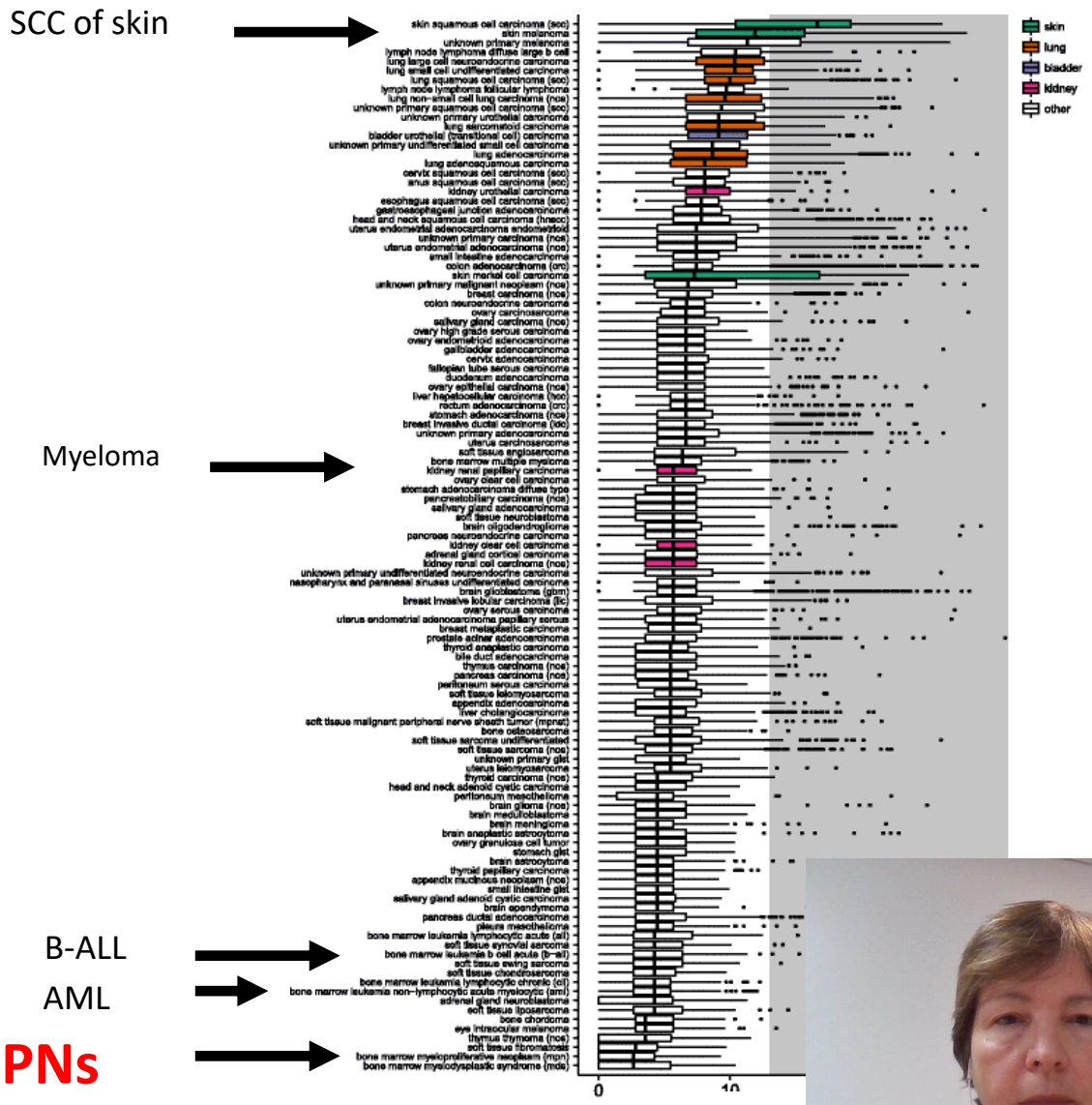
MPN Horizons
Understanding the New Complexity of MPNs
13-15 October
Zagreb, Croatia
2023
mpnan

How does a genetic understanding of MPNs affect prognosis for patients?

Claire Harrison

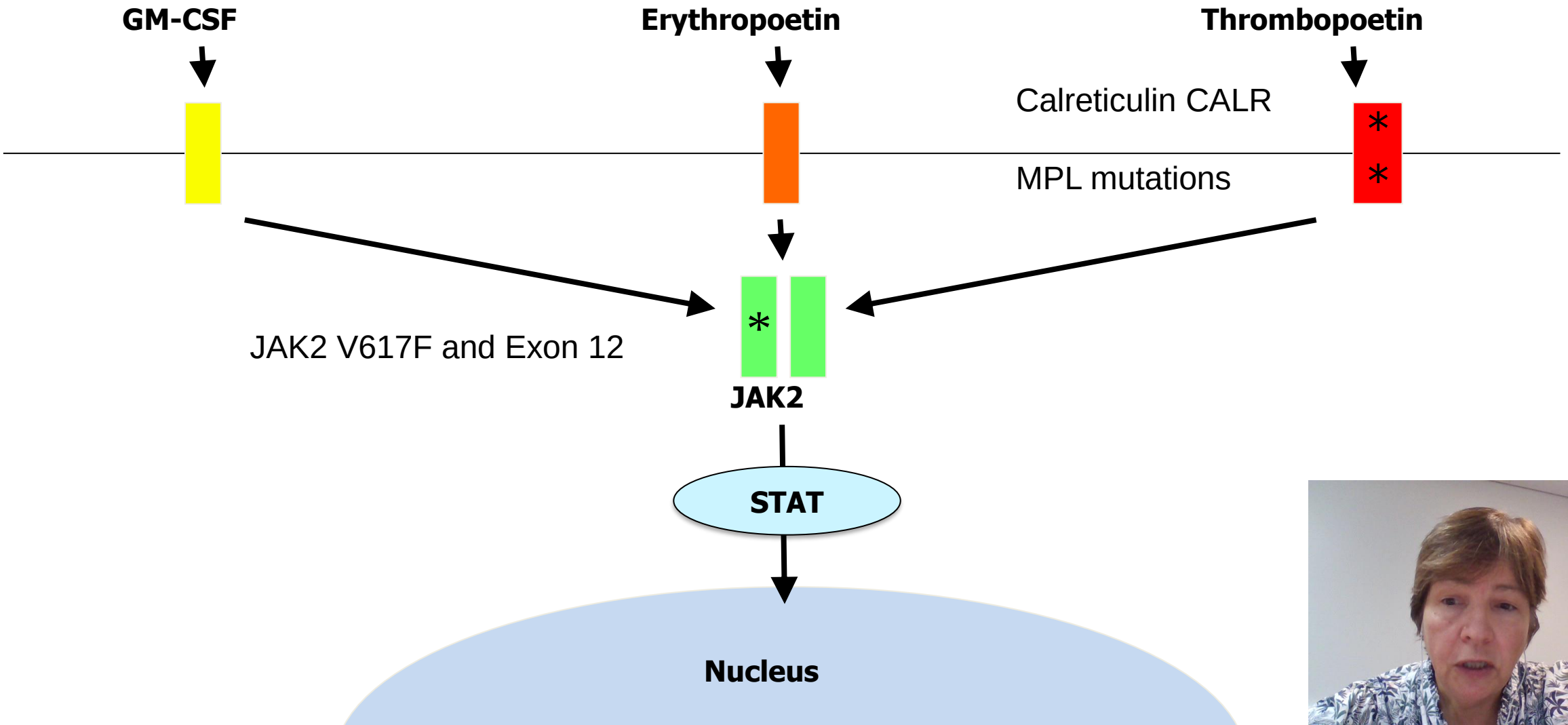
Genomic landscape of Ph- Myeloproliferative Neoplasms

- Relatively low genomic complexity

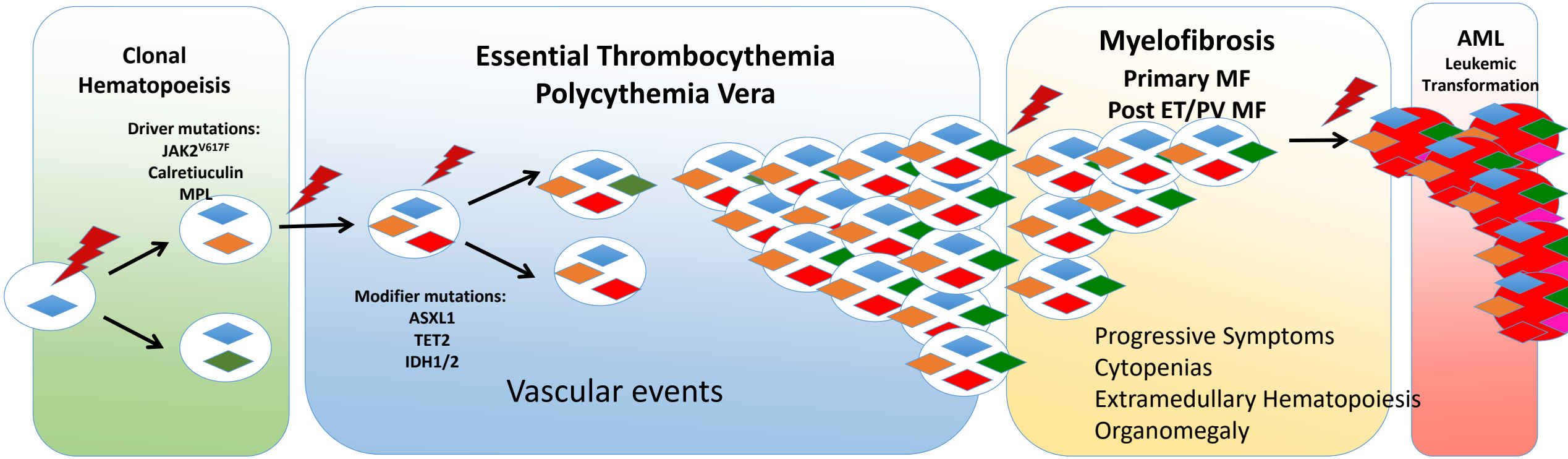


Chalmers et al. Genome Medic

JAK2: central physiological role in the signal transduction of hematopoietic growth factors & the pathogenesis of MPN



Myeloproliferative Neoplasms



Lead time: Typically years (>10) to ∞

Time: Variable 3-5 years comm

Normal Hematopoiesis

Beyond *JAK2 V617F* Mutation: Molecular Complexity of MPNs

Mutations affecting the JAK-STAT Signaling

JAK2
MPL
LNK
c-CBL
SOCS1-3

CALR

Mutations affecting the epigenetic regulation

TET2
EZH2
ASXL1
IDH1/2
DNMT3A
JAK2V617F

Mutations associated with Leukemic transformation

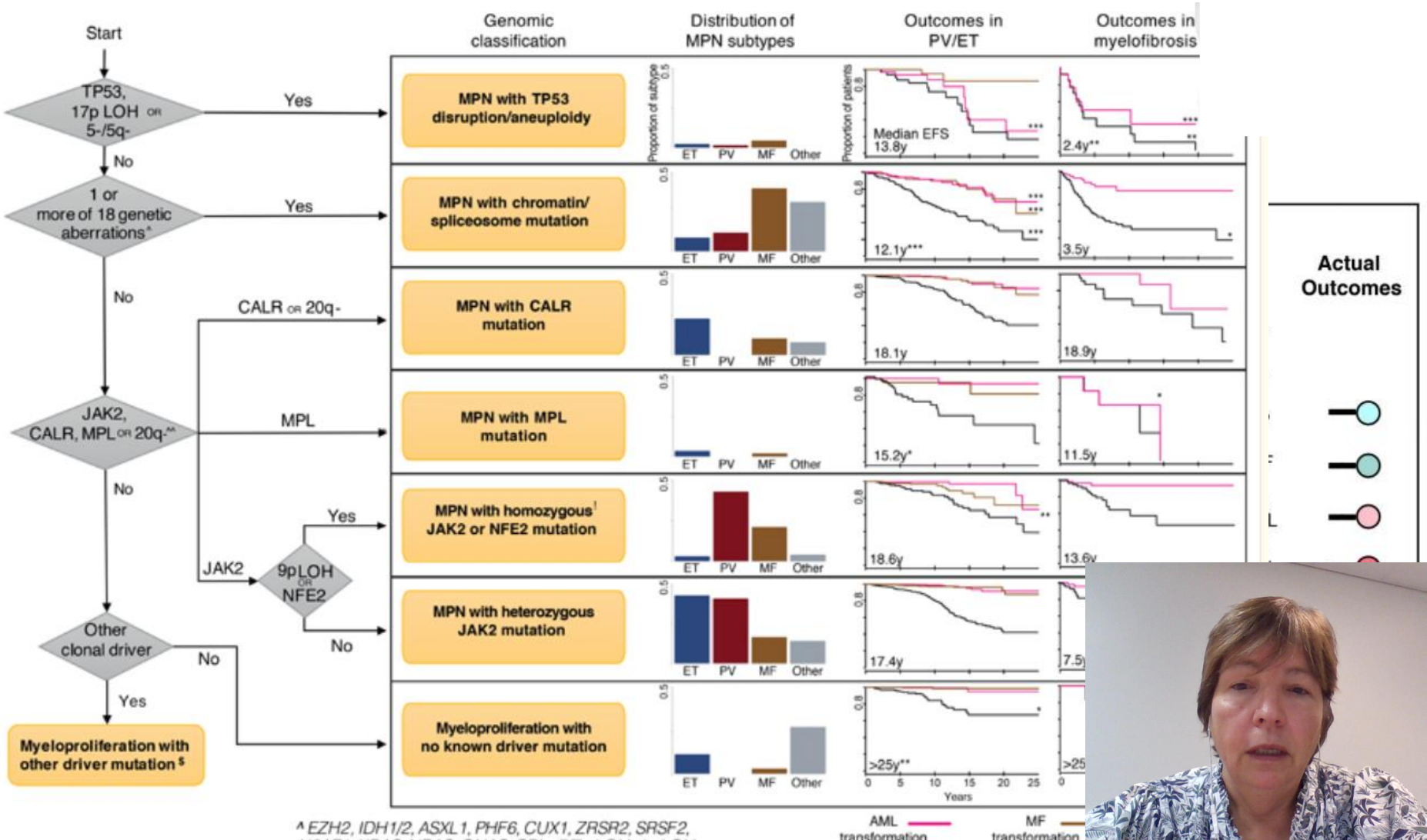
IDH1/2
IKZF1
TP53
NF1
RUNX1
NRAS
KRAS
DN

The NEW ENGLAND JOURNAL of MEDICINE

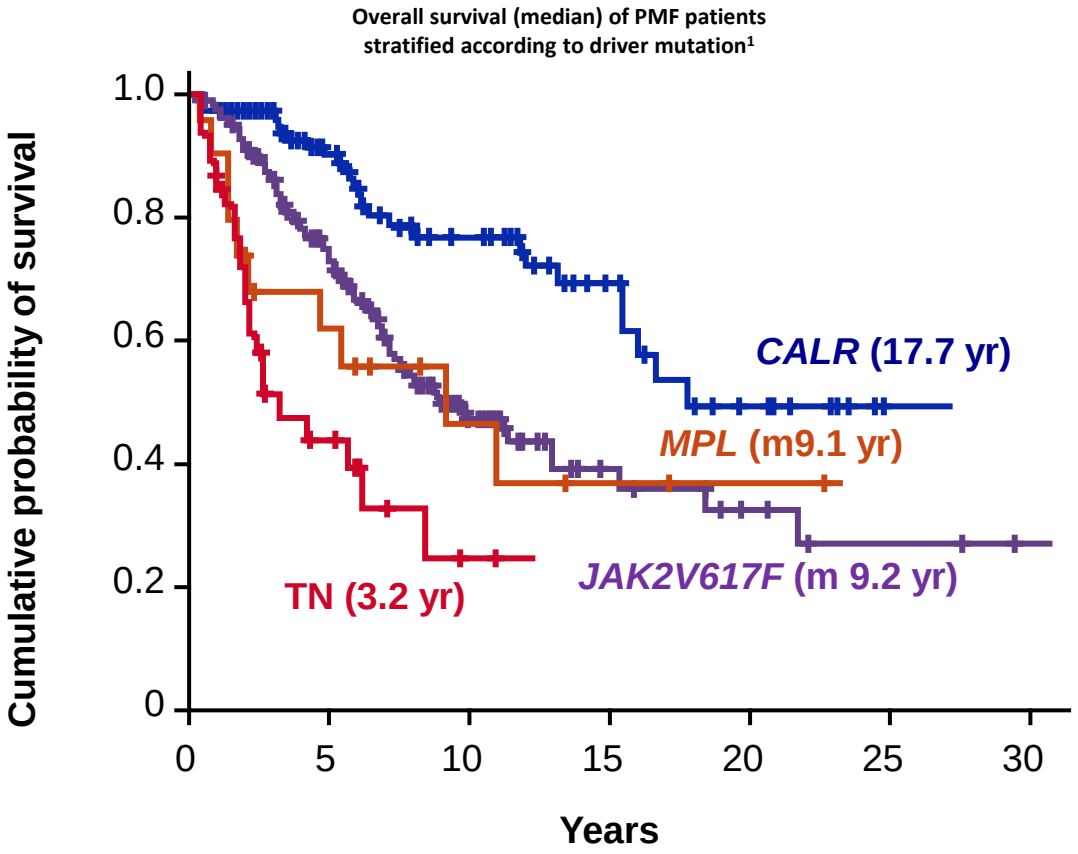
ORIGINAL ARTICLE

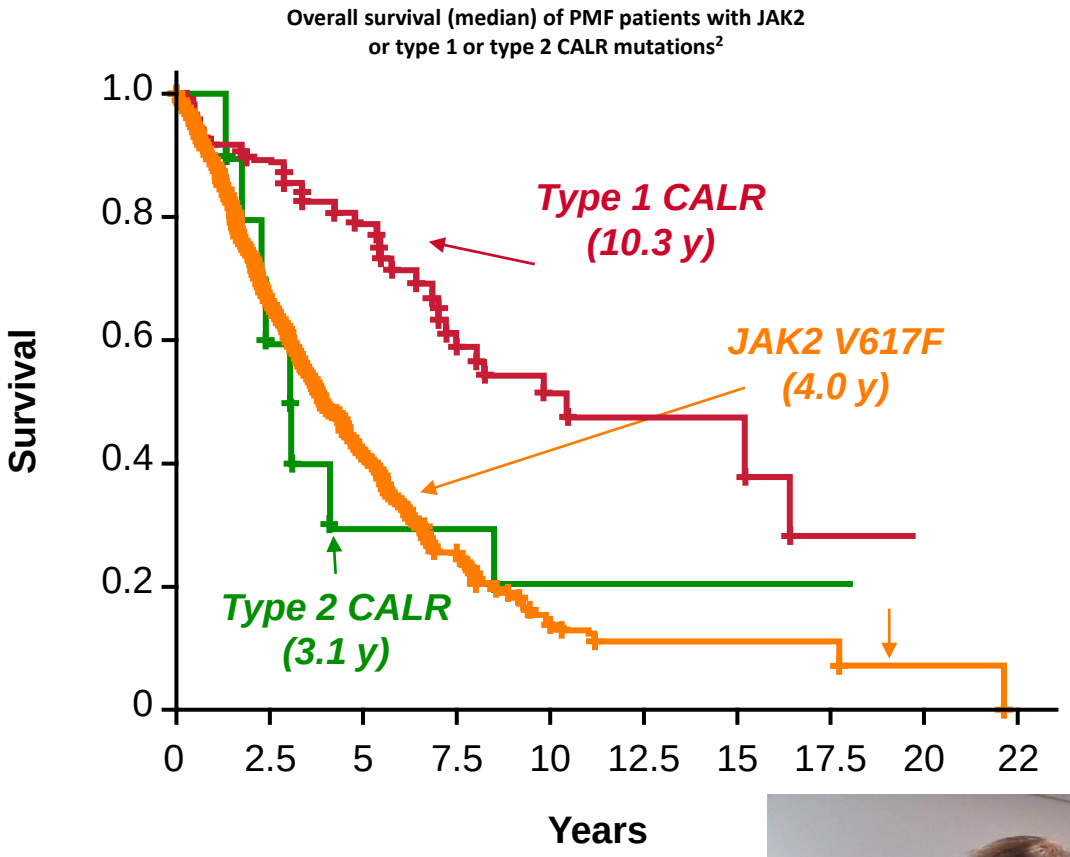
Classification and Personalized Prognosis in Myeloproliferative Neoplasms

J. Grinfeld, J. Nangalia, E.J. Baxter, D.C. Wedge, N. Angelop
A.L. Godfrey, E. Papaemmanuil, G. Gundem, C. MacLean, J
S. O'Meara, J.W. Teague, A.P. Butler, C.E. Massie, N. Will
C.L. Andersen, H.C. Hasselbalch, P. Guglielmelli, M.F
A.M. Vannucchi, C.N. Harrison, M. Gerstung, A.R. Green, a



Prognostic Significance of Phenotype Driver Mutations in Myelofibrosis





In ET, no difference between Type 1 and Type 2 CALR for overall sur

1. Rum
2. Tefferi A, (
3. Gug

MIPSS70 Risk Score:
Variables Associated with Reduced OS

Variables	HR (95% CI)	P	Weighted value
Hb <100g/L	1.9 (1.32–2.71)	<0.001	**1**
WBC >25x10^9/L	3.8 (2.21–6.64)	<0.001	**2**
PLT			
PB blasts ≥2%			**1**
Constitutional Symptoms	2.18 (1.57–3.03)	<0.001	**1**
Grade ≥2 BM fibrosis	1.9 (1.34–2.71)	<0.001	**1**
Absence *of CALR* Type1	1.9 (1.21–2.96)	0.005	**1**
HMR category[a]	1.8 (1.26–2.49)	0.004	**1**
≥2 HMR mutations[b]	3.95 (2.43–6.40)	<0.001	

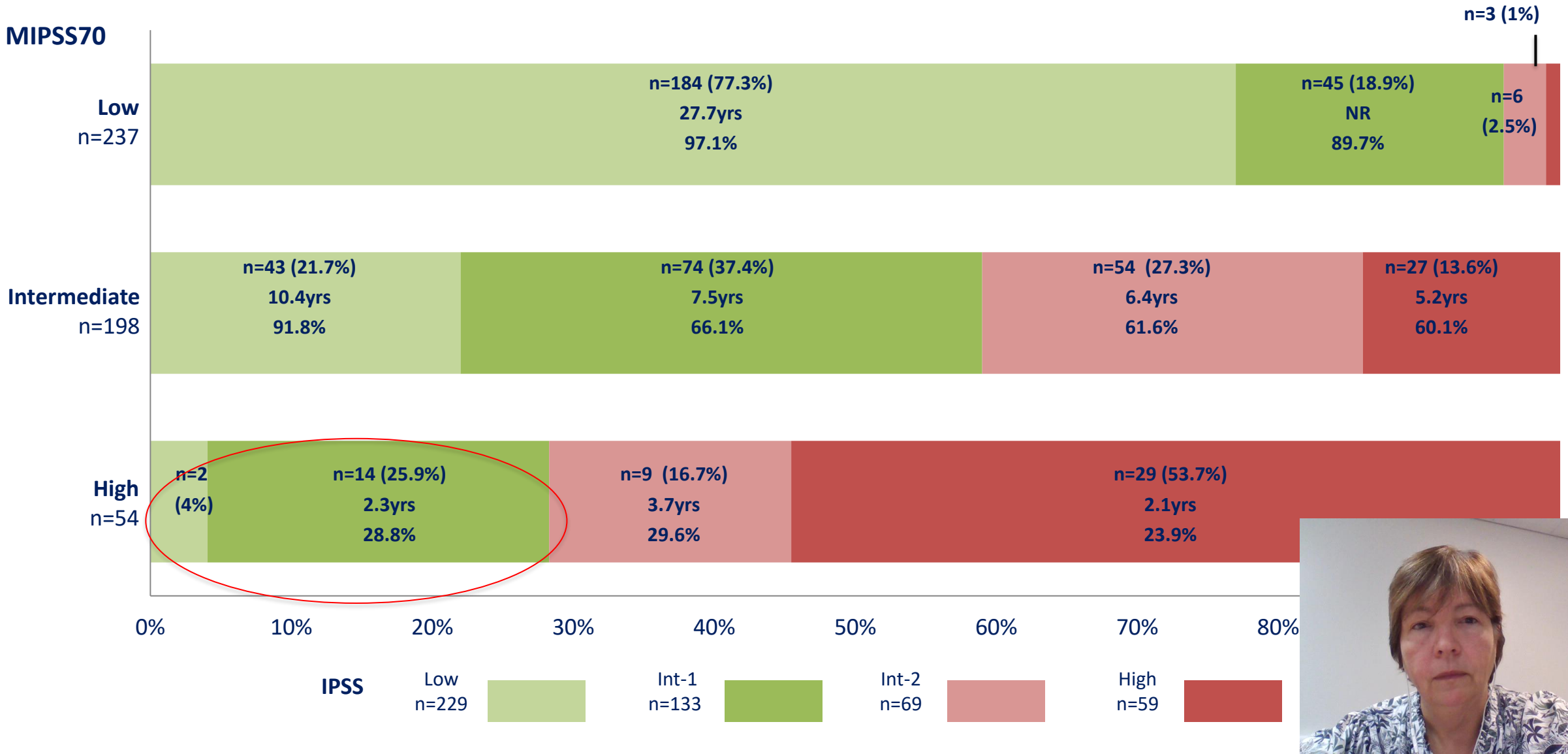
Molecular information is incorporated into MF prognostic scores

[a]Any mutation in: ASXL1, EZH2, SRSF2, IDH1/2, U2AF1 other bad mutations not included RAS

[b]Two or more mutated genes among: ASXL1, EZH2, SRSF2, IDH1/2
≥2 mutations in the same gene are counted as one

Guglielmelli P, et al

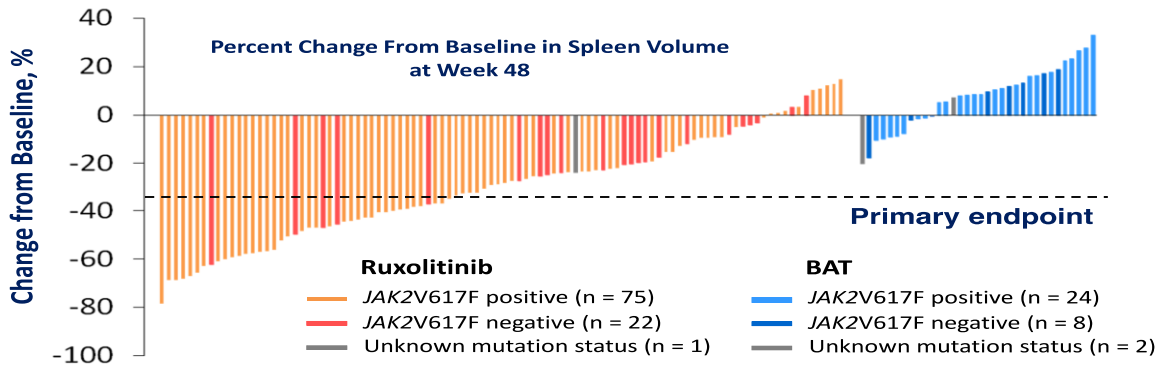
Patients' Redistribution Across IPSS and MIPSS70 Risk Scores…… improving prognostication



IMPACT OF GENETICS ON TREATMENT RESPONSE IN MYELOFIBROSIS

Spleen reduction is independent of driver mutation

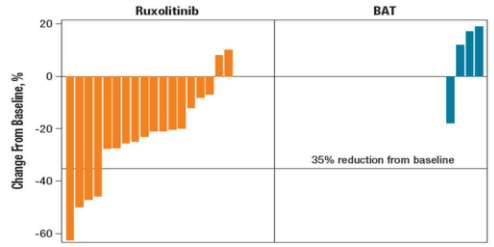
Regardless of *JAK2* V617F Mutation



- At week 48, most patients receiving ruxolitinib experienced spleen volume reductions, including *JAK2*V617F-positive (88% [66/75]) and *JAK2*V617F-negative (91% [20/22]) patients

Efficacy of Ruxolitinib in *CALR* Mutated Patients in COMFORT-II

- In *CALR*+ patients, a ≥35% reduction from baseline in spleen volume at week 48 was achieved by 20% in the ruxolitinib arm *vs* 0% in the BAT arm

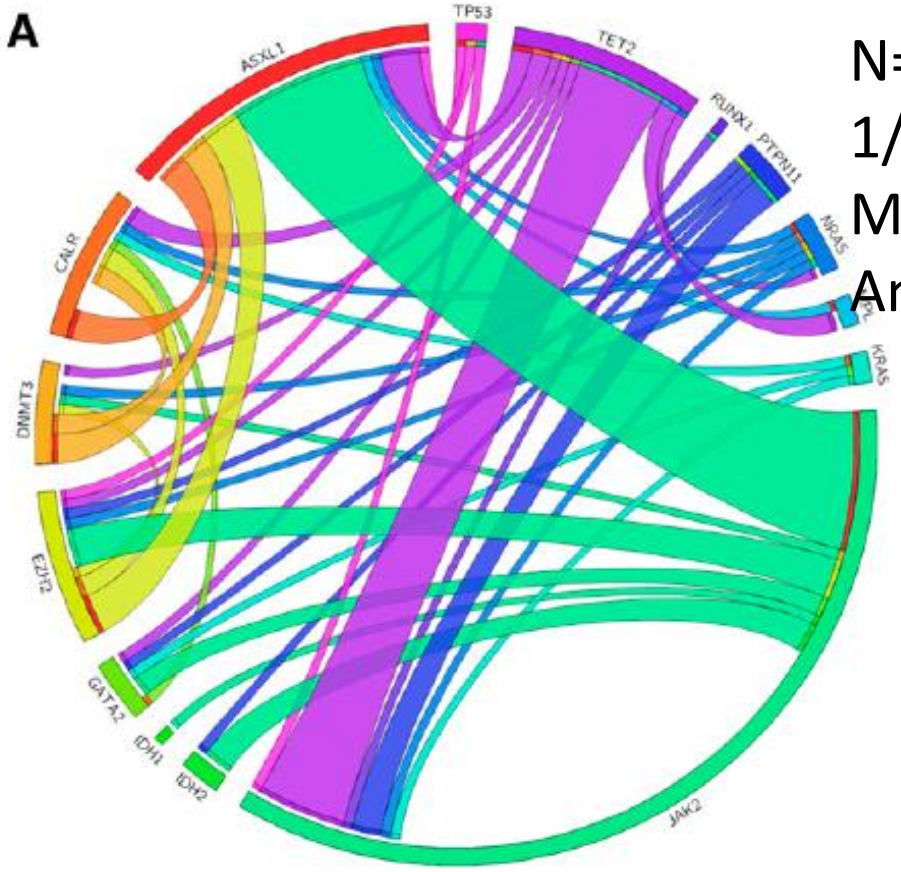


- The Kaplan-Meier–estimated probability of survival at 144 weeks was 0.76 in the ruxolitinib arm *vs* 0.50 in the BAT arm

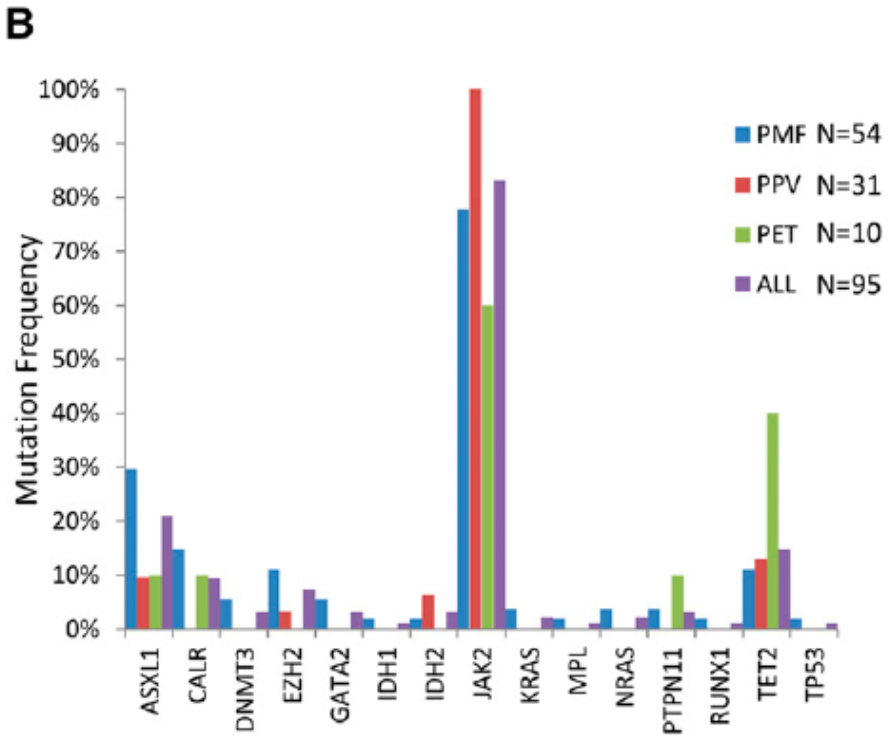
Analysis conducted on 29/166 (17.5%) patients, with baseline mutation status assessments, who were *CALR* +

Gugliel

Additional mutations: impact on ruxolitinib response



N=95; Phase 1/2 study at MD Anderson



≥3 mutations: 9-fold reduction
spleen response; shorter time t
discontinuation & reduc

Patel KP, et al. Blood 2015;126:790–7.

Prognosis after ruxolitinib discontinuation

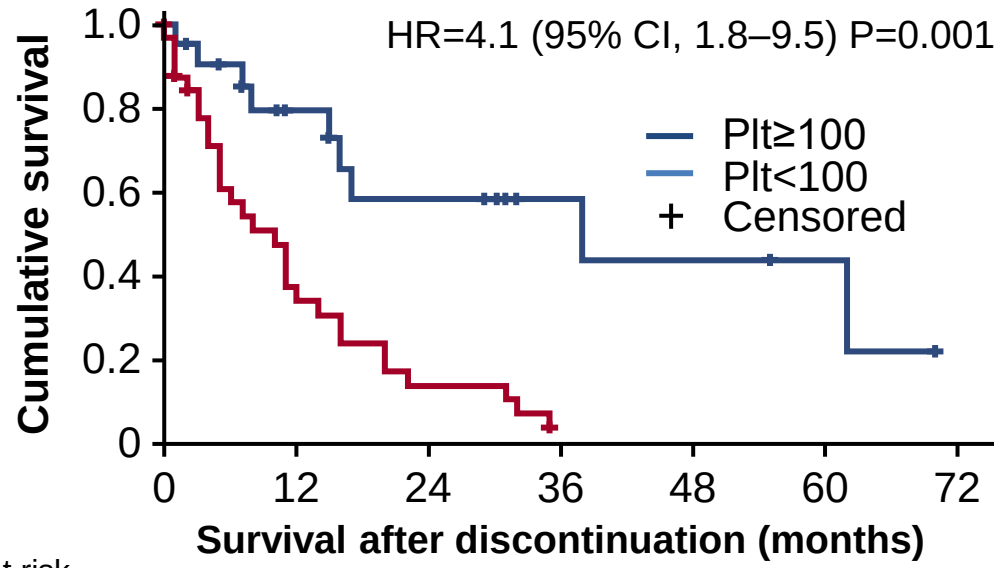
Regular Article blood

MYELOID NEOPLASIA

Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation

Kate J. Newberry,[1] Keyur Patel,[2] Lucia Masarova,[1] Rajyalakshmi Luthra,[2] Taghi Manshouri,[1] Elias Jabbour,[1] Prithviraj Bose,[1] Naval Daver,[1] Jorge Cortes,[1] Hagop Kantarjian,[1] and Srdan Verstovsek[1]

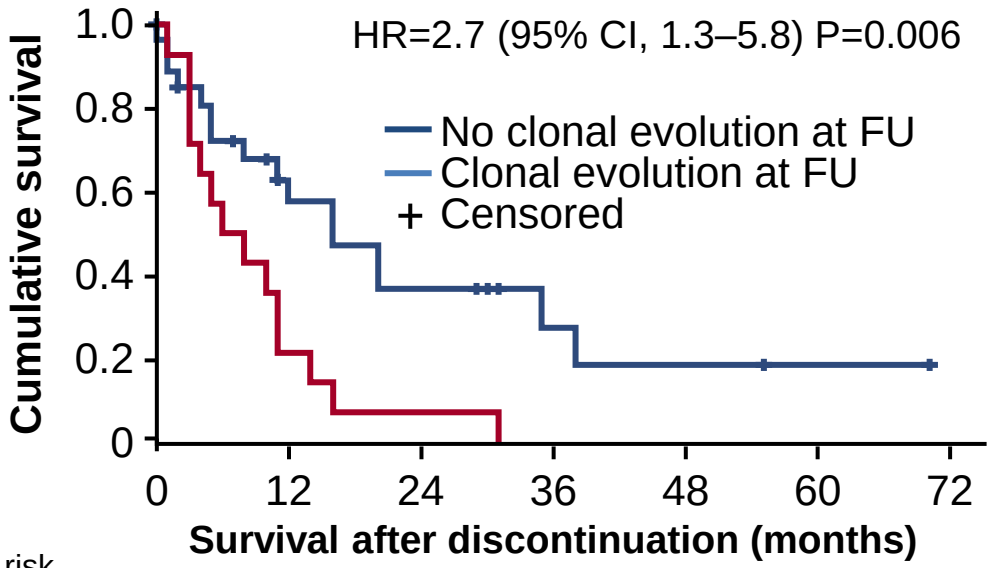
[1]Department of Leukemia and [2]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX



No. at risk

Plt≥100	23	12	7	4	3	1	0
Plt<100	33	10	4	0			

Plts <100 median survival 11/12



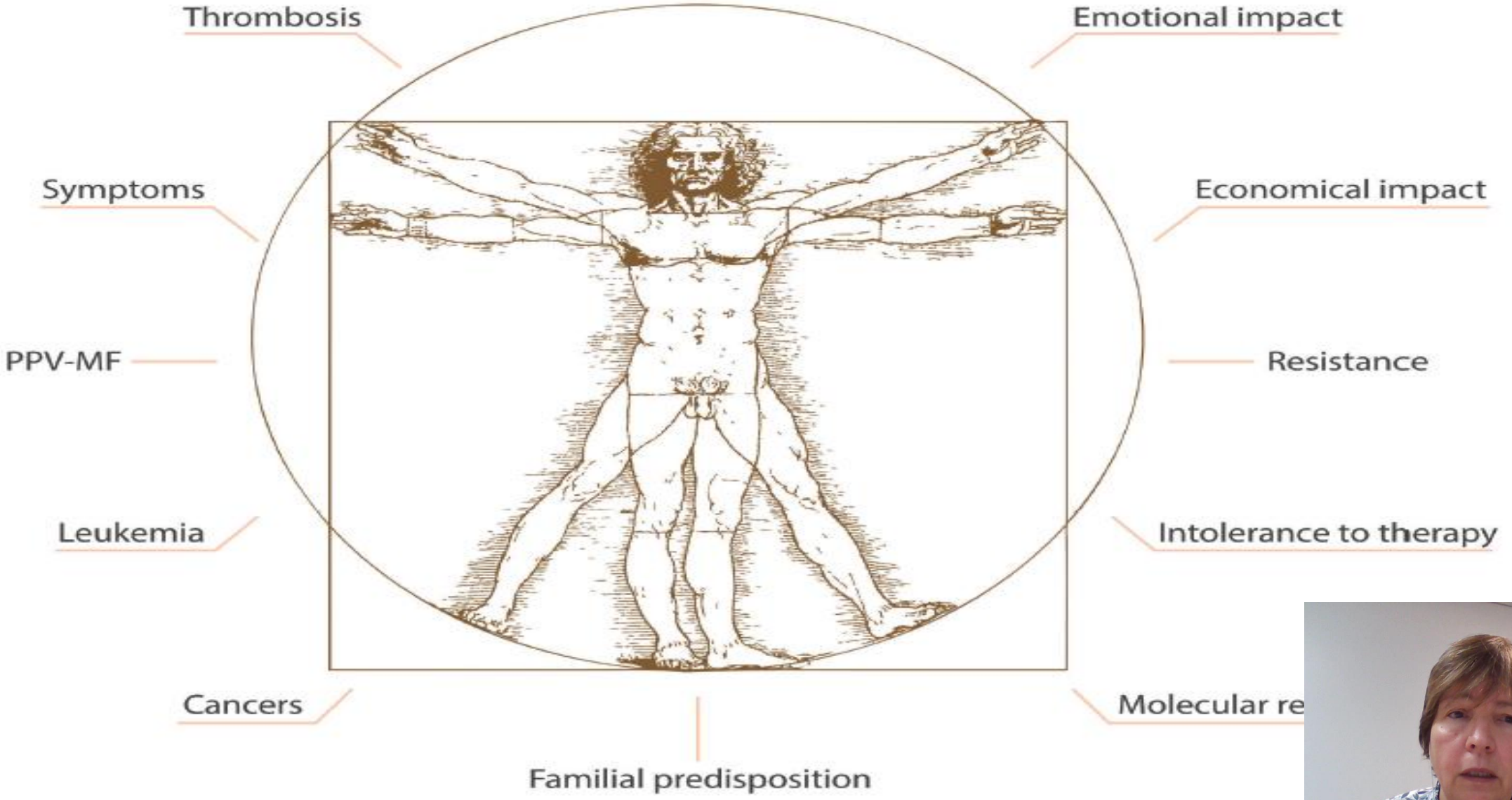
No. at risk

No CE	28	16	4	4	2
CE	14	3	3	1	0

Clonal evolution median

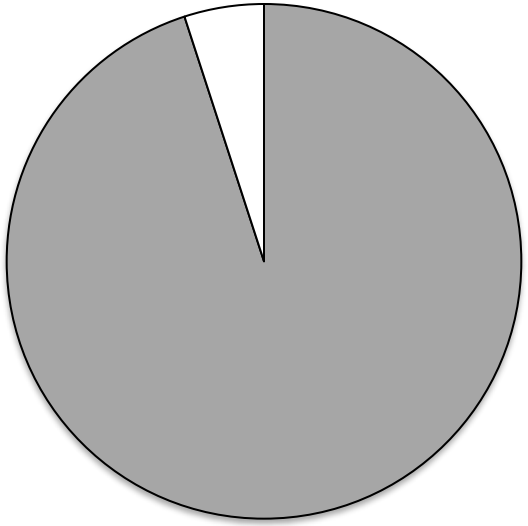
Newberry KJ

Impacts of PV and ET

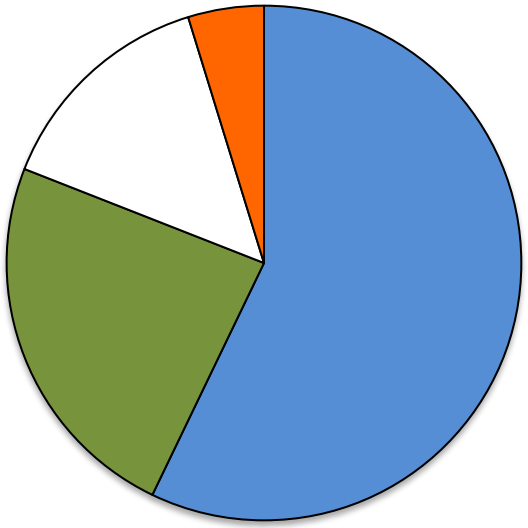


Vannucch

Genetic aberrations in MPN

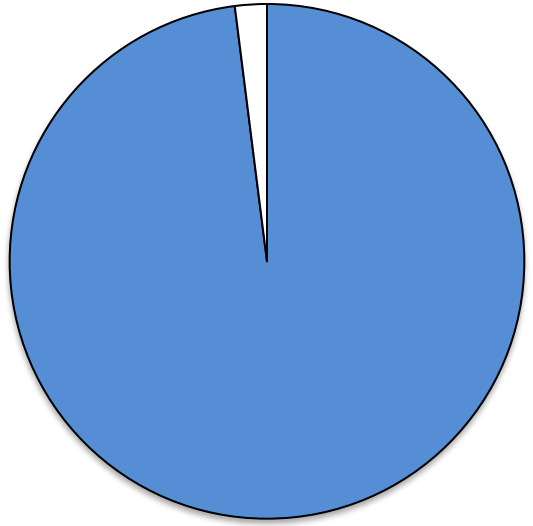


CML

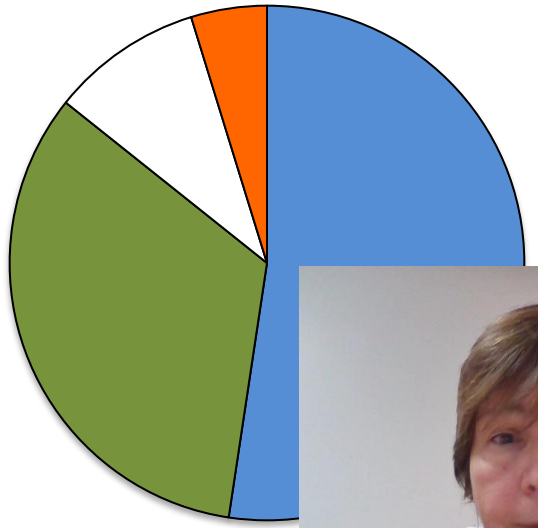


ET

- *BCR-ABL*
- *JAK2* exon 12 and 14
- *CALR* exon 9
- *MPL*
- JAK2-/MPL-/CALR- (triple-negative)

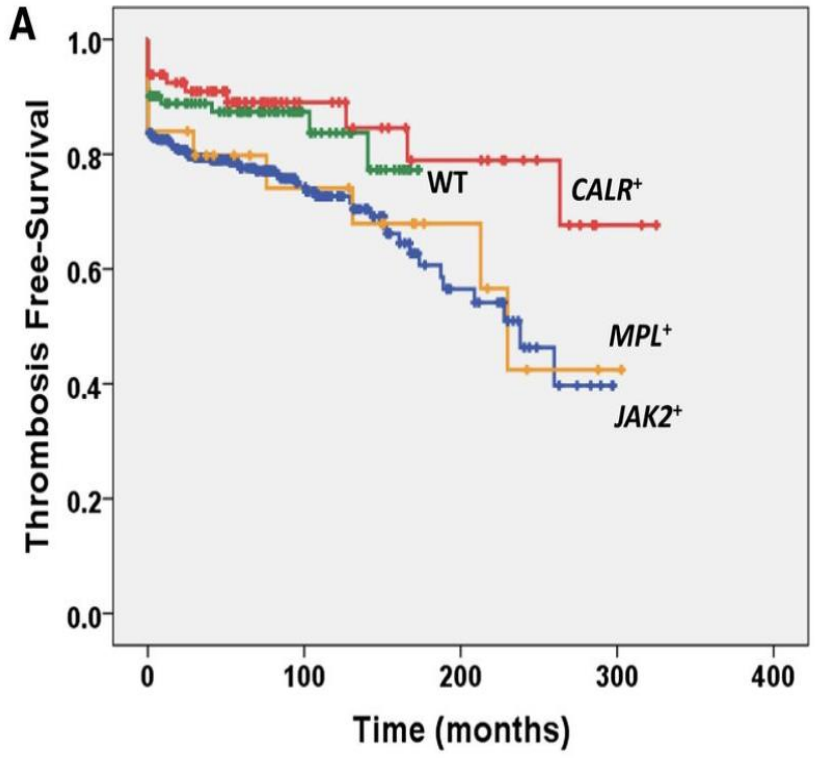


PV



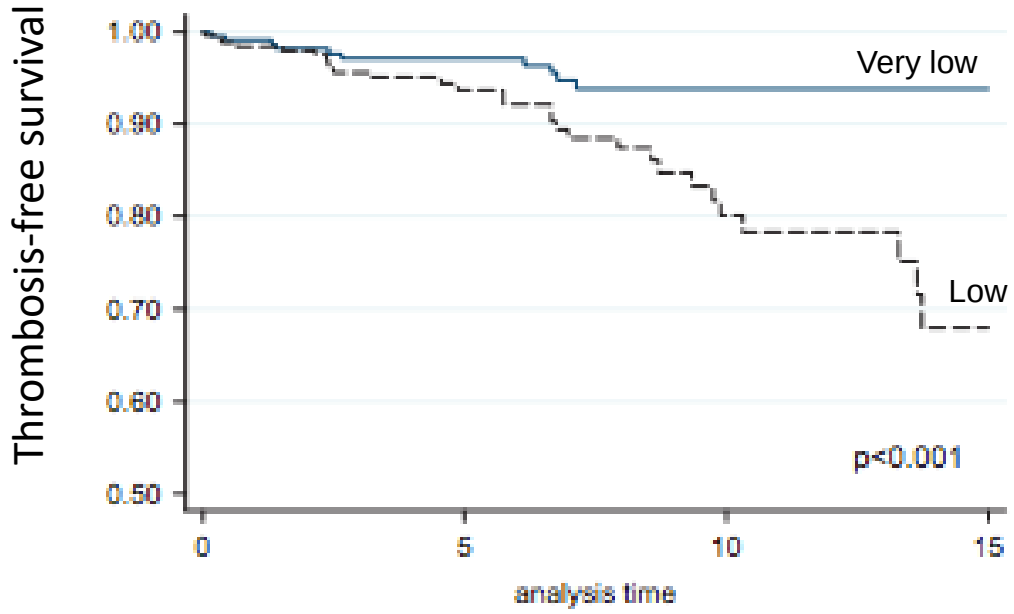
PMF

Molecular status in ET can impact risk of thrombosis



Campbell et al, Lancet 2005; Rotunno et al, Blood 2014; Rumi et al, Blood 2014

IPSET-thrombosis incorporates this



Very low: no thrombosis, age≤60, JAK2-neg
Low: no thrombosis, age≤60, JAK2-mutated

However:
- Based on retrospective data
- No prospective data on if/how should influence management

Barbui et al Blood Cancer J 2015

Transformation	Clinical risk factors	Genetic risk factors
Post PV MF	Age	*JAK2V617F* allele burden
	WBC	
	Disease duration	
	BM reticulin	
	Splenomegaly	
Post-ET MF	Age	*JAK2V617F* negative
	WBC	*ASXL1* mutation
	Anaemia	
	BM reticulin	

Prior th

Cerquozzi &
Blood Canc

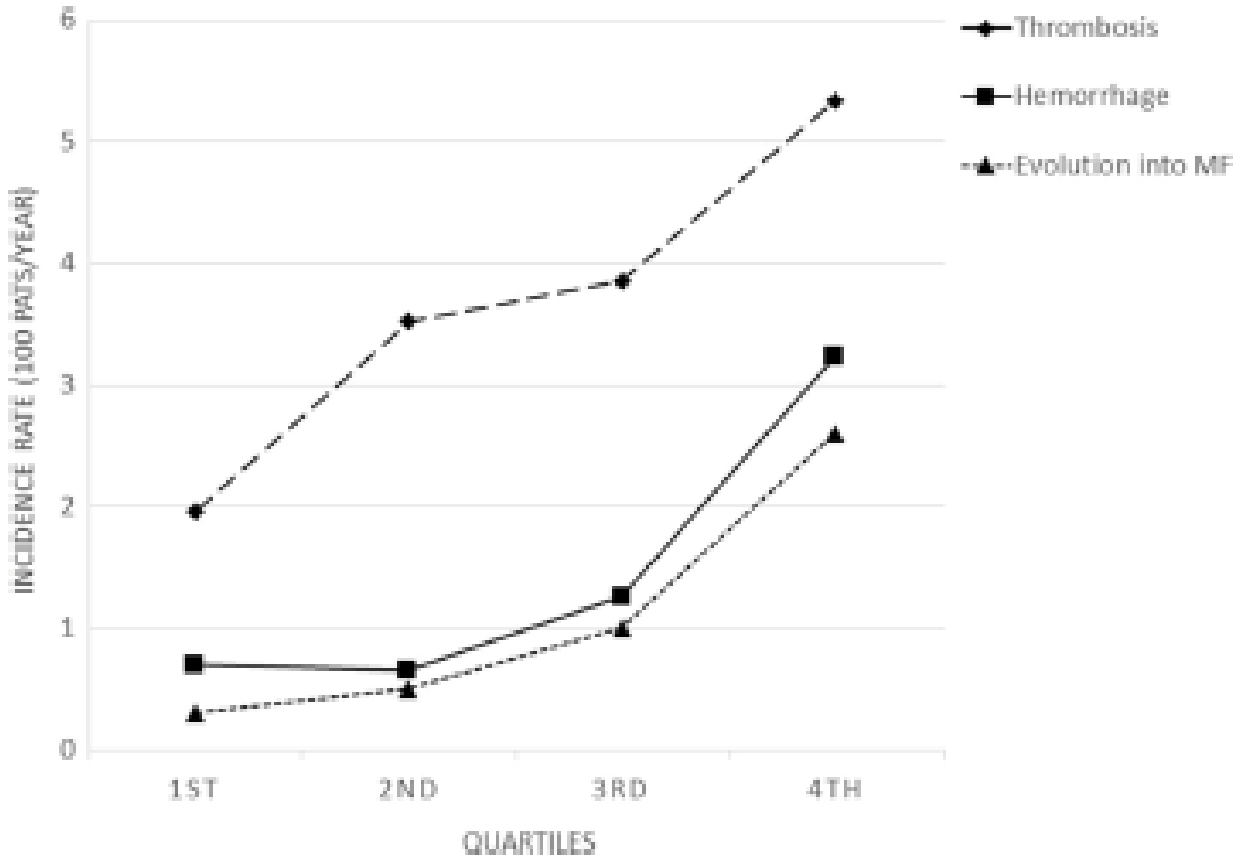
NEW LANGUAGE TO EXPLAIN

- Allele burden
- VAF = Variant allele frequency

- = % of total gene in sample which is mutated

- Eg JAK2 VAF of 25% means 75% of JAK2 is normal (wild type)

JAK2 V617F VAF and Rate of Thrombosis in PV



Bertozzi I et al, Ann Hematol 2017; 26:1297

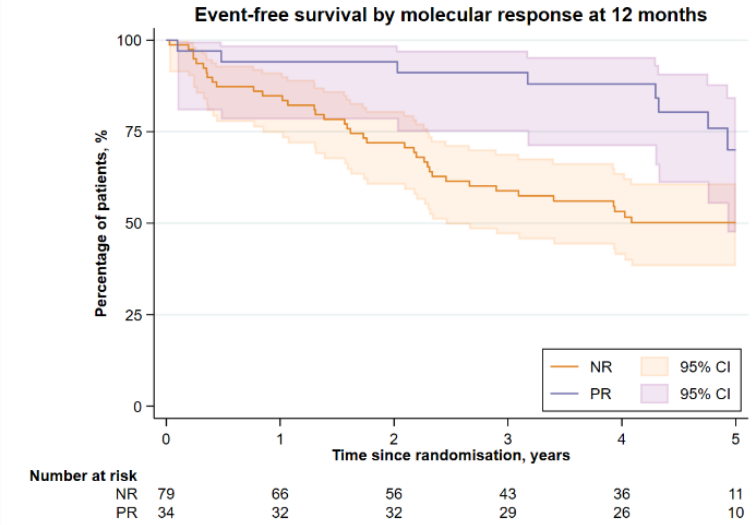
IS REDUCING THE VAF or ALLELE BURDEN IMPORTANT?

- Yes in other diseases eg CML definitely fundamental
- Yes after transplant
- New evidence from a UK PV study suggests YES reducing JAK2 VAF important but so was controlling all aspects of FBC

- Which treatments can lower the VAF
  - Many can not just interferon
  - Hydroxyurea (weak), RUXOLITINIB, some newer MF treatments too.

MAJIC PV: Concerning molecular response and clinical endpoints:

Molecular response at 1 year correlated with superior EFS – thrombosis, haemorrhage, transformation and death



Those with **durable molecular response** at last time point had significant improvements in **EFS, PFS and OS regardless of treatment arm**

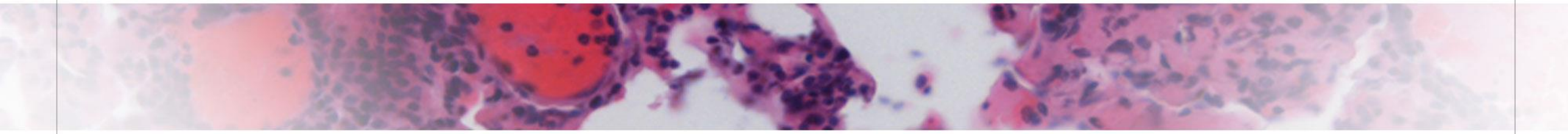
For ruxolitinib: all except thrombosis correlated with molecular response

For BAT there was no correlation

NEW FINDINGS

	Any				Ruxolitinib			BAT		
	Whole trial (n=127)	NR (n=74)	PR (n=53)	p-value	NR (n=31)	PR (n=39)	p-value	NR (n=43)	PR (n=14)	p-value
Thromboembolic event	38 (30%)	28 (38%)	10 (19%)	0.02	10 (32%)	7 (18%)	0.17	18 (42%)	3 (21%)	0.17
Haemorrhagic event	28 (22%)	23 (31%)	5 (9%)	0.004	9 (29%)	4 (10%		14		
Progression-free survival	35 (28%)	29 (39%)	6 (11%)	0.001	13 (42%)	3 (8%				
Event-free survival	53 (42%)	40 (54%)	13 (25%)	0.001	16 (52%)	8 (21%				
Overall survival	22 (17%)	18 (24%)	4 (8%)	0.01	8 (26%)	3 (8%				

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

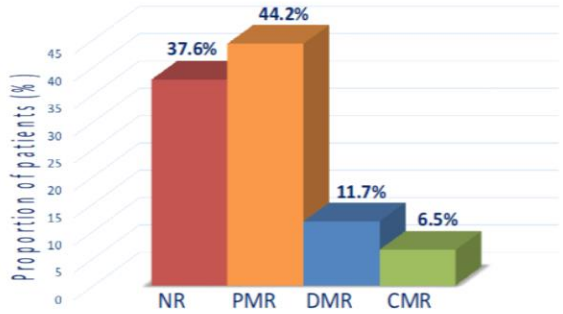


*JAK2*V617F Molecular Response to Ruxolitinib in Patients with PV and ET Is Associated with Lower Risk of Progression to Secondary Myelofibrosis

P. Guglielmelli, B. Mora, F. Gesullo, F. Mannelli, G. G. Loscocco, L. Signori, C. Passina, F. Pancani, I. Colugnat, R. Aquila, E. Nacca, P. Cicogna, F. Passamonti, and A.M. Vannucchi

CRIMM, Center Research and Innovation of Myeloproliferative Neoplasms, University of Florence, AOU Careggi, Florenc
Hematology, University Hospital Ospedale di Circolo e Fondazione Macchi – ASST Sette Laghi, University of Insubria

Categories of *JAK2* V617F Molecular Response



- A CMR was reached in 5 patients (6.5%), 3 (4.6%) and 2 (16%) with PV and ET; a DMR was reached in 9 patients (11.7%), 6 were PV (8.5%) and 3 ET (25%).

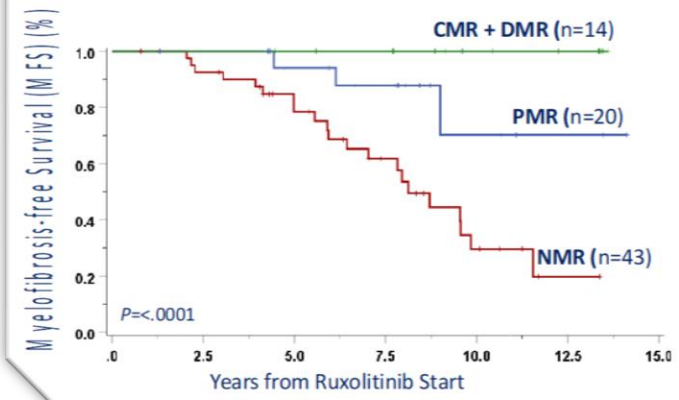
- No correlation between molecular response & response of Hct, platelets and spleen length reduction.
- Normalization of leukocyte count was more frequent with at least PMR (93.8% *vs* 62.5%, P=0.02).
- A baseline *JAK2*V617F VAF level of <60% was associated with a significantly greater likelihood to obtain CMR+DMR (37.1% *vs* 2.4%; P<0.0001) as well as PMR (60% *vs* 38.2%, P=0.01).

American Society *of* Hematology

Barosi G et al. Blood. 2013 Jun 6;121(23):4778-81

Molecular Response Is Associated with superior MF-Free Survival

- 24 patients (31.1%) progressed to sMF after a median of 6.0y (2-11.5). 34% were PV and 16.6% ET.



Category	sMF events	MFS (median) yr	HR (95% CI)
CMR+DMR	0	NR	ref
PMR	3	NR	3.6 (0.4-34.6)
NMR	21	8.1 (6.9-9.4)	19.9 (2.4-166.7)

- All 3 pts who progressed to AML were NMR.

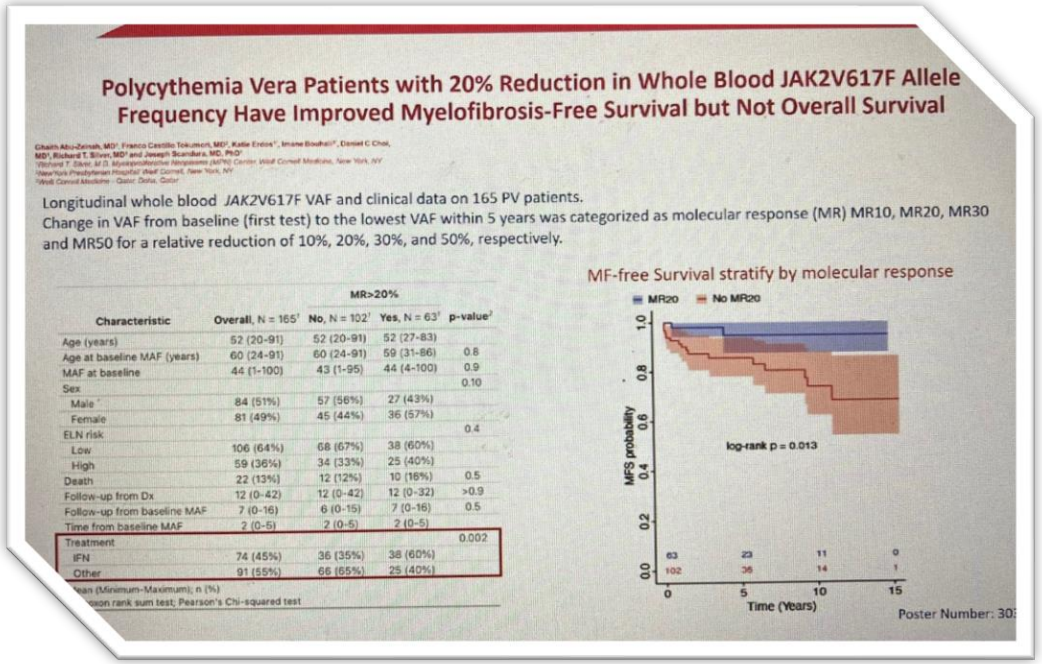
American Society *of* Hematology

- **2 other ASH abstracts link MF free survival and variably defined molecular response**
- **Should this lead to an immediate change in practice?**

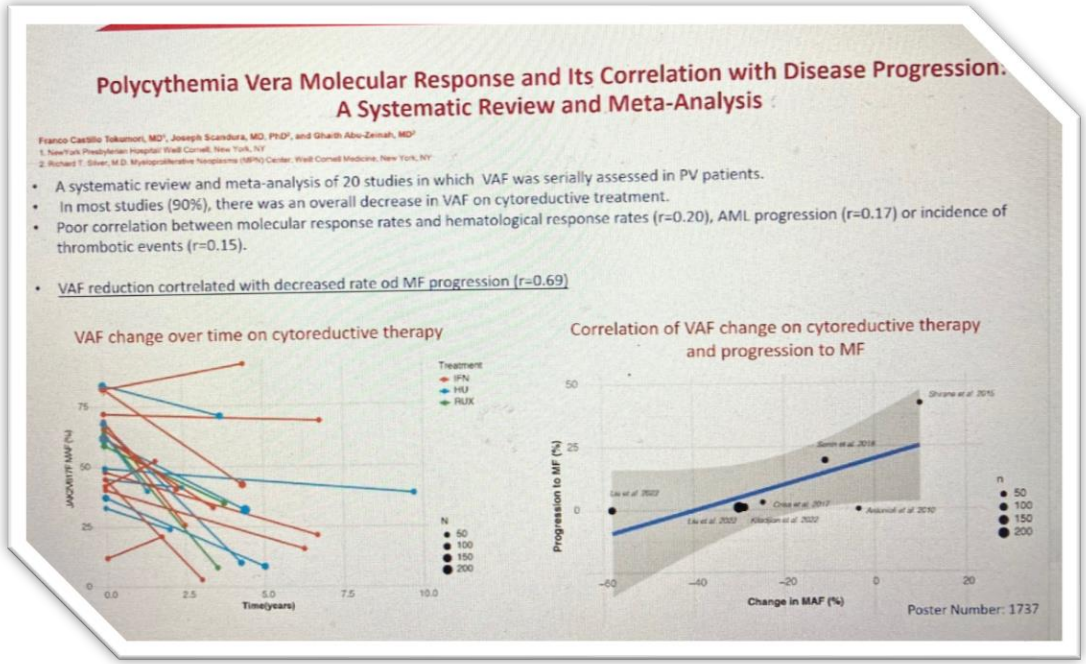
NO

- MAJIC PV also demonstrates haem response is important
- Needs careful thought and guidance..

Other data presented at ASH also suggested benefits of molecular response impacting clinical outcome:



Abu-Zeinah 3034



Tokumori 1737

Single cohort and systematic review and meta-analysis s
>20% reduction linked to reduction in PPV MF

Should this lead to an immediate change in practice?

- **NO**
- MAJIC PV also demonstrates haem response is important
- Needs careful thought and guidance..

Take away messages genetics and MPN:

- Genetic tests are an important fundamental in the diagnosis and management of MPN
- Genomic discoveries have radically altered diagnostics, prognostics and the therapeutic paradigm
- Some emergent data that altering allele burden is important
- MORE DATA TO FOLLOW
- WATCH THIS SPACE