Myeloproliferative Neoplasms

Prognostication and therapeutic implications

2022 Indy Hematology Review

Ayalew Tefferi, MD
Barbara Woodward Lips Professor of Medicine
Mayo Clinic, Division of Hematology
Rochester, MN

I have nothing to declare

Objectives

- Contemporary prognostic models
- Risk-based treatment strategies

Diseases to be covered

- Essential thrombocythemia
- Polycythemia vers
- Myelofibrosis

2022 International Consensus Classification (ICC) system for Myeloid neoplasms and Acute leukemia

Daniel A. Arber, MD
Chair
University of Chicago, Chicago, IL, USA

Pathology co-chairs:

Attilio Orazi
Texas Tech University Health Sciences Center,
El Paso, El Paso, USA

Robert P. Hasserjian
Massachusetts General Hospital,
Boston, USA

Clinical advisory committee co-chairs:

Mario Cazzola
University of Pavia, Pavia, Italy

Hartmut Dohner
University of Ulm, Ulm, Germany

Ayalew Tefferi
Mayo Clinic, Rochester, USA

What is new:

Primary AML is now diagnosed in the presence of ≥10% blasts BM or PB
Diagnosis of secondary AML, with antecedent CML, MPN, or MDS, still requires presence of ≥20% blasts
There are now multiple genetic subcategories of AML

New MDS subcategories

MDS with excess blasts 5-9% (2-9% PB)
MDS-SF3B1 (>10% VAF)
MDS-del(5q)
MDS-NOS without or with single-lineage or multi-lineage dysplasia

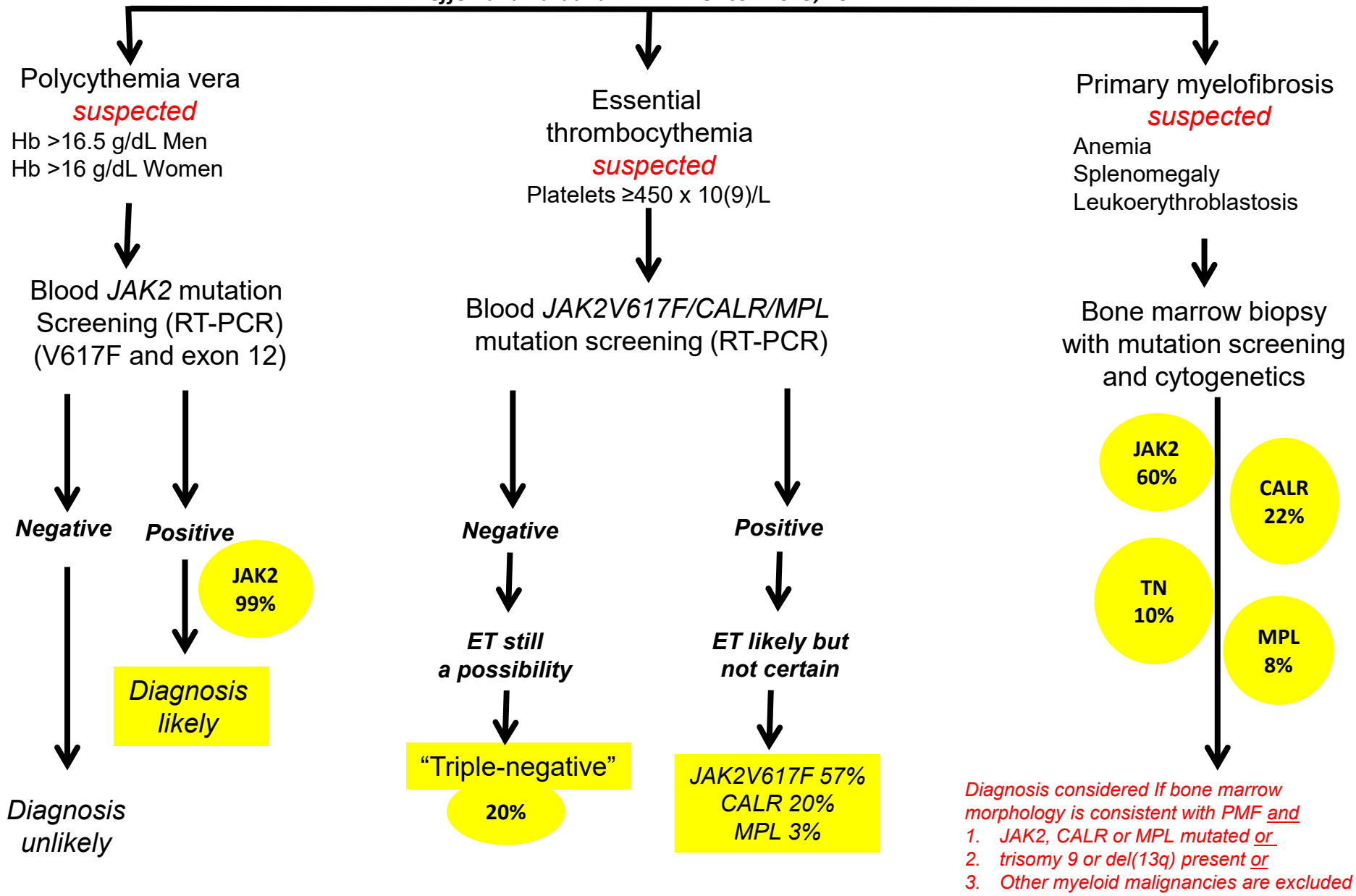
MDS with excess blasts-2 is now classified as MDS/AML, 10-19% blasts
AML, MDS or AML/MDS + *TP53* mutation are now classified as "myeloid neoplasms with *TP53* mutation"
CMML diagnosis now requires ≥0.5 x 10(9)/L PB monocytes and ≥10% fraction, with evidence of clonality

The good news is that MPN classification remained mostly unchanged

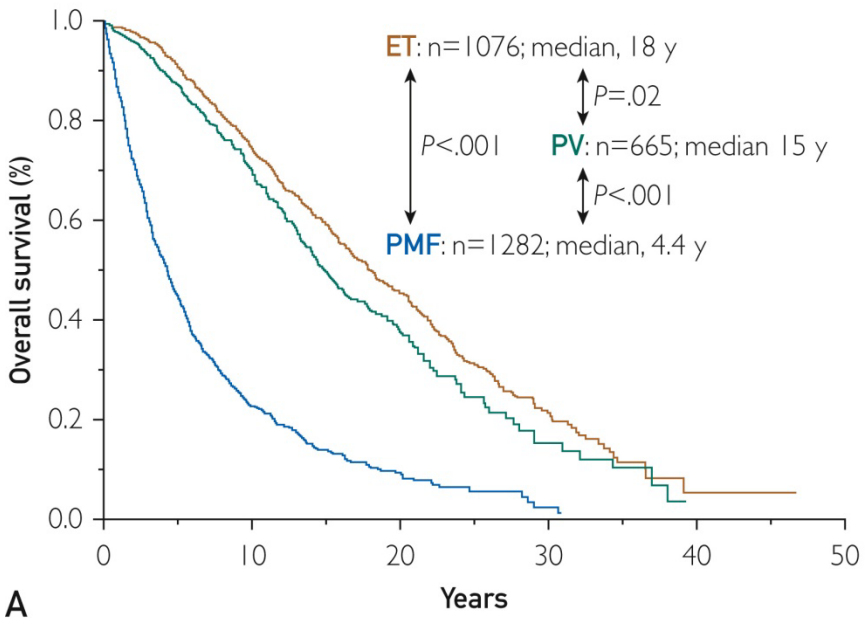
Arber et al. Blood. 2022 (in press)
Arber et al. Am J Hematol. 2022;97:514

Practical algorithm for diagnosis of myeloproliferative neoplasms

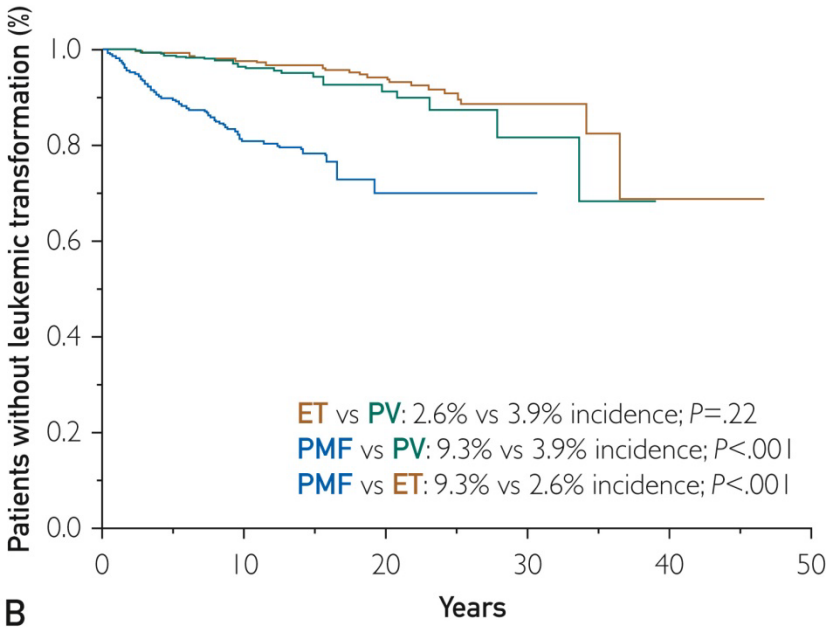
Tefferi and Pardanani. JAMA Oncol. 2015;1:97



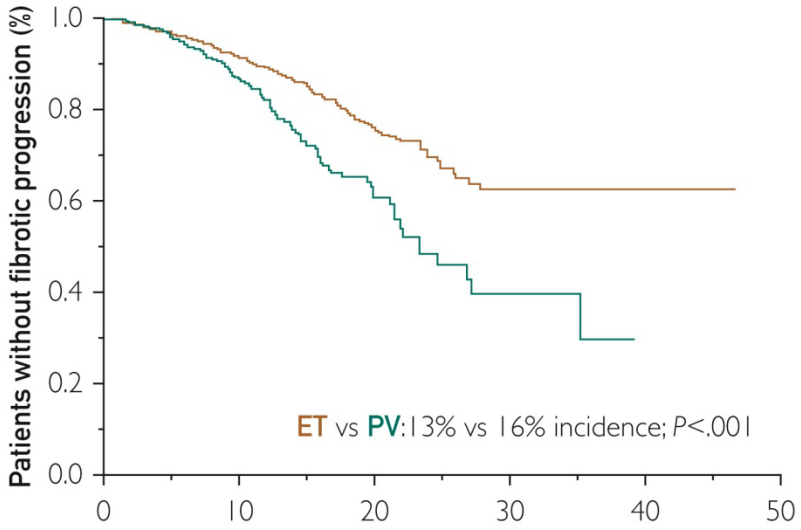
Overall (A), leukemia-free (B), myelofibrosis-free (C), and thrombosis-free (D) survival for 3,023 Mayo Clinic patients with myeloproliferative neoplasms (ET; PMF; PV) seen between 1967 and 2017. Median f/u = 20 years

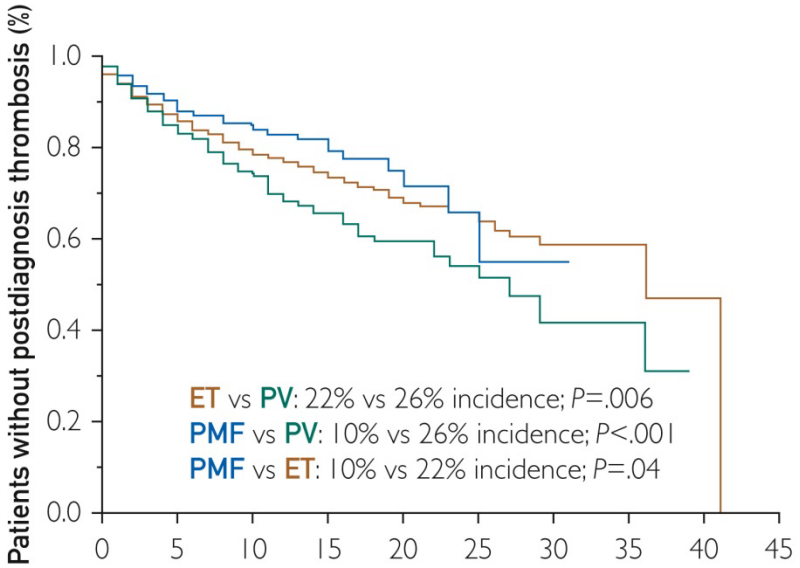


A



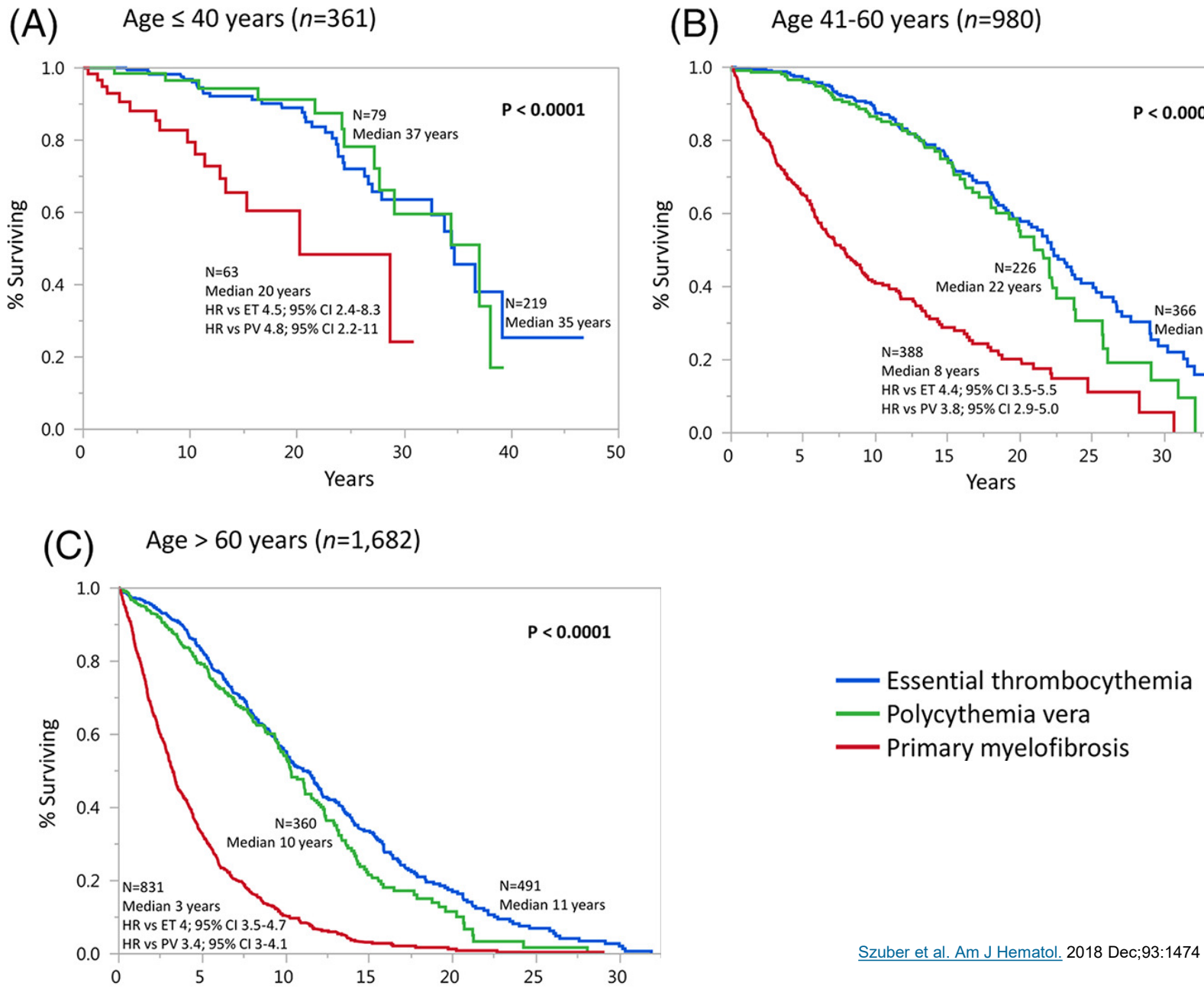
B





Szuber et al. Mayo Clin Proc. 2019;94:599-610.

Age and survival in myeloproliferative neoplasms

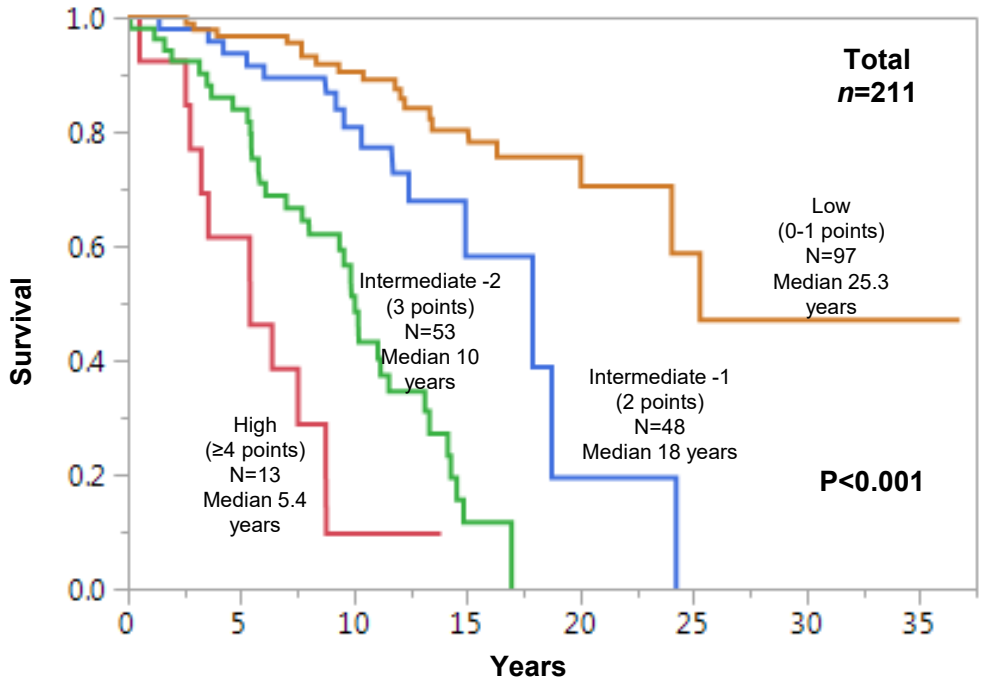


Szuber et al. Am J Hematol. 2018 Dec;93:1474

Mutation-enhanced international prognostic score (MIPSS-PV)

Risk factors:

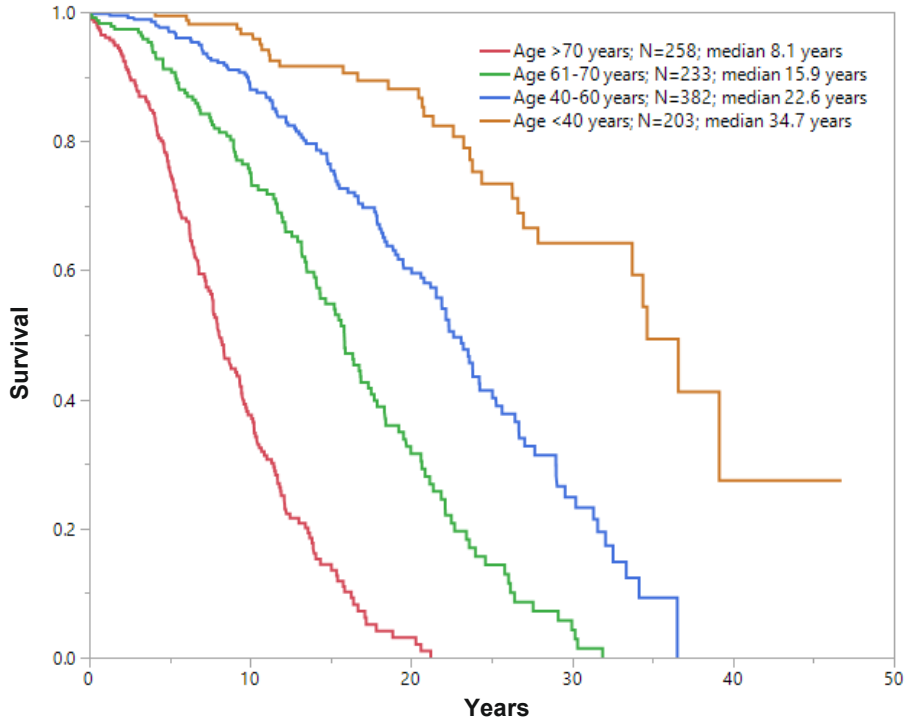
1. *Age >60 years (2 points),*
2. *Leukocyte count ≥11 x 10^9/l (1 point), incidence 50%*
3. *Abnormal karyotype (1 point), incidence 20%*
4. *SRSF2 mutations (2 points), incidence 3%*



Tefferi et al. *BJH* 2020;189:291

ET prognostication

Age-stratified survival among 1,076 Mayo Clinic patients with ET



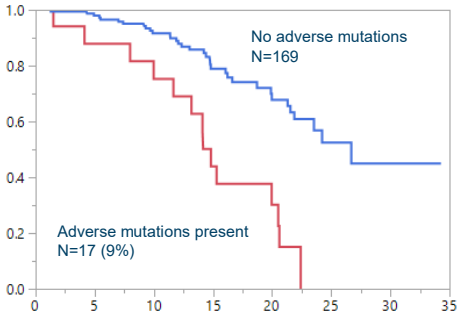
Age-independent risk factors in ET

- *Leukocytosis*
- *Male sex*
- *SF3B1, SRSF2, U2AF1 and TP53 mutations*

MIPSS-ET

Tefferi et al. BJH 2020;189:291

Mutation effect in 186 patients age 40-60 years, based on merged analysis of 451 total informative cases from the Mayo Clinic and University of Florence

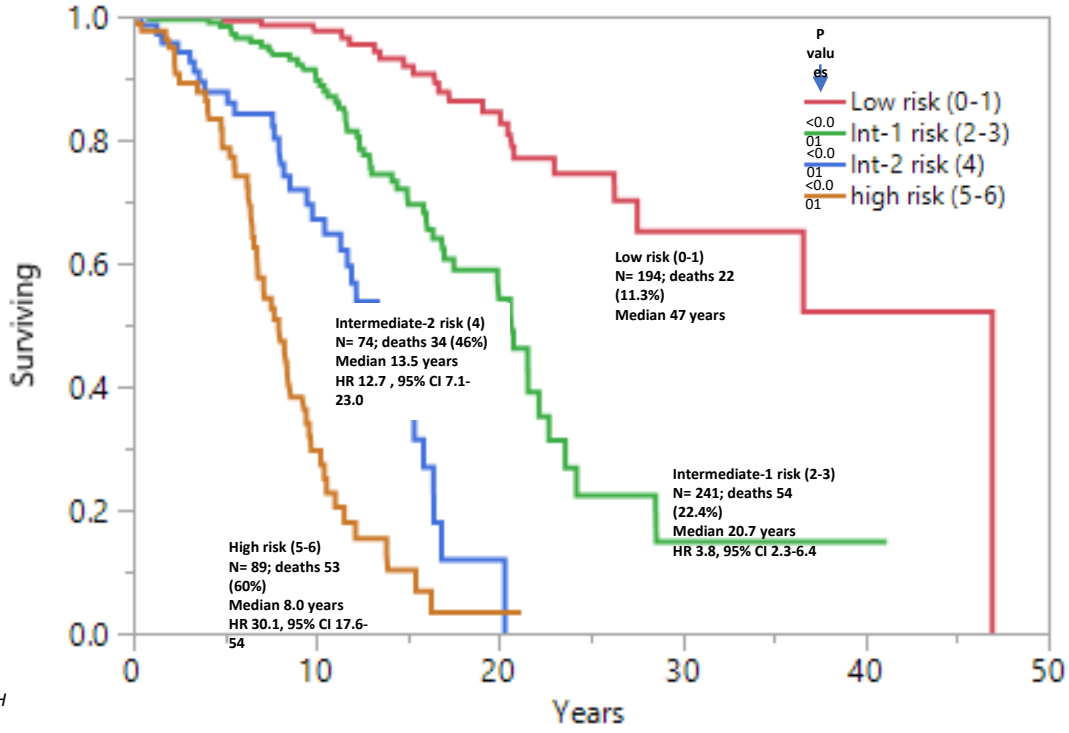


Tefferi and Pardanani, *NEJM* 2019;381:2135

The new 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 x 10(9)/L = 1 point
Absolute neutrophil count ≥8 x 10 (9)/L = 1 point

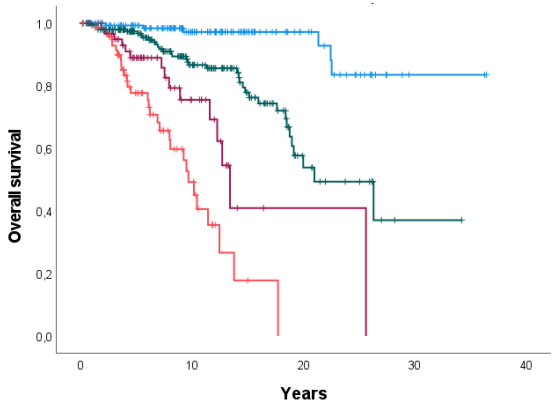


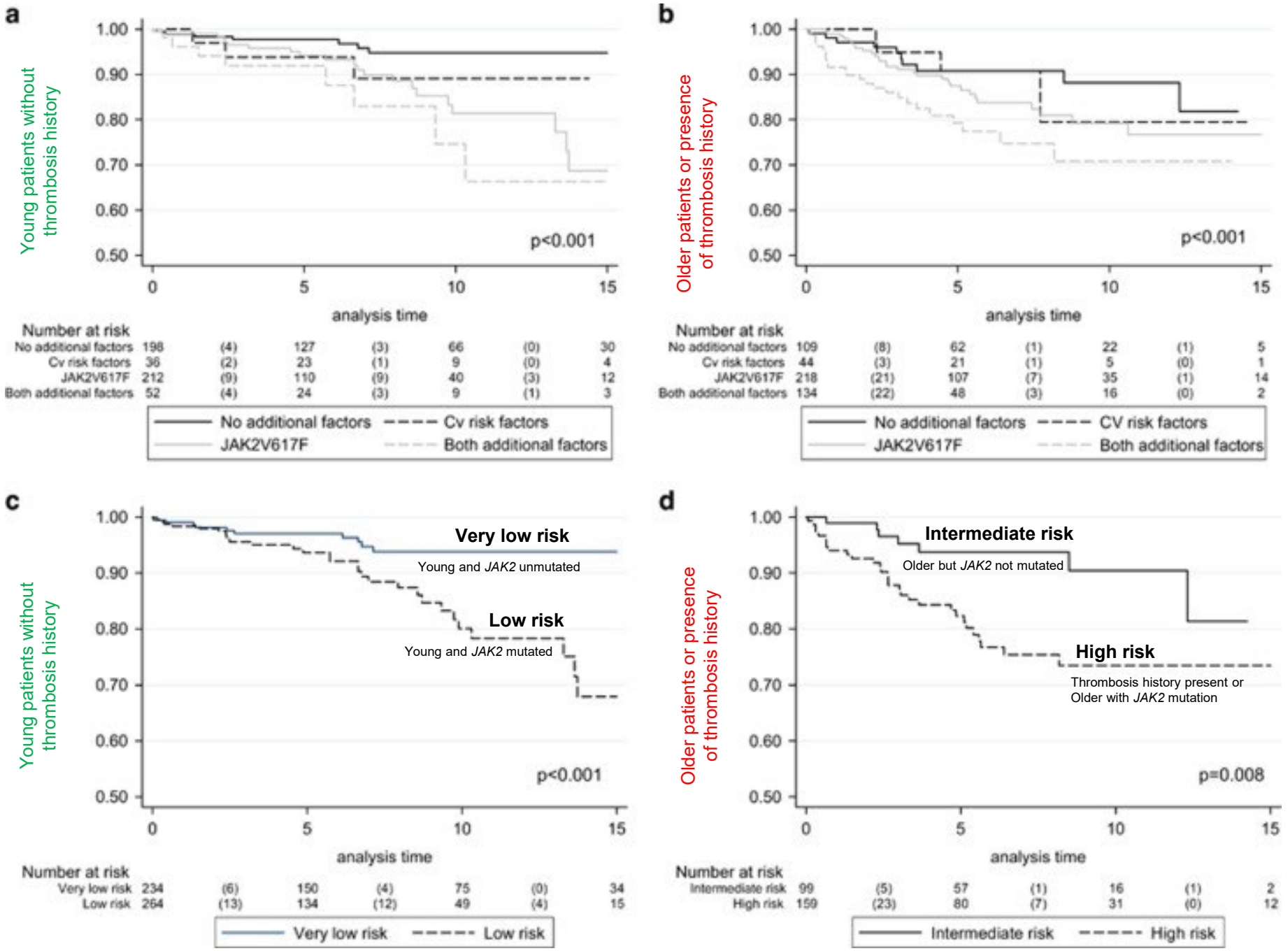
At risk	59	24	7	1	3
	8	3	3	4	

Tefferi et al. ASH 2021

Validation cohort

Overall survival data among 485 University of Florence patients with essential thrombocythemia

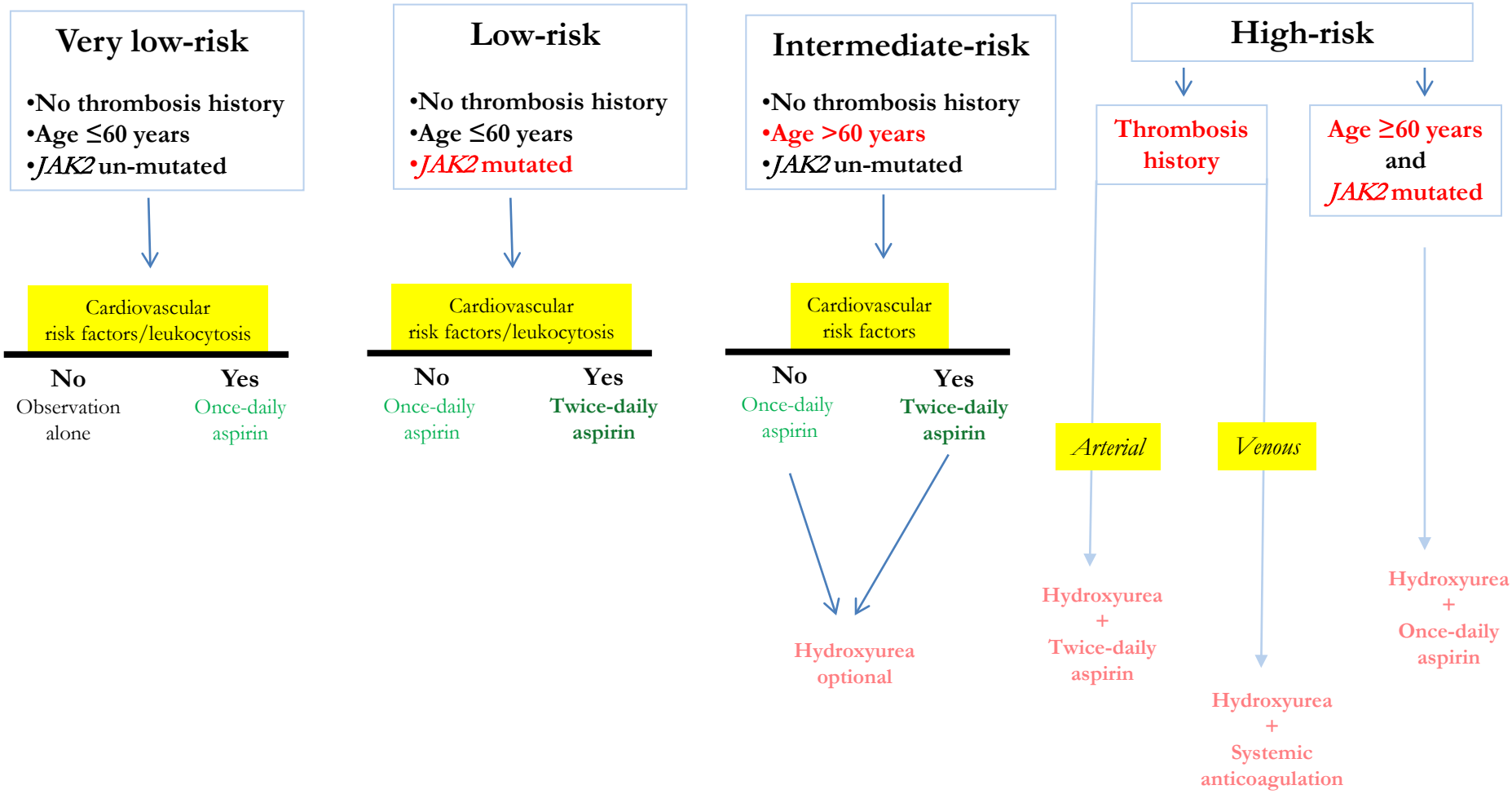




Revised IPSET: Barbui et al. Blood Cancer J. 2015 Nov; 5(11): e369

Current Treatment Algorithm in Essential Thrombocythemia

Blood Cancer J. 2018 Jan 10;8(1):2



Additional points:

-Must consider the possibility of AvWS before instituting aspirin therapy, especially in the presence of extreme thrombocytosis

-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

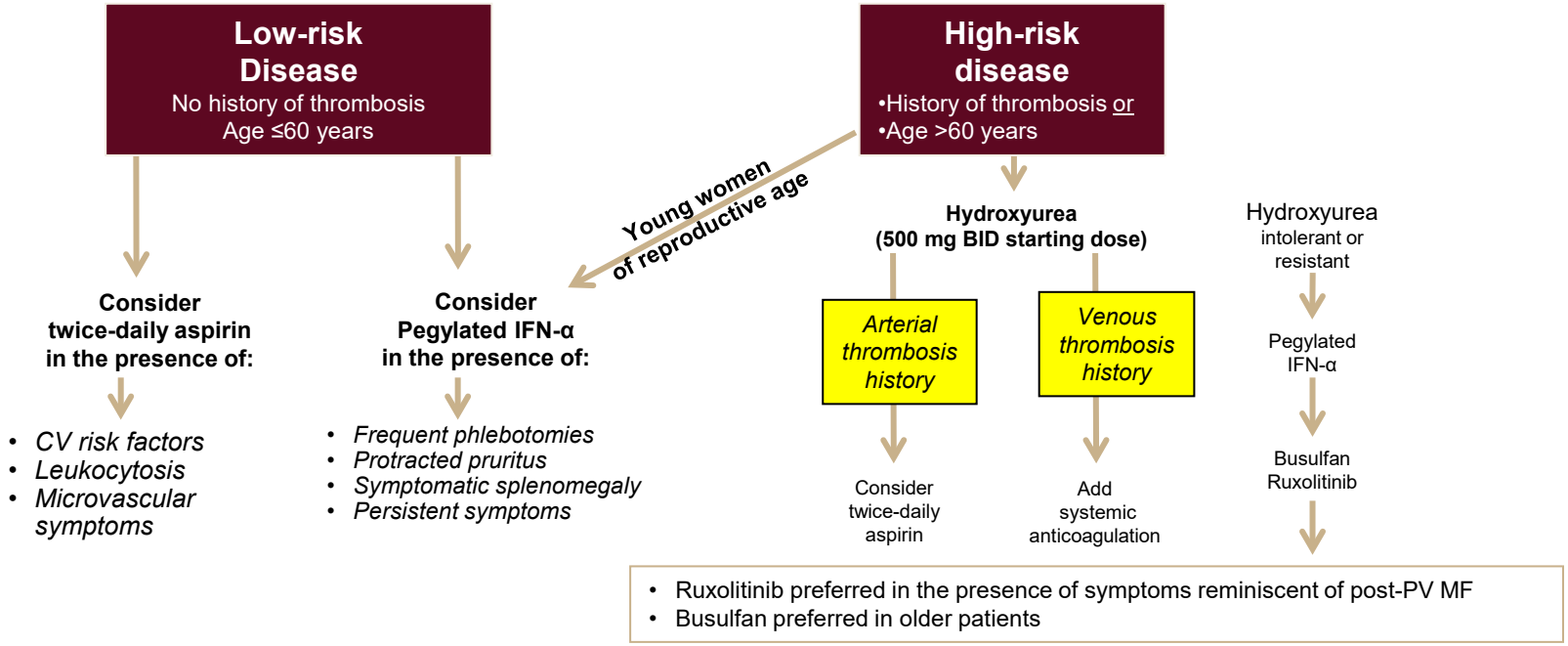
Vascular events among 27 low-risk patients with essential thrombocythemia presenting with extreme thrombocytosis (≥ 1500 x10^9/L), stratified by initial treatment reports

Variables	All patients n=27	Observation alone n=5	Aspirin alone n=5	Cytoreduction alone n=7	Aspirin + cytoreduction n=7
Driver mutation status, n (%)					
-JAK2V617F	8 (30)	1 (20)	1 (20)	1 (14)	4 (57)
- CALR	14 (52)	3 (60)	3 (60)	5 (71)	2 (29)
Median f/u in years (range)	15.3 (0.5-46.9)	11.2 (4.4-24.3)	15.5 (7.5-27.5)	10.0 (0.5-22.3)	19.5 (4.1-41.2)
Major thrombosis, n (%)					
- Arterial thrombosis	2 (7)	0	0	1 (14)	1 (14)
- Venous thrombosis	1 (4)	1 (20)	0	0	0
Major hemorrhage, n (%)	3/26 (12)	1 (20)	0	0	1 (14)

Gangat et al. Blood Advances (in press)
Gangat et al. AJH 2021;96:E93
Tefferi et al. Am J Hematol. 2021;96:E182

Current Treatment Approach in Polycythemia Vera

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



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

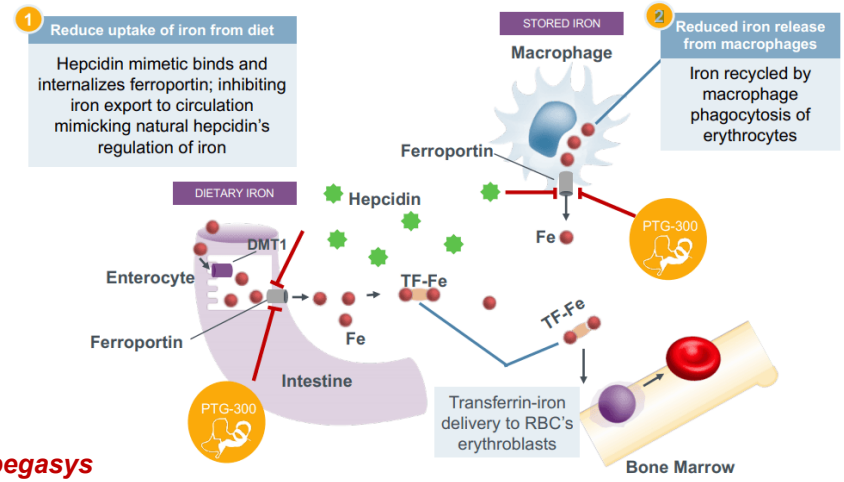
New Drugs in PV

Ropeginterferon (Ropeg)

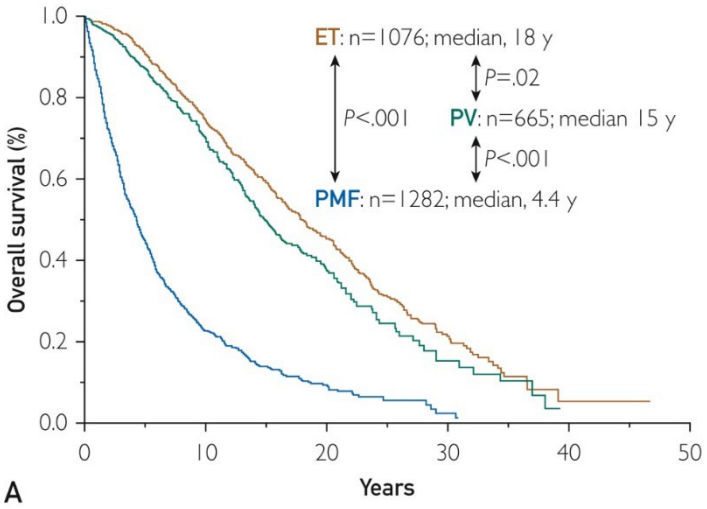
- **High-risk disease**
  - Ropeg (Besremi®) vs HU in PV phase-3…***Gisslinger et al. Lancet Hematology 2020;7:e196***
    - CHR…43% vs 46%... Ropeg associated with more side effects and lower *JAK2* allele burden
  - Pegasys (Peg-rIFN-α2a) vs HU…***Mascarenhas et al. Blood. 2022 May 12;139(19):2931…***168 patients with PV (87) or ET (81)
    - CR 35% vs 37%, at 12 months; 30% vs 28% in PV…
      - Pegasys better at Hct control and reduction of *JAK2* allele burden
      - HU better at histopathologic responses and less grade 3 or 4 adverse events.
- **Low-risk disease**…**Barbui et al. *Lancet Hematology* 2021;8:e175; Ropeg** *better Hct control than phlebotomy alone relevance?...f/u 1 yr*

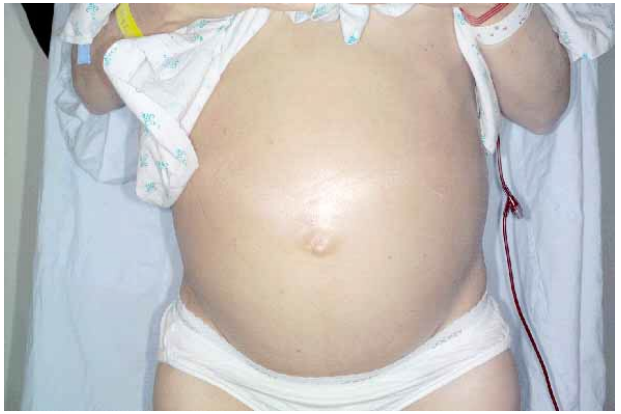
PTG-300 (Rusfertide; hepcidin mimetic) Kremyanskaya et al. *Blood* 136, 2020

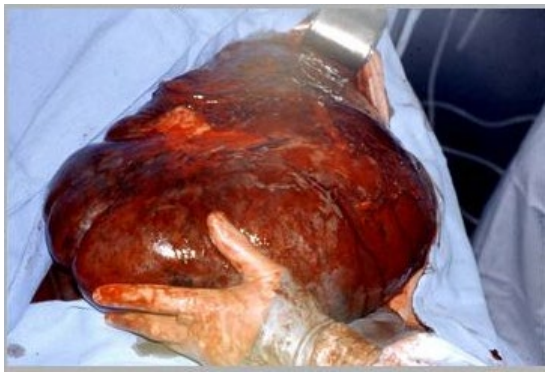
- *Weekly SC injection*
- *Marked reduction in phlebotomy need and reversal of iron deficiency*
- *No effect on platelet or leukocyte count*
- ***High-risk disease…***
  - ***dubious role since broader myelosuppression is secured by cytoreductive therapy***
- ***Low-risk disease…uncertain role in the context of alternative therapy with pegasys***



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

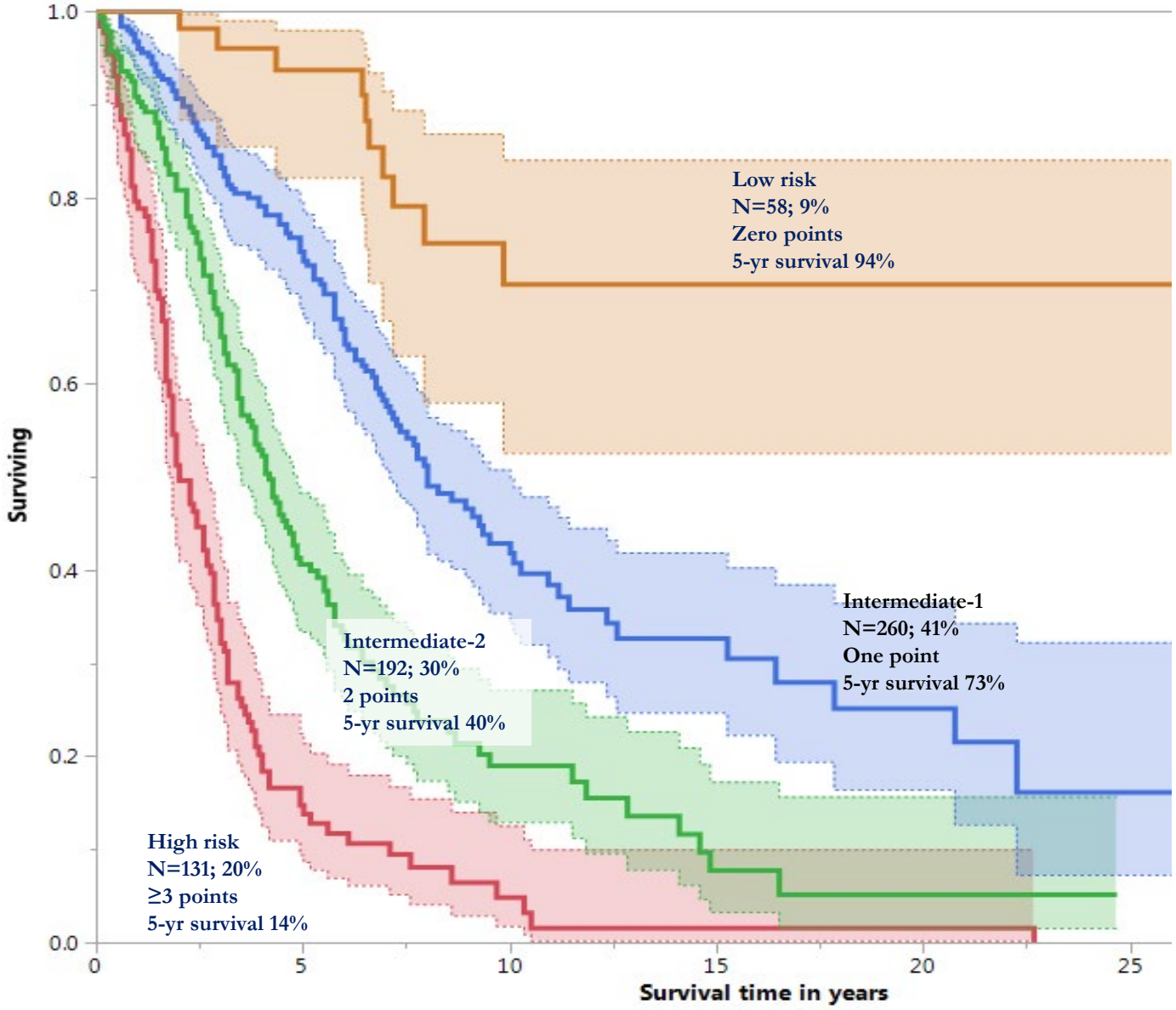
Prognostication in myelofibrosis

1. **Mutation-enhanced international prognostic scoring system version 2.0 (MIPSS*v2*)**
2. **Genetics-inspired IPSS (GIPSS)**

Guglielmelli et al. J Clin Oncol. 2018;36:310
Tefferi et al. J Clin Oncol. 2018;36:1769

GIPSS

genetically-inspired prognostic scoring system-stratified survival data in 641 patients with primary myelofibrosis



Karyotype:
Very high risk = 2 points
Unfavorable = 1 point

High risk mutations:
ASXL1 mutation = 1 point
SRSF2 mutation = 1 point
U2AF1 Q157 mutation = 1 point

Driver mutations:
Type 1/like *CALR* absent = 1 point

Very high Risk karyotype	Favorable karyotype
-7	NN
+21	-Y
+19	13q-
12p-	+9
11q-	20q-
i(17q)	1(dup)
Inv(3)	

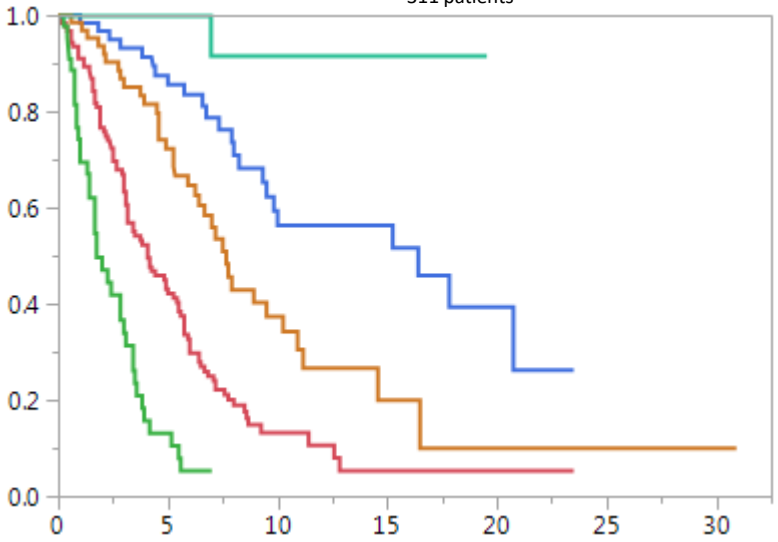
Tefferi et al. Leukemia. 2018;32:1631

Survival data on Mayo Clinic patients with primary myelofibrosis stratified by MIPSS70+ *version 2.0 (MIPSSv2)*

Risk categories: very high risk ≥9 points; high risk 5-8 points; intermediate risk 3-4 points; low risk 1-2 points; and very low risk zero points

Age 70 years or younger

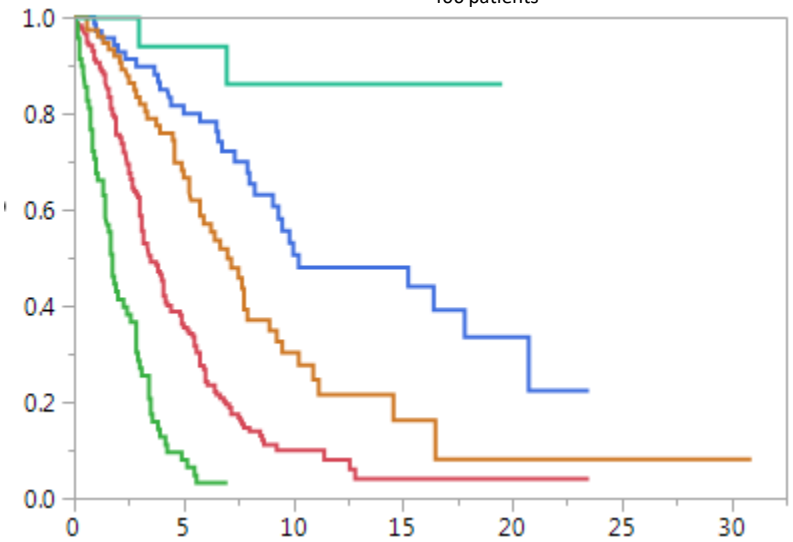
311 patients



- Very high risk; *n*=44; median 1.8 years; 10-year survival <5%
- High risk; *n*=124; median 4.1 years; 10-year survival 13%
- Intermediate risk; *n*=64; median 7.7 years; 10-year survival 37%
- Low risk; *n*=61; median 16.4 years; 10-year survival 56%
- Very low risk; *n*=18; median not reached; 10-year survival 92%

All ages

406 patients



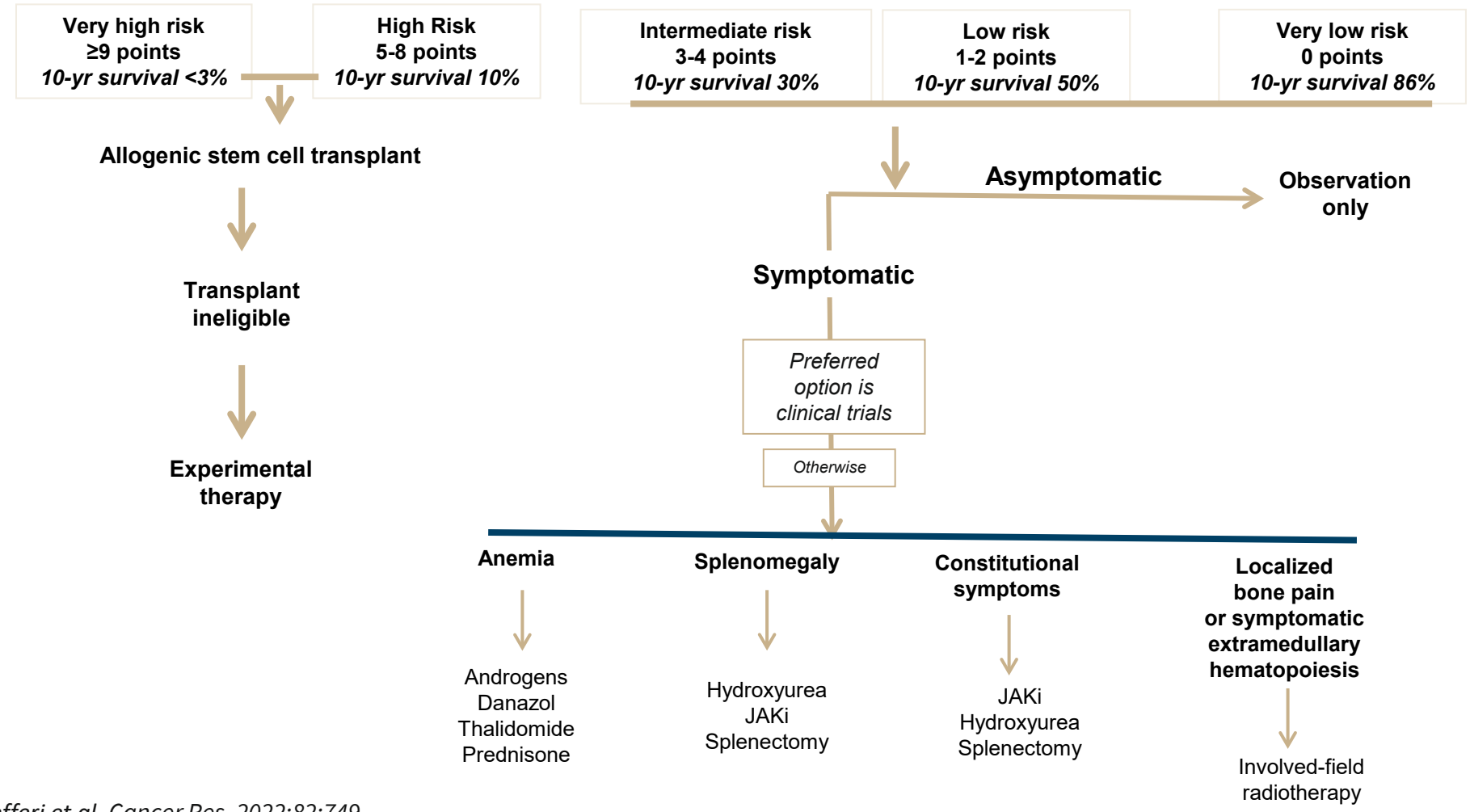
- Very high risk; *n*=69; median 1.8 years; 10-year survival <3%
- High risk; *n*=172; median 3.5 years; 10-year survival 10%
- Intermediate risk; *n*=76; median 7 years; 10-year survival 30%
- Low risk; *n*=70; median 10.3 years; 10-year survival 50%
- Very low risk; *n*=19; median not reached; 10-year survival 86%

Very high risk karyotype	**4 points**
Unfavorable karyotype	**3 points**
≥2 HMR mutations	**3 points**
One HMR mutation	**2 points**
Type 1/like CALR absent	**2 points**
Constitutional symptoms	**2 points**
Severe anemia	**2 points**
Moderate anemia	**1 point**
≥2% circulating blasts	**1 point**

Tefferi et al. J Clin Oncol. 2018;36:1769

Current Treatment Algorithm in Myelofibrosis (Risk-adapted)

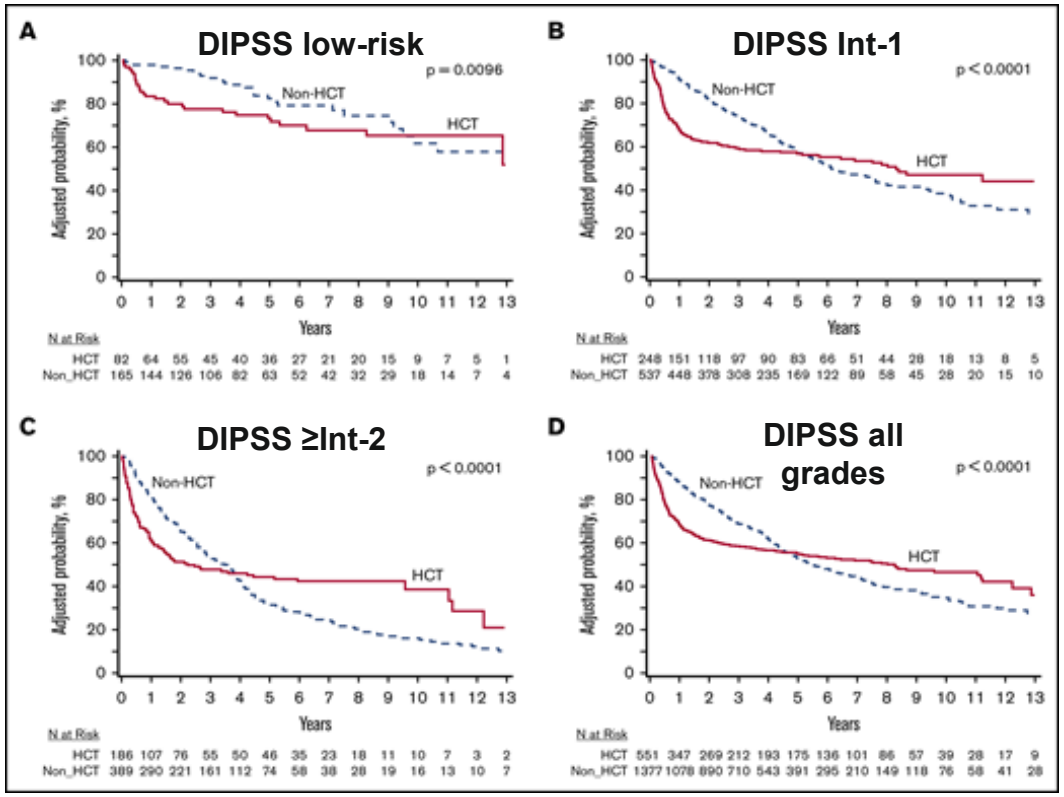
MIPSS70+ version 2.0
***Karyotype**: Very high risk 4 points; unfavorable 3 points;*
Mutations:: ≥2 high risk 3 points; one high risk 2 points;
***Type 1 CALR mutation**: absent 2 points;*
***Clinical risk factors**: constitutional symptoms 2 points; severe anemia 2 points; moderate anemia 1 point; ≥2% circulating blasts 1 point*



Tefferi et al. Cancer Res. 2022;82:749

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.

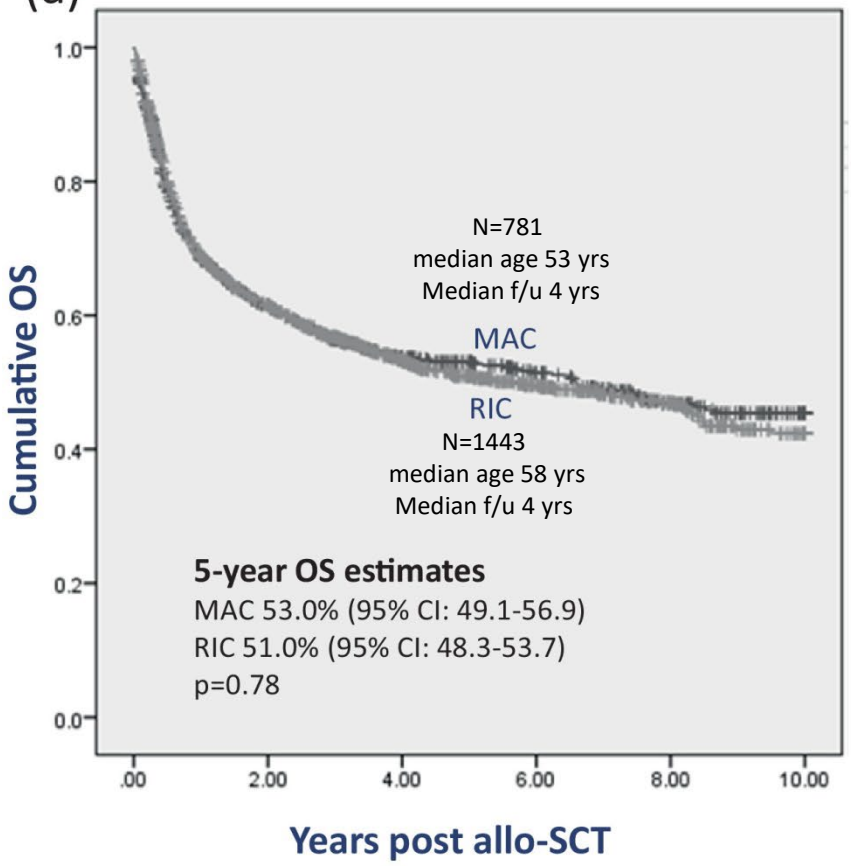
RIC vs MAC

Retrospective study by the ESBMT of 2224 MF patients
who underwent allogeneic stem cell transplantation between 2000 and 2014

McLornan et al. Biol Blood Marrow Transplant 2019;25:2167

(a)

~40% related and 60% unrelated donors



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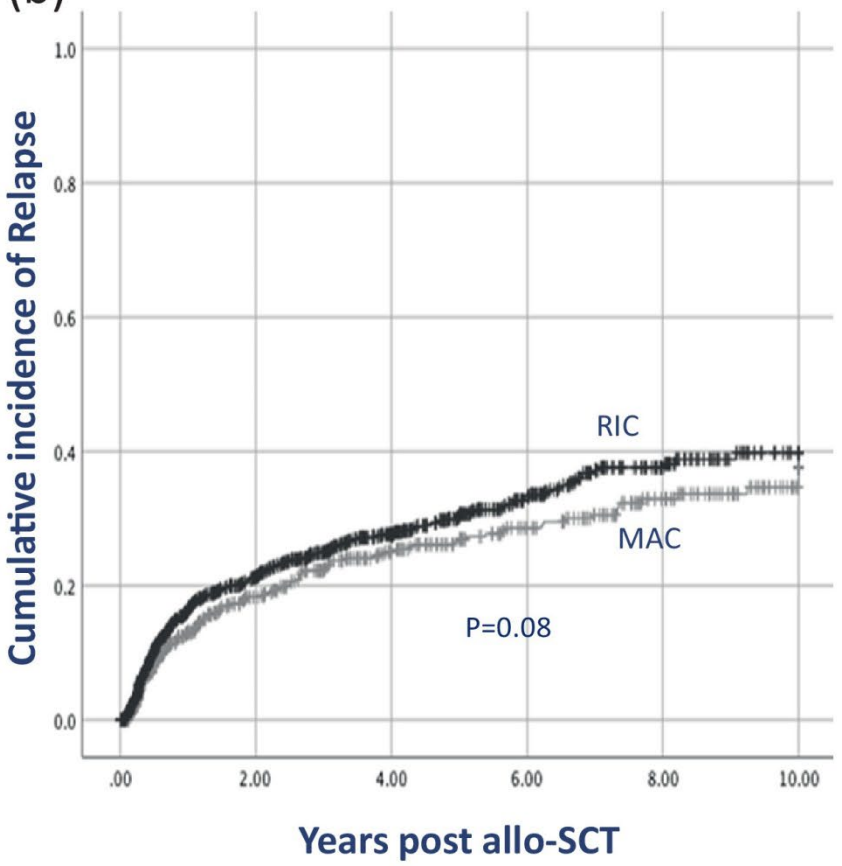


GVHD-free and relapse-free survival was 32% for MAC and 26% for RIC

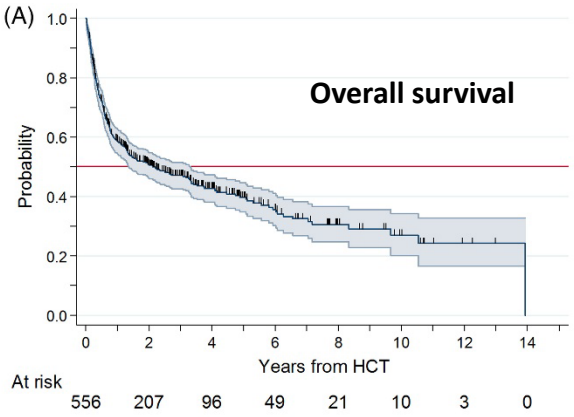
556 patients with myelofibrosis age ≥65 years undergoing allogeneic hematopoietic cell transplantation

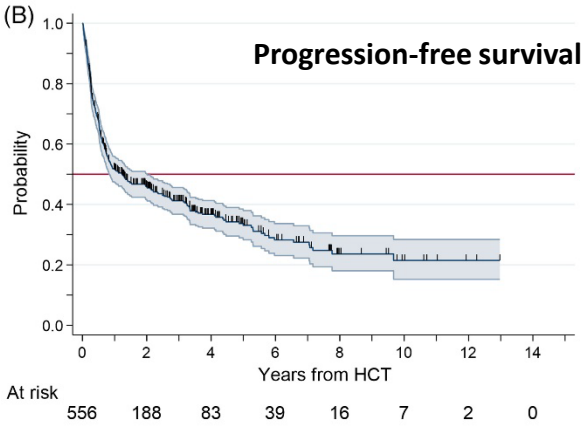
Hernández-Boluda et al. AJH 2021;96:1186

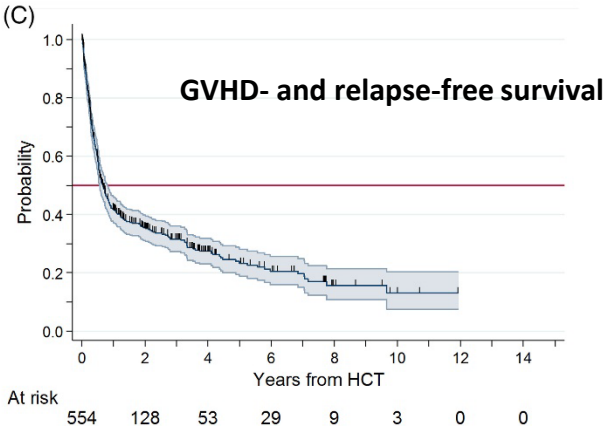
Median age 67 years (range, 65–76)
83% DIPSS high or intermediate-2 risk
Median f/u 3.4 years
Deaths 55% (n=306; GVHD 106; relapse/prog 80; infection 69)
Survival rates at 1, 3, and 5 years were 59%, 49%, and 40%
Relapse/progression at 1, 3, and 5 years was 18%, 22%, and 25%

5-year risk-adjusted survival of non-transplant cohort 33%

Syngeneic	1 (0)
HLA-matched related	134 (24)
HLA-mismatched related	5 (1)
Haploidentical	22 (4)
HLA-matched unrelated	255 (46)
HLA-mismatched unrelated	71 (13)
Unrelated, HLA-match unknown	61 (11)
Cord blood	5 (1)

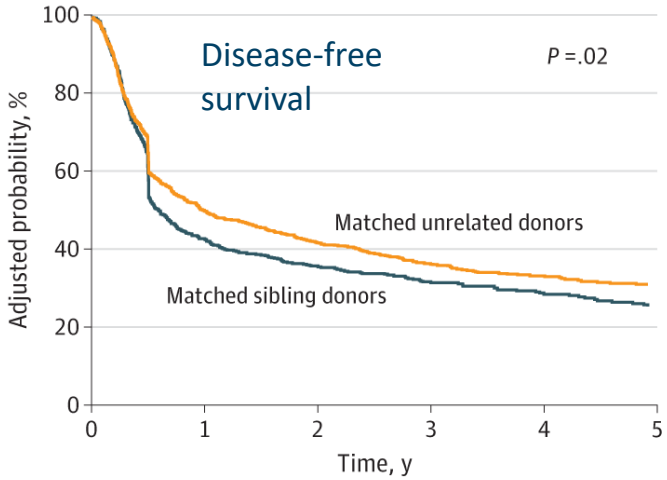






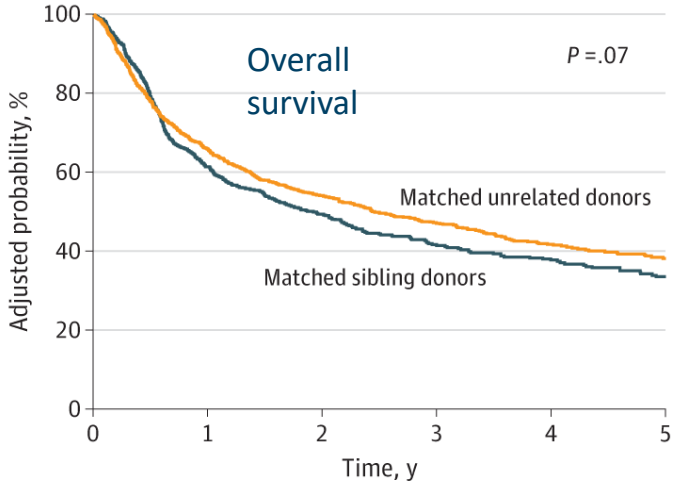
Relapse and Disease-Free Survival in Patients With Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation Using Older Matched Sibling Donors vs Younger Matched Unrelated Donors

Subramanian et al. JAMA Oncology online January 13, 2022



No. at risk

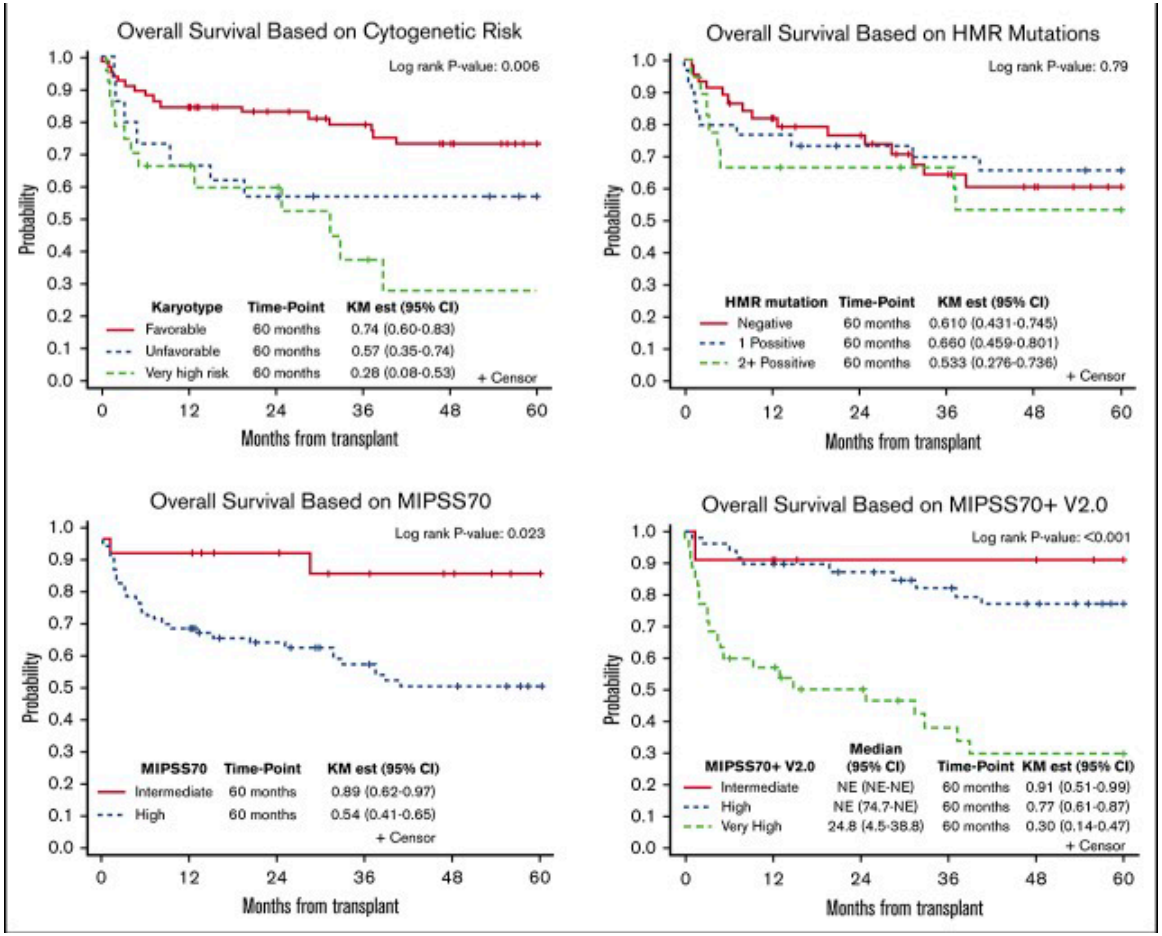
Matched unrelated donors	1110	528	363	253	161	96
Matched sibling donors	644	262	182	131	94	53



No. at risk

Matched unrelated donors	1115	696	476	325	201	121
Matched sibling donors	646	384	261	181	127	70

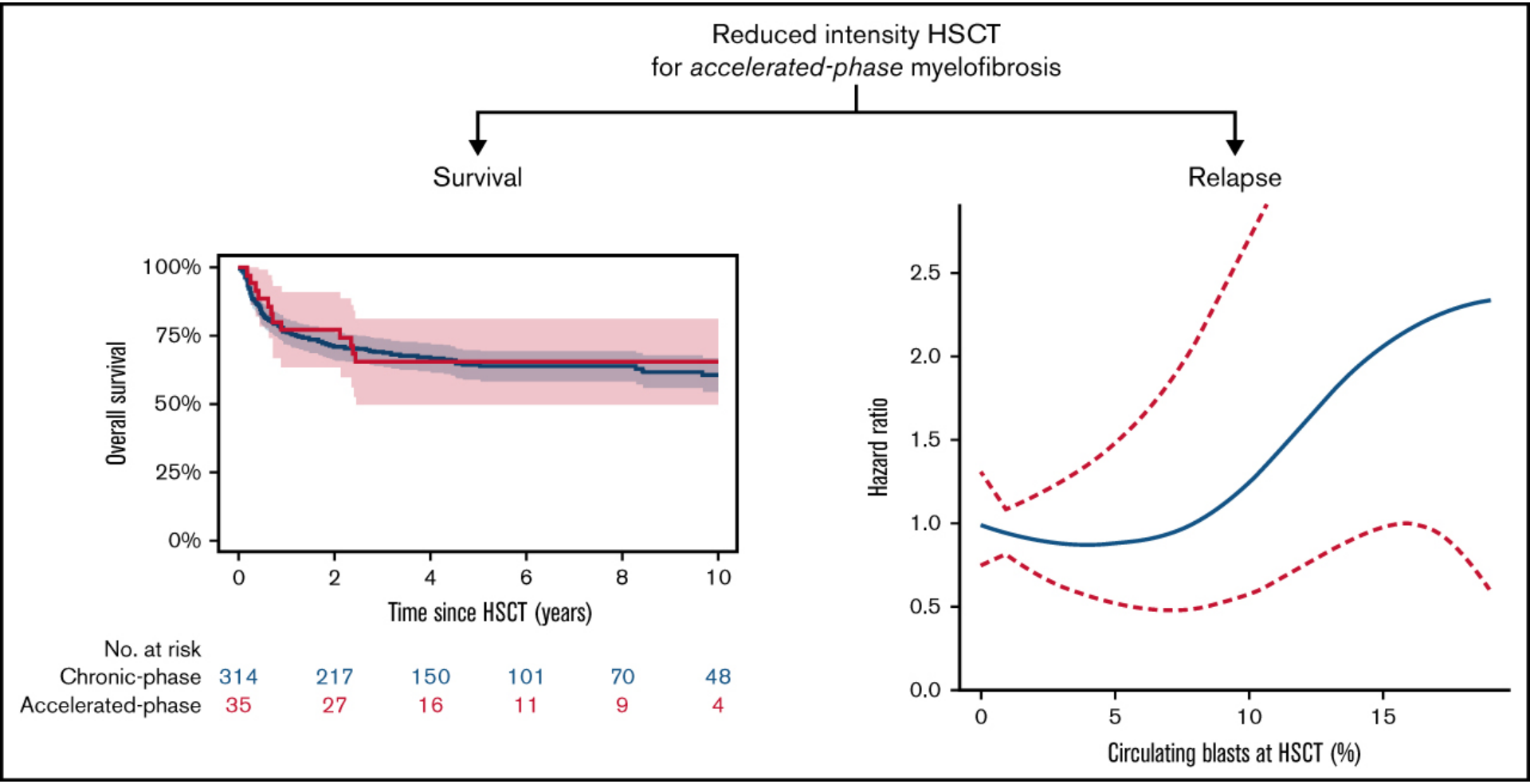
110 MF patients with allo-HCT at City of Hope



Ali et al. Blood Adv. 2019; 3: 83.

Reduced intensity hematopoietic stem cell transplantation for accelerated-phase myelofibrosis (peripheral blood blasts 10-19%)

Donor source was matched unrelated (n = 174), HLA-identical sibling (n = 89), or mismatch related or unrelated (n = 86).



Gagelmann et al. Blood Adv 2022;6:1222

Phase-3 tested JAK2 inhibitors in myelofibrosis

N Engl J Med. 2010 Sep 16;363(12):1117 (ruxolitinib phase-2)
JAMA Oncol. 2015 Aug;1(5):643 (fedratinib phase-3)
Leukemia. 2018 Apr;32(4):1035-1038 (momelotinib phase-2)
Blood. 2015 Apr 23;125(17):2649-55 (pacritinib phase-2)

2013 revised IWG-MRT response rates for 166 JAKi treated Mayo Clinic patients

	CR	PR	1-2-3 years discontinuation rates
Momelotinib (*n*=100)	0%	1%	31%-52%-71%
Ruxolitinib (*n*=51)	0%	0%	49%-71%-86%
Fedratinib (*n*=15)	0%	0%	20%-67%-80%

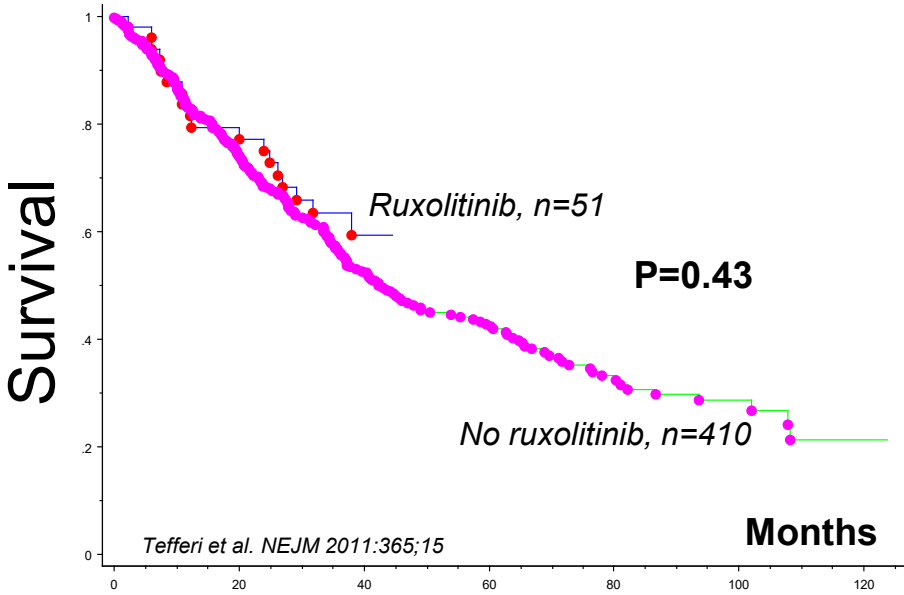
Leukemia 2014

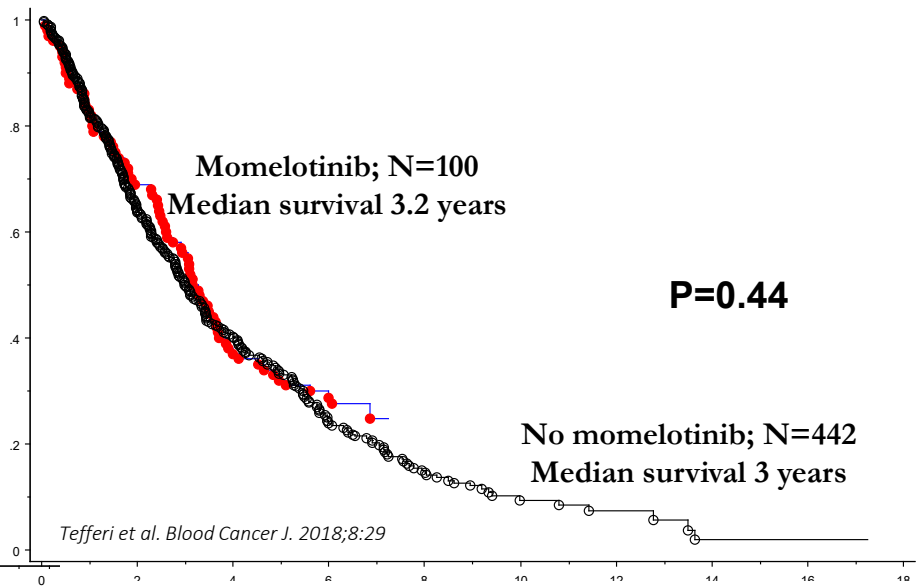
	JAK targets	Other targets	Symp. resp.	Spleen resp.	Anemia resp.	Side effects	
Ruxolitinib *FDA approved 11/16/2011*	JAK1 JAK2	TRK-B, ACK1 FAK, LCK RET	Yes	28-42% (MRI)	NR	↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections	*COMFORT-1 vs placebo COMFORT-2 vs BAT*
Fedratinib (SAR302501) *FDA approved 8/16/2019*	JAK2	FLT3, RET, ACK1 JNK1	Yes	36% (MRI)	NR	↓Hgb/Plts Nausea/Diarrhea ↑LFTs/Lipase/amylase Encephalopathy	*JAKARTA-1 vs placebo*
Pacritinib (SB1518) FDA approved 2/28/2022	JAK2	FLT3	Yes	19% (MRI)	NR	Diarrhea/Nausea	*PERSIST-1 vs BAT (no rux)*
Momelotinib (CYT387) **Phase-3 completed**	JAK1 JAK2	PKD3, PKCμ CDK2, ROCK2 JNK1, TBK1 ALK-2 (ACVR1)	Yes	27% MRI	53%	↓Plts 1st dose effect ↓BP/dizzy Neuropathy/Headache ↑LFTs/Lipase/Amylase	*SIMPLIFY-1 vs ruxo*

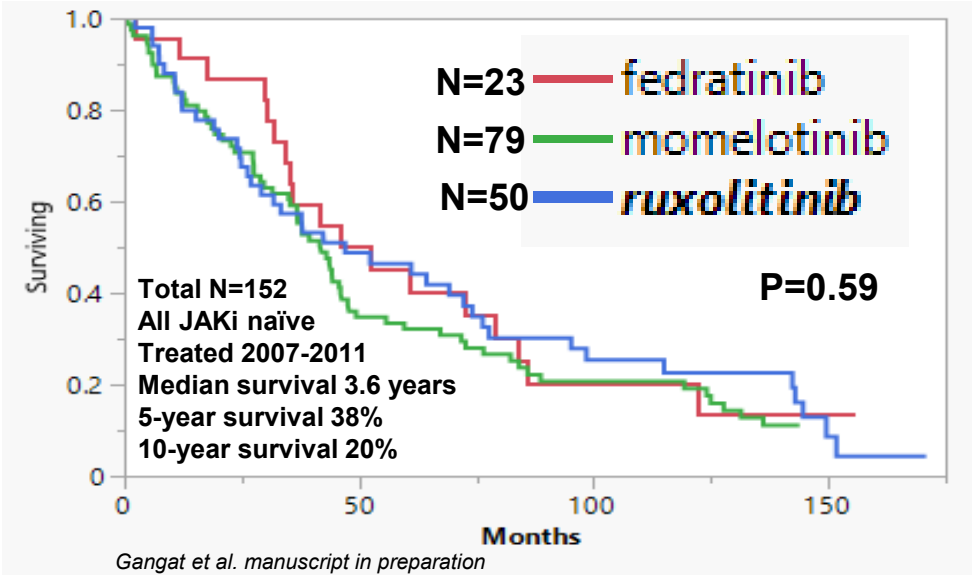
31% vs 20% Tx-indep. vs danazol

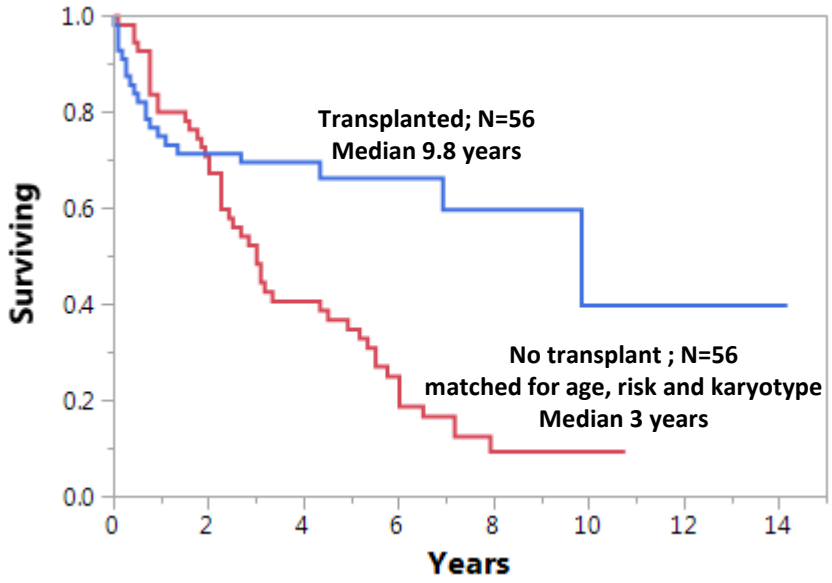
MOMENTUM vs danazol in JAKi treated

Survival impact of JAKi in myelofibrosis: Mayo Clinic studies (retrospective comparisons with risk-adjusted controls)









Fedratinib in myelofibrosis patients meeting stringent criteria for ruxolitinib failure

Study	Treatment	Spleen volume response ≥35%	Grade ¾ Toxicity
Retrospective analysis of JAKARTA-2 *High/intermediate risk MF with platelets ≥50k* N=79 patients meeting stringent criteria of resistance or intolerance to ruxolitinib Relapsed = 18; Refractory = 47; Intolerant = 14	Fedratinib 400 mg/day (initial dose 400 mg/d) Median duration 24 weeks	 28% 32% 29%	**Anemia** 44% (rux-relapsed), 49% (rux-refractory), 29% (rux-intolerant) **Thrombocytopenia** 28% (rux-relapsed), 19% (rux-refractory), 14% (rux-intolerant) **Fedratinib discontinuation** 22% (rux-relapsed), 17% (rux-refractory), 29% (rux-intolerant)

Harrison et al. AJH 2020;95:594

Clinical characteristics at time of fedratinib initiation and outcomes for 28 patients with myelofibrosis relapsed/refractory to ruxolitinib; retrospective review of real-world experience

*Gangat et al. BJH 2022;*doi: 10.1111/bjh.18284. Online ahead of print

Variables	All patients (n=28)	Patients switched from ruxolitinib ≥20 mg twice daily (n=11)	Patients switched from ruxolitinib <20 mg twice daily (n=17)	P-value
Age in years, median (range)	73 (52-85)	72 (53-85)	74 (52-84)	0.68
Splenomegaly, n (%)	24 (86)	8(73)	16(94)	0.12
Spleen size in cm (median, range) (based on imaging, US/CT/MRI)	23 (16.6-34)	29.7 (17.5-34)	22.1 (16.6-33.5)	0.05
Dose of fedratinib (median, range)	400 (100-400)	400 (100-400)	400 (300-400)	0.16
Duration of therapy in months, (median, range)	8.0 (1.0- 29.2)	4.2 (1.0-29.2)	9.0 (1-24.1)	0.88
Response*, n (%)				
- Spleen, n evaluable =24	3 (13%)	0/9(0%)	3/16(19%)	0.08
- Symptom, n evaluable =25	8 (32%)	1/9 (11%)	7/16 (44%)	0.07
				0.01
Duration of response in months, (median, range)	7.8 (0-25.8)	6.0 (0-25.8)	8.5 (1.4-12.6)	0.16
Treatment discontinuation, n (%)	15 (54)	6(55)	9(53)	0.93
Allogeneic transplant, n (%)	4 (14)	3(27)	1(6)	0.12
Toxicity, n (%)				
- Gastrointestinal	6 (21)	3(27)	3(18)	0.55
- Anemia, Grade 3	7 (25)	1(9)	6(35)	0.10
- Thrombocytopenia, Grade 3/4	6 (21)	3(27)	3(18)	0.55
- Renal insufficiency	4 (14)	2(18)	2(12)	0.64
- Increased lipase	1 (4)	1(9)	0(0)	0.16

Ongoing challenges and investigations

Drugs other than JAK2 inhibitors

- *CPI-0610 (BET inihibitor)*
- *Luspatercept (SMAD inhibitor)*
- *Imetelstat (telomerase inhibitor)*
- *Bomedemstat (LSD1 inhibitor; histone demethylase specific for H3K4)*
- *Navitoclax (BCL-2/BCL-X inhibitor)*
- *Tagraxofusp (SL-401; IL3RA/CD123-directed cytotoxin-IL3 fused to diphtheria toxin)*
- *Alisertib (aurora kinase inhibitor)*
- *Buparlisib/Parsaclisib (PI3/AKT inhibitors)*

- Pre-transplant management of the spleen
  - No specific intervention
  - Splenectomy
  - Splenic irradiation
  - Ruxolitinib
- Palliative treatment options after ruxolitinib
  - Splenectomy
  - Other JAKi - *Momelotinib, Fedratinib, Pacritinib*

Tefferi et al. Cancer Res. 2022;82:749