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Biology of High risk Myeloproliferative Neoplasms

Naseema Gangat MD

Assistant Professor of Medicine
Mayo Clinic College of Medicine
Rochester, MN

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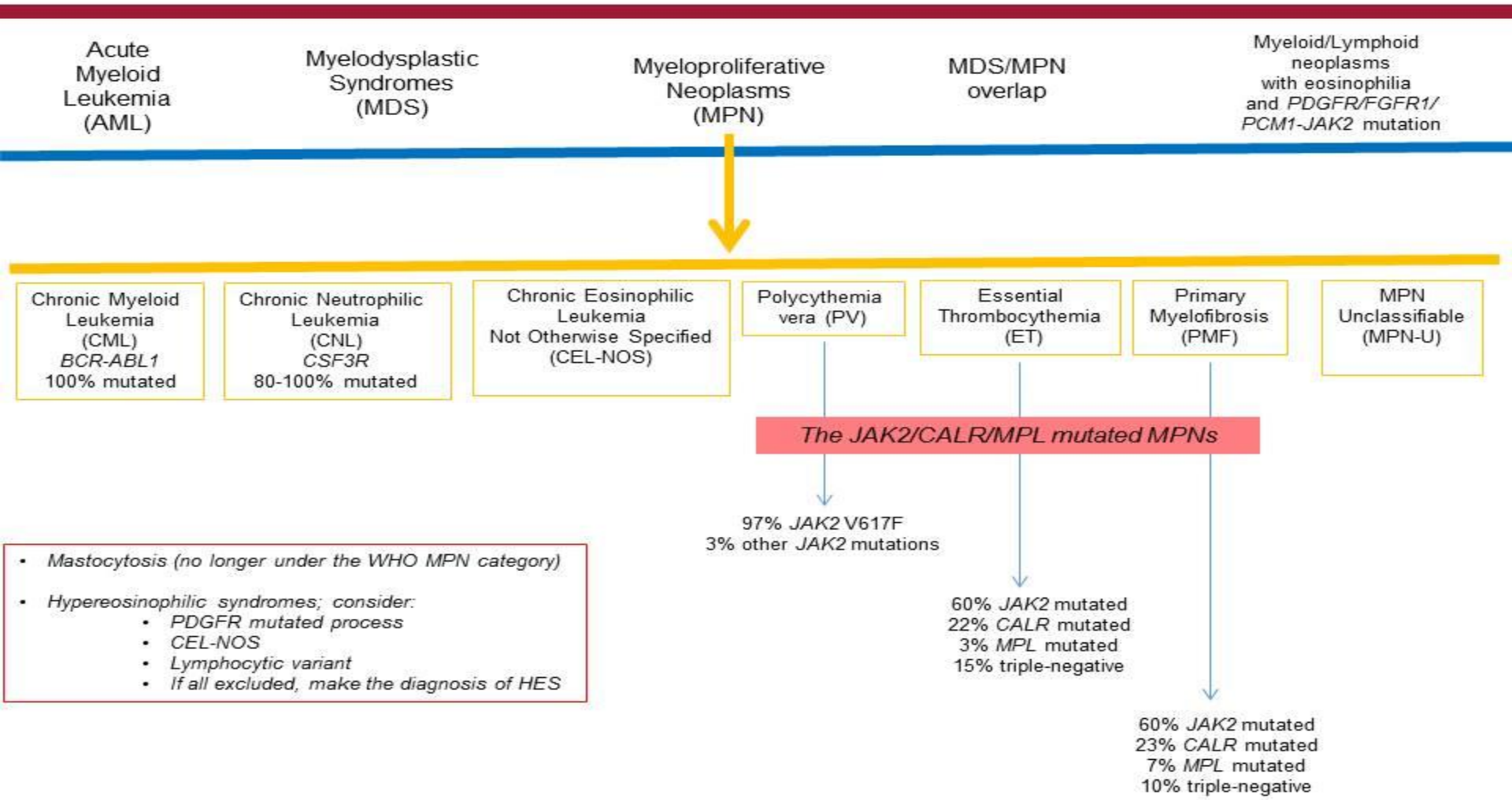
Disclosures

Principal investigator role	Janssen, Gilead Sciences, Takeda, Celgene
Employee	None
Consultant	None
Major Stockholder	None
Speakers' Bureau	None
Scientific Advisory Board	None

Objectives

- WHO 2016 classification of MPN
- Impact of mutations in MPN
- Genetic prognostication in MPN

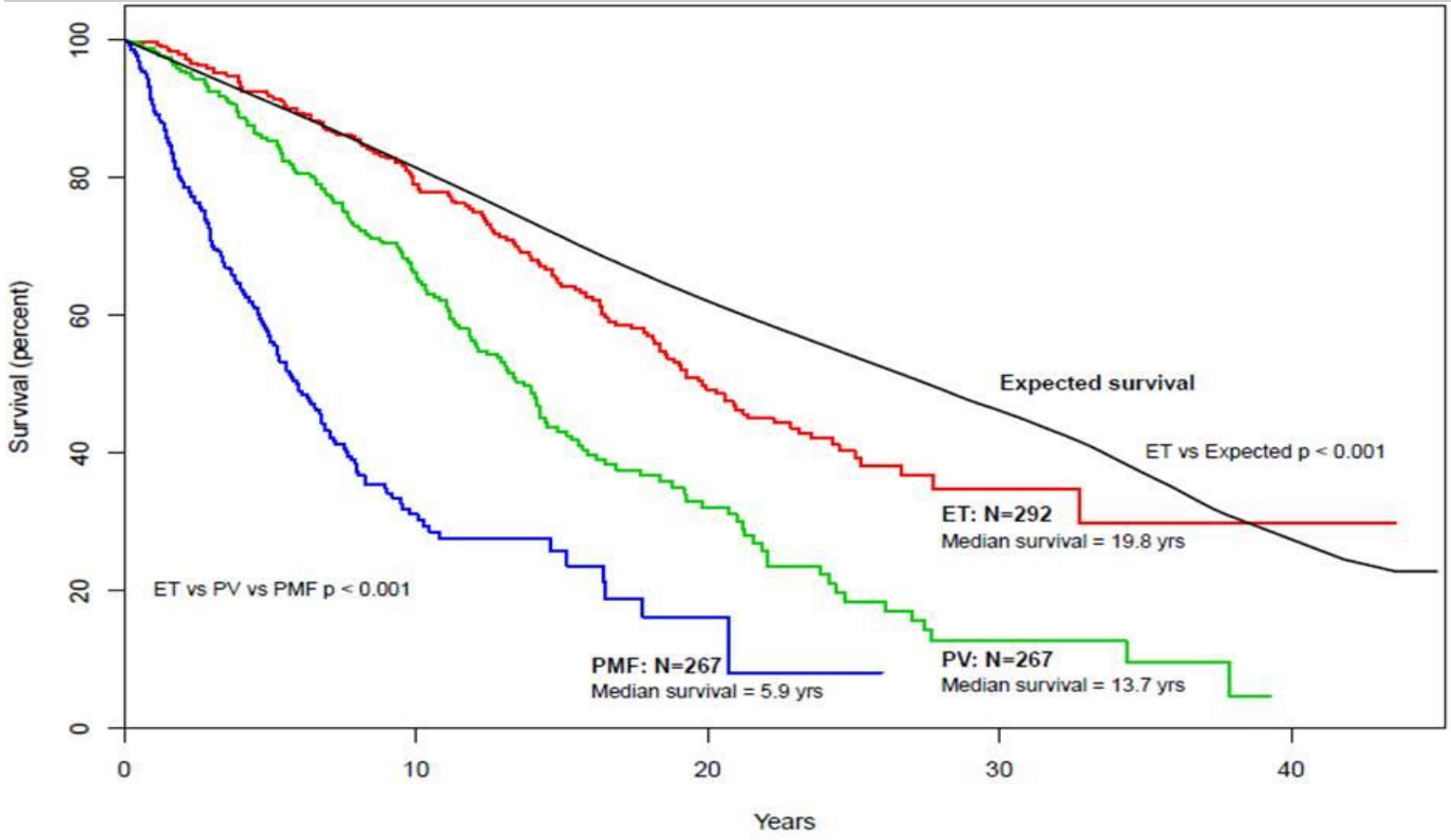
WHO Classification of MPN



Blood 2016

Survival in MPN

Comparison of survival in 826 Mayo Clinic patients with essential thrombocythemia vs polycythemia vera vs primary myelofibrosis.



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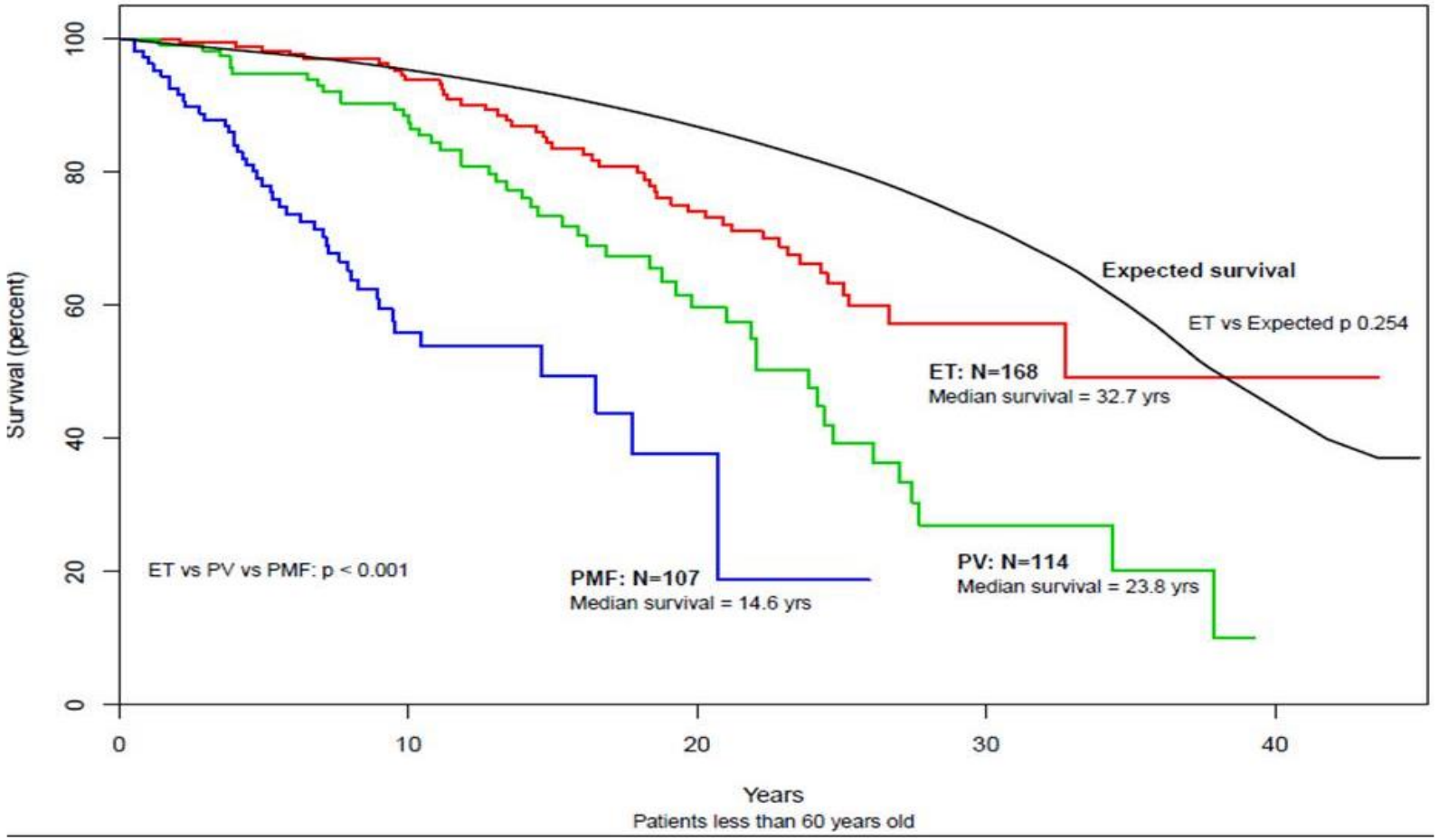
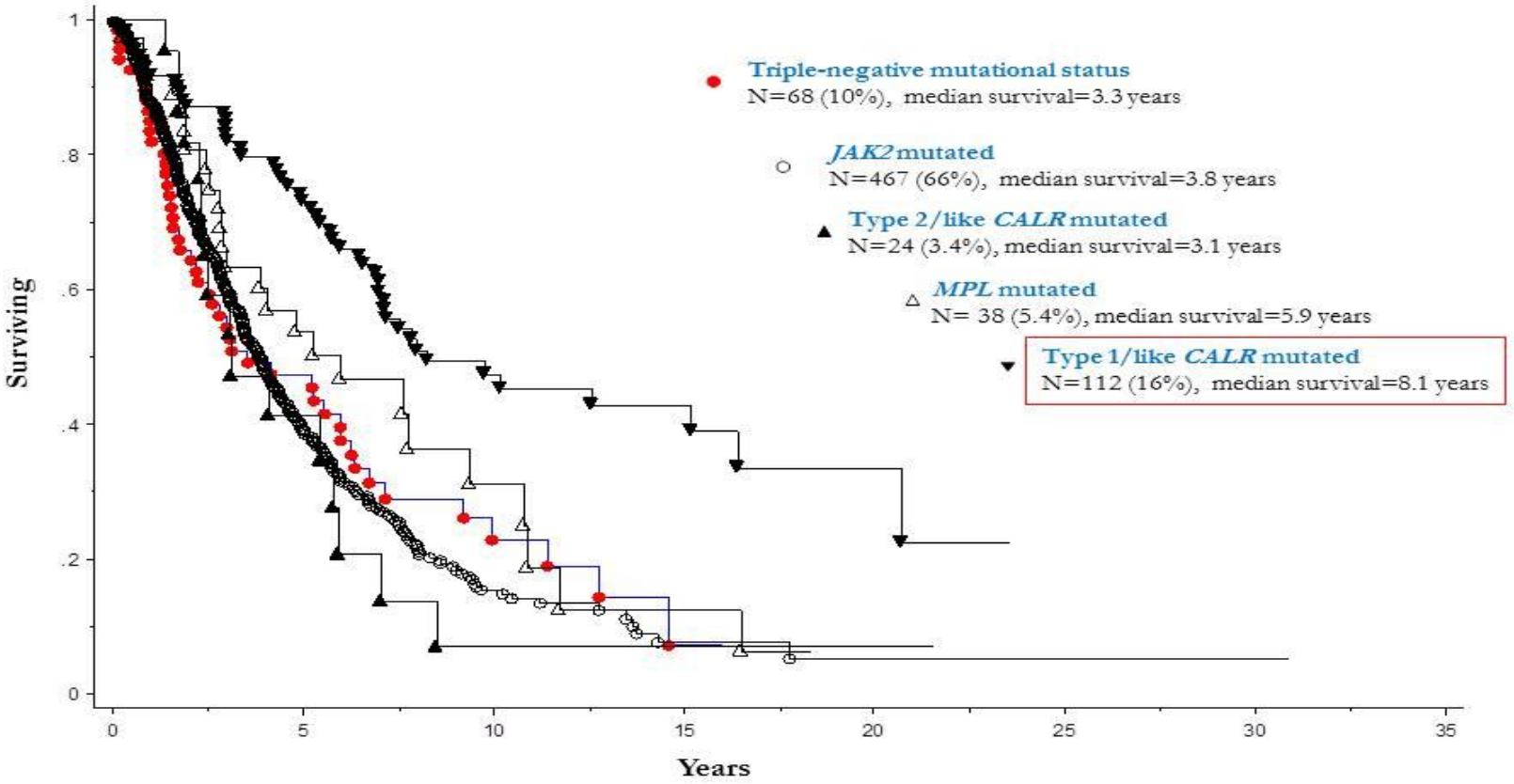
Blood 2014

Survival in young patients with MPN



Blood 2014

Survival of 709 primary myelofibrosis patients stratified by driver mutational status

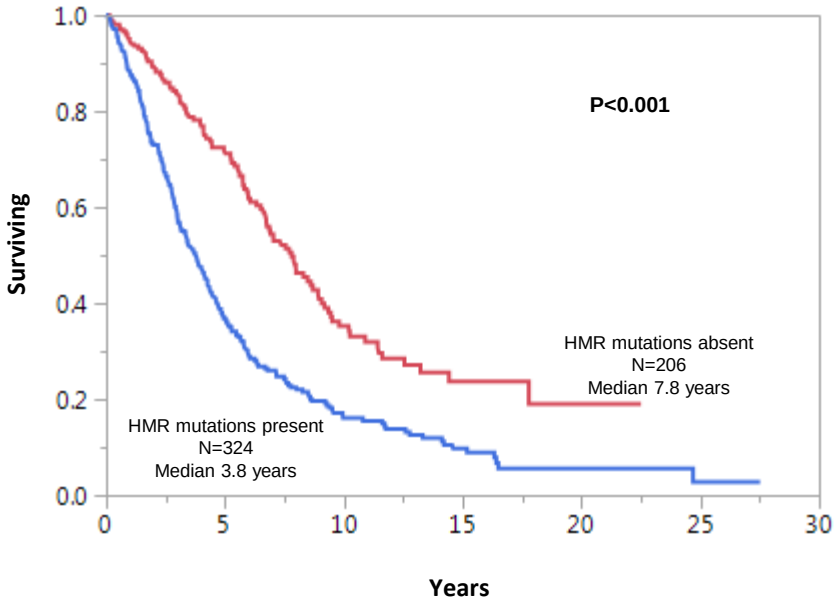


Am J Hematol 2018

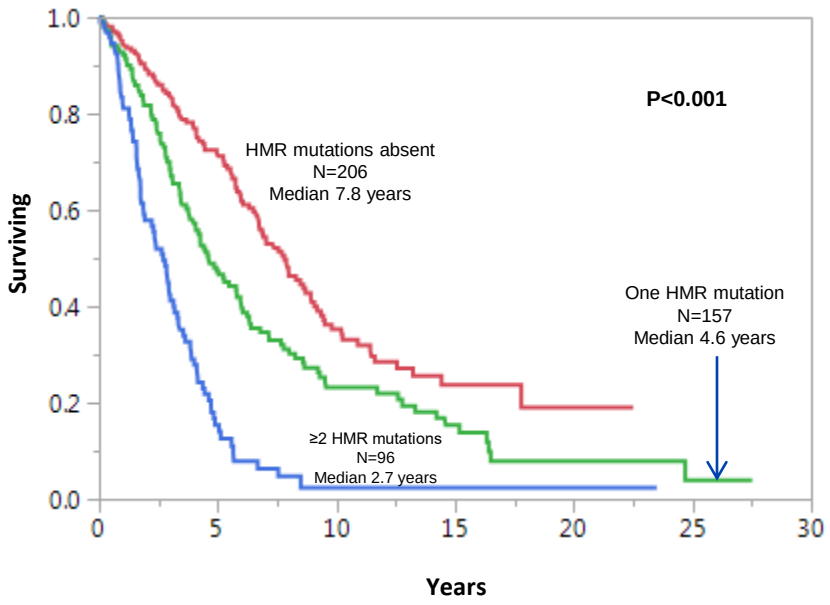
Survival of 530 patients with primary myelofibrosis stratified by the presence or absence of high molecular risk (HMR) mutations

ASXL1, SRSF2, U2AF1Q157, EZH2, IDH1 and IDH2

N=530



N=459



JCO 2018

Contemporary prognostic models in PMF

Prognostic score	Variables	Assessment
IPSS (Blood 2009)	Age Anemia Leukocytosis Circulating blast % Constitutional symptoms	At diagnosis
DIPSS (Blood 2010)	Same as above	Anytime
DIPSS plus (JCO 2011)	Same as above + Red cell transfusion need Thrombocytopenia Unfavorable karyotype	Anytime
MIPSS70/MIPSS70 plus (Mutation/karyotype enhanced) **MIPSS70 plus version 2.0** **(JCO 2017, JCO 2018)**	Clinical + histologic+ genetic variables	Anytime
GIPSS (Genetically inspired) (Leukemia 2018)	Cyto-molecular genetics	Anytime

Revised Three-tiered Cytogenetic stratification in PMF

Unfavorable karyotype	
DIPSS plus	complex karyotype, single or two abnormalities Including 8,7/7q-, i(17q),5/5q-, 12p-, inv(3) or 11q23rearrangement
MIPSS70 plus	any abnormal karyotype **except** normal karyotype sole abnormalities 20q-, 13q-, +9, chr. 1 translocation/ duplication, -Y, sex chromosome abnormality other than -Y

Three tiered cytogenetic risk groups	
Very high risk (VHR)	• single/multiple abnormalities of -7, inv(3)/3q21, i(17q), 12p-/12p11.2 or 11q-/11q23 • Single/multiple autosomal trisomies other than +9 and +8
Unfavorable	• sole abnormalities of +8 or 7q- • sole translocations not involving chromosome 1 • sole abnormalities not otherwise classified • monosomal karyotype without VHR abnormality • complex non-monosomal without VHR abnormality • Single/multiple 5q- abnormalities • Two abnormalities without VHR abnormality
Favorable	• Normal karyotype • sole abnormalities of 20q-,13q-, +9 • sole sex chromosome abnormalities including -Y • sole chromosome 1 translocations/duplications

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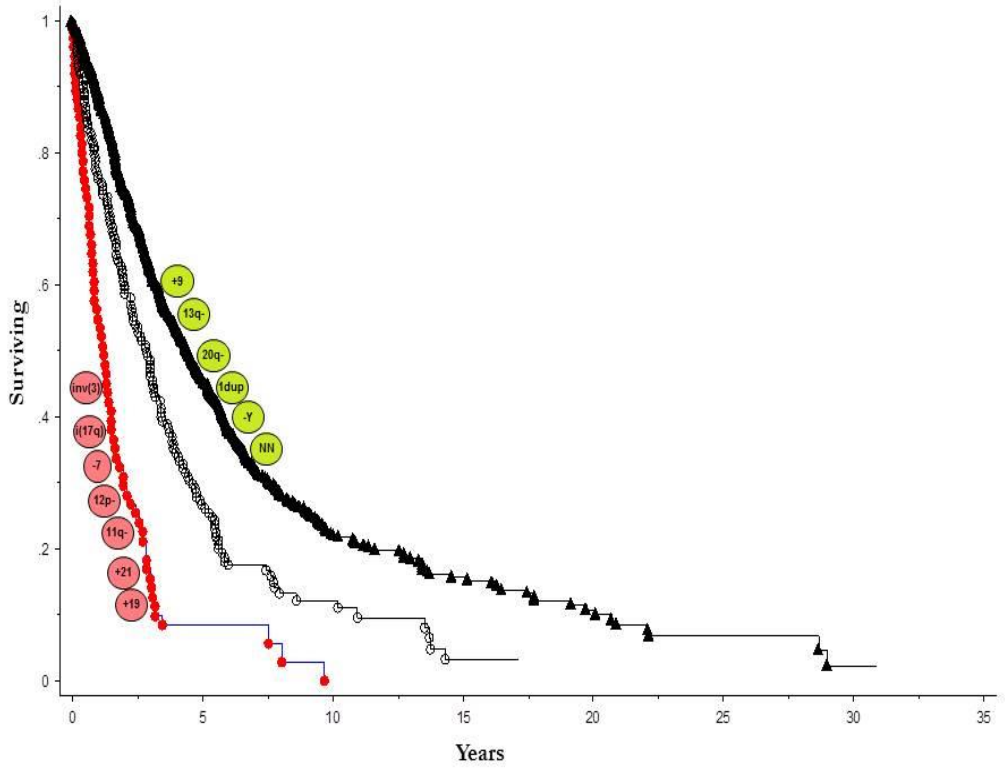
Leukemia 2018

Survival of 1,002 patients with primary myelofibrosis stratified by the revised three-tiered cytogenetic risk model



Very high risk category (VHR); N=75; median survival 1.2 years

Unfavorable risk category; N=190; median survival 2.9 years

Favorable risk category; N=737; median survival 4.4 years

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Leukemia 2018

MIPSS70 plus Version *2.0*

Clinical variables

- Sex and severity adjusted anemia

severe anemia
< 8g/dl (F)
< 9 g/dl (M)
moderate anemia
8-9.9 g/dl (F)
9-10.9 g/dl (M)

- Blasts ≥ 2%

- Constitutional symptoms

Genetic variables

- *U2AF1* Q157, *ASXL1, SRSF2, EZH2, IDH1/2,* absence of type 1 *CALR*

- ≥ 2 HMR

- 3 tiered cytogenetics (VHR, unfavorable)

Very high risk karyotype 4 points
Unfavorable karyotype 3 points
≥2 HMR mutations 3 points

One HMR mutation 2 points
Type 1/like CALR mutation absent 2 points
Constitutional symptoms 2 points
Severe anemia 2 points

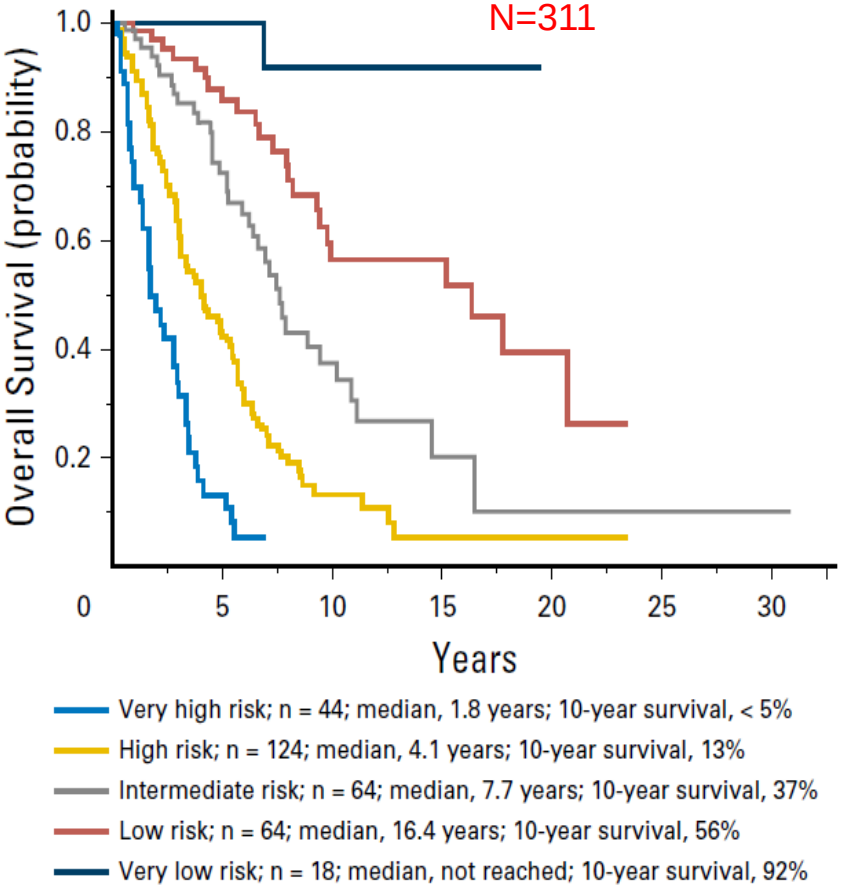
Moderate anemia 1 point
≥2% circulating blasts 1 point

http://www.mipss70score.it/

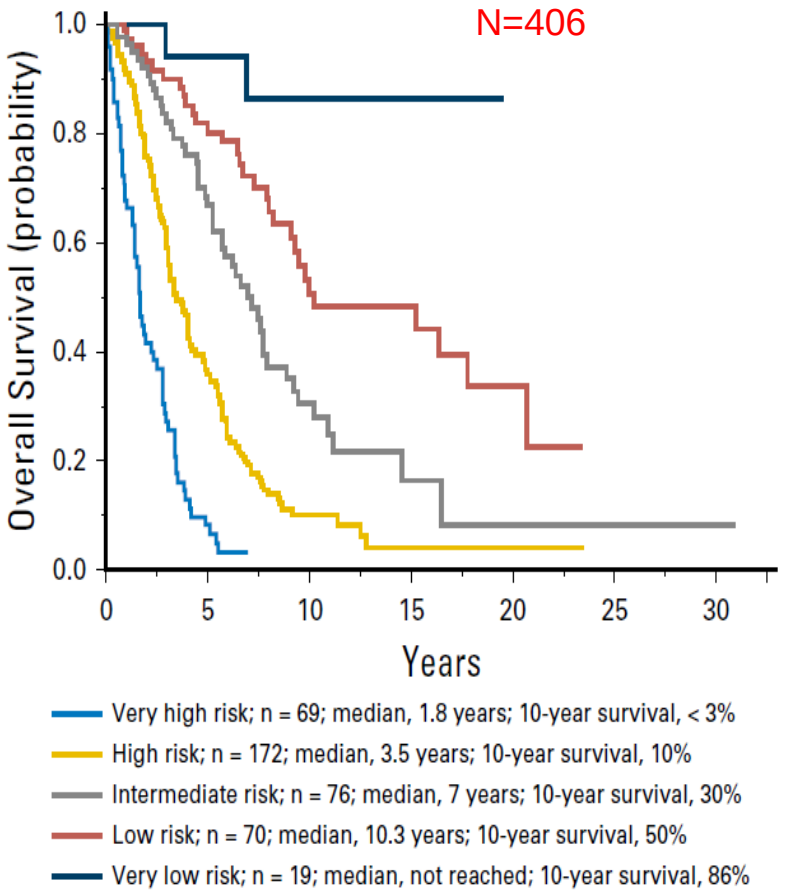
MIPSS70 plus Version *2.0*

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**

Patients < 70 years
N=311

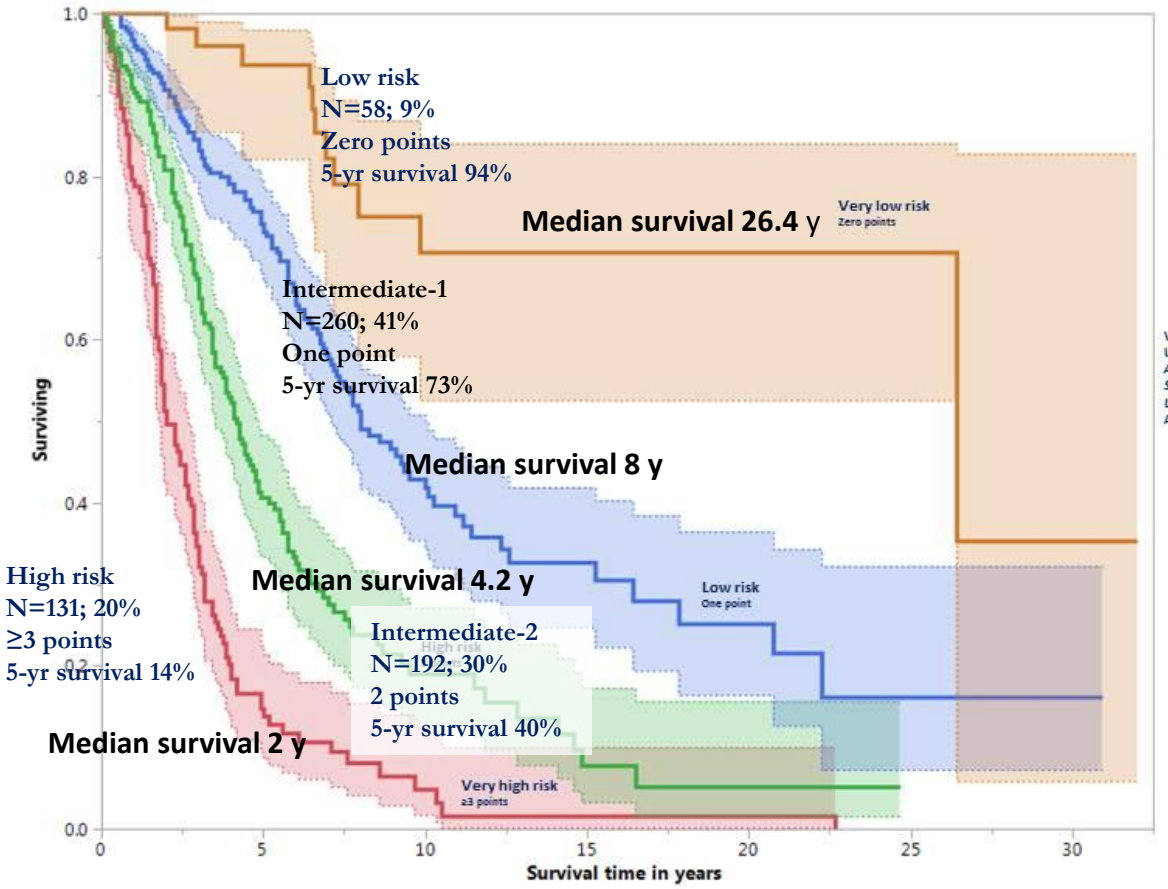


All patients
N=406



JCO 2018

Genetically inspired prognostic score (GIPSS)



Very high risk karyotype = 2 points
Unfavorable karyotype = 1 point
ASXL1 mutation = 1 point
SRSF2 mutation = 1 point
U2AF1 Q157 mutation = 1 point
Absence of type 1/like *CALR* = 1 point

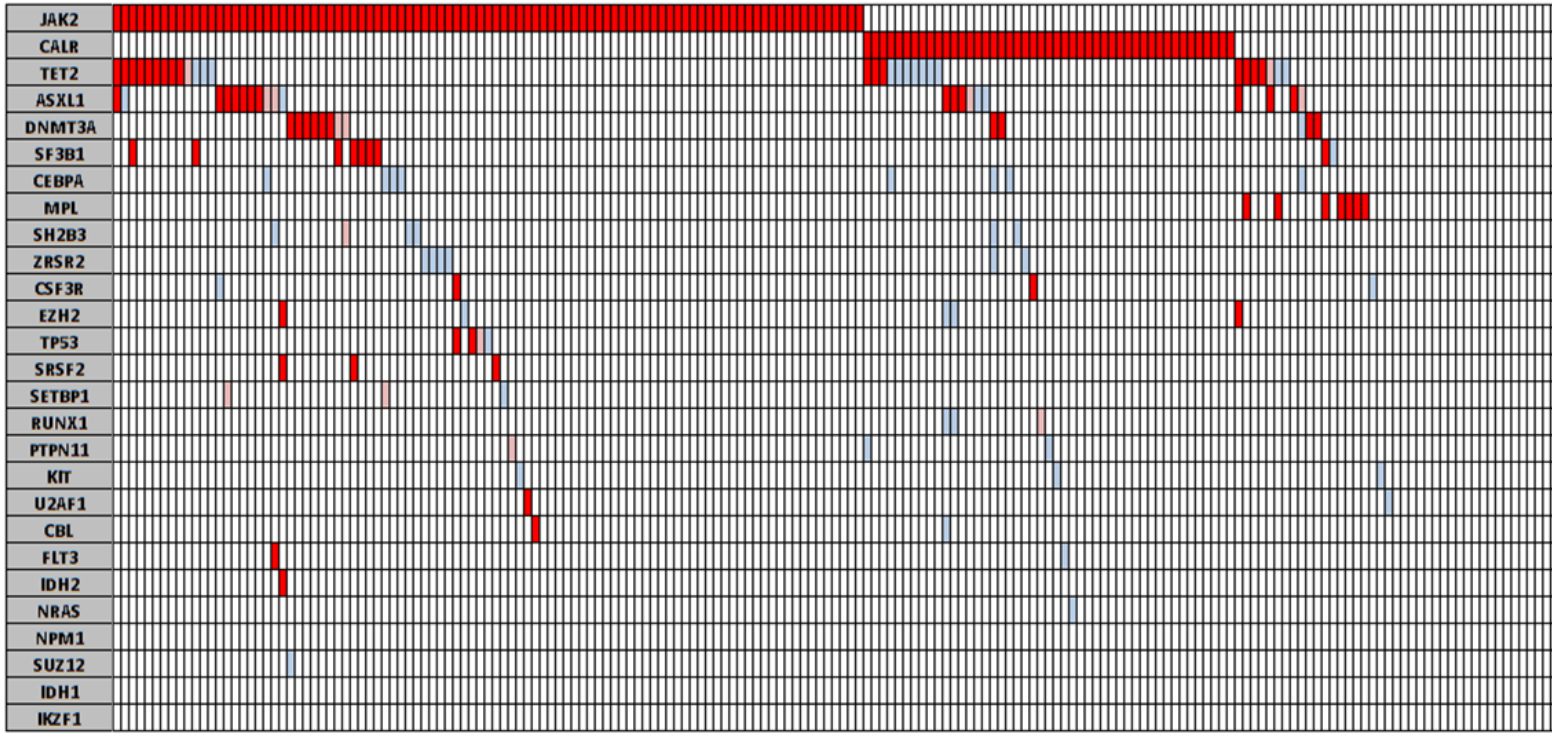
Karyotype:
Very high risk = 2 points
Unfavorable = 1 point

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

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

Leukemia 2018

Targeted deep sequencing in 183 patients with ET

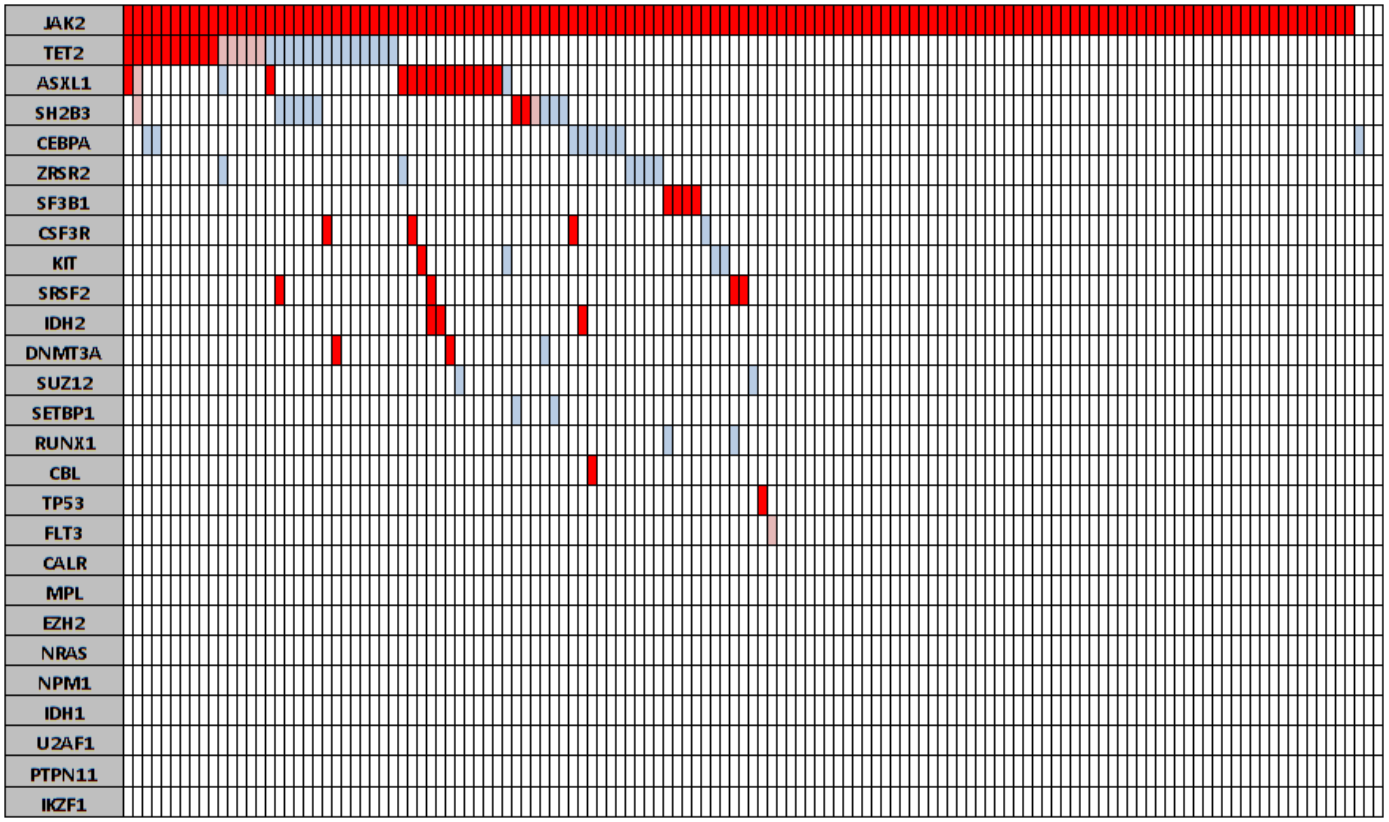


	Total #	% Total
JAK2	95	52%
CALR	47	26%
TET2	30	16%
ASXL1	20	11%
DNMT3A	11	6%
SF3B1	9	5%
CEBPA	8	4%
MPL	7	4%
SH2B3	6	3%
ZRSR2	6	3%
CSF3R	5	3%
EZH2	5	3%
TP53	4	2%
SRSF2	3	2%
SETBP1	3	2%
RUNX1	3	2%
PTPN1	3	2%
KIT	3	2%
U2AF1	2	1%
CBL	2	1%
FLT3	2	1%
IDH2	1	1%
NRAS	1	1%
NPM1	0	0%
SUZ12	0	0%
IDH1	0	0%
IKZF1	0	0%

RED: Sequence variants previously associated with a hematologic malignancy and shown to be somatic
PINK: Sequence variants previously associated with a hematologic malignancy and with ≤1% minor allele frequency in current databases for single nucleotide polymorphisms
BLUE: Sequence variants with ≤1% minor allele frequency in current databases for single nucleotide polymorphisms

1. Prevalence of mutations/variants other than *JAK2/CALR/MPL* = 53%
2. Driver mutational status did not affect prevalence
3. Most frequent were *ASXL1* and*TET2*
4. 41%, 8% and 4% harbored 1, 2 or ≥3 such mutations

Targeted deep sequencing in 133 patients with PV



	Total #	% Total
JAK2	130	98%
TET2	29	22%
ASXL1	16	12%
SH2B3	12	9%
CEBPA	8	6%
ZRSR2	6	5%
SF3B1	4	3%
CSF3R	4	3%
KIT	4	3%
SRSF2	4	3%
IDH2	3	2%
DNMT3A	3	2%
SUZ12	2	2%
SETBP1	2	2%
RUNX1	2	2%
CBL	1	1%
TP53	1	1%
FLT3	1	1%
CALR	0	0%
MPL	0	0%
EZH2	0	0%
NRAS	0	0%
NPM1	0	0%
IDH1	0	0%
U2AF1	0	0%
PTPN1	0	0%
IKZF1	0	0%

RED: Sequence variants previously associated with a hematologic malignancy and shown to be somatic
PINK: Sequence variants previously associated with a hematologic malignancy and with ≤1% minor allele frequency in current databases for single nucleotide polymorphisms
BLUE: Sequence variants with ≤1% minor allele frequency in current databases for single nucleotide polymorphisms

1. Prevalence of mutations/variants other than *JAK2/CALR/MPL* = 53%
2. Most frequent were *ASXL1* and*TET2*
3. 30%, 20% and 3% harbored 1, 2 or ≥3 such mutations

Blood Advances 2016

Contemporary prognostic models in PV/ET

Prognostic assessment	Variables	
Survival in PV	Age Leukocytosis Venous thrombosis	Leukemia 2013
IPSET- thrombosis	Age *JAK2* mutation History of thrombosis Cardiovascular risk factors (diabetes, hypertension, tobacco use)	Blood 2012 Blood Cancer J 2015
IPSET- survival	Age Leukocytosis History of thrombosis	Blood 2012
MIPSS-ET/MIPSS-PV (Mutation-enhanced)	Clinical + genetic variables	Ongoing

Derivation of Mutation-enhanced MIPSS score in ET/PV

Variables	HR (95% CI)	Weighted value
ET		
Age > 60 years	6.7 (4.8-9.4)	4
Male	1.8 (1.4-2.4)	1
***SRSF2/SF3B1* mutations**	2.8 (1.8-4.3)	2
PV		
Age > 60 years	5.7 (3.3-10.1)	2
Leukocyte count ≥ 11x109	2.4 (1.5-3.9)	1
Abnormal karyotype	2.1 (1.1-3.6)	1
***SRSF2* mutations**	7 (2.3-17.4)	2

Mutation-enhanced MIPSS score in ET (MIPSS-ET)

Figure 1a: MIPSS-ET; *n*=502

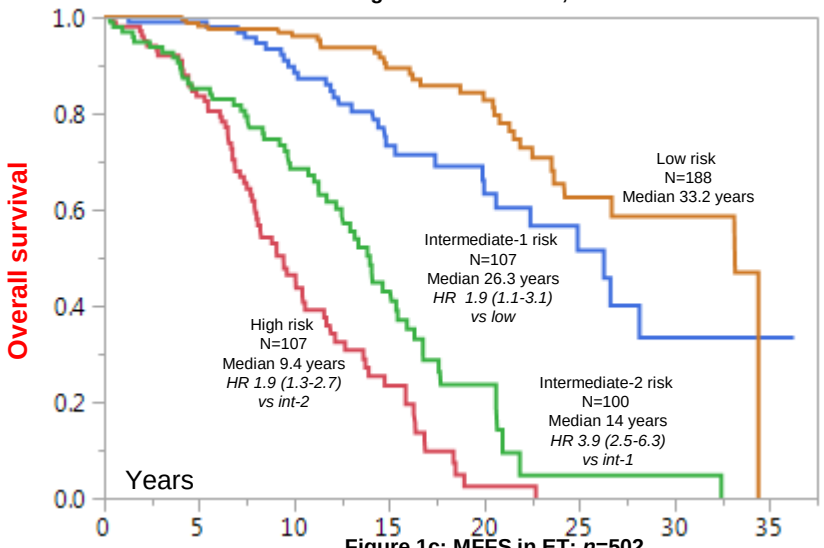


Figure 1b: LFS in ET; *n*=502

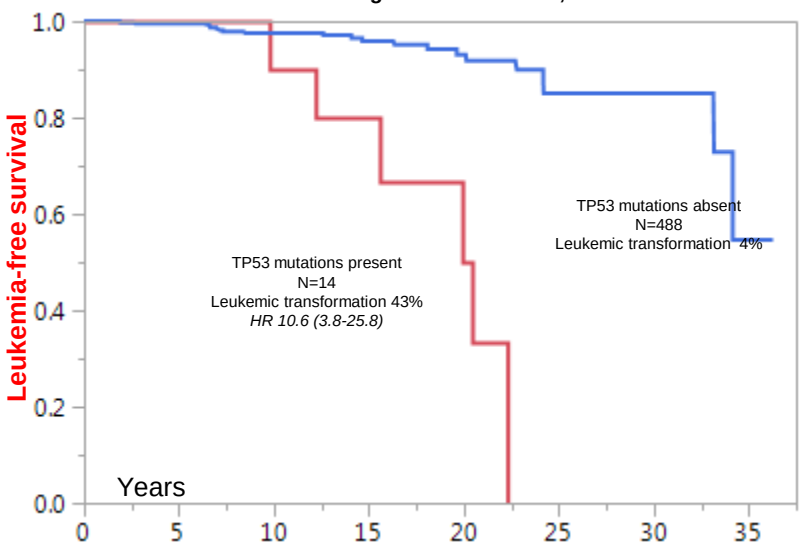
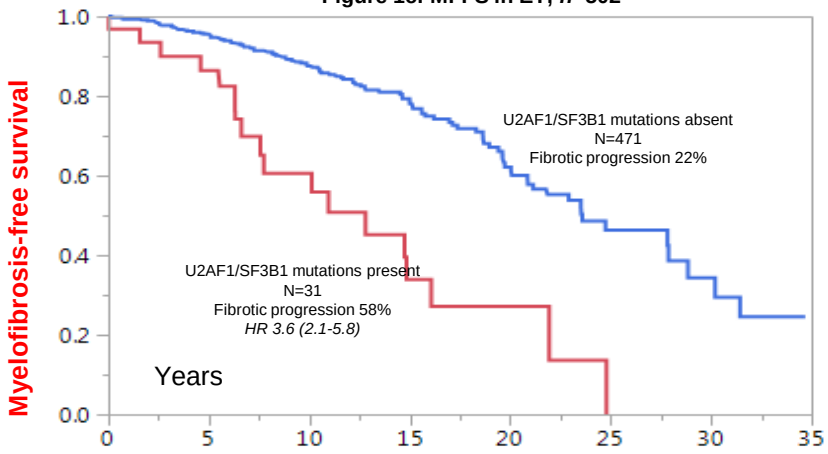


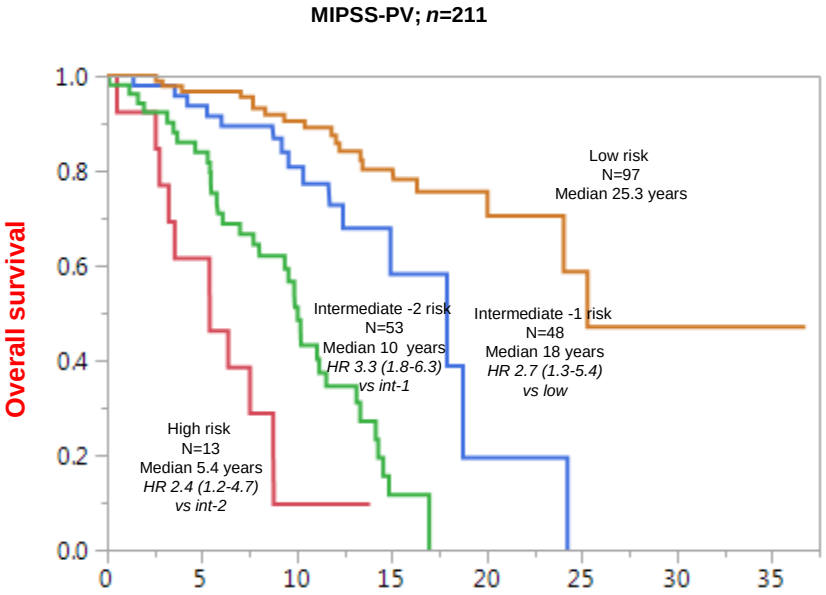
Figure 1c: MFFS in ET; *n*=502



Analysis was based on a combined dataset of 502 cases, informative for all listed risk factors, from the Mayo Clinic and University of Florence.

ET survival risk factors: *SRSF2/SF3B1 mutations (2 points), age >60 years (4 points) and male sex (1 point) — low "0" points; intermediate-1 "1-2 points"; intermediate-2 "3-4 points"; high "≥5" points*

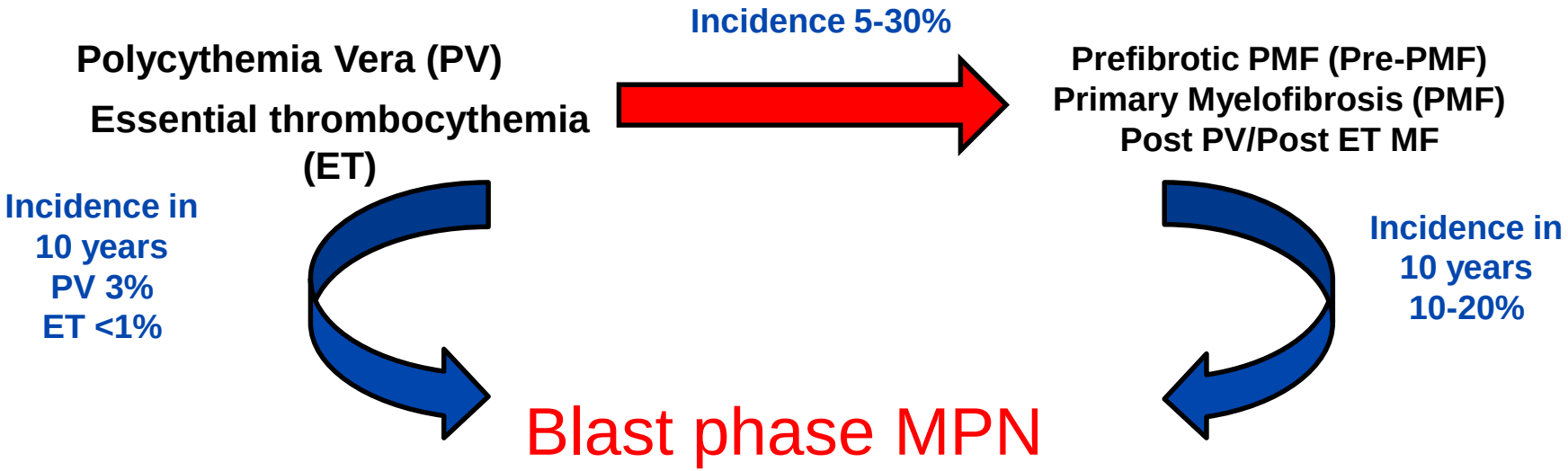
Mutation-enhanced MIPSS score in PV (MIPSS-PV)



Analysis was based on a combined dataset of 211 cases, informative for all listed risk factors, from the Mayo Clinic and University of Florence.

PV survival risk factors: *SRSF2 mutations (2 points), age >60 years (2 points), leukocyte count ≥11 x 10^9/l (1 point) and abnormal karyotype (1 point) — low "0-1" points; intermediate-1 "2" points; intermediate-2 "3" points; high "≥4" points*

Blast Phase MPN: Incidence & Risk factors

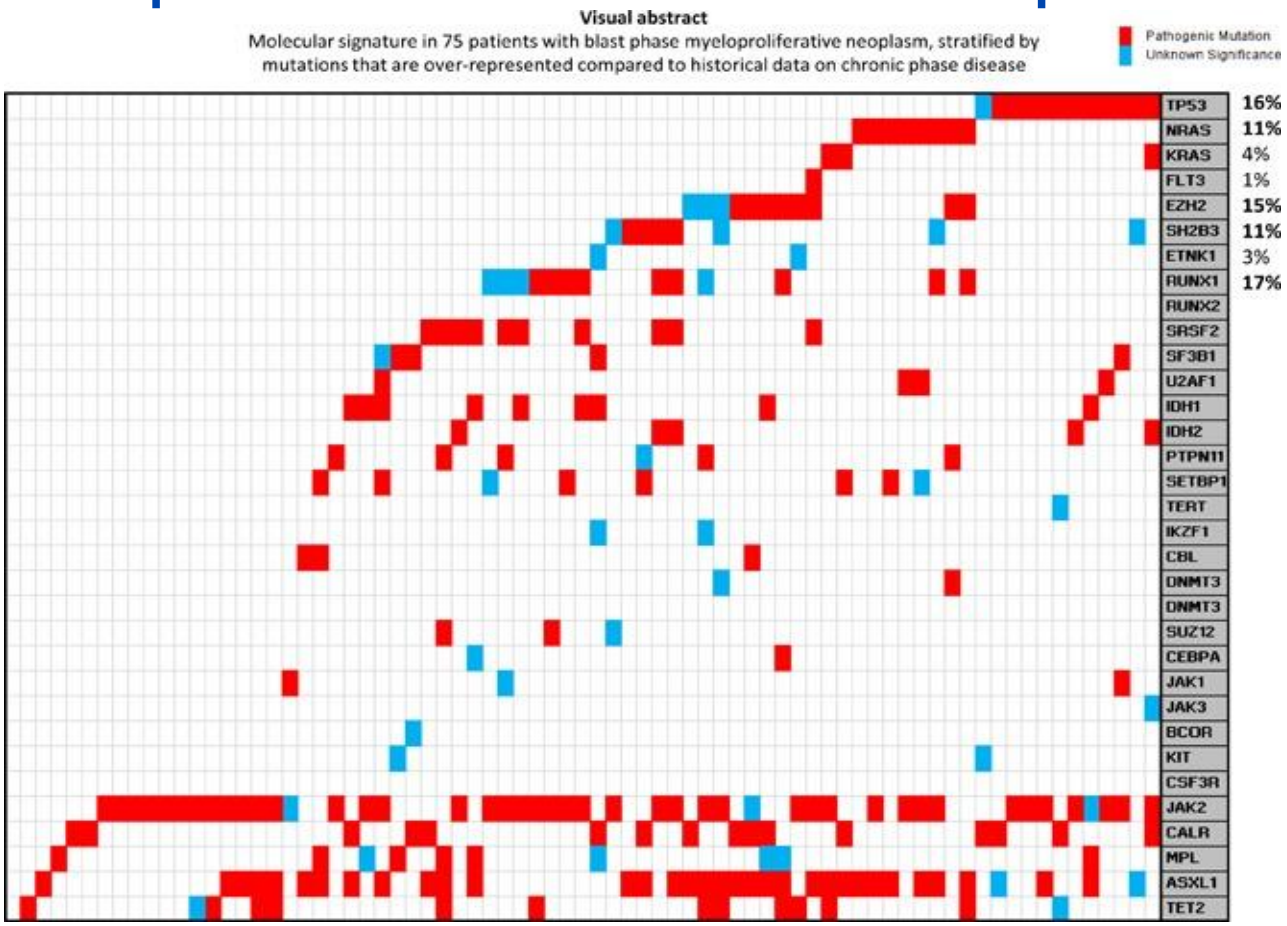


PV: leukocytosis, age, abnormal karyotype, *SRSF2* or *IDH2* mutations and radiophosphorous, chlorambucil or pipobroman tx.
ET: anemia, extreme thrombocytosis, age, leukocytosis, and *TP53* or *EZH2* mutations

unfavorable karyotype, thrombocytopenia, excess circulating blasts, marked leukocytosis, transfusion-requiring anemia, age increased interleukin-8 and C-reactive protein
triple-negative , *ASXL1*, *SRSF2*, *IDH1/2*, *RUNX1*, *CEBPA* or *SH2B3* and absence of *CALR* type 1-like mutation

Leukemia 2018

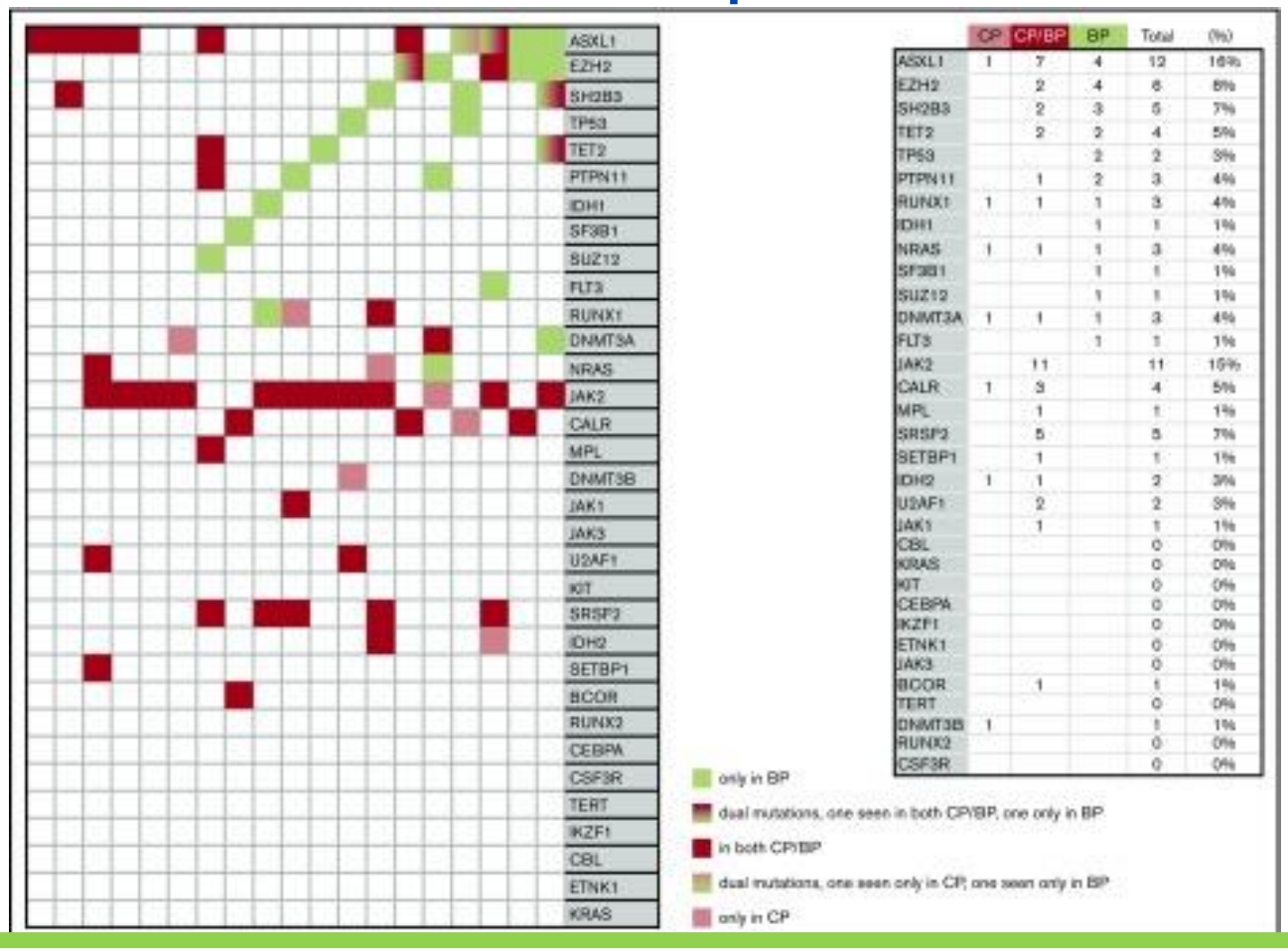
Blast phase MPN: Molecular profile



1. Prevalence of *JAK2/CALR/MPL* mutations = 57%/20%/9%
2. 85% harbored other mutations/variants
3. Enriched in *TP53, RUNX1, EZH2, NRAS, SH2B3* mutations

Blood Advances 2018

Blast phase vs chronic phase MPN: Molecular profile



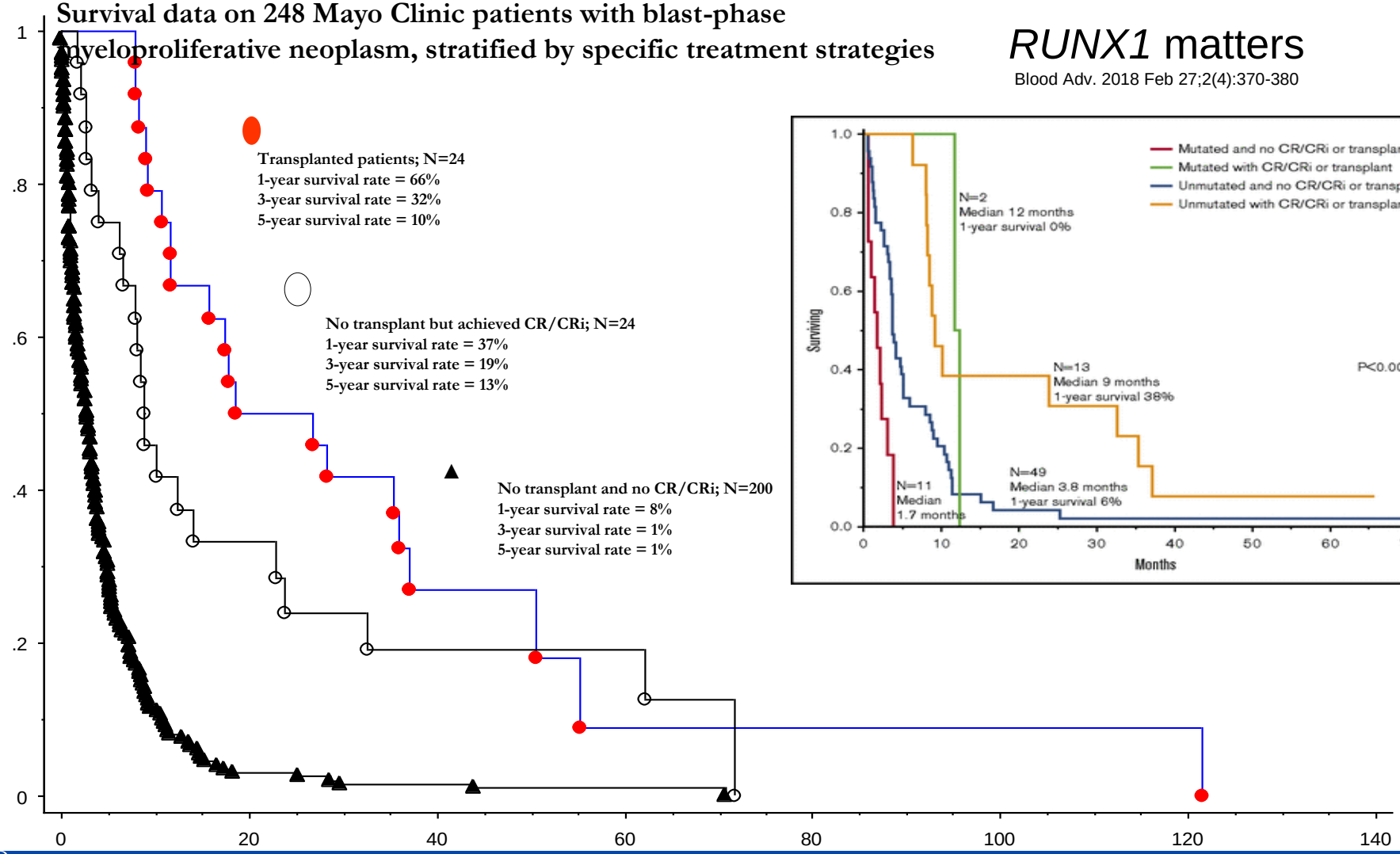
	CP	CP/BP	BP	Total	(%)
ASXL1	1	7	4	12	16%
EZH2		2	4	6	8%
SH2B3		2	3	5	7%
TET2		2	2	4	5%
TP53			2	2	3%
PTPN11		1	2	3	4%
RUNX1	1	1	1	3	4%
IDH1			1	1	1%
NRAS	1	1	1	3	4%
SF3B1			1	1	1%
SUZ12			1	1	1%
DNMT3A	1	1	1	3	4%
FLT3			1	1	1%
JAK2		11		11	16%
CALR	1	3		4	5%
MPL		1		1	1%
SRSF2		5		5	7%
SETBP1		1		1	1%
IDH2	1	1		2	3%
U2AF1		2		2	3%
JAK1		1		1	1%
CBL				0	0%
KRAS				0	0%
KIT				0	0%
CEBPA				0	0%
IKZF1				0	0%
ETNK1				0	0%
JAK3				0	0%
BCOR		1		1	1%
TERT				0	0%
DNMT3B	1			1	1%
RUNX2				0	0%
CSF3R				0	0%

Mutations with 2 or more instances of acquisition in blast phase disease included *TP53*, *EZH2*, *LNK*, *ASXL1*, *PTPN11*, and *TET2*

Blood Advances 2018

Blast Phase MPN

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



RUNX1 matters

Blood Adv. 2018 Feb 27;2(4):370-380

Leukemia 2018

Summary

- During prognostication of patients with primary myelofibrosis (PMF), one can simply start with the genetics only GIPSS prognostic model
  - *Very high risk (VHR) karyotype automatically puts a patient into high risk category and no additional prognostic information might be needed*
  - *In the absence of VHR karyotype, high risk category assignment requires three adverse genetic features: absence of type 1/like CALR, unfavorable karyotype, high molecular risk mutation such as ASXL1, SRSF2 and U2AF1 Q157*
- About 10% of patients with PMF do not to display any adverse genetic features and their 5-year survival is over 90%

Summary

- MIPSS70+ *version 2.0* includes clinical risk factors (anemia, circulating blasts, constitutional symptoms), in addition to genetic risk factors used in GIPSS, and offers additional information on prognosis

- MIPSS-ET and MIPSS-PV includes clinical risk factors (age/male gender, age/leukocytosis respectively), in addition to genetic risk factors

- Mutation patterns in blast phase MPN point to specific mutations (*TP53*, *EZH2*, *LNK*, *ASXL1*, *PTPN11*, and *TET2)* with potential pathogenetic relevance

- *RUNX1* mutations predict inferior survival in blast phase MPN

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Questions & Discussion

