Myelofibrosis: chronic and blast phase

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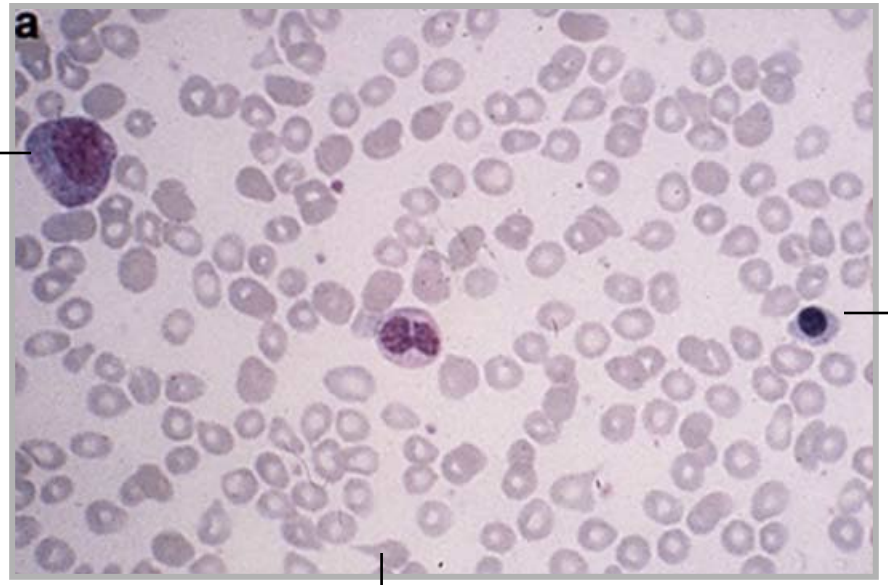
I have nothing to disclose

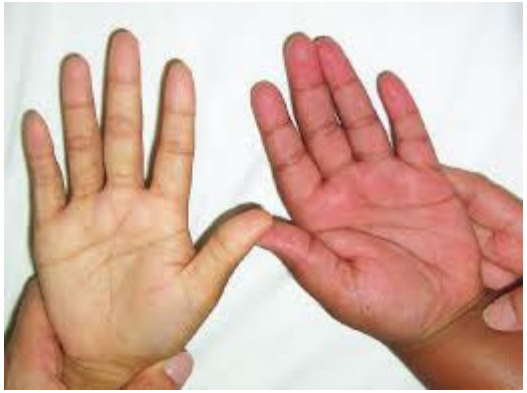
When does one suspect Myelofibrosis?



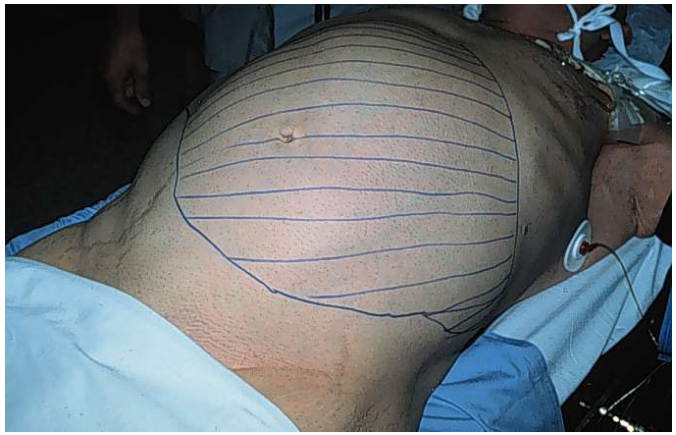
Immature myeloid cells

Nucleated red cells

Tear-drop erythrocytes



Anemia



Marked splenomegaly

Objectives

- Practical overview
  - Diagnosis
  - Molecular prognostication
  - Risk-adapted treatment approaches
- In context discussion of selected ASH 2022 abstracts

International Consensus Classification

Arber et al. Blood 2022;140:1200

Polycythemia vera

suspected

Hb >16.5 g/dL Men
Hb >16 g/dL Women

Blood *JAK2* mutation Screening (RT-PCR) (V617F and exon 12)

Negative

Diagnosis unlikely

Positive

JAK2 99%

Diagnosis likely

Essential thrombocythemia

suspected

Platelets ≥450 x 10(9)/L

Blood *JAK2V617F/CALR/MPL* mutation screening (RT-PCR)

Negative

ET still a possibility

"Triple-negative"

20%

Positive

ET likely but not certain

JAK2V617F 57%
CALR 20%
MPL 3%

Primary myelofibrosis

suspected

Anemia
Splenomegaly
Leukoerythroblastosis

Bone marrow biopsy with mutation screening and cytogenetics

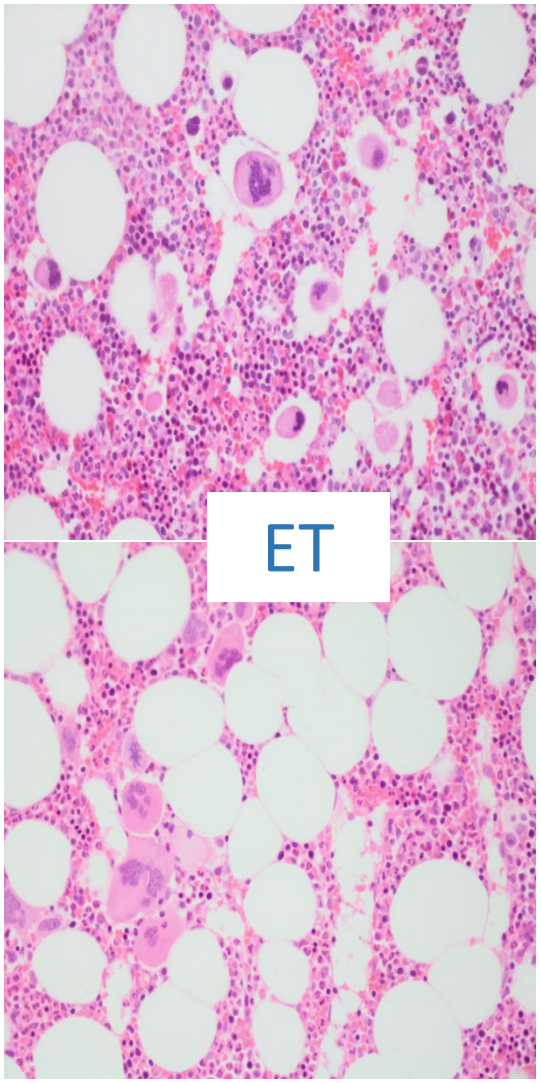
JAK2 60%
CALR 22%
TN 10%
MPL 8%

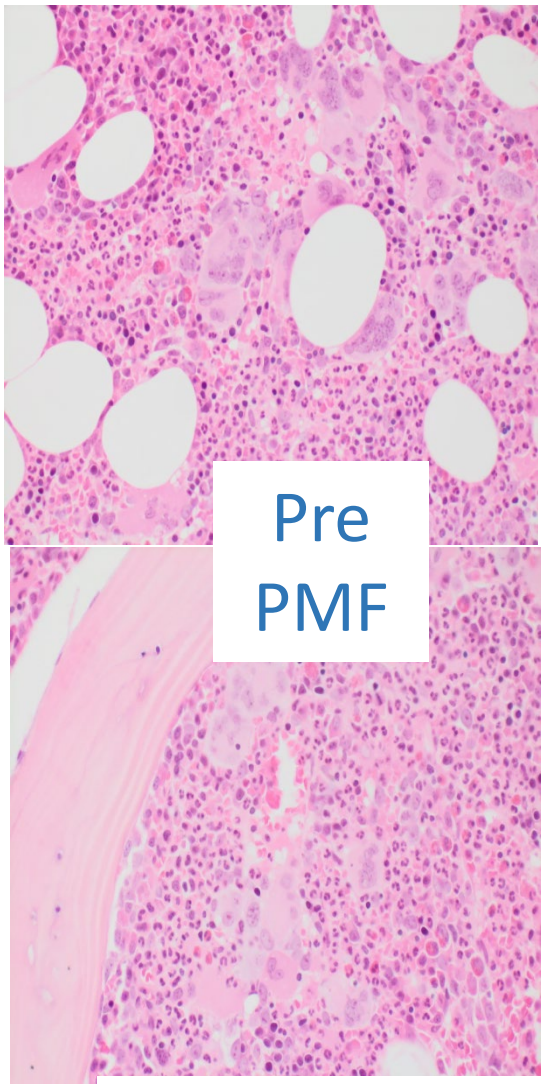
Diagnosis considered If bone marrow morphology is consistent with PMF and

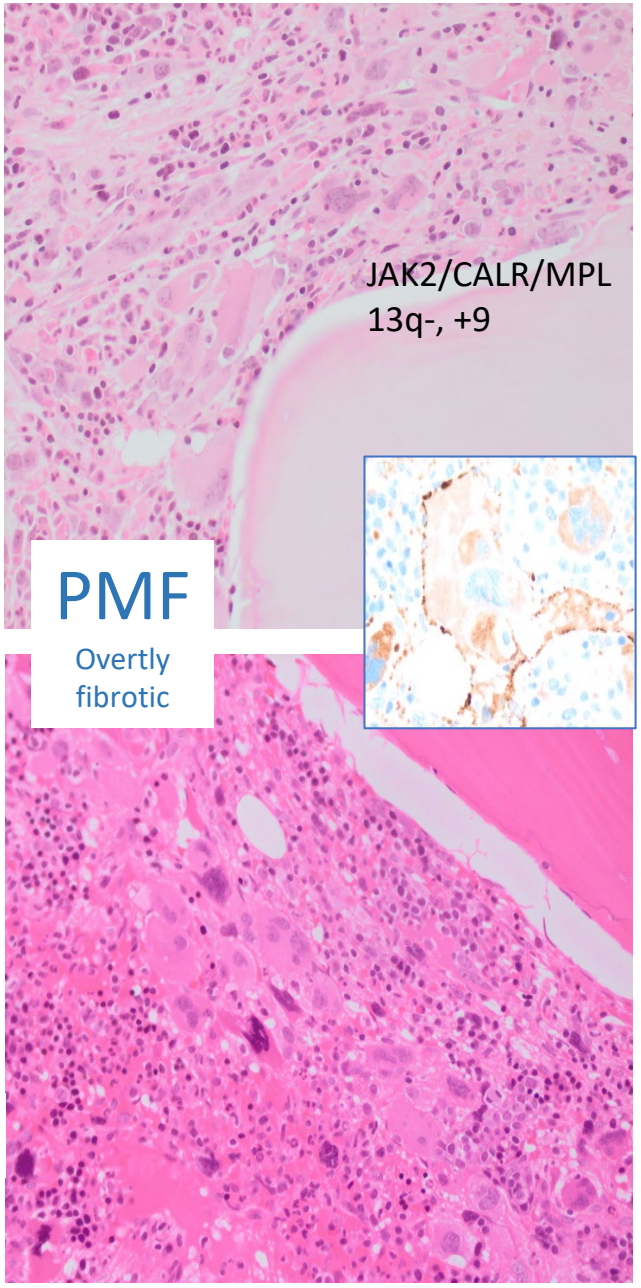
1. *JAK2, CALR or MPL mutated or*
2. *trisomy 9 or del(13q) present or*
3. *Other myeloid malignancies are excluded*

Tefferi, A. AJH; First published: 21 January 2023
https://doi.org/10.1002/ajh.26857

Bone marrow morphology in overt vs prefibrotic myelofibrosis (PMF) vs essential thrombocythemia (ET)



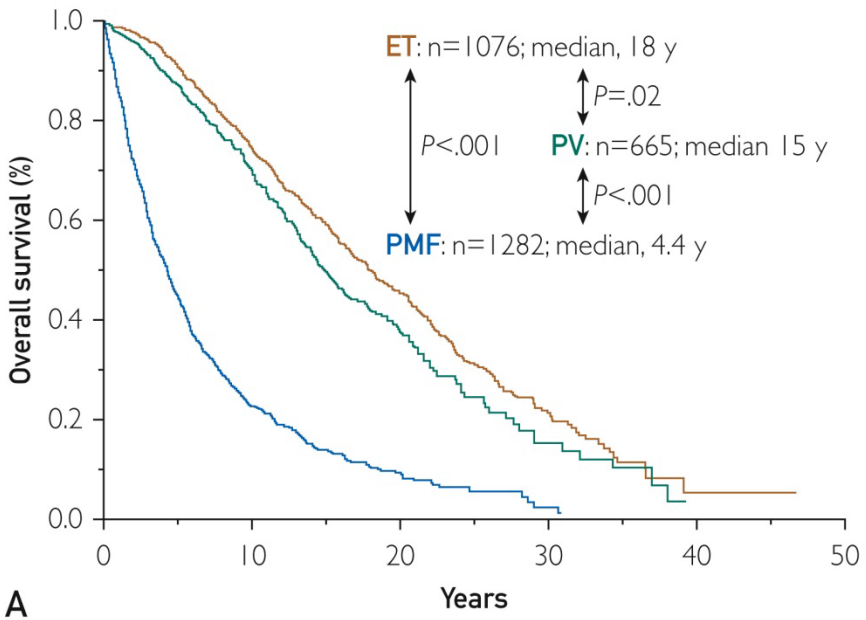




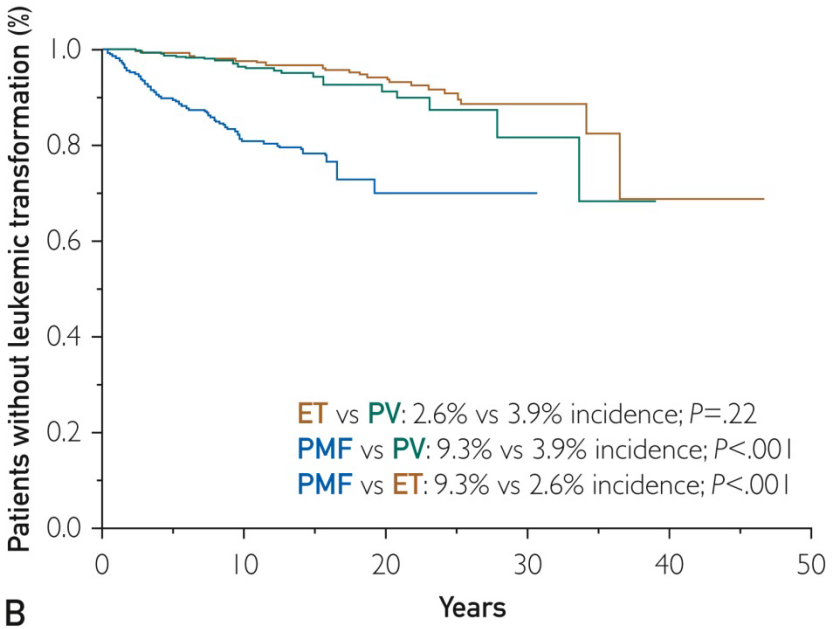
Courtesy Dr Anna Ruskova (Haematologist)
Auckland City Hospital, New Zealand

Tefferi, A. AJH; First published: 21 January 2023
https://doi.org/10.1002/ajh.26857

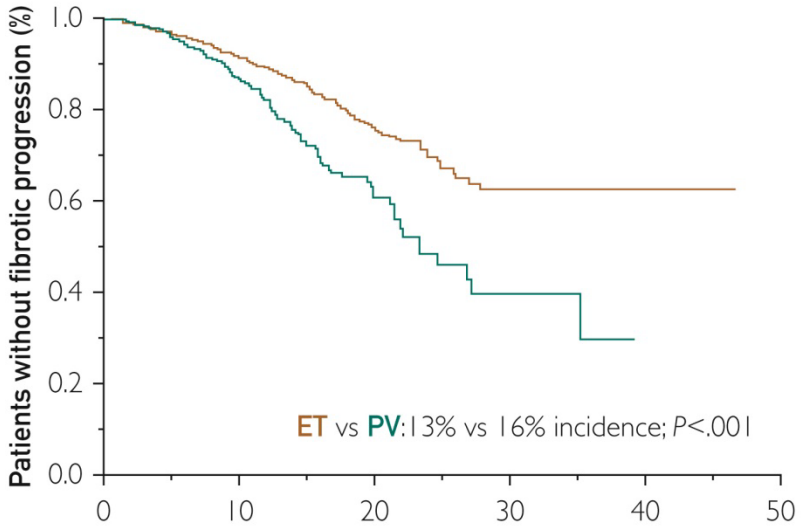
Overall (A), leukemia-free (B), myelofibrosis-free (C), and thrombosis-free (D) survival for 3,023 Mayo Clinic patients with myeloproliferative neoplasms (ET; PMF; PV) seen between 1967 and 2017. Median f/u = 20 years

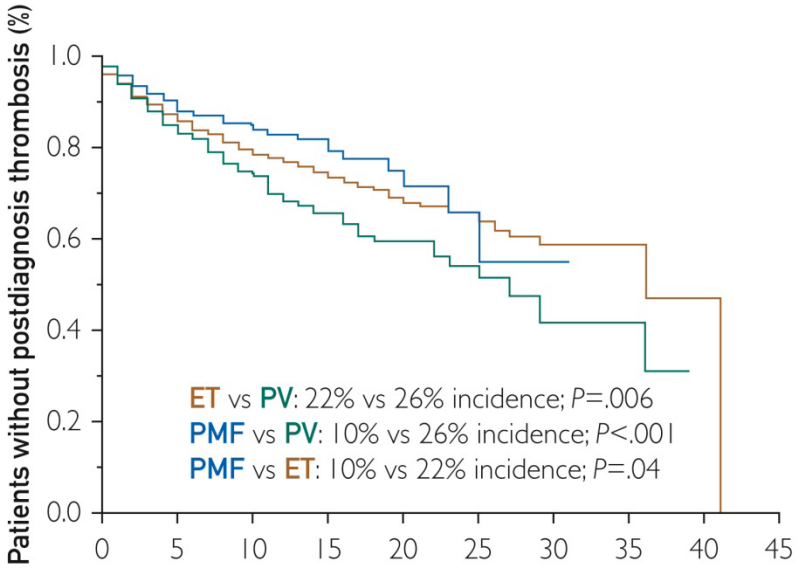


A



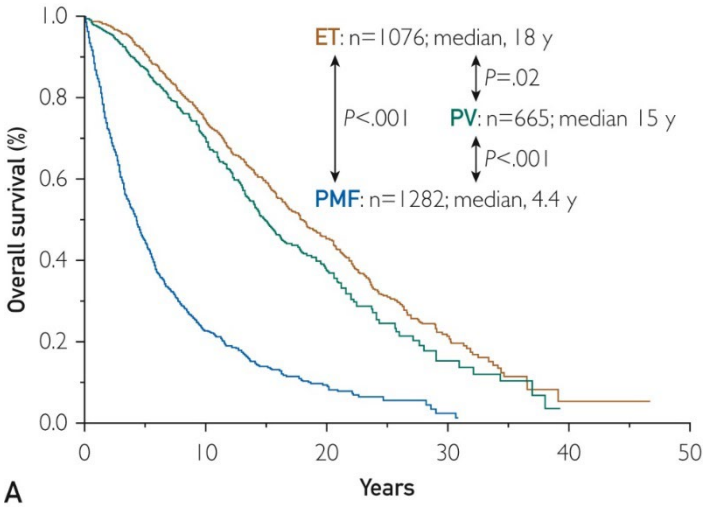
B

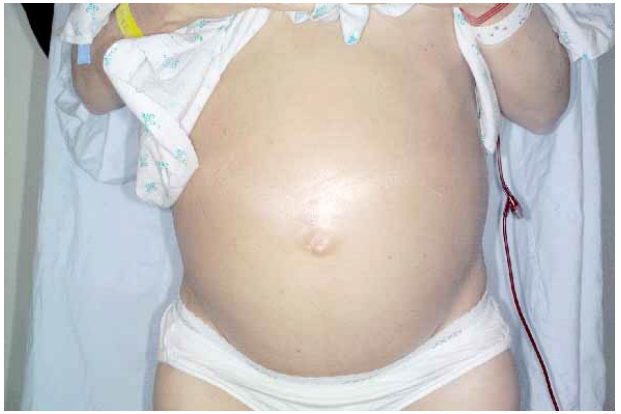


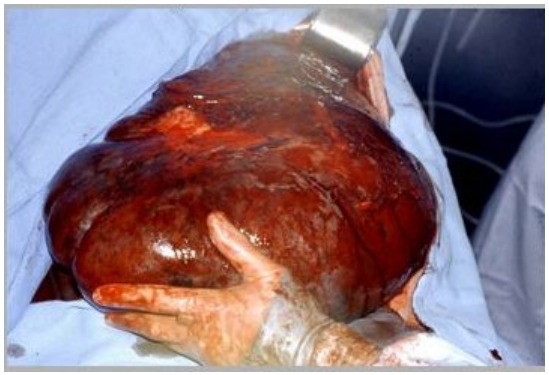


Szuber et al. Mayo Clin Proc. 2019;94:599-610.

Myelofibrosis
Disease complications







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

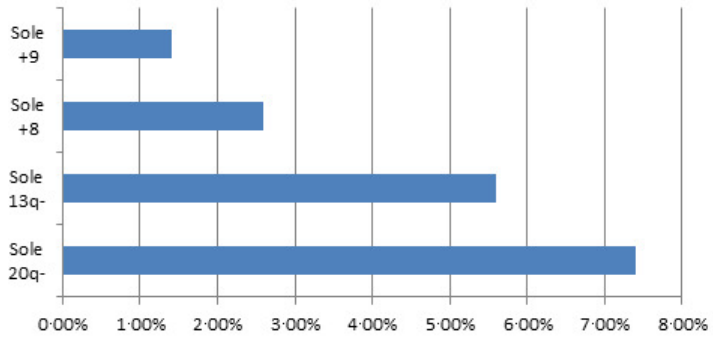
Szuber et al. Mayo Clin Proc. 2019;94:599

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

Recurrent genetic abnormalities in myelofibrosis

Abnormal karyotype at time of diagnosis ~ 30%

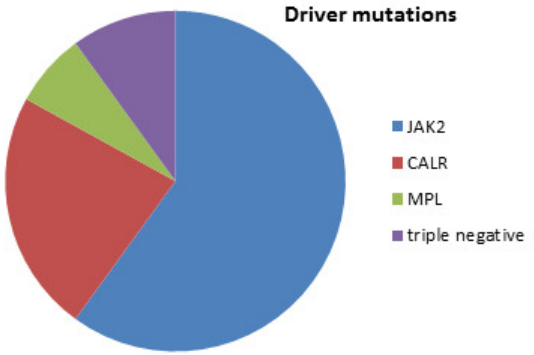


Revised cytogenetic risk stratification

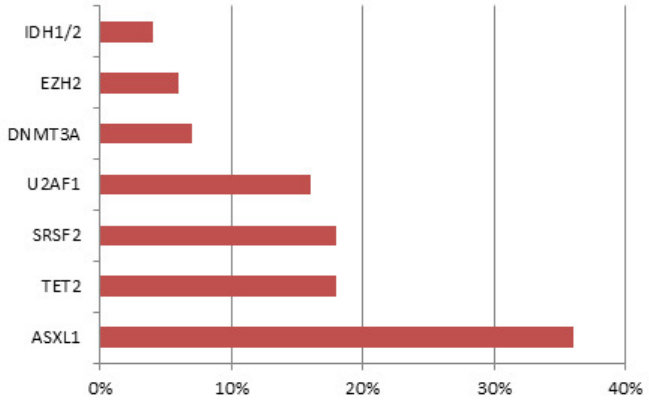
Very high risk karyotype
single/multiple abnormalities of -7, i(17q), inv(3)/3q21, 12p-/12p11·2, 11q-/11q23, or other autosomal trisomies

Unfavorable karyotype
all other abnormalities

Favorable karyotype
normal karyotype or sole abnormalities of 13q-, +9, 20q-, chromosome 1 translocation/duplication or sex chromosome abnormality including -Y;



Driver mutations frequency ~ 90%
JAK2 ~ 60%
CALR ~ 23%
MPL ~ 7%
TN ~ 10%



Other mutations frequency ~ 80%

High molecular risk aberrations
Absence of type 1 *CALR, ASXL1, SRSF2, EZH2, IDH1/2, U2AF1Q157*

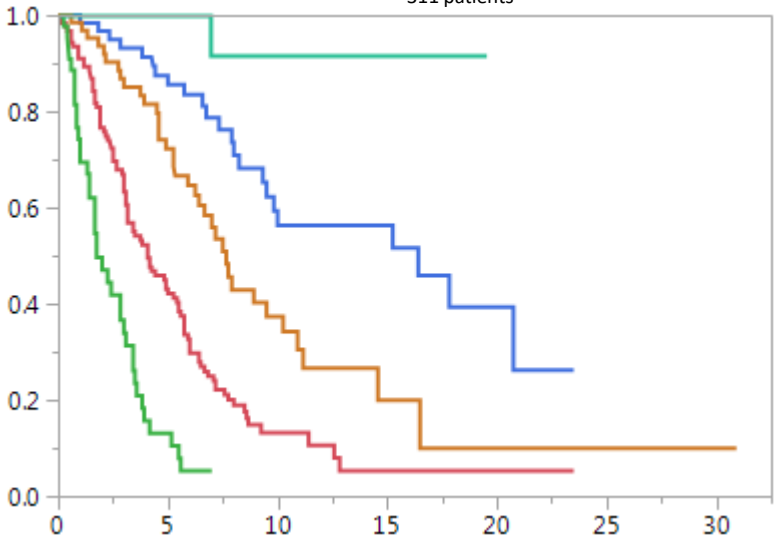
Gangat and Tefferi; BJH: 20 March 2020;
https://doi.org/10.1111/bjh.16576

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



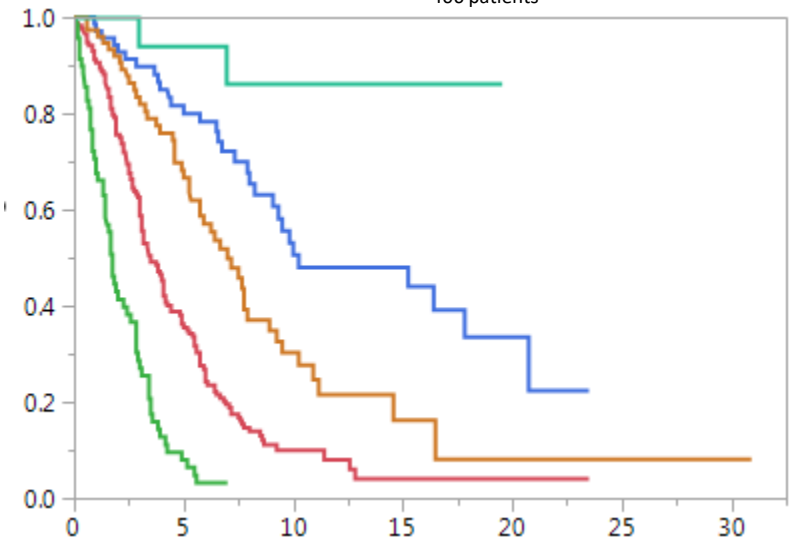
- Very high risk; *n*=44; median 1.8 years; 10-year survival <5%
- High risk; *n*=124; median 4.1 years; 10-year survival 13%
- Intermediate risk; *n*=64; median 7.7 years; 10-year survival 37%
- Low risk; *n*=61; median 16.4 years; 10-year survival 56%
- Very low risk; *n*=18; median not reached; 10-year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

Surviving

Years

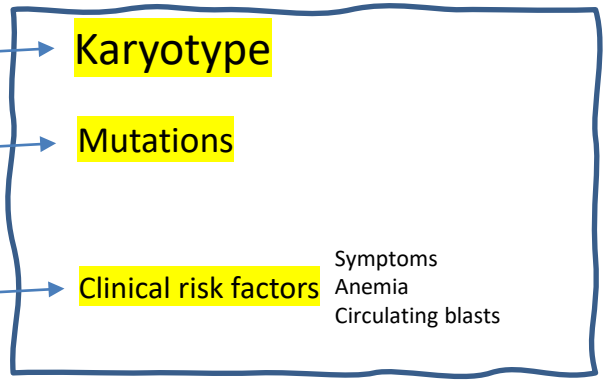
All ages

406 patients



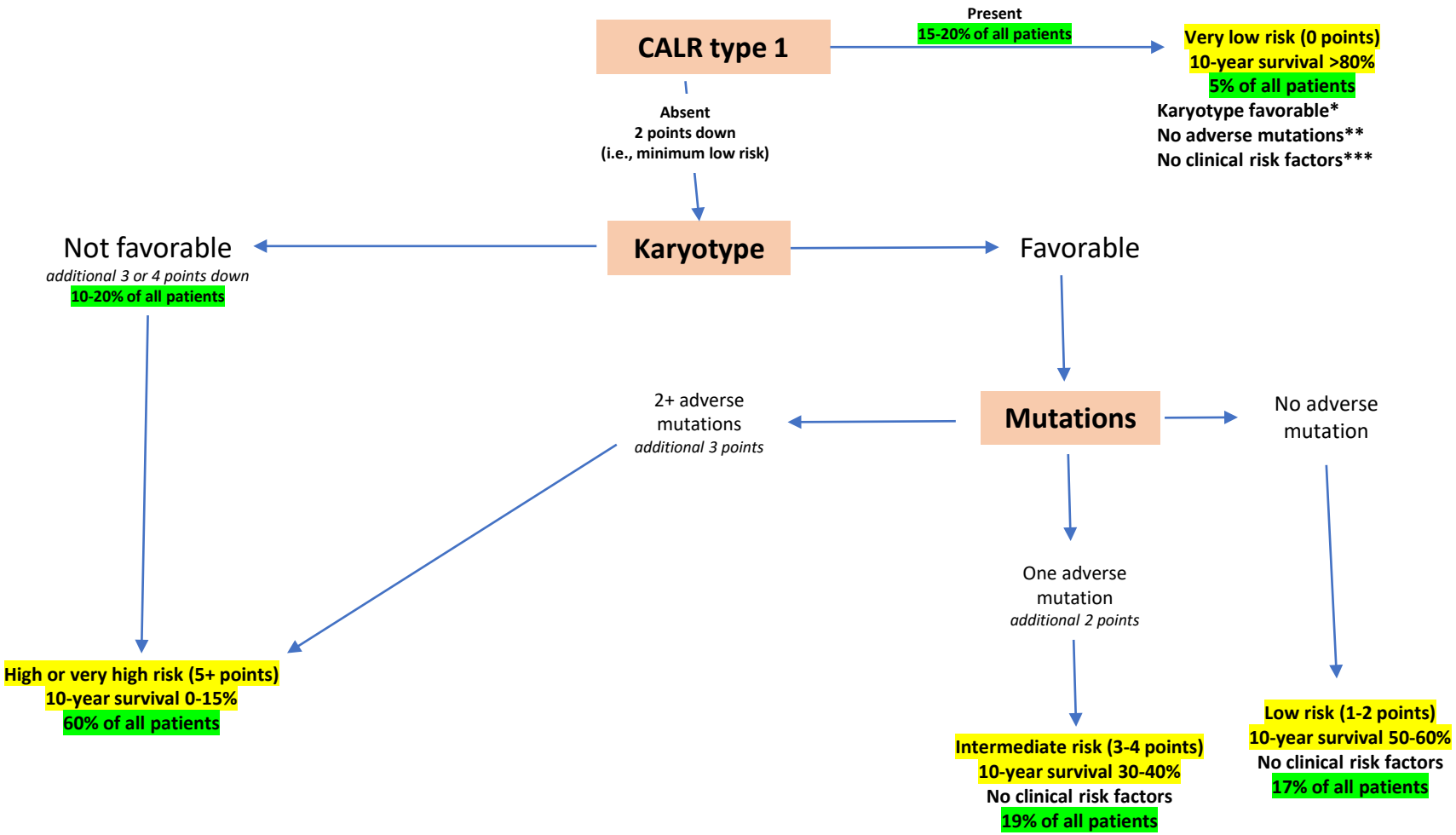
- Very high risk; *n*=69; median 1.8 years; 10-year survival <3%
- High risk; *n*=172; median 3.5 years; 10-year survival 10%
- Intermediate risk; *n*=76; median 7 years; 10-year survival 30%
- Low risk; *n*=70; median 10.3 years; 10-year survival 50%
- Very low risk; *n*=19; median not reached; 10-year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

Genetically-guided risk stratification in primary myelofibrosis (MIPSSv2)



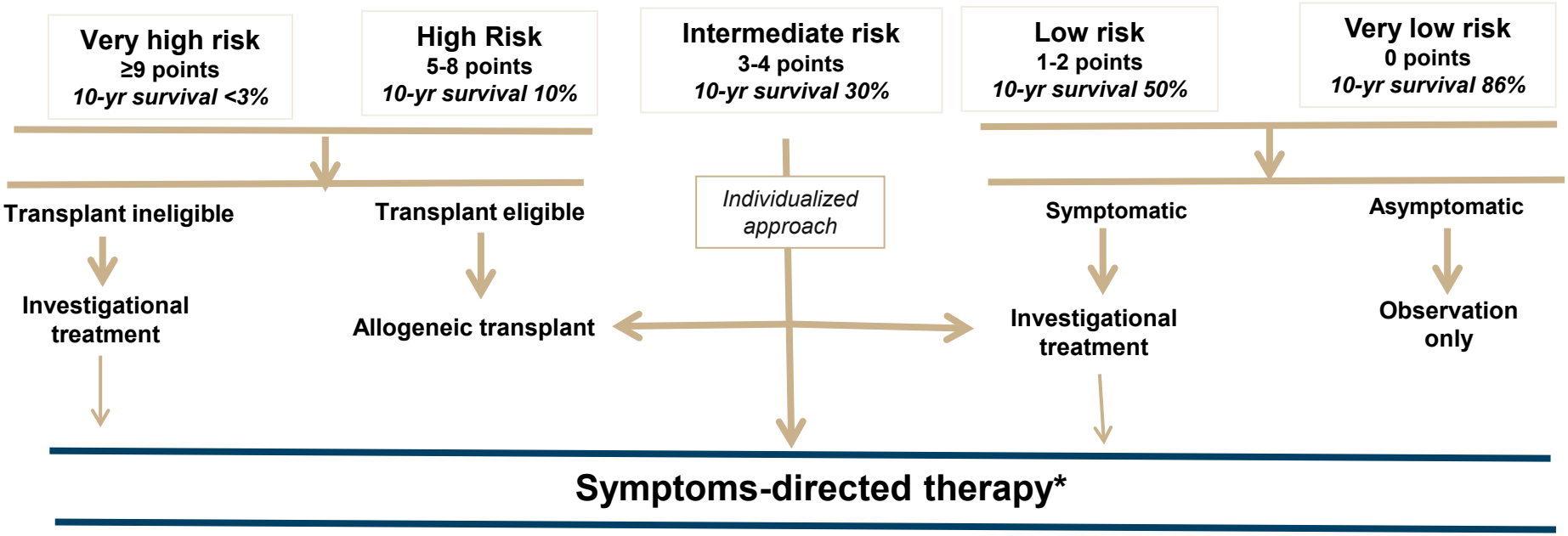
*Normal or any single abnormality of a sex chromosome, +9, 13q-, 20q-, or chromosome 1q abnormalities

***ASXL1*, *SRSF2*, *U2AF1*-Q157

*** i) Constitutional symptoms
ii) moderate or severe anemia <10 g/dL in women and <11 g/dL in men
iii) ≥2% circulating blasts

Tefferi Manuscript in preparation

Myelofibrosis: 2023 treatment algorithm



Tefferi, A. AJH; First published: 21 January 2023
https://doi.org/10.1002/ajh.26857

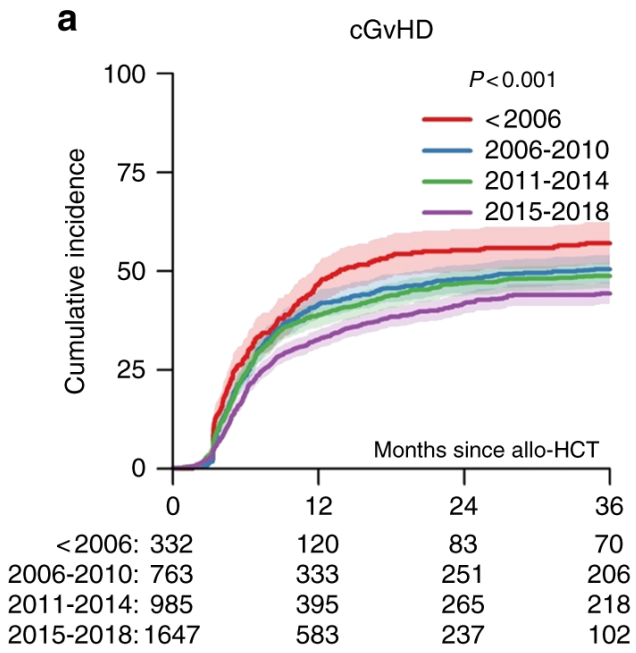
European registry-based study 1995-2018
4,412 MF patients

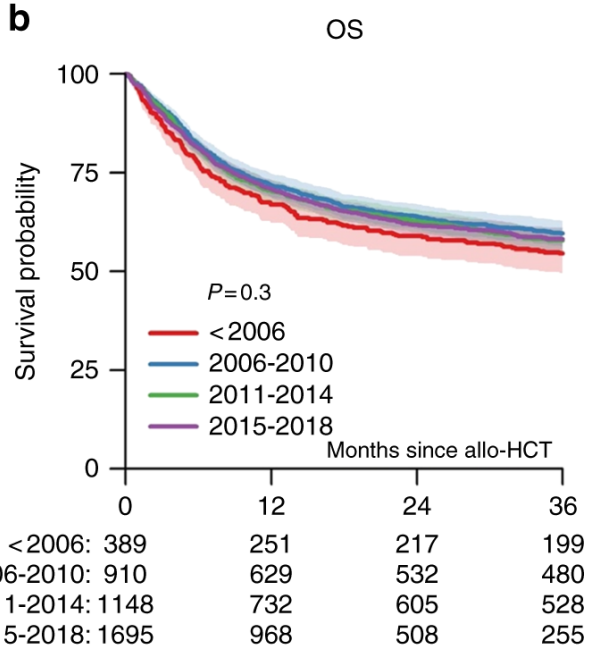
Changes over time:

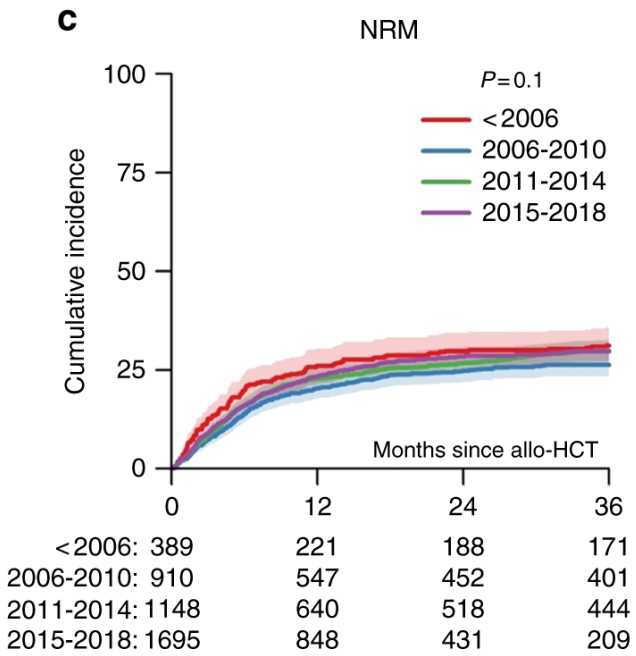
Median age 49 to 59 years
MUD use 23% to 45%
MMRD use 3% to 9%
aGVHD II-IV 35%-28%
Extensive CGVHD 36% to 23%

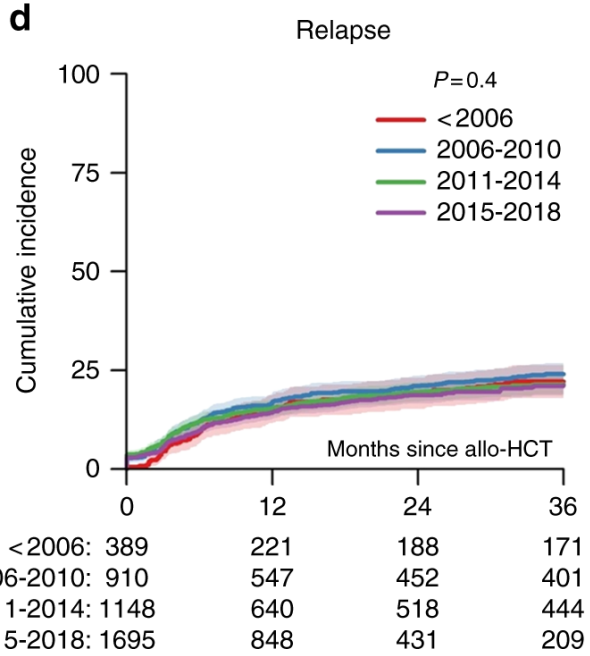
No significant change over time:

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









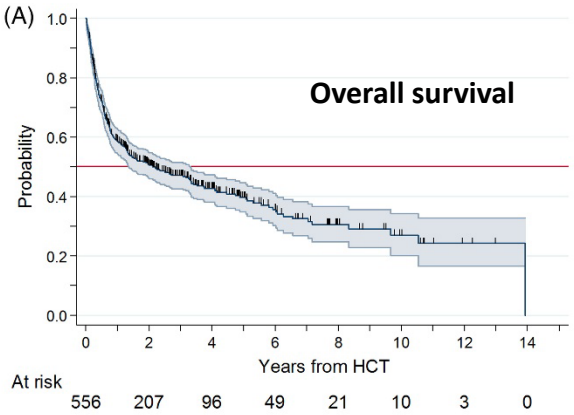
McLornan et al. BMT 2021;56:2160

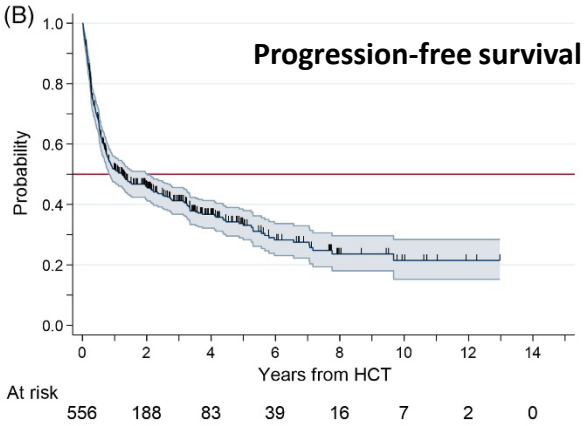
556 patients with myelofibrosis age ≥65 years undergoing allogeneic hematopoietic cell transplantation

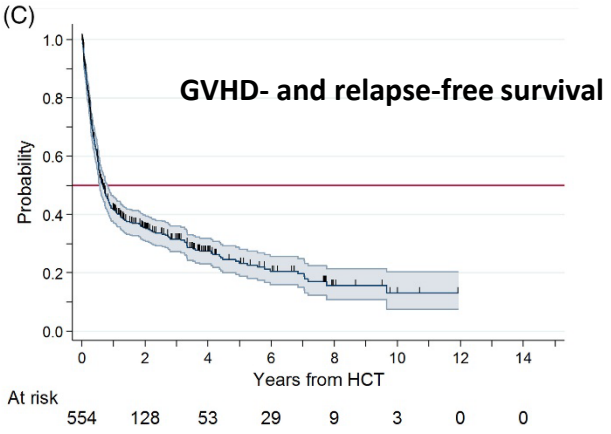
Median age 67 years (range, 65–76)
83% DIPSS high or intermediate-2 risk
Median f/u 3.4 years
Deaths 55% (n=306; GVHD 106; relapse/prog 80; infection 69)
Survival rates at 1, 3, and 5 years were 59%, 49%, and 40%
Relapse/progression at 1, 3, and 5 years was 18%, 22%, and 25%

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

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

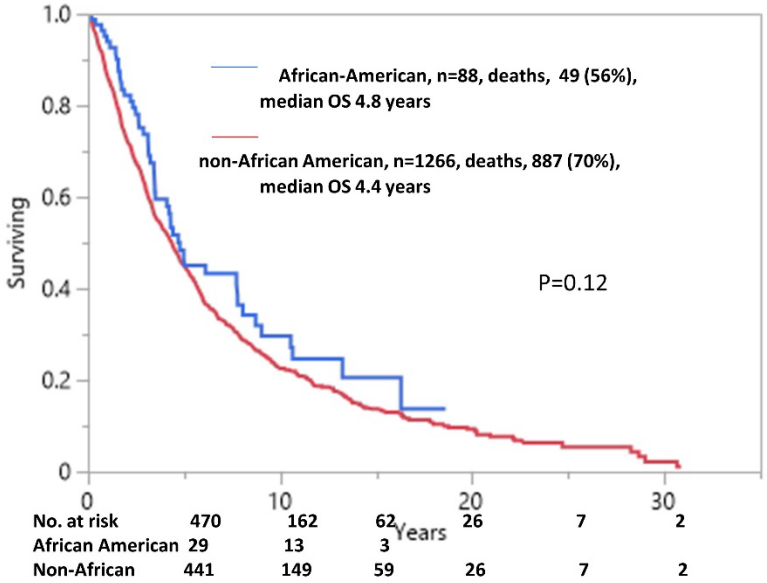






Hernández-Boluda et al. AJH 2021;96:1186

Figure 1a. Overall survival of 1,354 patients with primary myelofibrosis (PMF) stratified by race (Black African-American *vs* non-African American*) * 95% Caucasian



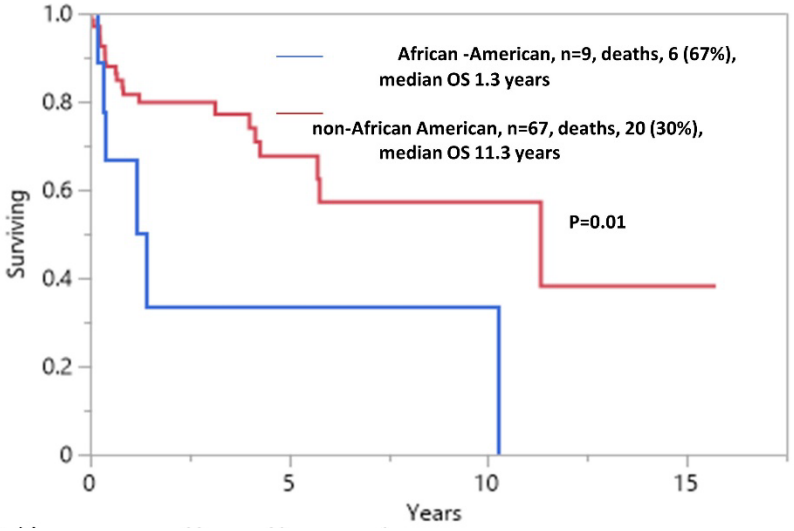
AA vs non-AA

Median age 61 vs 65 years
Females 52% vs 37%

Multivariate P-values

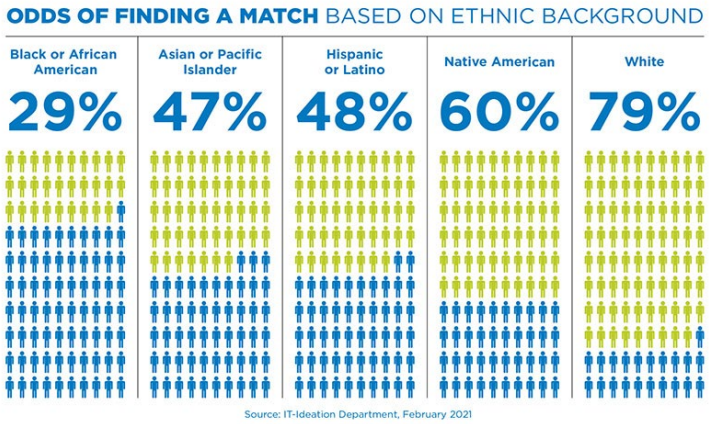
Race, p=0.73
DIPSS-plus risk, p<0.01
Type 1/like *CALR* mutation, p<0.01
***ASXL1* mutation, p=0.03**
***SRSF2* mutation, p<0.01**

Figure 1b. Post-transplant survival of 76 patients with primary myelofibrosis (PMF) stratified by race (Black African -American *vs* non-African American*) * 95% Caucasian



AA vs non-AA

MMUD/MMRD 44% vs 7%
MUD 33% vs 46%
MRD 22% vs 46%



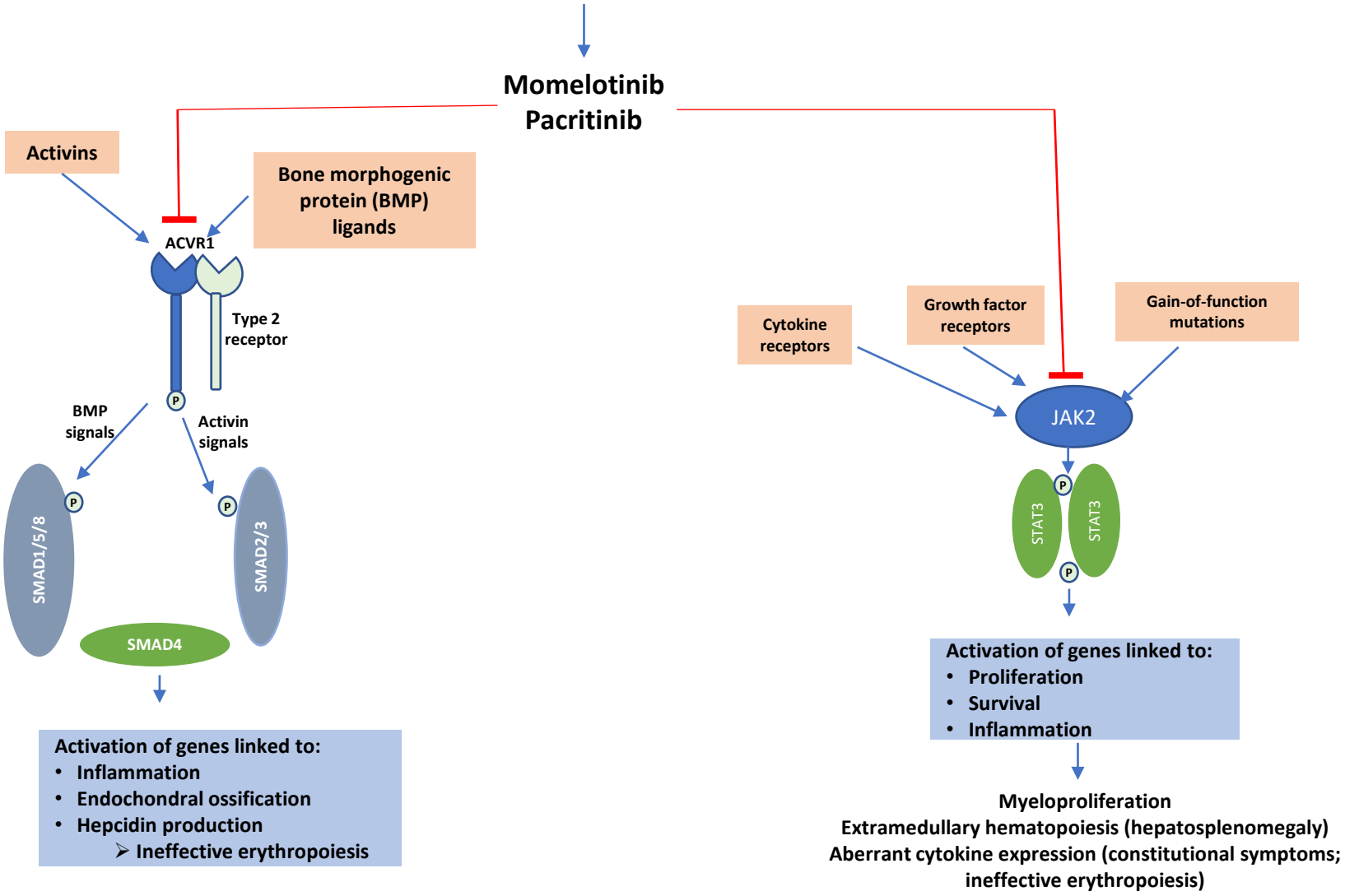
Gangat et al. Blood Advances 2023, https://doi.org/10.1182/bloodadvances.2022009611

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

Newer JAK2 inhibitors



Tefferi et al. Haematologica Early view Mar 2, 2023 https://doi.org/10.3324/haematol.2022.282612
Oh et al. Blood 140:1518-1521, 2022

MOMENTUM: Phase 3 randomized study of momelotinib (MMB 200 mg QD; n=130) **versus danazol (**DAN 600 mg QD (n=65) **in symptomatic and anemic myelofibrosis patients previously treated with a JAK inhibitor**

Week 24 Endpoint	Momelotinib	Danazol	p-value
Transfusion independence rate "at baseline" to "at week 24"	**13% to 31%**	**15% to 20%**	**<0.05**
Spleen response rate ≥35% "at week 24"	**23%**	**3%**	**<0.05**
Symptoms score response rate "at week 24"	**25%**	**9%**	**<0.05**

*Verstovsek et al. Lancet 2023;***401:269**

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)

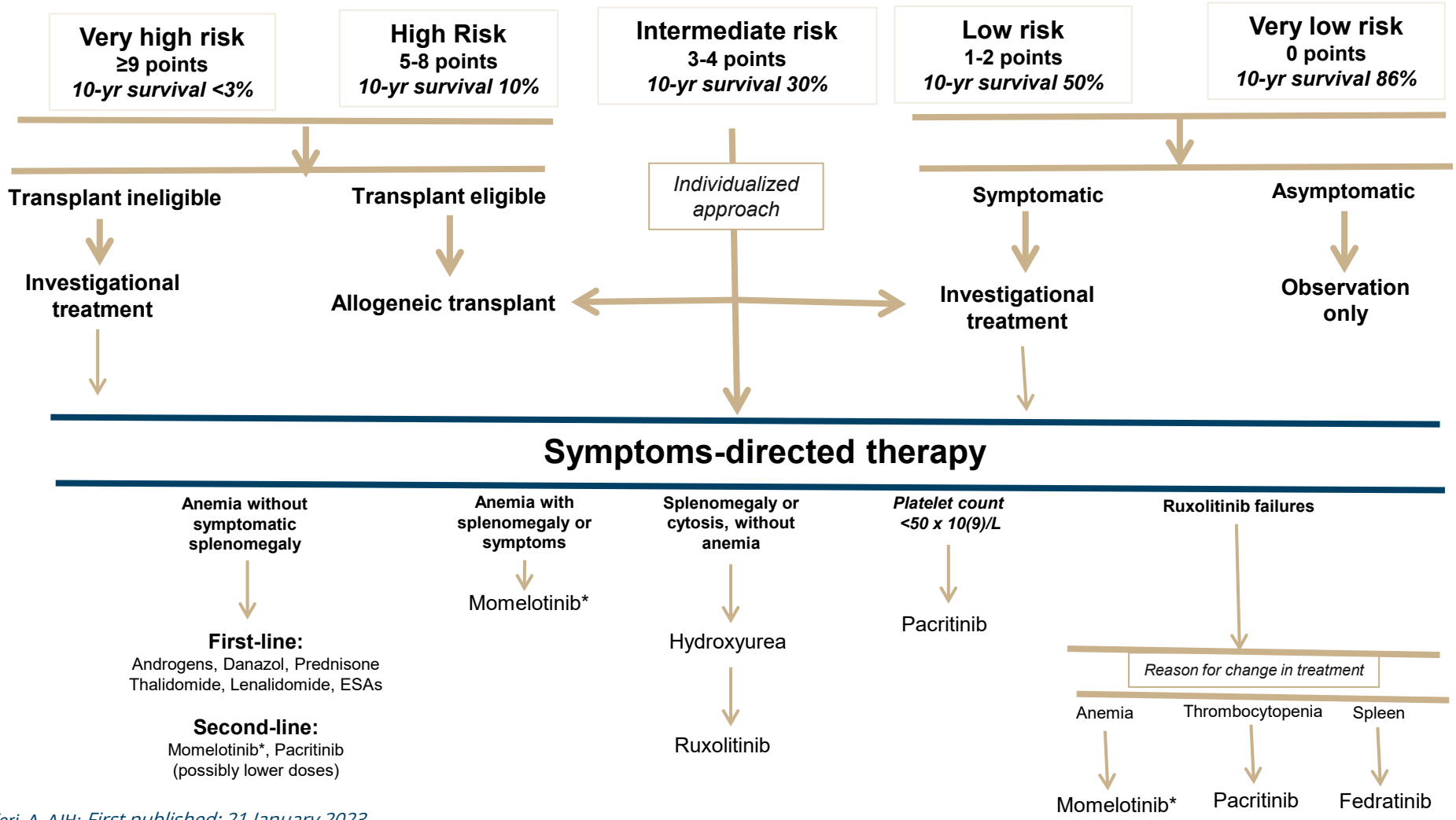
Harrison et al. AJH 2020;95:594

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

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

Gangat et al. BJH 2022;198:e54

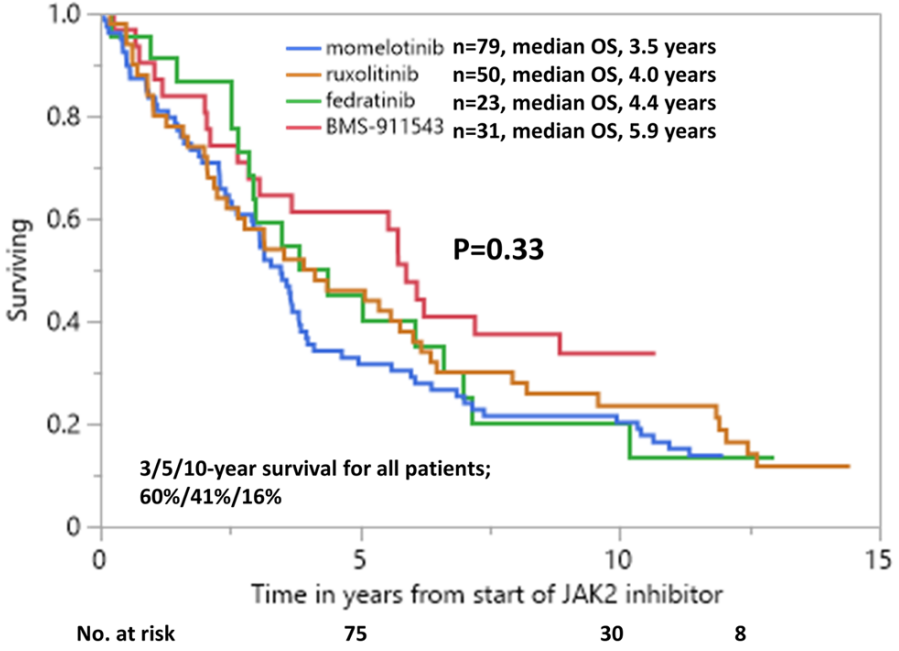
Myelofibrosis: 2023 treatment algorithm



Tefferi, A. AJH; First published: 21 January 2023
https://doi.org/10.1002/ajh.26857

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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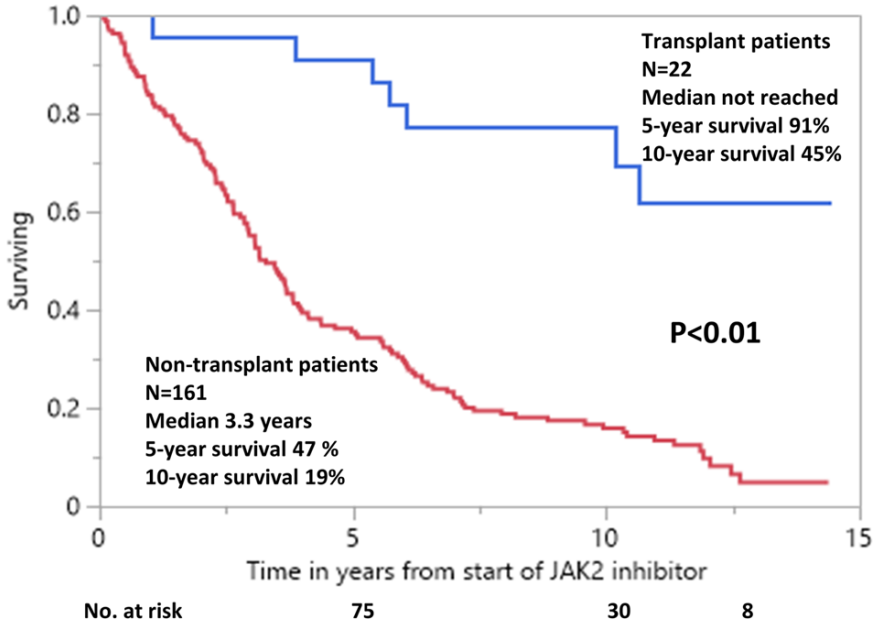


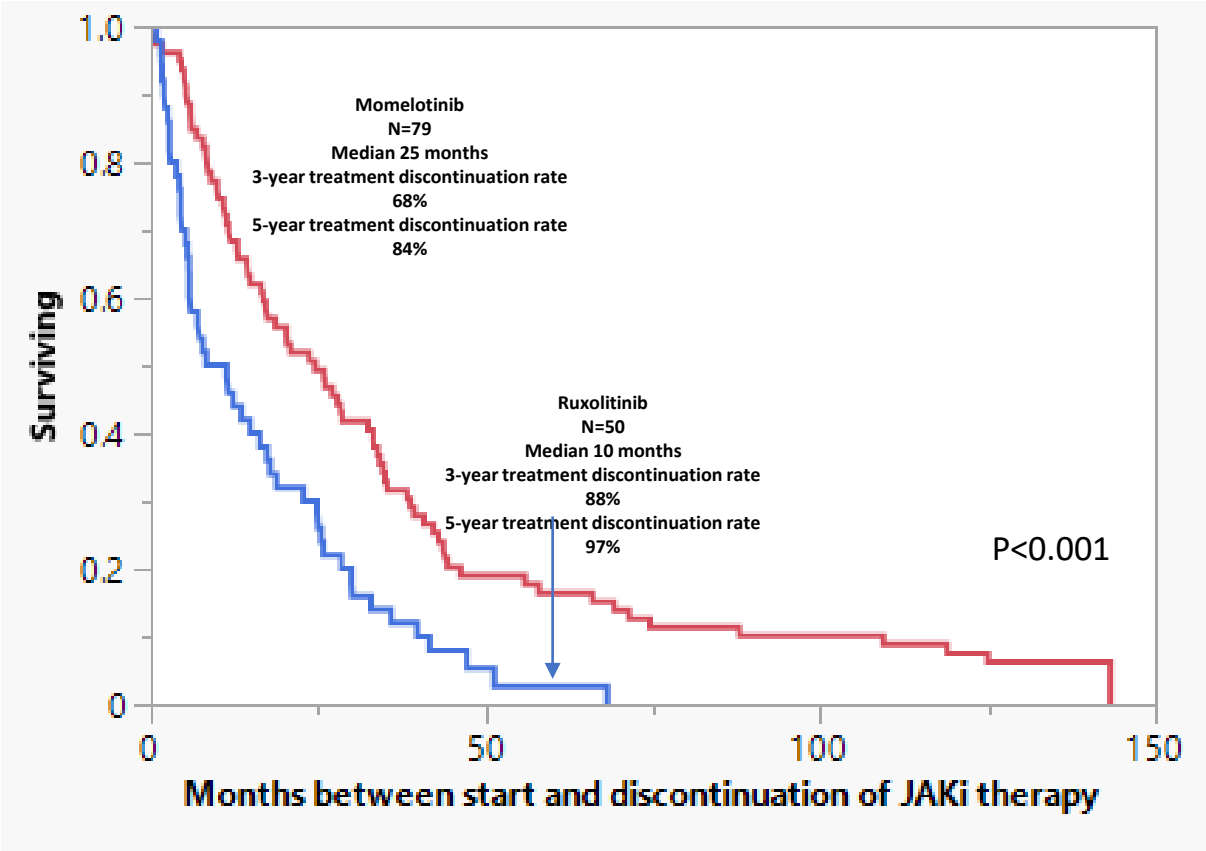
Predictors of inferior survival

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)*

Figure 2: On-treatment survival among 129 patients with high/intermediate risk myelofibrosis treated with either momelotinib or ruxolitinib



Tefferi et al. AJH. First published: 03 September 2022
https://doi.org/10.1002/ajh.26714

Summary of Novel Agents in clinical trials in myelofibrosis

Novel agent	Mechanism	SVR/TSS	Anemia response	Reduction in fibrosis	Status
Navitoclax + Ruxolitinib Abstract 237 (JAKi naïve) JCO 2022 (JAKi exposed)	bcl-2/bcl-X inhibitor	+/NR	NR	+	Phase 3 TRANSFORM 1/2
Pelabresib (CPI-0610) + Ruxolitinib Abstract 238 (JAKi naïve) Abstract 4344 (JAKi exposed)	Nuclear factor kappa B (NFκB) signaling	++	+	+	Phase 3 MANIFEST
Parsaclisib + Ruxolitinib Abstract 236 (JAKi exposed)	PI3Kδ inhibitor	++	NR	NR	Phase 3
Pegylated IFN-α + Ruxolitinib Abstract 235	Immunotherapy	+/NR	NR	-	Ongoing
Luspatercept +/- Ruxolitinib Blood 2019	TGF-β/SMAD signalling	NR	**+**	NR	Phase 3 Independence
Bomedemstat (Img-7289) Abstract 139	LSD1 inhibitor	++	**+**	+	Completed
Imetelstat JCO 2021	Telomerase inhibitor	Minimal/+	-	+	Phase 3 MYF3001 MYF1001

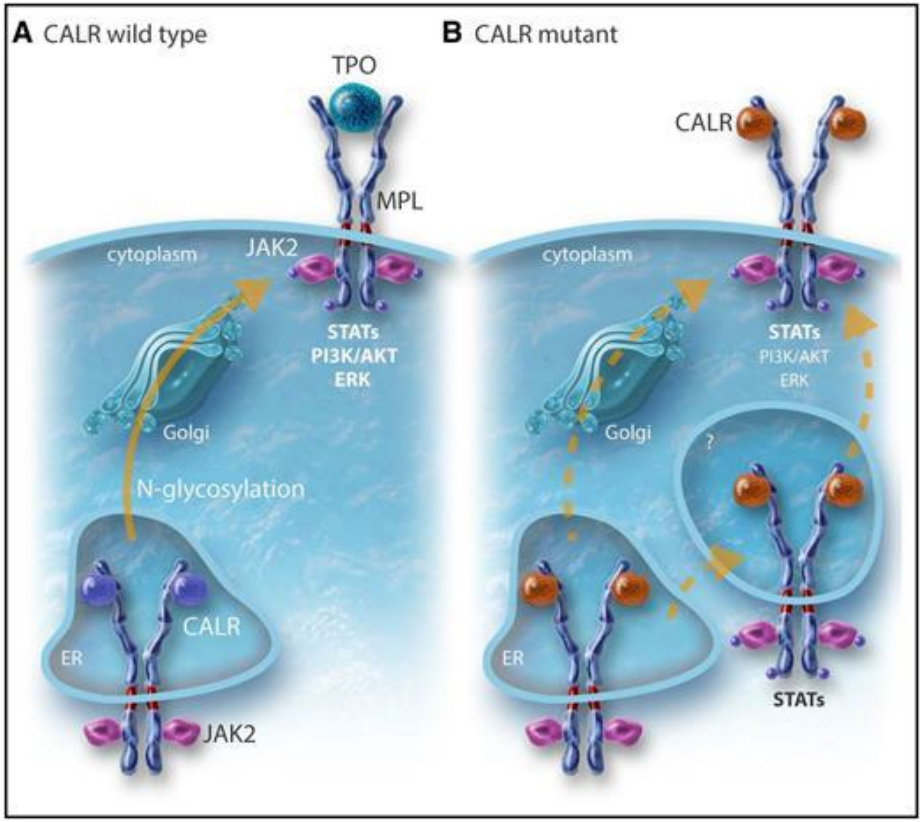
SVR, spleen volume reduction; TSS, total symptom score; NR, not reported

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 is planned in mut *CALR* MF and ET in 2023**

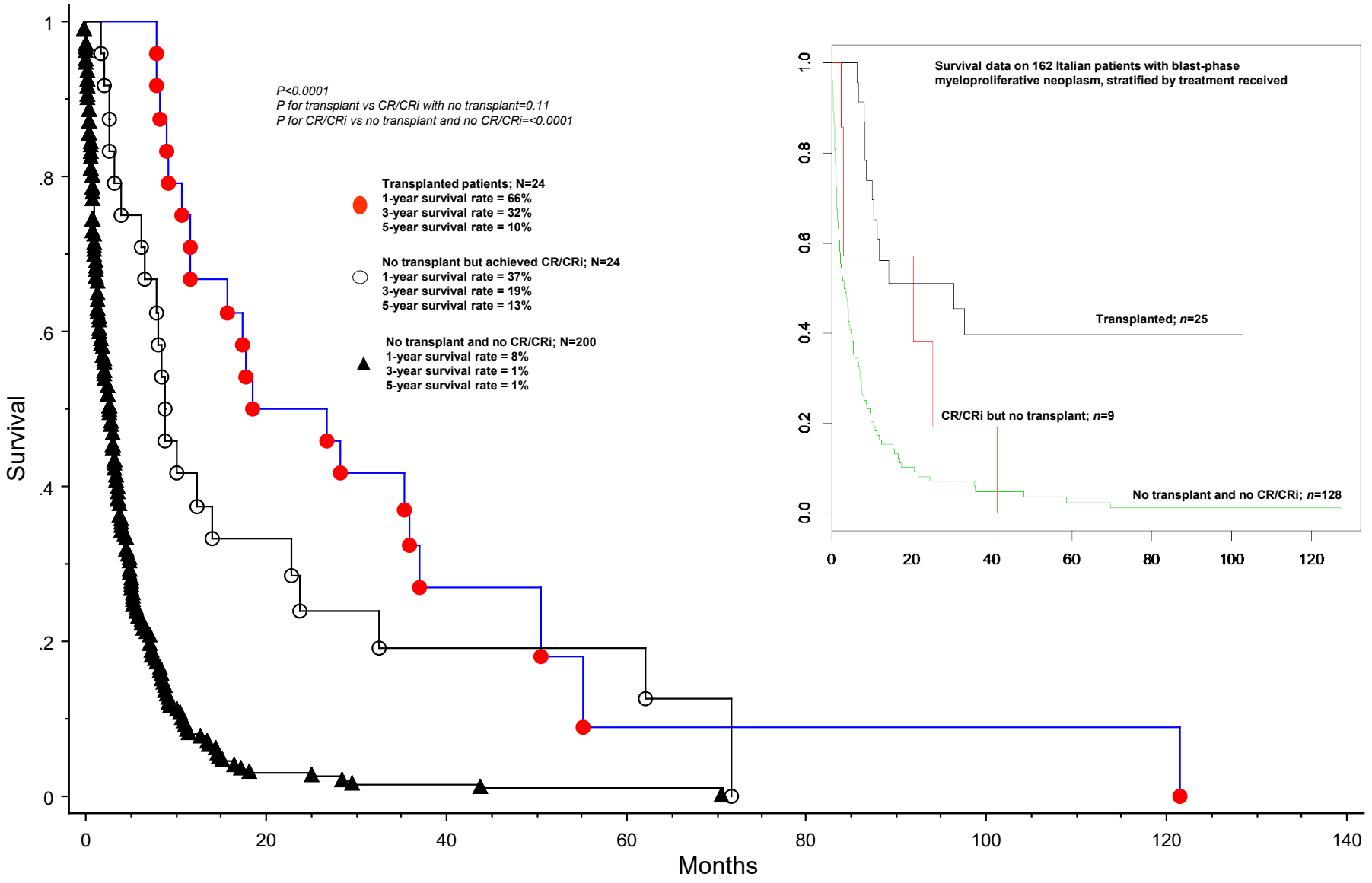
What can we expect?



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

ASH 2022
Plenary Abstract 6

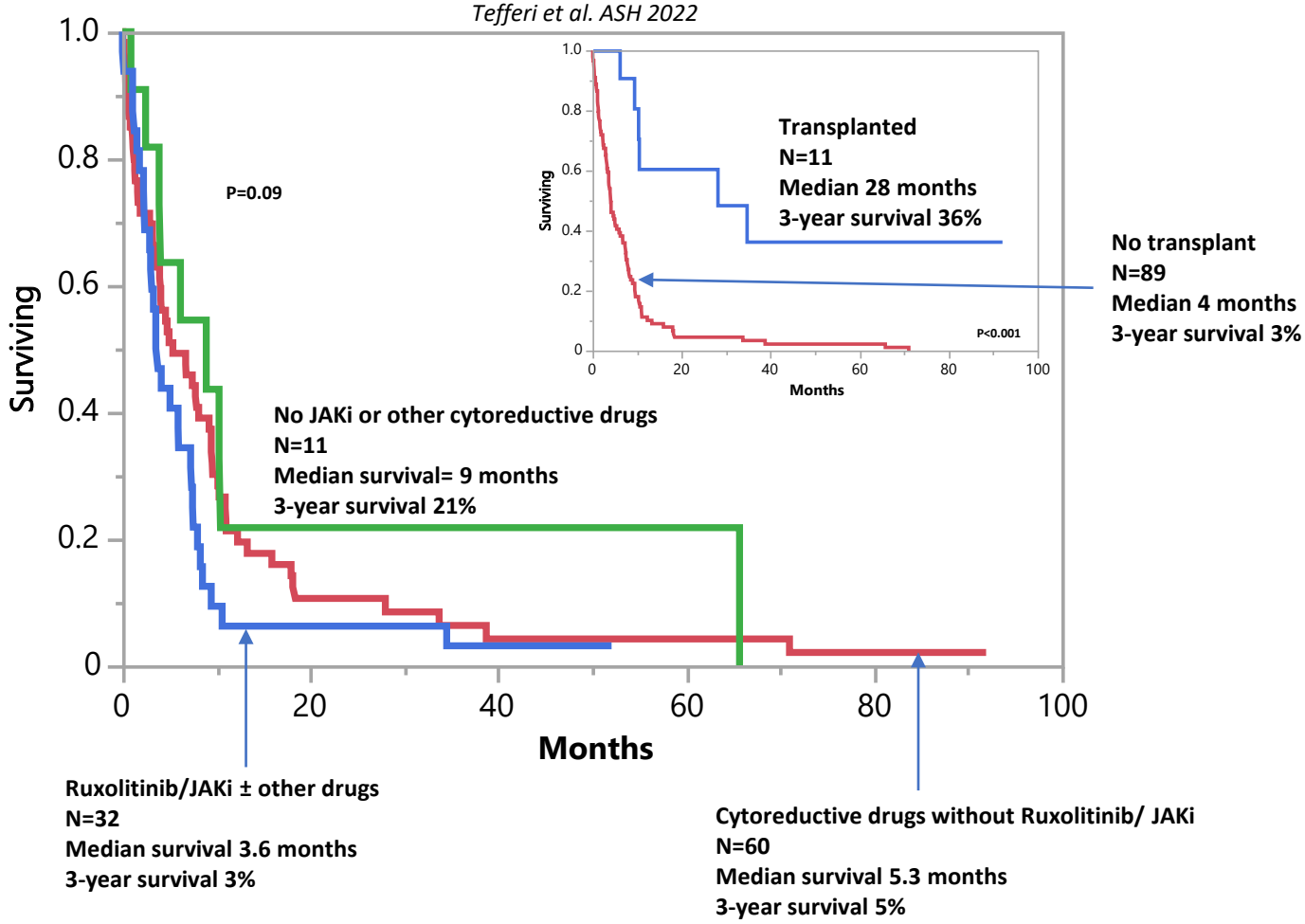
Survival data on 248 Mayo Clinic patients with blast-phase myeloproliferative neoplasm, stratified by specific treatment strategies



Tefferi et al. Leukemia 2018;32:1200

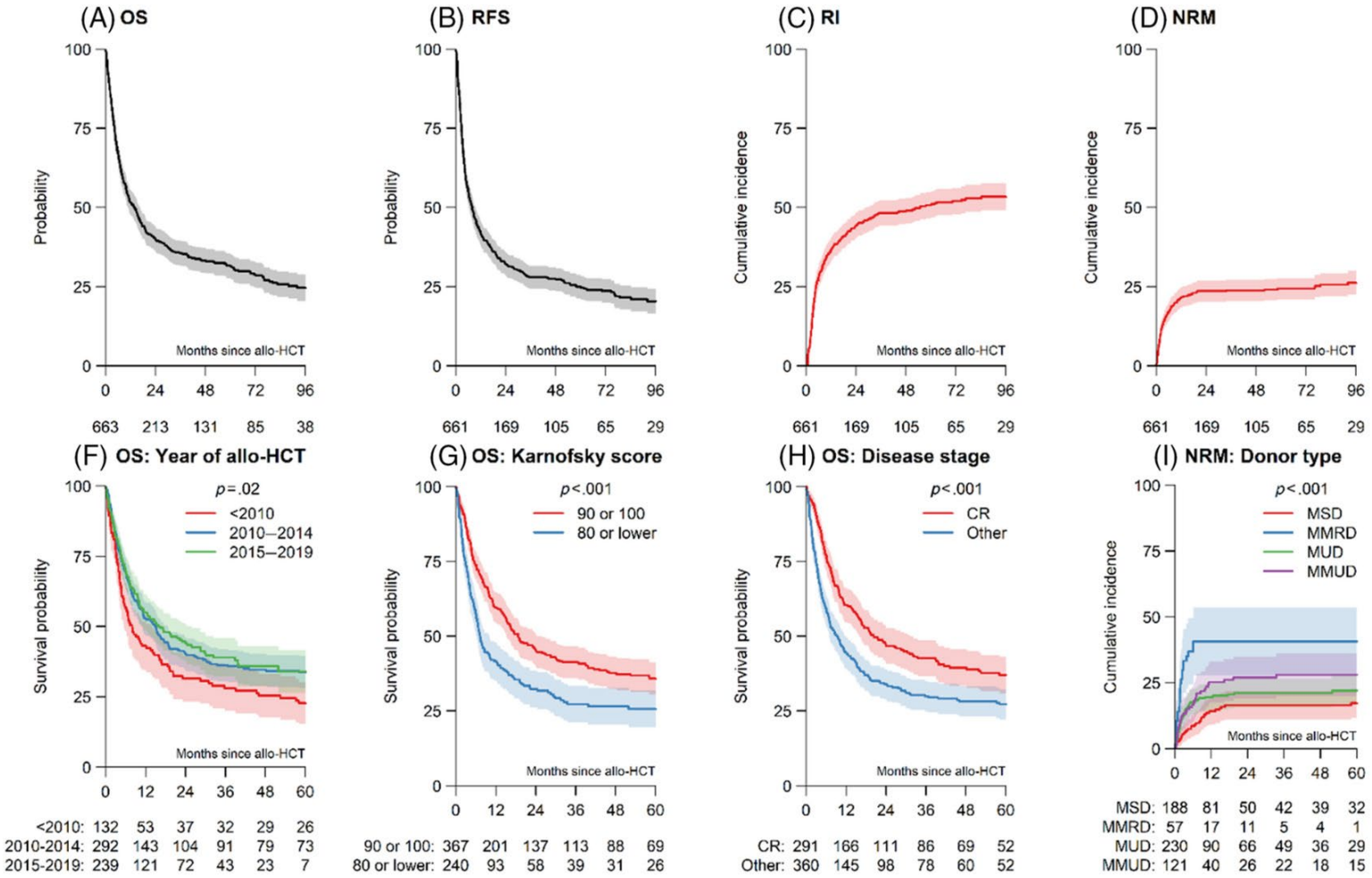
Survival in 103 patients with blast phase myeloproliferative neoplasm, **diagnosed in the ruxolitinib era of 2011 and beyond**, stratified by treatment received prior to leukemic transformation ("n" informative = 100)

Tefferi et al. ASH 2022



Abdelmagid et al. Haematologica 2023 https://doi.org/10.3324/haematol.2022.282627

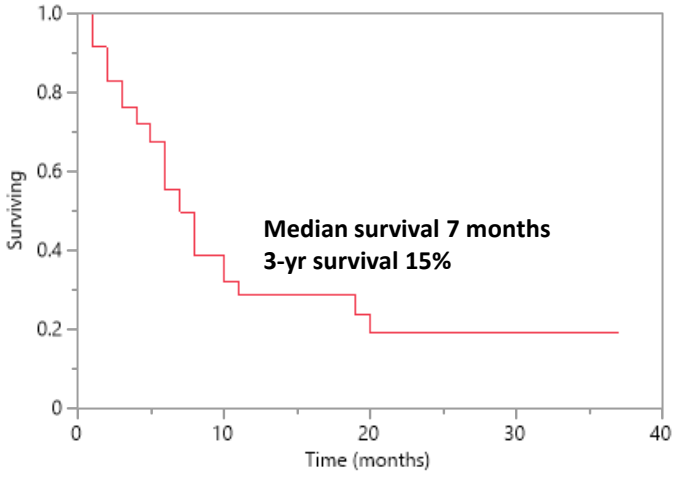
663 patients with MPN-BP allo-transplanted (2005-2019) with median f/u 62 months: 3-year survival 36%...increased to 60% if transplanted in CR and good performance status

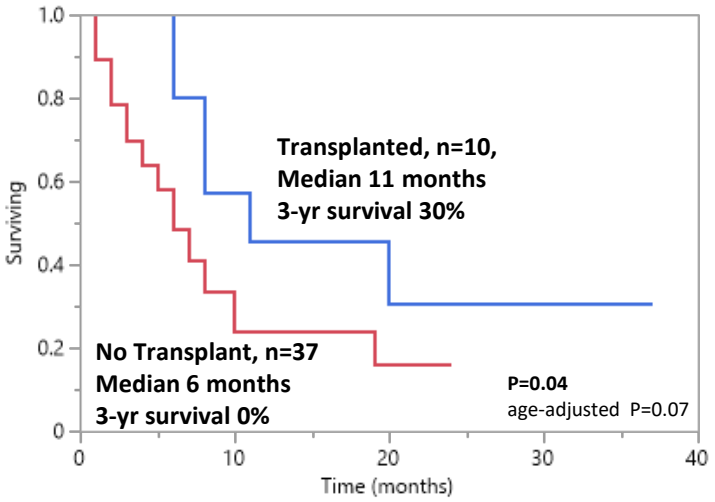


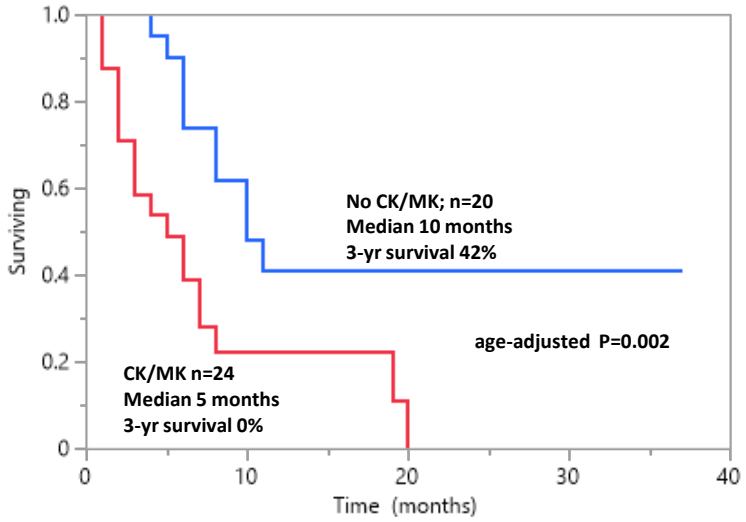
Orti et al. AJH 2023 First published: 06 January 2023; https://doi.org/10.1002/ajh.26833

Survival in 47 patients with blast phase myeloproliferative neoplasm receiving venetoclax + hypomethylating agent

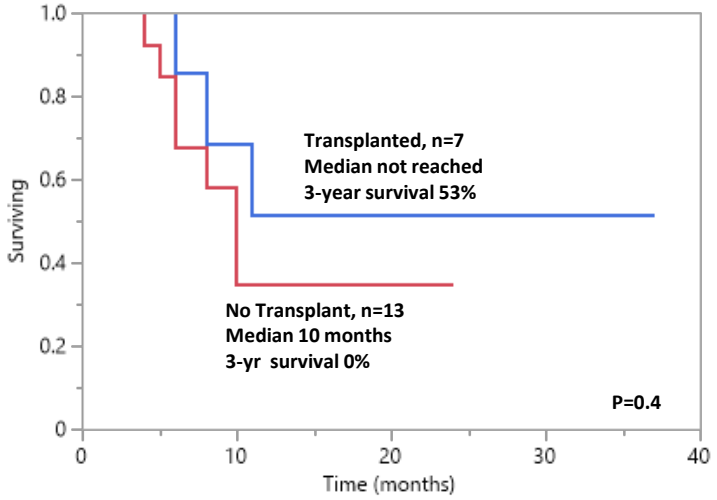
- **Predictors of response:** *TET2 mutations (70% vs 35%); absence of CK/MK (60% vs 29%); PMF/post-ET vs post-PV MF (55% vs 19%)*
- **Predictors of superior survival:** *CR/CRi; Transplant; IDH mutations, absence of CK/MK or N/KRAS mutations*





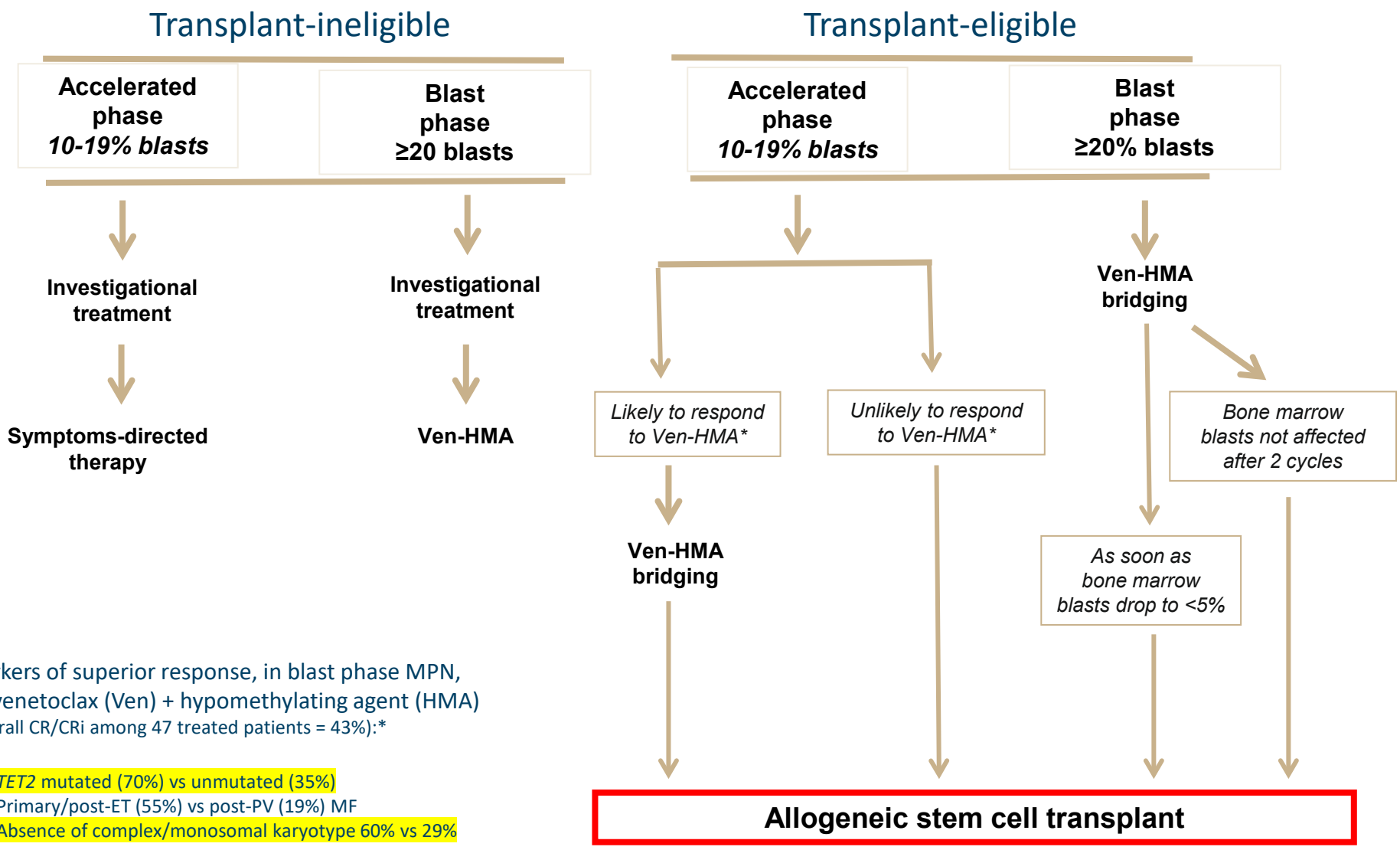


20 patients with MPN-BP without CK/MK treated with venetoclax plus hypomethylating agent stratified by allogeneic transplantation



Gangat et al. Haematologica Early view Dec 15, 2022 https://doi.org/10.3324/haematol.2022.282019

Current management approach in accelerated or blast phase myeloproliferative neoplasms



Markers of superior response, in blast phase MPN, to venetoclax (Ven) + hypomethylating agent (HMA)
(Overall CR/CRi among 47 treated patients = 43%):*

1. *TET2* mutated (70%) vs unmutated (35%)
2. Primary/post-ET (55%) vs post-PV (19%) MF
3. Absence of complex/monosomal karyotype 60% vs 29%

**Gangat et al.* Haematologica Early view Dec 15, 2022 https://doi.org/10.3324
Tefferi et al. Manuscript in preparation

Concluding remarks – thank God for transplant

- **Allogeneic transplant is the only treatment modality that can secure long-term survival in both chronic and blast phase myelofibrosis; *bone marrow registry needs 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 disease-modifying activity**
- **Regarding investigational new drugs for myelofibrosis, I see clouds but no smoke☺**