Myeloproliferative Neoplasms

Current Treatment Approaches

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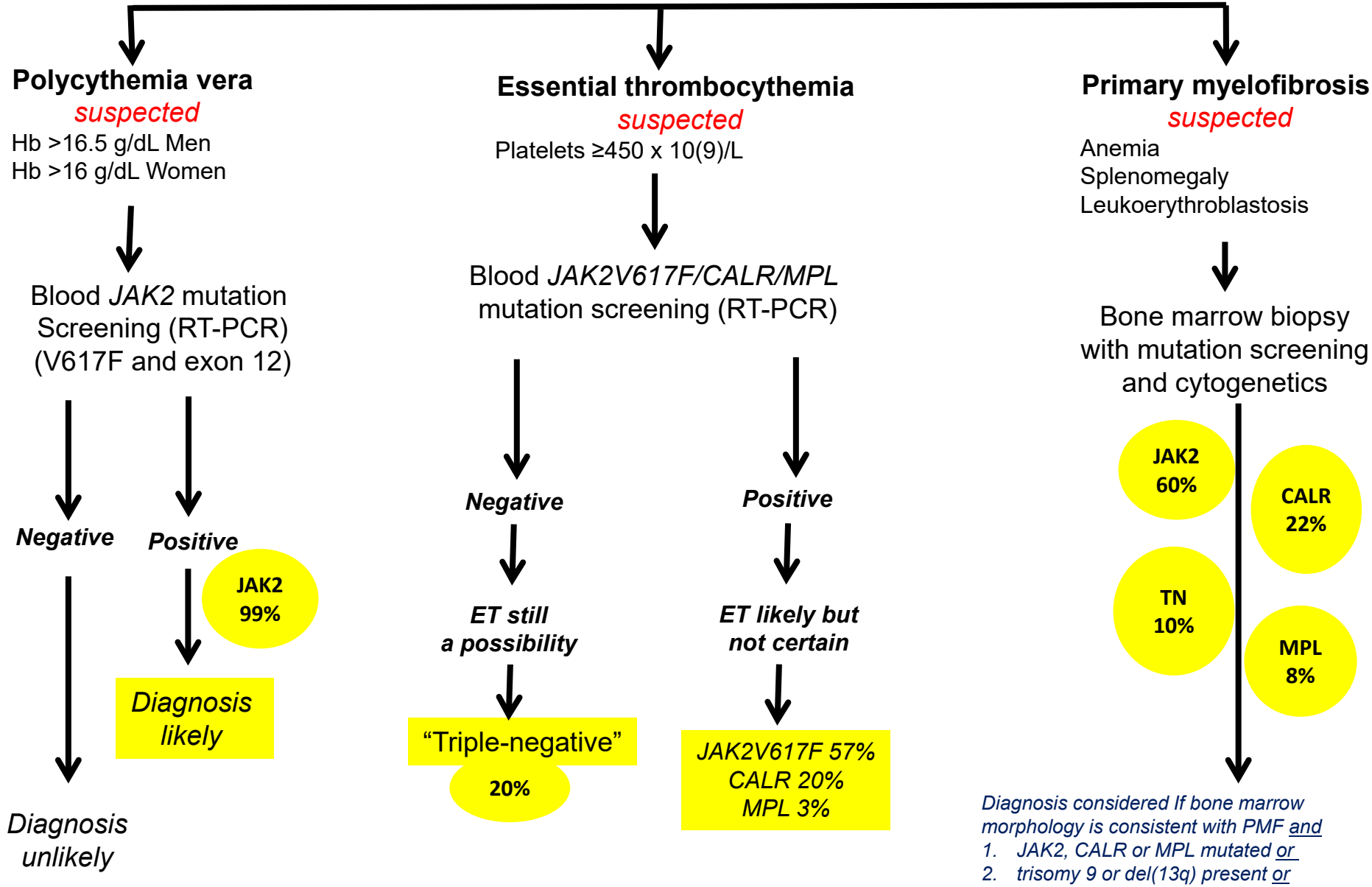
I have nothing to declare

International Consensus Classification

Arber et al. Blood 2022;140:1200

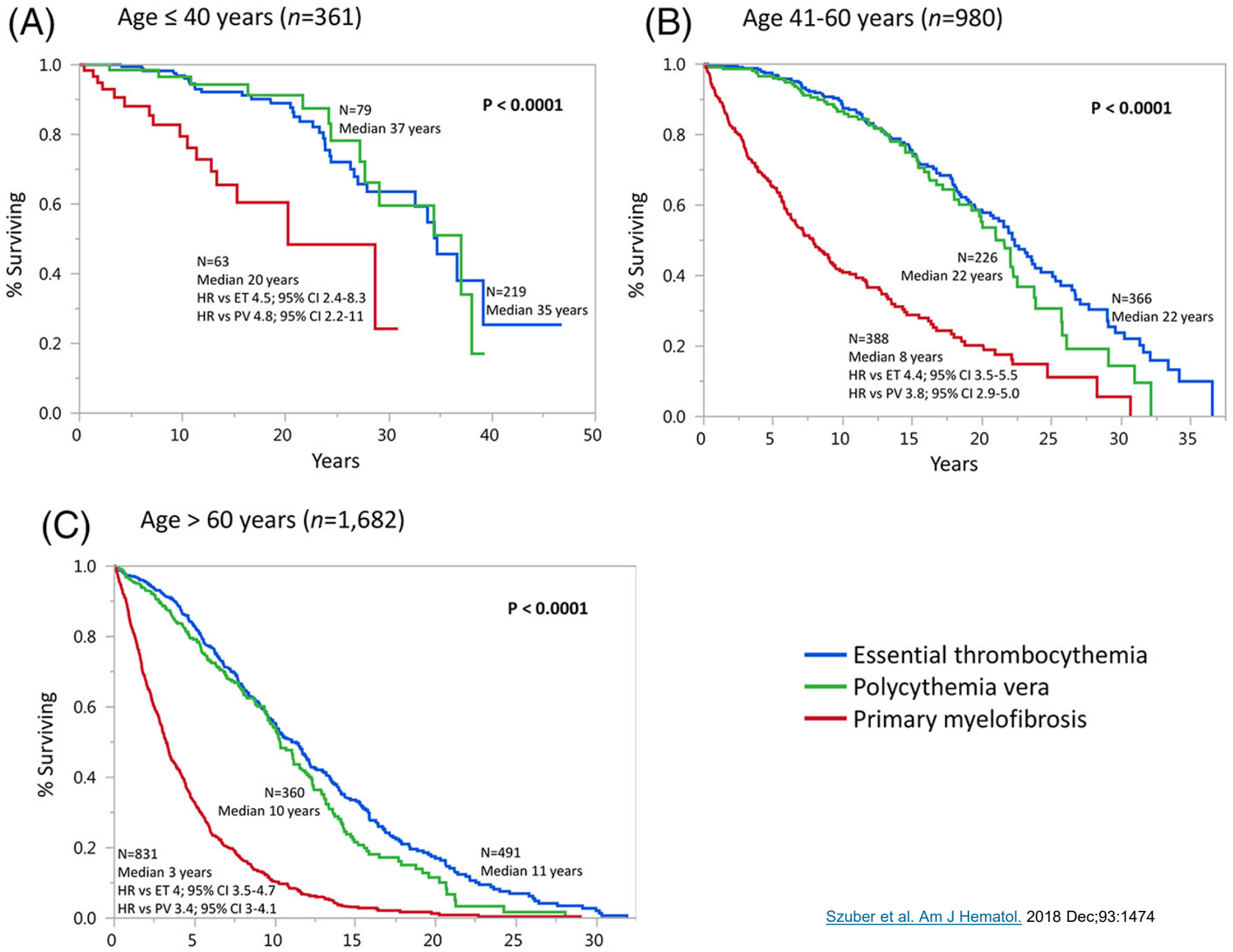


Diagnosis considered If bone marrow morphology is consistent with PMF and

1. *JAK2, CALR or MPL mutated or*
2. *trisomy 9 or del(13q) present or*
3. *Other myeloid malignancies are excluded*

Tefferi, A. AJH 2023;98:801

Age and survival in myeloproliferative neoplasms

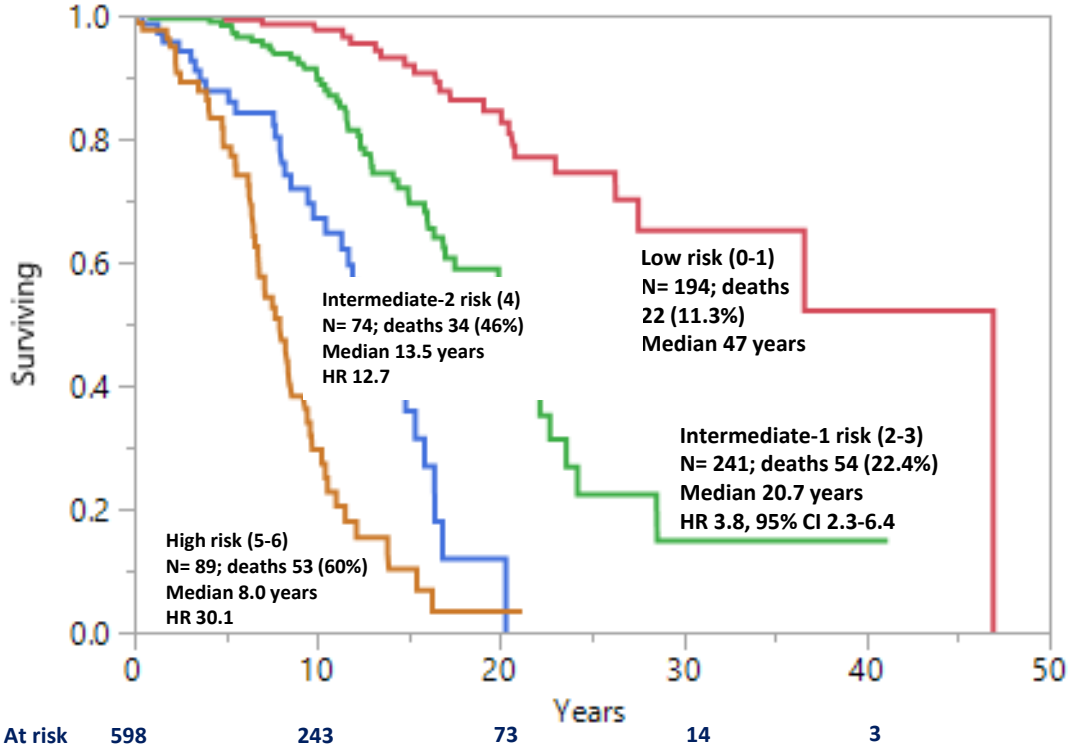


Szuber et al. Am J Hematol. 2018 Dec;93:1474

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

***A**ge >70 years = 4 points*
Age 50-70 years = 2 points
***A**bsolute lymphocyte count <1.7 x 10(9)/L = 1 point*
***A**bsolute neutrophil count ≥8 x 10 (9)/L = 1 point*



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

Tefferi et al. AJH 2023;98:1829

Traditionally low risk

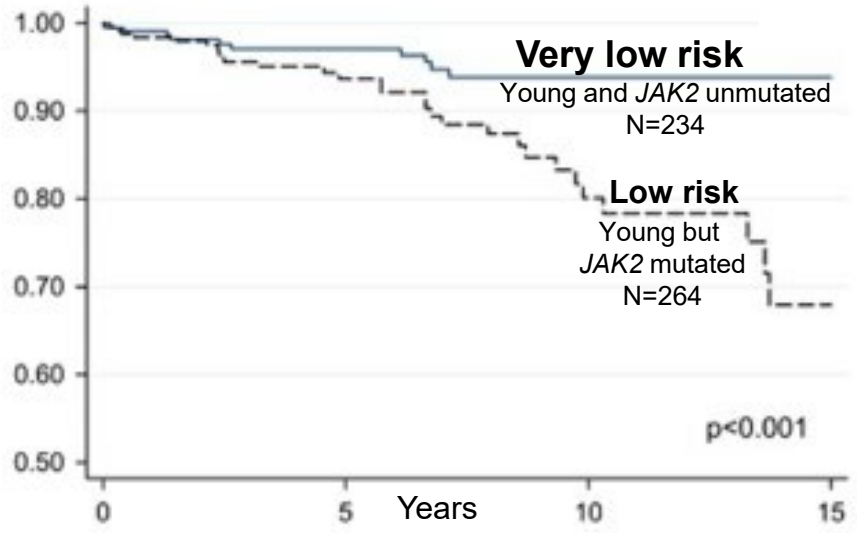
- *Age ≤60 years and*
- *No thrombosis history*

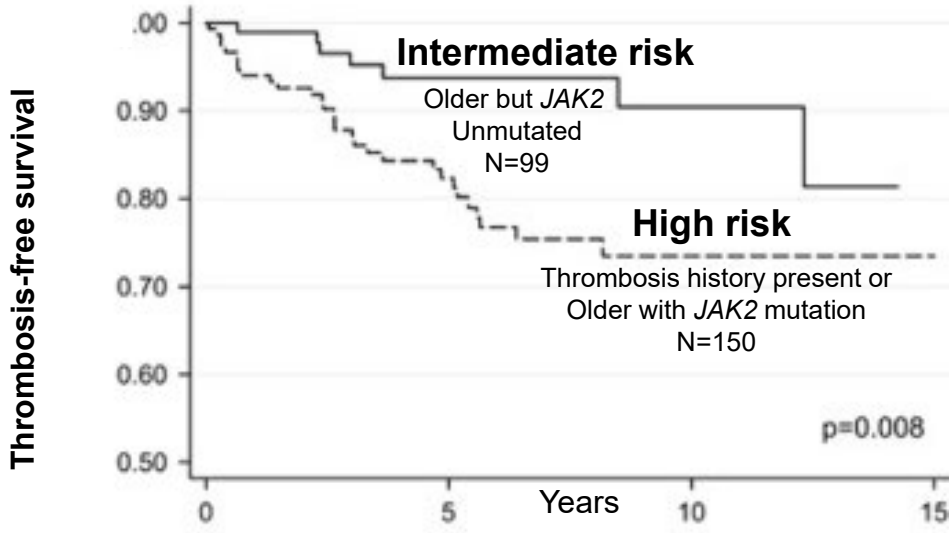
Traditionally high risk

- *Age >60 years or*
- *Presence of thrombosis history*

International prognostic score ET (IPSET)-thrombosis

4-tiered

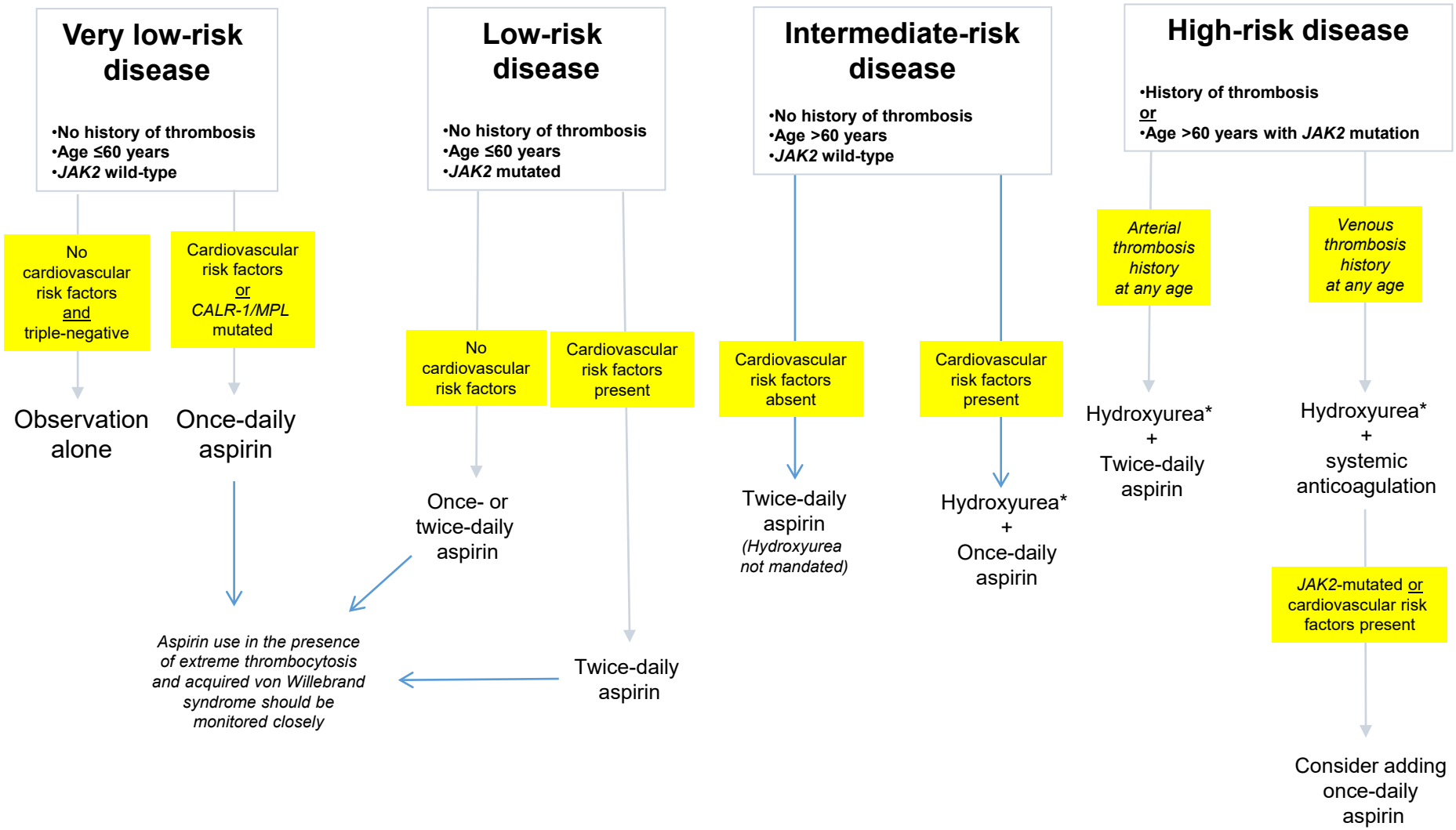




Barbui et al. Blood Cancer J. 2015 Nov; 5(11): e369

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

Bewersdorf et al. Leukemia. 2021 Jun;35(6):1643
Renso et al. Blood Cancer J. 2018 Jun 11;8(6):56
Alvarez-Larrán et al. Ann Hematol. 2014 Dec;93(12):2037
Palandri et al. Am J Hematol. 2009 Apr;84(4):215

Gangat and Tefferi. Am J Hematol. 2021 Mar 1;96(3):354
Sant'Antonio et al. Am J Hematol. 2020 Feb;95(2):156
Martinelli et al. Am J Hematol. 2014 Nov;89(11):E200-5
Tefferi et al. Am J Hematol. 2021 Jun 1;96(6):E182

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

Tefferi, Vannucchi, and Barbui
Leukemia. 2021;35:3339

Current Treatment Approach in Polycythemia Vera

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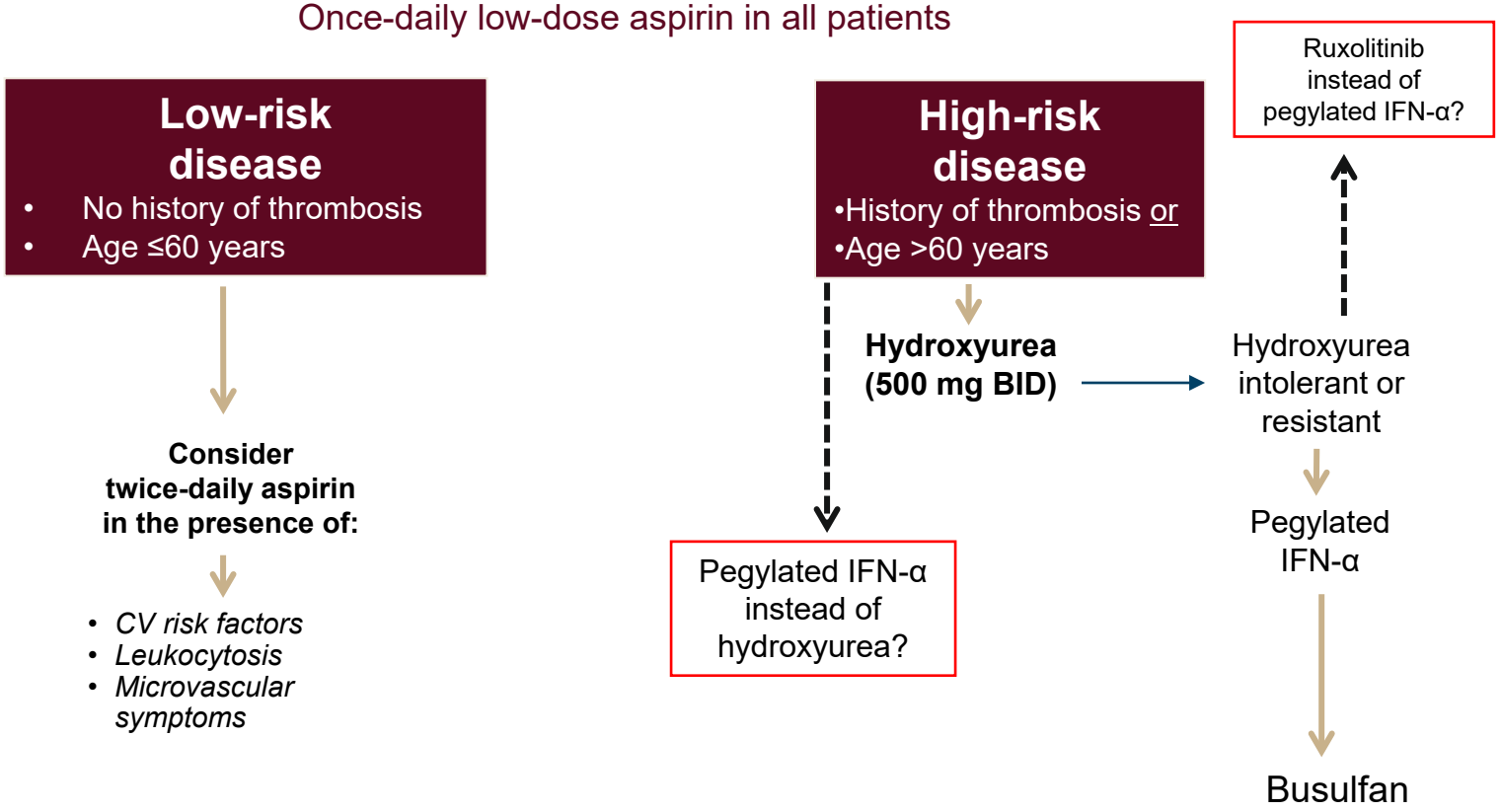

Tefferi, Vannucchi, and Barbui
Leukemia. 2021;35:3339

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. *Blood.* *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. *Lancet Haematol.* *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. *NEJM Evid. 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
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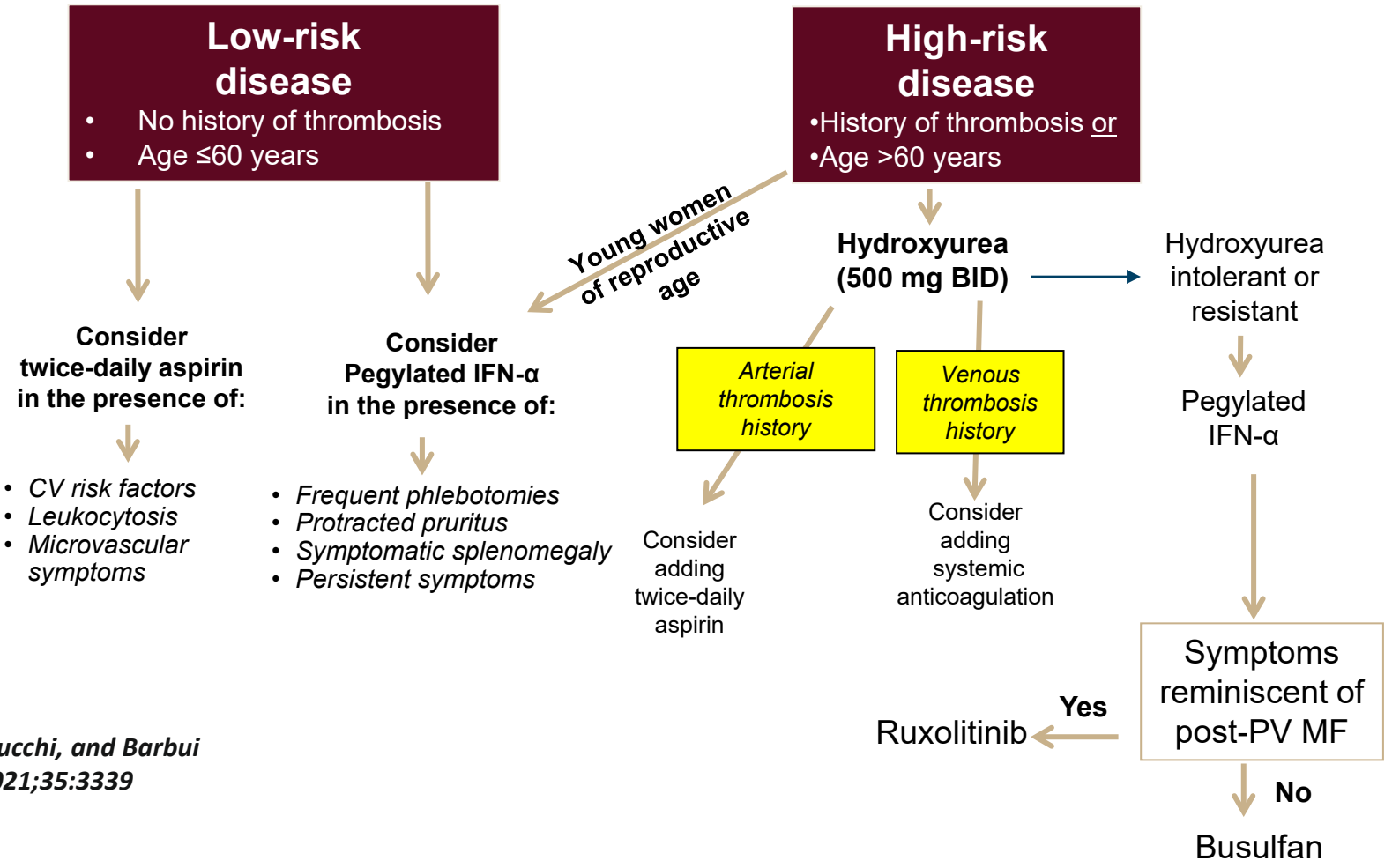
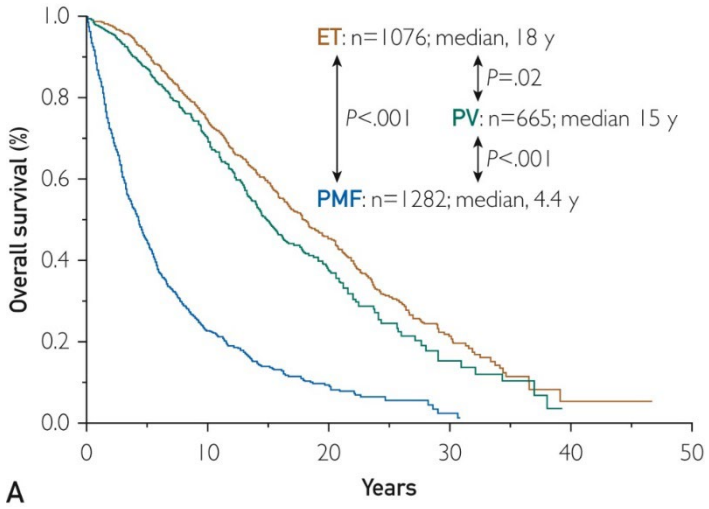
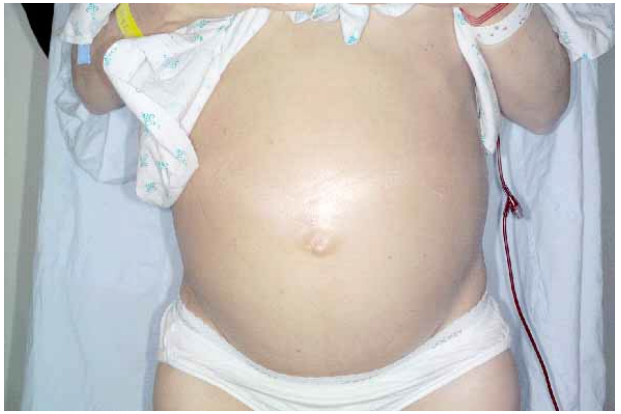
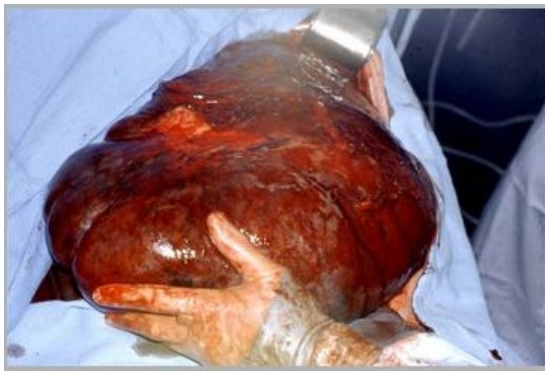


Tefferi, Vannucchi, and Barbui
Leukemia. 2021;35:3339

Disease Complications in Myelofibrosis







- **Anemia**
- **Splenomegaly**
- **Constitutional symptoms**
- **Cachexia**

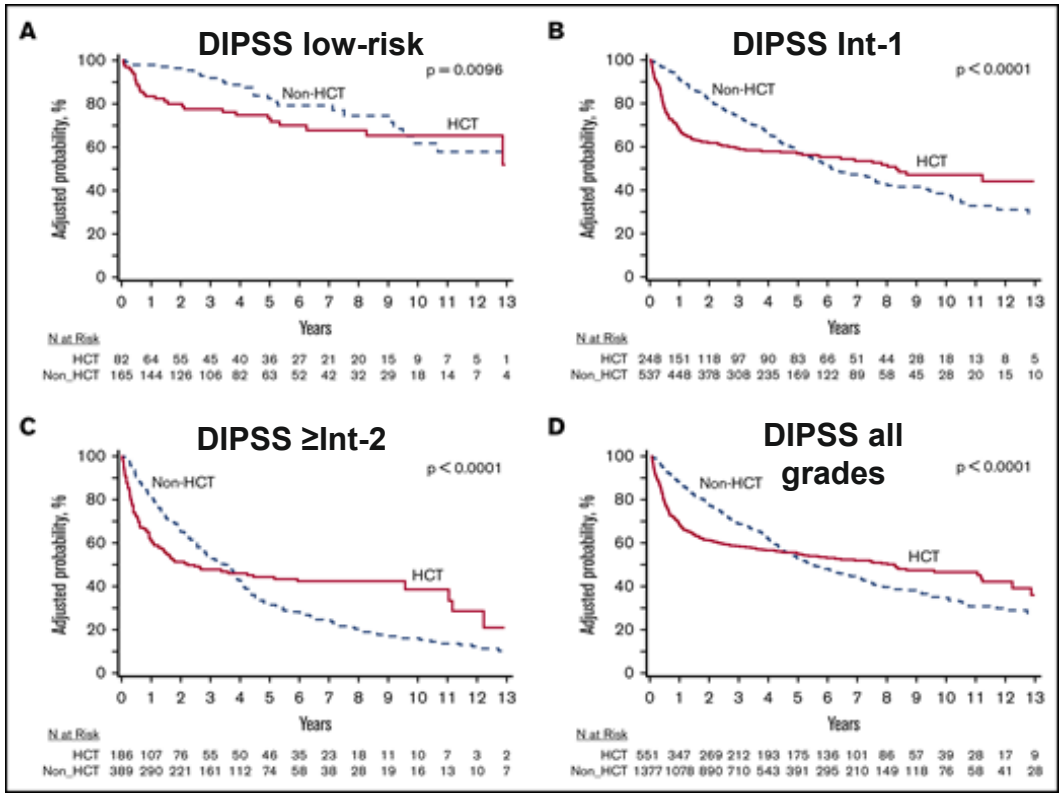
Szuber et al. Mayo Clin Proc. 2019;94:599

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



Gowin K et al. Blood Adv 2020;4: 1965.

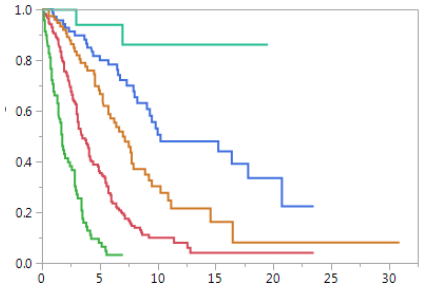
Figure 1:

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

Tefferi et al. J Clin Oncol. 2018;36:1769
Tefferi, A. BMT 2023; doi.org/10.1038/s41409-023-02112-2

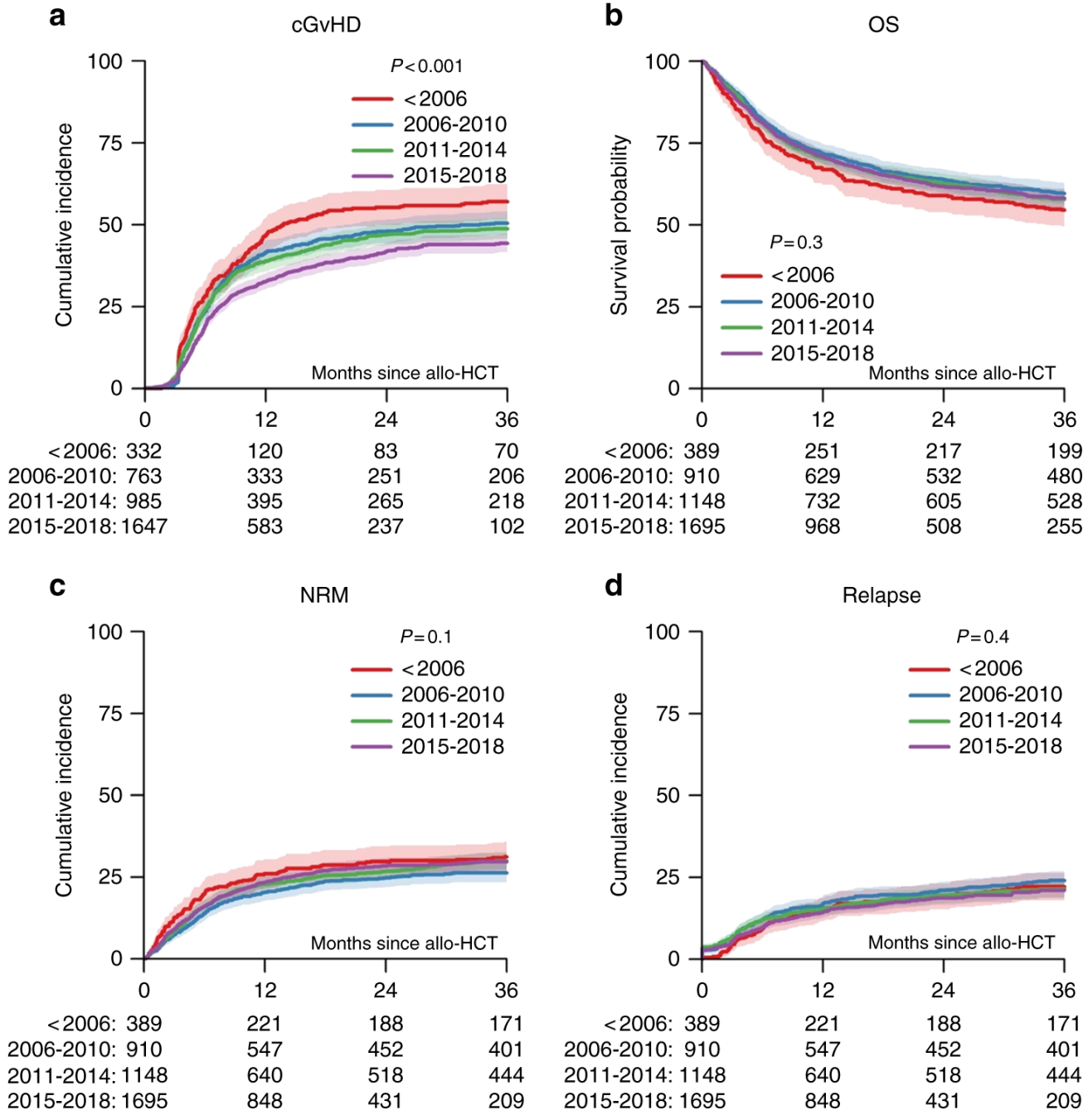
European registry-based study 1995-2018
4,412 MF patients

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:

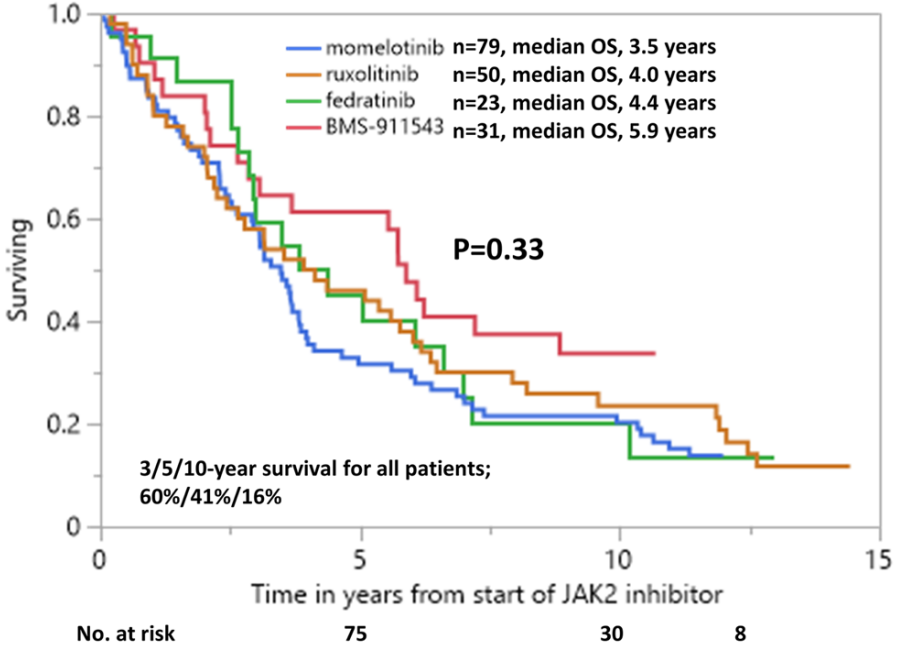
3-year OS 55% to 58%
RFS 47% to 49%
Relapse rate 22% to 21%
NRM 31% to 30%
Primary graft failure 25 to 4%
Secondary graft failure 4% to 7%
Stem cell source



McLornan et al. BMT 2021;56:2160

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

a



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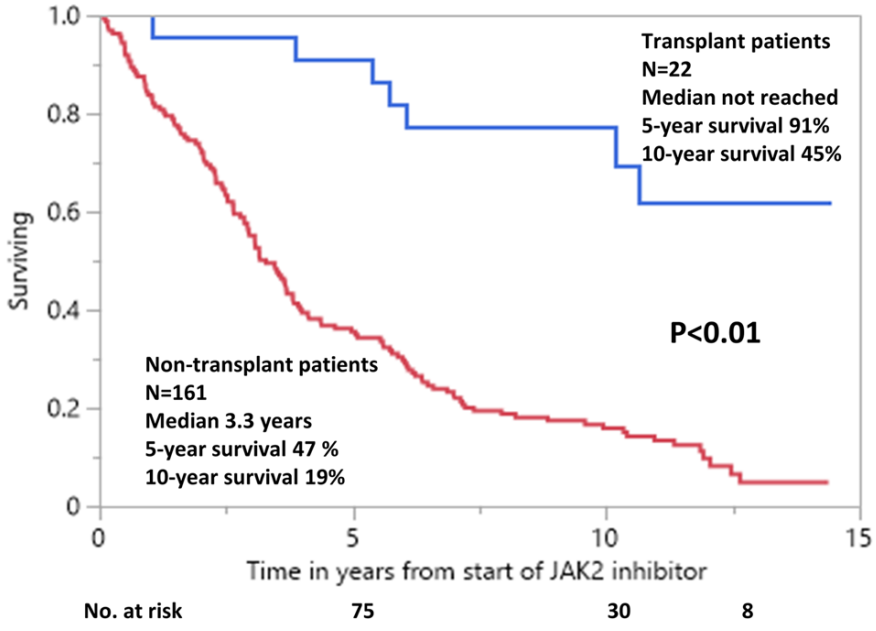


Predictors of inferior survival

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

Gangat et al. Blood Cancer Journal ***volume 13****, Article number: 3 (2023)*

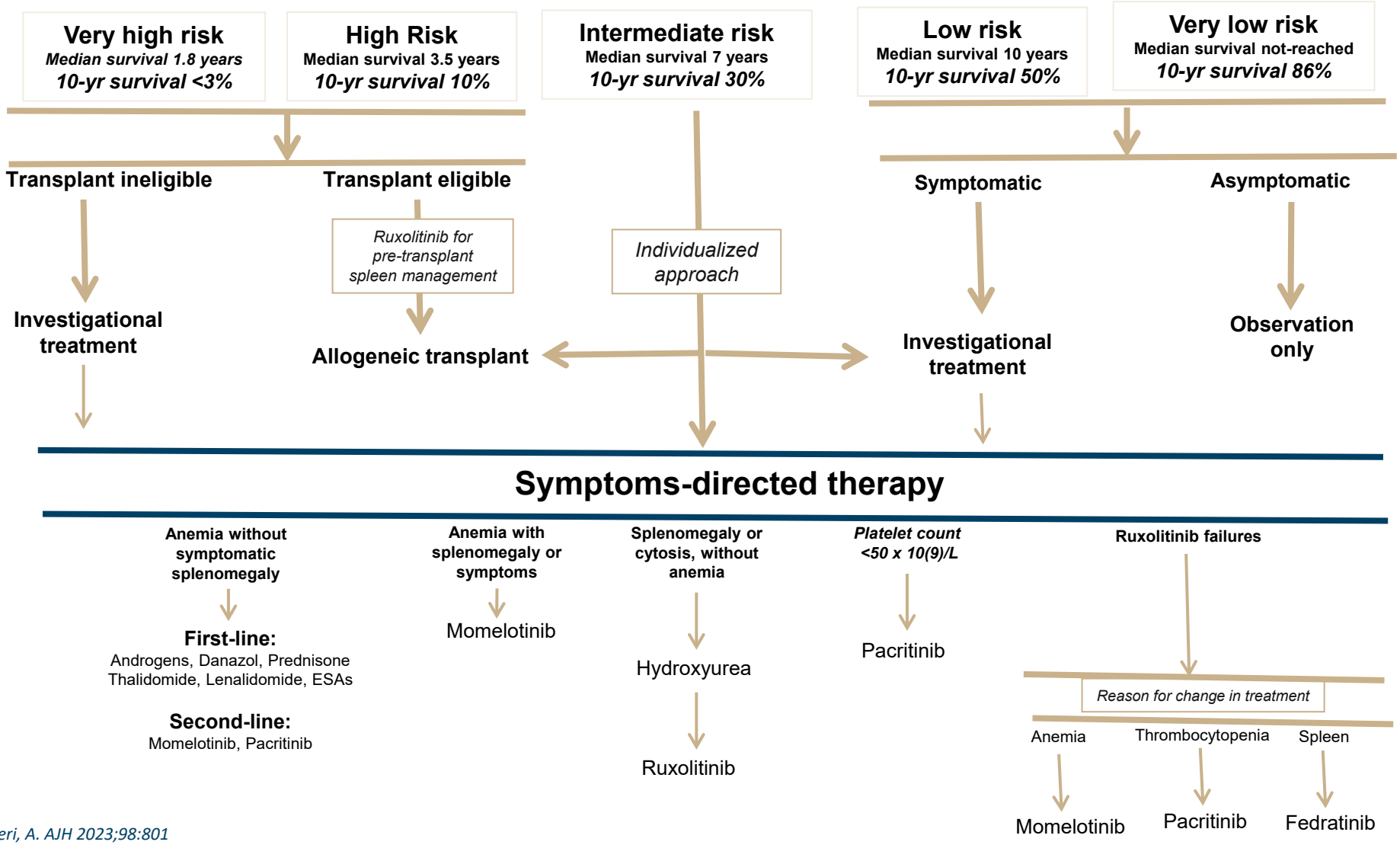
JAK2 inhibitors in myelofibrosis: activity in JAKi-naïve patients

	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) *Ruxo vs mom*	36% (JAKARTA-1) *Pardanani et al. JAMA Oncology 2015* *fed vs placebo*	19% (PERSIST-1) Mesa et al. Lancet Hematology 2017 *Pac vs BAT*	27% (SIMPLIFY-1) *Mesa et al. JCO 2017*
Transfusion resolution	More likely to cause anemia	More likely to cause anemia	25% (PERSIST-1)	46% (Mayo study) *Gangat et al. AJH 2022*
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)

Tefferi et al. Haematologica Early view Mar 2, 2023 https://doi.org/10.3324/haematol.2022.282612

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)*



Tefferi, A. AJH 2023;98:801

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
Spleen	**BMS-986158 + Ruxolitinib/Fedratinib (N=48)** Abstract 623 (JAKi naïve + exposed)	Bromodomain and extra-terminal (BET) inhibitor	++/NR	-	+	GI ↓ Platelet count Anemia
Spleen	**Selinexor + Ruxolitinib (N=14)** Abstract 622 (JAKi naïve)	Nuclear export XPO1 inhibitor	++/++	NR	NR	GI ↓ Platelet count Anemia
Spleen	**INCB057643 +/- Ruxolitinib (N=29)** Abstract 750 (JAKi exposed)	Bromodomain and extra-terminal (BET) inhibitor	+/+	+	NR	↓ Platelet count Anemia GI
Spleen	**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
Anemia	**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
Anemia	**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 (AcRIIA-Fc)

Momelotinib
Pacritinib

Activins
TGF-β
GDF

Bone morphogenic protein (BMP) ligands

ACVR1

ALK inhibitor

Type 2 Receptor (BMPR2/ACVR2A, ACVR2B)

Anti-HJV mAb

BMP signals

Activin signals

SMAD1/5/8

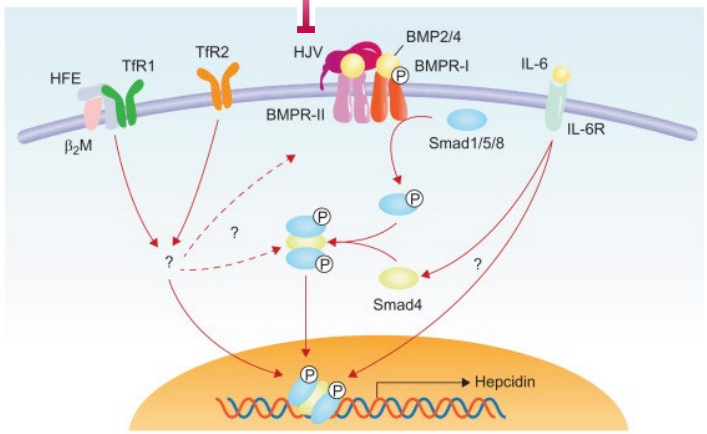
SMAD2/3

Luspatercept
Sotatercept

SMAD4

Activation of genes linked to:
- **Inflammation**
- **Endochondral ossification**
- **Hepcidin production**
  - ➢ **Ineffective erythropoiesis**

anti-HJV mAb



Cytokine receptors

Growth factor receptors

Gain-of-function mutations

JAK2

STAT3

STAT5

Activation of genes linked to:
- **Proliferation**
- **Survival**
- **Inflammation**

Myeloproliferation
Extramedullary hematopoiesis (hepatosplenomegaly)
Aberrant cytokine expression (constitutional symptoms; ineffective erythropoiesis)

Tefferi et al. Haematologica Mar 2, 2023 https://doi.org/10.3324/haematol.2022.282612

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

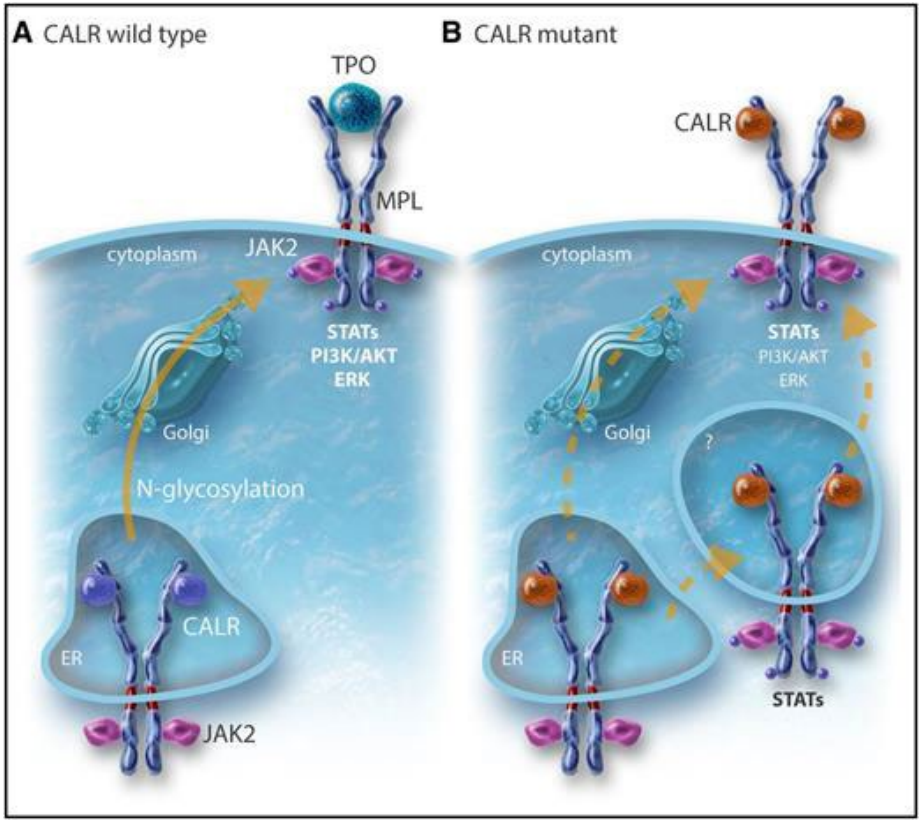
- **Fully human IgG1**
- **Selective binding to mutant *CALR***
- **Inhibited *CALR* induced signaling**
- **Inhibited pSTAT5 in CD34+ mut *CALR* cells not wild type**
- **Inhibited proliferation of mut *CALR* HSPC/megakaryocytes**
- **Murine model of ET: reduction in mut *CALR* platelets**
- **Restored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