Myeloproliferative Neoplasms

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

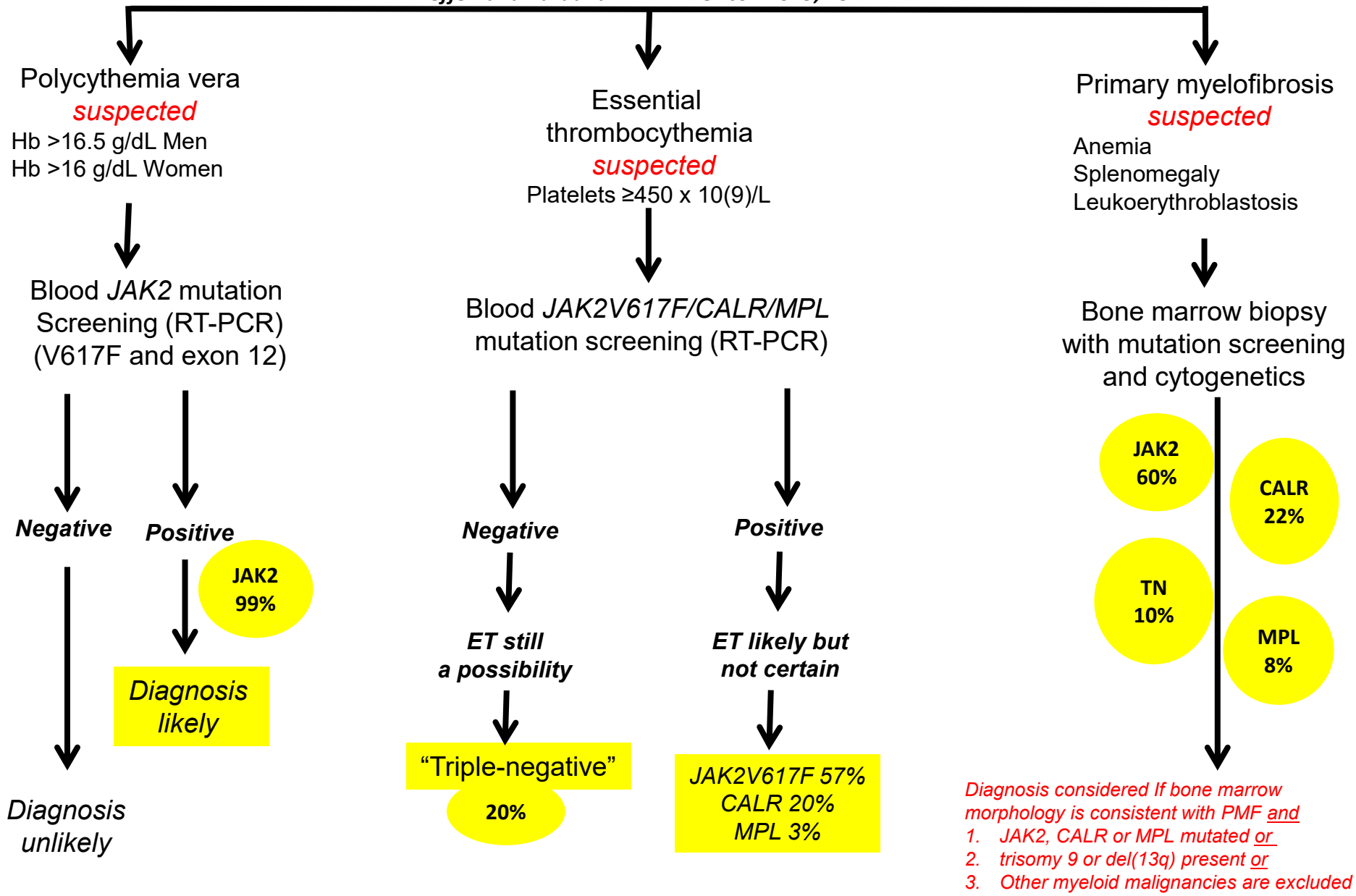
Objectives

- **MPN**
  - **Diagnosis**
  - **Prognostication**
  - **Treatment algorithms**

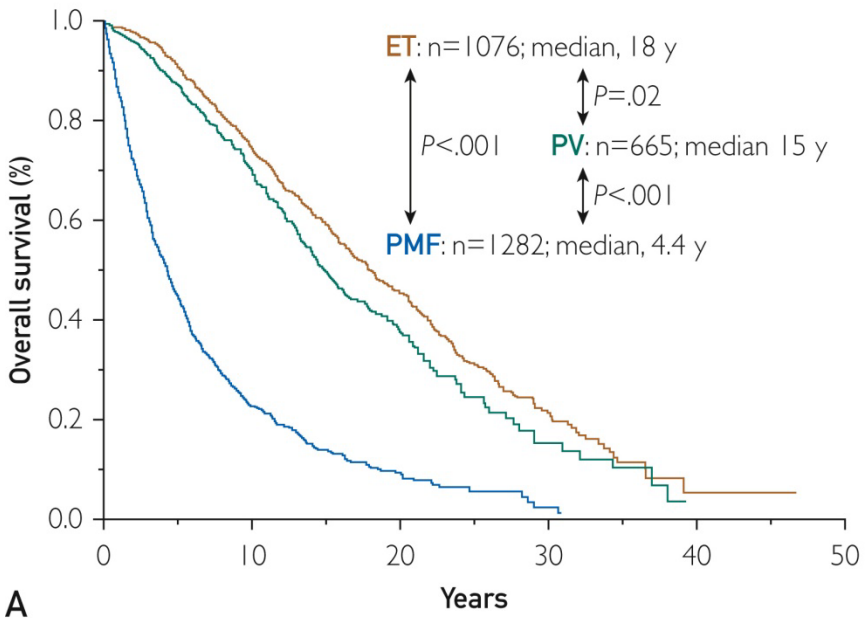
- **COVID infection and vaccine experience in patients with MPN**

Practical algorithm for diagnosis of myeloproliferative neoplasms

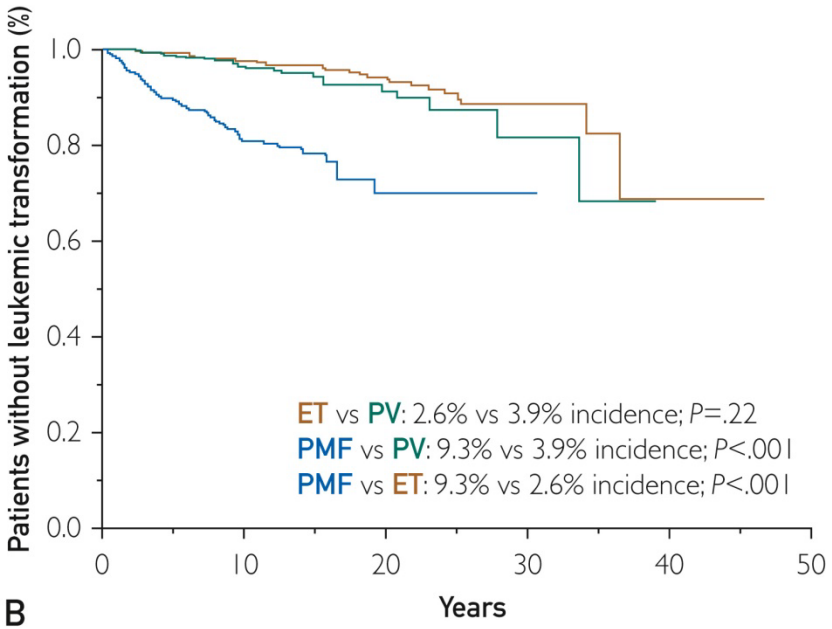
Tefferi and Pardanani. JAMA Oncol. 2015;1:97



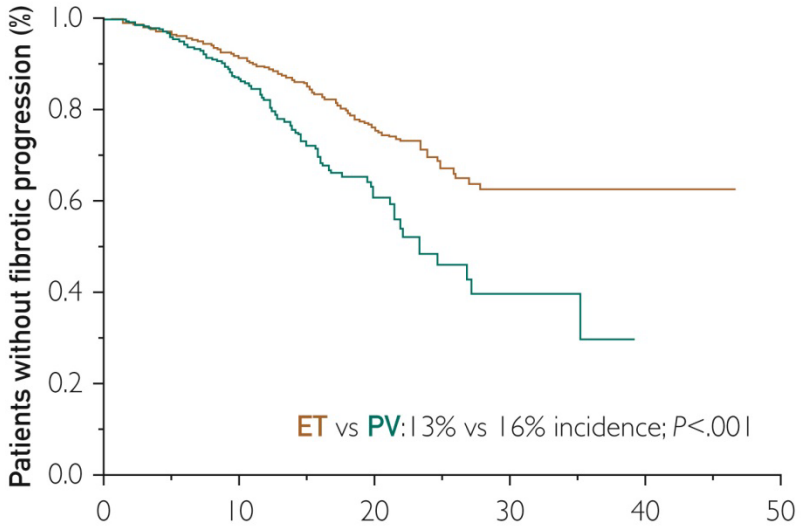
Overall (A), leukemia-free (B), myelofibrosis-free (C), and thrombosis-free (D) survival for 3,023 Mayo Clinic patients with myeloproliferative neoplasms (ET; PMF; PV) seen between 1967 and 2017. Median f/u = 20 years

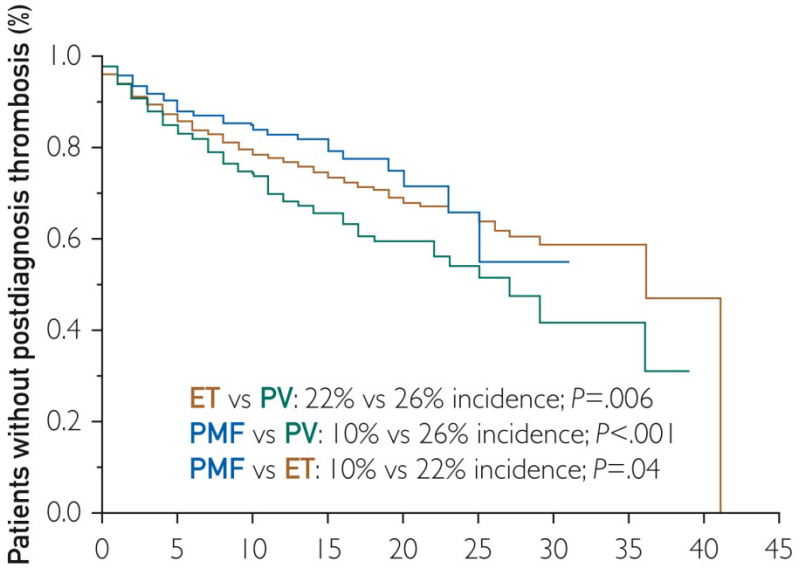


A



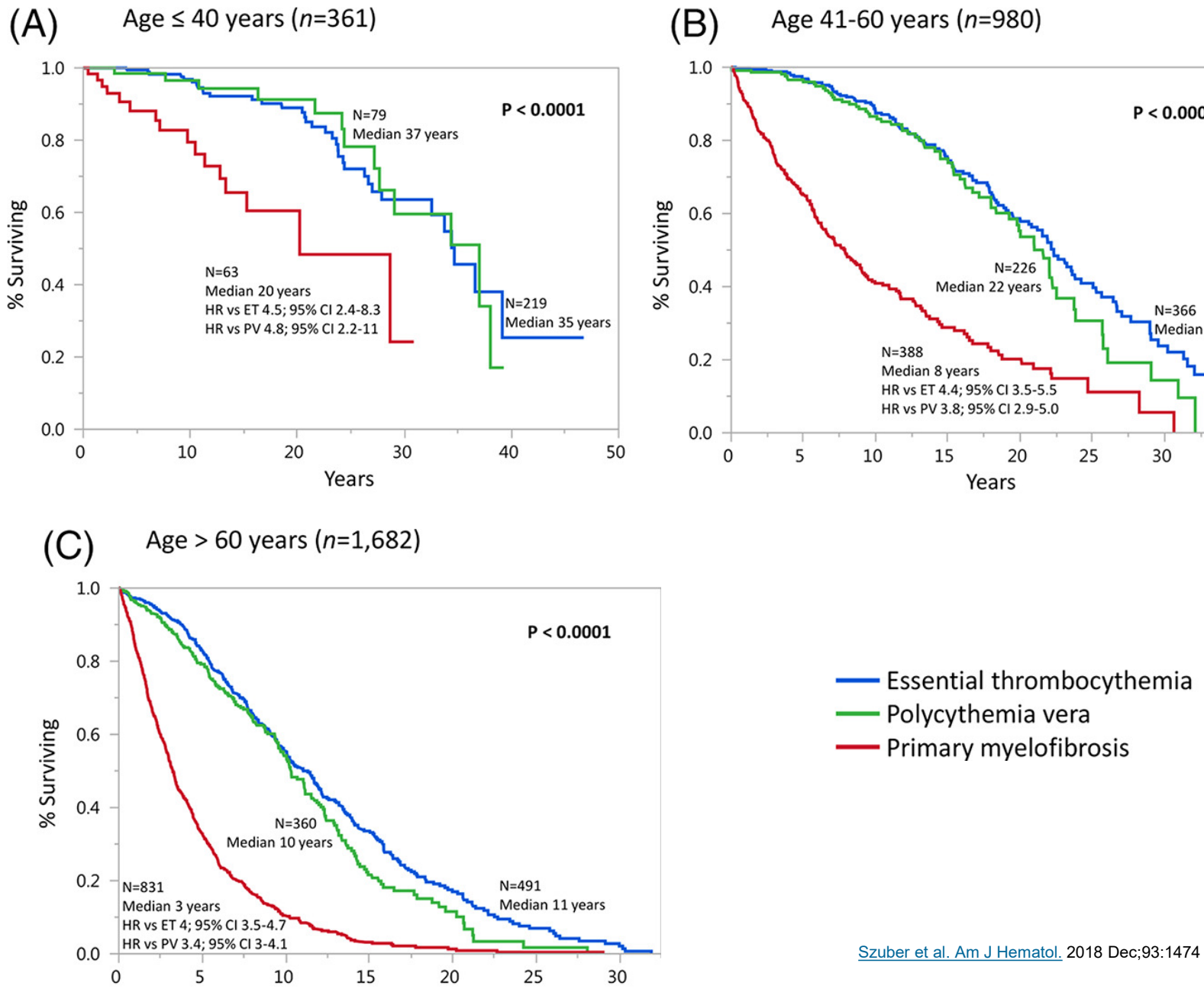
B





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

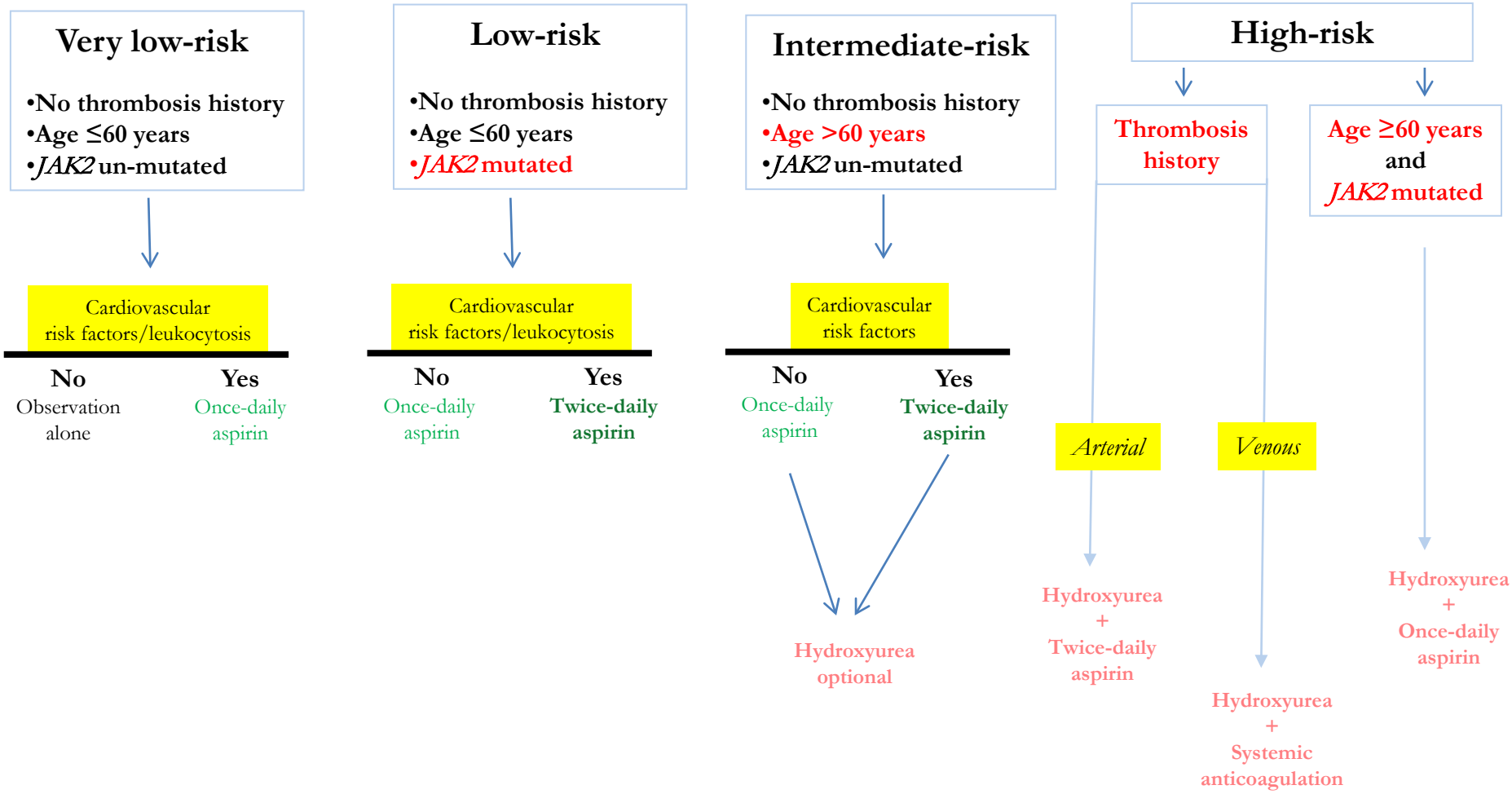
Age and survival in myeloproliferative neoplasms



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

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

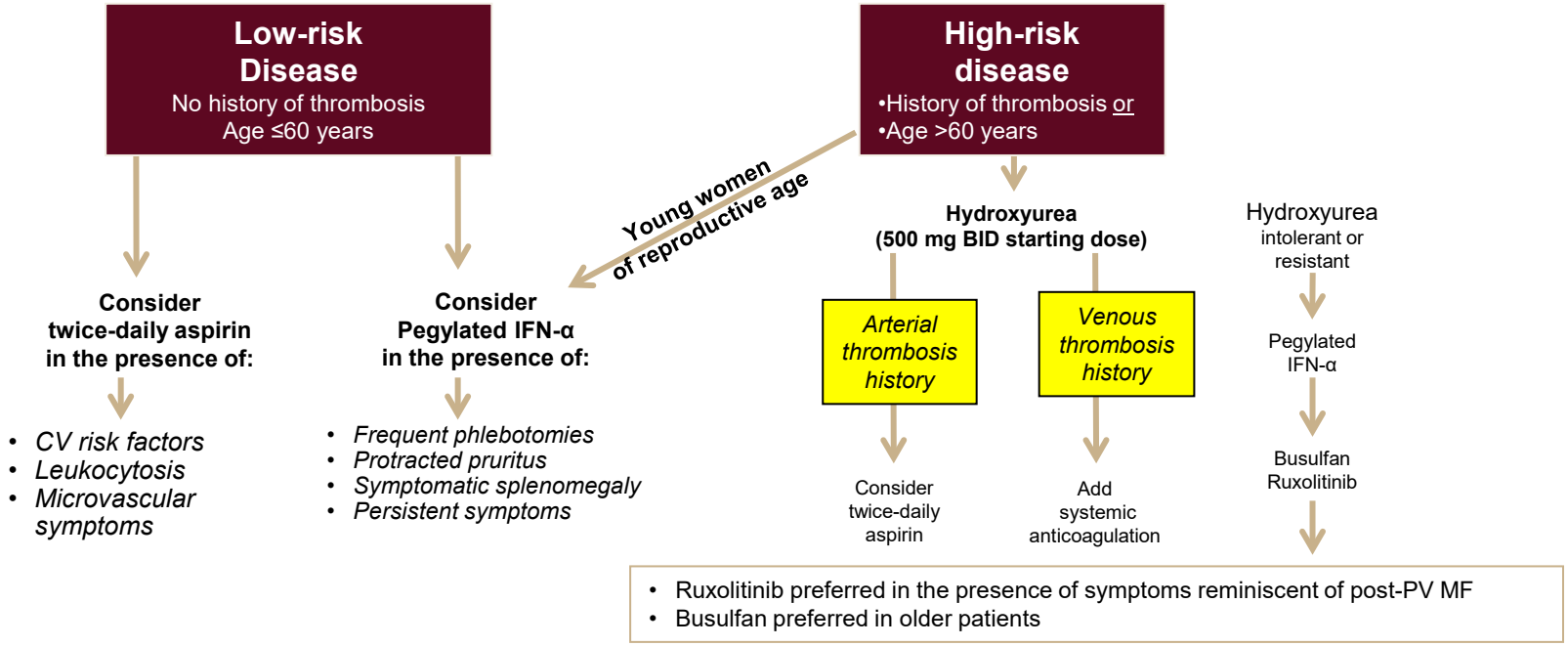
4. Management of platelet millionaires with otherwise low-risk disease
   - No evidence of value for cytoreductive therapy
   - Avoid use of aspirin in patients with clinically evident acquired von Willebrand syndrome
   - Treat the patient and not the platelet count

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

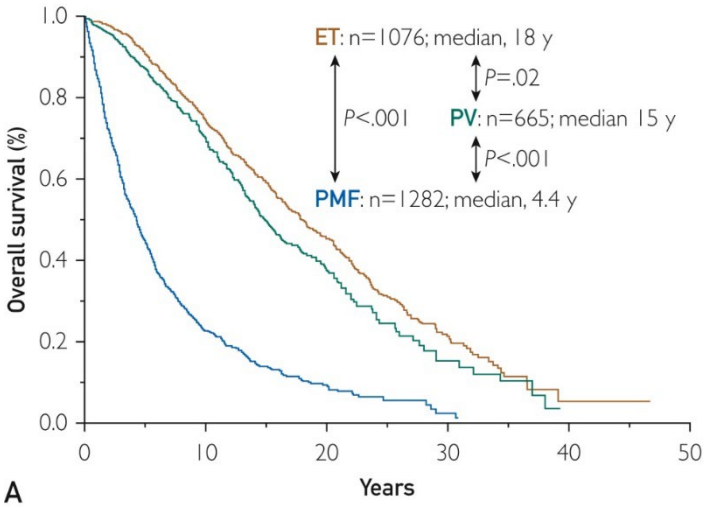
Current Treatment Approach in Polycythemia Vera

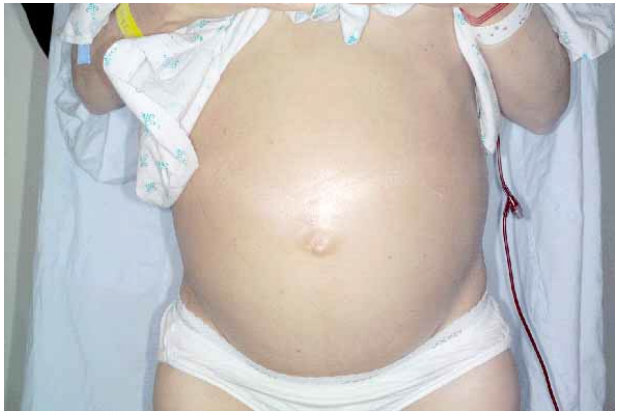
Scheduled phlebotomy to keep hematocrit <45% in all patients
+
Once-daily low-dose aspirin in all patients

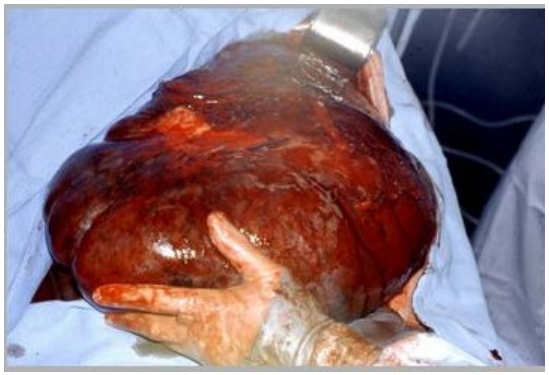


Tefferi, Vannucchi, and Barbui
Leukemia. 2021;35:3339

Disease Complications in Myelofibrosis







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

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

Therapeutic options in myelofibrosis

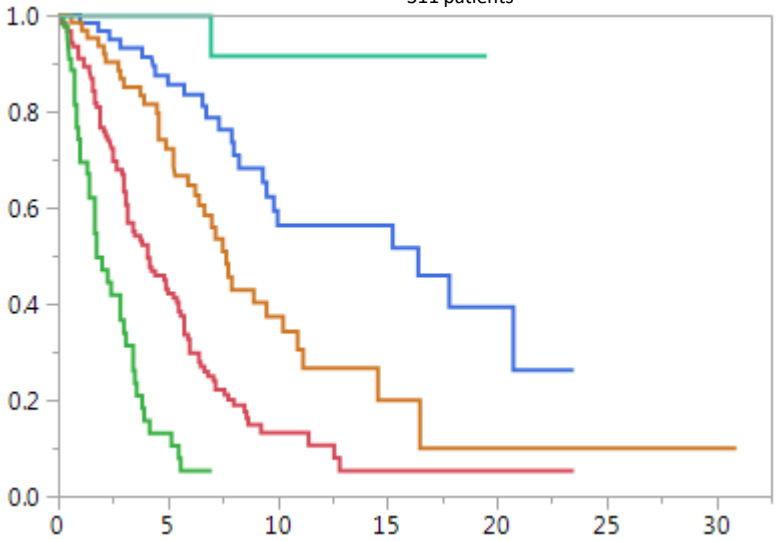
- **Curative or with potential to improve survival**
  - ✓ Allogeneic hematopoietic cell transplant (allo-HCT)
- **Palliative**
  - ✓ Observation alone (watch-and-wait)
  - ✓ Treatment for anemia
    - Thalidomide ± prednisone
    - Androgens
    - Danazol
    - ESAs
    - Lenalidomide/pomalidomide
  - ✓ Treatment for symptomatic splenomegaly
    - Hydroxyurea
    - JAK2 inhibitors
    - Splenectomy
  - ✓ Treatment for constitutional symptoms
    - JAK2 inhibitors
  - ✓ Involved field radiotherapy for extra-medullary hematopoiesis
  - ✓ Experimental therapy

Survival 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

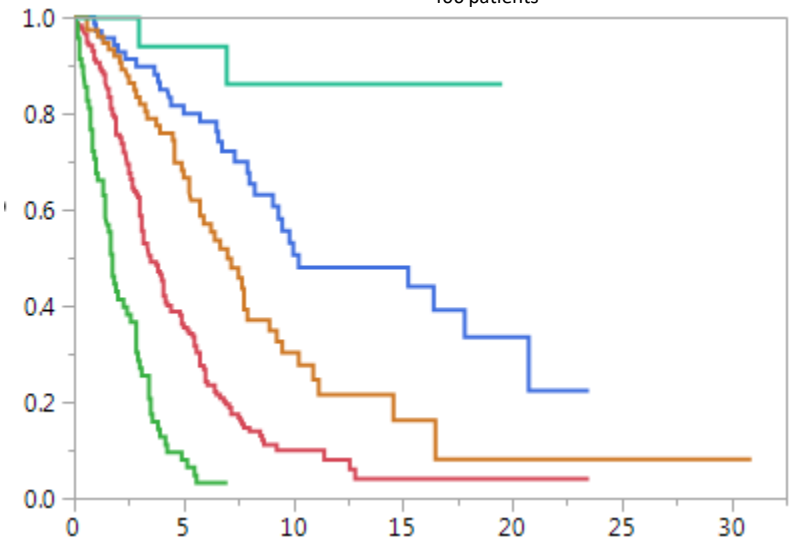
311 patients



- 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



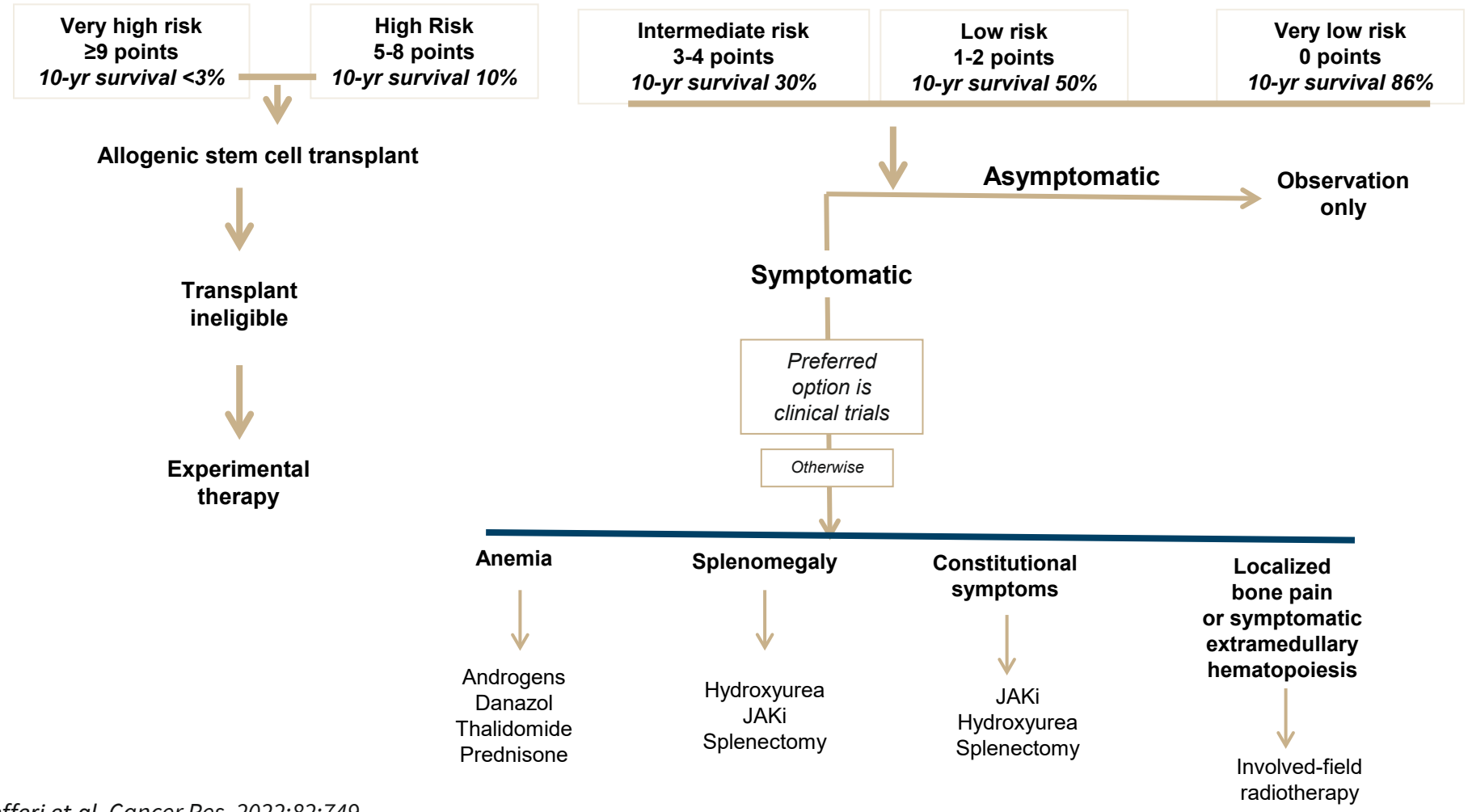
- Very high risk; *n*=69; median 1.8 years; 10-year survival <3%
- High risk; *n*=172; median 3.5 years; 10-year survival 10%
- Intermediate risk; *n*=76; median 7 years; 10-year survival 30%
- Low risk; *n*=70; median 10.3 years; 10-year survival 50%
- Very low risk; *n*=19; median not reached; 10-year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

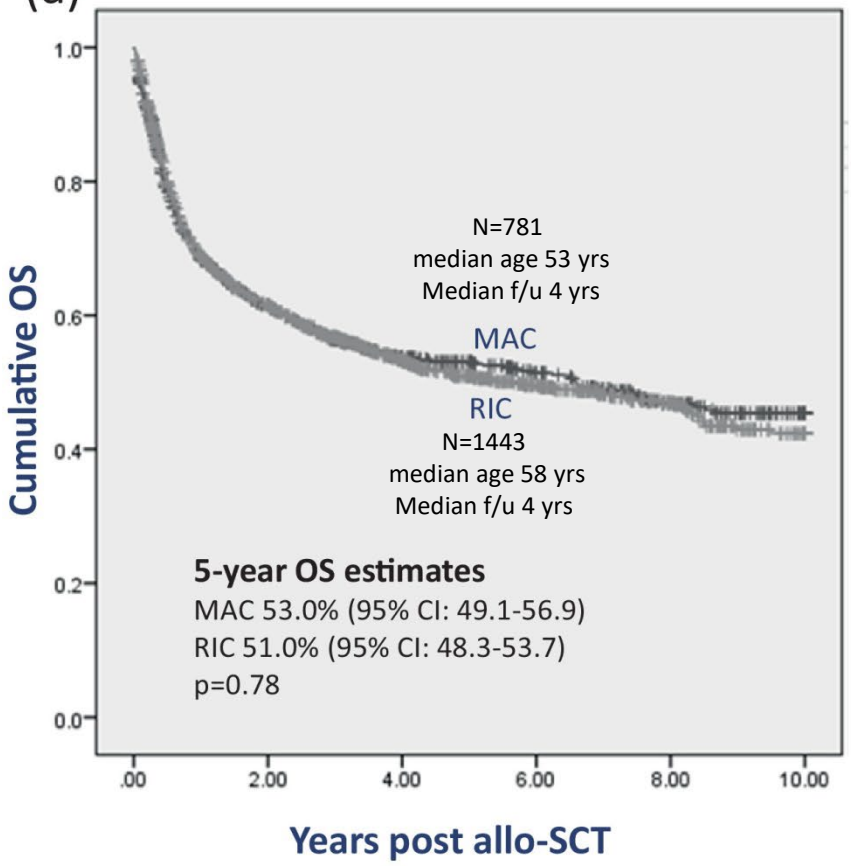
RIC vs MAC

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

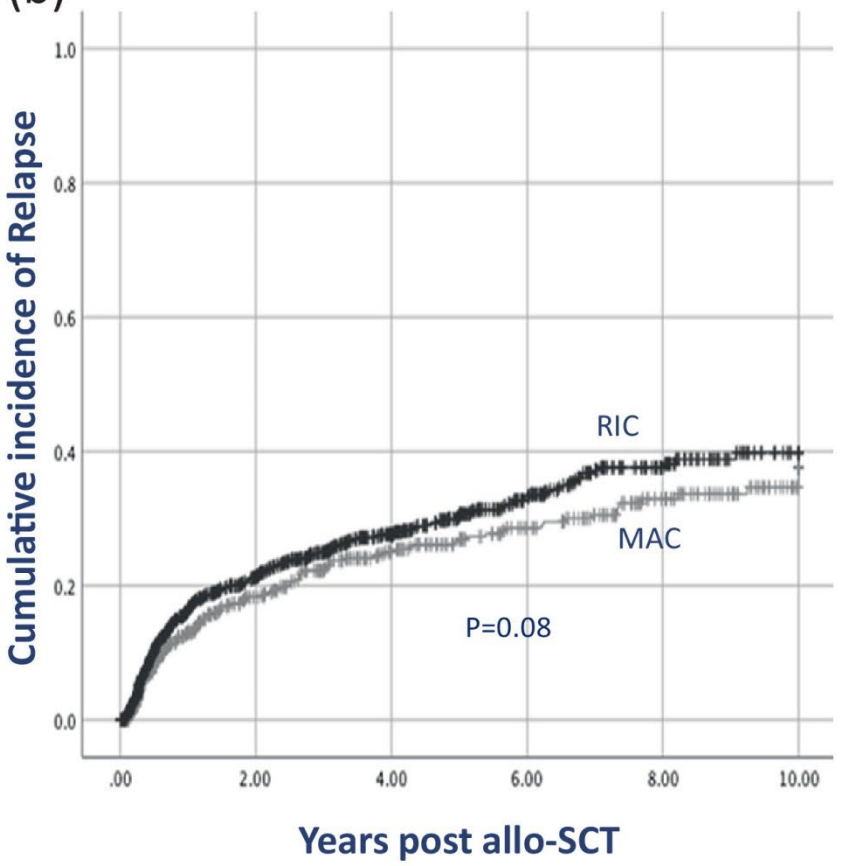
McLornan et al. Biol Blood Marrow Transplant 2019;25:2167

(a)

~40% related and 60% unrelated donors



(b)



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

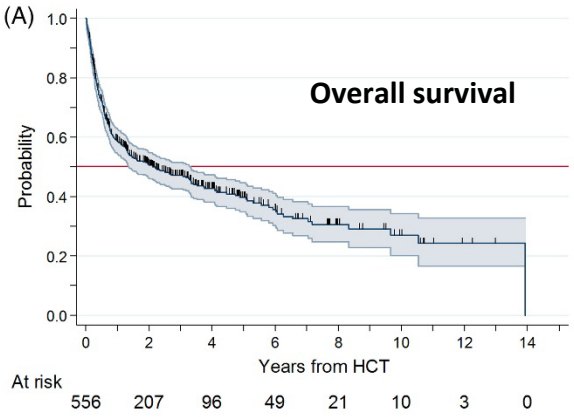
556 patients with myelofibrosis age ≥65 years undergoing allogeneic hematopoietic cell transplantation

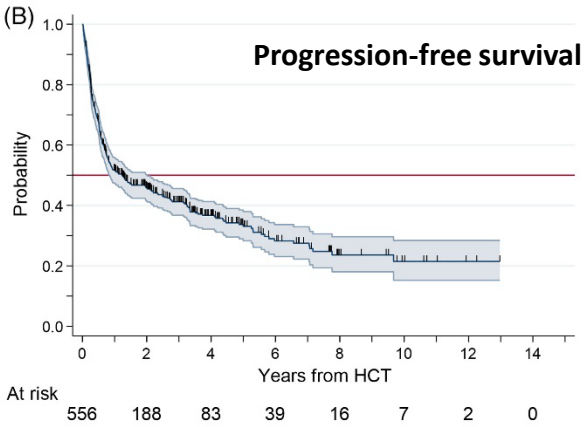
Hernández-Boluda et al. AJH 2021;96:1186

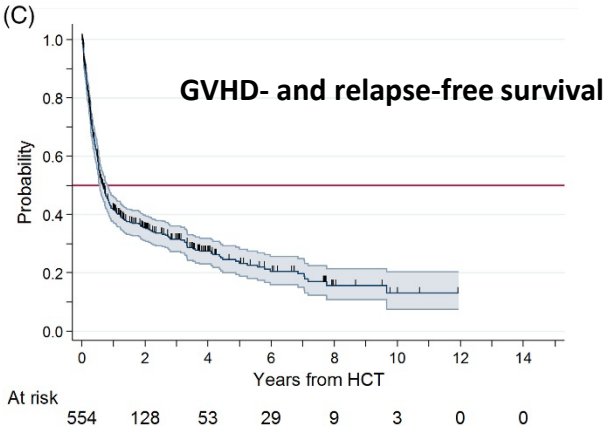
Median age 67 years (range, 65–76)
83% DIPSS high or intermediate-2 risk
Median f/u 3.4 years
Deaths 55% (n=306; GVHD 106; relapse/prog 80; infection 69)
Survival rates at 1, 3, and 5 years were 59%, 49%, and 40%
Relapse/progression at 1, 3, and 5 years was 18%, 22%, and 25%

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)







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%

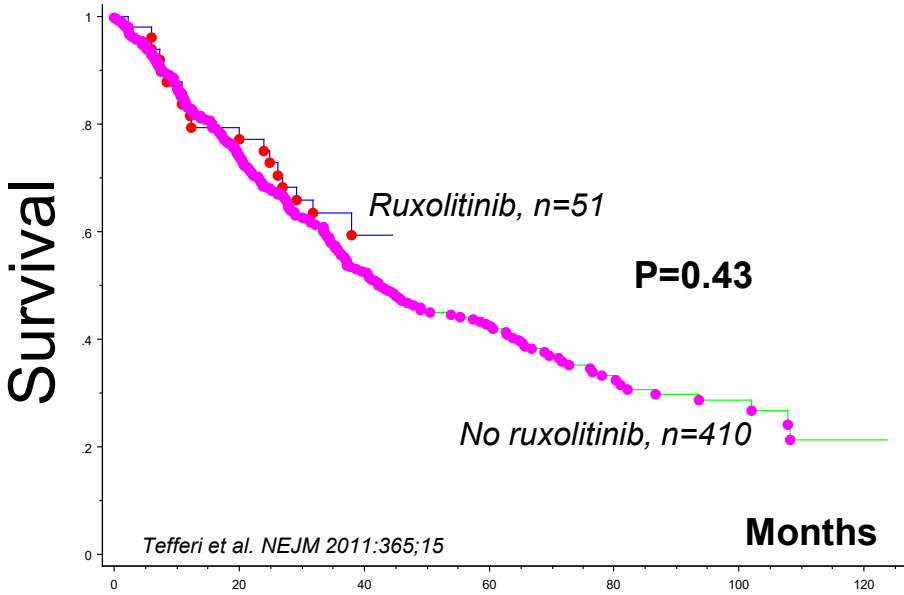
Leukemia 2014

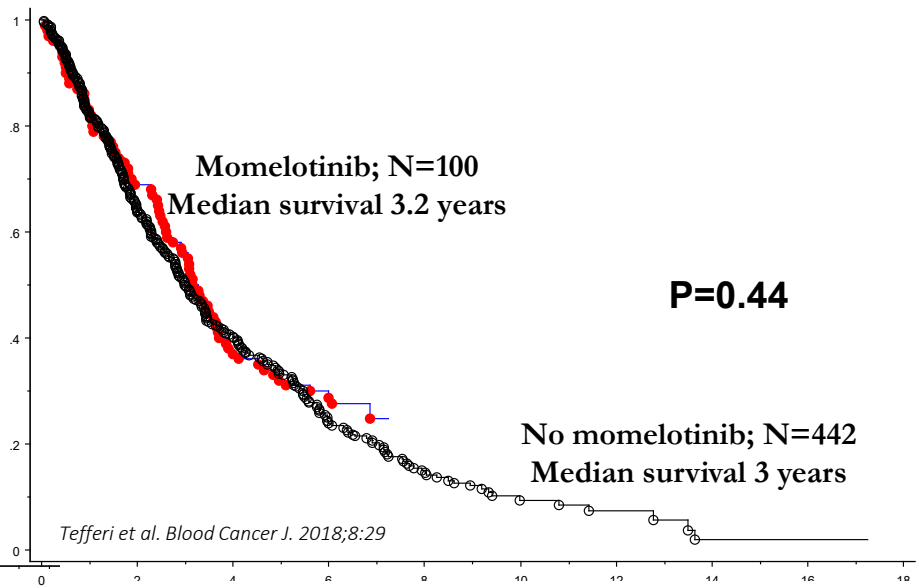
	JAK targets	Other targets	Symp. resp.	Spleen resp.	Anemia resp.	Side effects	
Ruxolitinib *FDA approved 11/16/2011*	JAK1 JAK2	TRK-B, ACK1 FAK, LCK RET	Yes	28-42% (MRI)	NR	↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections	*COMFORT-1 vs placebo COMFORT-2 vs BAT*
Fedratinib (SAR302501) *FDA 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*

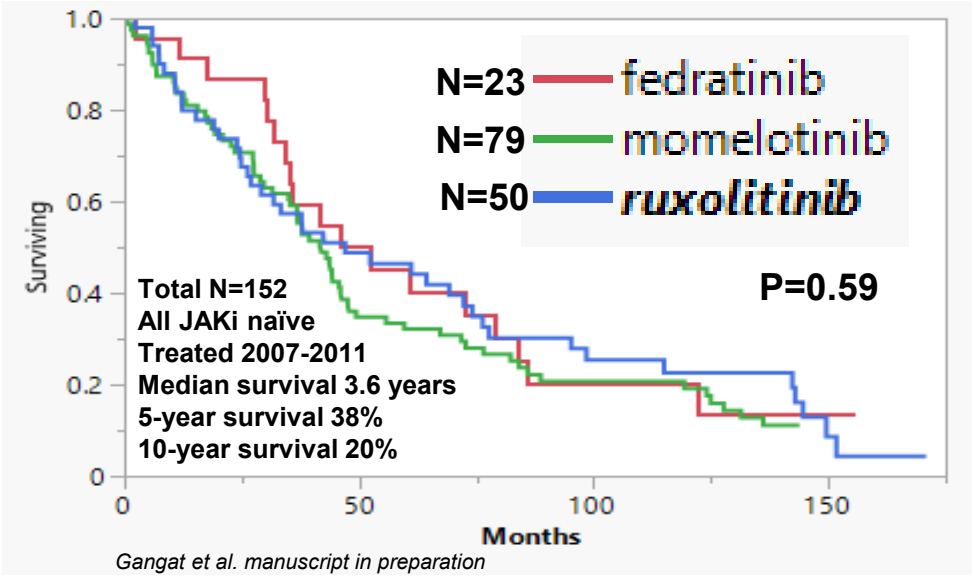
31% vs 20% Tx-indep. vs danazol

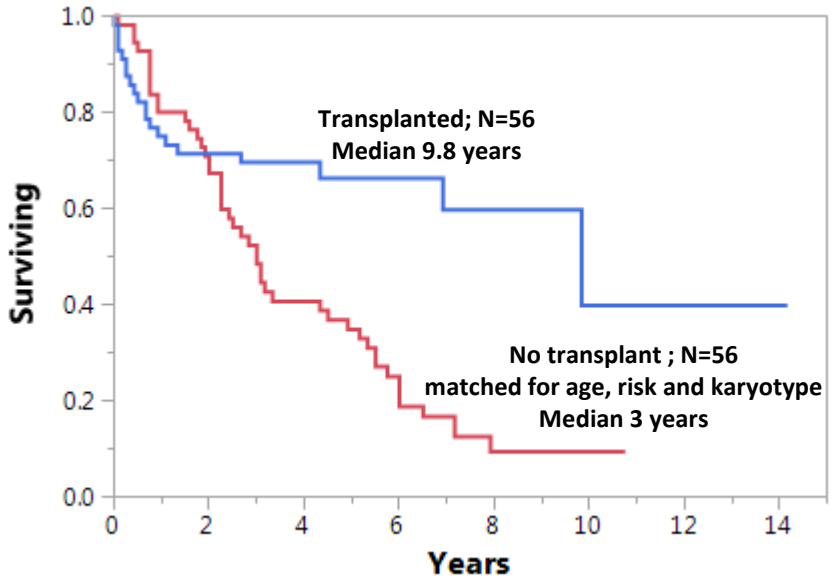
MOMENTUM vs danazol in JAKi treated

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









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

Practice points regarding ruxolitinib or related JAKi therapy

Indications

1. Marked splenomegaly that is symptomatic and resistant to hydroxyurea
2. Severe constitutional symptoms including pruritus, night sweats, fatigue and cachexia

Side effects include…

1. Anemia
2. Thrombocytopenia
3. Immunosuppression
4. Opportunistic infections
5. Protracted myelosuppression

Special concerns

1. **Poor immune response to COVID vaccination***
2. Might compromise future eligibility for clinical trials because of protracted myelosuppression
3. Benefit lasts for an average of approximately one year; might be best to try HU first
4. **BEWARE** of withdrawal symptoms that might include SIRS and overt and immediate relapse of splenomegaly/symptoms

COVID-19 and MPN

UK national survey
77 MPN patients with COVID-19 (median age 74)
ET 28
PV 18
MF 27
MPN-U 4

45% died

Salisbury et al. Leukemia. 2021; 35(8): 2424–2430

European MPN-COVID study first and second wave
Barbui et al. Leukemia. 2022;36:897

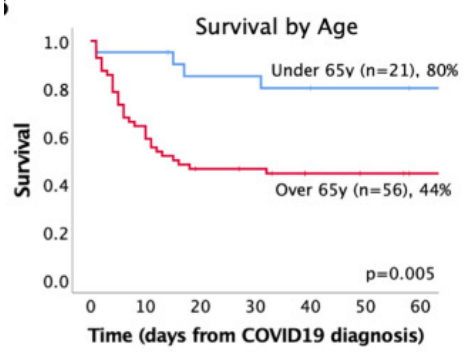
Total 479 patients

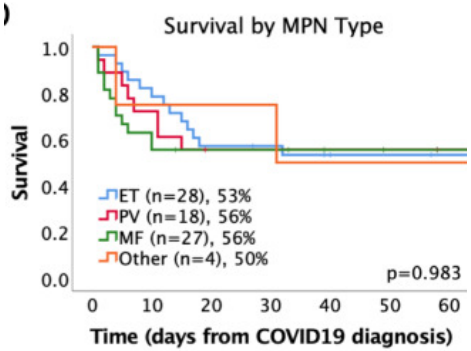
- 161 ET
- 135 PV
- 134 PMF
- 49 pre-PMF

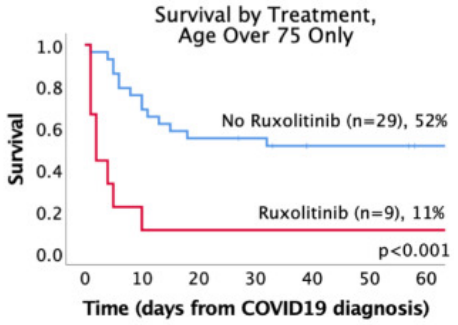
Predictors of death

- Age >70 years
- Male sex
- Severity of COVID-19
- Ruxolitinib discontinuation

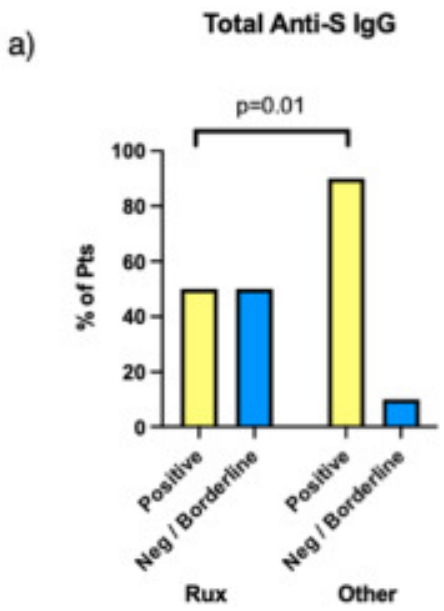
Venous thrombotic complications were more likely to occur in ET

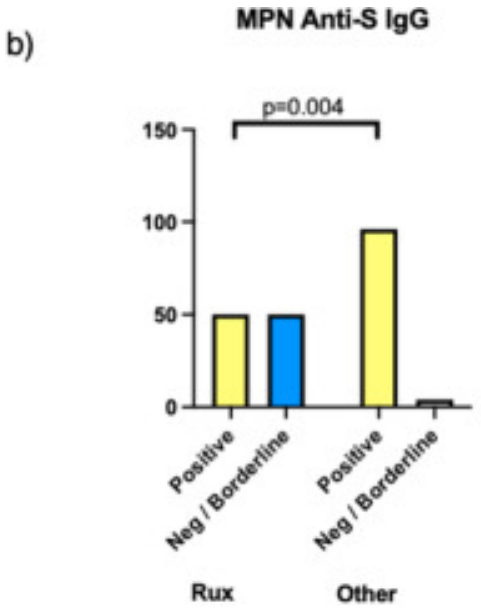




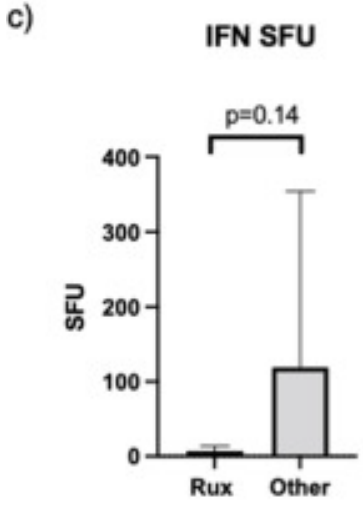


Effect of Ruxolitinib treatment on antibody and T cell response to COVID vaccination (median 6.4 weeks from 2nd dose)
(Harrington et al. Blood Cancer J. 2022; 12: 73)





61 patients total
24 CML
11 ET
13 PV
13 MF



What do I advice my patients:

1. COVID-19 is just the beginning
2. Make social distancing and masking, as necessary, a permanent habit
3. Follow vaccine guidelines
4. Ruxolitinib and other JAK inhibitors are immunosuppressants
   - Increase mortality from infection
   - Compromise vaccine response
5. If not on JAKi, consider alternative therapy, if possible
6. If already on JAKi, do not discontinue; consider evusheld/paxlovid
   - Note drug-drug interactions with paxlovid…decrease ruxo by 50%
7. Hydroxyurea or interferon-alpha do not appear to be deleterious