Treatment advances for patients with myelofibrosis (MF) and value of patient-reported symptoms

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fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GIMEMA International Meeting

New Frontiers in Hematologic Research: Quality of Life and Artificial Intelligence

Disclosures of Harrison

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	x				x	x	
GSK	x				x	x	
Incyte	x				x	x	SSC
Keros			x			x	DMC
Takeda			x			x	
Geron						x	
Johnson and Johnson						x	
Syntara			xx				
SOBI						x	
MSD						x	
AOP	x		x		x	x	

Patient Reported Outcomes in myelofibrosis can mean a number of things but has become synonymous with “Disease related symptoms”

As we will discuss these have enabled a healthy focus upon PRO and importance of QoL

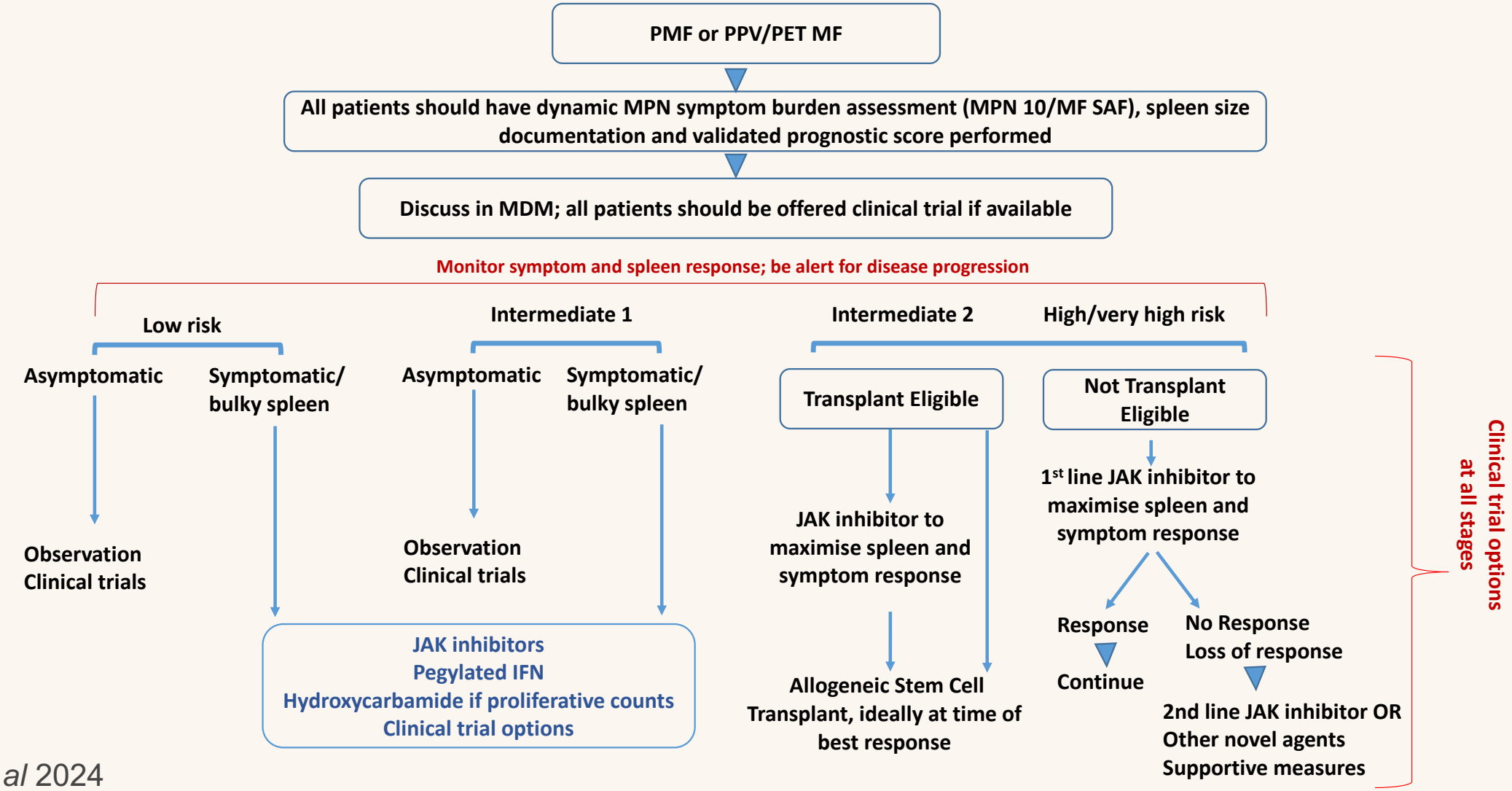
But

Symptoms do not EQUAL Quality of Life

And

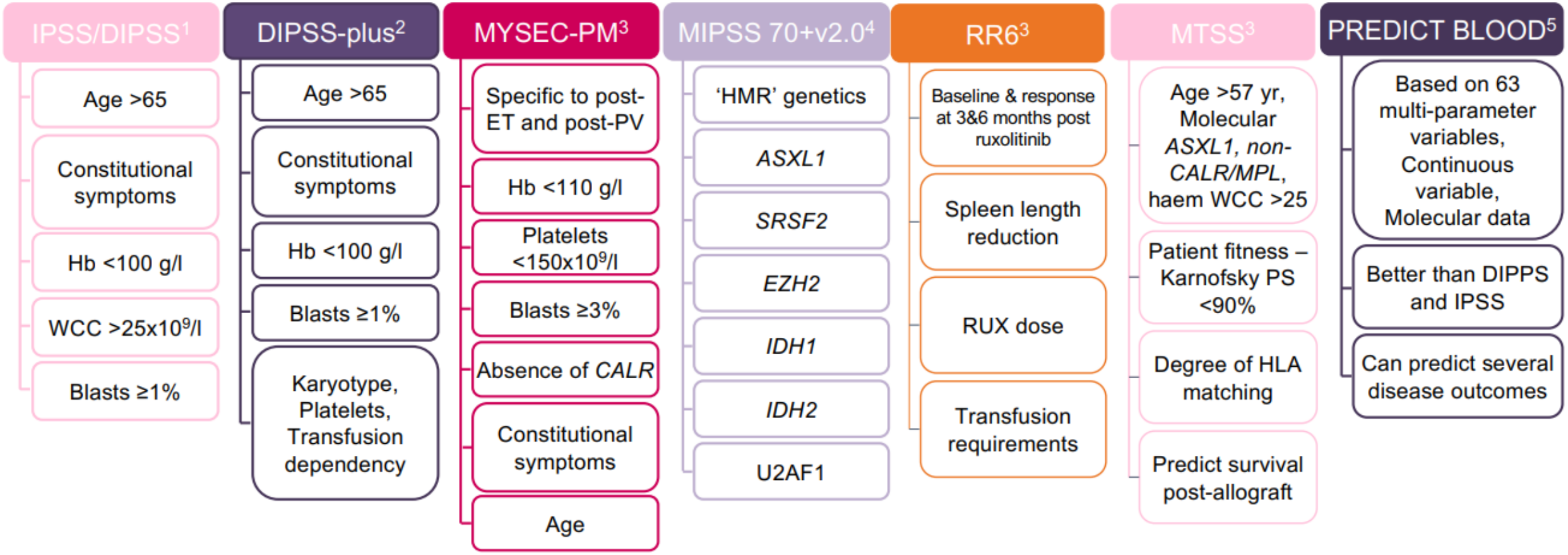
We should consider that functional cure with allo-ASCT may involve substantial perhaps temporary reduction in QoL

Myelofibrosis Management in 2025…. Same as in 2024 but changing



McLornan *et al* 2024

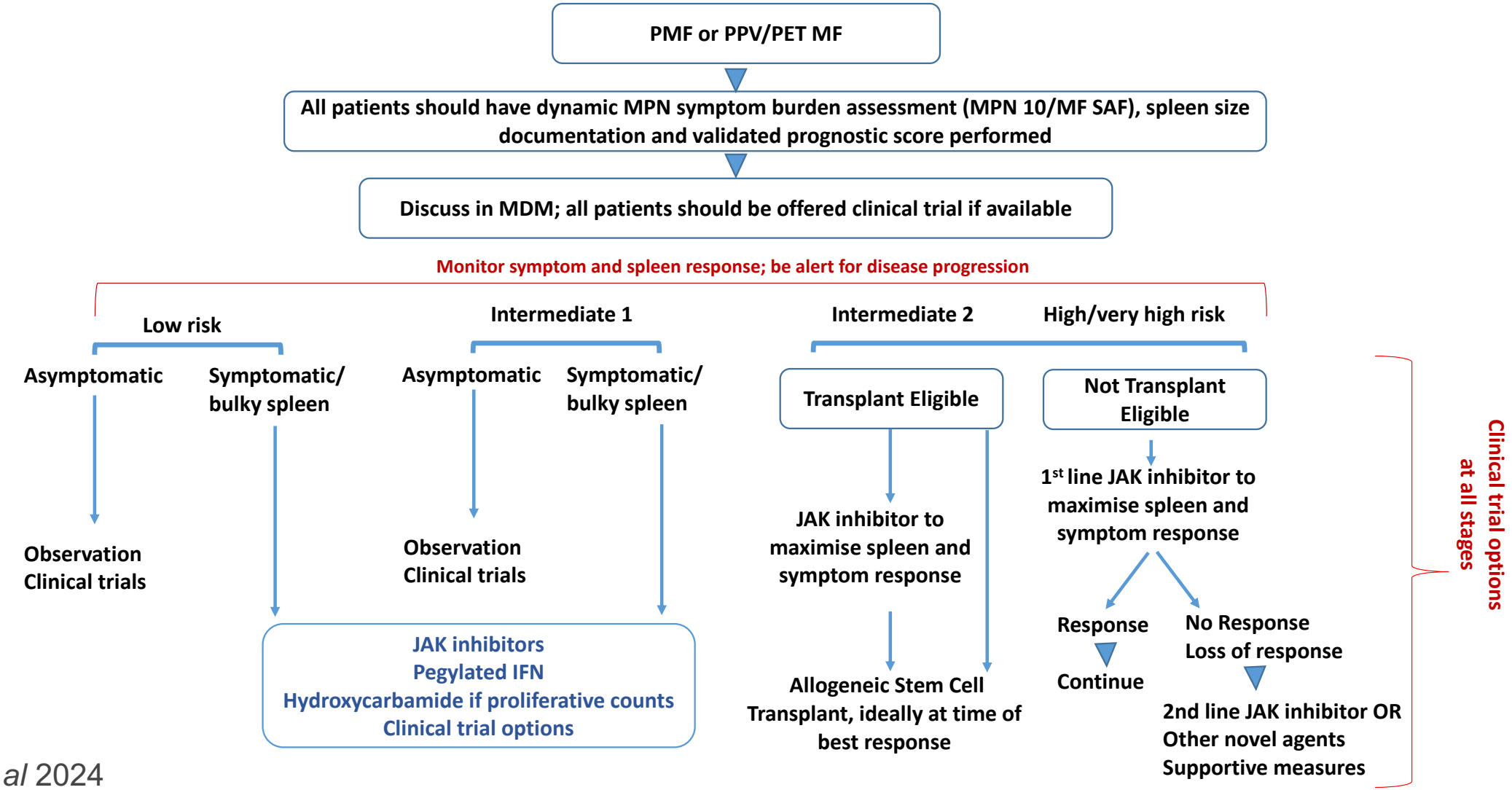
Incorporation of symptoms into prognostic scores in MF



DIPSS=Dynamic International Prognostic Scoring System; Hb=haemoglobin; HLA=human leukocyte antigen; HMR=high molecular risk; IPSS=International Prognostic Scoring System; MIPSS=Mutation-Enhanced International Prognostic Scoring System; MTSS=myelofibrosis transplant scoring system; MYSEC=myelofibrosis secondary to polycythaemia and essential thrombocythemia-prognostic model; PMF=primary myelofibrosis; PS=performance status; WCC=white cell count.

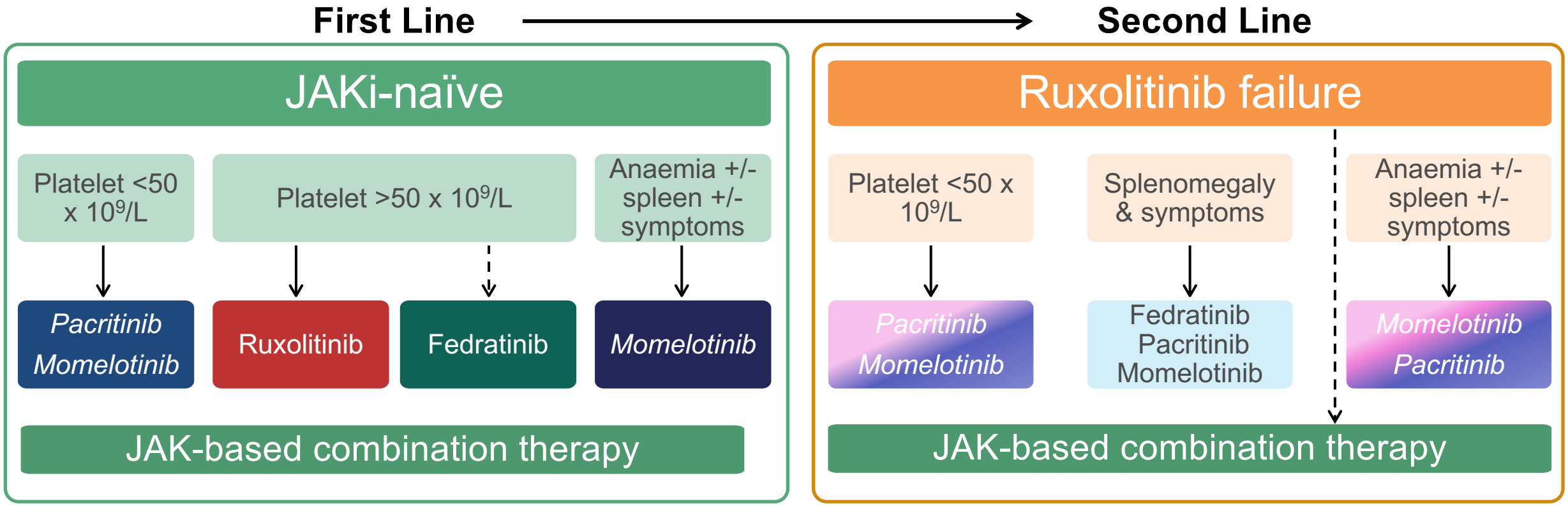
1. Passamonti F, at al. *Blood*. 2010;115:1703–1708; 2. Gangat N, et al. *J Clin Oncol*. 2011;29:392–397; 3. Duminuco A, et al. *J Clin Med*. 2023;12:2188;
4. MIPSS70 score. Available from: http://www.mipss70score.it [Last accessed: May 2024]; 5. Grinfeld J, et al. *N Engl J Med*. 2018;379:1416–1430.

Myelofibrosis Management in 2025



McLornan *et al* 2024

POTENTIAL POSITIONING OF JAK INHIBITORS IN MF



Pacritinib is approved by the FDA but are not currently approved in UK
Fedratinib is only available second line

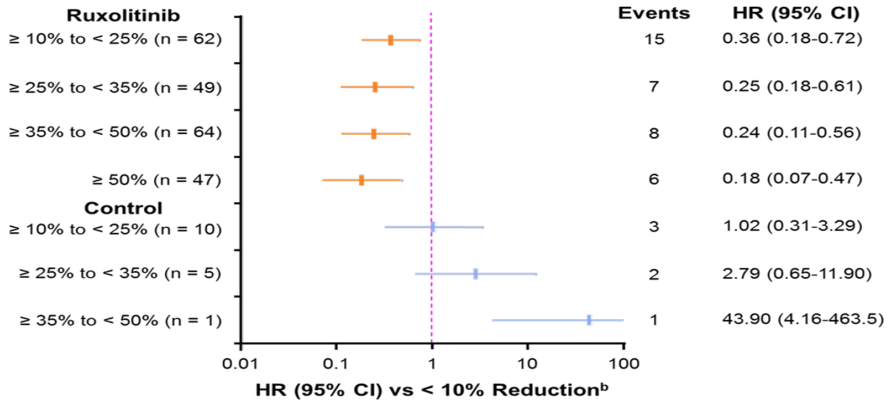
Clinical Variables Predictive of Survival Benefit / Outcome in Patients Receiving JAK Inhibitor Therapy?

Treatment goal……..

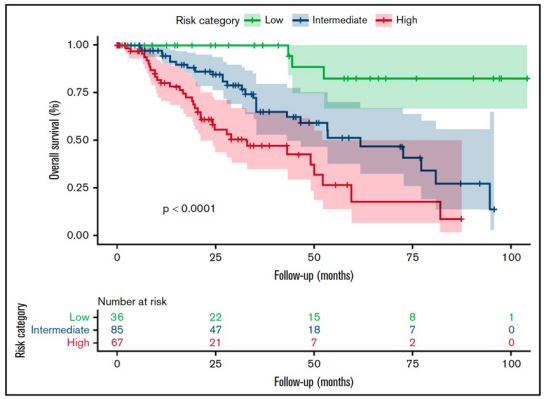
- Spleen size reduction (for ruxolitinib, pacritinib, momelotinib, and fedratinib)
- Transfusion independence (for momelotinib)

On treatment events, complications dose etc

- Requirement for transfusion and dose of ruxolitinib <20mg BID (for patients who have been on RUX for ≥6 months) – in line with the RR6 prognostic score
- Emergence of clonal progression (following discontinuation of ruxolitinib) and specifically, clones such as RAS and TP53



[a] Includes patients known to be alive at week 24.
[b] Category includes patients with a < 10% reduction from baseline in spleen volume at week 24 or no assessment (ruxolitinib, n = 64; control, n = 189); among these patients, there were 26 deaths (events) in the pooled ruxolitinib group and 63 deaths in the control group.



BID, twice daily; JAK, Janus kinase; RR6, Response to Ruxolitinib After 6 Months; RUX, ruxolitinib.

Can we do better than JAKi monotherapy in MF?

What will the outcome of mCALR and more specific JAKi therapies be?

Is combination upfront better or is it better to “rescue” with a combination?

> **Soon we should expect results from studies with Imetelstat, Navetamadlin, Selinexor…. And others..**

Utility of other JAK inhibitors as combo partners ?

How do we define sufficient benefit for success and then adoption?

Comparison of two completed phase 3 upfront combination trials

P	Transform 1 (BCL_2)	Manifest 2 (BETi)
	RUX +/- Navitoclax N = 252	RUX +/- Pelabresib N= 431
Risk Int 1/ Int 2/ High (%)	5%/ 85%/ 10%	59% / 35%/ 6%
Discontinuations	30% / 35% (control)	27.1% / 25% (control)
Mean RUX dose	20mg / 30mg est*	29.3mg /31.3 mg
SVR35%	63.2% vs 31.5% (p<0.0001)	65.9% vs 35.2% (p<0.001)
TSS50	39.2% / 41.7%	52.3% vs 42.3 (p=0.216)
Mean absolute change in TSS	+1.4 (p NS)	-1.94 (p=0.0545)
* Anaemia response** / Fibrosis improvement***	Not stated	9.3% vs 5.6% 38.5 vs 24.2 (OR 2 [1.14-3.93])

Pemmaraju et al EHA 2024; Rampal et al EHA 2024

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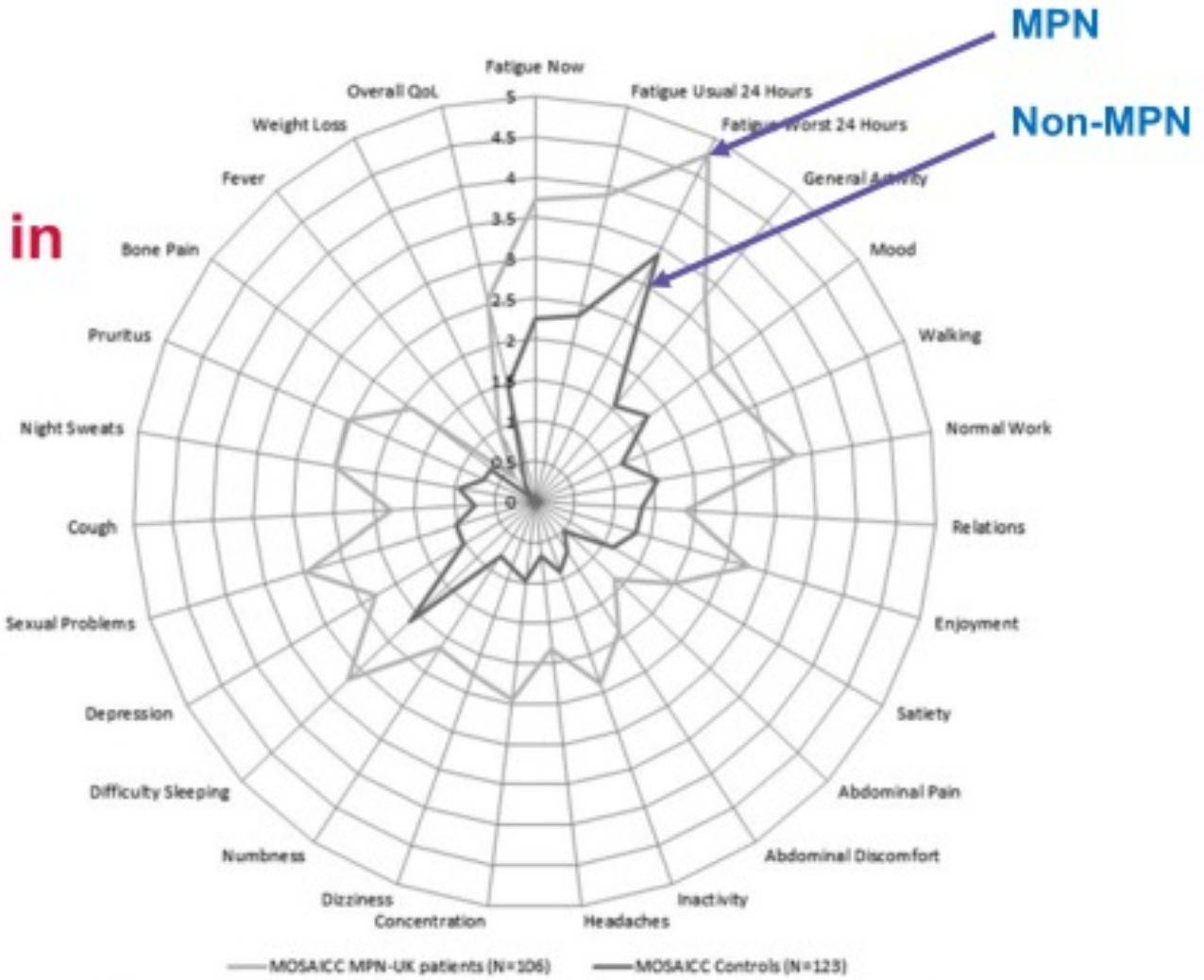
What is the reliability of symptoms as an endpoint in MPN?

- Symptoms are not MPN specific
- Fatigue is a dominant symptom but not MPN specific



Comparison of MOSAICC MPN-UK patient and control reported symptom scores.

Anderson AJH 2015

myMPNvoice App
work of Patrick Harrington

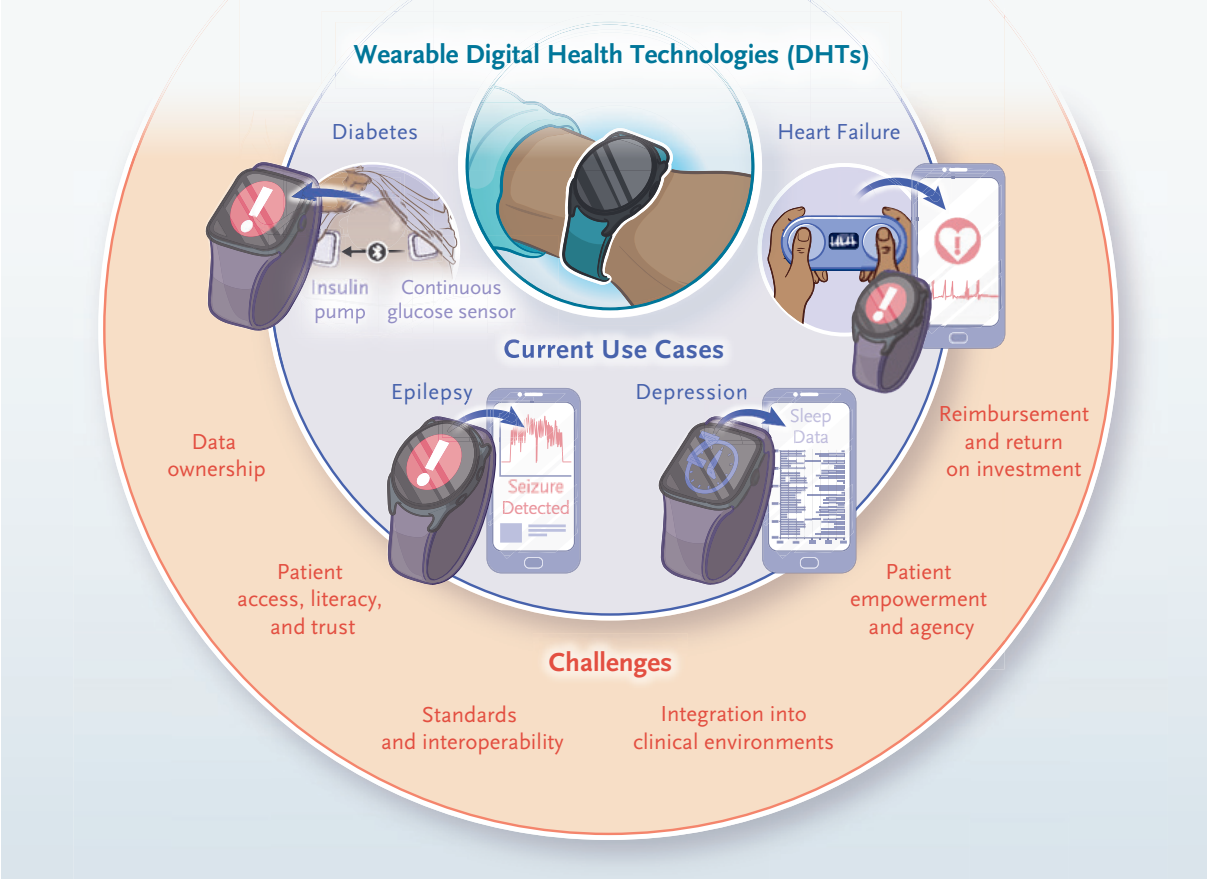
Aim:

To better understand lived experience of patients with MPN:

Through:

- Patient-reported outcomes
- Biometrics linked to wearable device
- Electronic health record data extraction

Potential Applications of Wearable Devices in Healthcare



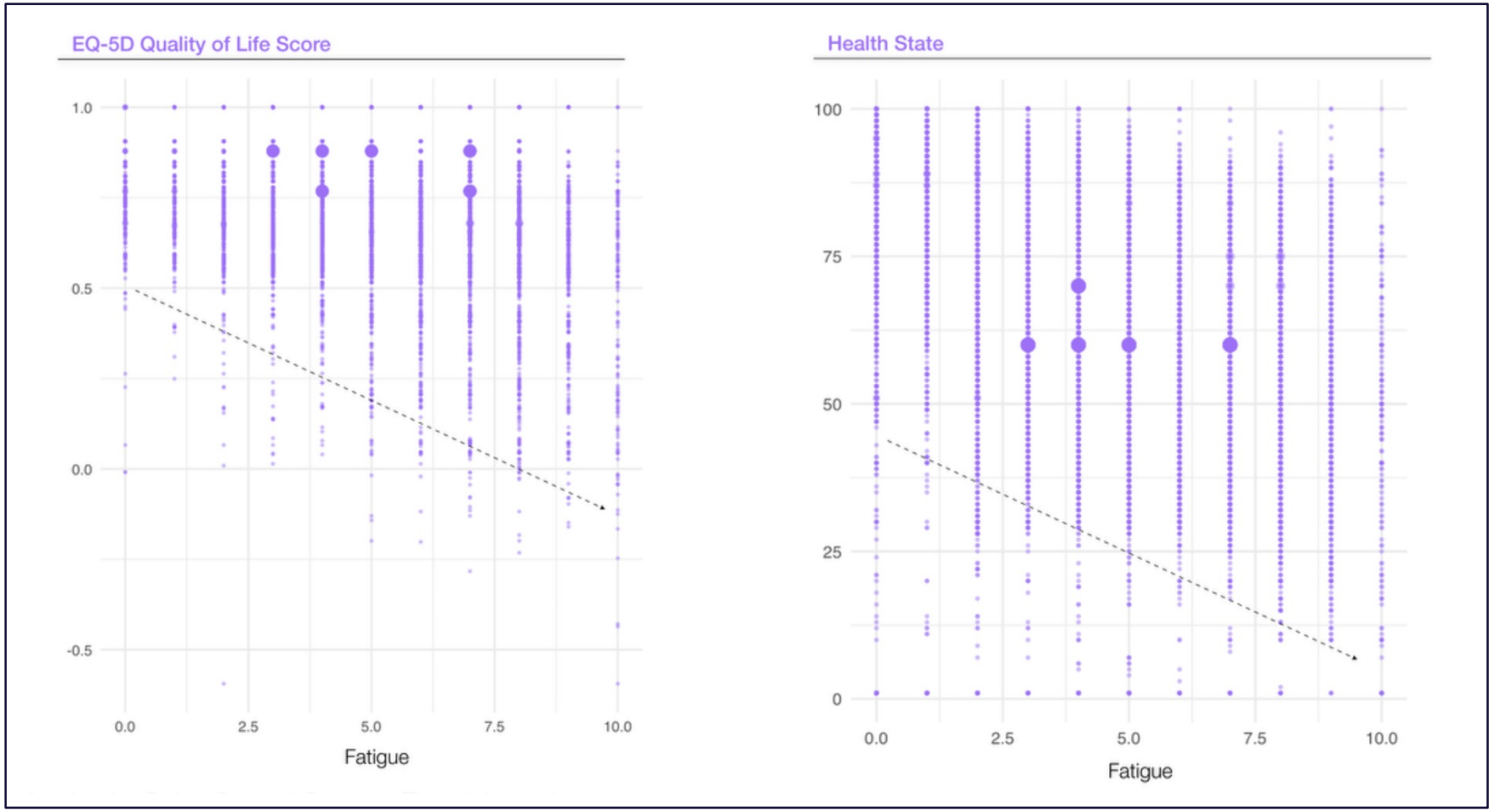
Ginsburg et al. N Engl J Med 2024;390:1118-27.

Biometric Data

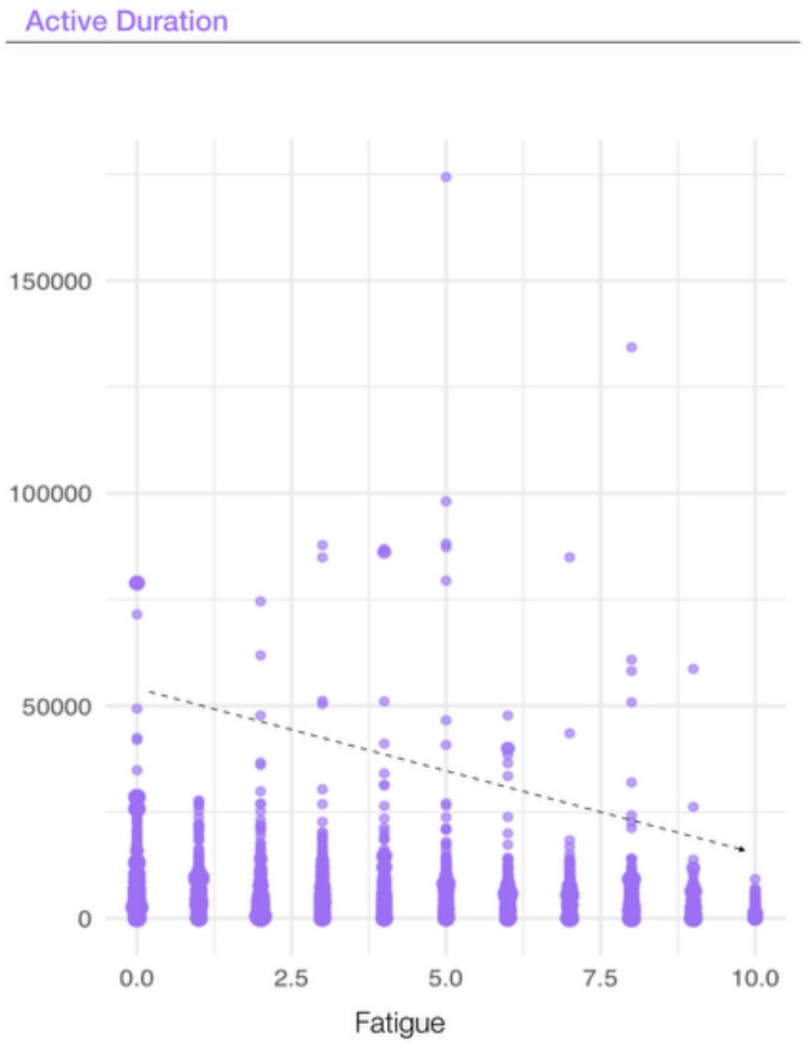
Remote monitoring data is pulled from the Withings ScanWatch2 and App into the MyMPN Voice App

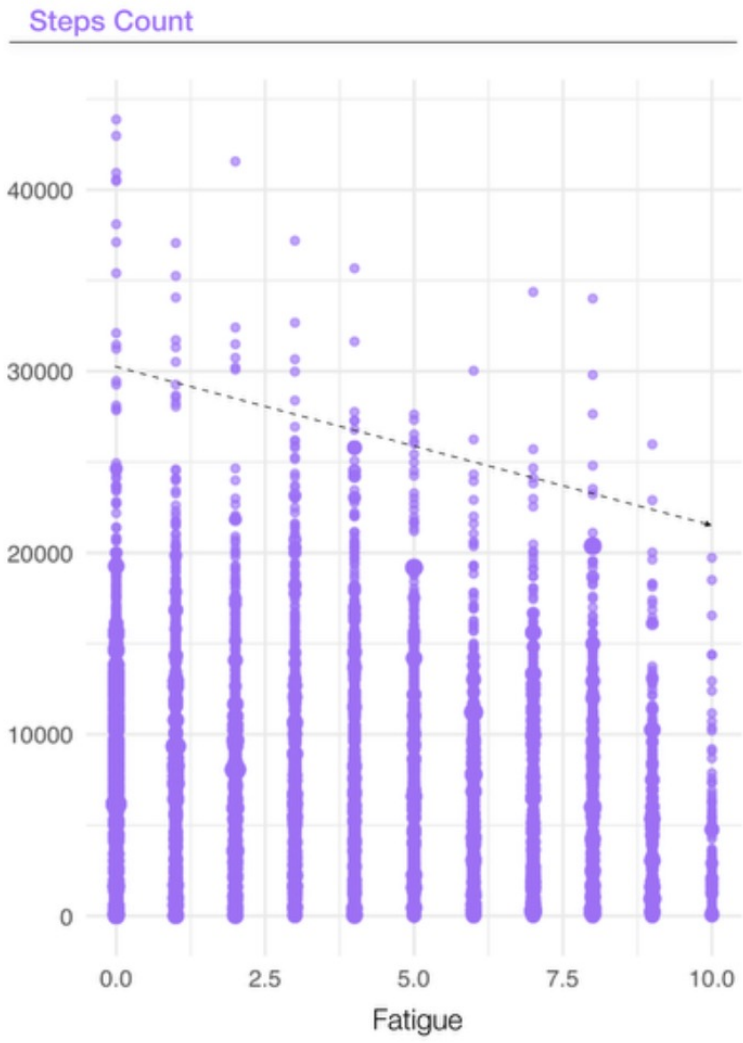
Fatigue and Correlation with other Patient Reported Outcome Data

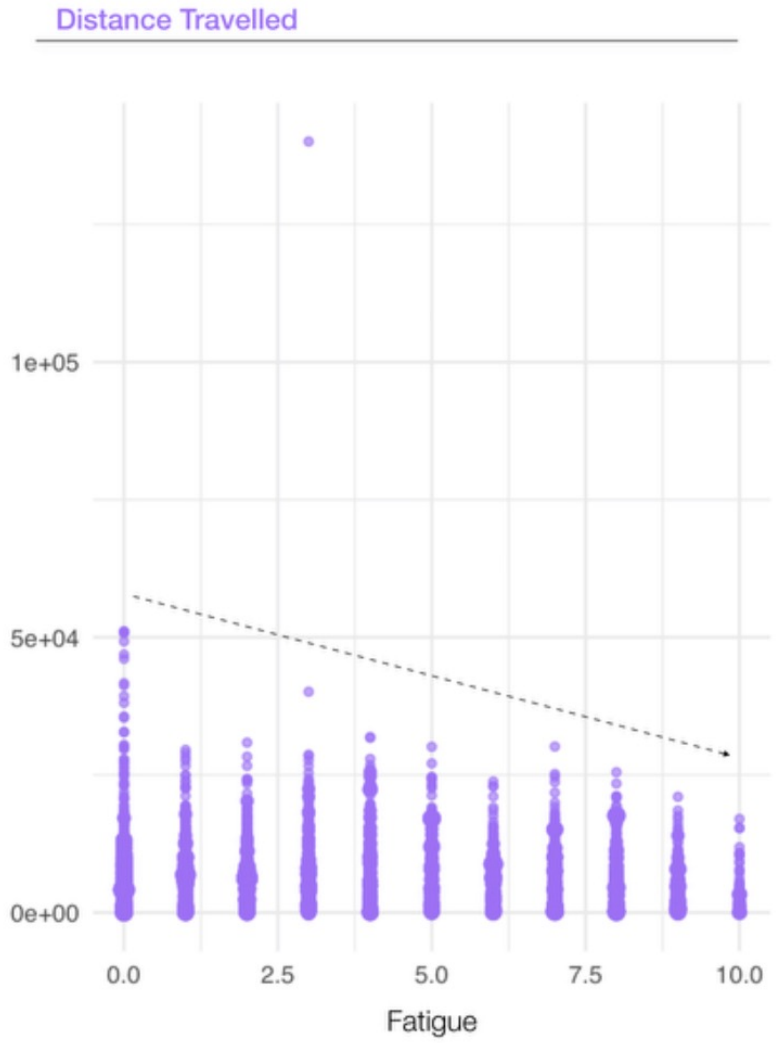
- Persistent, subjective sense of tiredness related to cancer or cancer therapy that interferes with usual functioning
- Most common symptom occurring in 81-95% percent of MPN patients



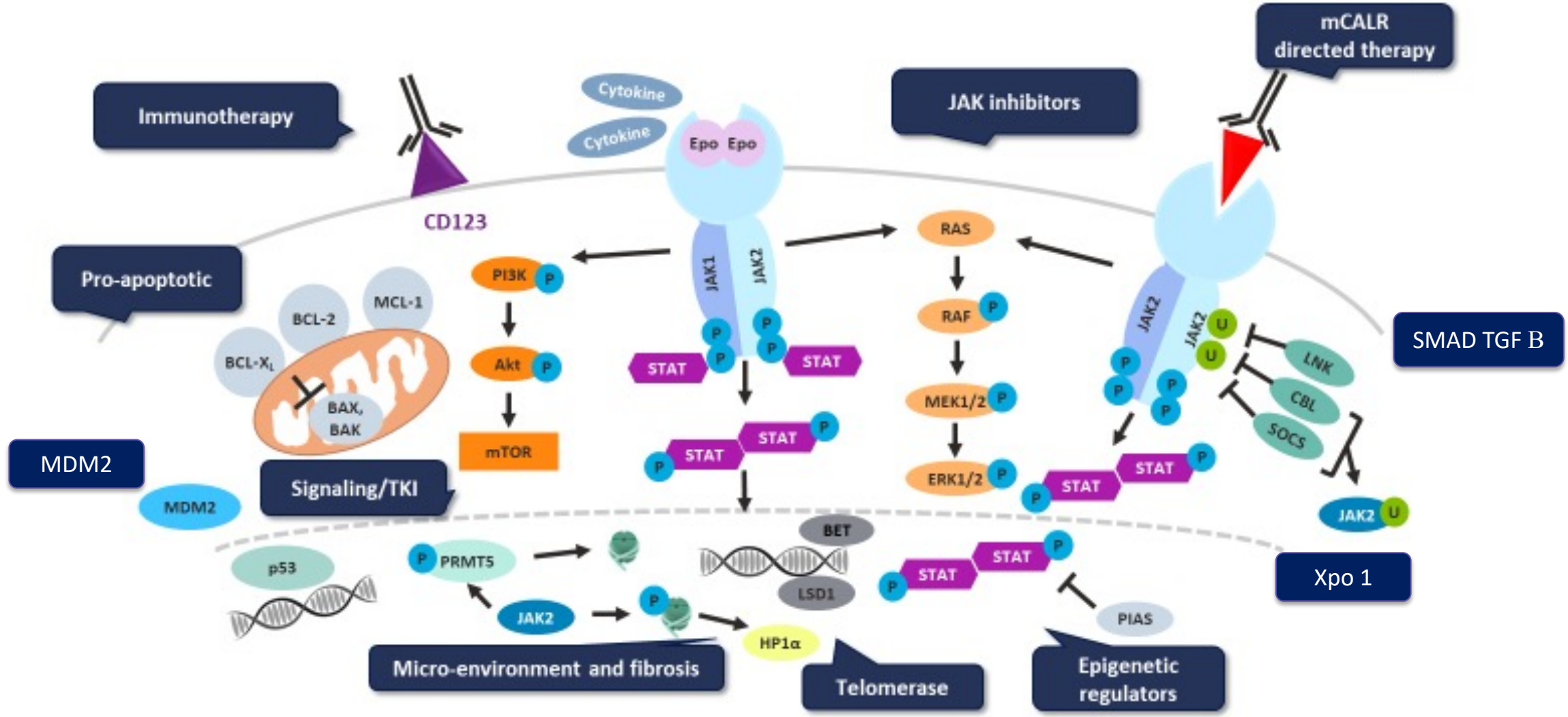
Fatigue a major area of unmet need in MPN correlates with Biometric Data







Future therapies for the treatment of MF..



TKI, tyrosine kinase inhibitor.

Adapted from: Daver N & Assi R. *Oncol Hematol Rev* 2016; **12**:71–74; McLornan DP & Harrison CN. *Br J Haematol* 2020; **191**:21–36; Schieber M, *et al. Blood Cancer J* 2019; **9**:74; Tremblay D & Mascarenhas J. *Cells* 2021; **10**:1034.

CALR Mutation Discovery to Phase 1 Clinical Trial in <10 yrs

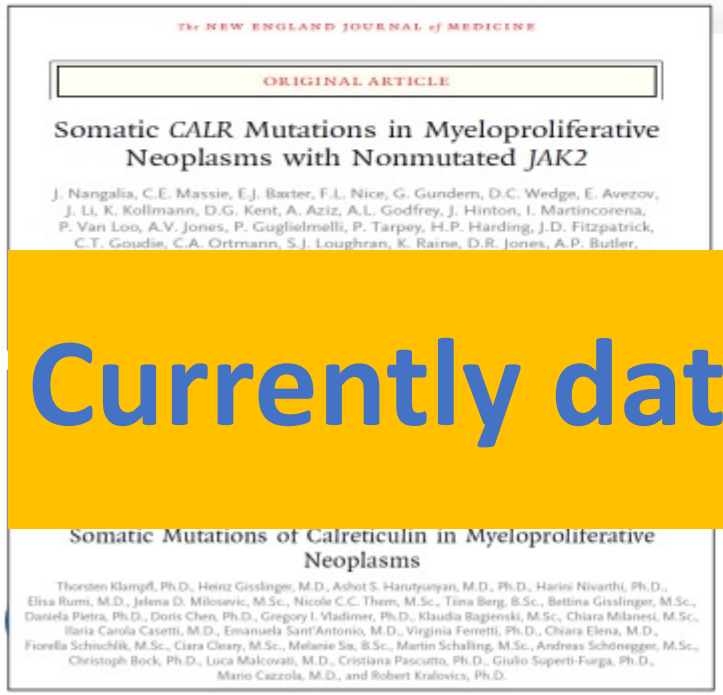
2013
DISCOVERY OF mutCALR

2023
PHASE 1 MONOCLONAL ANTIBODY INCA033989

LESS THAN 10 YEARS

1st

- **First mutCALR oncogene-targeted therapy**
- **Developed for patients with MPNs**


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

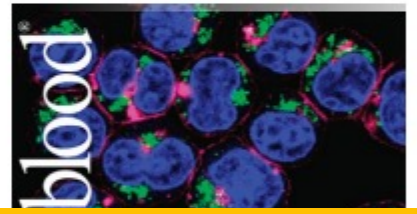
Somatic *CALR* Mutations in Myeloproliferative Neoplasms with Nonmutated *JAK2*

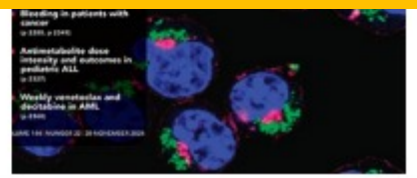
J. Nangalia, C.E. Massie, E.J. Baxter, F.L. Nice, G. Gundem, D.C. Wedge, E. Avezov, J. Li, K. Kollmann, D.G. Kent, A. Aziz, A.L. Godfrey, J. Hinton, I. Martincorena, P. Van Loo, A.V. Jones, P. Guglielmelli, P. Tarpey, H.P. Harding, J.D. Fitzpatrick, C.T. Goudie, C.A. Ortmann, S.J. Loughran, K. Raine, D.R. Jones, A.P. Butler,

Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms

Thorsten Klampfl, Ph.D., Heinz Gisslinger, M.D., Ashot S. Harutyunyan, M.D., Ph.D., Harini Nivarthi, Ph.D., Elisa Rumi, M.D., Jelena D. Milosevic, M.Sc., Nicole C.C. Them, M.Sc., Tina Berg, B.Sc., Bettina Gisslinger, M.Sc., Daniela Pietra, Ph.D., Doris Chen, Ph.D., Gregory I. Vladimer, Ph.D., Klaudia Bagienski, M.Sc., Chiara Milanesi, M.Sc., Ilaria Carola Casetti, M.D., Emanuela Sant'Antonio, M.D., Virginia Ferretti, Ph.D., Chiara Elena, M.D., Fiorella Schischlik, M.Sc., Ciara Cleary, M.Sc., Melanie Six, B.Sc., Martin Schalling, M.Sc., Andreas Schönegger, M.Sc., Christoph Bock, Ph.D., Luca Malcovati, M.D., Cristiana Pascutto, Ph.D., Giulio Superti-Furga, Ph.D., Mario Cazzola, M.D., and Robert Kralovics, Ph.D.


2022
American Society of Hematology
Helping hematologists conquer blood diseases worldwide

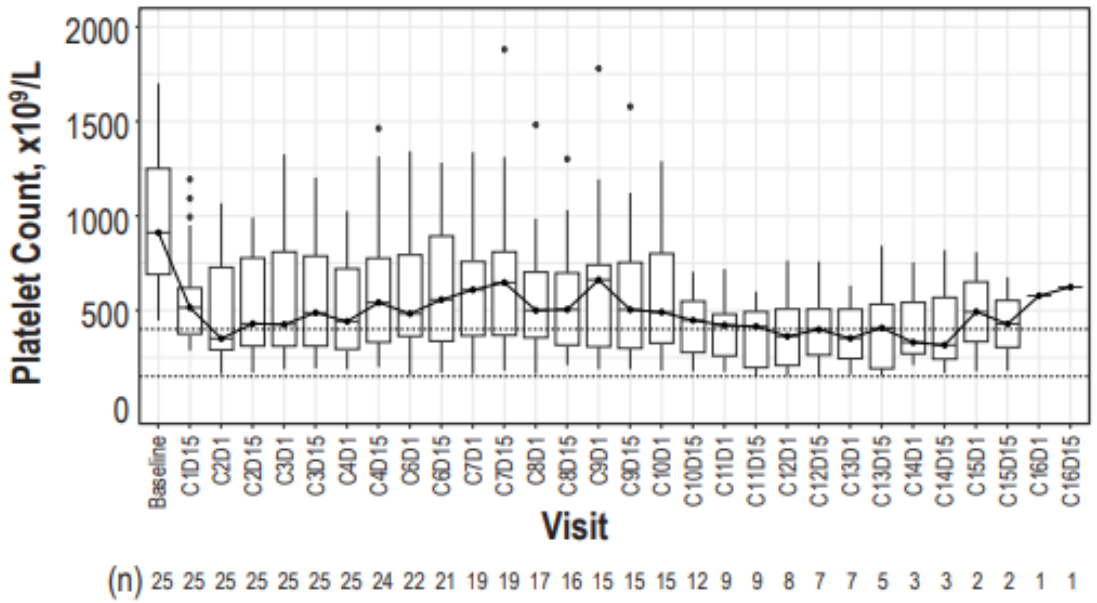




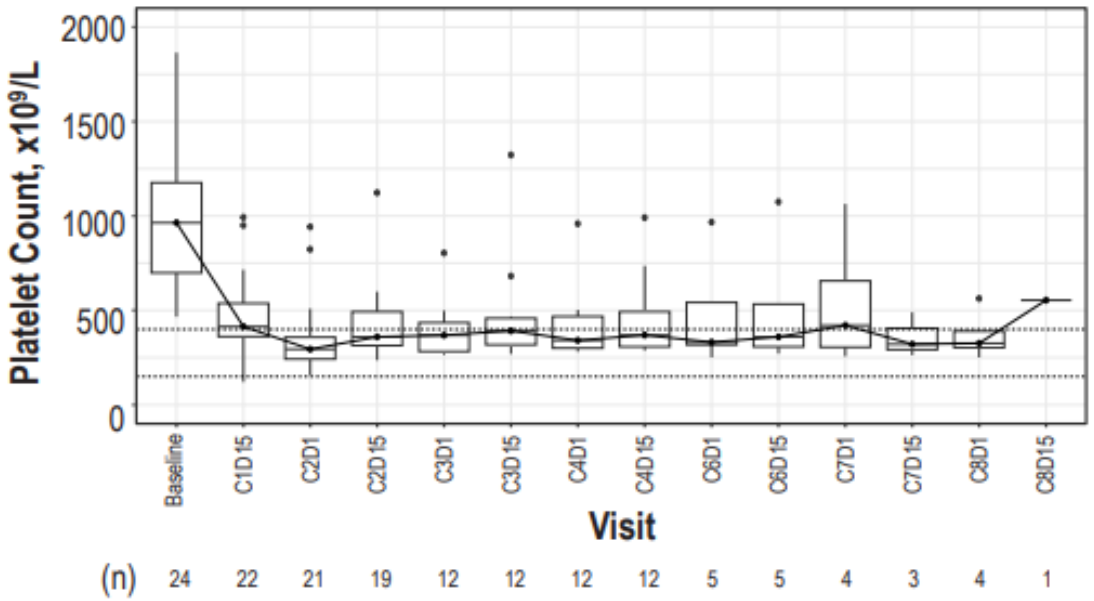
Currently data only available for ET….

Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

Doses 24-250 mg*



Doses 400-2500 mg†

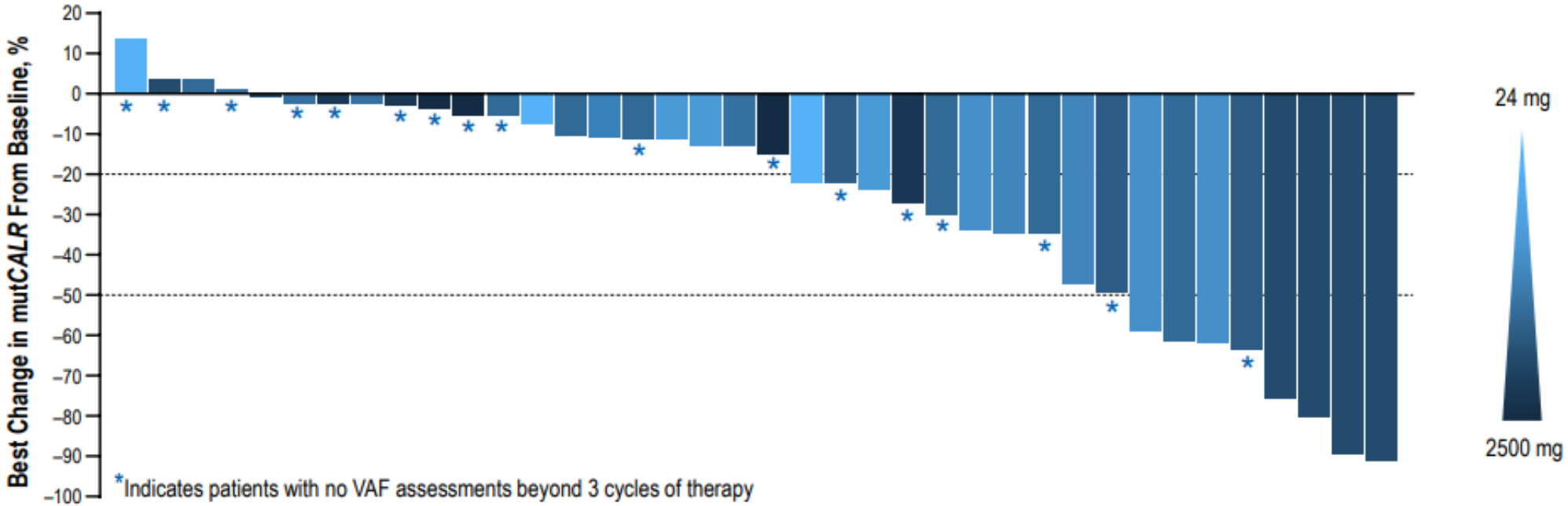


- Of the 31 patients that enrolled with concomitant cytoreductive therapy (hydroxyurea or anagrelide), 20 (65%) discontinued it and remained on study
- Thrombocytopenia was not observed in any patient
- Doses of ≥400 mg produced higher frequency of platelet count normalization

Dotted lines indicate upper and lower limit of normal. Boxes denote the first and third quartiles, lines represent the median. Number of patients with available data at each visit is noted below the x axis. *24 mg (n=3), 50 mg (n=3), 70 mg (n=3), 100 mg (n=3), 200 mg (n=5), 250 mg (n=8). †400 mg (n=5), 750 mg (n=9), 1500 mg (n=6), 2500 mg (n=4). C, cycle; D, day.

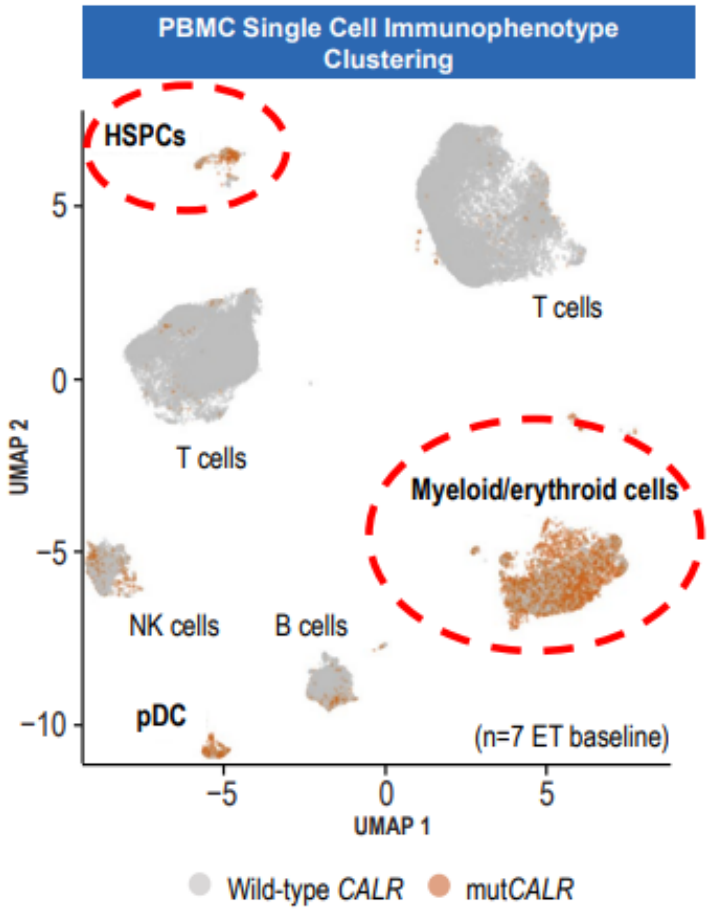
Molecular Responses Are Rapid and Frequent

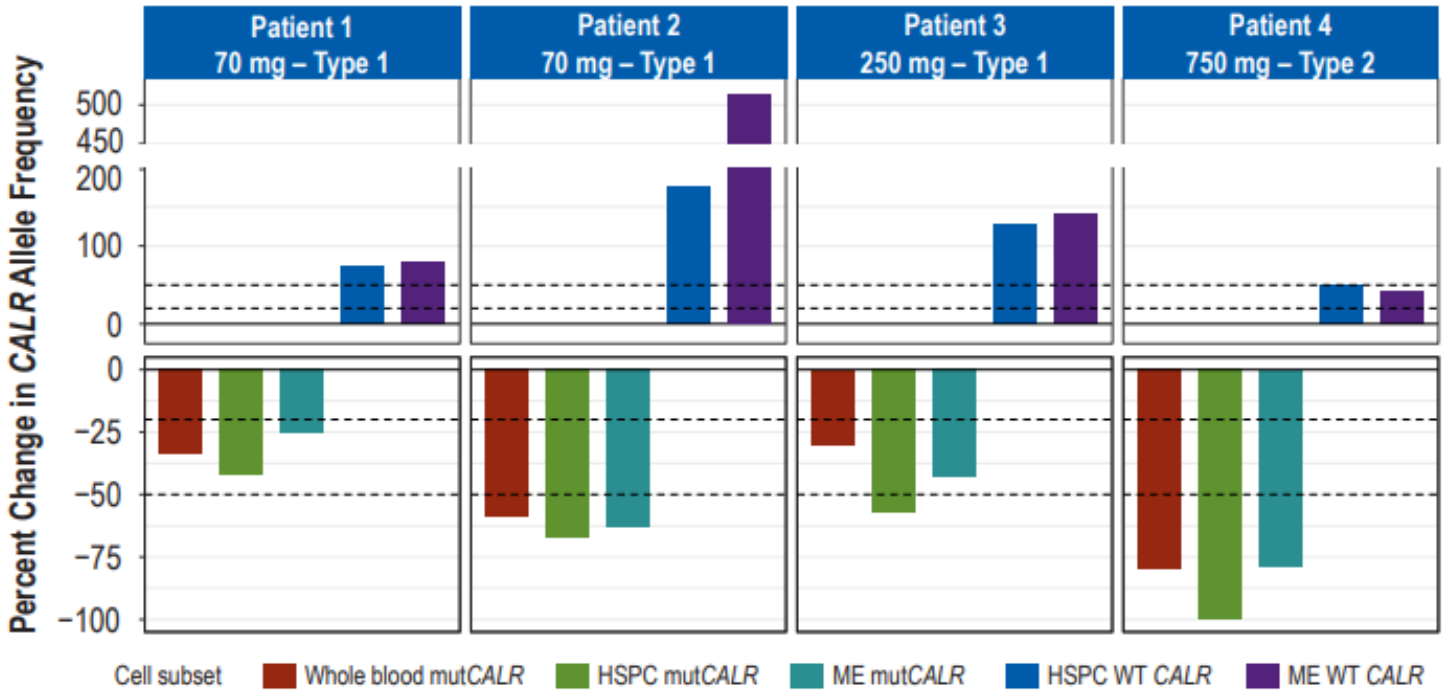
- A reduction in mut*CALR* VAF from baseline occurred in 34/38 (89%) evaluable patients
  - 18/38 (47%) achieved >20% best reduction in VAF
  - 8/38 (21%) achieved >50% best reduction in VAF
- A reduction of ≥20% VAF occurred within 6 cycles of therapy for all 18 responders
- All 18 molecular responders achieved a hematological response of CR or PR



Dotted lines represent 20% and 50% VAF thresholds. 1 cycle = 28 days or 2 doses. CR, complete response; mut*CALR*, mutations in calreticulin; PR, partial response; VAF, variant allele frequency.

Reduction of mut*CALR*+ HSPCs and Myeloid/Erythroid Cells in Clinical Responders

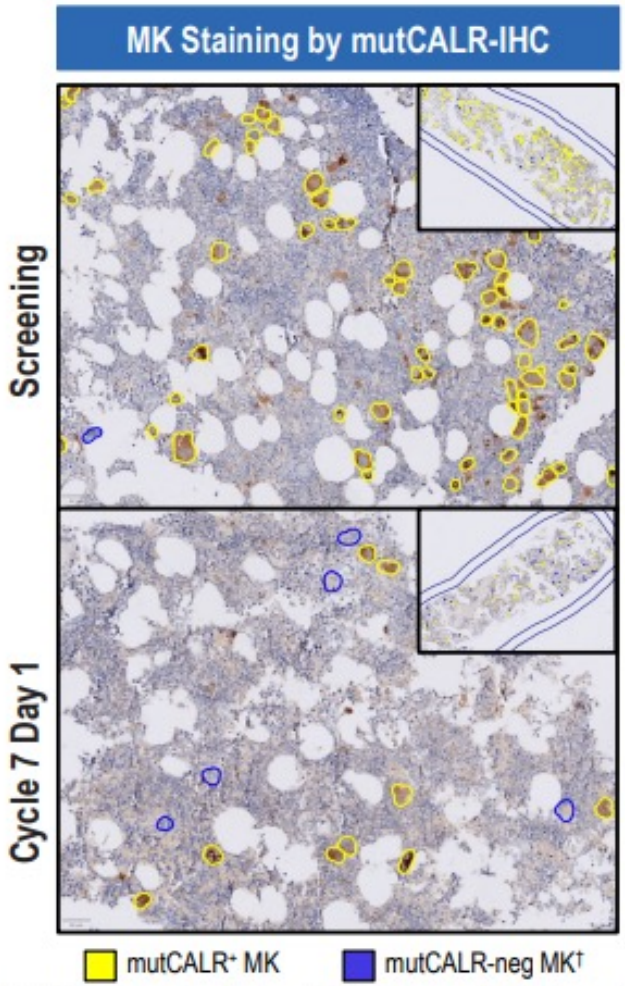


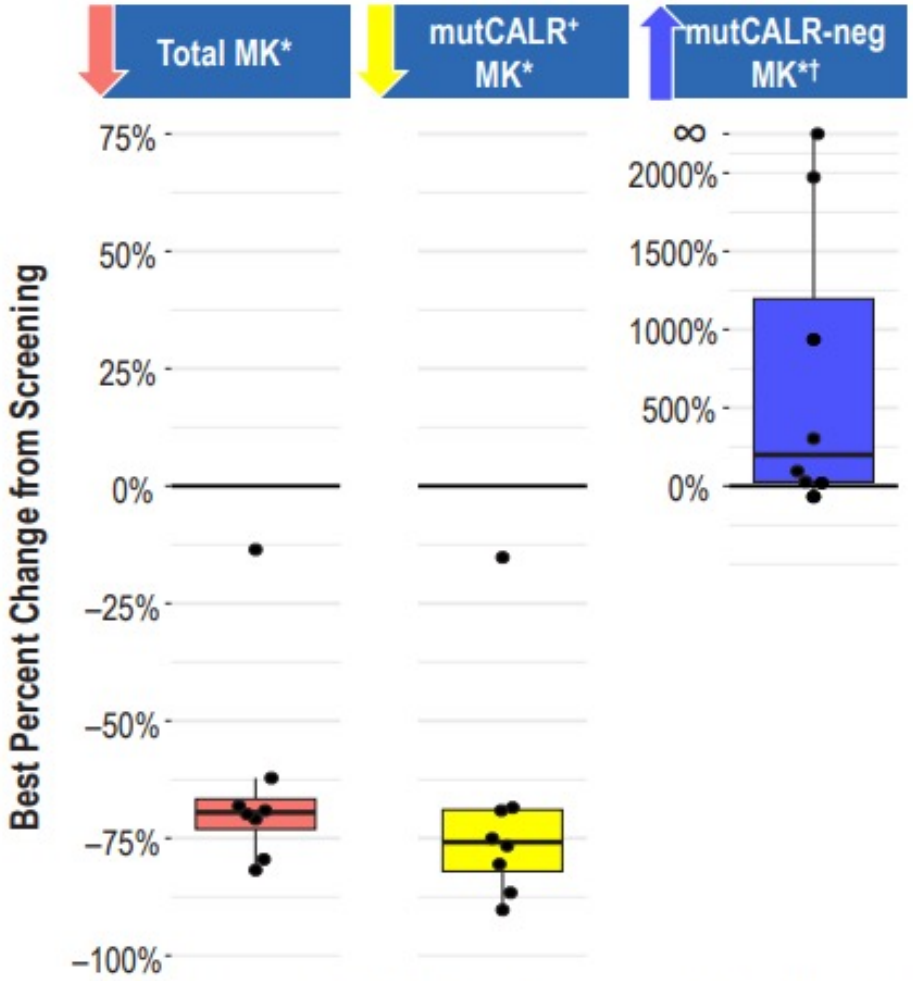


- Reduction of mut*CALR* VAF in HSPCs is deeper than in whole blood VAF
- Reduction of mutant populations (HSPC and ME) is accompanied by significant increases in *CALR* WT cell fractions indicating a shift to normal hematopoiesis

Single-cell sequencing (Tapestri™) conducted on PBMCs collected at C1D1 and C4D1. Cells were clustered and visualized using a UMAP based on cell surface expression of 46 proteins.
CALR, calreticulin; ET, essential thrombocythemia; HSPCs, hematopoietic stem/progenitor cells; ME, myeloid/erythroid; mut*CALR*, mutations in calreticulin; NK, natural killer; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cells; scDNA, single-cell deoxyribonucleic acid; UMAP, Uniform Manifold Approximation and Projection; WT, wild-type; VAF, variant allele frequency.

Reduction in mutCALR⁺ Megakaryocytes in the Bone Marrow of Clinical Responders





In 8 patients with hematologic response after 6 cycles of treatment:

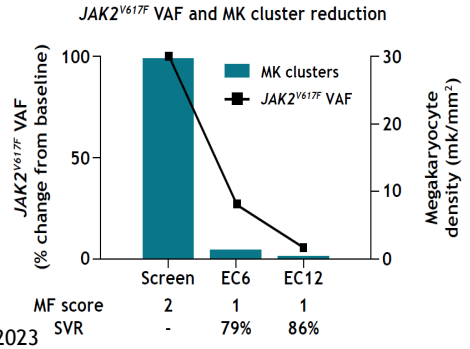
- Total number of megakaryocytes (MK) decreased
- Fraction of mutCALR⁺ MKs decreased
- Fraction of mutCALR negative MKs increased

*Best % change in total, mutCALR⁺, or mutCALR-neg MKs in hematologic responders with available data (n=8), dose range 24 mg-250 mg. †Undetectable mutCALR protein by IHC. Bone marrow biopsies stained for mutCALR using mutant-specific IHC. MKs quantified by semi-automated pathology scoring. CALR, calreticulin; IHC, immunohistochemistry; MK, megakaryocytes; mutCALR, mutations in

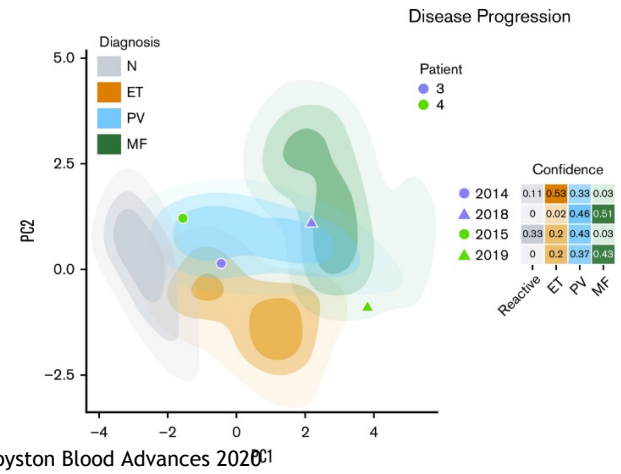
What are potential candidates for defining improved response in MF….. ?

- Better or more durable spleen response
- Change in driver mutation (or indeed non-driver mutation)
- Change in BM fibrosis / megakaryocytes etc

  AI algorithms may beneficial



Lee-Hoeflich ASH 2023



Royston Blood Advances 2020

- Uncertain if we should beat TSS with JAKi


THANK
YOU

International colleagues:

Ruben Mesa
Serge Verstovsek
Jean Jacques Kiladjian
Andreas Reiter
Alessandro Vannucchi
Steffen Koschmeider
Jean Christophe Ianotto
Yan Beauverd
Francesco Passamonti
Tiziano Barbui
John Mascarenhas
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Beth Psaila
Bridget Wilkins
Jyoti Nangalia
Donal McLornan
Joanne Ewing
Andrew McGregor
Rebecca Frewin
Joanna Baxter
Clodagh Keohane
Sonia Fox & B'ham CTU
& many more

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GSTT MPN team and patients

GUY'S INTERNATIONAL CENTRE OF EXCELLENCE IN MYELOID DISORDERS G-ICEMD
MPN • AML • MDS • SM • CML • CEL

MPN voice

Global MPN friends and collaborators