p=0.72

TN p=0.19

Traditionally low risk

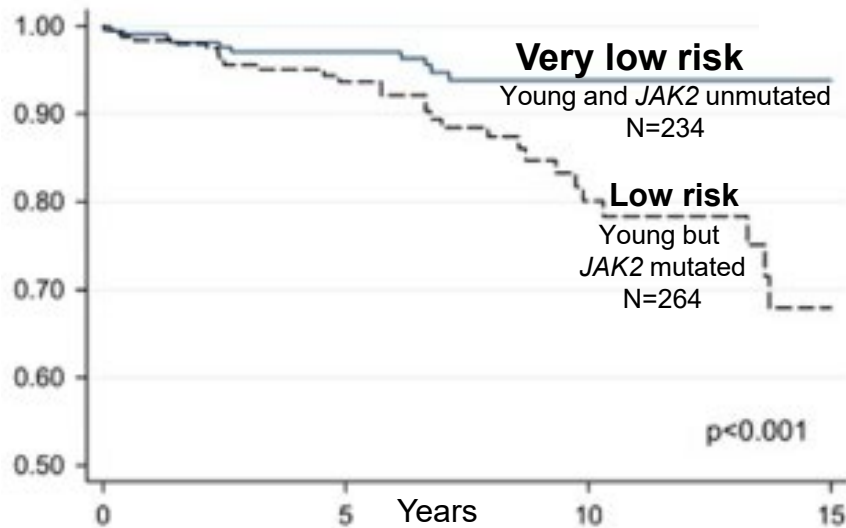
- Age ≤ 60 years and
- No thrombosis history

Traditionally high risk

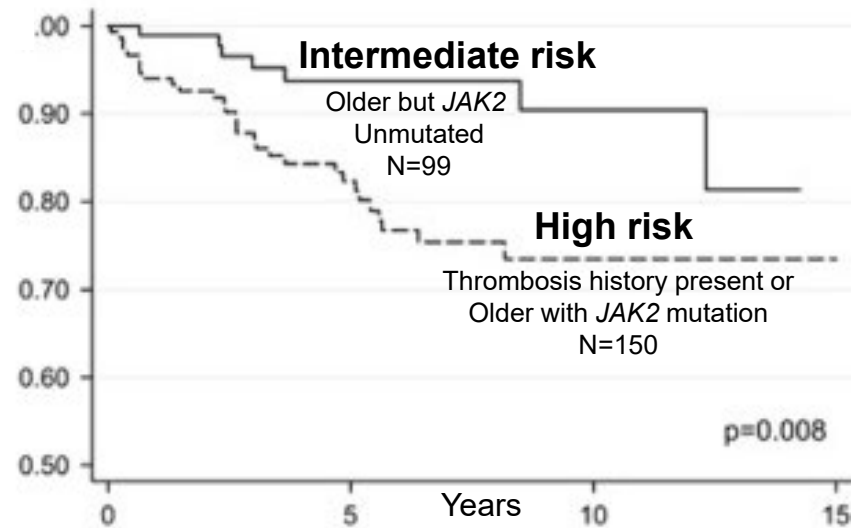
- Age >60 years or
- Presence of thrombosis history

International prognostic score ET (IPSET)-thrombosis

4-tiered



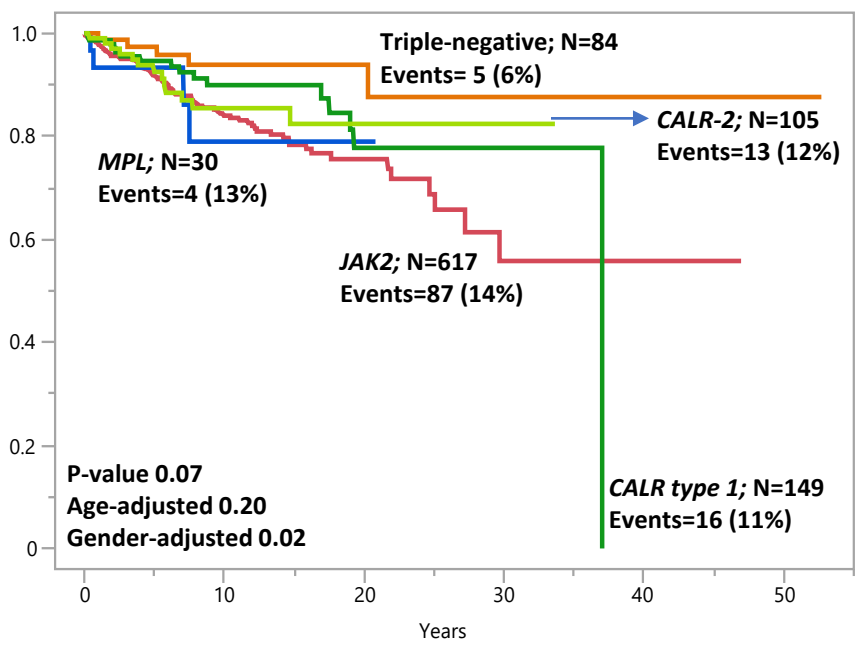
Thrombosis-free survival



New information:
One thousand patients with essential thrombocythemia
 Triple-negative had the lowest risk of arterial or venous thrombosis
CALR-1 vs CALR-2 carries higher risk of arterial thrombosis

Gangat, N., et al. *Blood Cancer J.* 14, 11 (2024). <https://doi.org/10.1038/s41408-023-00972>

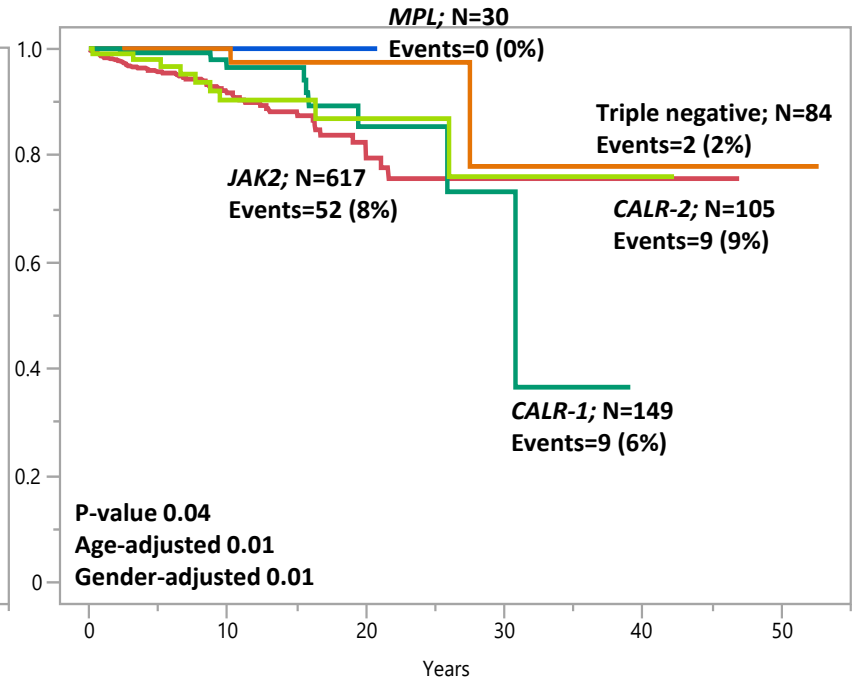
Arterial Thrombosis-free survival in 985 patients with essential thrombocythemia stratified by driver mutation



P-value

- JAK2 vs CALR type 1= 0.12**
- JAK2 vs CALR type 2=0.32**
- JAK2 vs triple negative= 0.02**
- JAK2 vs MPL= 1.0**
- CALR type 1 or type 2 vs MPL= 0.46/0.61**
- CALR type 1 vs triple negative =0.18**
- CALR type 2 vs triple negative= 0.12**

Venous Thrombosis-free survival in 985 patients with essential thrombocythemia stratified by driver mutation

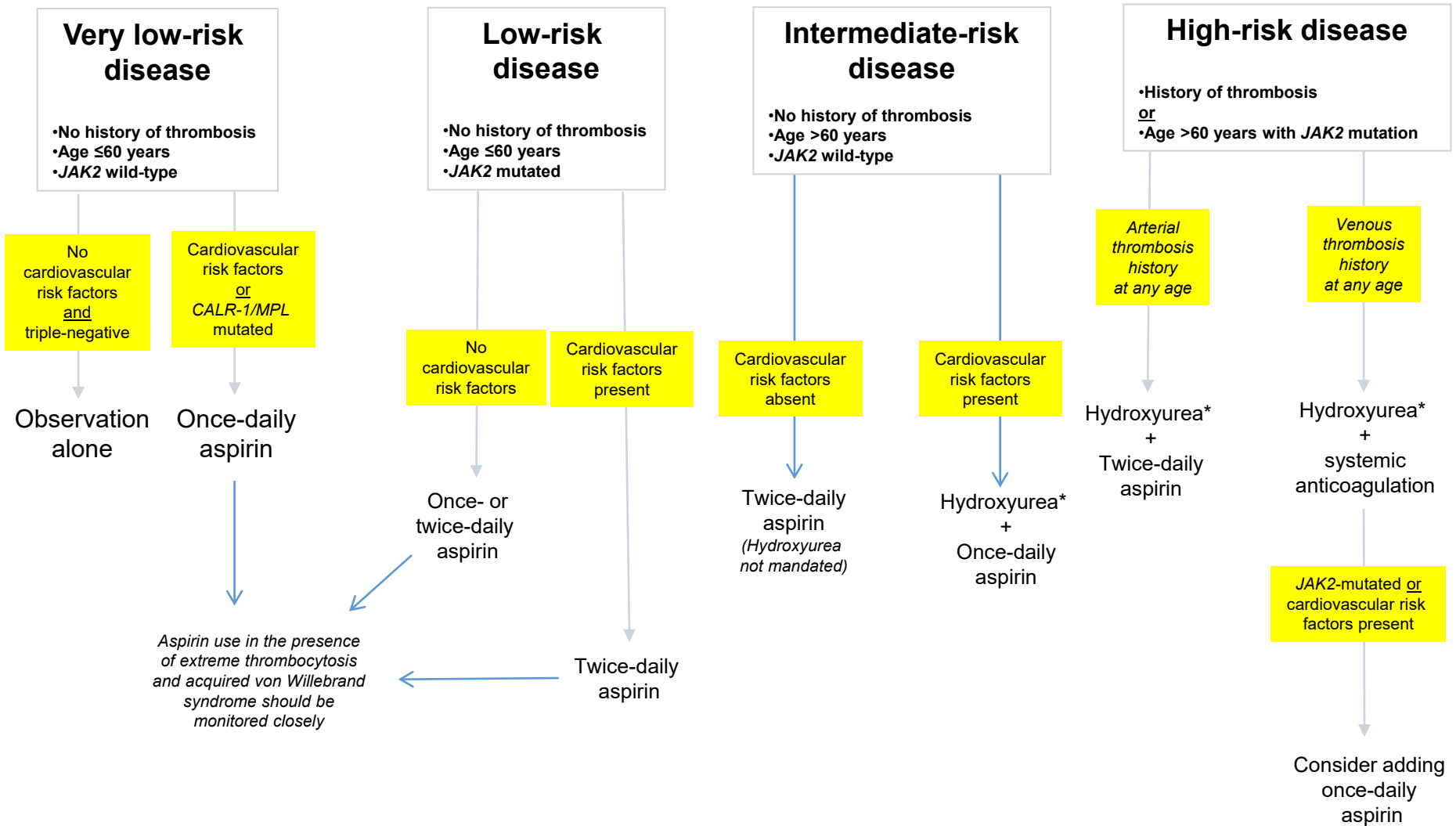


P-value

- JAK2 vs CALR type 1= 0.14**
- JAK2 vs CALR type 2=0.50**
- JAK2 vs triple negative= 0.03**
- JAK2 vs MPL= 1.0**
- CALR type 1 or type 2 vs MPL= 0.99**
- CALR type 1 vs triple negative =0.17**
- CALR type 2 vs triple negative= 0.08**

Current Treatment Algorithm in Essential Thrombocythemia

Tefferi. et al. AJH 2024 in press



*Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN- α or busulfan

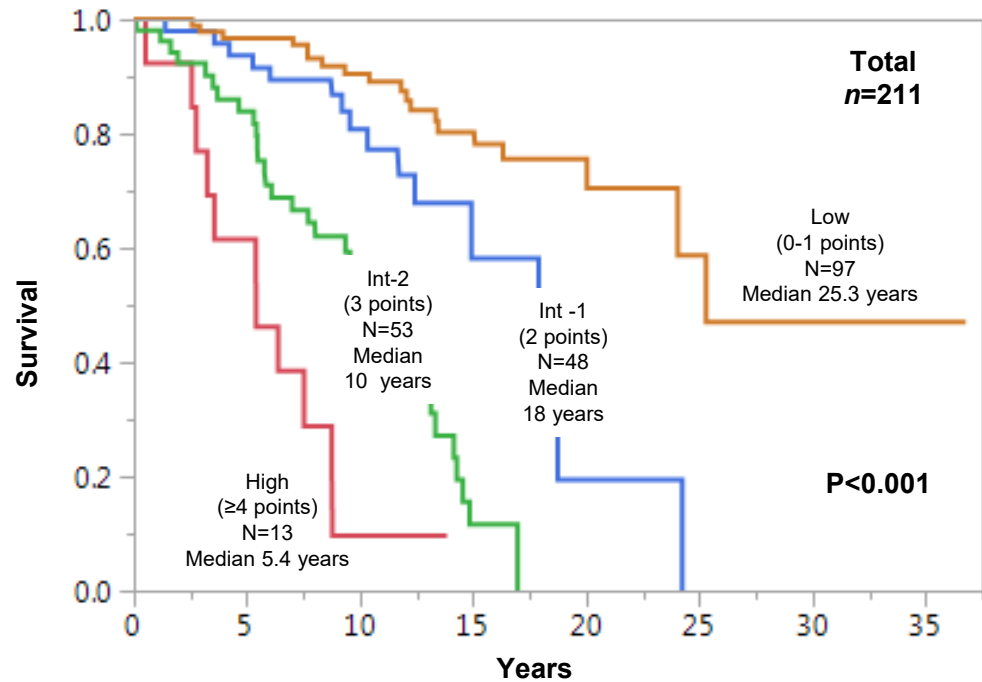
Additional practice points in essential thrombocythemia

1. What if you can't or don't want to use hydroxyurea
 - First choice-pegylated interferon alpha
 - Second choice-busulfan
 - I do not advise use of anagrelide or ruxolitinib in ET
2. Management before or during pregnancy
 - Low-risk...low-dose aspirin only
 - High-risk...pegylated IFN + low-dose aspirin
 - LMWH use reserved for patients with venous thrombosis history
3. Management of splanchnic vein or cerebral vein thrombosis
 - Systemic anticoagulation advised (DOAC vs warfarin)
 - Consider adding aspirin in the presence of risk factors for arterial thrombosis
 - Additional value of cytoreductive therapy uncertain-to be decided case by case
4. Management of platelet millionaires with otherwise low-risk disease
 - No evidence of value for cytoreductive therapy
 - Avoid use of aspirin in patients with clinically evident acquired von Willebrand syndrome
 - Treat the patient and not the platelet count

Mutation-enhanced international prognostic score (MIPSS-PV)

Risk factors:

1. Age >60 years (2 points),
2. Leukocyte count $\geq 11 \times 10^9/l$ (1 point), incidence 50%
3. Abnormal karyotype (1 point), incidence 20%
4. **SRSF2 mutations** (2 points), incidence 3%



Current Treatment Approach in Polycythemia Vera

Scheduled phlebotomy to keep hematocrit <45% in all patients
+
Once-daily low-dose aspirin in all patients

Low-risk disease

- No history of thrombosis
- Age ≤60 years

Consider twice-daily aspirin in the presence of:

- *CV risk factors*
- *Leukocytosis*
- *Microvascular symptoms*

High-risk disease

- History of thrombosis or
- Age >60 years

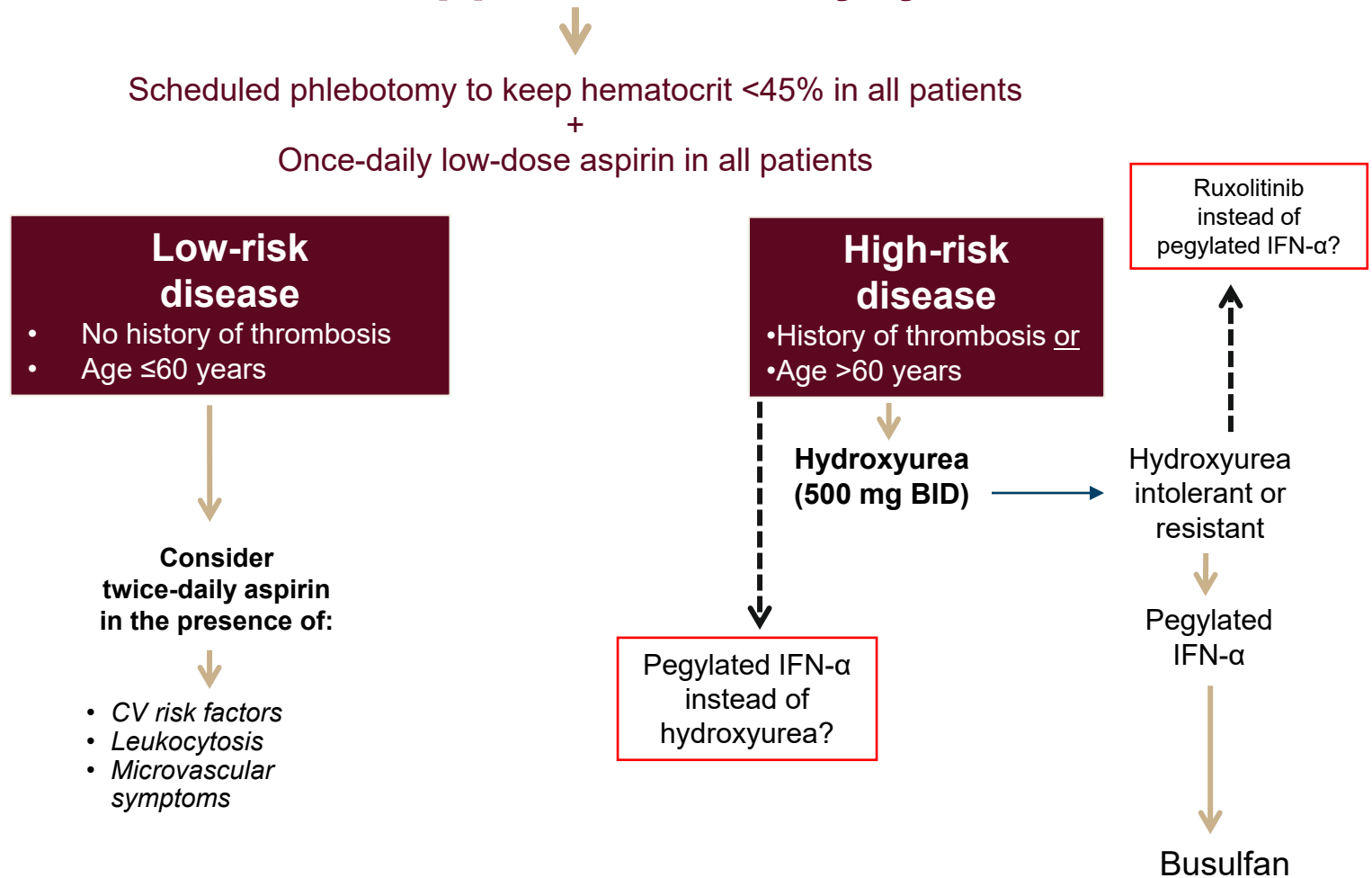
Hydroxyurea (500 mg BID)

Hydroxyurea intolerant or resistant

Pegylated IFN- α

Busulfan

Current Treatment Approach in Polycythemia Vera



Consideration of pegylated interferon for upfront therapy in both low-risk and high-risk PV

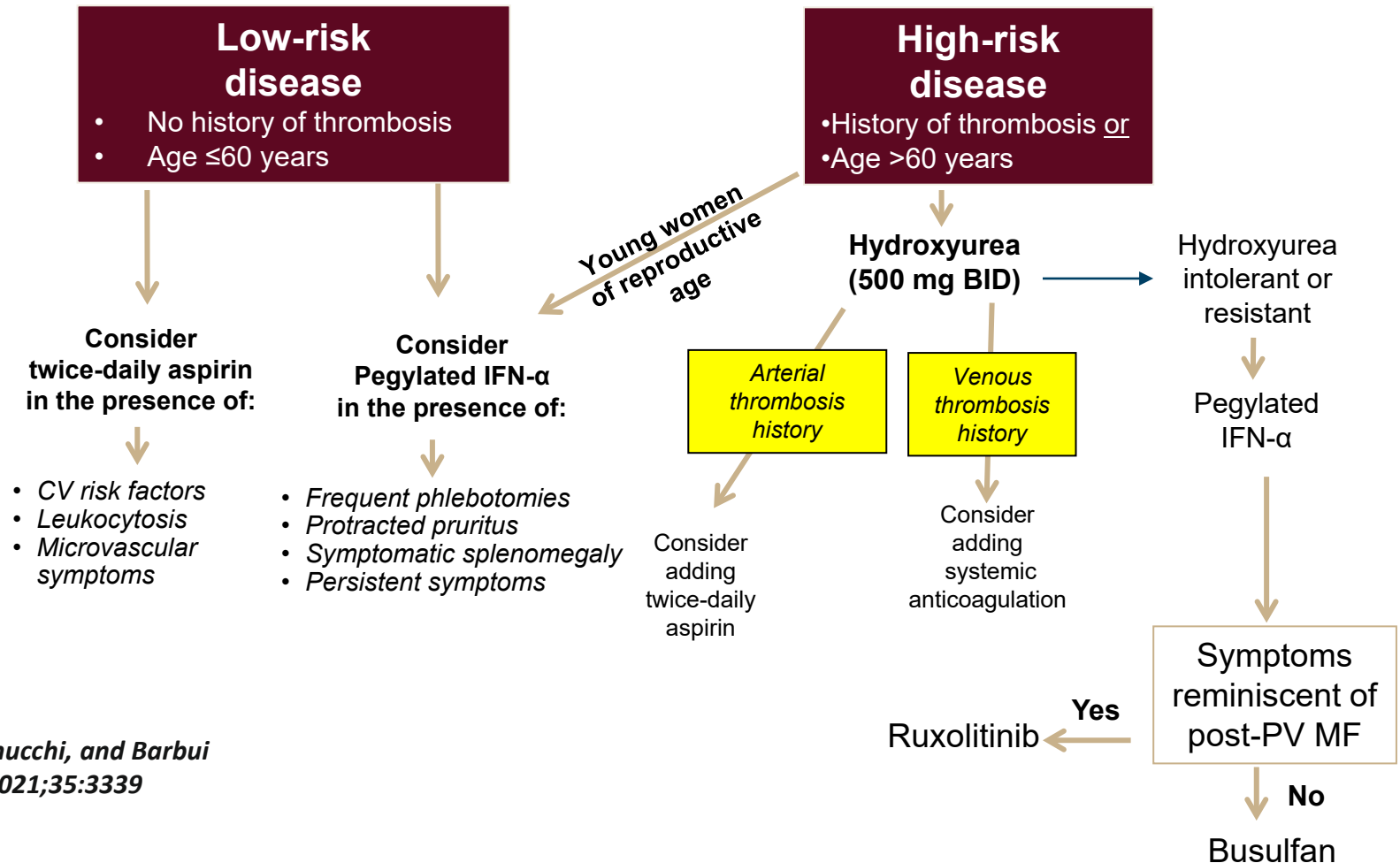
Studies	Treatment arm	Comparator	Efficacy	Toxicity	Meaningful endpoints
Phase-3 high-risk PV/ET Mascarenhas et al. <i>Blood</i> . 2022; 139: 2931	Peg-rIFN-α2a	Hydroxyurea	CHR 35 VS 37% ORR 78 vs 70% Hct control 65 vs 43% Peg-IFN better with JAK2 VAF reduction HU better with histologic remission 23 vs 5%	Peg-IFN more Toxic than HU: ≥ grade 3 AEs 46% vs 28%	Disease progression and thrombosis were Infrequent In both arms
Phase-3 high-risk PV Gisslinger et al. <i>Lancet Haematol</i> . 2020; 7: e196	Ropeg.	Hydroxyurea	CHR 21 VS 28% Hematologic response 43% vs 46% Responses to Ropeg Improved over time JAK2 VAF lower with Ropeg	TEAEs were Reported Similar Dose red 40% Drug int 23% Drug dis 8%	F/U too short to comment Impact on survival or thrombosis
Phase-2 randomized Low-risk PV Barbui et al. <i>NEJM Evid</i> . 2023; 2:Doa2200335.	Ropeg. + Phlebotomy + ASA	Phlebotomy + ASA	Hct control at 1-year: 81% vs 59% JAK2 VAF change Baseline to 12-mos 34.0% (18.0-57.0) to 18.0% (8.0-35.0)	Treatment-emergent side effects 55% vs 6%	F/U too short to comment Impact on survival or thrombosis + Cross-over design

HU resistant/intolerant PV

Studies	Rx arm	Other arm	Efficacy	Toxicity
Phase-2 PV/ET Yacoub et al. Blood. 2019; 134: 1498	Peg-IFN N=50/65	N/A	ORR 69% ORR PV only 60% CHR PV only 22% Median reduction in JAK2 VAF at CR -6% (-84% to 47%)	Usual Peg-IFN Toxicity
Phase-3 RESPONSE Vannucchi et al. NEJM 2015;372	Ruxolitinib N=110	BAT HU 60% No Rx 15% N=112	Hct control 60% vs 20% Spleen control 40% vs 1% CHR 24% vs 4% Symptoms 49% vs 5% Week 32 mean VAF -12%; week 112 -35%	Shingles 6.4% vs 0% Number of events too small to comment on progression/SCC
Phase-3 RESPONSE-2 without splenomegaly Passamonti et al. Lancet Oncol. 2017;18:88	Ruxolitinib N=74	BAT HU 49% No Rx 28% N=75	Hct control 62% vs. 19% Spleen control N/A CHR 23% vs 5% Symptoms 45% vs 23% JAK2 VAF change not reported	Number of events too small to comment on progression and Shingles/SCC
Phase-2 randomized MAJIC-PV Harrison et al. JCO 2023 doi:10.1200	Ruxolitinib N=93	BAT HU 66% alone or combo N=87	CR: 43% vs 26% >50% reduction in VAF: 14% vs 18% at 1-yr 56% vs 25% at 4-yrs 3-yr survival 88% vs 87% (p=NS) PFS 84% vs 75% (p=NS) EFS better with ruxolitinib and CR	Shingles 9% vs 3% SCC 6% vs 0% AML 4% vs 0%

Current Treatment Approach in Polycythemia Vera

Scheduled phlebotomy to keep hematocrit <45% in all patients
+
Once-daily low-dose aspirin in all patients



Hepcidin inducers

mAb against Matriptase-2 (TMPRSS6), a regulator of HJV/hepcidin production
Matriptase mutations cause IRIDA (high hepcidin anemia)

New drugs in PV

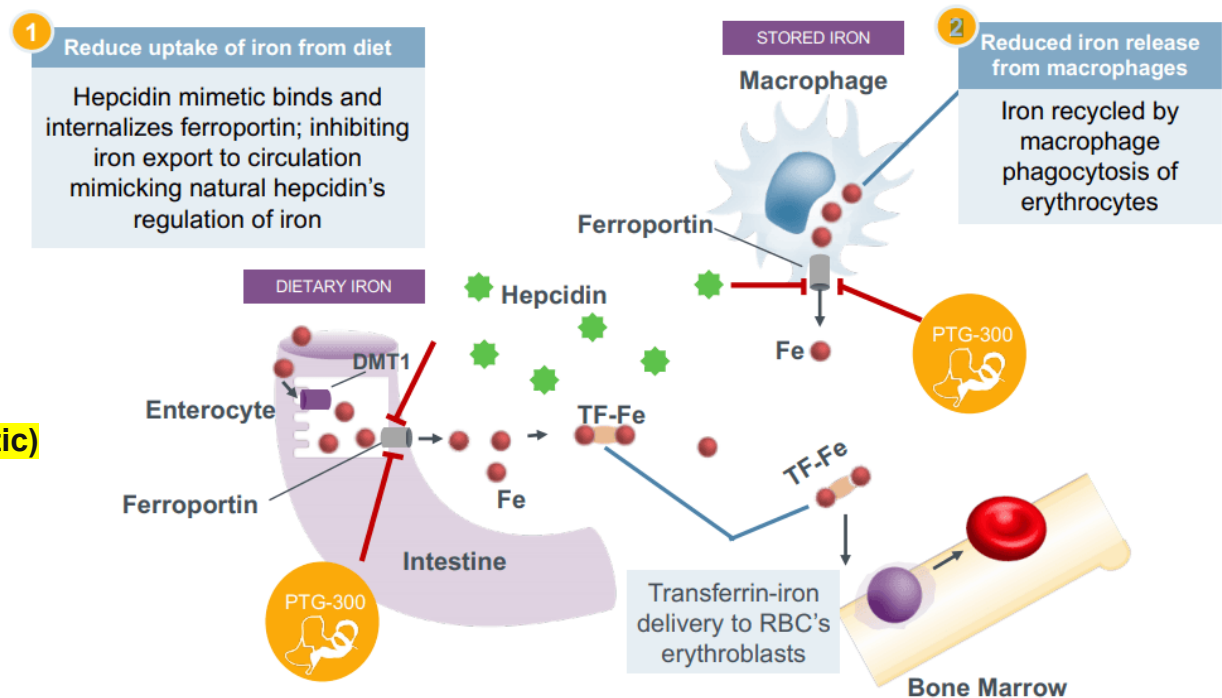
Hepcidin mimetics

Rusfertide

PTG-300 (Rusfertide; hepcidin mimetic)

Hoffman et al. ASCO 2022

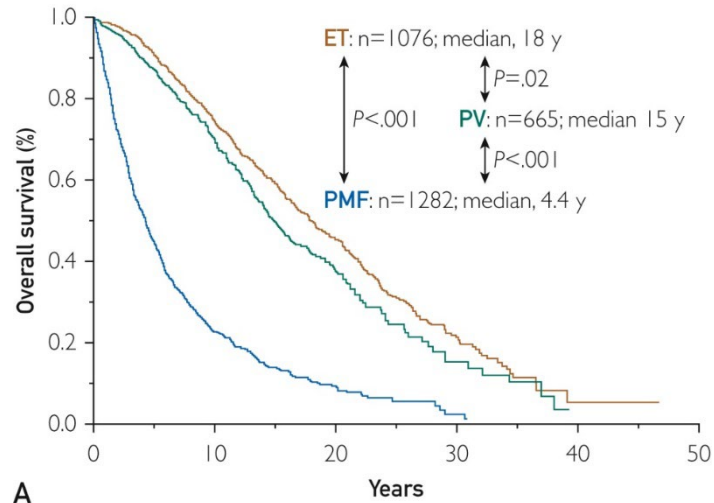
- Phase-2 study of 63 patients
- Weekly SC injection 10-120 mg
- Marked reduction in phlebotomy need and reversal of iron deficiency
- Injection site reactions
- Phase-3 study ongoing



Personal perspective

- **High-risk disease...dubious role since broader myelosuppression is secured by cytoreductive therapy**
- **Low-risk disease...patient preference and should be assessed in the context of alternative therapy with pegylated IFN, which, by the way, also controls leukocytosis, thrombocytosis, and splenomegaly**

Disease Complications in Myelofibrosis



A

- Anemia
- Splenomegaly
- Constitutional symptoms
- Cachexia

Therapeutic options in myelofibrosis

- **Curative or with potential to improve survival**

- ✓ Allogeneic hematopoietic cell transplant (allo-HCT)

- **Palliative**

- ✓ Observation alone (watch-and-wait)
- ✓ Treatment for anemia
 - Thalidomide ± prednisone
 - Androgens
 - Danazol
 - ESAs
 - Lenalidomide/pomalidomide
- ✓ Treatment for symptomatic splenomegaly
 - Hydroxyurea
 - JAK2 inhibitors
 - Splenectomy
- ✓ Treatment for constitutional symptoms
 - JAK2 inhibitors
- ✓ Involved field radiotherapy for extra-medullary hematopoiesis
- ✓ Experimental therapy

Survival following allogeneic transplant in patients with myelofibrosis (CIBMTR and MPN Research Consortium study)

551 patients transplanted vs 1377 not transplanted

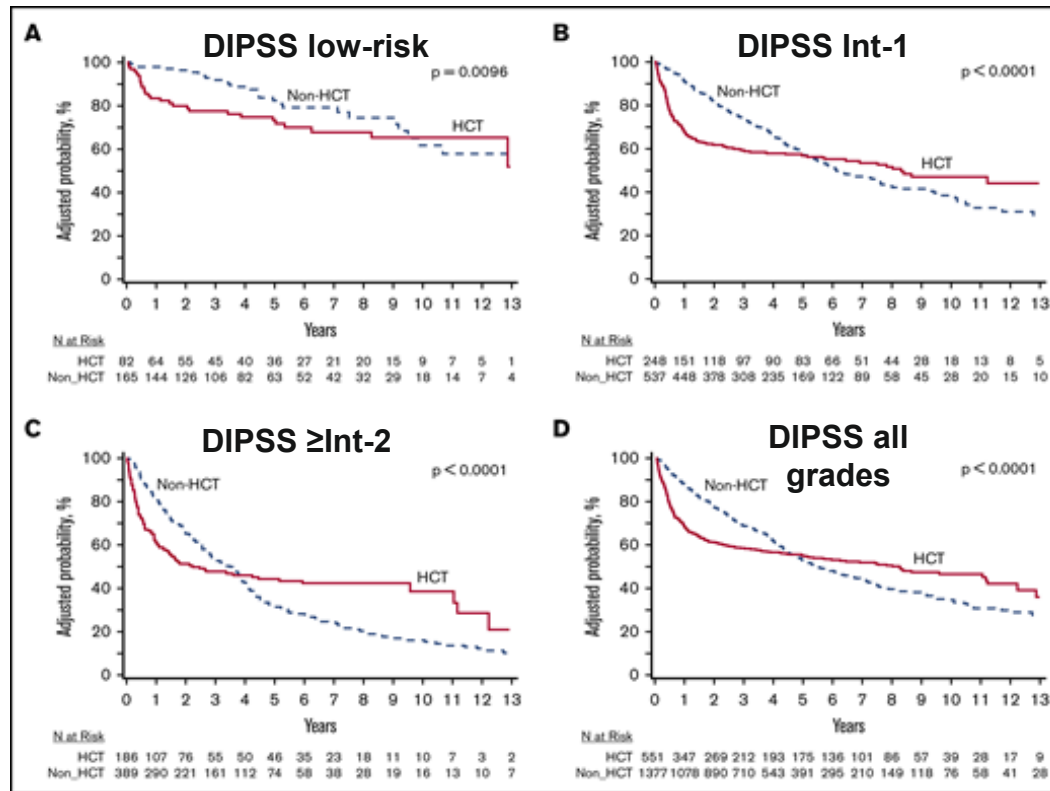


Figure 1:

Mutation/karyotype-enhanced international prognostic scoring system for primary myelofibrosis (MIPSSv2)

≥5 points

High/very high risk
Median survival 1.8-3.5 years
10-year survival 0-10%

3-4 points

Intermediate risk
Median survival 7 years
10-year survival 30%

≤2 points

Low/very low risk
Median survival 10 years-not reached
10-year survival 50-86%

CALR type 1/like mutation

Absent
2 points

Present
0 points

Karyotype

Very high risk

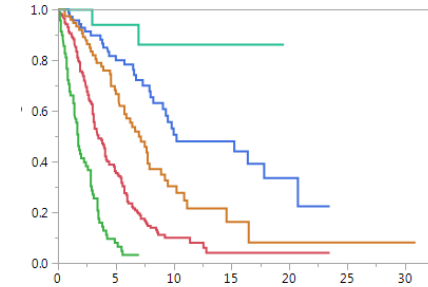
-7,i(17q),inv(3), 12p, 11q23, other autosomal trisomies
4 points

Unfavorable

Not favorable or very high risk
3 points

Favorable

Normal, sole 13q-, +9, 20q-, 1q+, -Y
0 points



High molecular risk mutations

ASXL1, SRSF2, U2AF1

Two
3 points

One
2 points

None
0 points

Clinical risk factors

Constitutional symptoms
2 points

Severe Anemia
Hgb <9 g/dL male
<8 g/dL female
2 points

Moderate Anemia
Hgb 9-10.9 g/dL male
8-9.9 g/dL female
1 point

Circulating blasts ≥2%
1 point

None of the above
0 points

European registry-based study 1995-2018

4,412 MF patients

Changes over time:

Median age 49 to 59 years

MUD use 23% to 45%

MMRD use 3% to 9%

aGVHD II-IV 35%-28%

Extensive CGVHD 36% to 23%

No significant change over time:

3-year OS 55% to 58%

RFS 47% to 49%

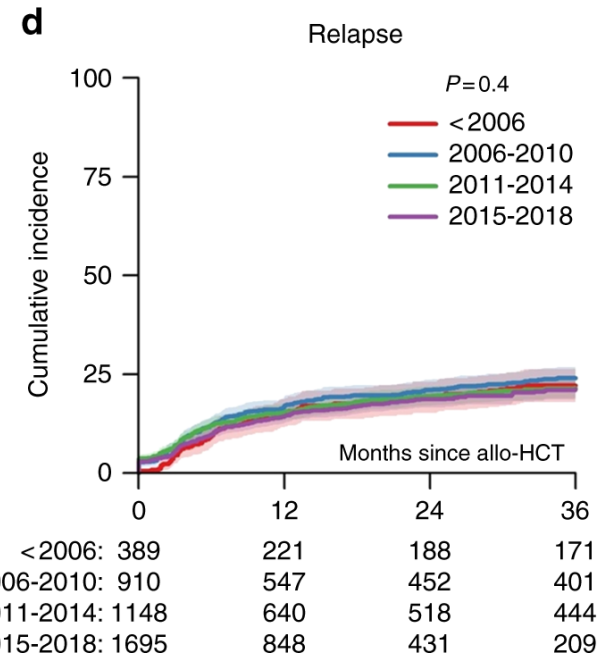
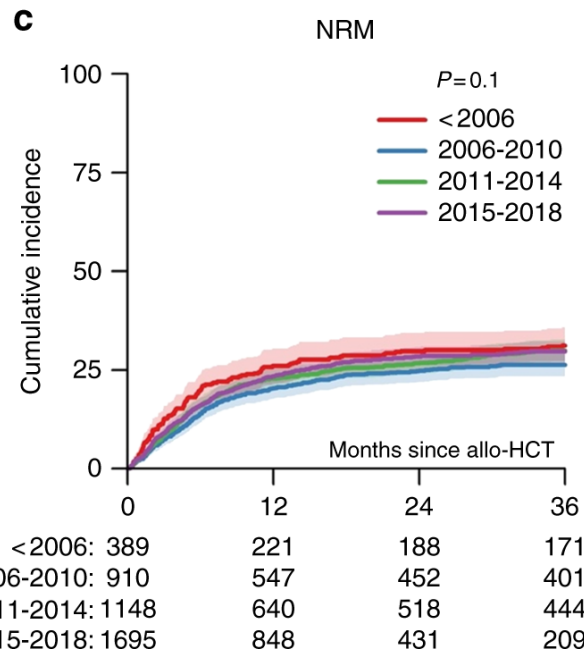
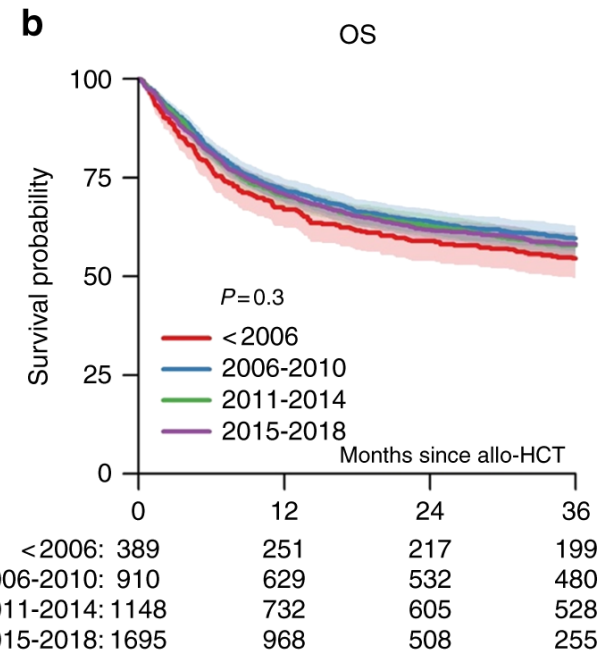
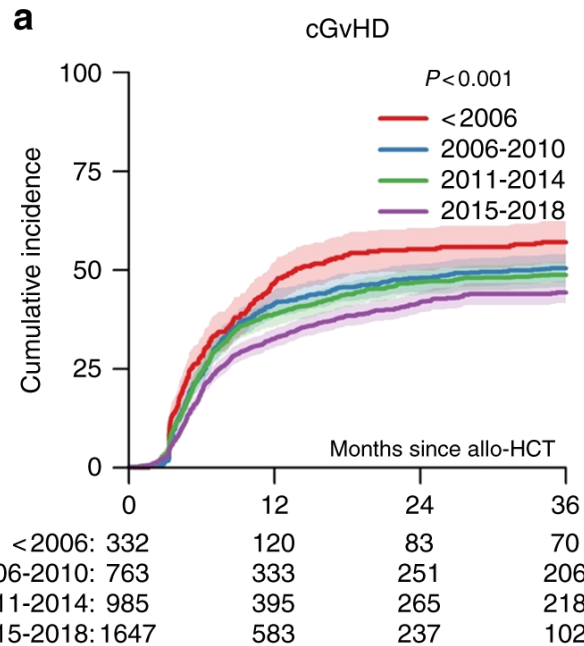
Relapse rate 22% to 21%

NRM 31% to 30%

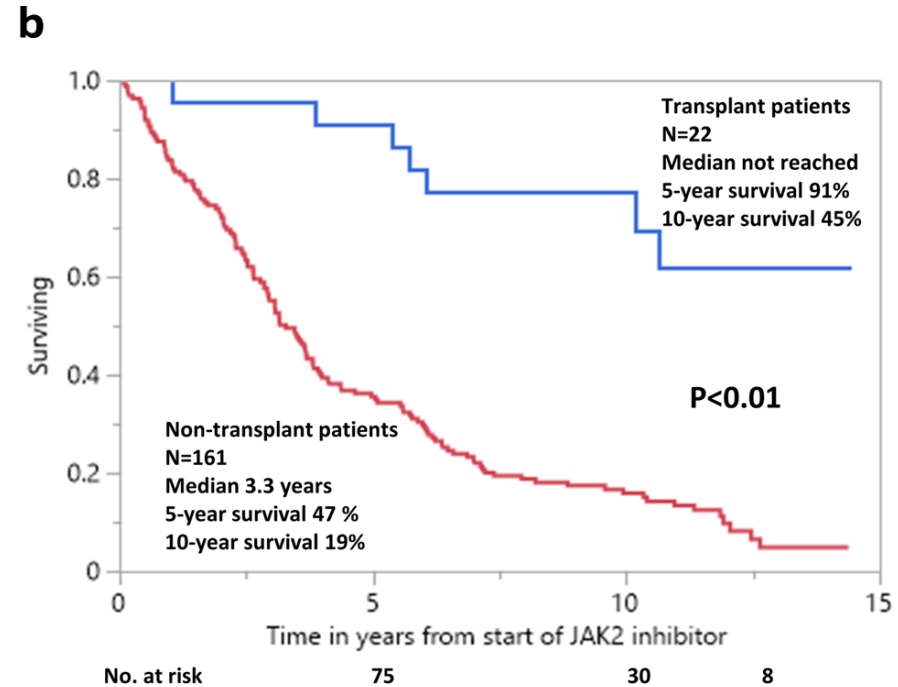
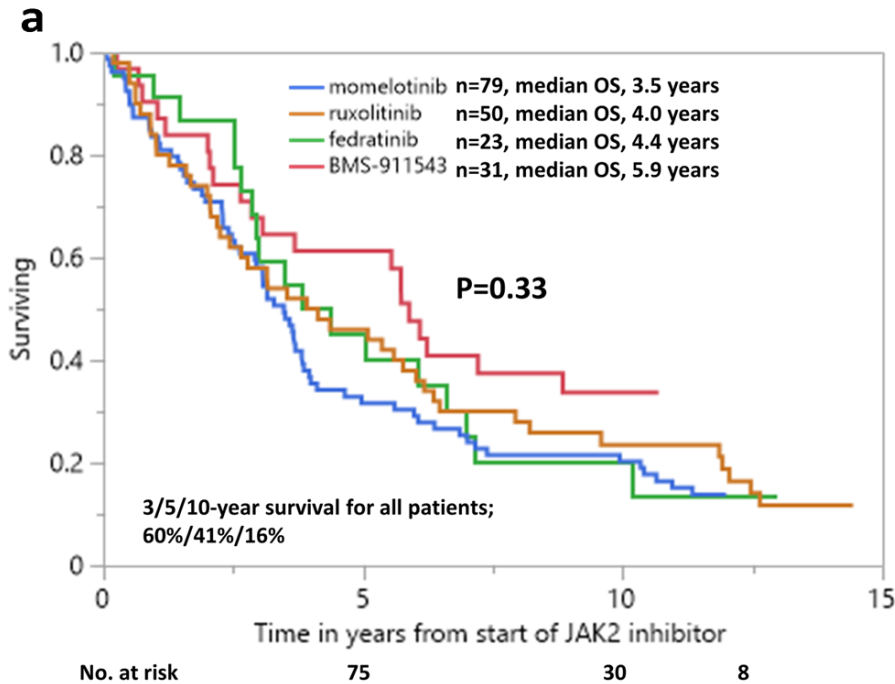
Primary graft failure 25 to 4%

Secondary graft failure 4% to 7%

Stem cell source



Determinants of survival and retrospective comparisons of 183 clinical trial patients with JAKi-naïve myelofibrosis treated with momelotinib, ruxolitinib, fedratinib or BMS- 911543 JAK2 inhibitor



Predictors of inferior survival

- Age > 65 years
- Transfusion-dependent anemia
- Unfavorable karyotype
- Absence of Type 1/like *CALR* mutation**
- Presence of *ASXL1/SRSF2* mutation**
- Absence of Spleen response**
- Absence of Anemia response**

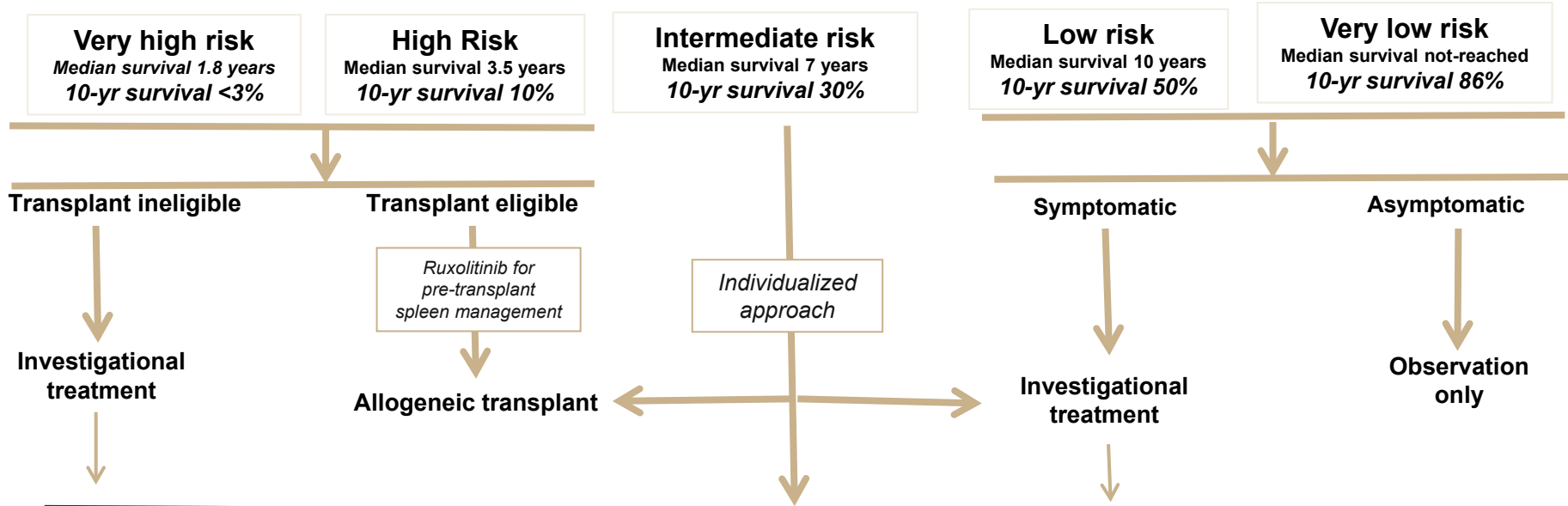
Bold font represents variables retaining significance on multivariable analysis

JAK2 inhibitors in myelofibrosis: activity in JAKi-naïve patients

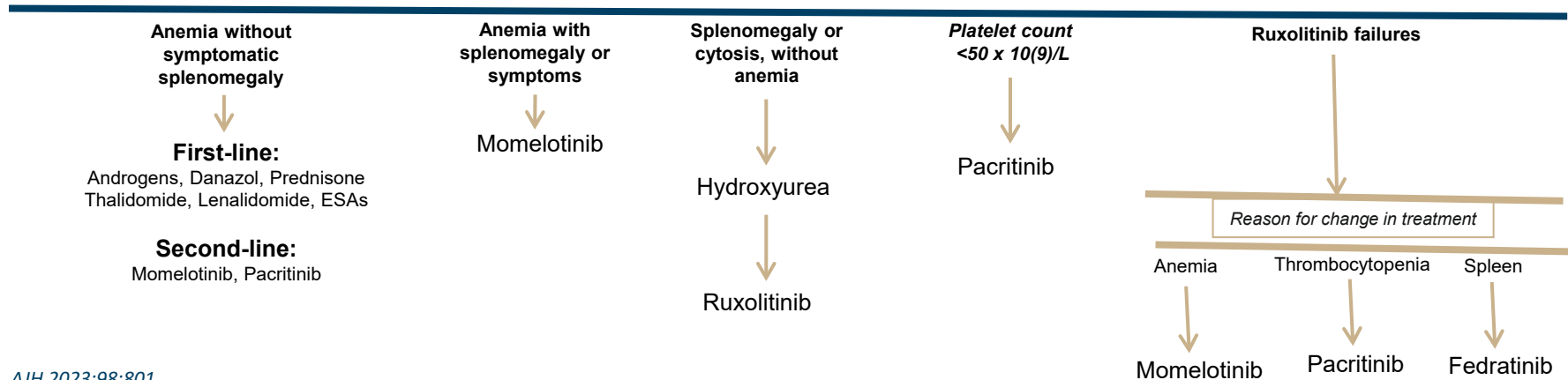
	Ruxolitinib (FDA 2011)	Fedratinib (FDA 2019)	Pacritinib (FDA 2022)	Momelotinib (FDA pending)
Dose & Schedule	20 mg BID (Plts >200 x10 ⁹ /l) 15 mg BID (Plts 150-200 x10 ⁹ /l)	400 mg BID (Plts ≥50 x10 ⁹ /l)	200 mg BID (Plts <50 x10 ⁹ /l)	Approval pending (200 mg QD)
SVR ≥35%	29% (SIMPLIFY-1) <i>Ruxo vs mom</i>	36% (JAKARTA-1) <i>Pardanani et al.</i> <i>JAMA Oncology 2015</i> <i>fed vs placebo</i>	19% (PERSIST-1) <i>Mesa et al.</i> <i>Lancet Hematology 2017</i> <i>Pac vs BAT</i>	27% (SIMPLIFY-1) <i>Mesa et al.</i> <i>JCO 2017</i>
Transfusion resolution	More likely to cause anemia	More likely to cause anemia	25% (PERSIST-1)	46% (Mayo study) <i>Gangat et al. AJH 2022</i>
Symptom response	42% (SIMPLIFY-1)	36% (JAKARTA-1)	19% (PERSIST-1)	28% (SIMPLIFY-1)
Adverse effects	Anemia Thrombocytopenia Withdrawal Opportunistic COVID vaccines	Anemia Thrombocytopenia GI symptoms ↑LFTs/amylase/lipase Wernicke's (Rare event)	GI symptoms Edema Pneumonia Cardiac failure	Thrombocytopenia ↑LFTs/amylase/lipase Peripheral neuropathy First-dose effect (Dizziness, Hypotension, Flushing, Nausea)

Risk-adapted treatment algorithm for myelofibrosis: 2024 edition

Based on risk category per the mutation/karyotype-enhanced international prognostic scoring system for primary myelofibrosis (MIPSSv2)*



Symptoms-directed therapy



Ruxolitinib in combination with navitoclax or pelabresib in myelofibrosis: activity in JAKi-naïve patients (ASH 2023)

	Ruxolitinib n=155	Navitoclax + Ruxolitinib n=125	Ruxolitinib + Placebo n=127	Pelabresib + Ruxolitinib n=214	Ruxolitinib + Placebo n=216
	COMFORT-1 Median follow-up: 8 months	TRANSFORM-1 Median follow-up: 14.9 months		MANIFEST-2 Median follow-up: 11.3 months	
Patient Characteristics	IPSS High 58% Intermediate 2 41%	DIPSS-plus High 10% Intermediate-2 83% Intermediate-1 6%	DIPSS-plus High 9% Intermediate 2 87% Intermediate-1 4%	DIPSS High 5% Intermediate 2 35% Intermediate-1 60%	DIPSS High 7% Intermediate 2 34% Intermediate-1 59%
High molecular risk	Not available	48%	43%	39%	49%
Transfusion-dependent	22%	4%	3%	16%	12%
Dose & Schedule	20 mg BID (Plts >200 x10 ⁹ /l) 15 mg BID (Plts 150-200 x10 ⁹ /l)	Ruxolitinib 15-20 mg BID (90% with dose reduction) + Navitoclax 100/200 mg QD	Ruxolitinib 15-20 mg BID (61% with dose reduction) + Placebo	Day 1-21 Ruxolitinib 10-15 mg BID (median dose 29.3 mg daily) + Day 1-14 Pelabresib 125 mg QD	Day 1-21 Ruxolitinib 10-15 mg BID (median dose 31.3 mg daily) + Day 1-14 Placebo
SVR ≥35%	42%	63%	32%	66%	35%
		P<0.0001		P<0.001	
Anemia response	-	-	-	9%	6%
Symptom Response	46%	39%	42%	52%	46%
		P=0.29		P=0.22	
Adverse effects	Grade ≥3 thrombocytopenia 13% Grade ≥3 neutropenia 7%	Grade ≥3 thrombocytopenia 51% Grade ≥3 neutropenia 38%	Grade ≥3 thrombocytopenia 15% Grade ≥3 neutropenia 4%	Thrombocytopenia 32% Grade ≥3 thrombocytopenia 9% Dysgeusia 18%	Thrombocytopenia 23% Grade ≥3 thrombocytopenia 6% Dysgeusia 4%
Discontinuation rate	14%	30%	35%	27%	25%

Summary of Novel Agents in phase 1/2 clinical trials in myelofibrosis

	Novel agent	Mechanism	SVR/TSS	Anemia response	Reduction in fibrosis	Toxicity
Spleen	TP-3654 (N=31) Abstract 626 (JAKi exposed)	PIM1 Kinase inhibitor	+ / ++	-	+	GI ↓ Platelet count Anemia
	BMS-986158 + Ruxolitinib/Fedratinib (N=48) Abstract 623 (JAKi naïve + exposed)	Bromodomain and extra-terminal (BET) inhibitor	++ / NR	-	+	GI ↓ Platelet count Anemia
	Selinexor + Ruxolitinib (N=14) Abstract 622 (JAKi naïve)	Nuclear export XPO1 inhibitor	++ / ++	NR	NR	GI ↓ Platelet count Anemia
	INCB057643 +/- Ruxolitinib (N=29) Abstract 750 (JAKi exposed)	Bromodomain and extra-terminal (BET) inhibitor	+ / +	+	NR	↓ Platelet count Anemia GI
	Bomedemstat (MK3543) + Ruxolitinib (N=35) Abstract 621 (JAKi naïve)	Lysine-specific demethylase-1 (LSD) inhibitor	+ / +	+	NR	↓ Platelet count Anemia GI
Anemia	Luspatercept +/- Ruxolitinib (N=95) Abstract 7016 (JAKi naïve + exposed)	Transforming growth factor-beta (TGF-β) ligand trap	NR / +	+ (TD on ruxolitinib)	NR	Hypertension
	Zilurgisertib (INCB000928) +/- Ruxolitinib (N=46) Abstract 624 (JAKi naïve + exposed)	Activin Receptor-like Kinase-2 (ALK2/ACVR1) inhibitor	NR	+ (none in TD)	NR	↓ Platelet count
	DISC-0974 (N=11) Abstract 4564 (JAKi naïve + exposed)	Anti-hemojuvelin (HJV) antibody	NR	++	NR	None to low incidence of diarrhea
Fibrosis	PXS-5505 (N=23) Abstract 634 (JAKi naïve + exposed)	Lysyl oxidase (LOX) inhibitor	- / +	+	Collagen + Reticulin -	GI ↓ Platelet count Anemia

SVR, spleen volume reduction; TSS, total symptom score; NR, not reported; GI, gastrointestinal, TD, transfusion-dependent

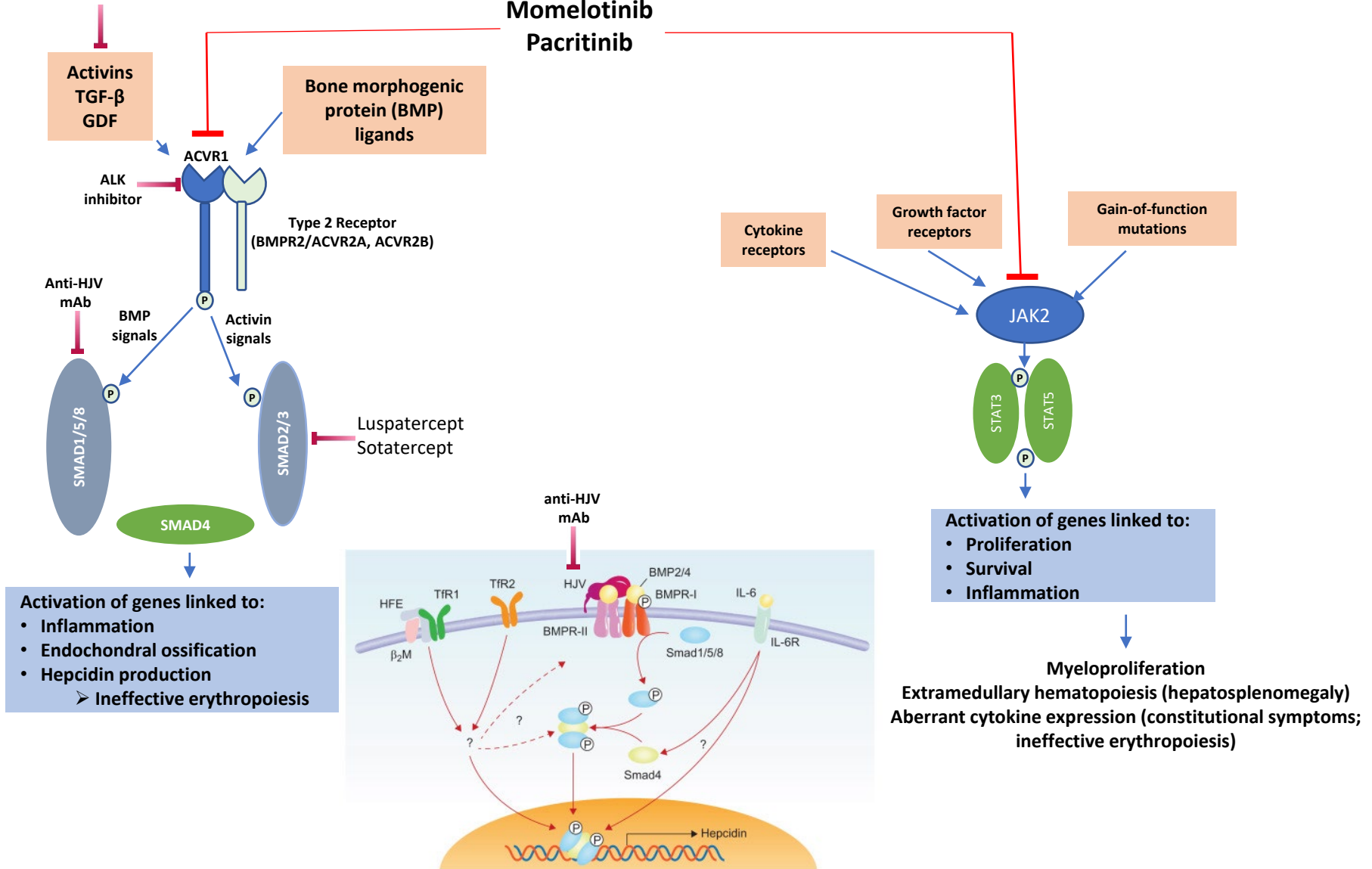
Newer JAK2 inhibitors

ACVR1: Activin A receptor type 1 (aka. ALK2)

Activin receptor ligand traps

Luspatercept (ActRIIB-Fc)
Sotatercept (ActRIIA-Fc)

Momelotinib
Pacritinib



Discovery of INCA033989, A Mutant Calreticulin (CALR)-specific monoclonal antibody

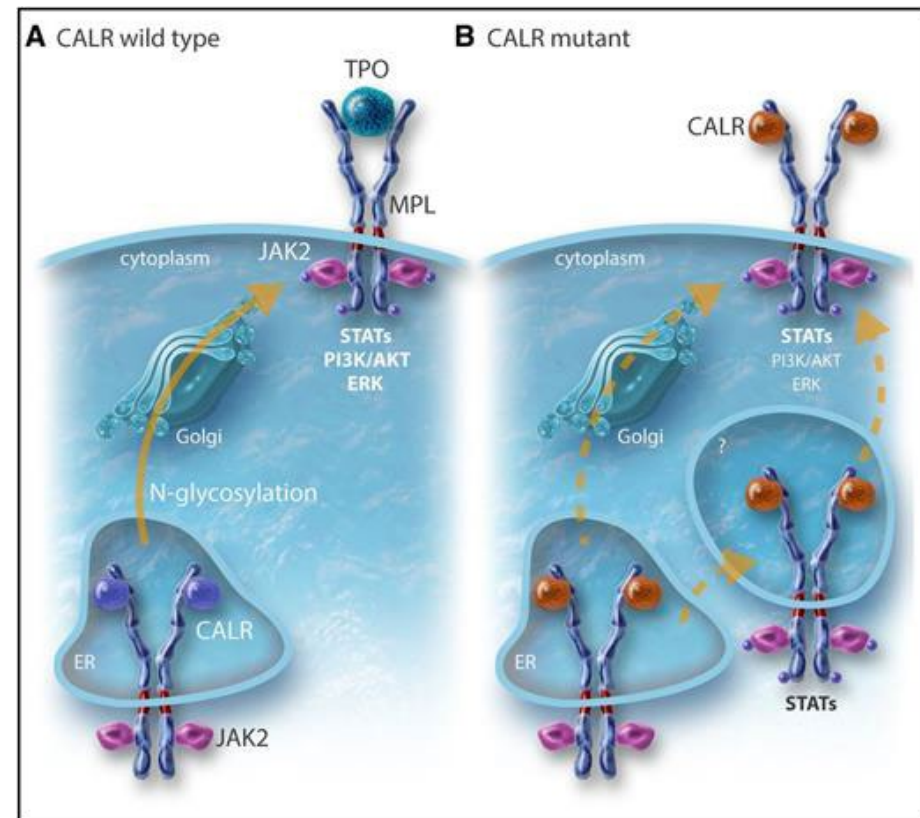
- Fully human IgG1
- Selective binding to mutant *CALR*
- Inhibited *CALR* induced signaling
- Inhibited pSTAT5 in CD34+ mut *CALR* cells not wild type
- Inhibited proliferation of mut *CALR* HSPC/megakaryocytes
- Murine model of ET: reduction in mut *CALR* platelets
- Restored normal megakaryopoiesis

- Phase 1 study in mut *CALR* ET and MF currently ongoing
- NCT06034002 LIMBER trial (recruiting)
- Study start December 2023
- Estimated completion date October 2028

- JNJ-88549968 phase-1 bispecific T-cell/mutant *CALR*
- NCT06150157 (recruiting)
- Study start December 2023
- Estimated completion date November 2026

- Mutant *CALR* peptide vaccine NCT03566446
- Study start date June 2018
- Recruitment completed April 2021

What can we expect?



Vainchenker and Kralovics. *Blood* (2017) 129 (6): 667–679.

Concluding remarks on MPN therapy 2024

- **Less is always more in the management of ET and PV**
- **Allogeneic transplant is the only treatment that secures long-term survival in myelofibrosis – bone marrow registries need more diverse donors**
- **Newer JAK2 inhibitors target the triad of QoL offenders in myelofibrosis: anemia, splenomegaly and constitutional symptoms/cachexia but, have not yet shown to be disease-modifying – treatment paradigms need to be revisited**
- **Regarding investigational new drugs for myelofibrosis, I see lots of cloud but no rain, yet☺**