Programme de la journée

8h00 – 8h30	***Accueil***
8h30 – 8h45	**Introduction :** Dr méd. Olivier Lebeau
8h45 – 9h30	**"Néoplasies myéloprolifératives : polycythémie thrombocytose myélofibrose leucémie myéloïde chronique"** Pr Dr méd. Jakob Passweg, Hôpital Universitaire, Bâle
9h30 – 9h45	**Discussion**, modérateur : Dr méd. Christian Monnerat
9h45 – 10h15	*Pause*

UNI BASEL

Prof Jakob R Passweg

Universitätsspital Basel

Leucémies chroniques

MPN

Il en a trop

LCM PV ET MFP

CEL

Mastocytose

Table 1. Major ICC categories of myeloid neoplasms and acute leukemias

Myeloproliferative neoplasms

Chronic myeloid leukemia

Polycythemia vera

Essential thrombocythemia

Primary myelofibrosis

- Early/prefibrotic primary myelofibrosis
- Overt primary myelofibrosis

Chronic neutrophilic leukemia

Chronic eosinophilic leukemia, not otherwise specified

Myeloproliferative neoplasm, unclassifiable

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement

Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement

Myeloid/lymphoid neoplasm with *FGFR1* rearrangement

Myeloid/lymphoid neoplasm with *JAK2* rearrangement

Myeloid/lymphoid neoplasm with *FLT3* rearrangement

Myeloid/lymphoid neoplasm with *ETV6::ABL1*

Mastocytosis

Myelodysplastic/myeloproliferative neoplasms

SMD

Il y en a pas assez

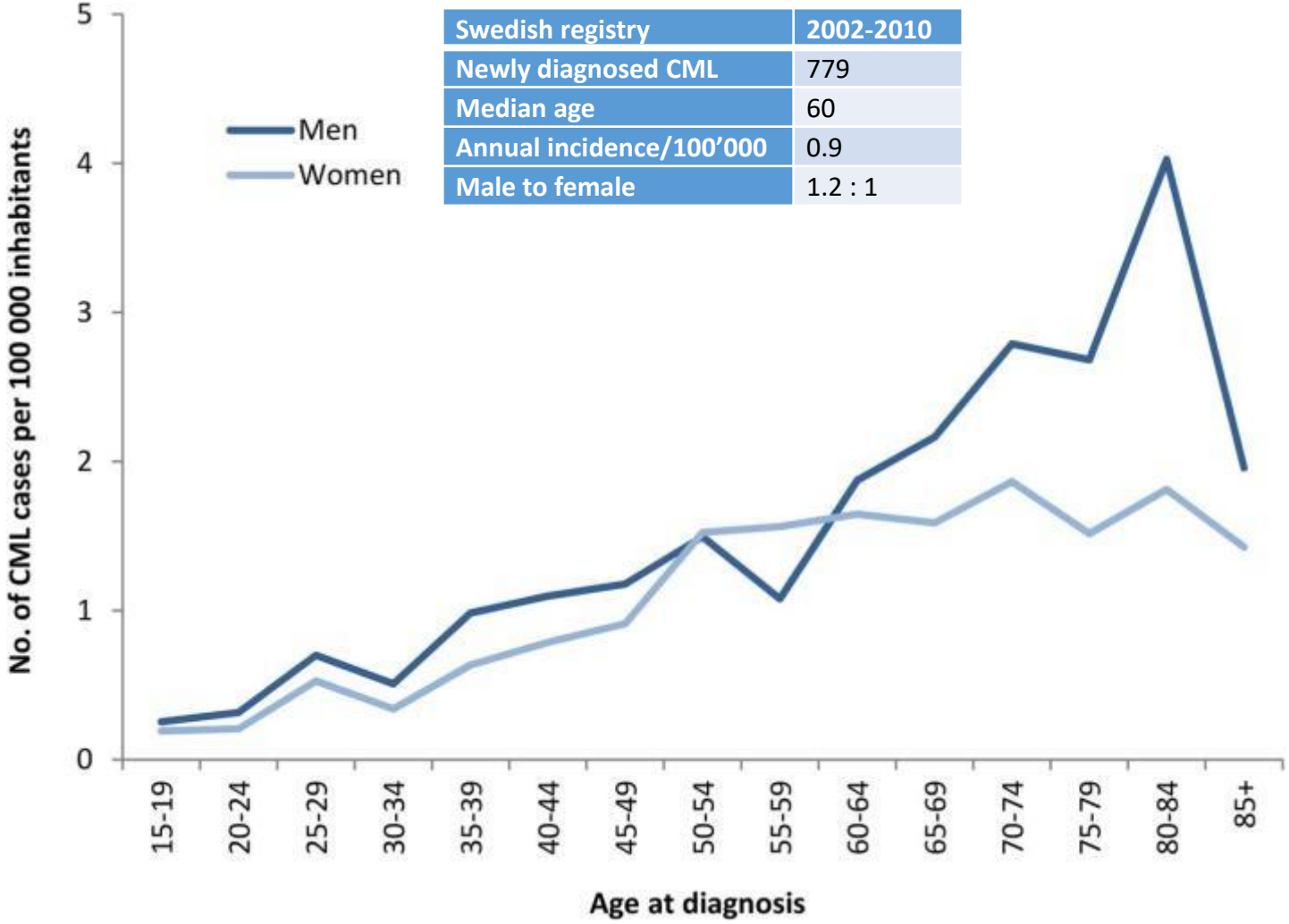
LMC: maladie modèle

Genotype-Phenotype

Clonal Evolution

Targeted Treatment

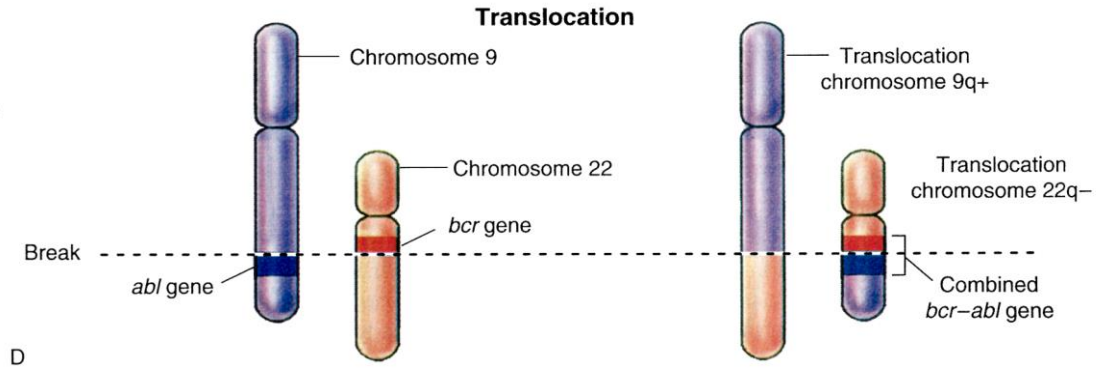
Age- and sex-specific incidence of CML per 100 000 inhabitants, year 2002-2010.

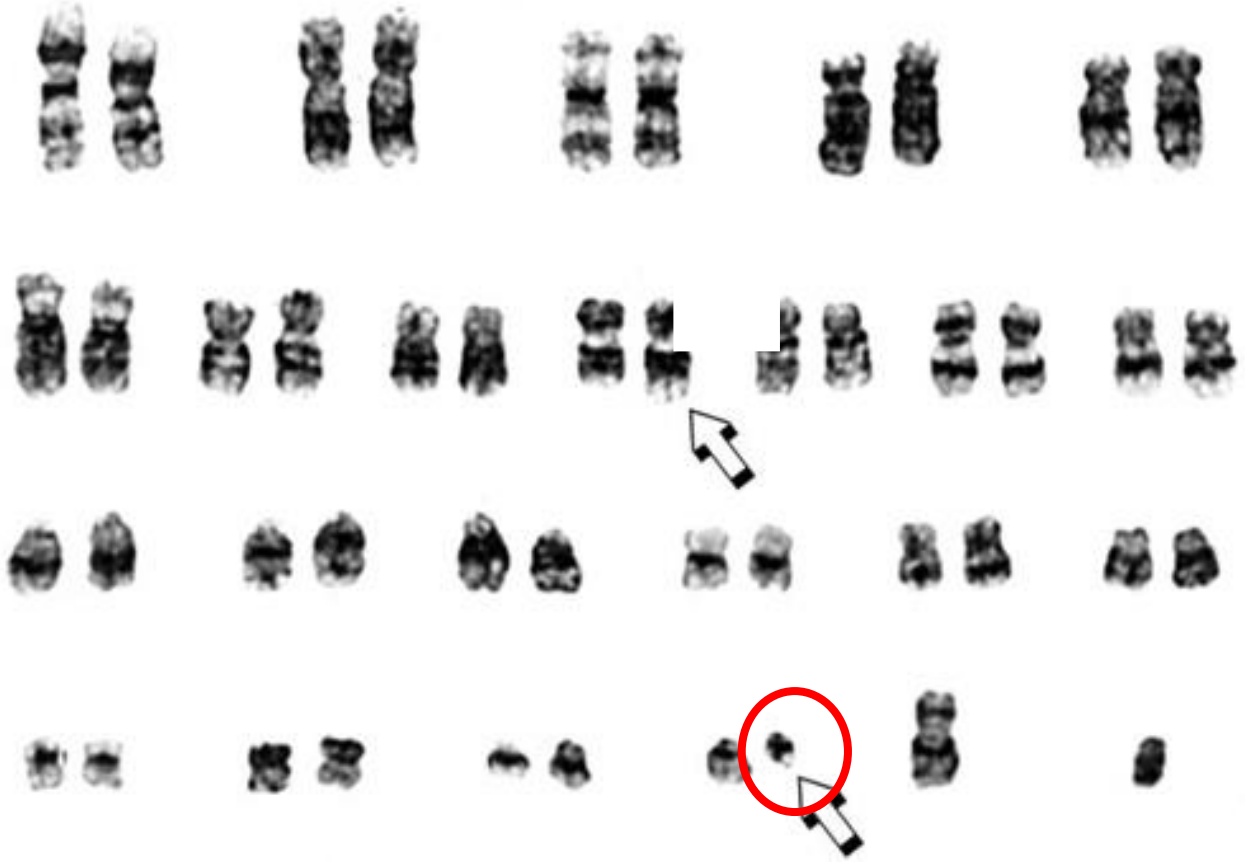


Swedish registry	2002-2010
Newly diagnosed CML	779
Median age	60
Annual incidence/100'000	0.9
Male to female	1.2 : 1

Höglund, M. et al. *Blood* 2013;122:1284-1292

Diagnosis of CML



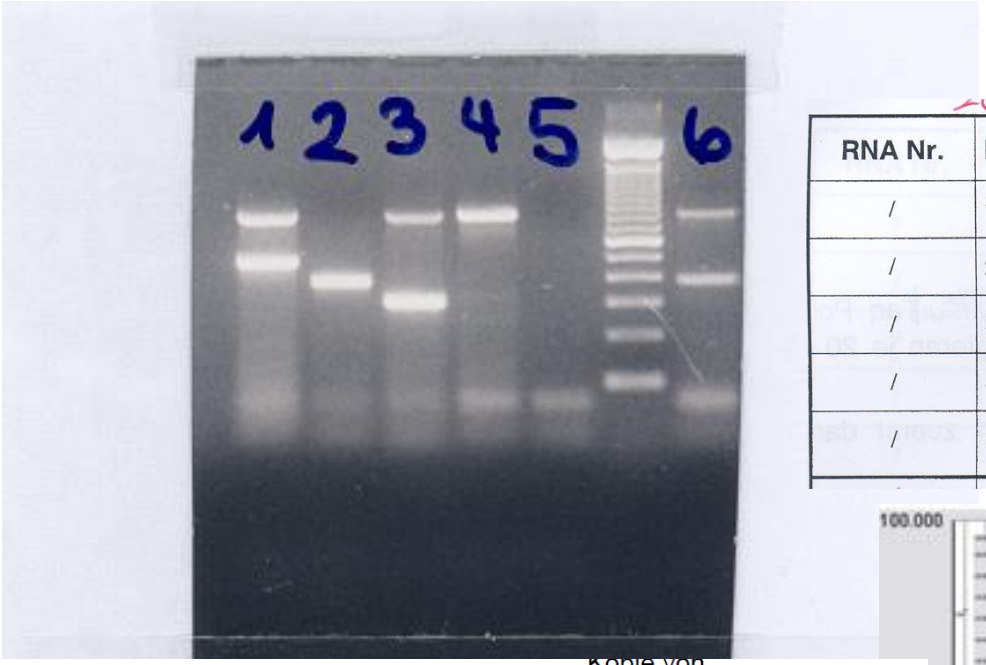


Philadelphia chromosome

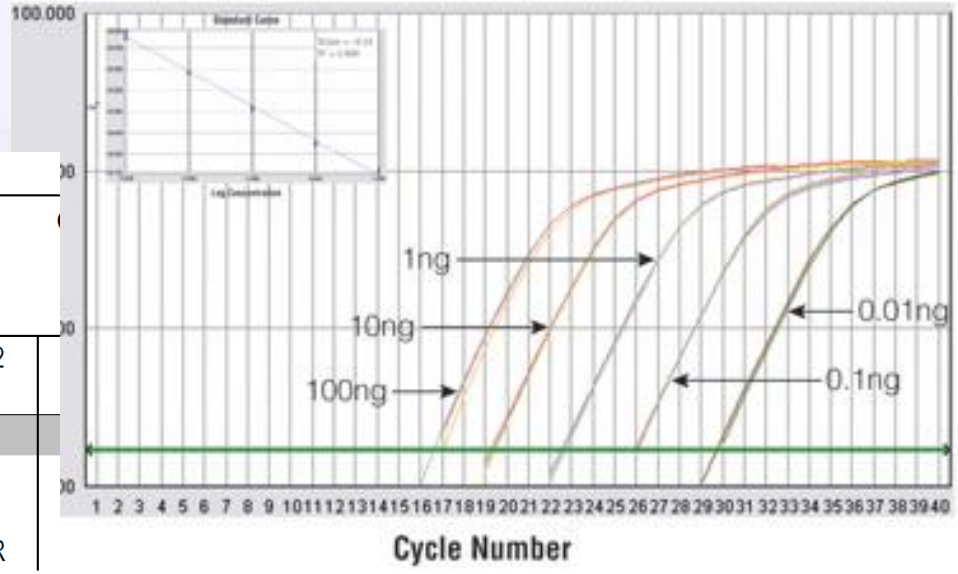
1960 - Nowell P.C. & Hungerford D.A
1972 – Rowley J

Diagnosis of CML

Molecular diagnostic multiplex PCR: qualitative result for BCR-ABL



RNA Nr.	Name		Material	Ergebnis	Nested
/	1. SD1	481 bp minor breakpoint	IQ	e1a2	-
/	2. K 562	385bp major breakpoint	IQ	b3a2	-
/	3. BV 173	310bp major breakpoint	IQ	b2a2	-
/	4. HL60	808bp normales bcr	IQ	Kontrollbande	-
/	5. Blank		IQ	Keine Bande	-



Kopie von

Typ Fusionstranskript: **BCR ::ABL1, e14a2 (b3a2)** **Klinische Angaben:**

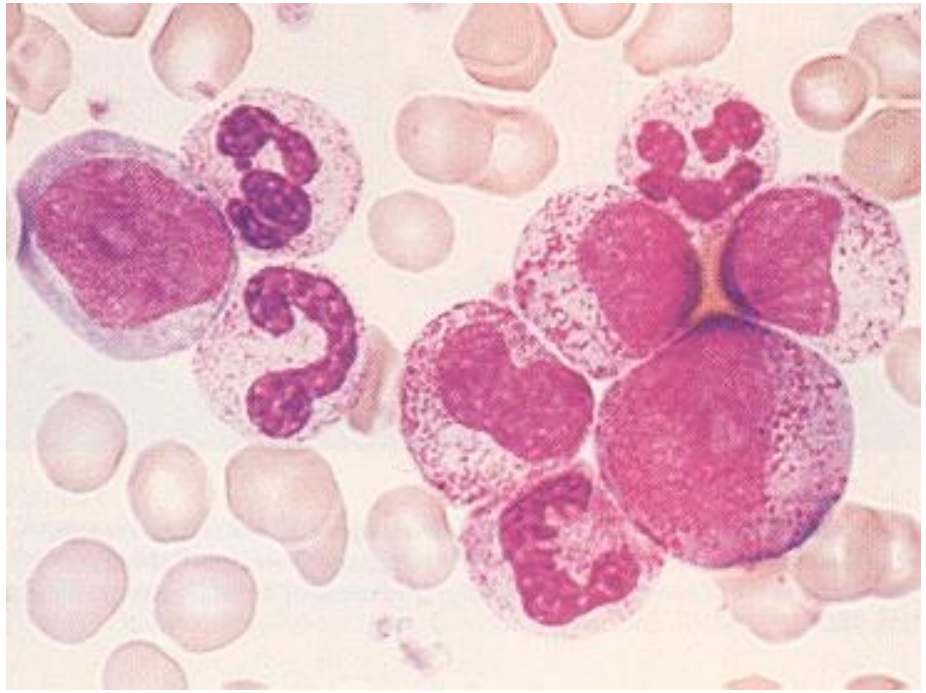
Conversion Factor: **0.173**

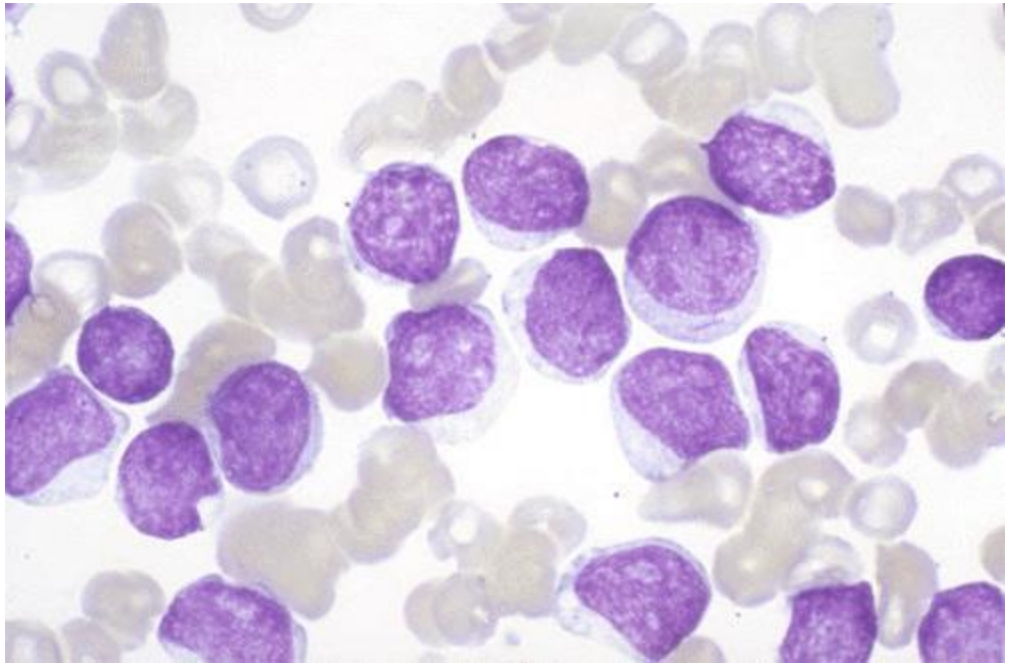
Entnahmedatum	31.10.2022	01.09.2022	04.07.2022	10.05.2022
Auftragsnummer	43781060	43686084	43588159	43506606
RNA Nr. (PB)	**221800**	221461	221112	220810
% IS Ratio BCR::ABL1 / ABL1	**0.05877**	0.21093	2.79526	18.60221
ABL1-Kopienanzahl (PB)	**36661**	29497	39624	40197
Molecular Response	**MR 3.0**	keine MMR	keine MMR	keine MMR

Chronic Phase

Blast Crisis

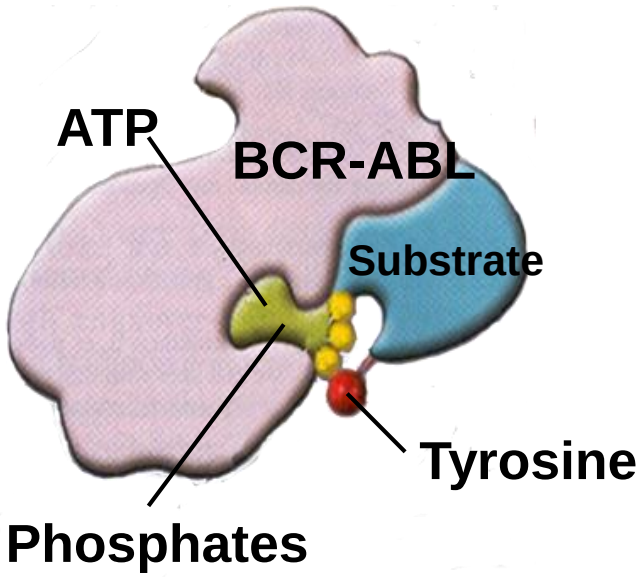
Accelerated Phase

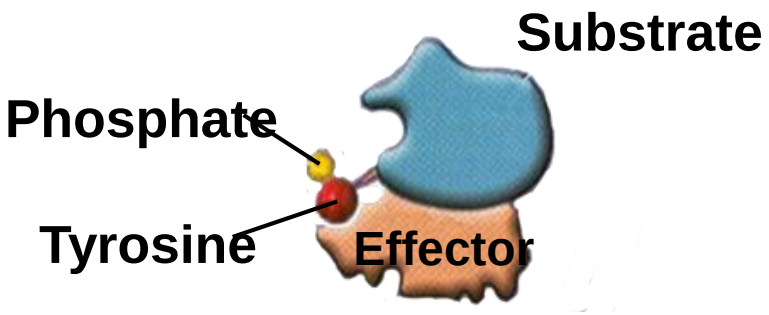




Chronic myeloid leukemia

Generations of TKI





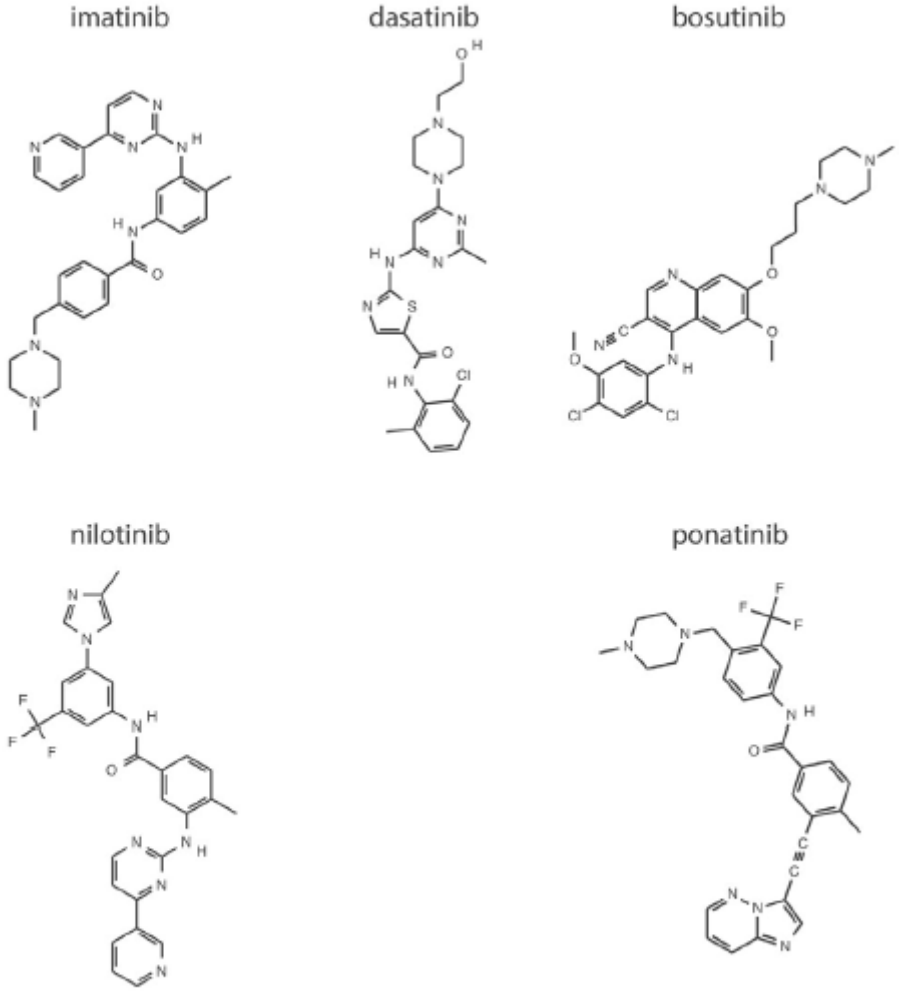
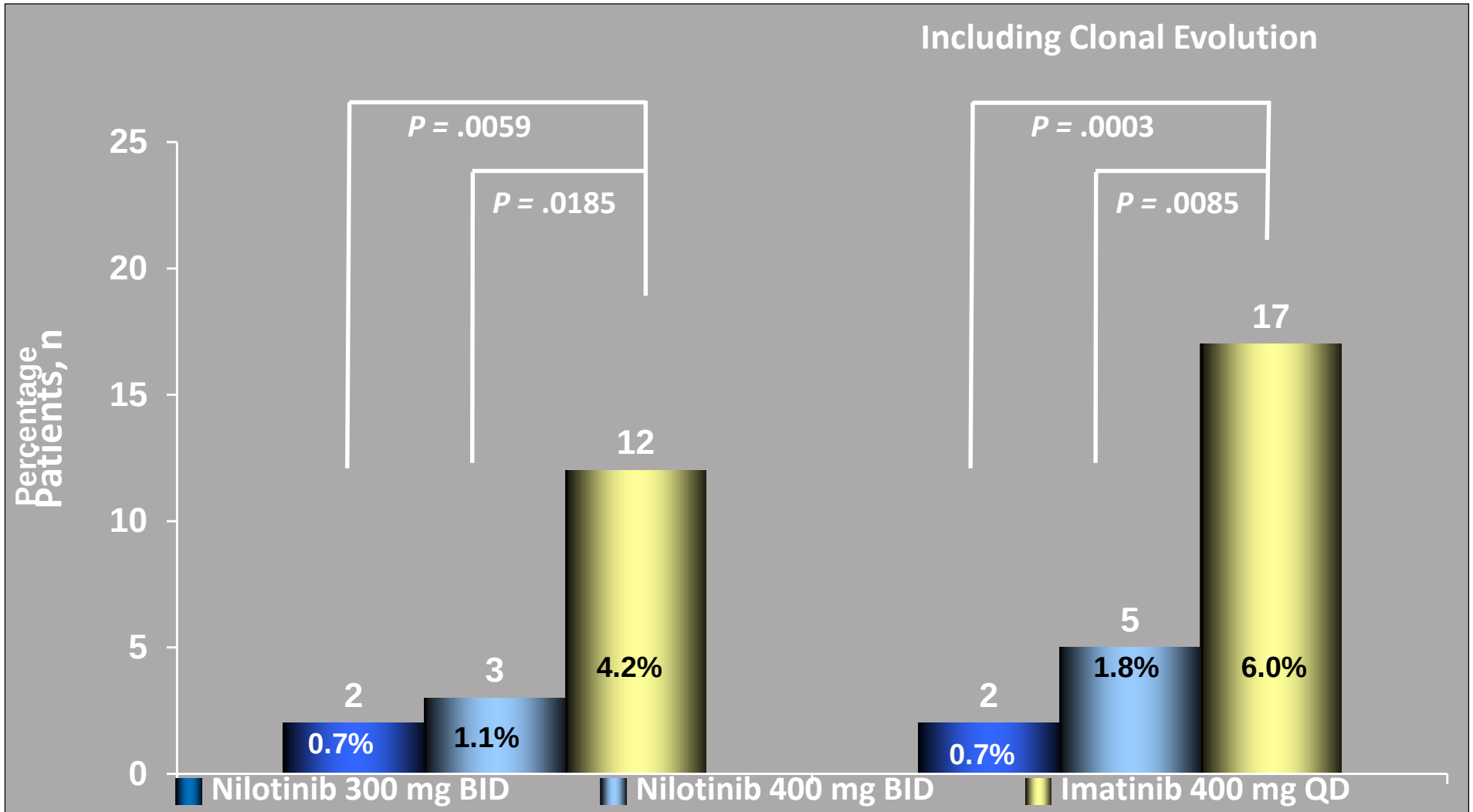


Figure 8. Chemical structures of imatinib, nilotinib, dasatinib, bosutinib and ponatinib.

Mughal et al, Haematologica 2016

Progression to AP/BC on Treatment

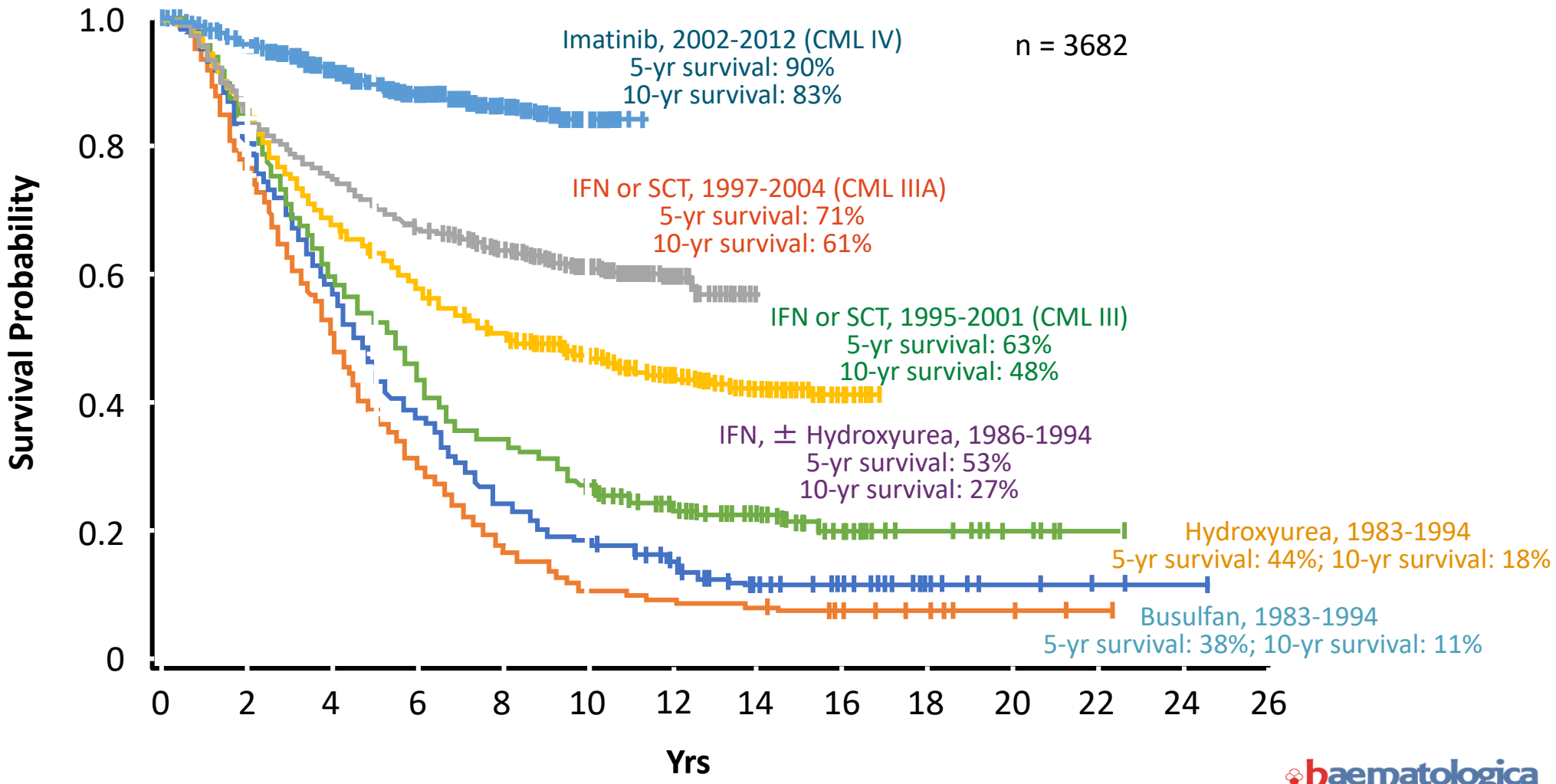


- No new progressions on treatment were observed since the 2-year analysis
- Nilotinib has a significantly lower risk of progression than imatinib

Data cutoff: 27Jul2011.

Clark RE, et al. *Haematologica*. 2012;97(s1):237 [abstract 0583].

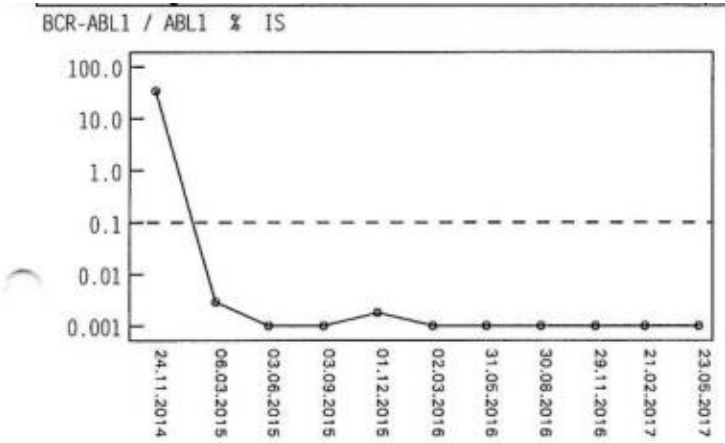
Survival With CML Over Time: The German CML-Study Group Experience



Hehlmann. Haematologica 2016;101:657.

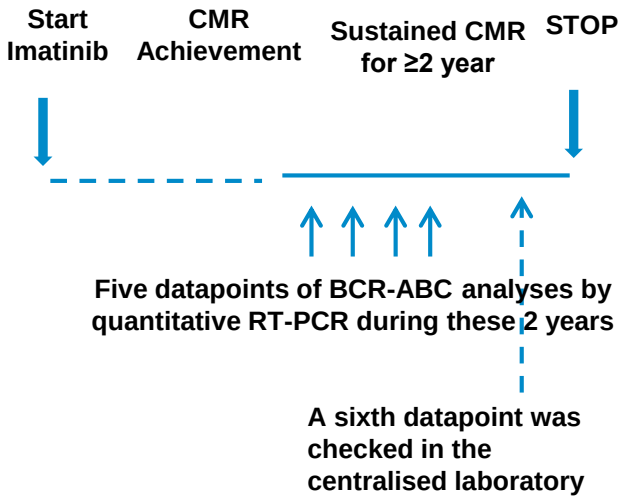
haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

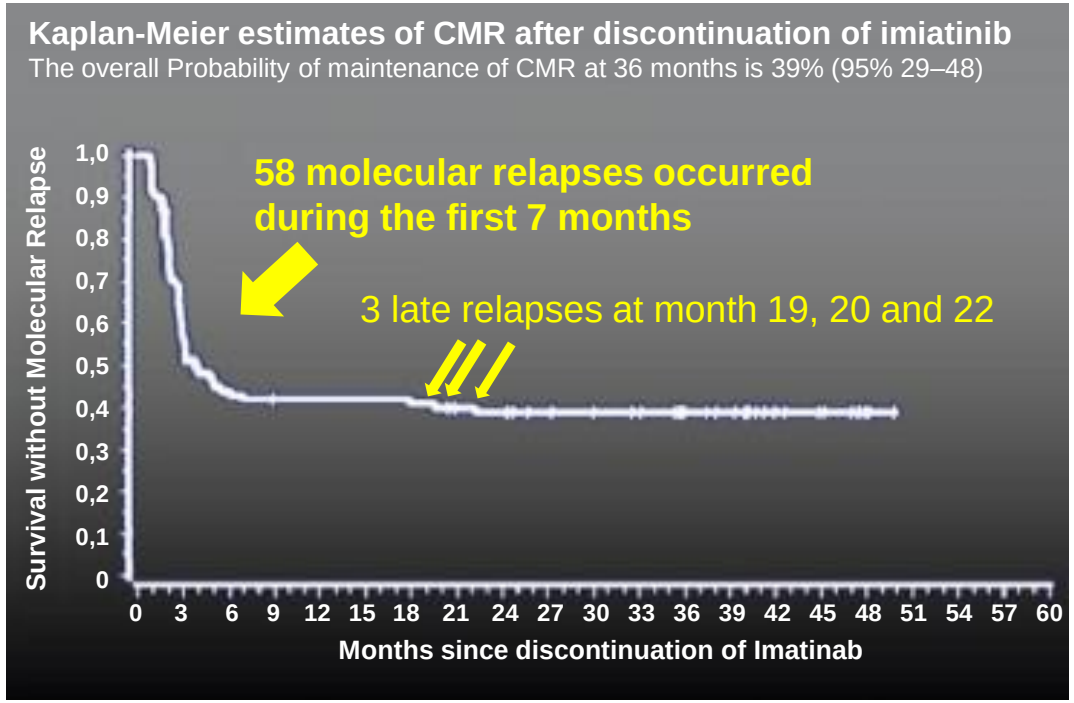
Monitoring of deep molecular response?



ANR	Proben-entnahme	BCR-ABL1 / ABL1 % IS	
994736	24.11.2014	33.443	
993150	06.03.2015	0.003	
999192	03.06.2015	<0.001	n.quant
996473	03.09.2015	<0.001	n. det
993350	01.12.2015	0.002	
990970	02.03.2016	<0.001	n. det
998575	31.05.2016	<0.001	n.quant
995954	30.08.2016	<0.001	n. det
994501	29.11.2016	<0.001	n. det
992165	21.02.2017	<0.001	n.quant
990855	23.05.2017	<0.001	① n. det

n = 100 patients





Quantitative RT-PCR from peripheral blood was done every month in the first year and every 2 months after 1 year.

Mahon FX et al. Lancet Oncol 2010; 11:1029-1035.

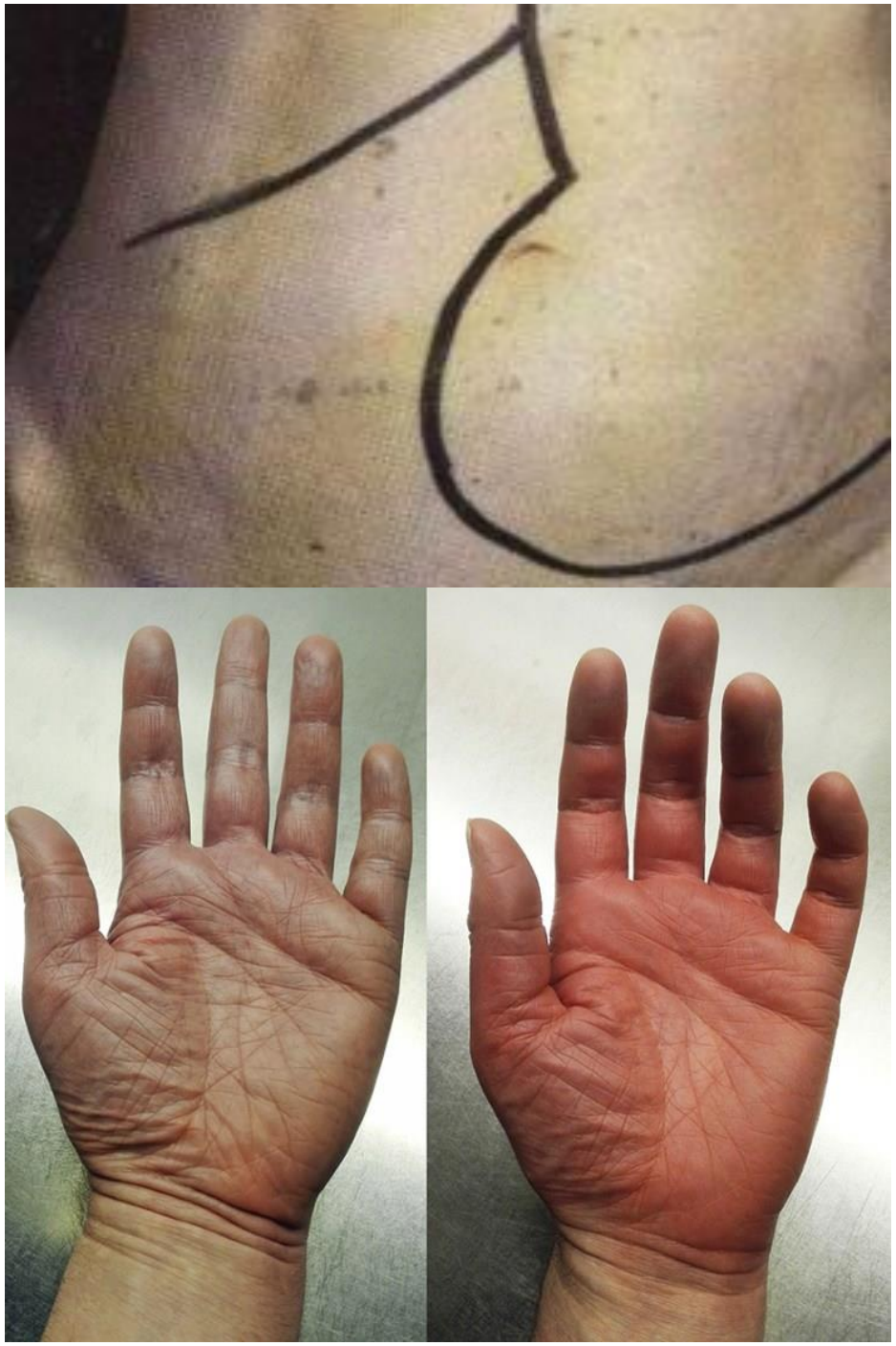
NMP: maladie modèle

Genotype-Phenotype

Mutation «driver»

Monosomie uniparentale

Cancer Stem Cell



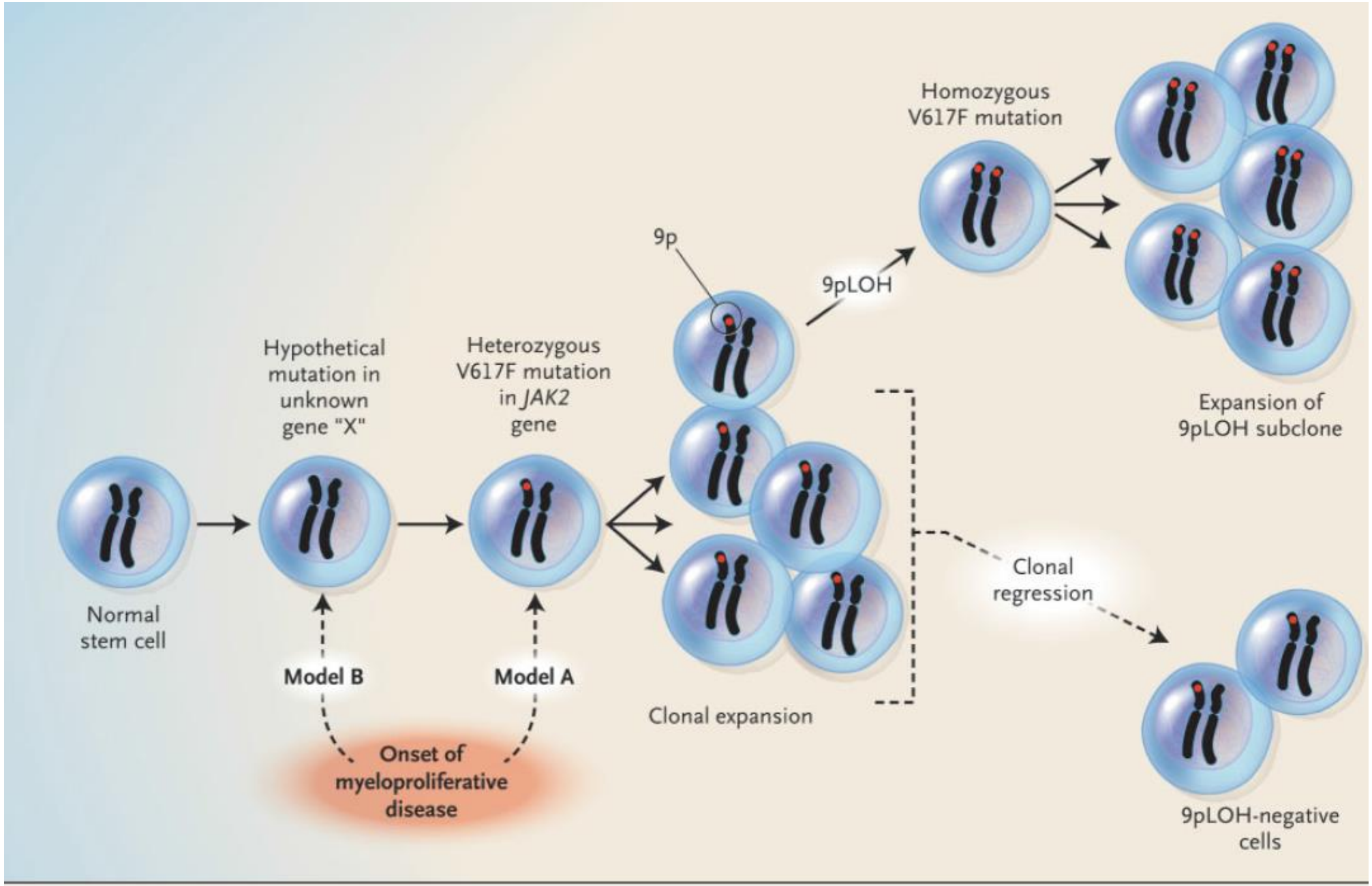
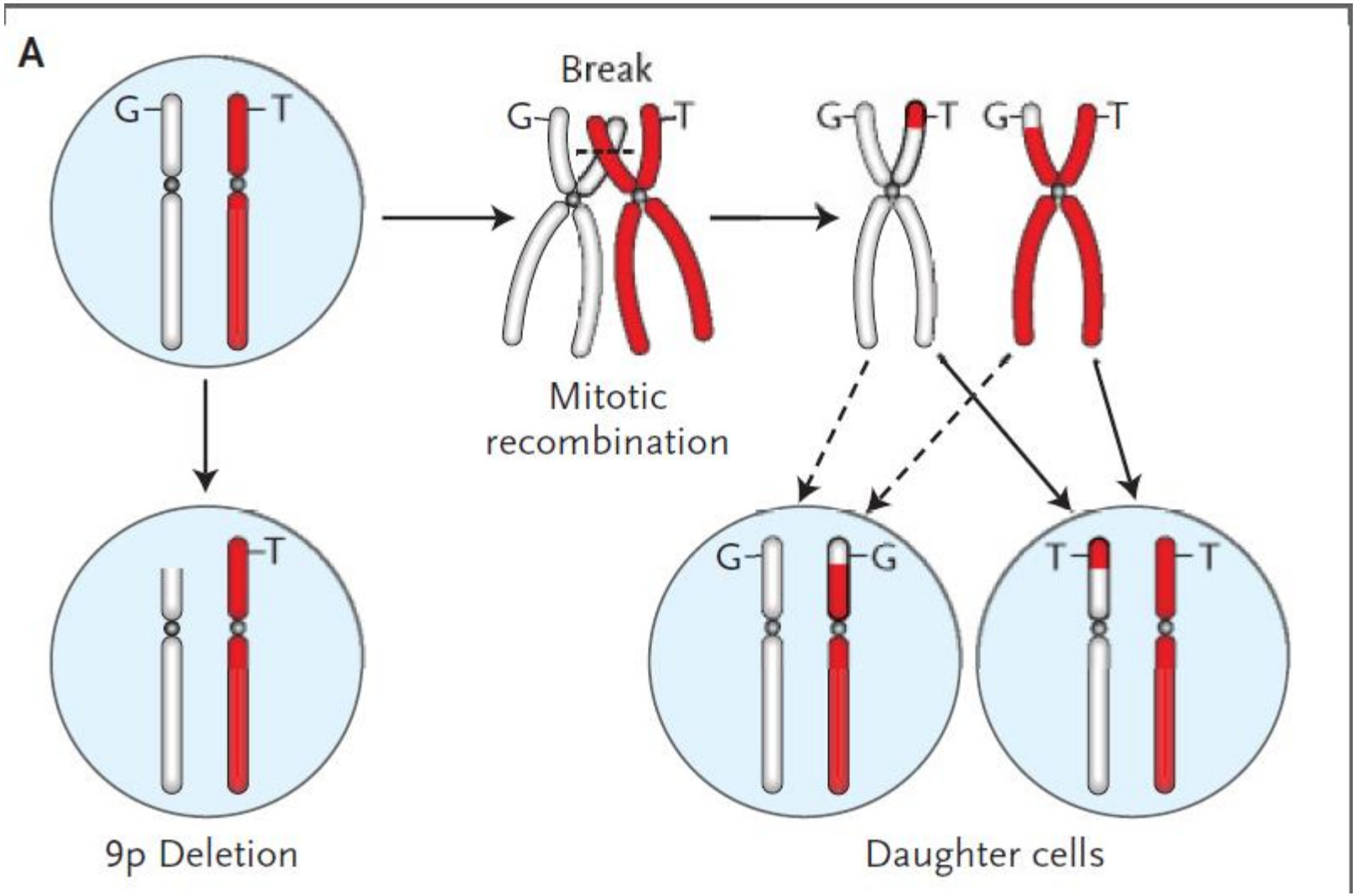
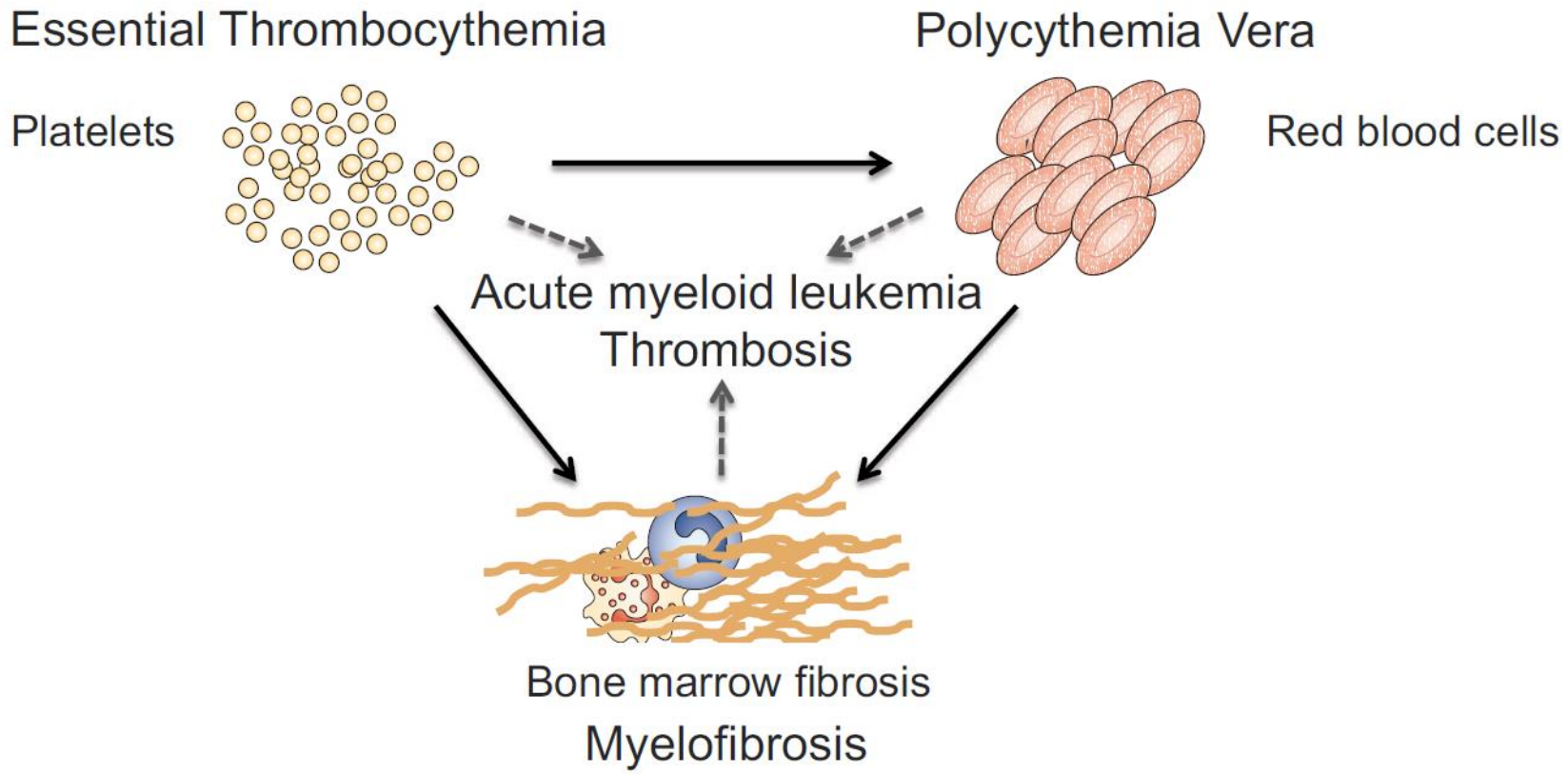


Figure 5. Possible Roles of the *JAK2* V617F Mutation in Myeloproliferative Diseases.


A
G
T
Break
G
T
G
T
G
T
Mitotic
recombination
T
9p Deletion
G
G
T
T
Daughter cells

NMP: 3 maladies; une cause commune?

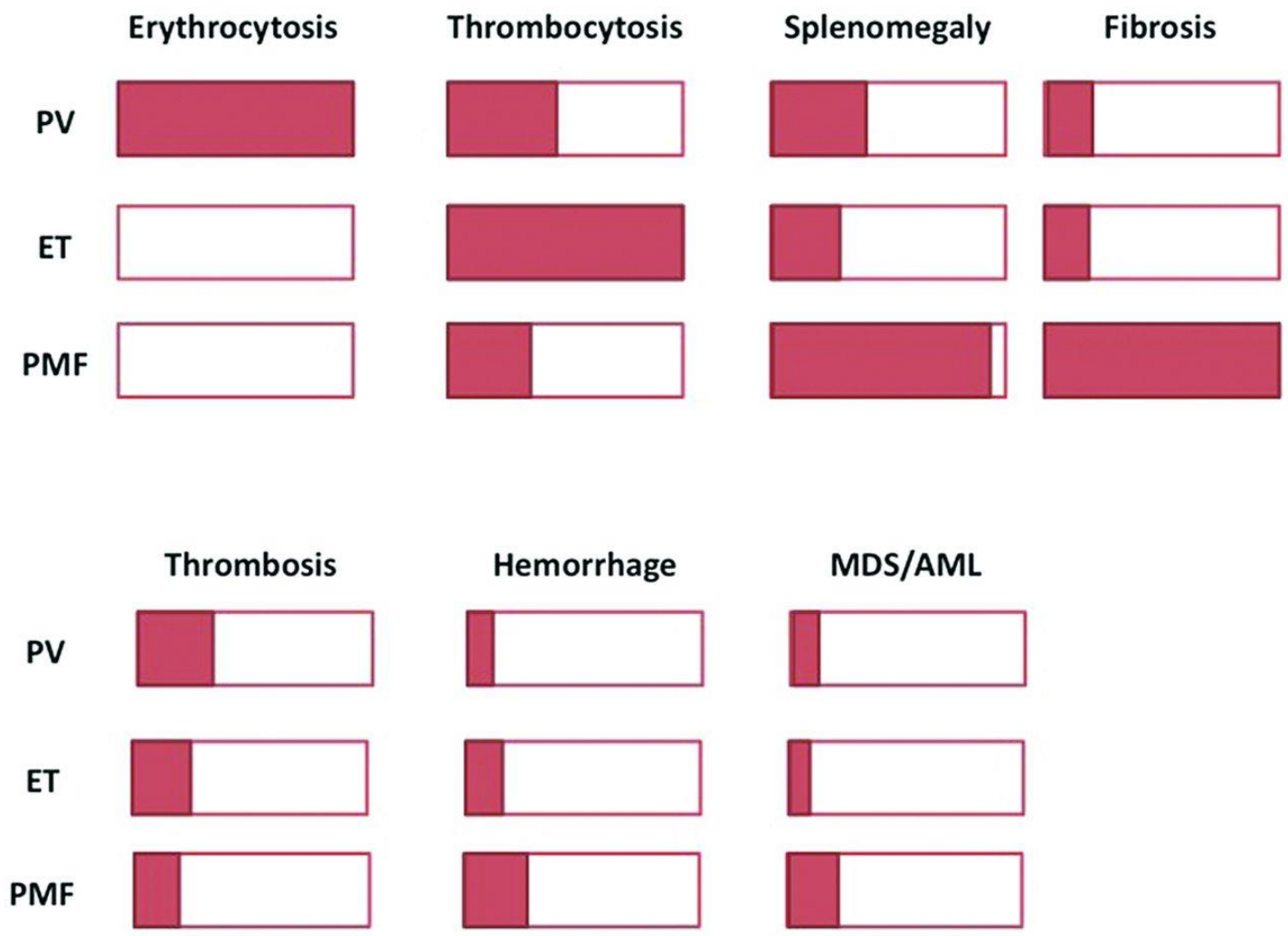


P

JAK2
Calreticulin
MPL
Triple négatif

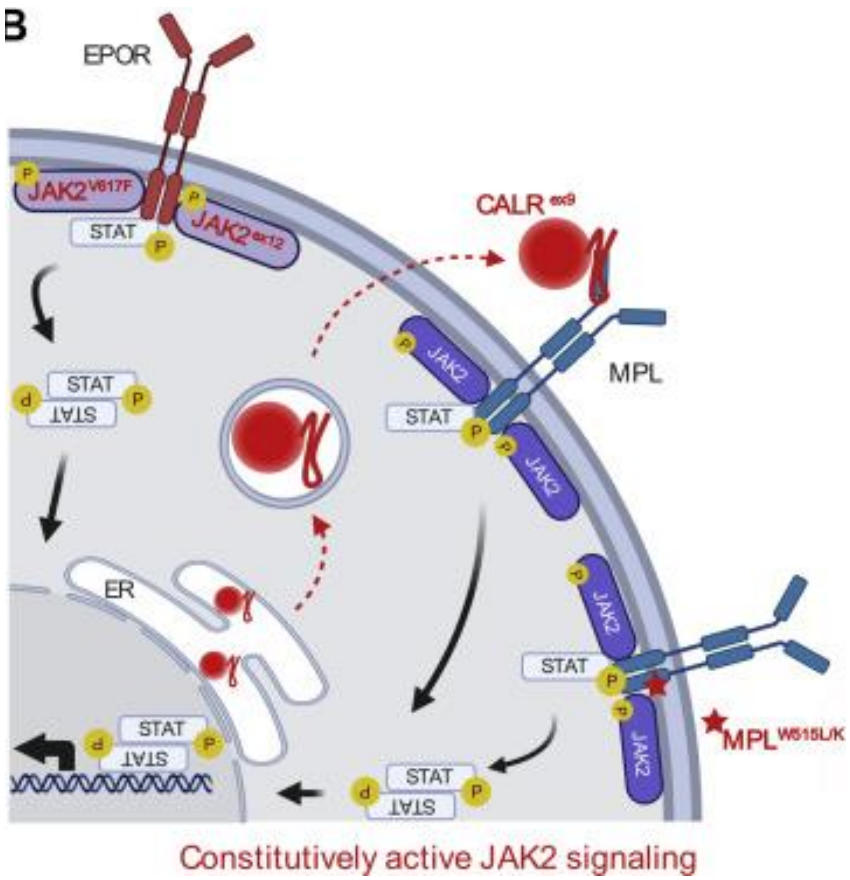
sLMA

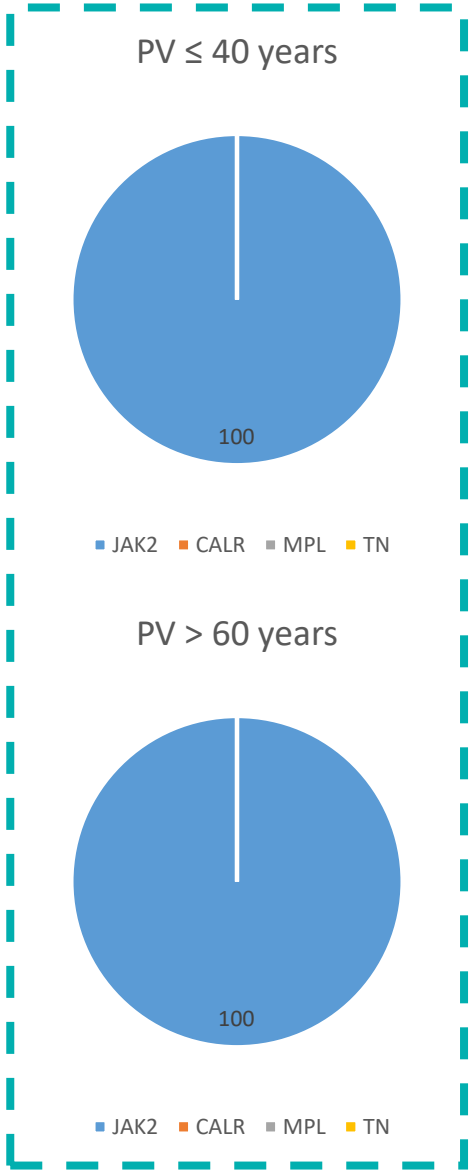
Overlaps in clinical presentation and evolution.

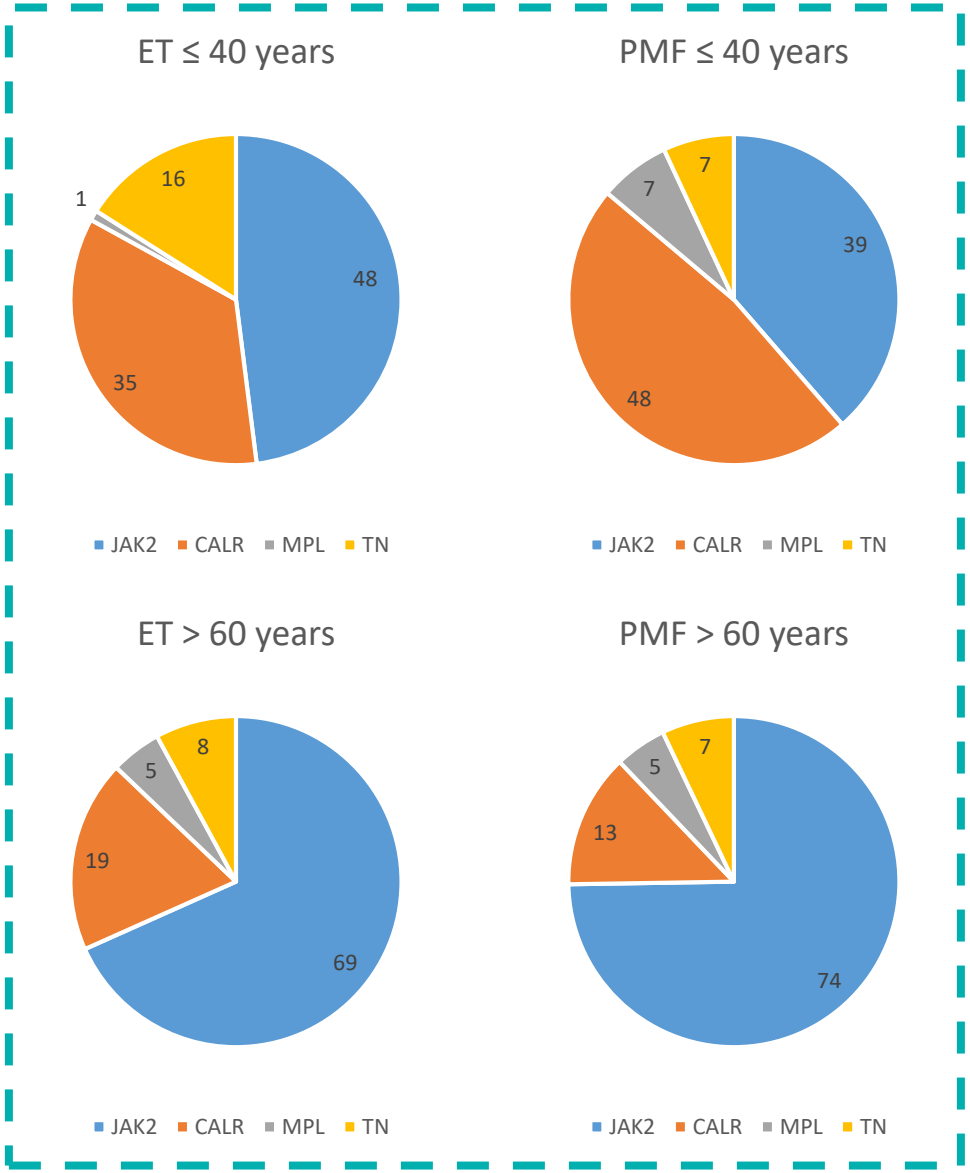


Kiladjian J Hematology 2012;2012:561-566

Genetics – driver mutations







Szuber, Vallapureddy, Penna et al. Am J Hematol. 2018 Dec;93(12):1474-1484.
Sobas M, Kiladjian, Beauverd et al. Blood Adv. 2022 Sep 13;6(17):5171-5183

Mutations frequents

	Driver-Mutationen	zusätzliche Mutationen	Ungünstige Mutationen
ET	JAK2 V617F (50-60%) CALR (30%) MPL (3-8%) Triple-neg (15%)	TET2 (10-15%) ASXL1 (5-10%) DNMT3A (5%) SF3B1 (3%)	SH2B3, SF3B1, U2AF1, TP53, IDH2, EZH2
prePMF/ PMF	JAK2 V617F (50-65%) CALR (25-30%) MPL (8-10%) Triple-neg (-12%)	ASXL1 (-35%) TET2 (20%) SRSF2 (-20%) U2AF1 (16%) ZRSR2 (10%) SF3B1 (10%) DNMT3A (5-15%)	ASXL1, SRSF2, CALR type 2

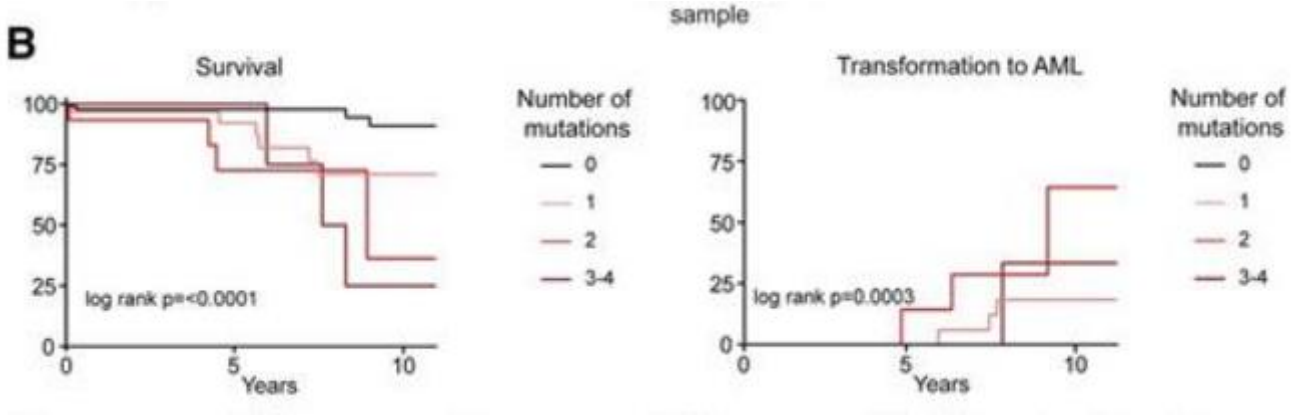
MYELOID NEOPLASIA

(*Blood*. 2014;123(14):2220-2228)

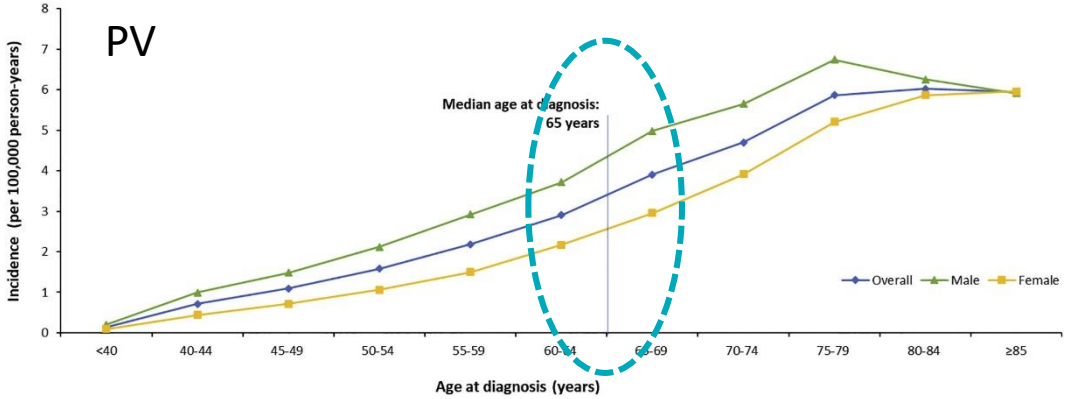
Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms

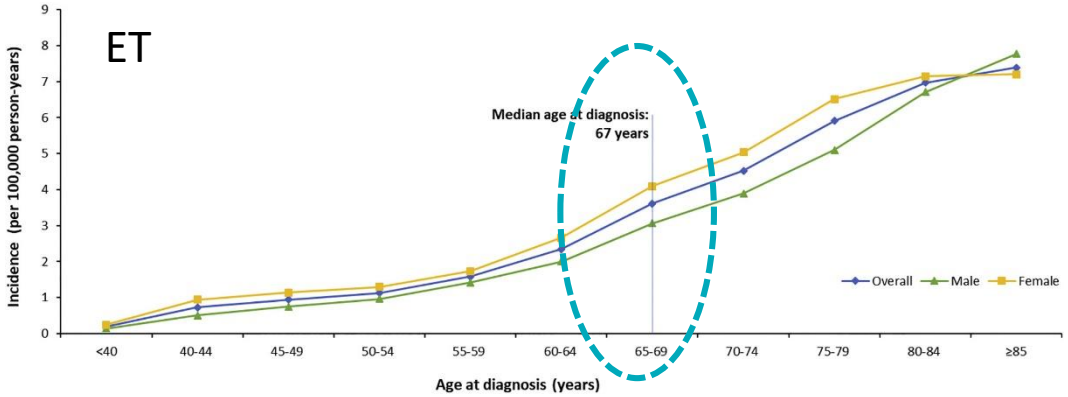
Pontus Lundberg,[1] Axel Karow,[1] Ronny Nienhold,[1] Renate Looser,[1] Hui Hao-Shen,[1] Ina Nissen,[2] Sabine Girsberger,[3] Thomas Lehmann,[3] Jakob Passweg,[3] Martin Stern,[1,3] Christian Beisel,[2] Robert Kralovics,[4,5] and Radek C. Skoda[1,3]

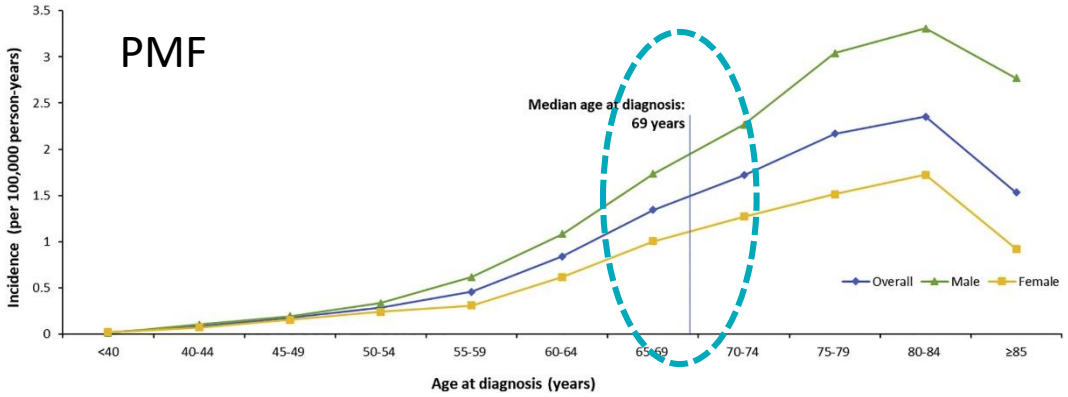
[1]Experimental Hematology, Department of Biomedicine, University Hospital of Basel, Basel, Switzerland; [2]Department of Biosystems Science and Engineering, Swiss Federal Institute of Technology, Zurich, Switzerland; [3]Division of Hematology, University Hospital Basel, Basel, Switzerland; [4]CeMM Research Center for Molecular Medicine, Austrian Academy of Sciences, Vienna, Austria; and [5]Division of Hematology and Blood Coagulation, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria



Âge moyenne







Shallis, Wang, Davidoff et al. Blood Rev. 2020 Jul;42:100706.

JEM

J. Exp. Med. 2014 Vol. 211 No. 11 2213-2230

Article

Myeloproliferative neoplasms can be initiated from a single hematopoietic stem cell expressing *JAK2*-V617F

Pontus Lundberg,[1] Hitoshi Takizawa,[2] Lucia Kubovcakova,[1] Guoji Guo,[3] Hui Hao-Shen,[1] Stephan Dirnhofer,[4] Stuart H. Orkin,[3] Markus G. Manz,[2] and Radek C. Skoda[1]

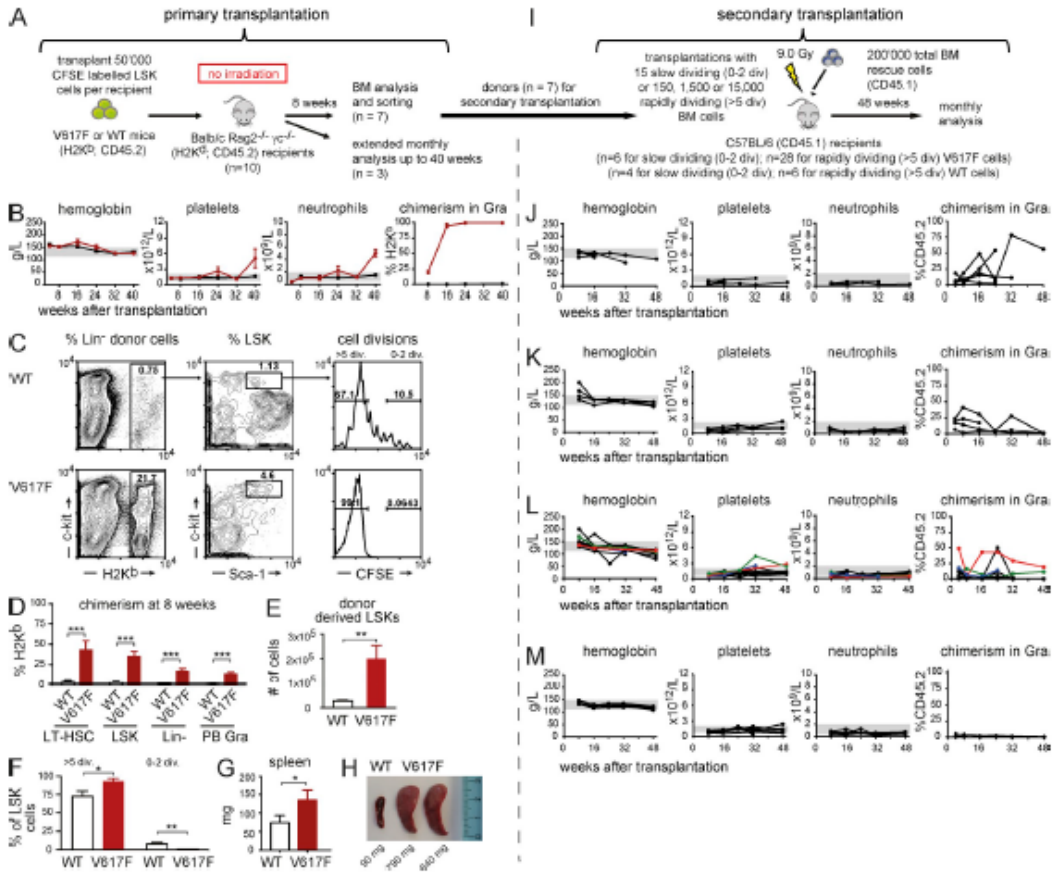


Figure 2. Analysis of cell cycling of BM progenitor cells transplanted into nonconditioned immune-compromised BALB/c Rag2−/− γc−/−

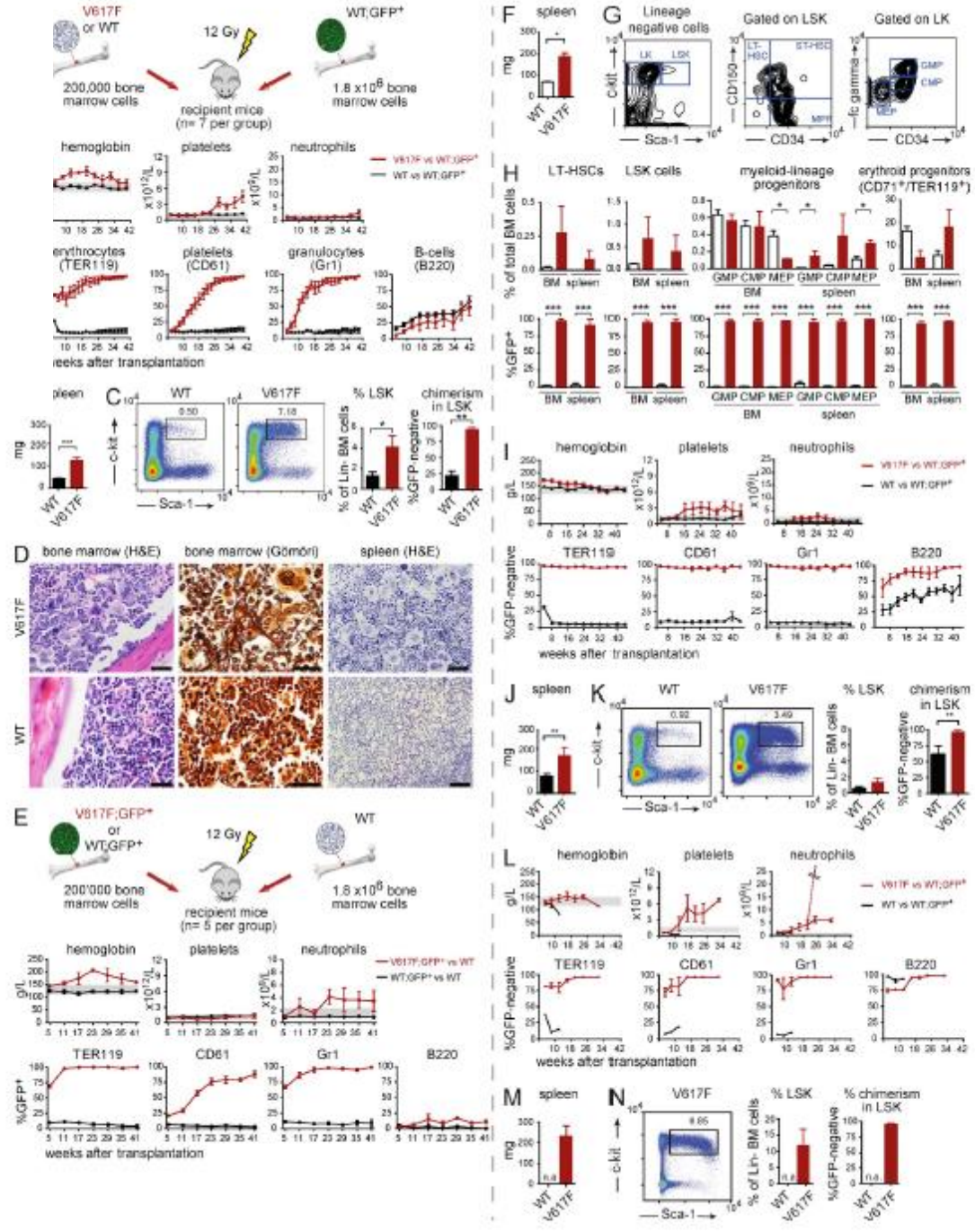


Figure 1. Competitive transplantations with *JAK2*-V617F (V617F) and WT BM cells. (A–D) Transplantation experiments in which GFP is expressed

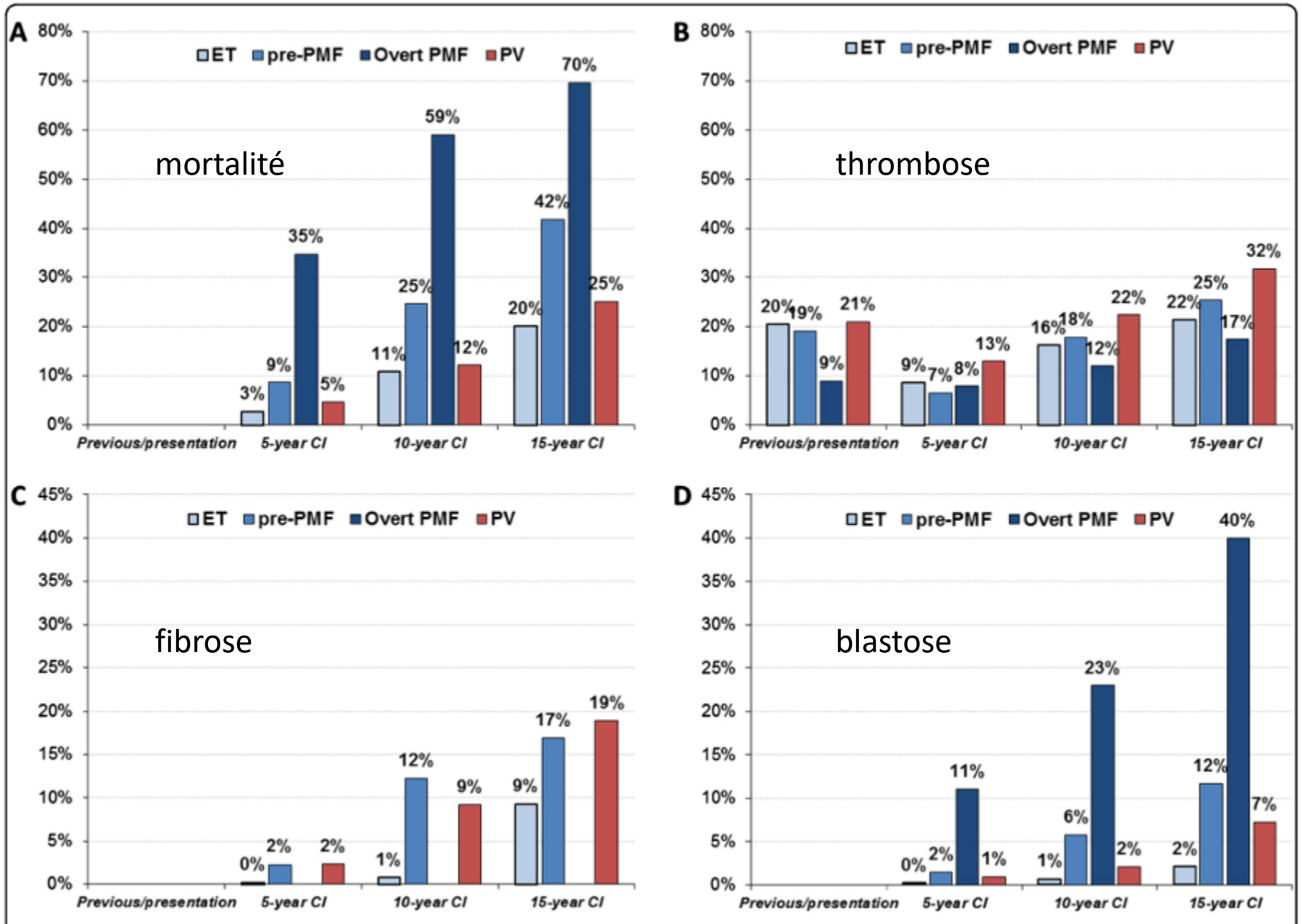


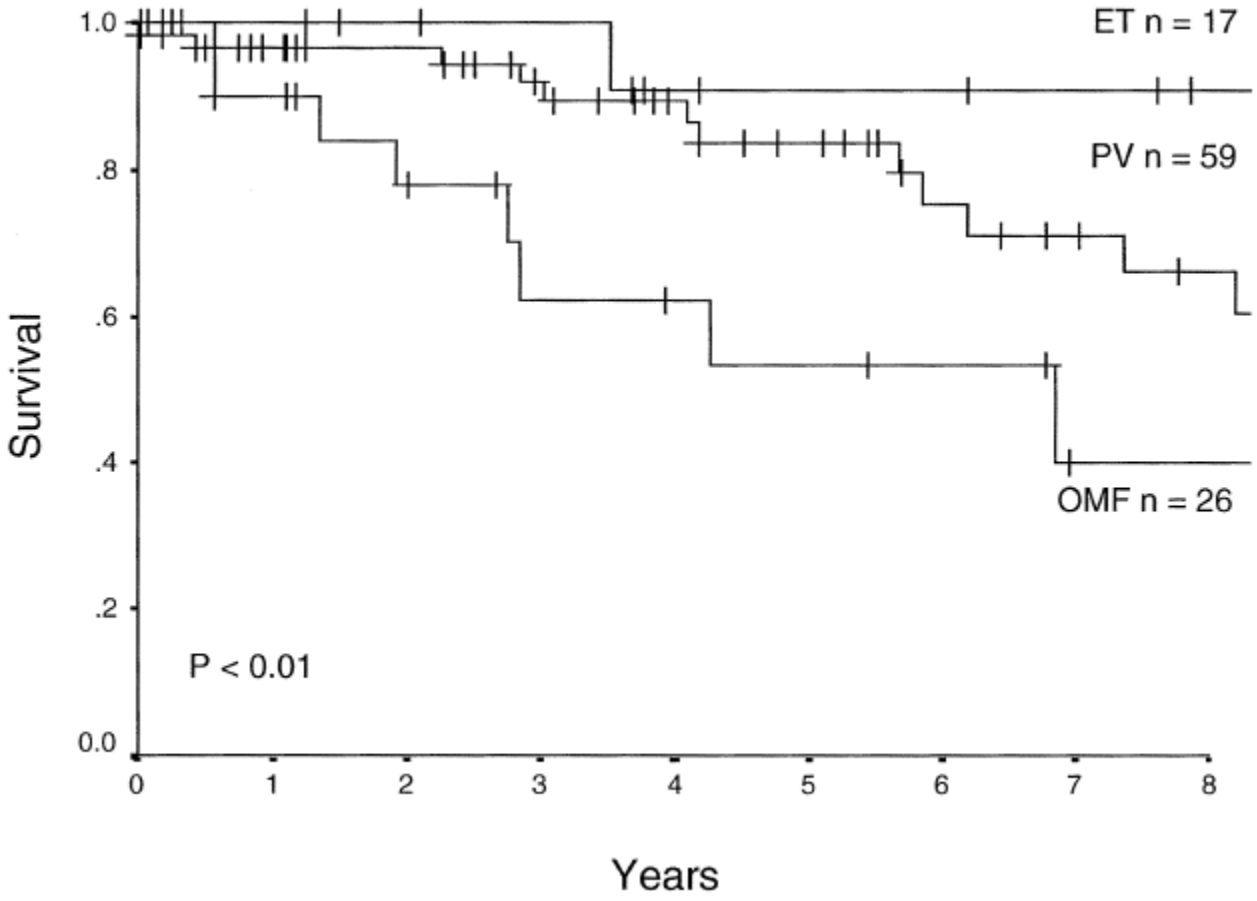
Fig. 1 Mortality **a**, major arterial and venous thrombotic complications **b**, myelofibrosis **c**, and Blast transformation **d** in ET, Pre-PMF, overt PMF and PV cohorts. Prevalence of previous events and cumulative incidence (CI) during follow-up calculated at 5, 10, and 15 years from diagnosis. For PMF, two different data sets were considered: $n = 707$ for panel **a**, **b**[18] and $n = 383$ for panel **d**[14] and regarding PV for all panels[110]

Ann Hematol (2000) 79:312–318

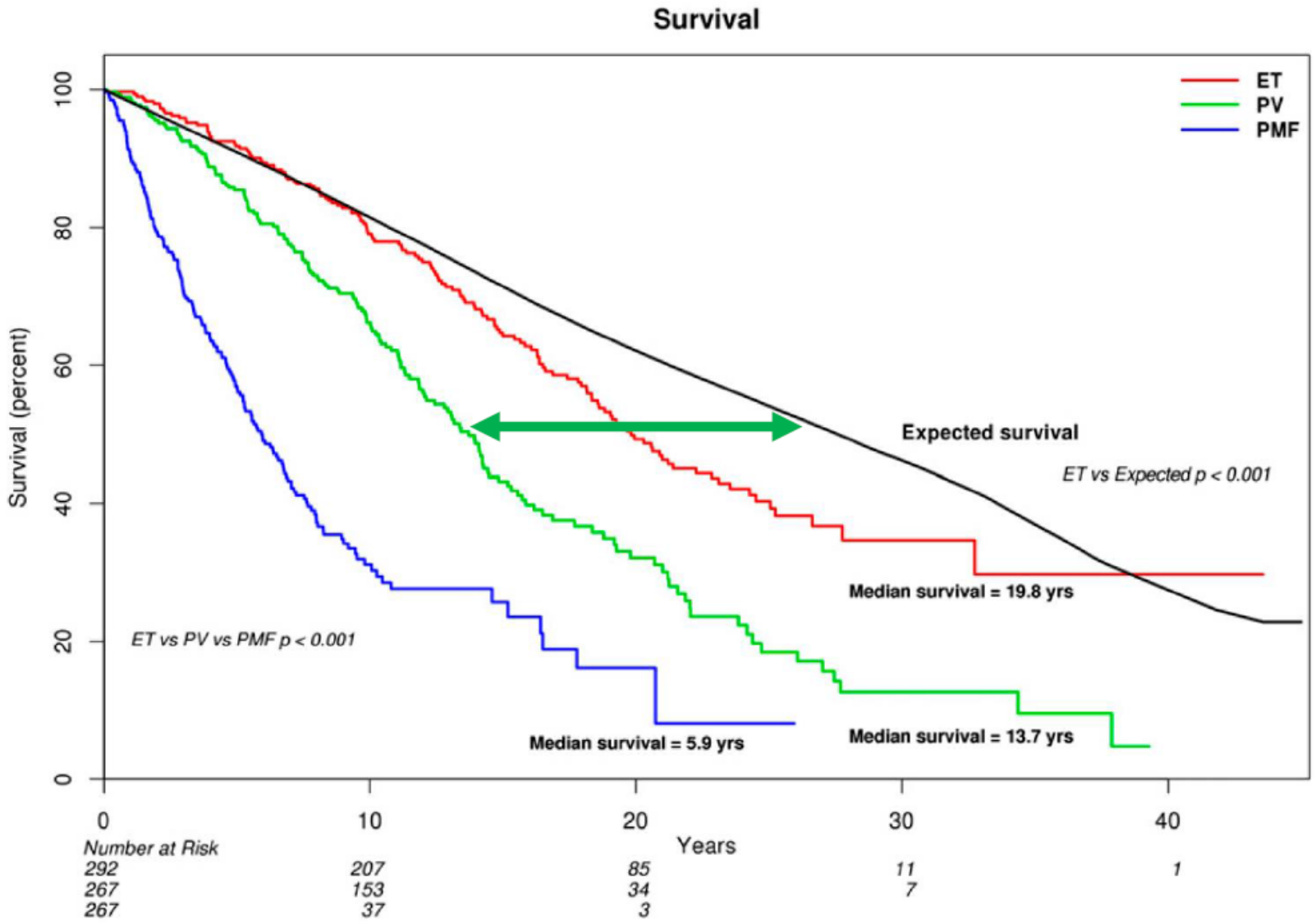
ORIGINAL ARTICLE

S. Brodmann · J.R. Passweg · A. Gratwohl
A. Tichelli · R.C. Skoda

Myeloproliferative disorders: complications, survival and causes of death



Survie Patients avec SMP comparé au standard pour l'âge

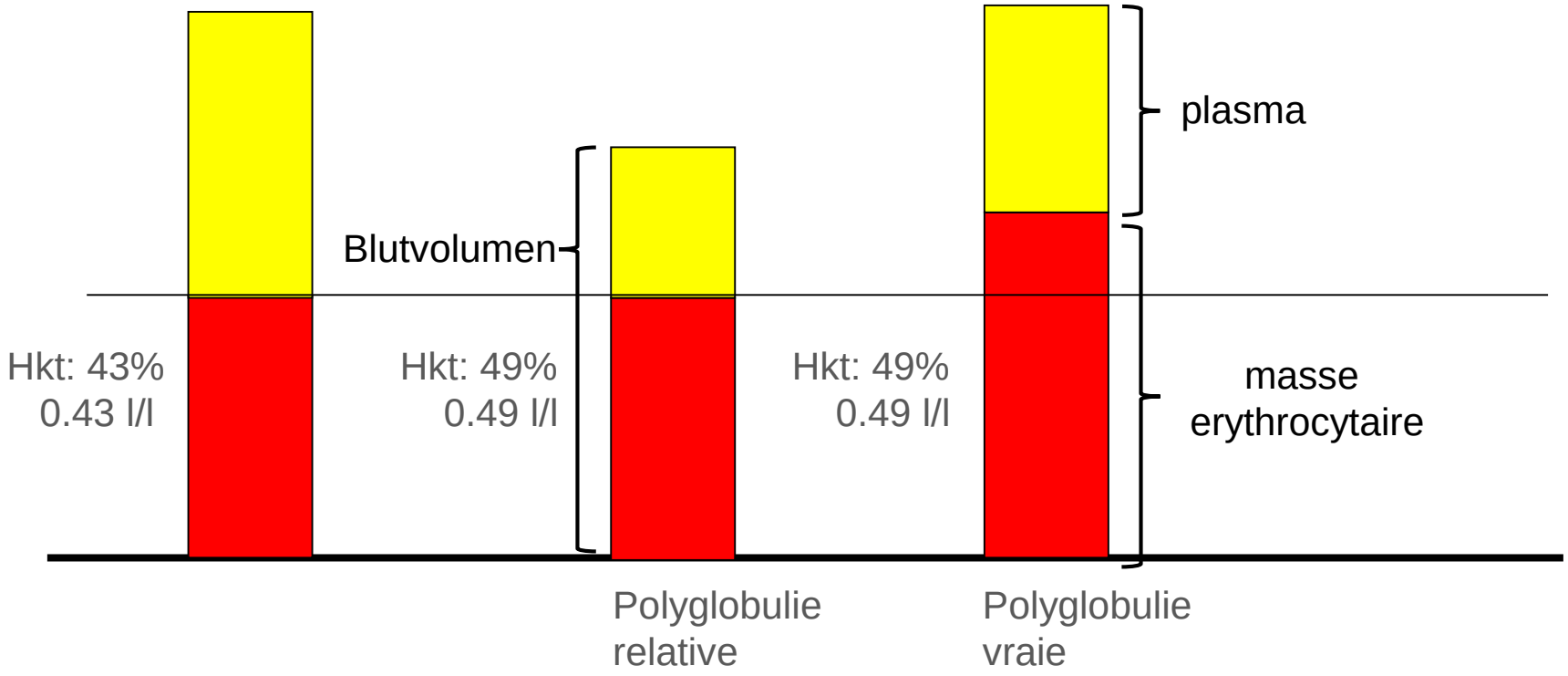


n=826pts

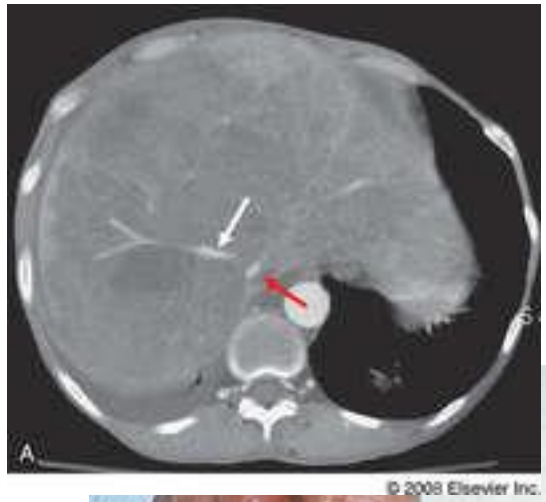
Tefferi et al., Blood 2014;124:2507-13.

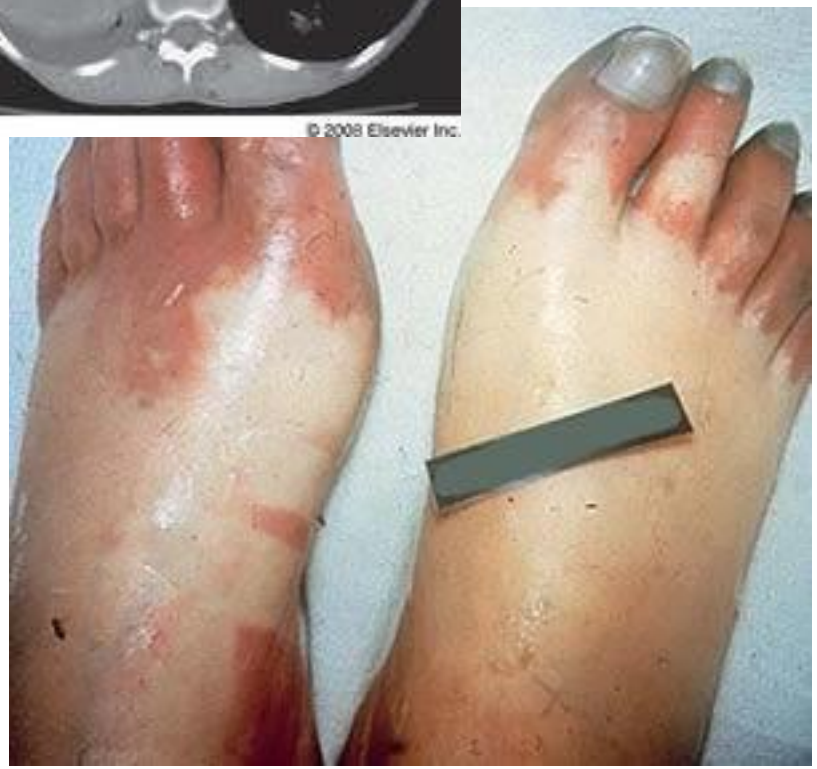
Investiguer quand?

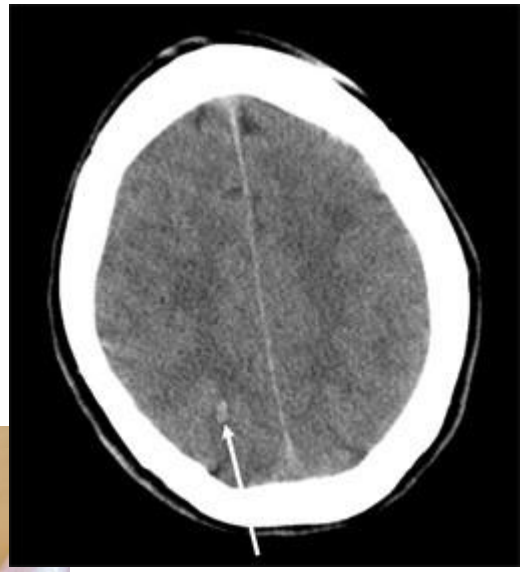
Wert	Werte	Referenz	Einheit
Hämatokrit	49	36 - 46	%
Hämoglobin	172	120 - 160	g/l
RBC	4.5	4.0 - 5.2	x 10^{12}/l



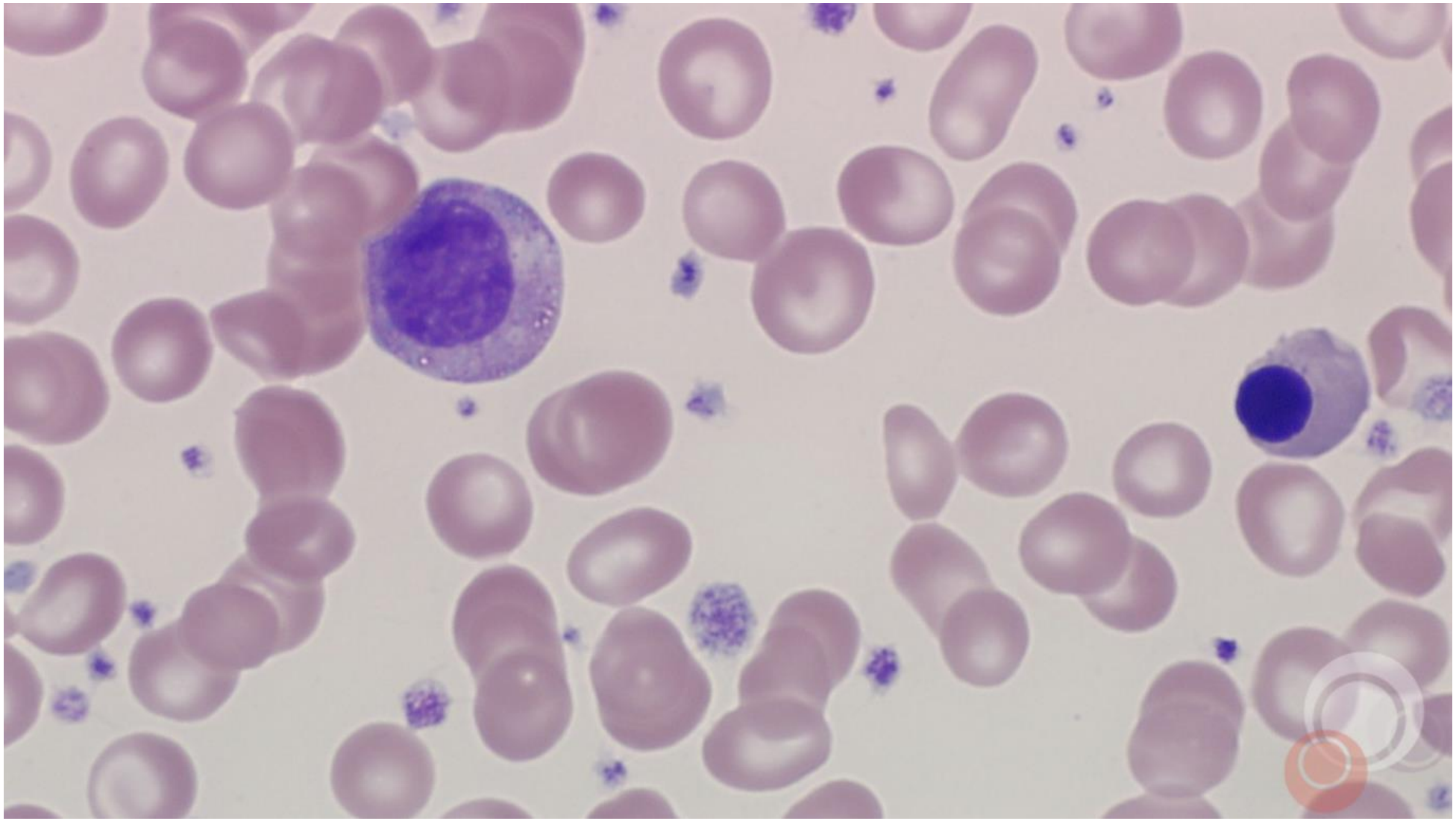
Raynaud
Erythromelalgie
Cyanose, necrose acrale
Thromboembolie atypique
Budd Chiari
Thrombose veine porte
Thrombose veine sinusale







FS leukoerythroblastaire



Polycythaemia vera

The diagnosis of polycythaemia vera requires either all 3 major criteria or the first 2 major criteria plus the minor criterion.

Major criteria

1. Elevated haemoglobin concentration (> 16.5 g/dL in men; > 16.0 g/dL in women) or elevated haematocrit (>49%[a] in men; >48% in women)
2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)[b]
3. Presence of *JAK2* V617F or *JAK2* exon 12 mutation

Minor criterion

Subnormal serum erythropoietin level.

---

[a] Haematocrit for diagnosis in the absence of a *JAK2* mutation. A higher haematocrit target could be considered (e.g., 0.52) in men before further investigation may be required.

[b] Major criterion 2 (bone marrow biopsy) may not be required in patients with sustained absolute erythrocytosis (haemoglobin concentrations of > 18.5 g/dL in men or > 16.5 g/dL in women or haematocrit values of > 0.555 in men or > 0.495 in women), if major criterion 3 and the minor criterion are present.

The determination of the red cell mass with ^{51}Cr-labeled red cells is not a method for routine clinical use.

Essential thrombocythaemia

The diagnosis of essential thrombocythaemia requires that either all major criteria or the first 3 major criteria plus the minor criterion are met.

Major criteria

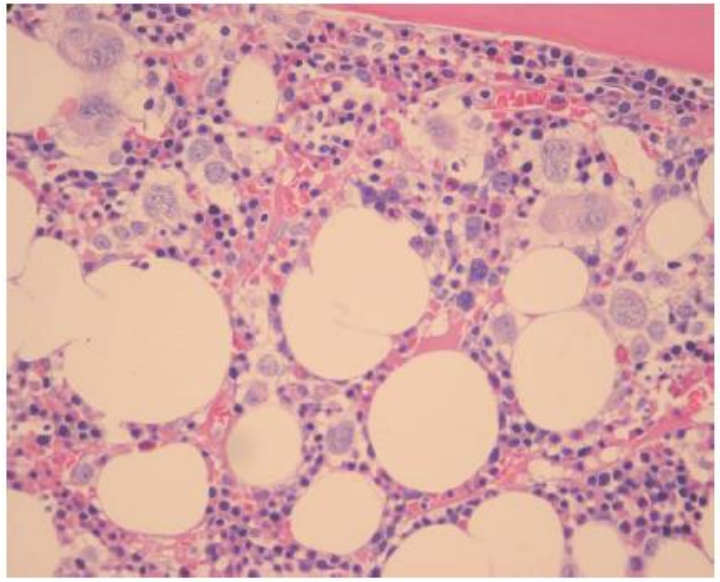
1. Platelet count ≥ 450×10^9/ L
2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; very rarely a minor (grade 1) increase in reticulin fibres
3. WHO criteria for *BCR*::*ABL1*+ CML, polycythaemia vera, primary myelofibrosis, or other myeloid neoplasms are not met
4. *JAK2*, *CALR*, or *MPL* mutation

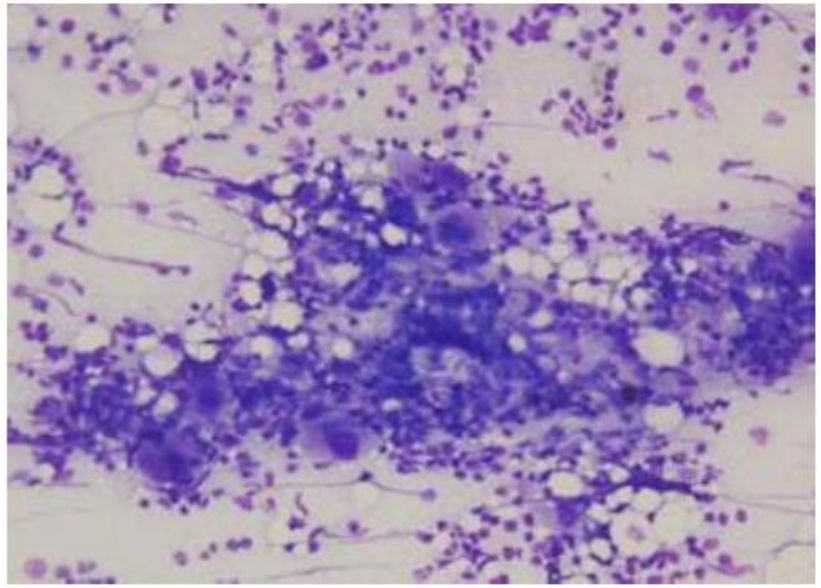
Minor criterion

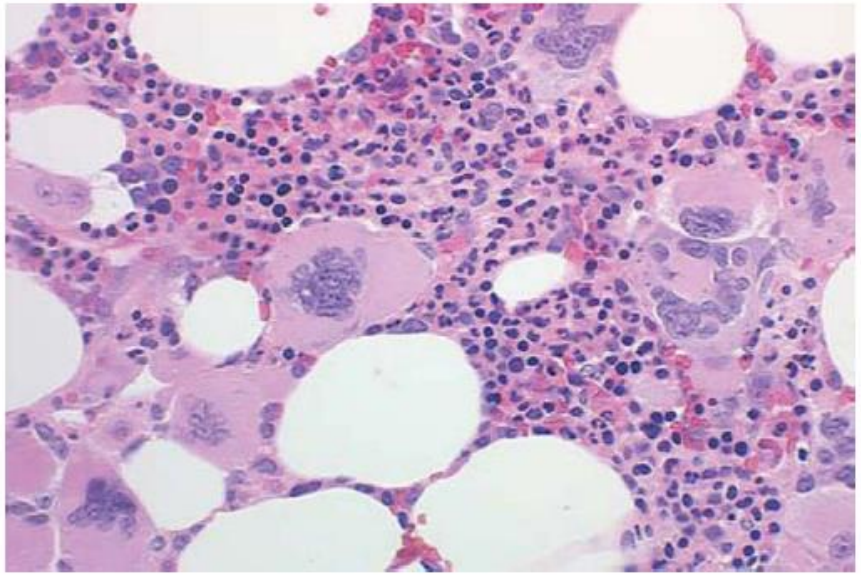
1. Presence of a clonal marker or
2. Exclusion of reactive thrombocytosis

Knochenmark bei essentieller Thrombozytämie (ET)

- Zellgehalt normal bis nur/ leicht ↗
- Megakaryozyten
  - gesteigert
  - in Nestern gelagert
  - Hypersegmentierte Kerne (Polyploidie)







Pre-fibrotic primary myelofibrosis

The diagnosis of pre-fibrotic primary myelofibrosis requires that all 3 major criteria and at least 1 minor criterion are met.

Major criteria

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade > 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
2. WHO criteria for *BCR*::*ABL1*+ CML, polycythaemia vera, essential thrombocythaemia, myelodysplastic syndromes, or other myeloid neoplasms are not met
3. JAK2, CALR, or MPL mutation OR
   Presence of another clonal marker OR
   Absence of minor reactive bone marrow reticulin fibrosis

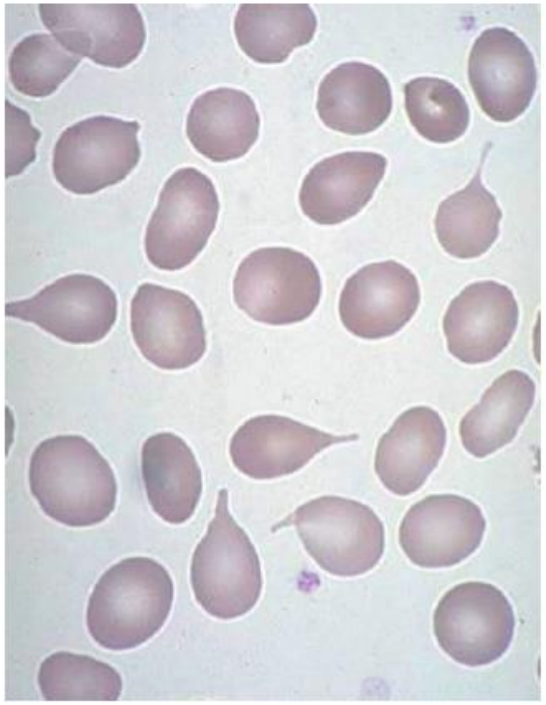
Minor criteria

Presence of at least one of the following, confirmed in 2 consecutive determinations:

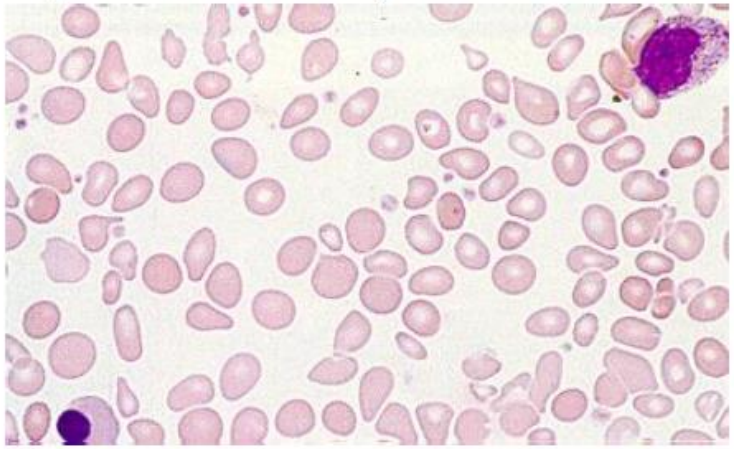
- Anaemia not attributed to a comorbid condition
- Leukocytosis $\geq 11 \times 10^9$/ L
- Splenomegaly detected clinically and/or by imaging
- Lactate dehydrogenase level above the upper limit of the institutional reference range
- Leukoerythroblastosis

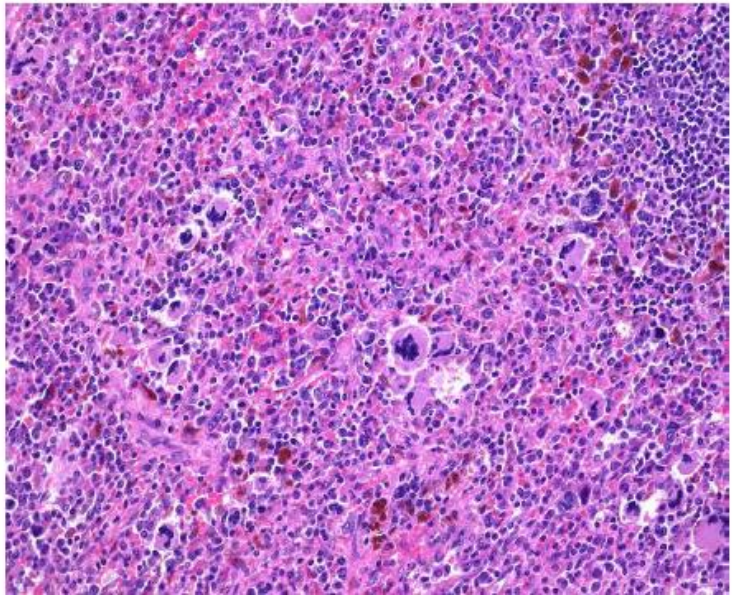
Morphologische Argumente für eine primäre Myelofibrose (PMF)

Tränenformen

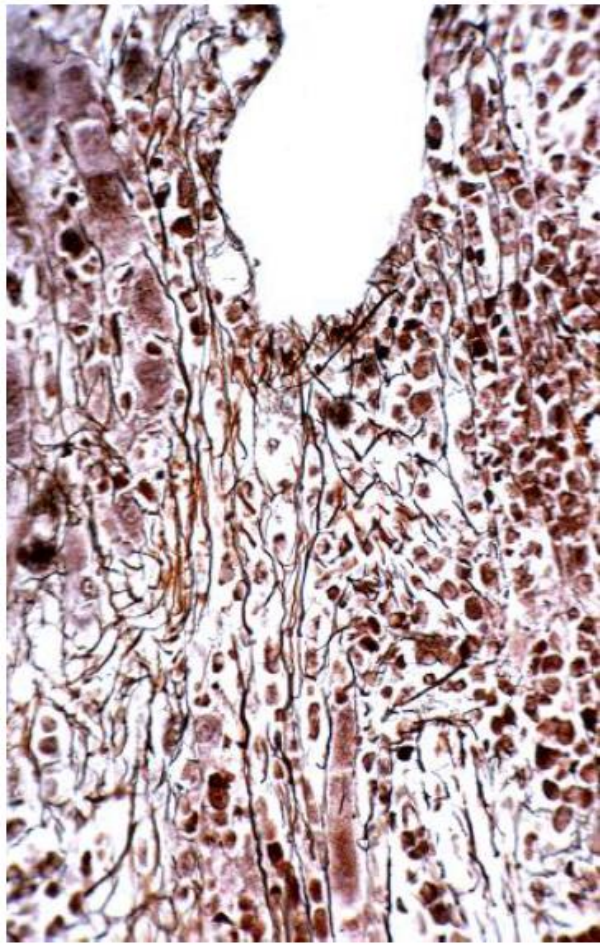


Leuko-erythroblastäres Blutbild:
Erythroblasten + myeloische Vorstufen





Hyperzelluläres Knochenmark



Knochenmark-Fibrose

Overt primary myelofibrosis

The diagnosis of overt primary myelofibrosis requires that all 3 major criteria and at least 1 minor criterion are met.

Major criteria

1. Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grades 2 or 3
2. WHO criteria for essential thrombocythaemia, polycythaemia vera, *BCR*::*ABL1*+ CML, myelodysplastic syndrome, or other myeloid neoplasms are not met
3. JAK2, CALR, or MPL mutation OR
   Presence of another clonal marker OR
   Absence of reactive myelofibrosis

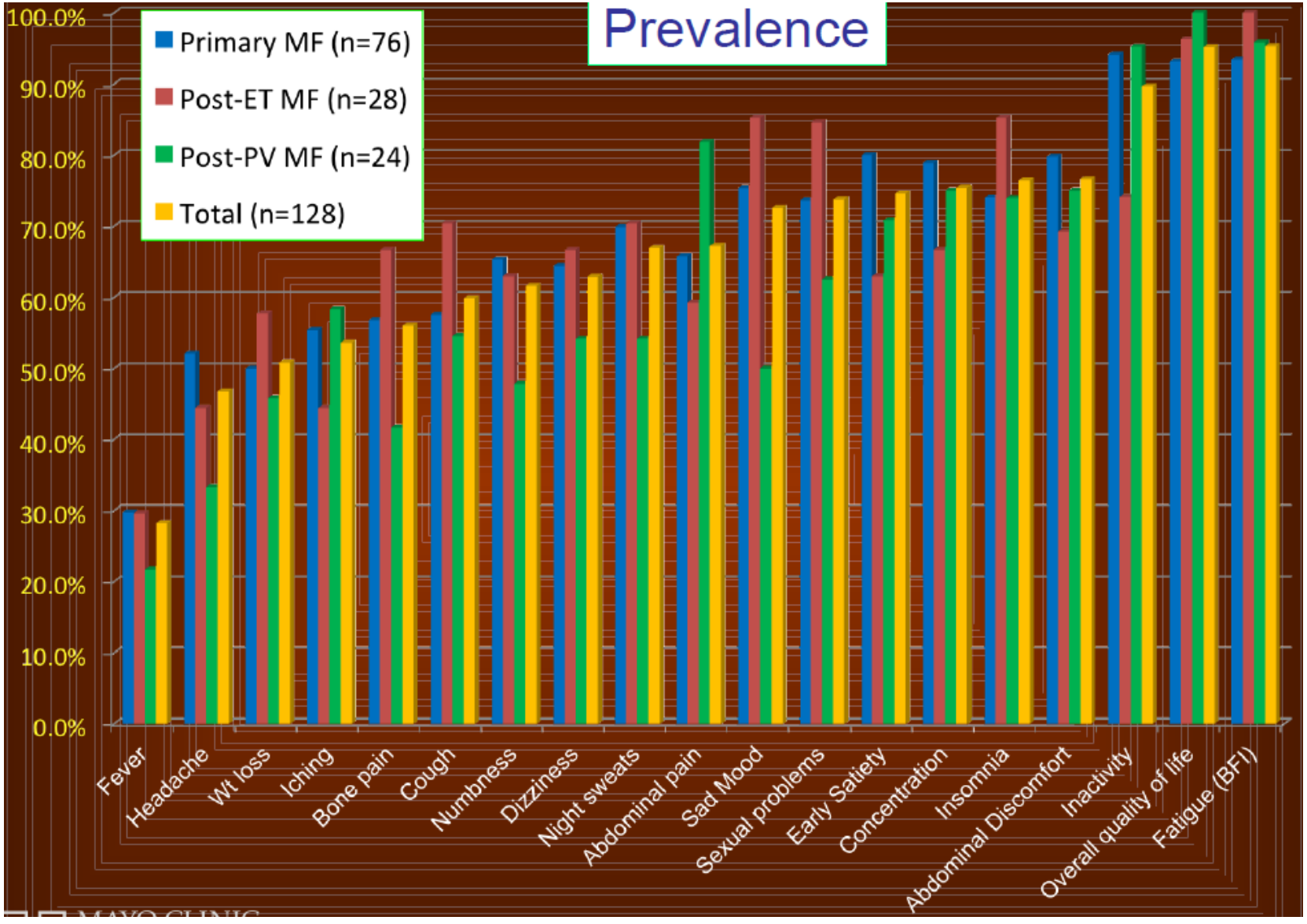
Minor criteria

Presence of at least one of the following, confirmed in 2 consecutive determinations:

- Anaemia not attributed to a comorbid condition
- Leukocytosis $\geq 11 \times 10^9$/L
- Splenomegaly detected clinically and/or by imaging
- Lactate dehydrogenase level above the upper limit of the institutional reference range
- Leukoerythroblastosis

Symptomes Myelofibrose

phase hypercellulaire, phase hypocellulaire tardive

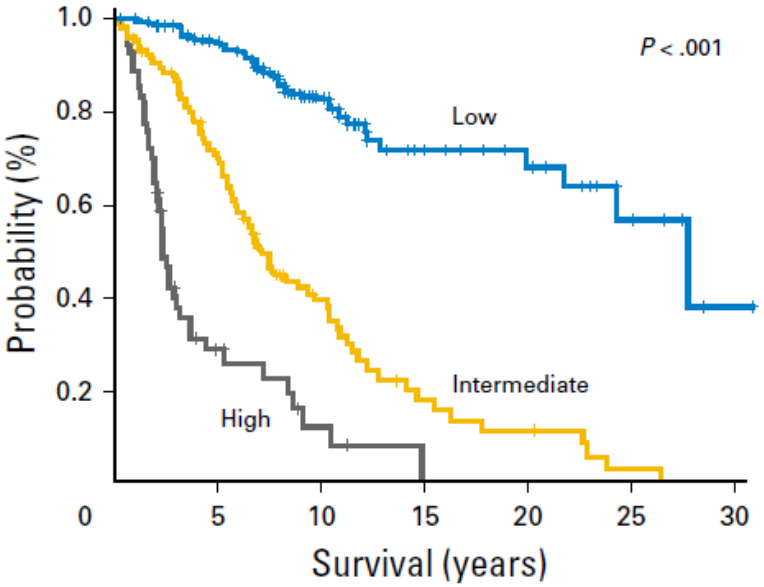


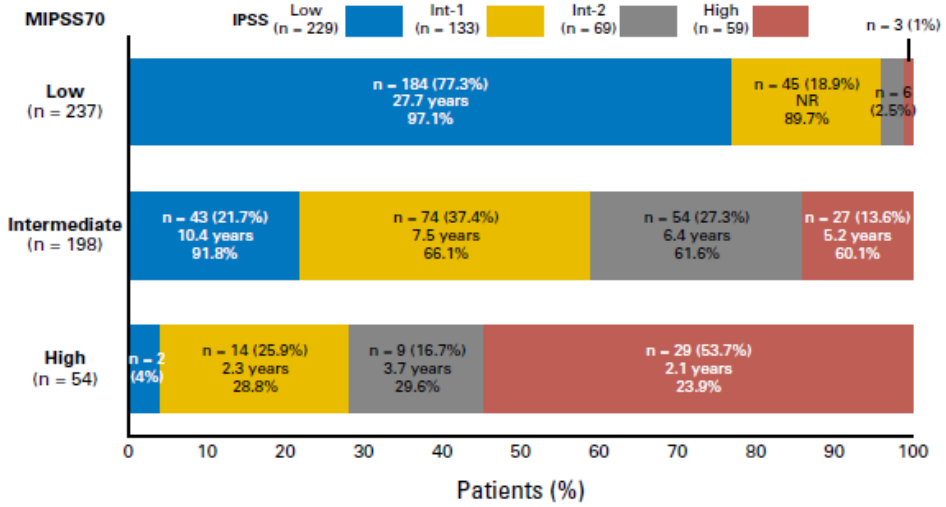
MIPSS70: a three - category prognostic model

Table 3. OS by MIPSS70 and MIPSS70-Plus Prognostic Scores in Training and Validation Cohorts

	Training Cohort				Validation Cohort			
Category (score range)	No. (%) of Patients	Median (range) OS (years)	HR (95% CI)	*P*	No. (%) of Patients	Median (range) OS (years)	HR (95% CI)	*P*
MIPSS70	Italian cohort				Mayo cohort			
Low (0-1)	238 (48.6)	27.7 (21.7-33.7)	1.00		27 (12.8)	Not reached	1.00	
Intermediate (2-4)	198 (40.4)	7.1 (6.2-8.1)	5.5 (3.8 to 8.0)	< .001	105 (49.8)	6.3 (0.1-23.5)	4.4 (1.8 to 11.1)	< .001
High (≥ 5)	54 (11.0)	2.3 (1.9-2.7)	16.0 (10.2 to 25.1)	< .001	79 (37.4)	3.1 (0.05-14.6)	9.9 (3.9 to 24.7)	< .001

#	Question
1	Severe Anemia (hemoglobin <80g/L)
2	Moderate Anemia (hemoglobin 80-100g/L)
3	Leucocytosis >25x10⁹/L
4	Thrombocytopenia (platelet count <100x10⁹/L)
5	Peripheral blood blast count ≥2%
6	Bone marrow fibrosis grade ≥2
7	Constitutional symptoms
8	Absence of CALR type 1/like mutation
9	HMR[1] category
10	≥2 HMR mutated genes
11	Unfavorable karyotype[2]
12	Very High Risk karyotype[3]





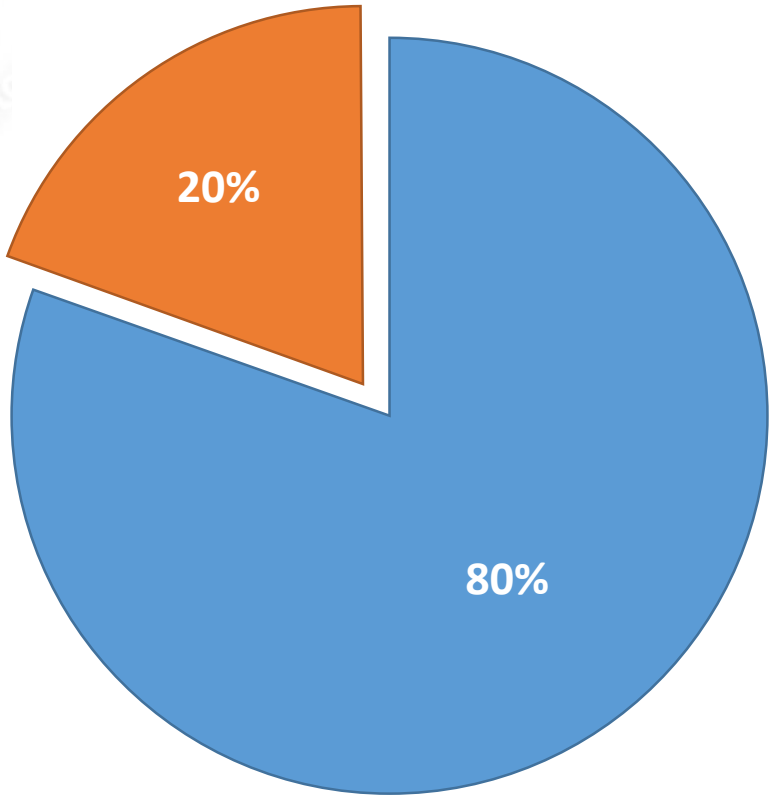
>> allo-HSCT recommended for high risk group

>> close monitoring recommended for intermediate risk group

Guglielmelli P et al, JCO Dec 9 2017

Selon âge les probèmes sont différents

- **Thrombotic risk**
- **Life expectancy**
- **Progression / transformation**
- **Symptoms and QOL**
- **Pregnancy**



- **Thrombotic risk**

Szuber, Vallapureddy, Penna et al. Am J Hematol. 2018 Dec;93(12):1474-1484.

Traitement - ET

- Indications:
  - Risque thromboembolique elevé:
    - Age > 60 st/p thrombose
    - IPSET-Thrombosis (Barbui T et al. Blood 2012;120(26):5126)

Risikofaktor	Punkte
Alter > 60 Jahre	1
Kardiovaskuläre RF	1
Frühere Thrombose	2
JAK2 V617F pos	2

- Tiefes Risiko: Score 0-1
- Mittleres Risiko: Score 2
- Hohes Risiko: Score $\geq$3

Traitement - ET

- Aspirin (100mg/d): tous les patients
  - Exception score 0?
  - Risque hémorrhagique: syndrome von Willebrand acquis (vWS)
- cytoreduction: à partir du risque intermédiaire Risiko (IPSET)
  - Oder Thrombozytose > 1000-1500 G/l (bzw vWS)
  - Standard Hydroxyurea (Litalir)
  - Patients jeunes < 40-50 Jahre évoquer Anagrelide
- Traiter facteurs de risque cardiovasculaire

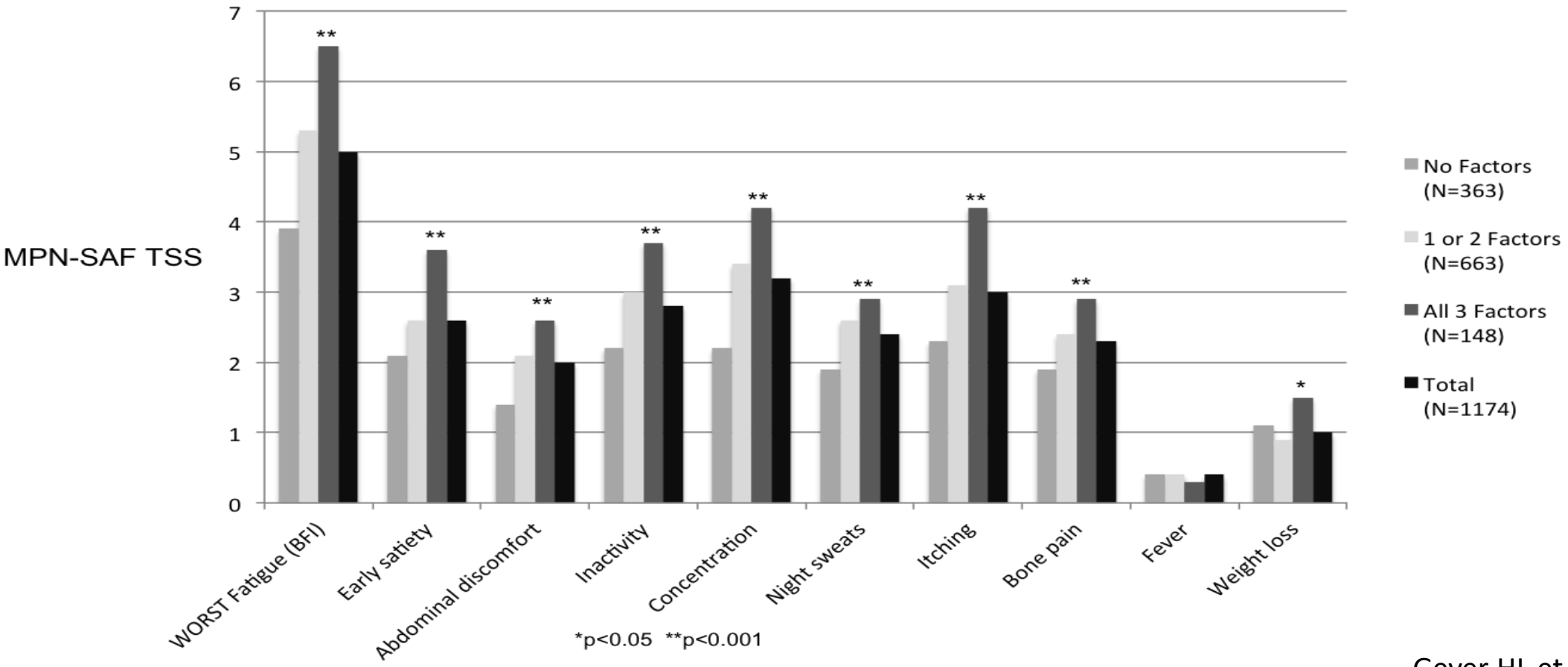
Survie IPSET

Risikofaktor	HR, CI 95%	Score 0	1	2
Alter (Jahre)	6.5, 3.9-10.7	<60		>60
Lc (G/l)	3.1, 2-4.7	<11	Mind 11	
Thrombose in Anamnese	2.9, 1.9-4.5	Nein	Ja	

Tiefes Risiko:	0 Punkte	medianes Überleben: no reached
Mittleres Risiko:	1-2 Punkte	17.5 – 24.5 Jahre
Hohes Risiko:	3-4 Punkte	7.1-14-7 Jahre

PV- symptoms 1344 patients

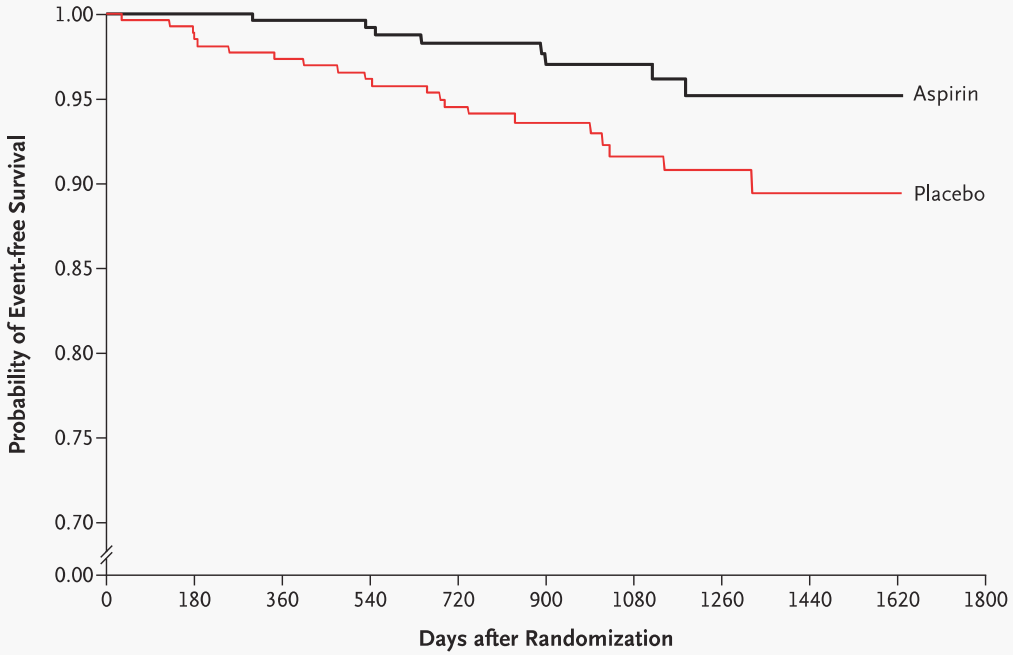
- Symptomes augmentent avec progression: (splenomegalie, phlebotomie, HU-traitement cytoréducteur).



Geyer HL et al. JCO

Traitement - PV

Aspirin (100mg/d): tous les patients



No. at Risk (No. of Events)											
Aspirin	253 (0)	250 (1)	249 (1)	231 (2)	212 (2)	153 (0)	112 (2)	81 (0)	24 (0)	1 (0)	0
Placebo	265 (4)	260 (3)	253 (3)	239 (4)	228 (2)	171 (3)	125 (1)	79 (1)	26 (0)	1 (0)	0

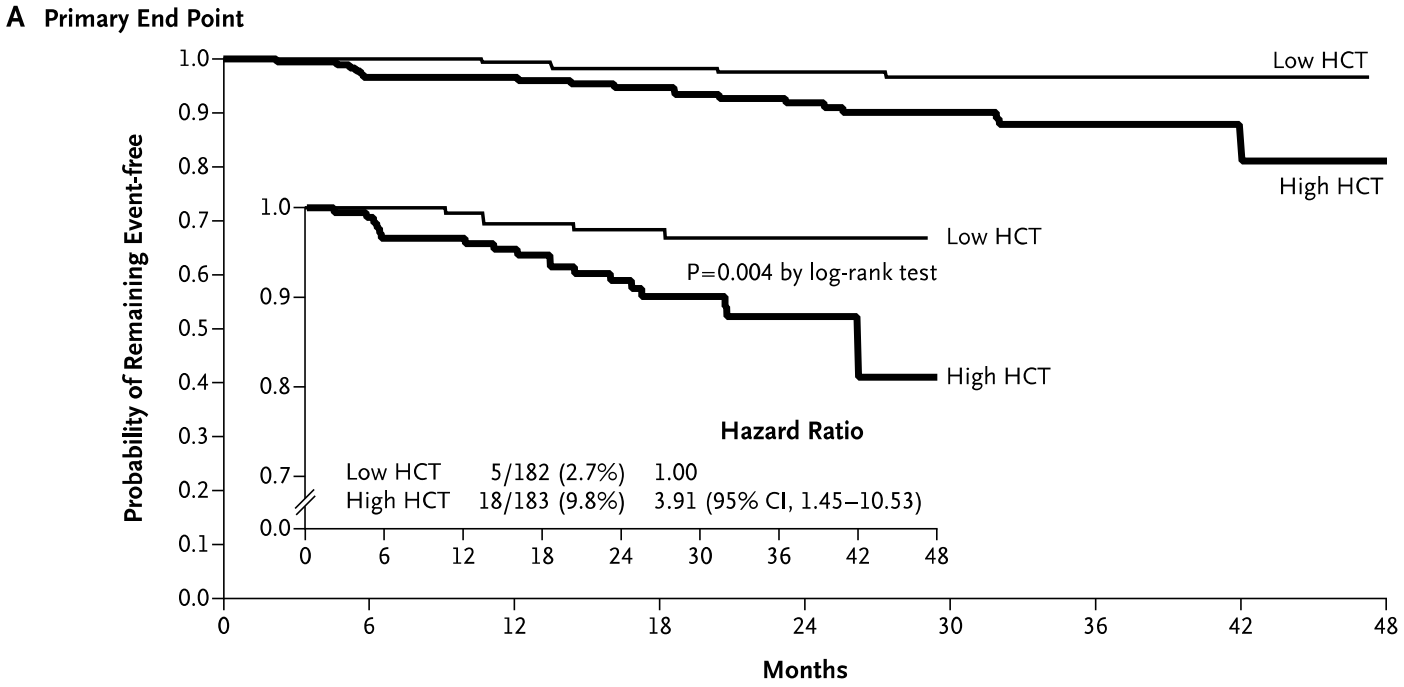
Étude ECLAP:
Risque réduit complications thromboemboliques aspirin

(RR 0.4; 95%, CI 0.18-0.91; p=.03)

Landolfi R et al. NEJM 2004;350(2)

Traitement - PV

Saigné itérative:

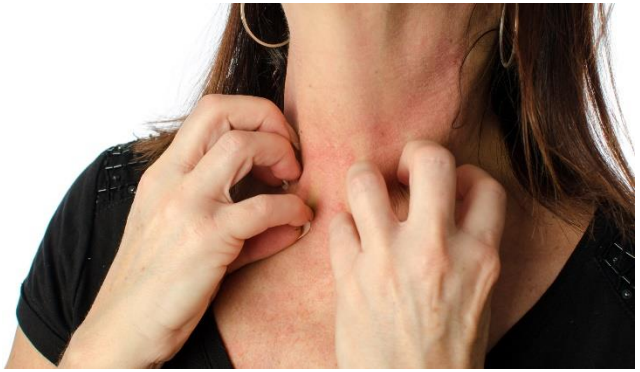


No. at Risk									
Low HCT	182 (0)	177 (1)	168 (2)	154 (1)	129 (1)	95 (0)	62 (0)	18 (0)	0
High HCT	183 (6)	168 (0)	160 (3)	143 (4)	110 (2)	92 (2)	54 (1)	12 (0)	1

But Hct <45%: Compilcations thromboemboliques diminués avec Hct = 50%

[1]Marchioli R et al. N Engl J Med 2013;368:22-33

PV Algorythme



Goals:
Relieve symptoms
Reduce risk for thrombosis/hemorrhage
Prevent/delay transformation

Manage CV risk factors
Low-dose aspirin
Phlebotomy: Hct <45%

Cytoreduction: Assess symptoms and risk

High Risk
Thrombosis hx or
age >60 yr

HU
Interferon
(including ropeg)

Worsening sx, poor
tolerance of PBT,
progressive cytosis

Lower Risk
Age ≤60 yr,
no thrombosis history

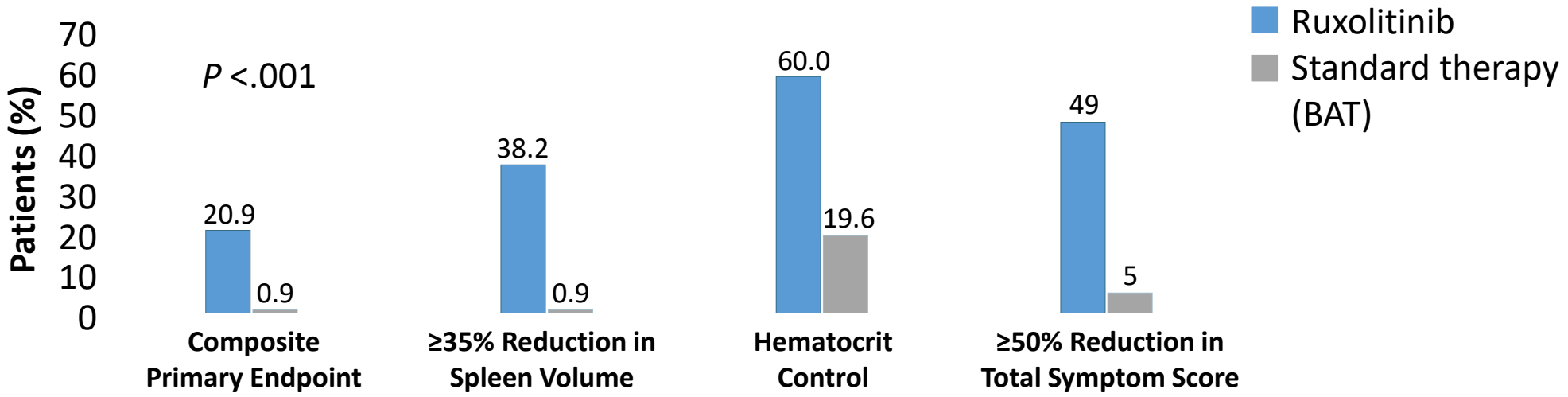
Intolerance or Resistance
Ruxolitinib
HU or IFN (if not previously used)
Busulfan (older patients)
Clinical trial

PV diagnosis per WHO criteria.

Stein. ASH SAP 7th ed.

RESPONSE: Ruxolitinib vs Standard Therapy in Patients With PV and HU Resistance/Intolerance

Wk 32 Data[1]

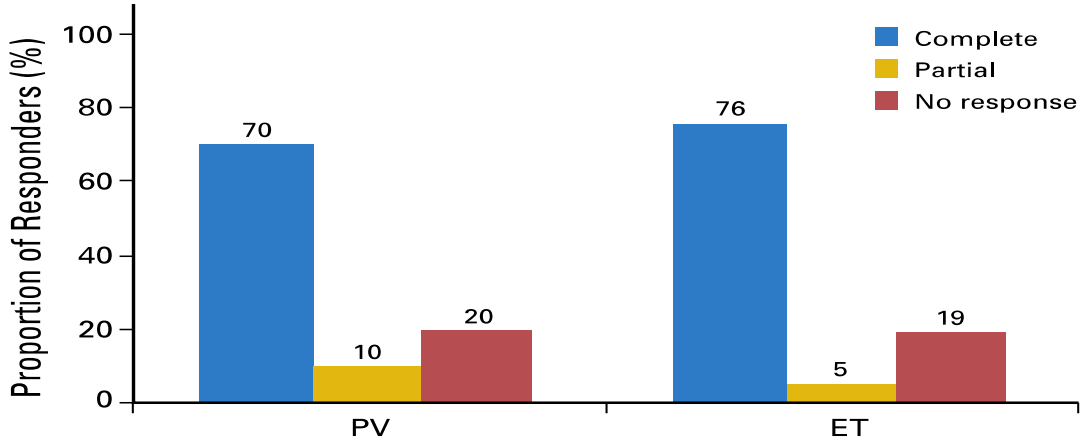


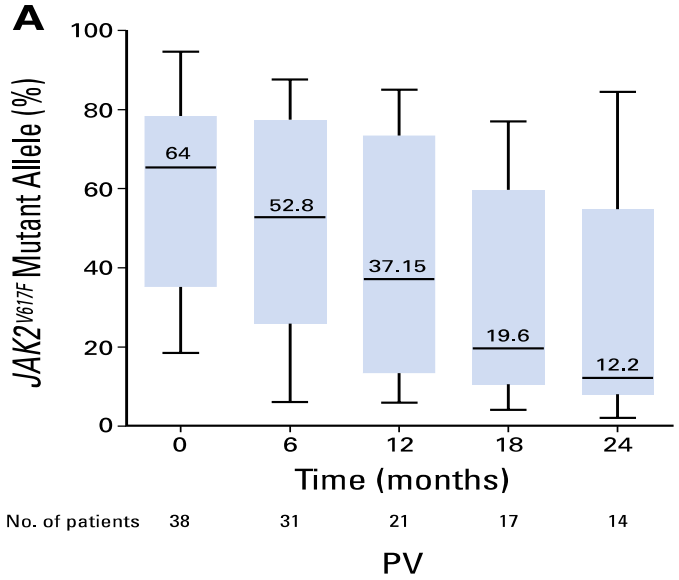
Longer-Term Follow-Up (5-Yr F/u)[2]	Of Interest (5-Yr F/u)[2]	AEs (5-Yr F/u)[2]
▪ 66% Rux-randomized completed therapy ▪ 65% Rux-crossover patients completed therapy	▪ Thrombosis, Rux-randomized and Rux-crossover vs BAT (100 patient-yr): 1.2 and 2.7 vs 8.2	▪ Rux vs BAT (100 patient-yr) • Anemia and TCP, rux: ~9% and 4% • Skin CA: 5.1 vs 2.7 ▪ ↑ Weight, rux: 4% to 6%, zoster: ~5%
Probability of maintaining overall clinicohematologic response: 67% Probability of maintaining CHR: 55%	MF transformation, Rux-randomized and Rux-crossover vs BAT: 2.1 and 1.8 vs 1.4	
▪ ~38% reduction in JAK2%	▪ AML, Rux-randomized and Rux-crossover vs BAT: 0.2 and 0.6 vs 0.0	

1. Vannucchi. NEJM. 2015;372:426. 2. Kiladjian. Lancet Haematol. 2020;7:e226.

Traitement - PV

- peg Interferon alfa-2a
  - Réponse hématologique 80% (70% CR)[2]
  - Réponse moléculaire 54% (CR 14%)[2]
  - 90ug/sem, bonne tolérance





1Kiladjian JJ et al. Blood 2006 Sep 15;108(6):2037-40
[2]Quintás-Cardama A et al. J Clin Oncol. 2009;27(32):5418- 5424.

Traitement - PV

- Ropeginterferon alfa-2b (51 PV Patienten)
  - T1/2- longue Injection tous les 2 sem
  - Réponse hémato 90% (CR 47%)
  - Réponse moléculaire 68% (CR 21%)
  - Absence de correlation entre dose et réponse

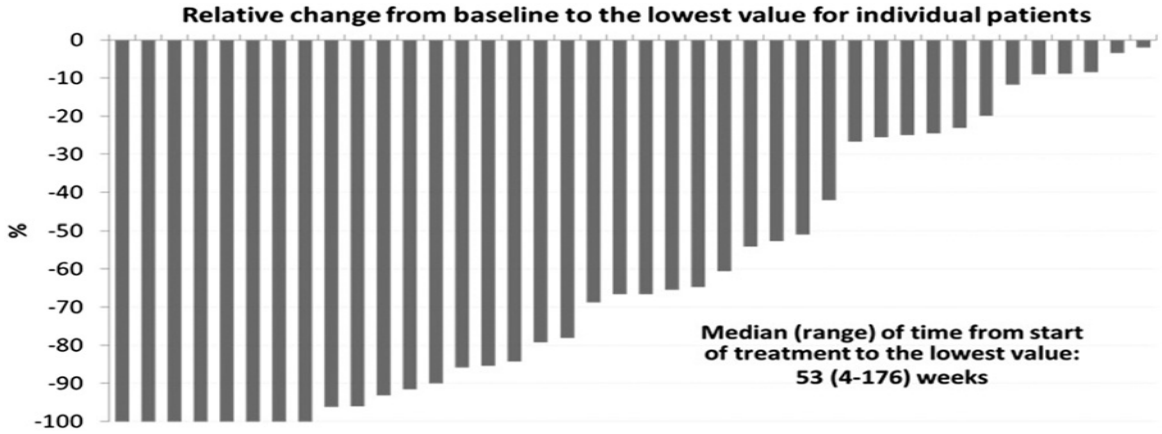


Figure 4. *JAK2* allelic burden for each patient (baseline allelic burden ≥20%), comparing the best individual response with baseline.

Gisslinger H. Blood. 2015 Oct 8;126(15):1762-9

A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia

John Mascarenhas,[1] Heidi E. Kosiorek,[2] Josef T. Prchal,[3] Alessandro Rambaldi,[4] Dmitriy Berenzon,[5] Abdulraheem Yacoub,[6] Claire N. Harrison,[7] Mary Frances McMullin,[8] Alessandro M. Vannucchi,[9] Joanne Ewing,[10] Casey L. O'Connell,[11] Jean-Jacques Kiladjian,[12] Adam J. Mead,[13] Elliott F. Winton,[14] David S. Leibowitz,[15] Valerio De Stefano,[16] Murat O. Arcasoy,[17] Craig M. Kessler,[18] Rosalind Catchatourian,[19] Damiano Rondelli,[20] Richard T. Silver,[21] Andrea Bacigalupo,[16] Arnon Nagler,[22] Marina Kremyanskaya,[1] Max F. Levine,[23] Juan E. Arango Ossa,[23] Erin McGovern,[23] Lonette Sandy,[1] Mohamad E. Salama,[24] Vesna Najfeld,[1] Joseph Tripodi,[1] Noushin Farnoud,[23] Alexander V. Penson,[23] Rona Singer Weinberg,[25] Leah Price,[26] Judith D. Goldberg,[26,27] Tiziano Barbui,[28] Roberto Marchioli,[29] Gianni Tognoni,[30] Raajit K. Rampal,[31] Ruben A. Mesa,[32] Amylou C. Dueck,[2] and Ronald Hoffman[1]

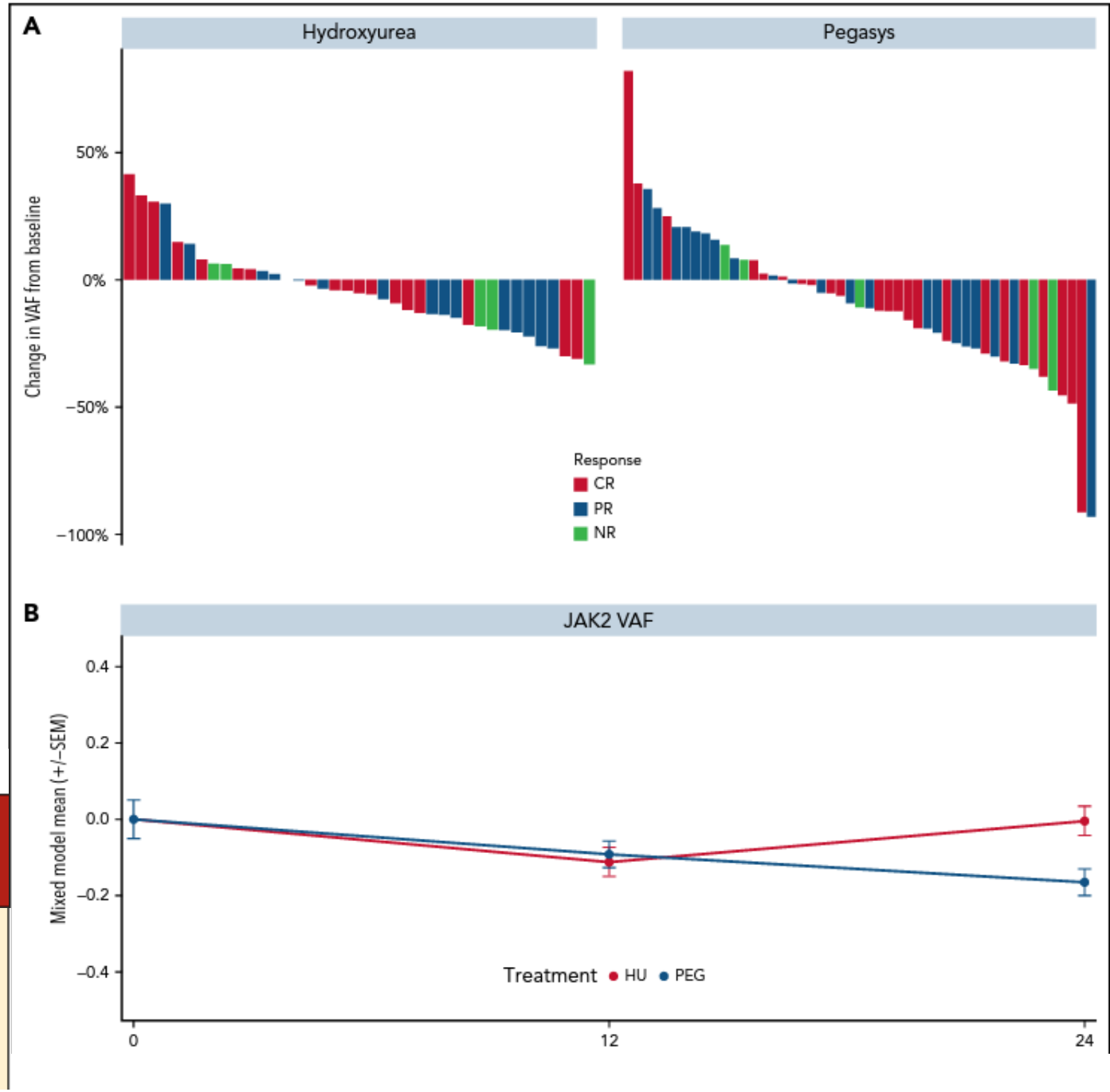
blood® 12 MAY 2022 | VOLUME 139, NUMBER 19 2931

KEY POINTS

- **Rates of thrombosis and progression were low in patients with ET/PV treated with either HU or IFN in this randomized study.**
- **PEG was more effective in normalizing counts and reducing *JAK2V617F* VAF in PV whereas HU induced more HPRs in ET.**

Table 2. Response by treatment arm

	HU (n = 86), %	PEG (n = 82), %	Difference in proportions for combined ET/PV, 95% CI (PEG – HU)	Rate ratio (95% CI)
36 mo	(n = 30)†	(n = 27)†		
Complete response	5 (17)	9 (33)	17%	2.0
ET	2 (17)	4 (40)	(−8 to 40)	(0.76, 5.23)
PV	3 (17)	5 (29)		
Overall response	14 (47)	16 (59)	13%	1.27
ET	4 (33)	6 (60)	(−15 to 38)	(0.77, 2.08)
PV	10 (56)	10 (59)		



PMF- Therapie: Jakavi

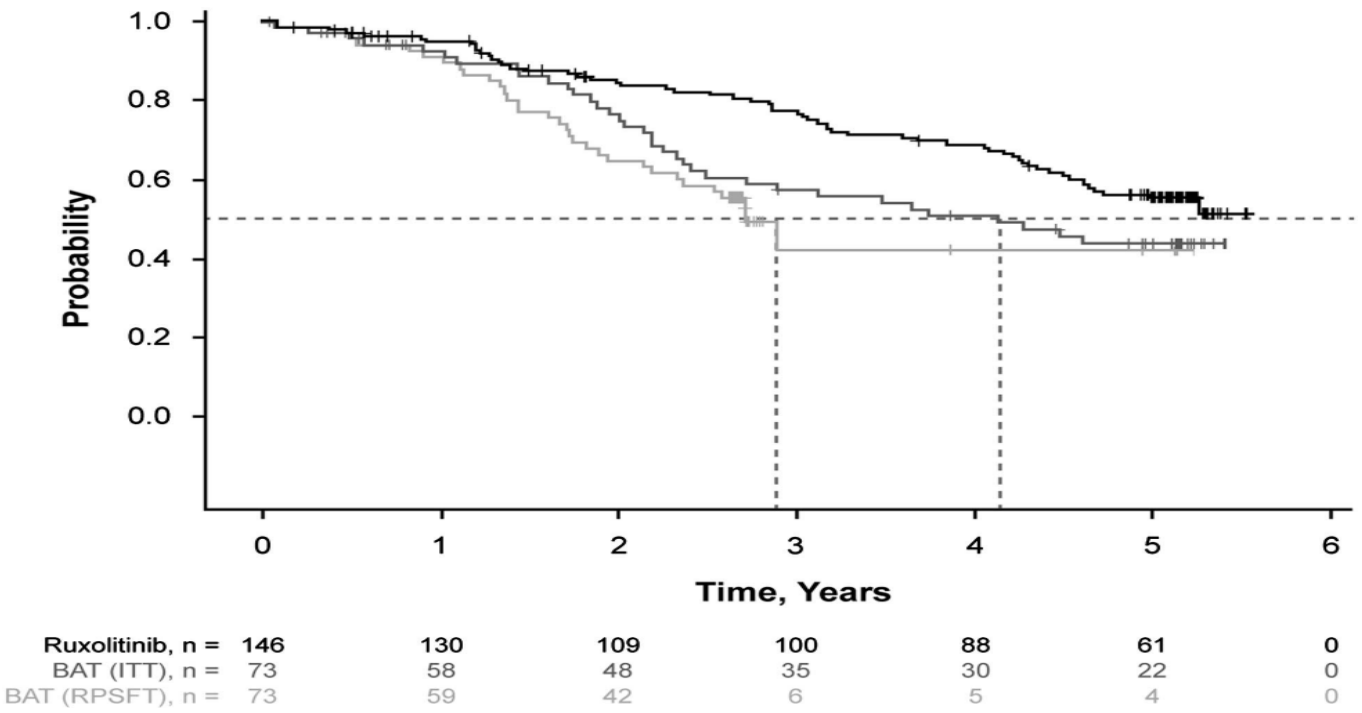
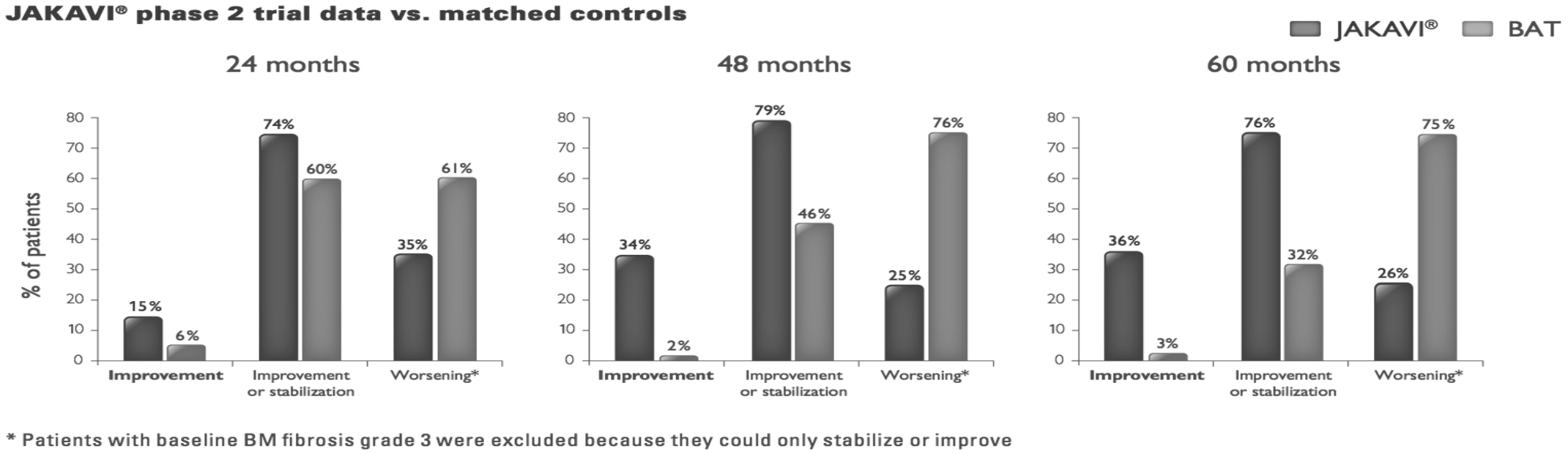


Figure 4. Kaplan–Meier analysis of OS by ITT analysis and RPSFT corrected for crossover from the BAT arm.

- Risque mortalité diminué de 42% Ruxolitinib vs BAT après 3.5 ans (ITT-Analyse)

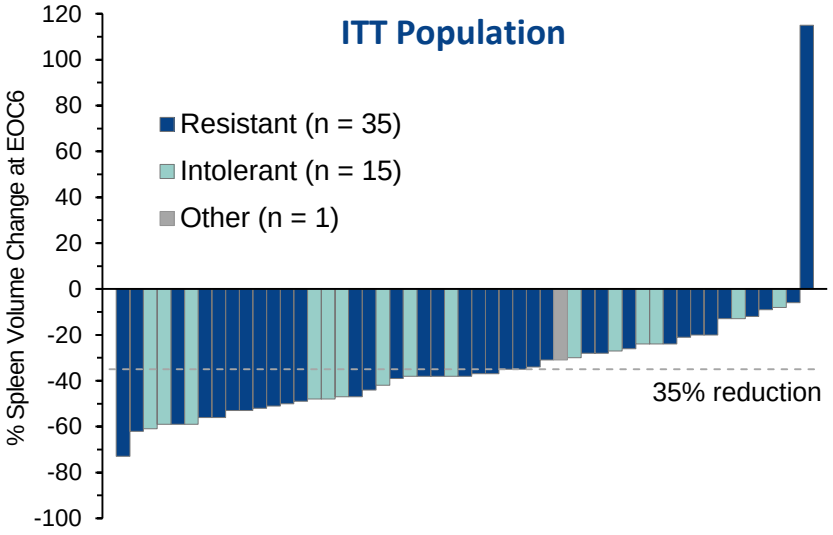
PMF- Therapie: Jakavi

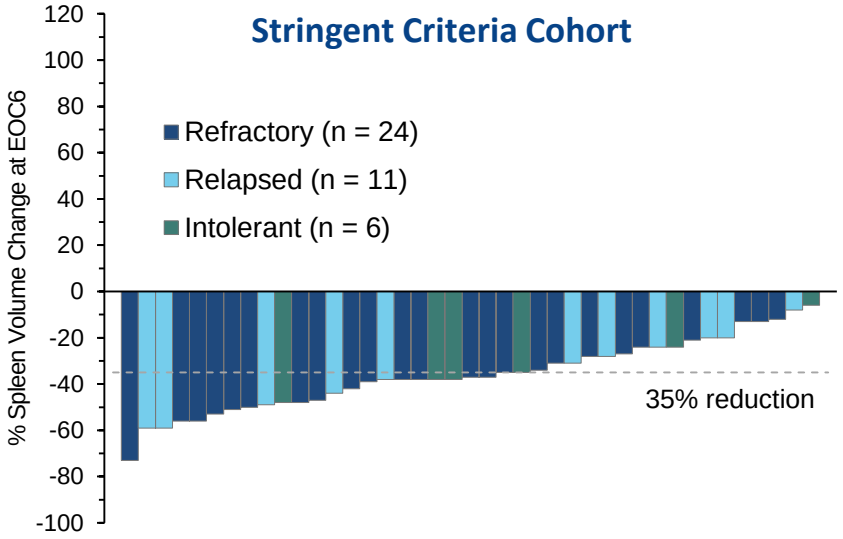


- Effet positif: fibrose, déposition collagène, ostéosclérose

Spleen VOLUME Responses Fedratinib

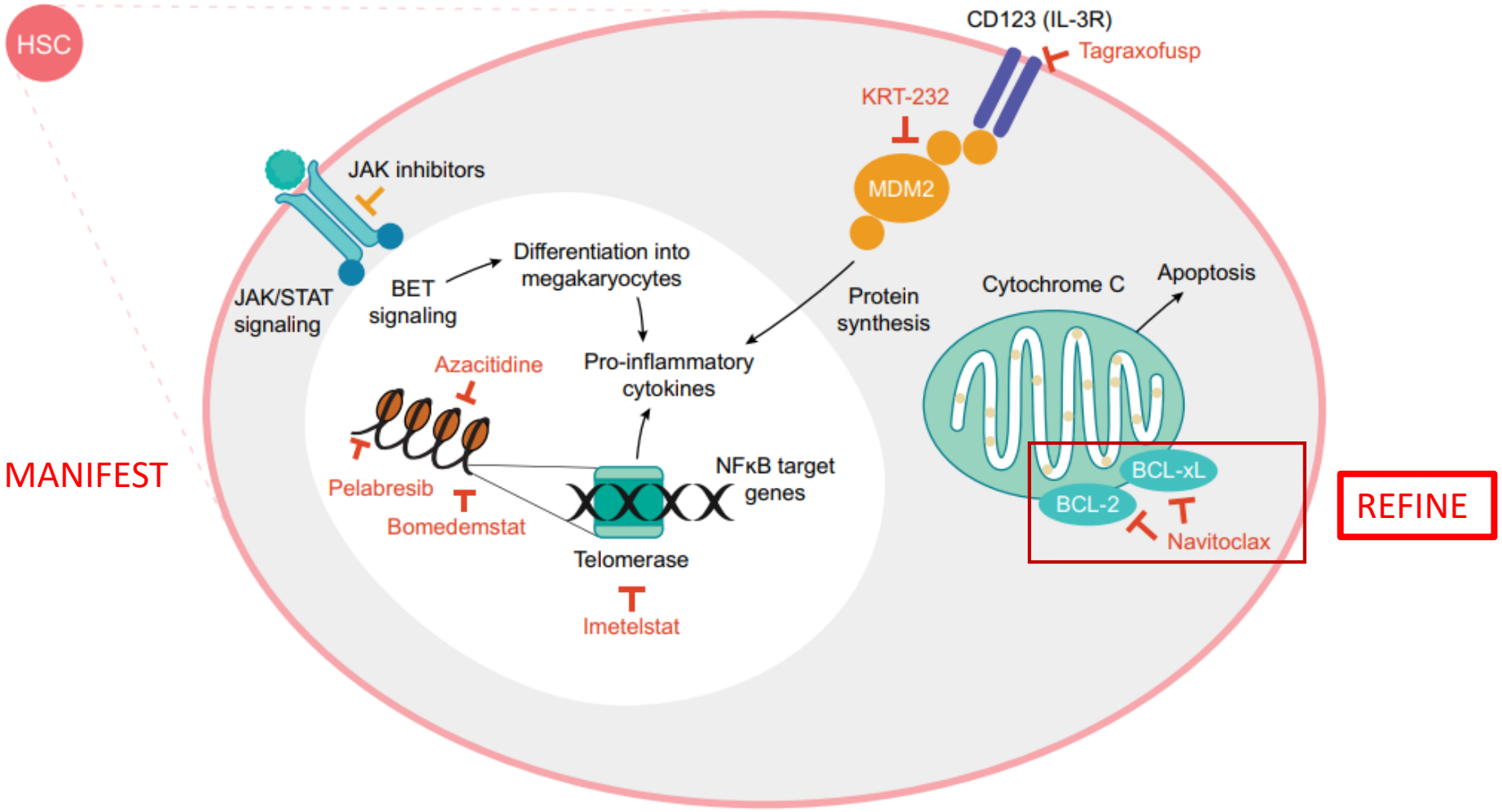
- Among patients with available spleen volume data at BL and EOC6, all but 1 patient experienced some degree of spleen reduction while on study
  - All patients in the Stringent Criteria Cohort experienced a spleen volume reduction from BL to EOC6





Harrison et al. Fedratinib Induces Spleen Responses in Patients with Myeloproliferative Neoplasm (MPN)-Associated Intermediate- or High-Risk Myelofibrosis (MF) Resistant or Intolerant to Ruxolitinib: An Updated Analysis of the Phase II JAKARTA2 Study. Abstract 353. *Poster presentation at the 7th Annual Meeting of the Society of Hematologic Oncology; September 11–14, 2019; Houston, Texas*

Potentially disease modifying drugs (red)



Pemmaraju et al., Cancer 2022

Merci de votre attention

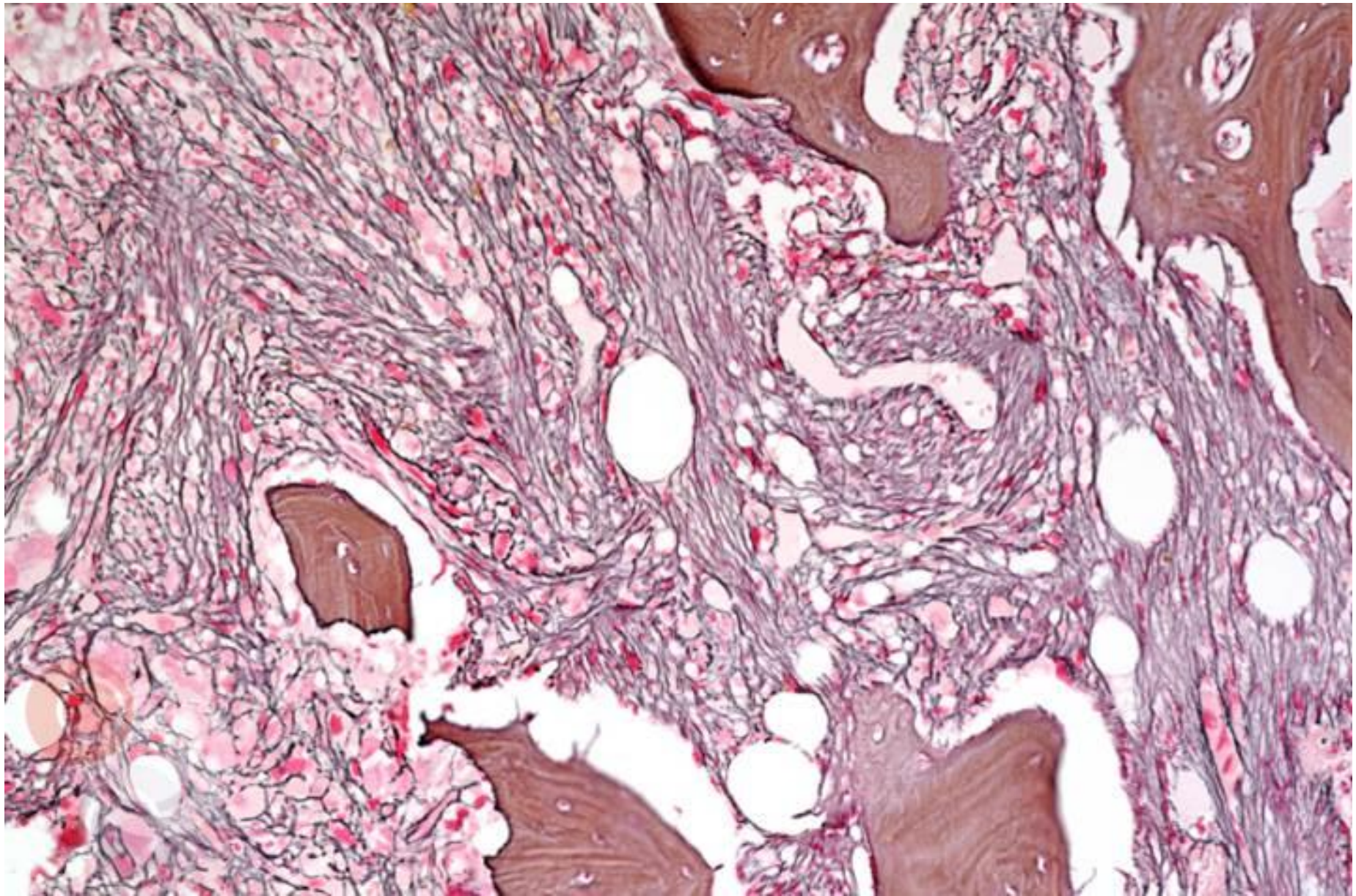


Table 3. Diagnostic criteria for polycythemia vera (PV) and post-PV myelofibrosis (Post-PV MF).

Polycythemia vera (PV)	Post-PV MF
Major criteria 1. Elevated hemoglobin concentration or Elevated hematocrit or Increased red blood cell mass[a)] 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation[b)] 3. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia **Minor criterion** ▪ Subnormal serum erythropoietin level	**Required criteria** 1. Previous established diagnosis of PV 2. Bone marrow fibrosis of grade 2 or 3 **Additional criteria** 1. Anemia (i.e., below the reference range given age, sex, and altitude considerations) or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (> 37.5 °C
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion[c)]	The diagnosis of Post-PV MF is established by all required citeria and at least two additional criteria

a) Diagnostic thresholds: hemoglobin: > 16.5 g/dL in men and > 16.0 g/dL in women
hematocrit: > 49% in men and > 48% in women
red blood cell mass: > 25% above mean normal predicted value

Table 4. Diagnostic criteria for essential thrombocythemia (ET) and post-ET myelofibrosis (Post-ET MF).

Essential thrombocythemia (ET)	Post-ET MF
Major criteria 1. Platelet count ≥ 450 x 10^9/L 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters[a)]; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis[b)] 3. Diagnostic criteria for *BCR::ABL1*-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, or other myeloid neoplasms are not met 4. *JAK2*, *CALR*, or *MPL* mutation[c)] **Minor criteria** 1. Presence of a clonal marker[d)] --or-- Absence of evidence of reactive thrombocytosis[e)]	**Required criteria** 1. Previous established diagnosis of ET 2. Bone marrow fibrosis of grade 2 or 3 **Additional criteria** 1. Anemia (i.e., below the reference range given age, sex, and altitude considerations) and a >2 g/dL decrease from baseline hemoglobin concentration 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Elevated lactate dehydrogenase (LDH) level above the reference range 5. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5 °C)
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria	The diagnosis of Post-ET MF is established by all required criteria and at least two additional criteria

Table 5. Diagnostic criteria for primary myelofibrosis (PMF).

Primary myelofibrosis, early/prefibrotic stage (prePMF)	**Primary myelofibrosis, overt fibrotic stage**
Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia[a)], bone marrow fibrosis grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. *JAK2*, *CALR*, or *MPL* mutation[b)] or Presence of another clonal marker[c)] or Absence of reactive bone marrow reticulin fibrosis[d)] 3. Diagnostic criteria for *BCR::ABL1*-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndromes, or other myeloid neoplasms are not met	**Major criteria** 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia[a)], accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. *JAK2*, *CALR*, or *MPL* mutation[b)] or Presence of another clonal marker[c)] or Absence of reactive myelofibrosis[d)] 3. Diagnostic criteria for essential thrombocythemia, polycythaemia vera, *BCR::ABL1*-positive chronic myeloid leukemia, myelodysplastic syndrome, or other myeloid neoplasms[e)] are not met
Minor criteria ▪ Anemia not attributed to a comorbid condition ▪ Leukocytosis ≥11 x 10^9/L ▪ Palpable splenomegaly ▪ Lactate dehydrogenase level above the above the reference range	**Minor criteria** ▪ Anemia not attributed to a comorbid condition ▪ Leukocytosis ≥11 x 10^9/L ▪ Palpable splenomegaly ▪ Lactate dehydrogenase level above the above the reference range ▪ Leukoerythroblastosis
The diagnosis of prePMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations	

Table 1. Myeloproliferative neoplasms.

Chronic myeloid leukaemia
Polycythaemia vera
Essential thrombocythaemia
Primary myelofibrosis
Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Juvenile myelomonocytic leukaemia
Myeloproliferative neoplasm, not otherwise specified

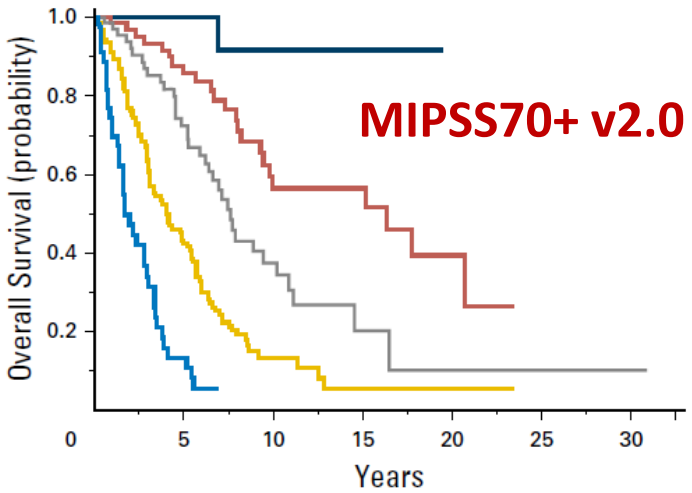
Mutation-enhanced IPSS scores (MIPSS)

	MIPSS70	MIPSS70+	MIPSS70+[v2.0]
Hb <10 g/dl	+	+	+
WBC ≥25 G/l	+		
Blasts ≥2% (PB)	+	+	+
Const. sympt.	+	+	+
PLT <100 G/l	+		
Fibrosis ≥°2	+		
Karyotype		+	++
HMR* mut.	++	++	++
CALR non-type-I	+	+	+

<8 g/dl vs. <10 g/dl (f)
<9 g/dl vs. <10 g/dl (m)

VHR** included

U2AF1 included



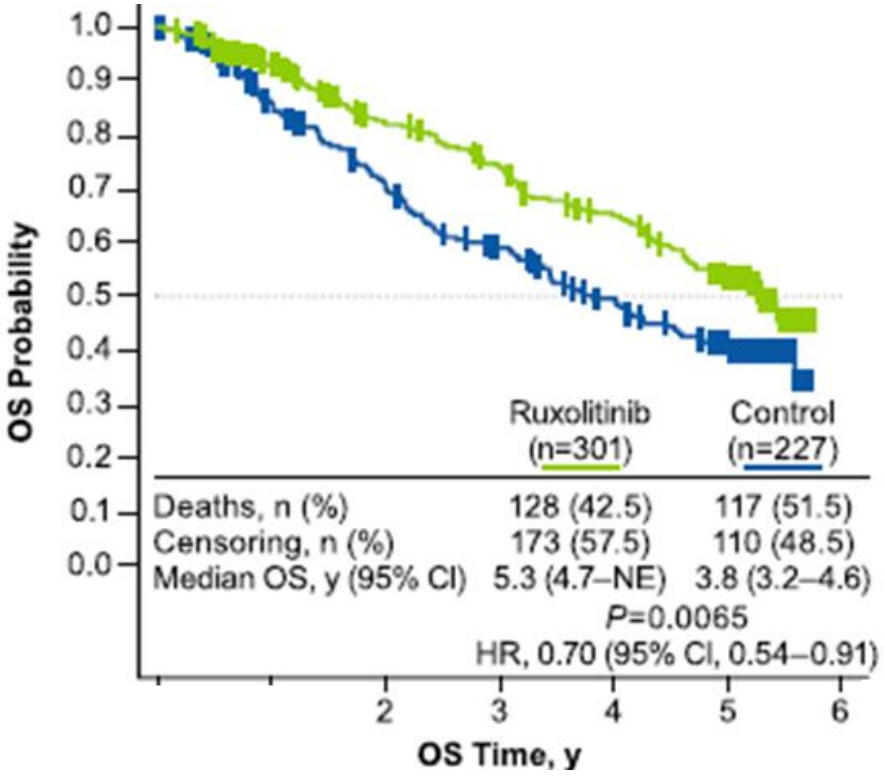
Very High Risk (≥9 pts)
High Risk (5-8 pts)
Intermediate Risk (3-4 pts)
Low Risk (1-2 pts)
Very Low Risk (0 pt)

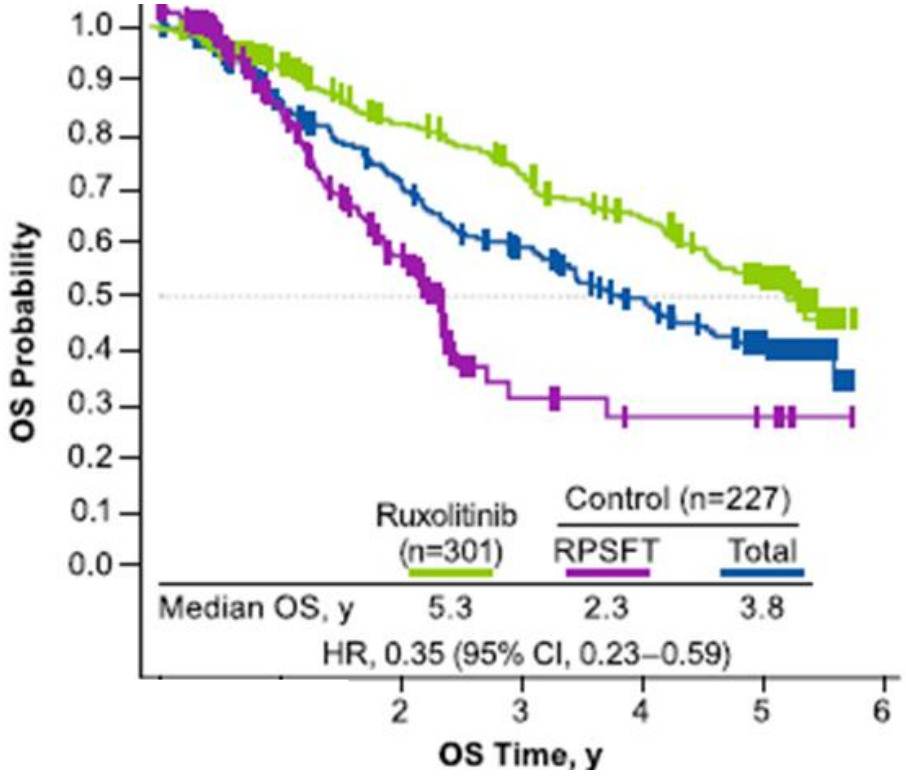
* High molecular risk: mutation in *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*

** Very high risk: -7, i(17q), inv(3), 12p-, 11q23 rearrangement

Guglielmelli et al., J Clin Oncol 2018; Tefferi et al., J Clin Oncol 2018

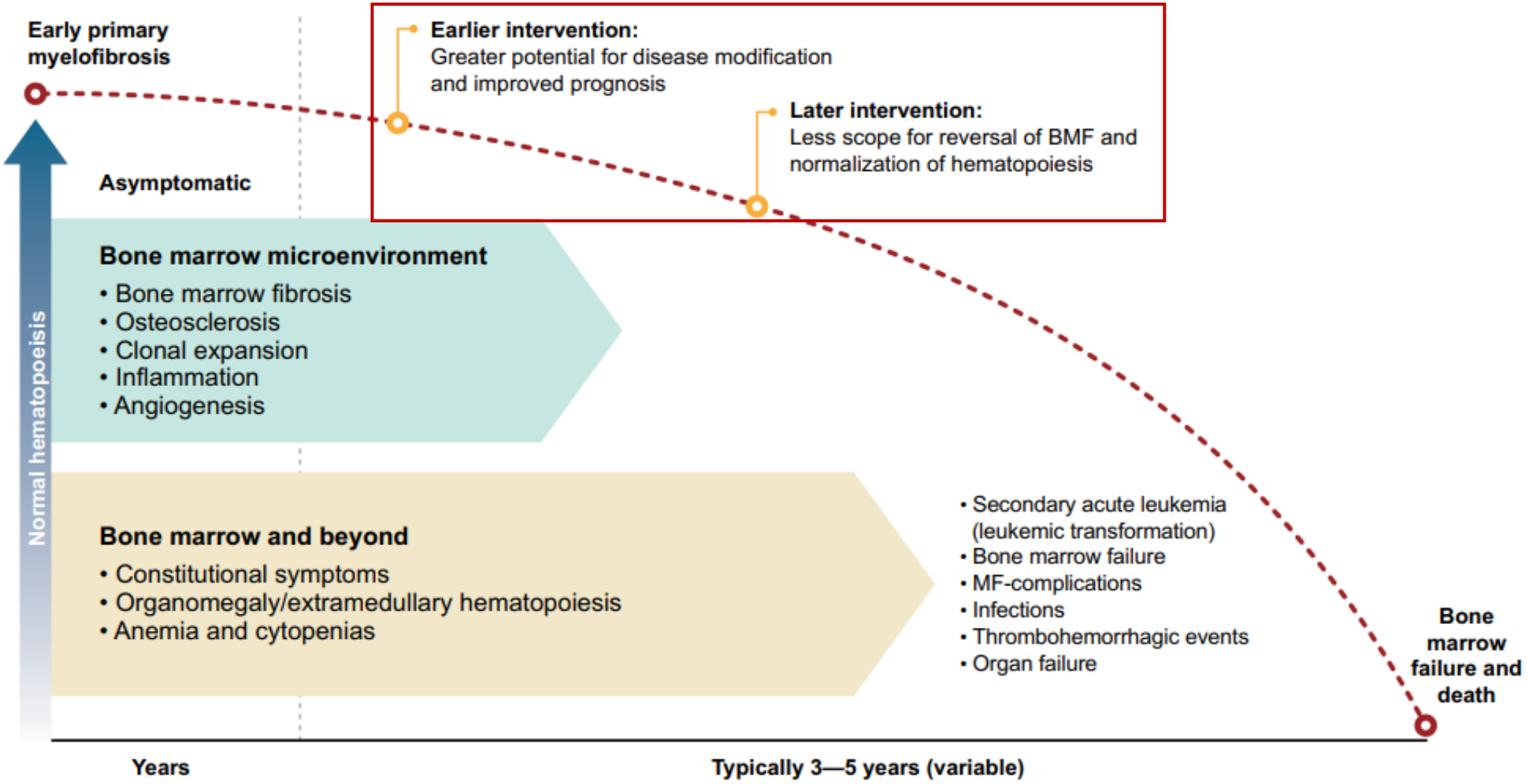
Ruxolitinib and overall survival in MF





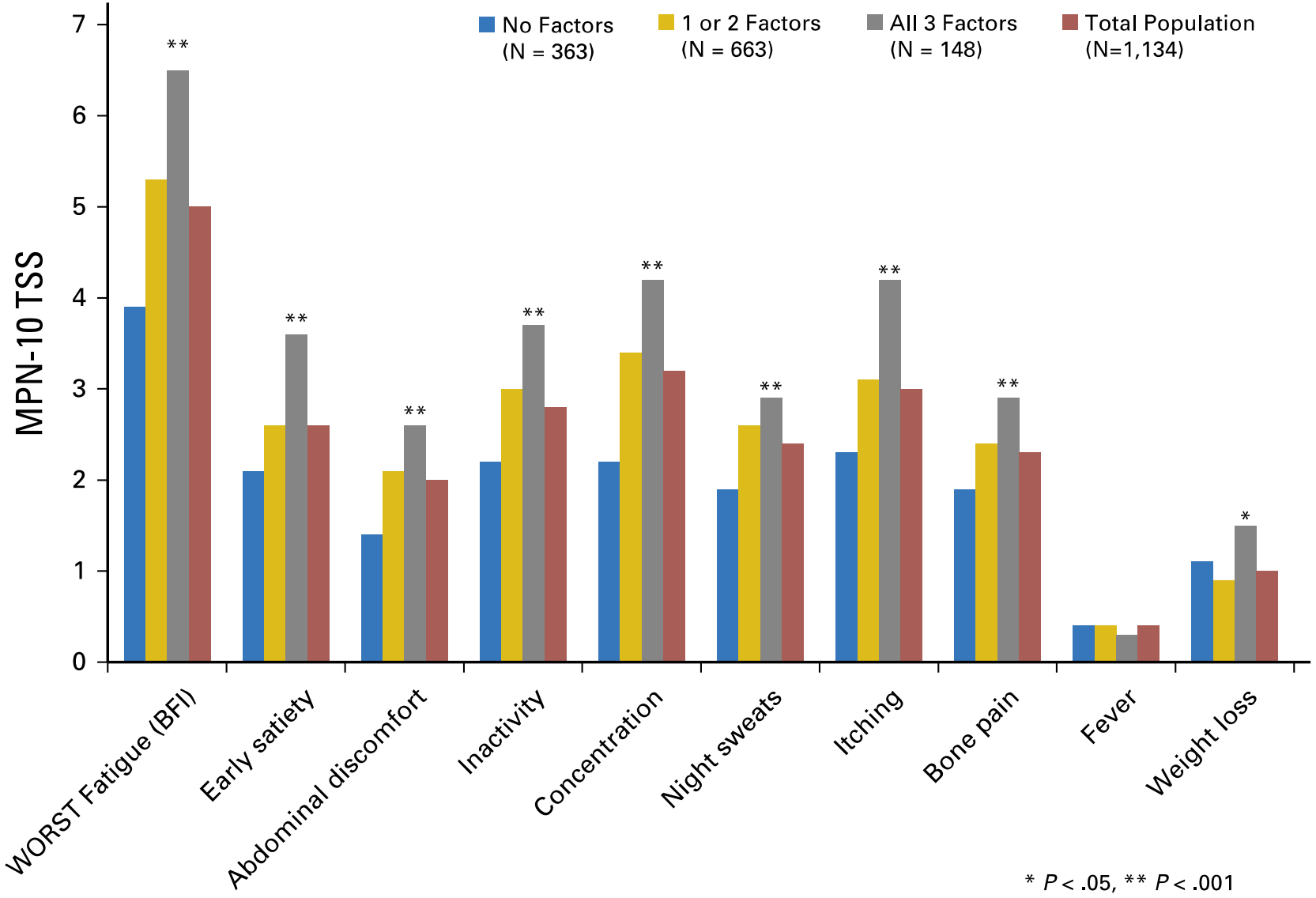
Verstovsek et al., J Hematol Oncol 2017

Course of MF and impact of intervention early vs. late



Pemmaraju et al., Cancer 2022

MPN-SAF TSS- Results in PV



Factors:

-Hydroxyurea use

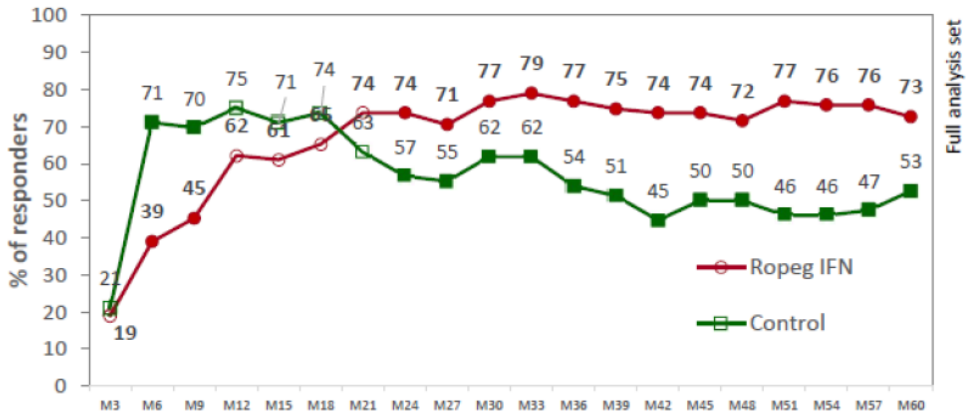
-Phlebotomy

-enlarged spleen

Geyer H et al. JCO 2015;34:151

Ropeg-IFNα vs. HU bei PV: hämatologisches Ansprechen

CHR with last observation carried forward (LOCF)

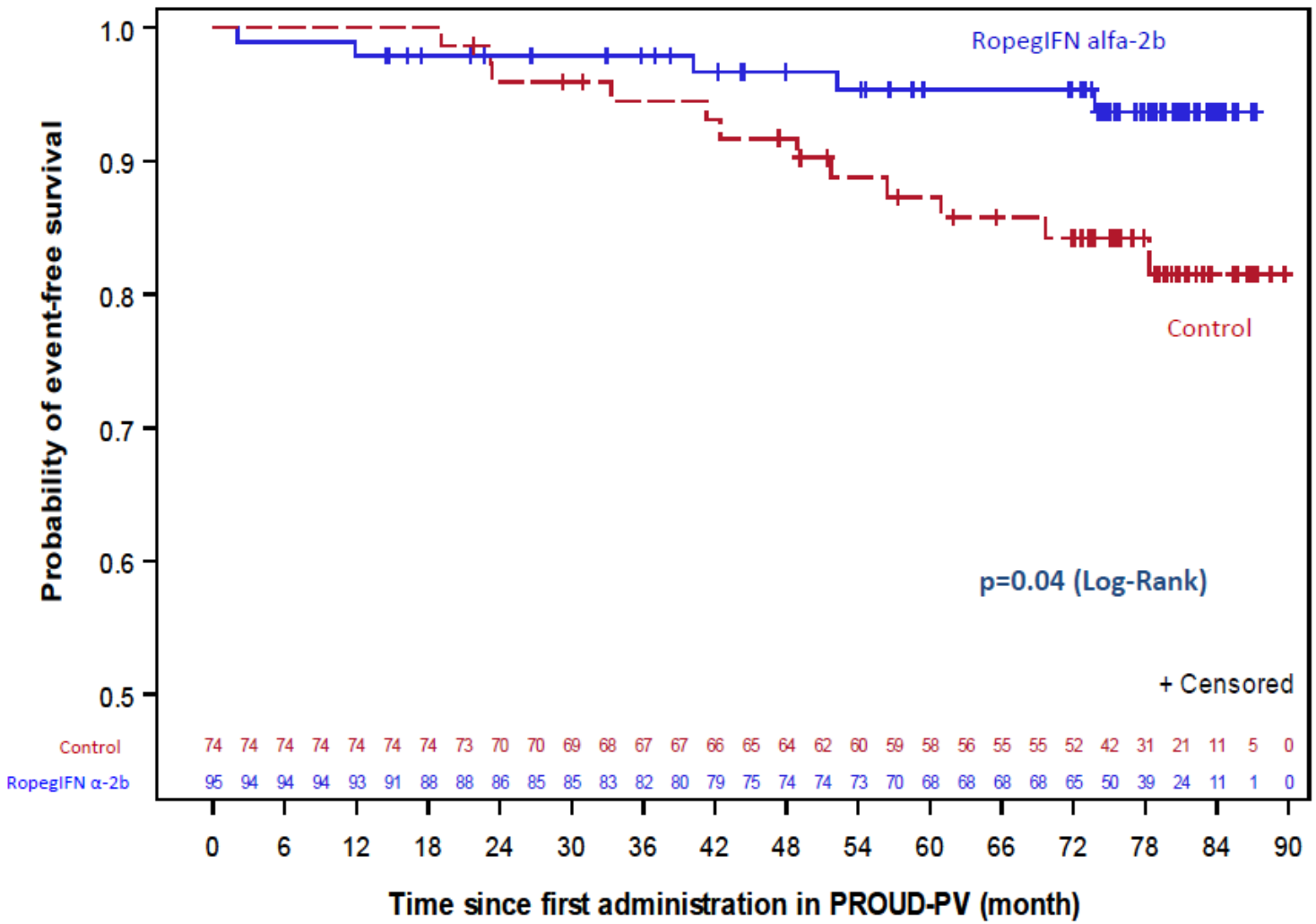


Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN /Control)
	Responder /N	Responder %	Responder/N	Responder %		
MONTH 12 (EOT in PR)	59	62.1%	57	75.0%	0.1	0.85 (0.70 to 1.04
MONTH 24 (LOCF)	70	73.7%	43	56.6%	**0.04**	1.27 (1.02 to 1.60)
MONTH 36 (LOCF)	73	76.8%	41	54.0%	**0.003**	1.43 (1.13 to 1.81)
MONTH 48 (LOCF)	68	71.6%	38	50.0%	**0.004**	1.46 (1.13 to 1.89)
MONTH 60 (LOCF)	69	72.6%	40	52.6%	**0.004**	1.43 (1.12 to 1.81)

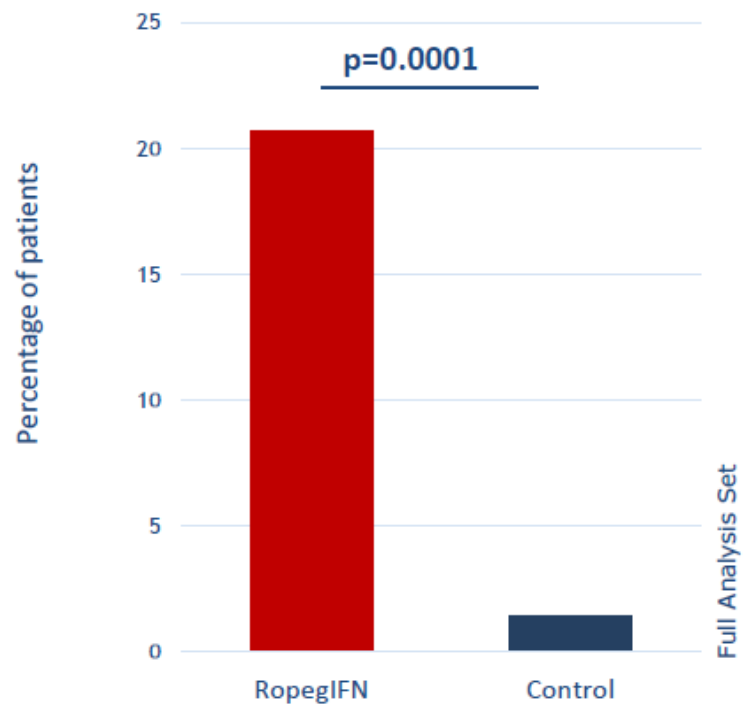
Kiladjian et al., Leukemia 2022; 36:1408-1411

Event-free survival

Risk events: death, disease progression and thromboembolic events

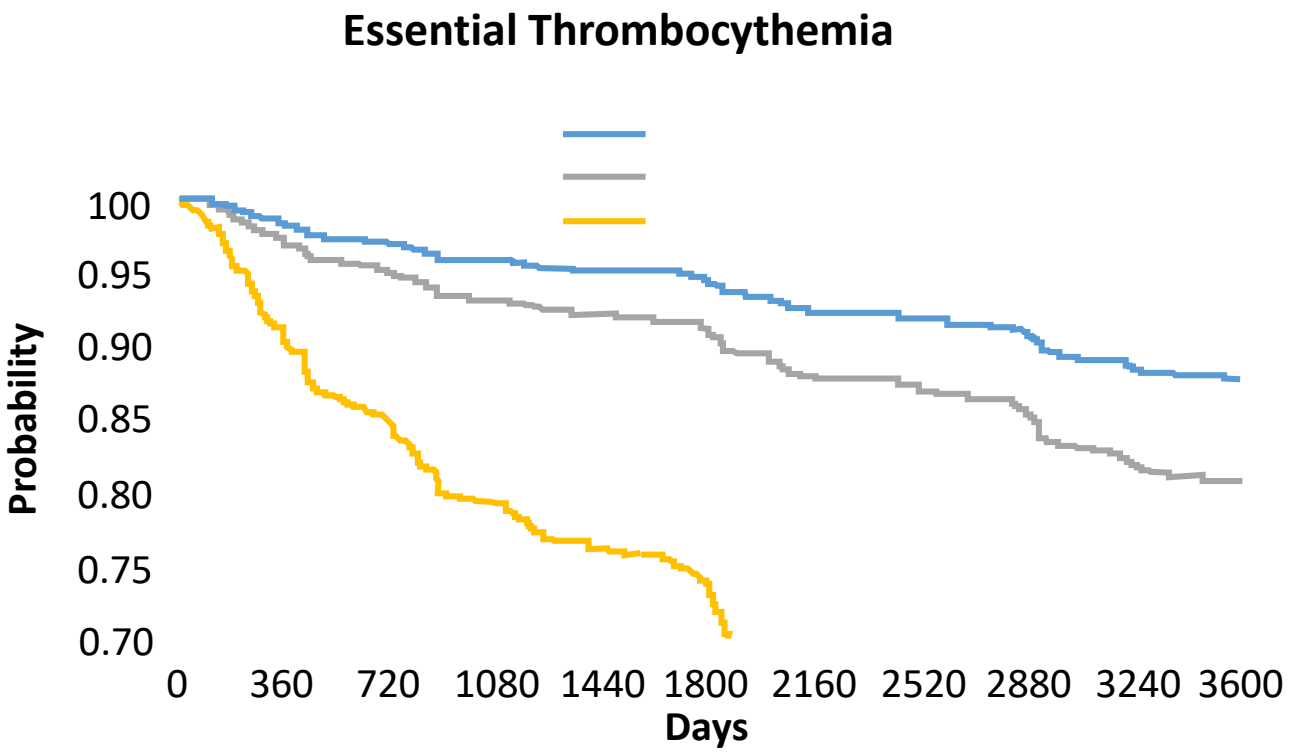


Patients with *JAK2*V617F allele burden <1% at 6 years*



Significance of Homozygosity for *JAK2* V617F

- *JAK2* V617F homozygous patients:
  - Older at diagnosis, larger spleen, **higher leukocyte count** and hematocrit
  - Aquagenic pruritus significantly more common
  - More frequent evolution into secondary myelofibrosis
  - Significantly higher risk of cardiovascular events than WT or HET



Vannucchi. Blood. 2007;110:840.

Slide credit: clinicaloptions.com