

Il profilo molecolare del paziente con mielofibrosi citopenica

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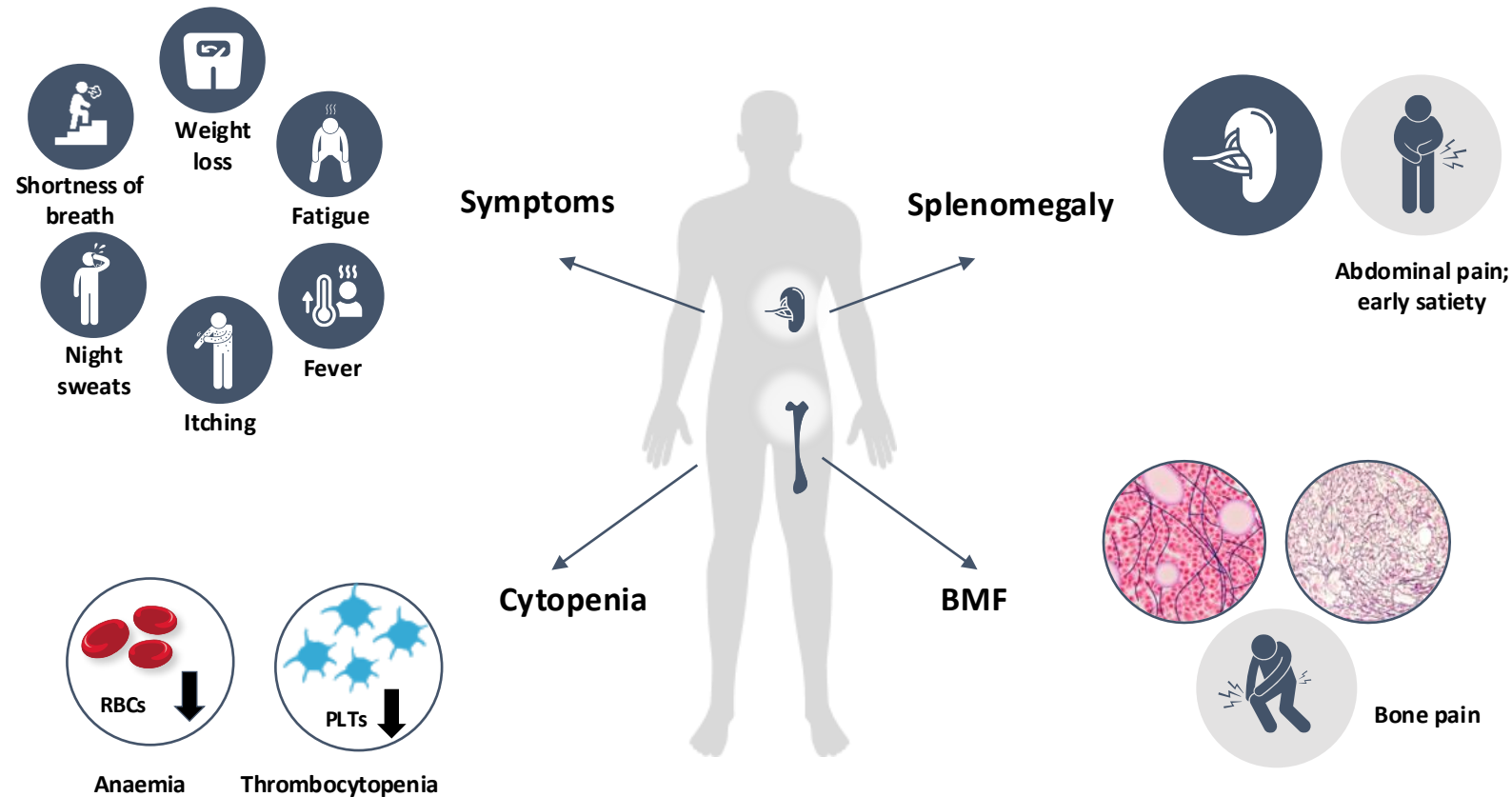


Regione
Lombardia

Disclosures

- FRANCESCO PASSAMONTI received honoraria during the last two years for lectures from Novartis, Bristol-Myers Squibb, Abbvie, GSK, AOP Orphan, Menarini Stemline, MSD, and for advisory boards from Novartis, Bristol-Myers Squibb/Celgene, GSK, Abbvie, Keros, Takeda, Sumitomo.

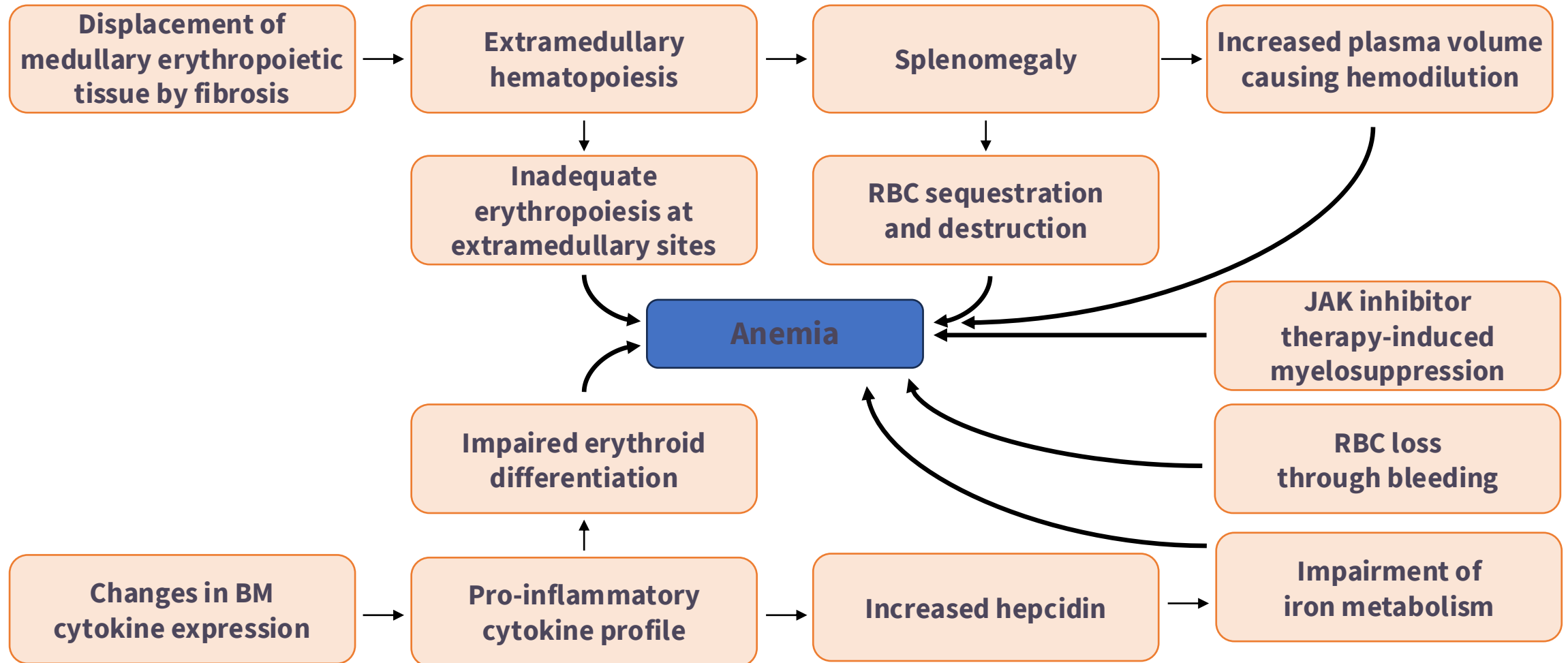
Key hallmarks and clinical presentation of myelofibrosis (MF)



Tefferi A. *Am J Hematol.* 2018;93:1551-1560. Mughal TI, et al. *Int J Gen Med.* 2014;7:89-101.
O'Sullivan JM, Harrison CN. *Clin Adv Hematol Oncol.* 2018;16:121-131.

Anemia in myelofibrosis

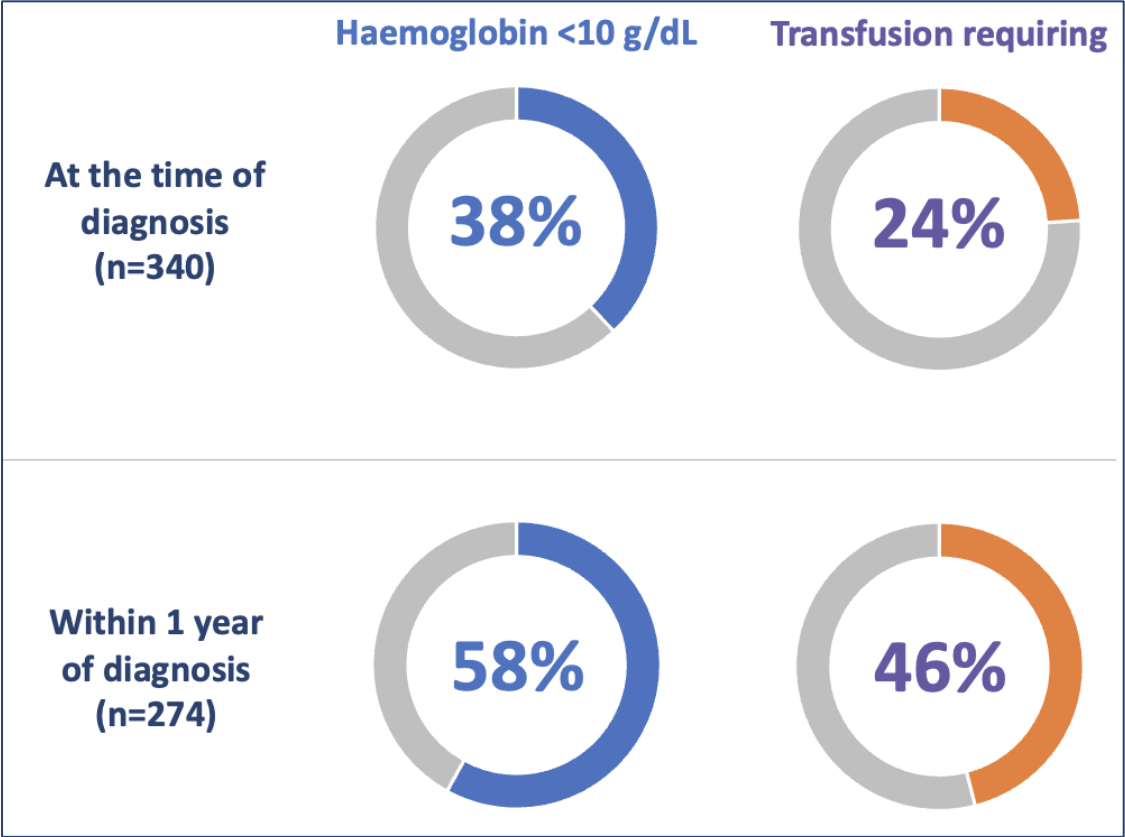
Anemia in myelofibrosis is multifactorial and has not been fully elucidated



Adapted from Naymagon *et al.*¹ in accordance with the Creative Commons Attribution License (CC BY 4.0).

Burden of anemia in patients with MF

PMF: the Mayo clinic experience



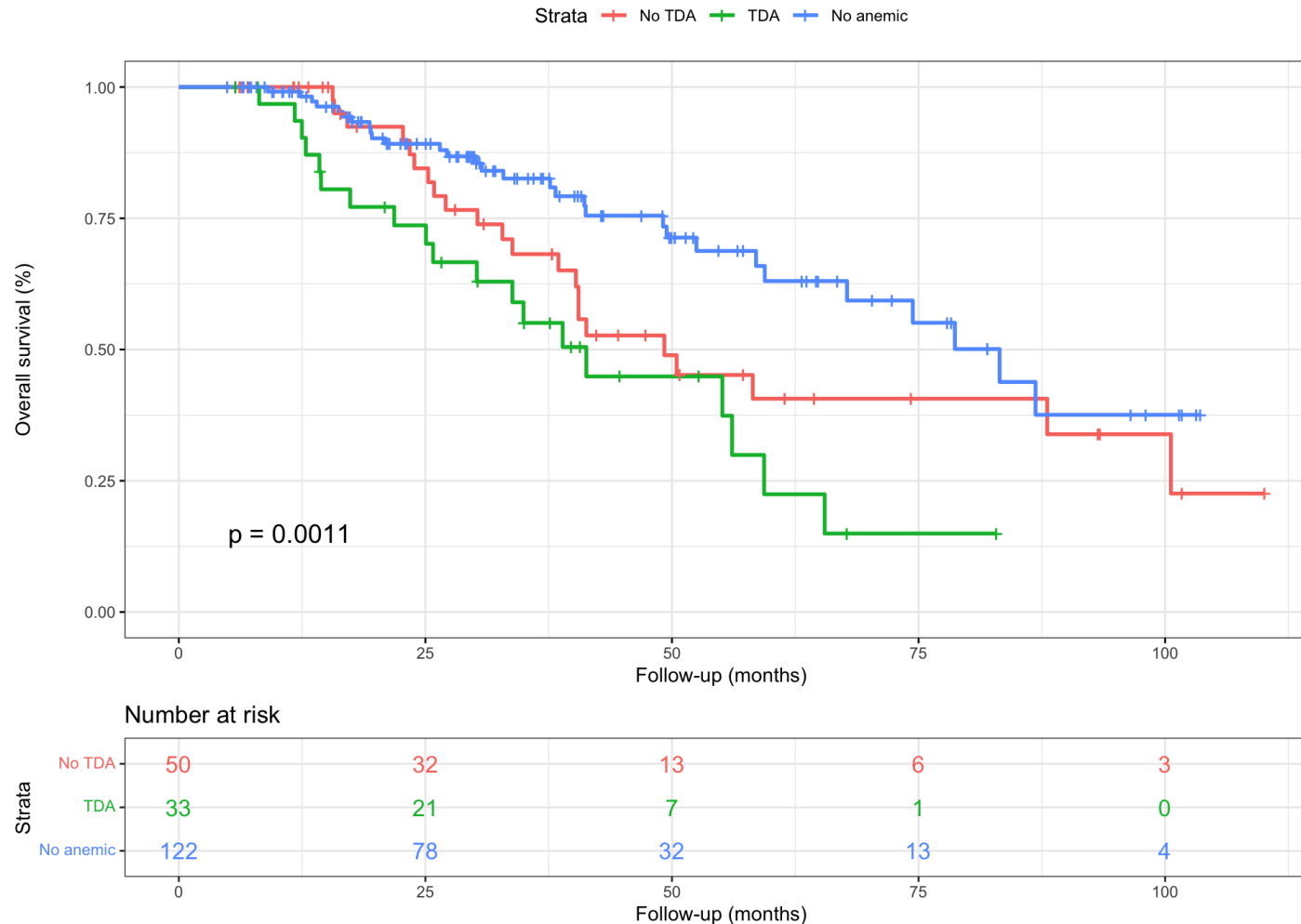
SMF: the MYSEC project

	Hb (g/dl), median (range)	Hb <10 (g/dl), n (%)	Hb <8 (g/dl), n (%)
SMF (1258)	11.1 (4.2-16.0)	363 (30.3)	62 (5.2)
PPV-MF (615)	11.9 (6.3-16.0)	131 (22.4)	17 (2.9)
PET-MF (643)	10.6 (4.2-16.0)	232 (37.7)	45 (7.3)
p-value	<0.0001	<0.0001	0.001

The revised IWG-ELN criteria proposed three strata for anemia definition

- A hemoglobin level of <10 g/dL, irrespective of gender, is considered a suitable key inclusion criterion for clinical trials targeting anemia
- TDA is defined as the need for ≥ 3 units of red blood cells/12 weeks
 - Patients requiring ≥ 6 units, within the 12-week preenrollment period constitute a high transfusion burden subcategory
- Non-TDA includes anemic subjects who do not qualify for TDA
- Dispense RBC transfusions if Hb to be <8.5 g/dL

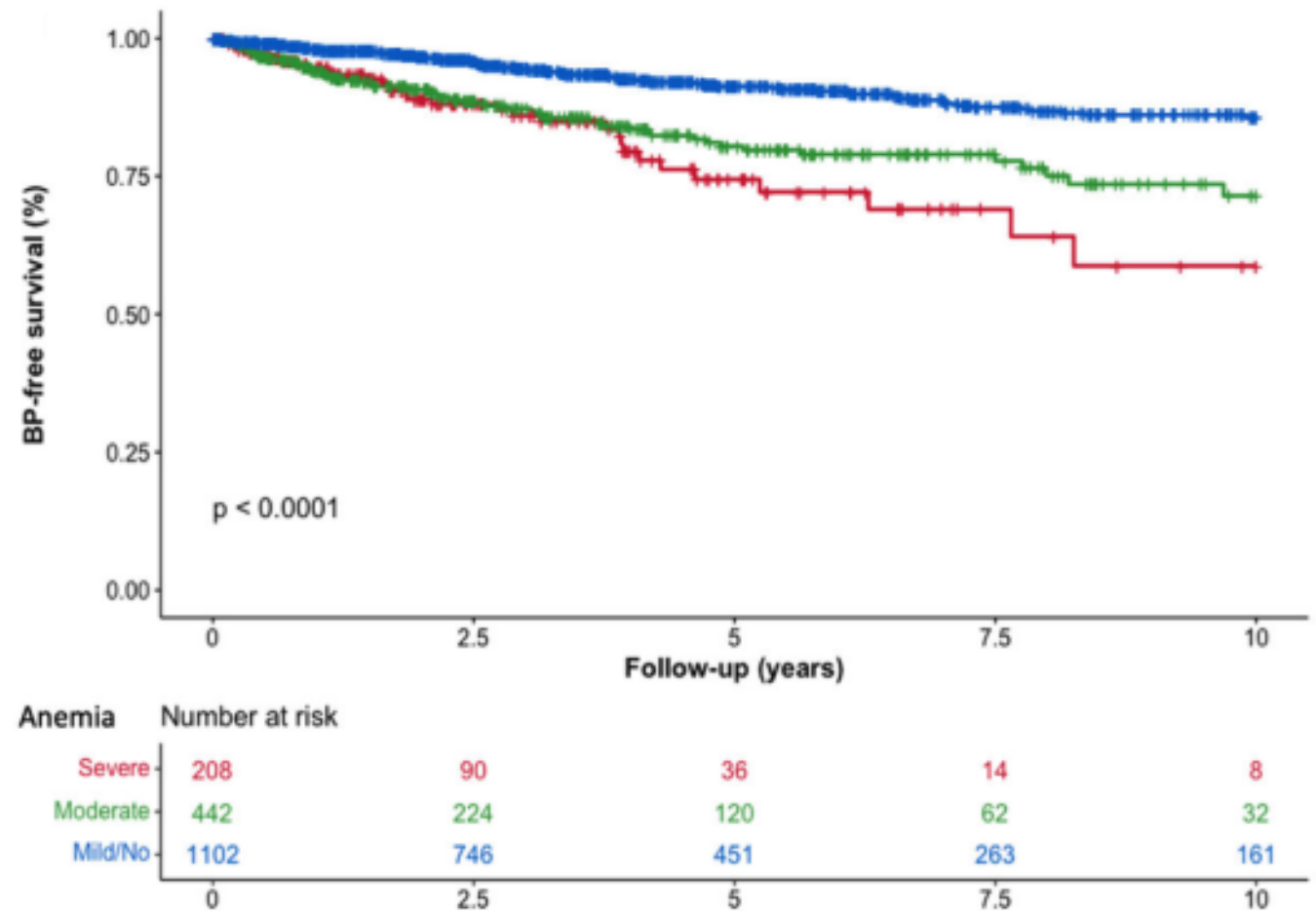
Actuarial survival curves according to baseline (at ruxolitinib start) anemia status



- Non-anemic
- Anemic but not transfusion-dependent (non-TDA)
- Transfusion-dependent (TDA)

A link between anemia and evolution to Blast-Phase MF

Association between blast phase-free survival (BP-FS) and anemia at time of MF diagnosis in 1,752 patients, according to severity¹



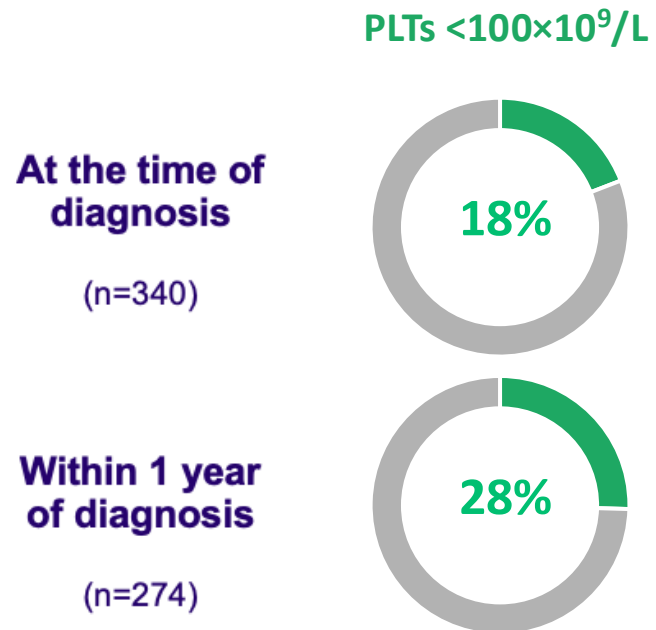
- BP-FS was associated with the presence and severity of anemia at MF diagnosis

Anemia and thrombocytopenia are often paired

Variable	Platelets $<50 \times 10^9/L$ (n=57)	Platelets $\geq 50 \times 10^9/L$ (n=834)	P-value
Age >65 years	75%	60%	0.019
Bleeding manifestations	19%	6%	<0.001
Constitutional symptoms	40%	34%	0.31
Hgb <80 g/L	35%	8%	<0.001
WBC $<4 \times 10^9/L$	26%	10%	<0.001
WBC $>25 \times 10^9/L$	14%	11%	0.47
Blasts $\geq 1\%$	57%	45%	0.069
Blasts $\geq 3\%$	21%	11%	0.022
Grade 3 bone marrow fibrosis	24%	11%	0.008
Unfavorable cytogenetics	17%	11%	0.35
JAK2 mutated	50%	64%	0.057
Int-2/High-risk IPSS	86%	60%	<0.001
Int-2/High-risk DIPSS+	100%	59%	<0.001

Burden of thrombocytopenia in patients with MF

PMF: the Mayo clinic experience



SMF: the MYSEC project

	PLT 50-100 ($\times 10^9/L$), n (%)
SMF (1258)	79 (6.6)
PPV-MF (615)	52 (8.9)
PET-MF (643)	27 (4.4)
p-value	0.002

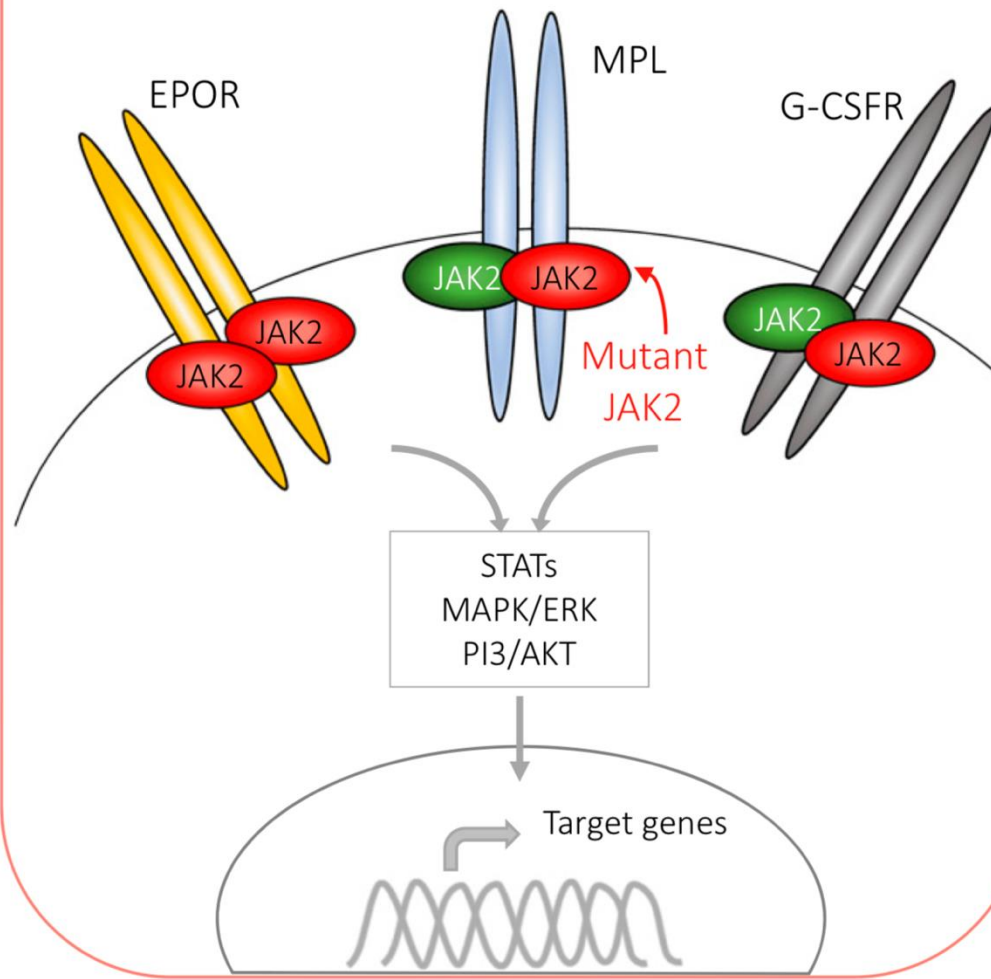
Cytopenias are included in currently used prognostic scores

Variables (weight)	DIPSS	DIPSS ⁺	MIPSS-70	MIPSS-70 ⁺ version 2.0	MYSEC-PM
Clinical features	Age >65 y (1) Constitutional symptoms (1)	Age >65 y (1) Constitutional symptoms (1) RBC transfusions need (1)	Constitutional symptoms (1)	Constitutional symptoms (2)	Age (0.15 × y of age) Constitutional symptoms (1)
Complete blood count	Hb <10 g/dL (2) WBC >25 × 10 ⁹ /L (1) Blasts ≥1% (1)	Hb <10 g/dL (1) WBC >25 × 10 ⁹ /L (1) Blasts ≥1% (1) PLT <100 × 10 ⁹ /L (1)	Hb <10 g/dL (1) WBC >25 × 10 ⁹ /L (2) Blasts ≥2% (1) PLT <100 × 10 ⁹ /L (2)	Severe anemia* (2) Moderate anemia† (1) Blasts ≥2% (1)	Hb <11 g/dL (2) Blasts ≥3% (2) PLT <150 × 10 ⁹ /L (1)

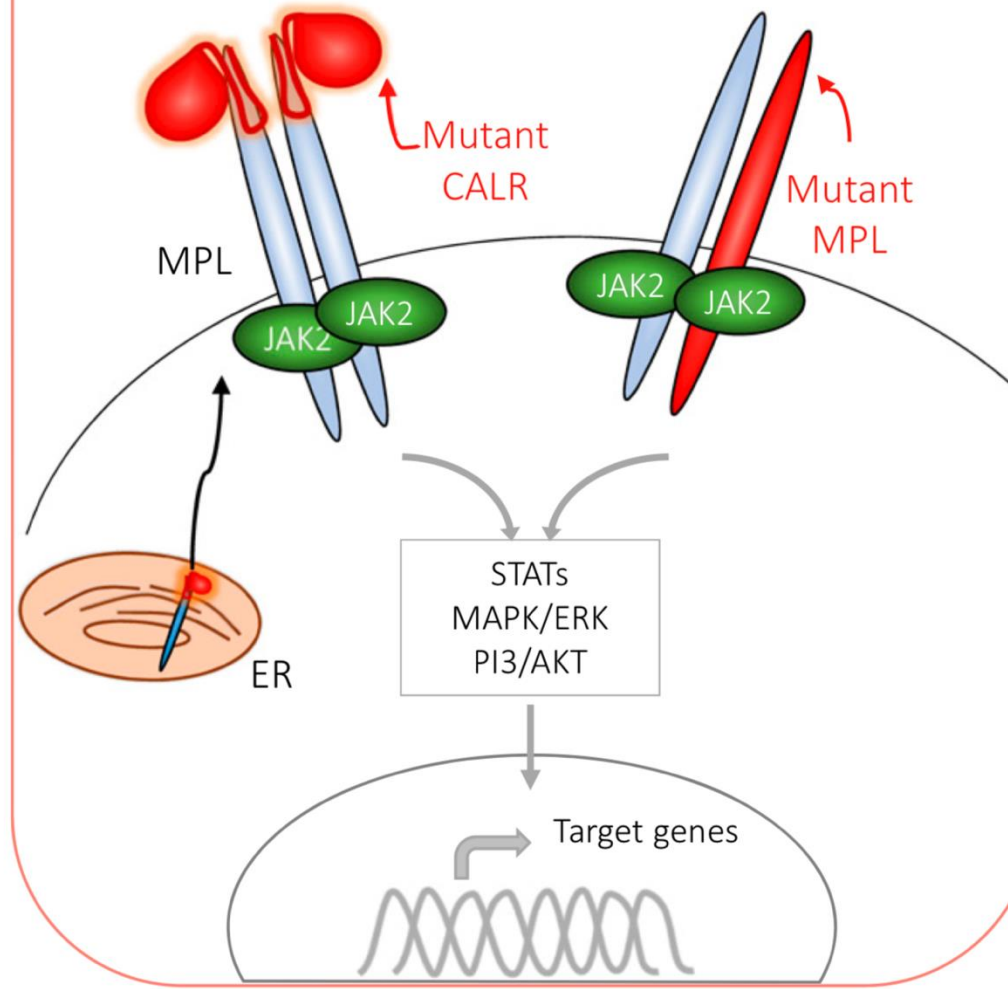
*Hb <8 g/dL in women and Hb <9 g/dL in men.

†Hb 8 to 9.9 g/dL in women and Hb 9 to 10.9 g/dL in men.

JAK2 mutations

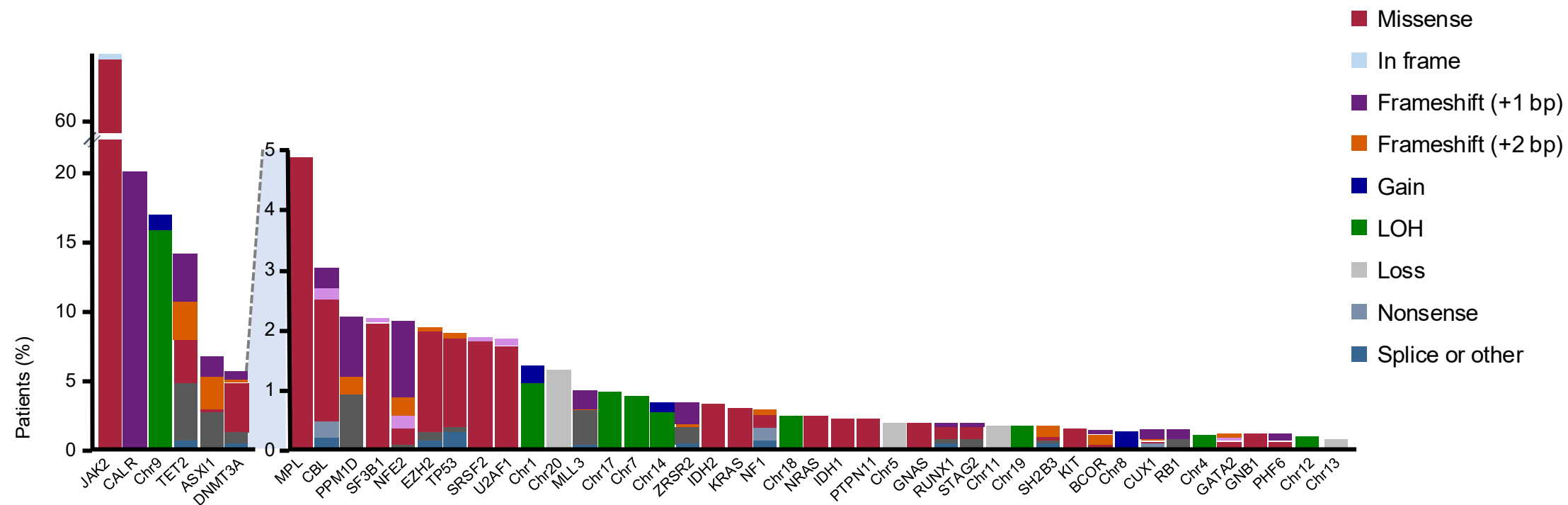


CALR and MPL mutations



The Mutation Profile of Chronic-Phase MPN

Recurrently mutated genes and chromosomal abnormalities



Myelofibrosis Presents Across a Spectrum of Disease

Emerging Characterization of Phenotypic Extremes¹

Proliferative MF

Better/Lower AML risk

More often secondary

Lower risk of cytopenias,
pronounced splenomegaly

Mostly *JAK2*,
low somatic mutations

Often high

Prognosis

Etiology of MF

Clinical Presentation

Mutational Landscape

JAK2^{V617F} Allele Burden

^aSomatic mutations in DNA methylation genes (eg, *TET2* and *DNMT3A*), epigenetic modifiers (eg, *IDH1/2*, *EZH2*, and *ASXL1*) and RNA splicing (eg, *SRSF2* and *U2AF1*).^{2,3}

Cytopenic MF

Poor/Higher AML risk

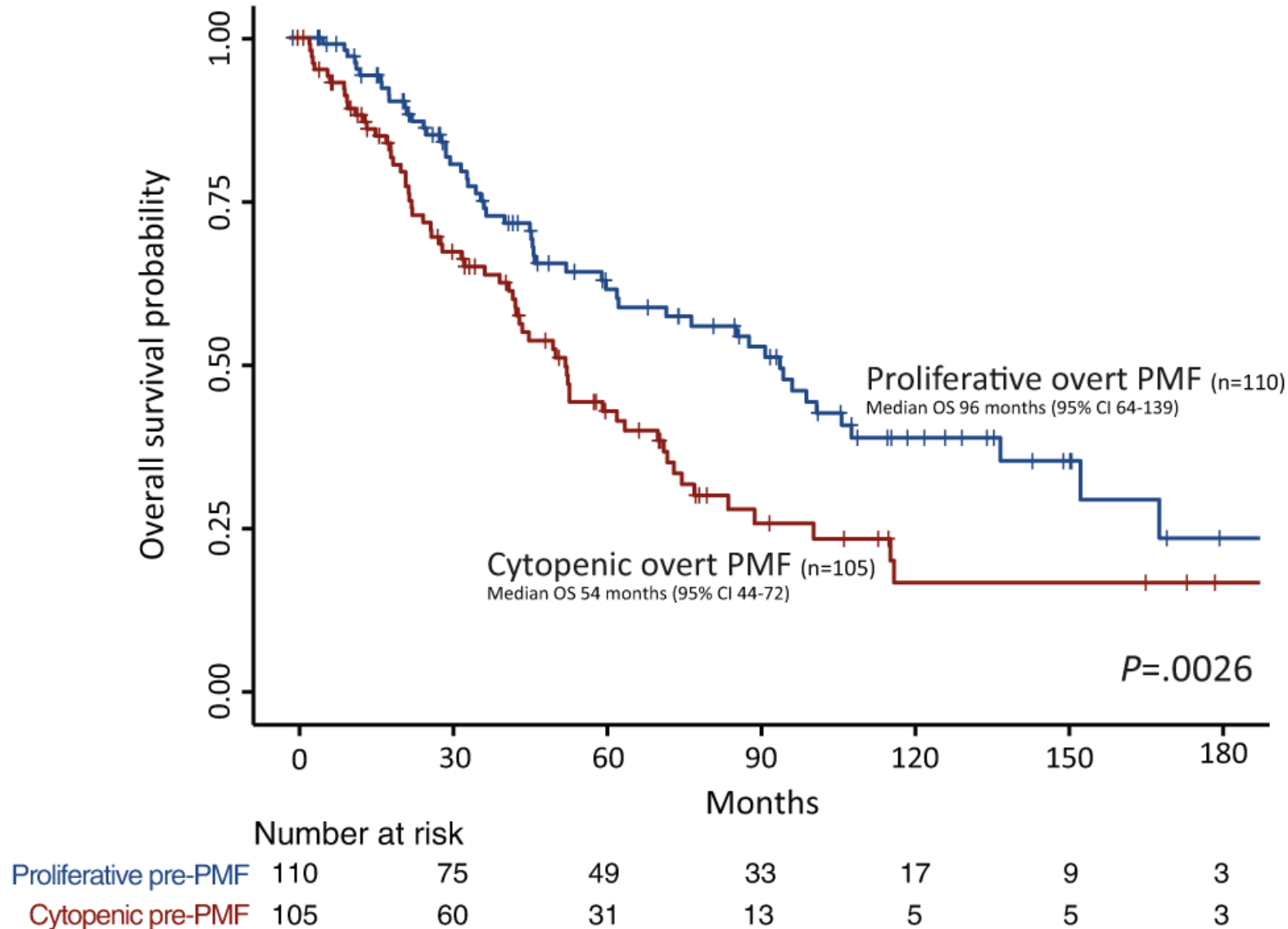
More often primary

Pronounced cytopenias, transfusion requirements, bleeding, infection, less pronounced splenomegaly

Variability in driver mutations
(*JAK2*, *CALR*, *MPL*, or triple-negative)
≥3 somatic mutations^a

Often low

Cytopenic MF is more aggressive vs. proliferative MF



Cytopenic MF is defined as any 1 of the following

- Leukocytes $<4 \times 10^9/L$
- Hemoglobin <11 g/dL and <10 g/dL for men and women, respectively
- Platelets $<100 \times 10^9/L$

Overt PMF with ≥ 2 cytopenias have a median OS of 43 months

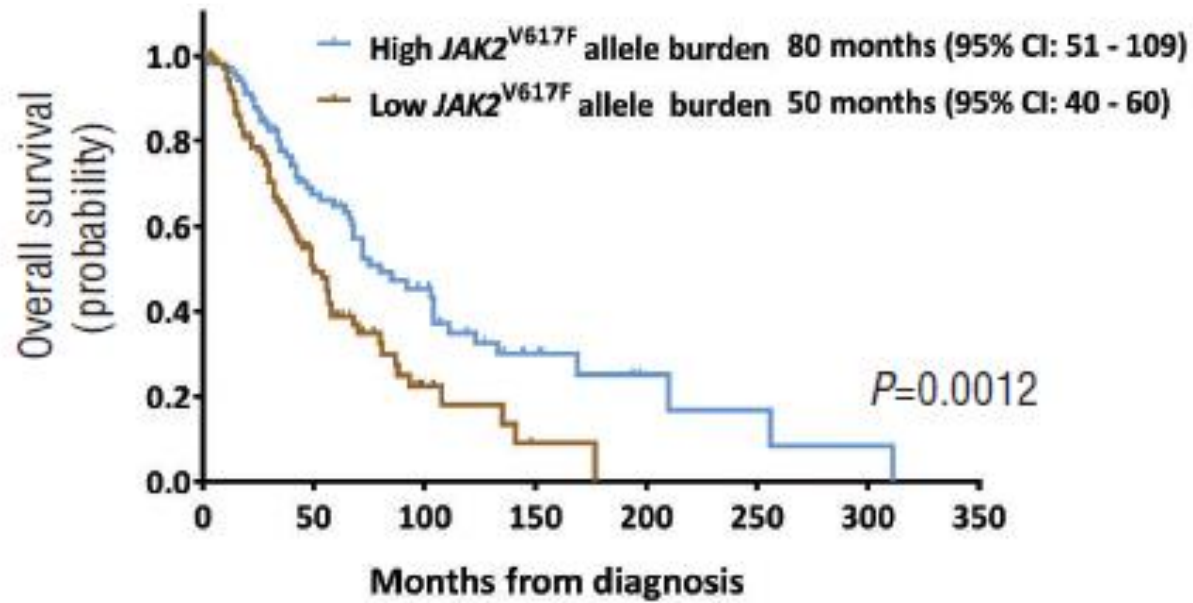
Prognostic impact of driver and high molecular risk nondriver mutations in primary mf

- Analysis of association between driver mutations and survival in patients with primary MF (N = 617)^[a]

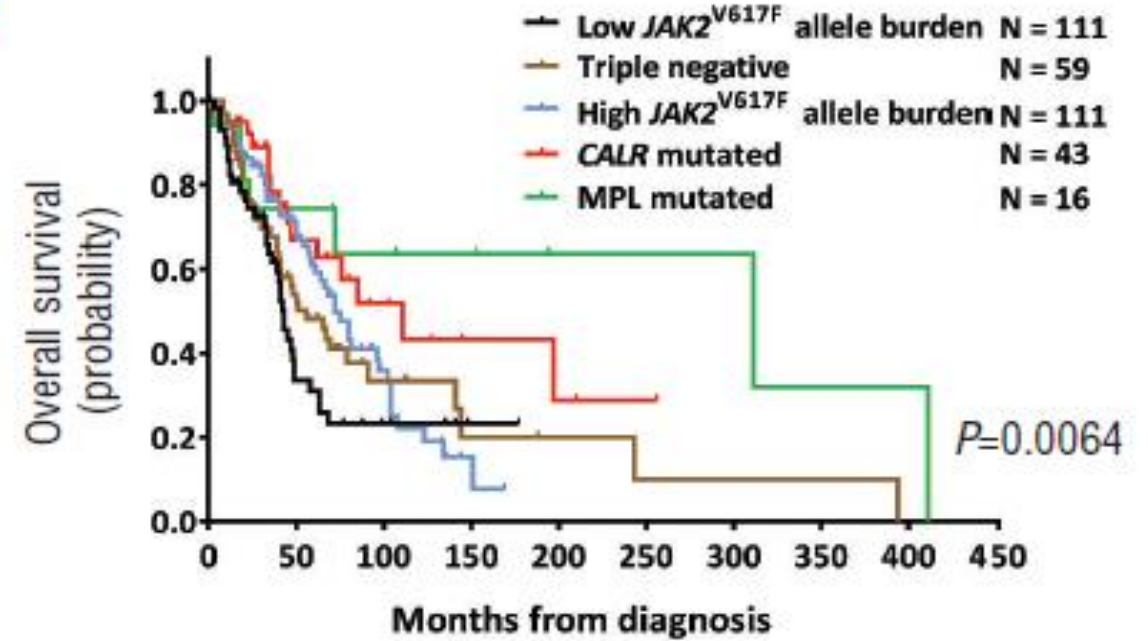
Driver Mutation	Patients, %	Median OS, y
<i>CALR</i> mutated	22.7	17.7
<i>JAK2</i> mutated	64.7	9.2
<i>MPL</i> mutated	4.0	9.1
Triple negative	8.6	3.2

- Analysis of association between set of nondriver mutations (*IDH*, *EZH2*, *ASXL1*, *SRSF2*) and survival in patients with primary MF (N = 797)^[b]
 - Presence of mutations predicted decreased survival; ≥ 2 mutations predicted worst survival

JAK2 VAFs <50% were associated with shorter survival

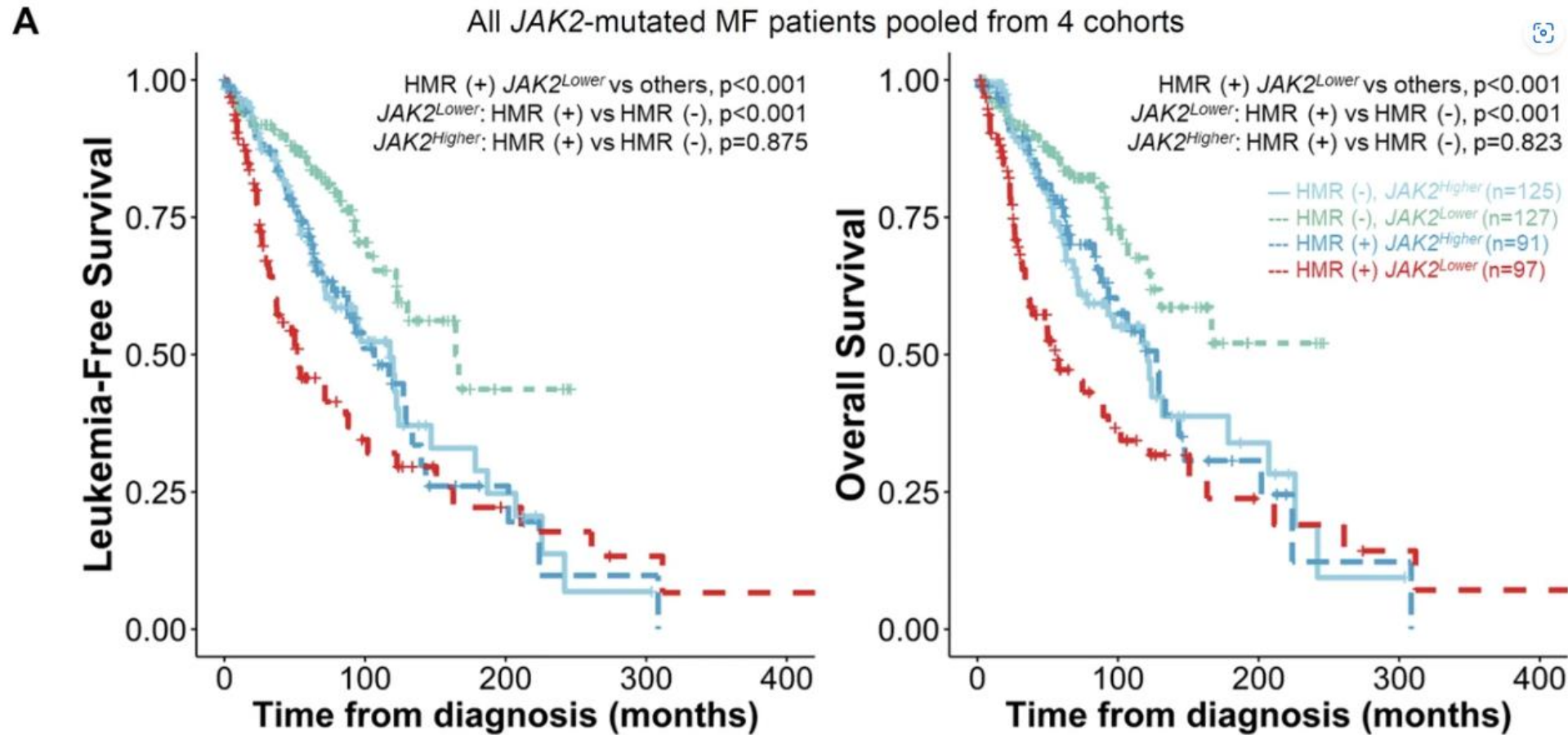


- JAK2 V617F ≥50%, mOS = 80 months (51-109)
- JAK2 V617F <50%, mOS = 50 months (40-60)

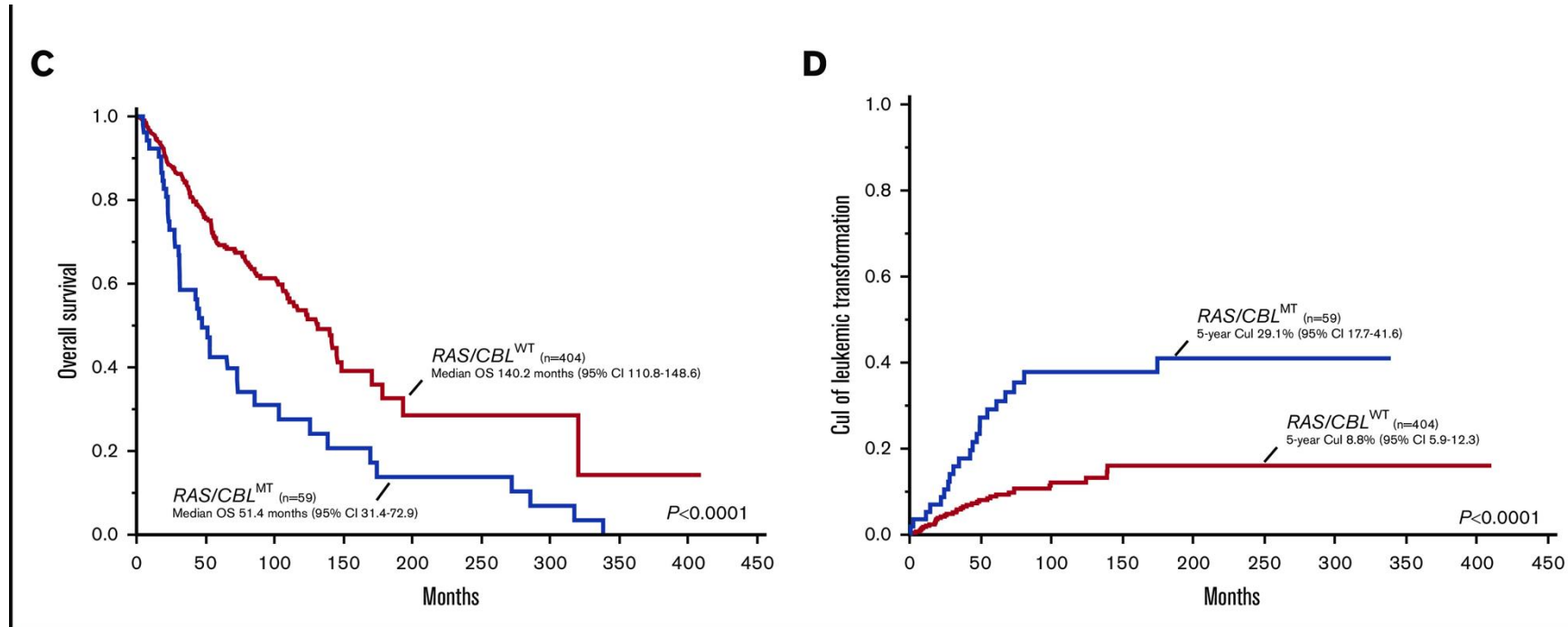


- JAK2 V617F ≥50%, mOS = 80 months (51-109)
- Triple negative, mOS = 56 months (35-77)
- JAK2 V617F <50%, mOS = 50 months (40-60)

HMR are detrimental only in the *JAK2V617F* low VAF



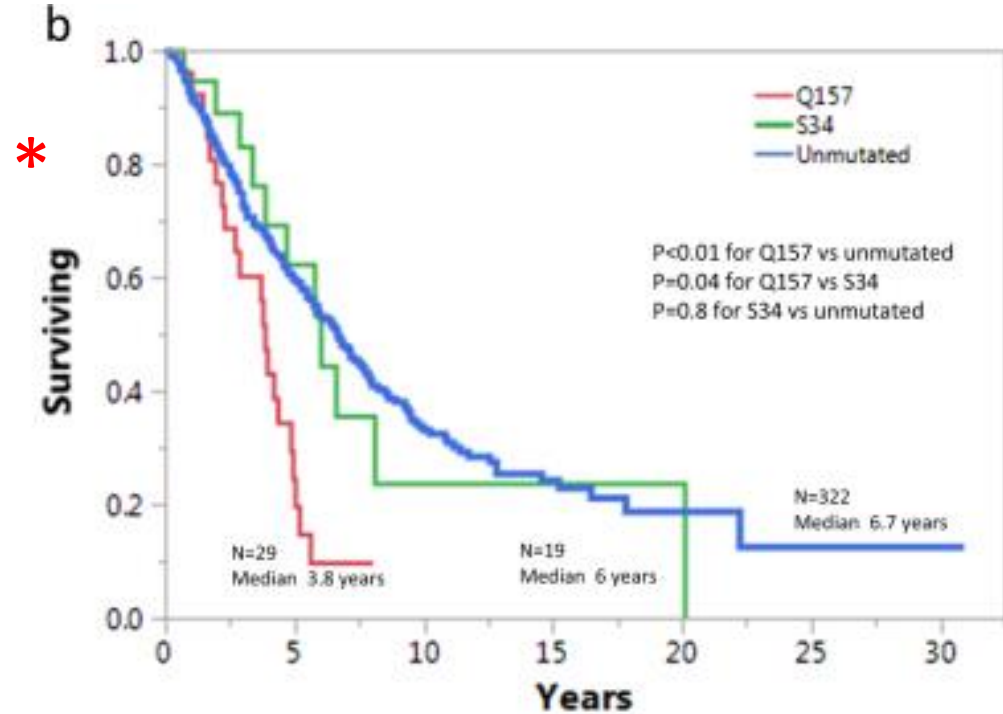
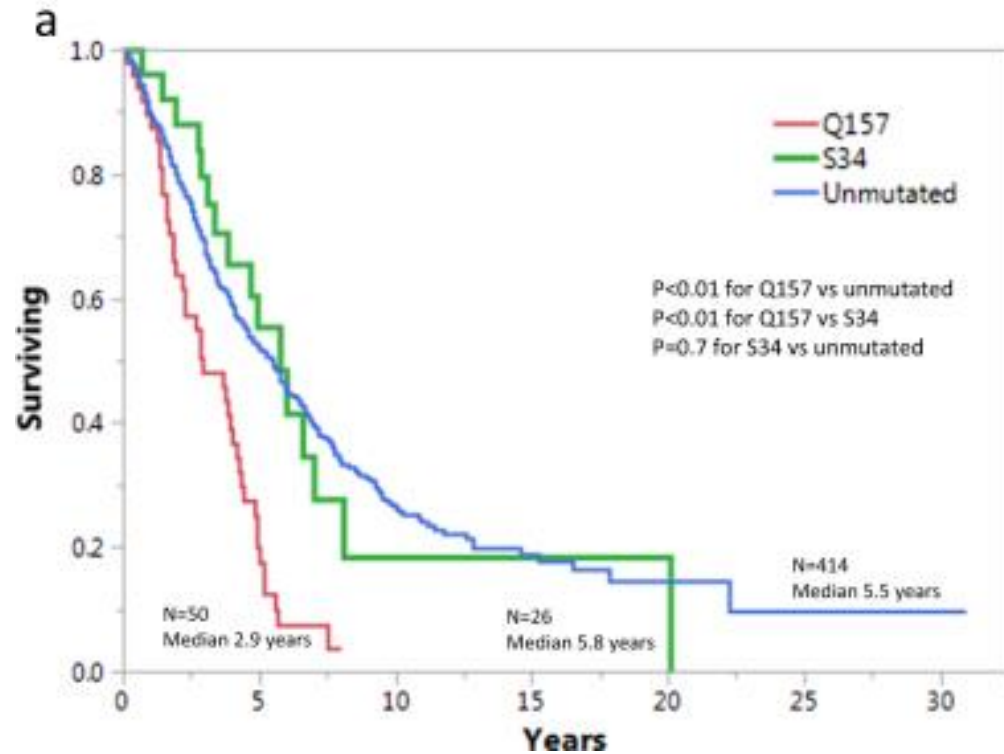
RAS/CBL+ adversely associated with cytopenic profile



U2AF1 associates with cytopenias and clusters with JAK2

Variables	All patients (n=250)	U2AF1 mutated (n=40)	U2AF1 wild-type (n=210)	P value
Constitutional symptoms; n (%)	86 (34.4)	18 (45)	68 (32.4)	0.12
Circulating blasts $\geq 1\%$; n (%)	143 (57.2)	14 (35)	115 (54.8)	0.07
Hemoglobin < 10 g/dl; n (%)	118 (47.2)	34 (85)	84 (40)	<0.0001
Transfusion requiring; n (%)	79 (31.6)	28 (70)	51 (24.3)	<0.0001
Leukocytes $> 25 \times 10^9/l$; n (%)	40 (16)	8 (20)	32 (15.2)	0.45
Leukocytes $< 4 \times 10^9/l$; n (%)	34 (13.6)	5 (12.5)	29 (13.8)	0.82
Platelets $< 100 \times 10^9/l$; n (%)	53 (21.2)	22 (55)	35 (16.7)	<0.0001
JAK2V617F-positive; n (%) 'N' evaluable=249	145 (58.2)	32 (80)	113(54.1)	0.002

U2AF1Q157, worse marker associated to cytopenic MF



The MYSEC-molecular prognostic model (MYSEC-mPM) and the karyotype- and mutation-enhanced MYSEC-kmPM to improve risk stratification in Secondary Myelofibrosis (SMF)

Context of Research

In SMF, OS is currently defined by the MYSEC-PM; the role of additional gene mutations and karyotype is unknown.

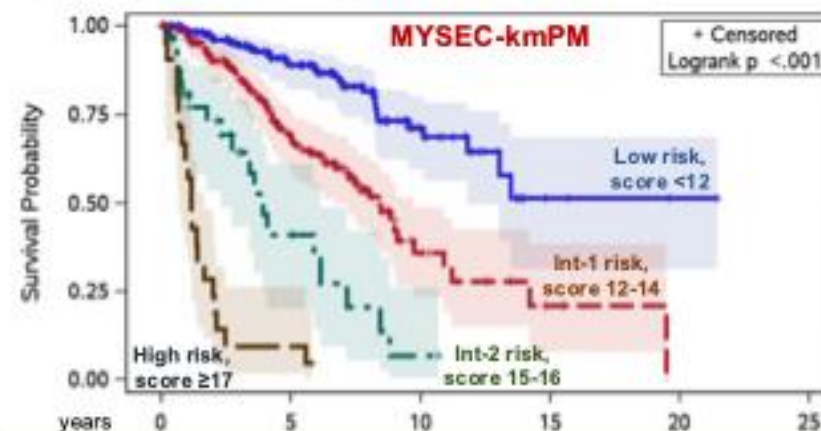
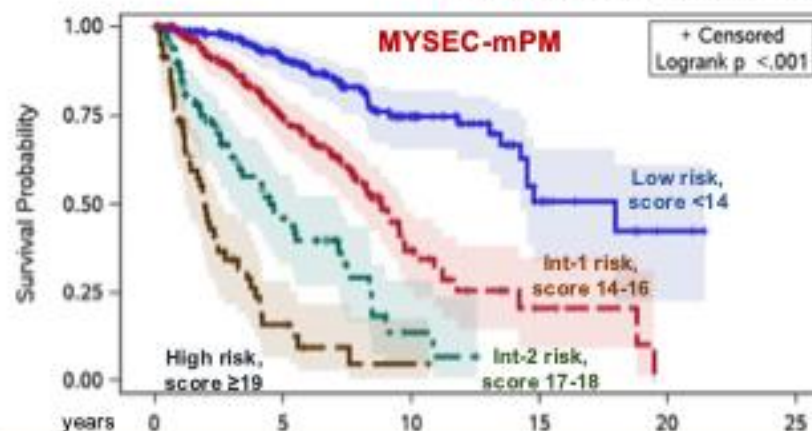
Aim of This Study

To develop molecular- and karyotype-enhanced prognostic models to predict OS in SMF within the MYSEC cohort.

Findings

- *U2AF1*, *TP53* or *SRSF2* (*UTS*) and *ASXL1* variants without *UTS* conferred worse OS, as well as complex/monosomal karyotype
- We integrated these genetic signatures with the MYSEC-PM to develop the **MYSEC-mPM (MYSEC-molecular PM)** and the **MYSEC-kmPM (karyotype- and mutation-enhanced MYSEC-PM)**

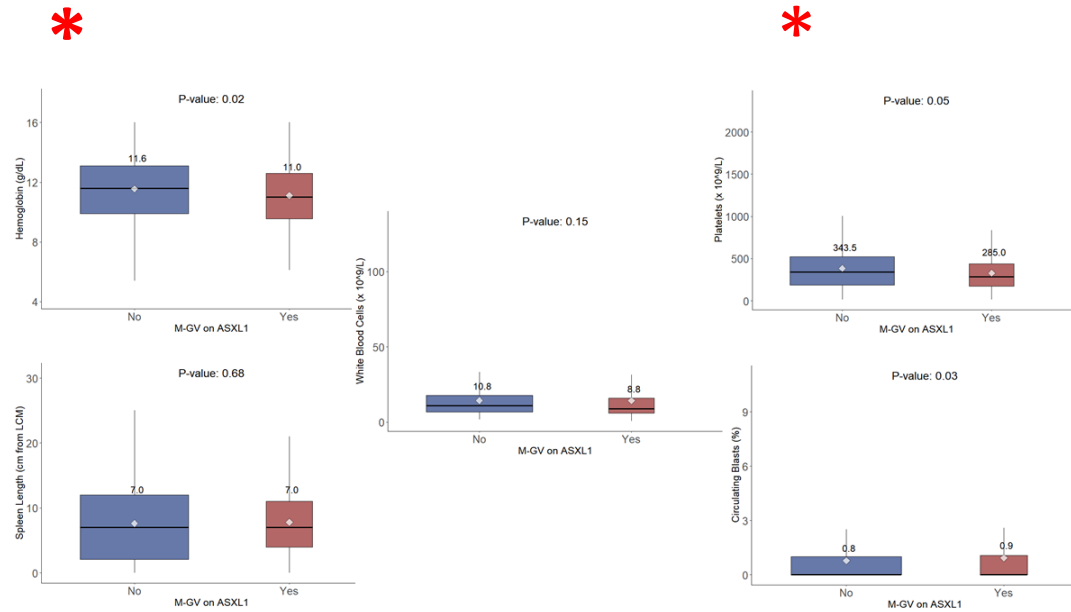
	MYSEC-mPM	MYSEC-kmPM
Variable	Points	Points
Age at SMF diagnosis	0.21 per year	0.17 per year
Hemoglobin <11 g/dl	1	1
Platelet <150 × 10 ⁹ /l	2	2
Circulating blast cells ≥3%	2	1
High molecular risk (<i>ASXL1</i> mut, no <i>UTS</i>)	1	1
Very high molecular risk (any <i>UTS</i> mut)	3	2
Complex/monosomal karyotype	-	2



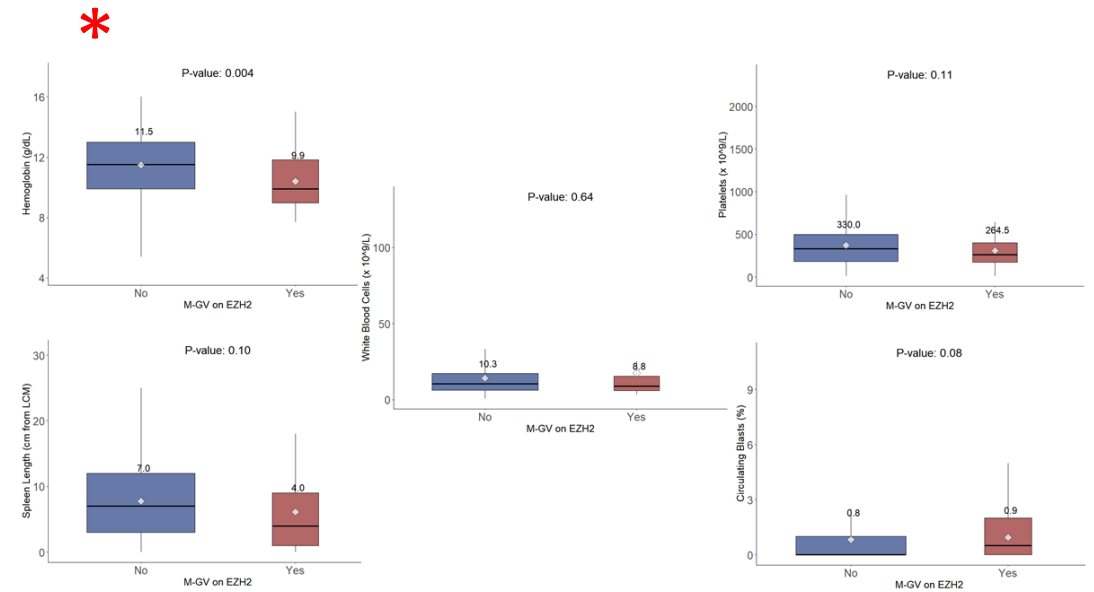
Conclusions: *ASXL1* mutations, *UTS* (*U2AF1*, *TP53*, *SRSF2*) variants and complex/monosomal karyotype worsen survival in SMF regardless of the MYSEC-PM. The new four-tiered MYSEC-mPM and MYSEC-kmPM scores, by integrating clinical and genetic profiles, outperform the MYSEC-PM.

Association between cytopenia and CGV in SMF

ASXL1 mutation

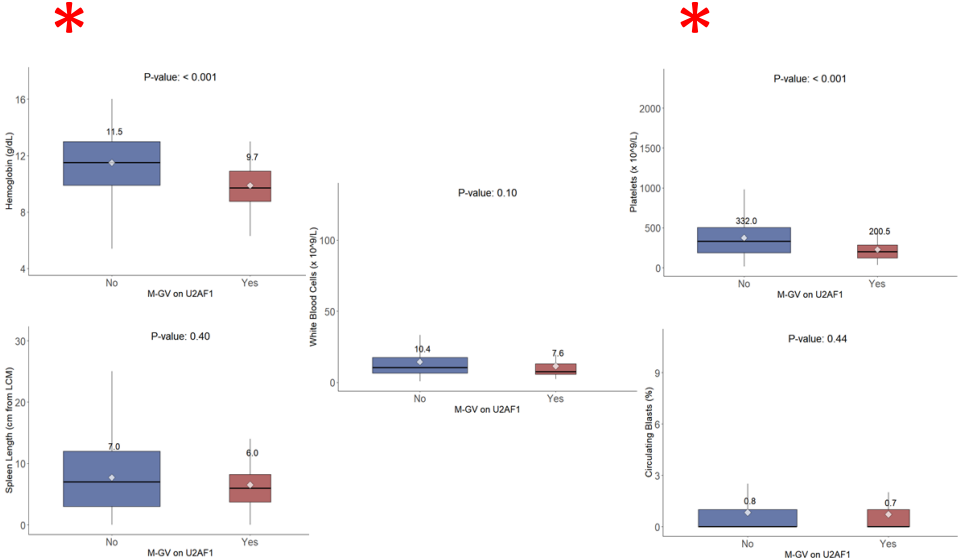


EZH2 mutation

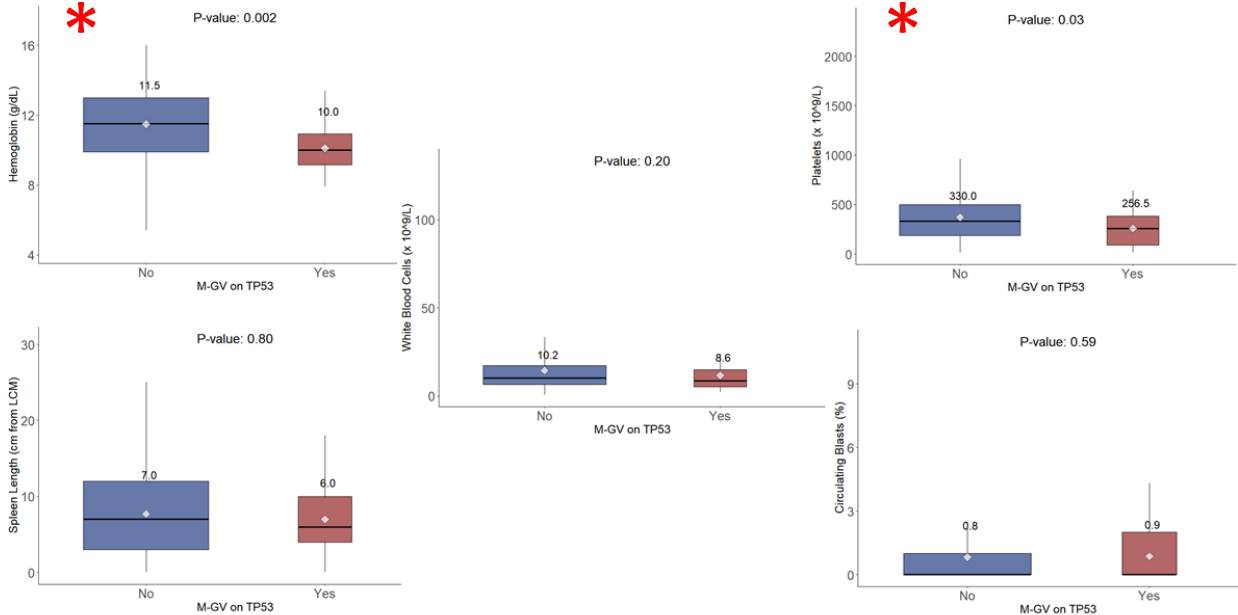


Association between cytopenia and CGV in SMF

U2AF1 mutation



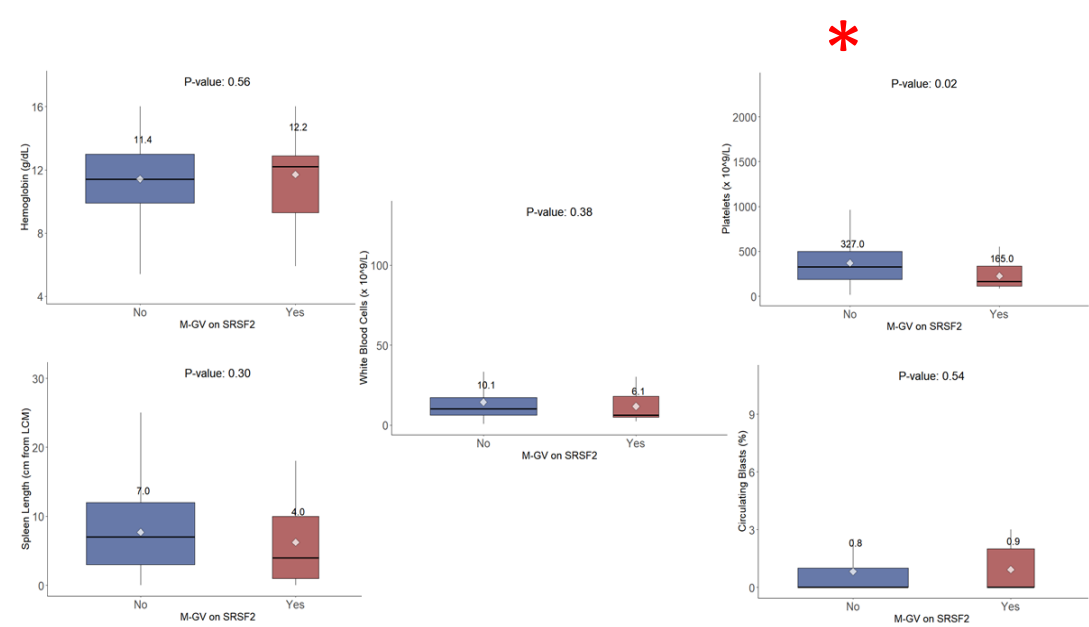
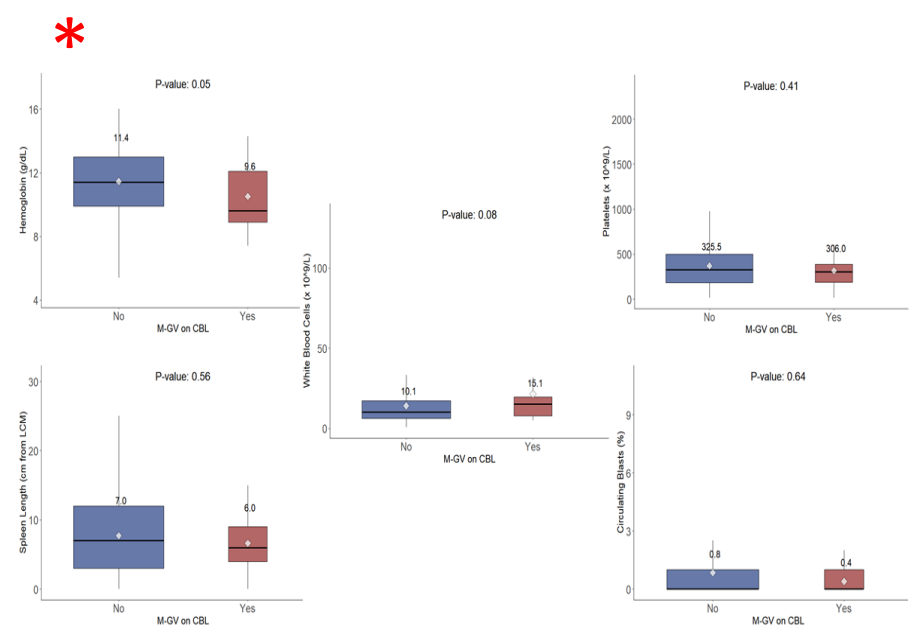
Tp53 mutation



Association between cytopenia and CGV in SMF

CBL mutation

SRSF2 mutation



Current treatments to address MF-related anemia

		Examples
RBC transfusion	Supplementation of mature RBCs via transfusion to raise Hb levels	
ESAs	Activate pro-erythroid signaling to stimulate erythropoiesis	EPO
Androgens	Enhance erythropoiesis and alleviate MF-related anemia	Danazol
Splenectomy	Removal of spleen to address splenomegaly and RBC destruction	
IMiD agents	Immunomodulators with pleiotropic effects, including promoting erythropoiesis	Thalidomide, lenalidomide, pomalidomide
JAK inhibitors	Prevent overactive JAK/STAT signaling due to mutation; can exacerbate MF-related anemia	Ruxolitinib, fedratinib, pacritinib, momelotinib
TGF-β i	Ligand trap for TGF- β super family members	Luspatecept, elritercept