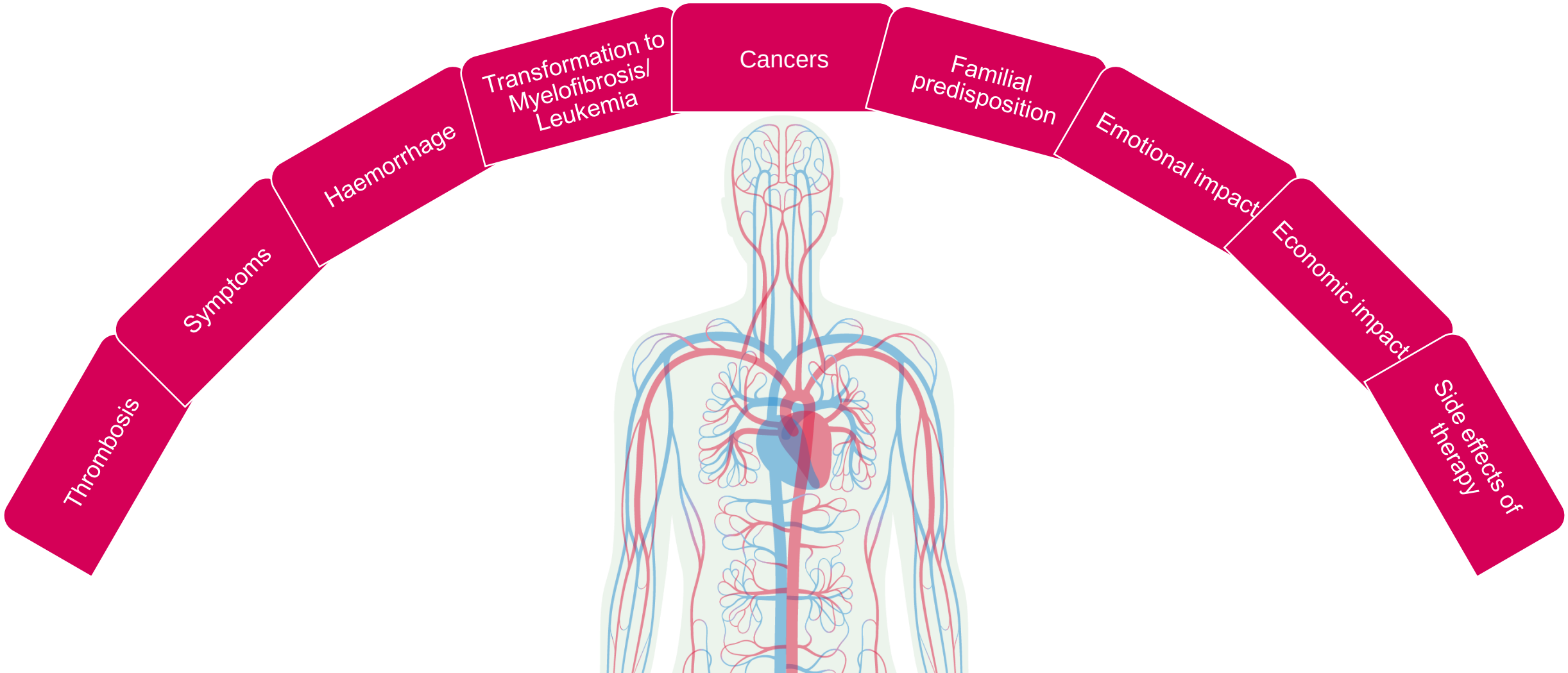
MPN Horizons
Understanding the New Complexity of MPNs
13-15 October
Zagreb, Croatia
2023
mpnan

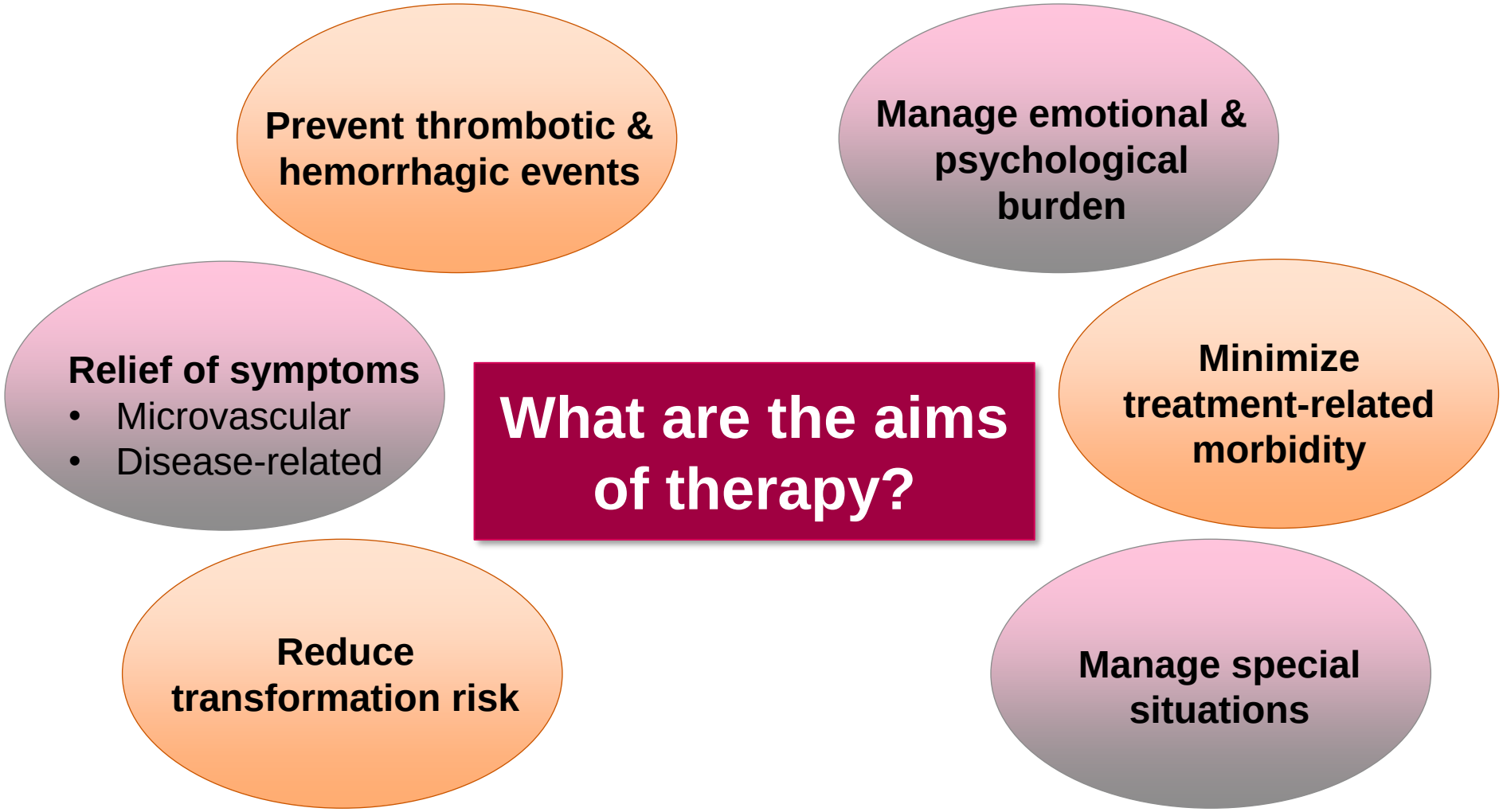
ET the future of treatment?

Claire Harrison

Impacts of Essential Thrombocythaemia diagnosis:



Aims of therapy:



Risk scores in ET

IPSET-thrombosis (revised)		MIPSS-ET		MPN personalised risk calculator
		Factor	Points¶	
Very low	No prior thrombosis + age ≤60 + JAK2-unmutated	Adverse mutation*	2	Available genomic data plus clinical factors (age, Hb, WBC, Plts, gender, prior thrombosis, splenomegaly)
Low	No prior thrombosis + age ≤60 years + JAK2-mutated	Age >60 yrs	3	
Intermediate	No thrombosis + age >60 + JAK2-unmutated	Male sex	1	
High	Thrombosis history (any age / genotype) or age >60 + JAK2-mutated	WBC ≥ 11 x 10^9/L	1	

¶Total score: 0-1=low risk; 2-5=intermediate risk; 6+=high risk. **SRSF2/SF3B1/U2AF1/TP53*

What is high-risk ET?

- IPSET
- Traditional age

(> 60 +/- thrombosis)

Also to consider:

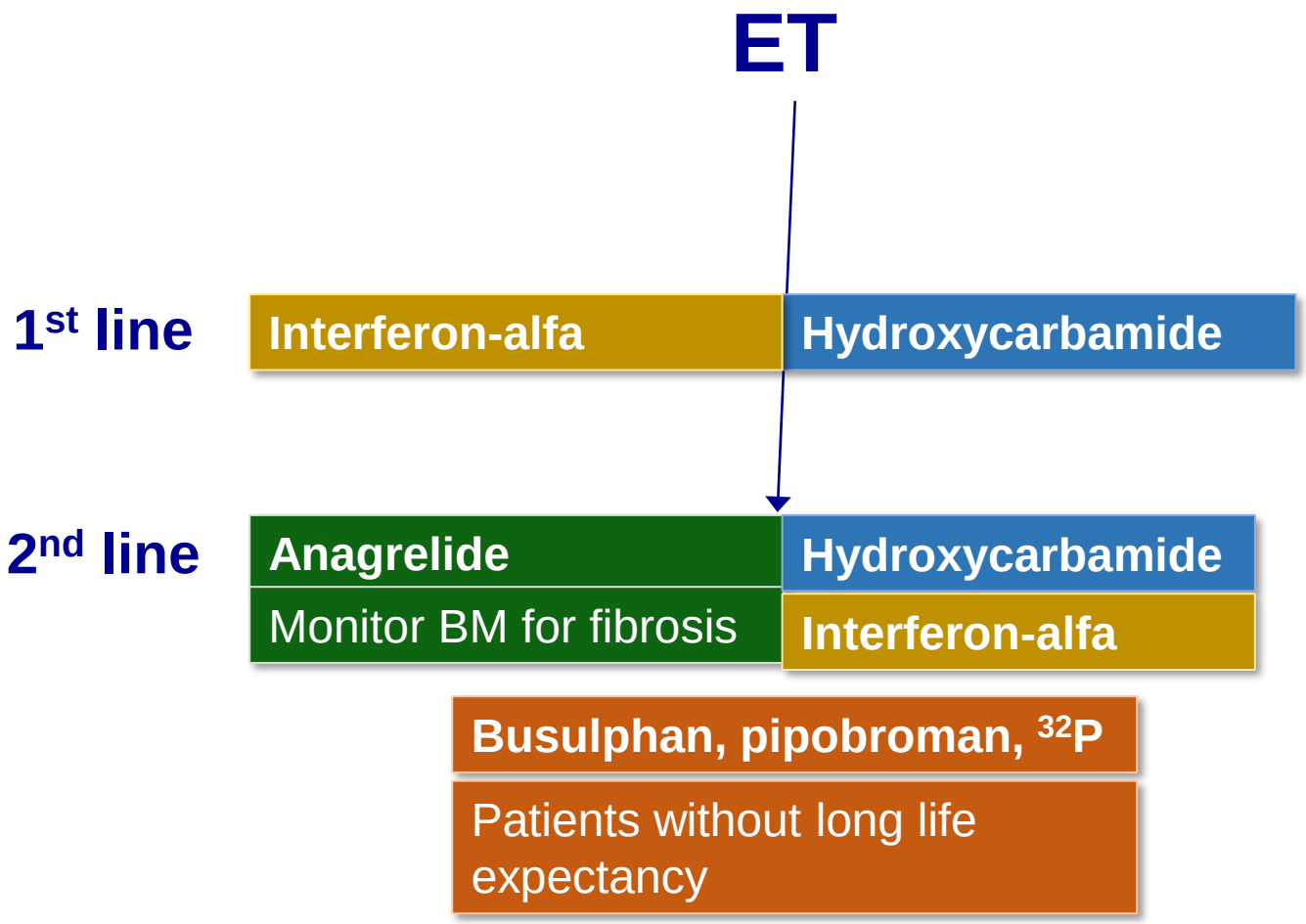
- ? High cardiovascular risk
- Symptoms

In addition:

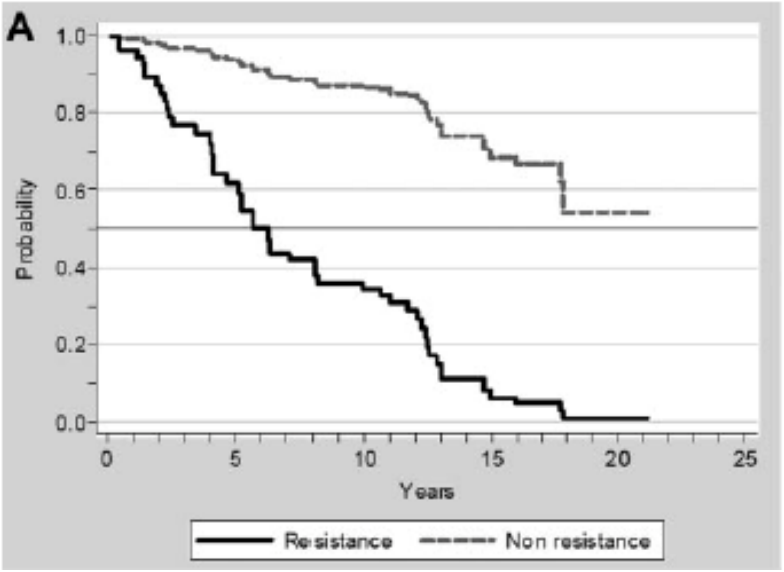
Currently unclear if we should really treat CALR-ET and triple negative ET in the same way as JAK2- or cMPL-ET

Despite IPSET score making most JAK negative ET intermediate risk despite count and age

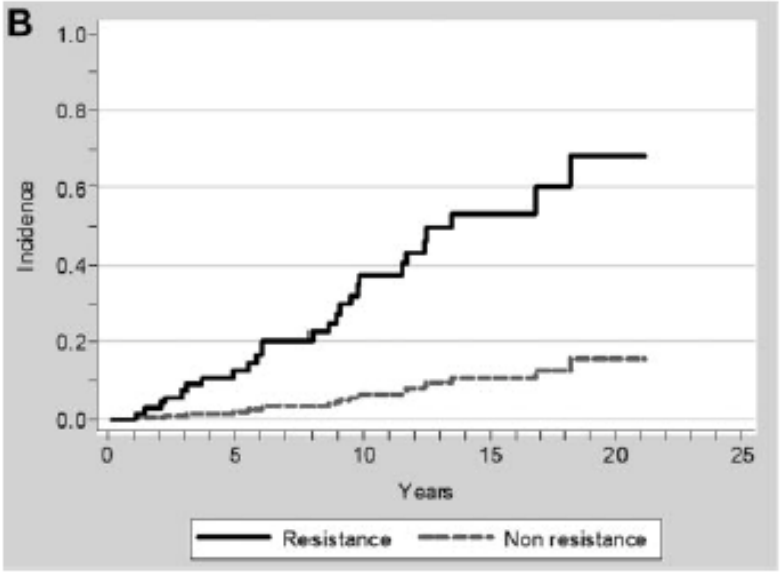
Cytoreduction in high-risk ET



Resistance to hydroxycarbamide: adverse prognosis



Increased risk of death
HR 5.6 (2.7-11.9)



Increased transformation to AML / MF
HR 6.8 (3.0-15.4)

	Myelofibrosis		Acute leukaemia	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Requirement for phlebotomies	1·2 (0·2–9·2)	0·8	–	–
Uncontrolled myeloproliferation	0·2 (0·02–2·2)	0·2	–	–
Progressive splenomegaly	9·1 (2·3–35·9)	0·002	–	–
Cytopenia	5·1 (1·9–13·7)	0·001	9·5 (2·6–34·5)	0·001
Extra-haematological toxicity	1·6 (0·7–3·6)	0·2	0·9 (0·2–4·3)	0·9

Alvarez-Larran et al Blood 2012, Br J Haem 2015

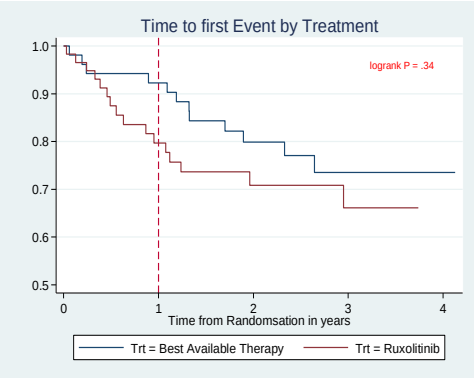
Alternatives for second line therapy

Ruxolitinib

MAJIC

- 110 ET refractory / intolerant to HC
- Randomised rux *vs* BAT

- No difference in CHR at 1 yr
- No difference in survival
- No difference in transformation, thrombosis or haemorrhage



Harrison et al, Blood 2017

Other second-line agents

- Anagrelide (alone or in combination)
- Busulphan
- Radioactive phosphorus
- Pipobroman

Current novel therapeutic approaches in ET trials

Pelabresib
BET inhibitor

MANIFEST study

Bomedemstat
LSD1 inhibitor

(Imago studies)

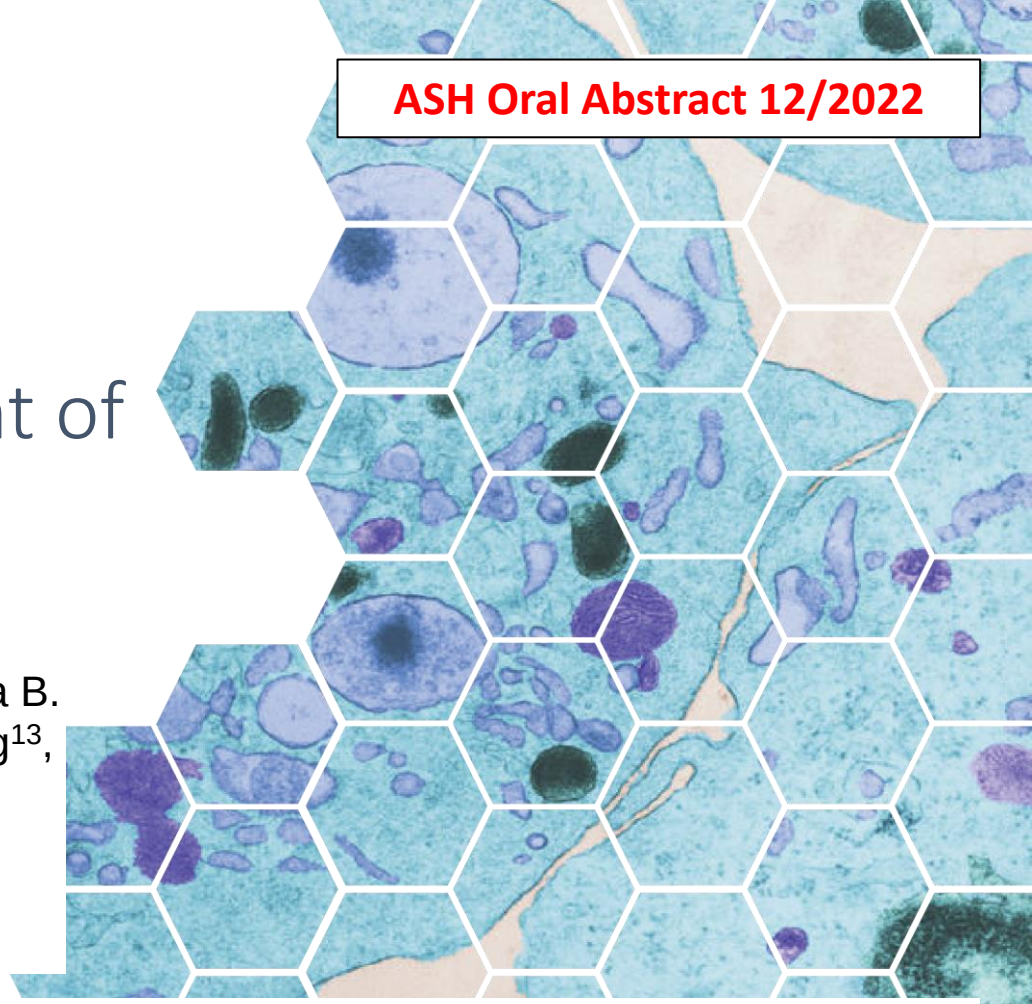
Calreticulin
Vaccination or immunotherapy

Pegylated Interferon
'BESREMi'
(Ropeginterferon 2b)
SURPASS ET study

IMAGO BIOSCIENCES

ASH Oral Abstract 12/2022

Phase 2 Study of the LSD1 Inhibitor Bomedemstat (IMG-7289) for the Treatment of Essential Thrombocythemia (ET)

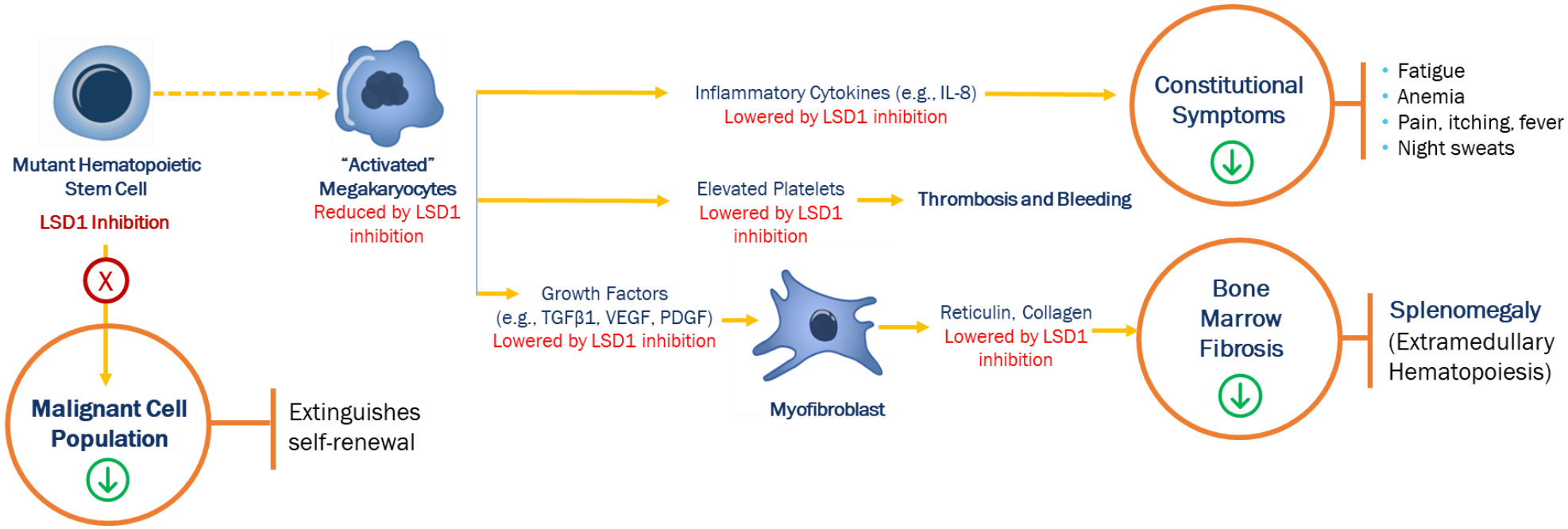


Harinder Gill*[1], Francesca Palandri [2], David M. Ross[3], Tara Cochrane[4], Courtney Tate[5], Steven W. Lane[6], Stephen R. Larsen[7], Aaron T. Gerds[8], Anna B. Halpern[9], Jake Shortt[10], James M. Rossetti[11], Kristen M. Pettit[12], James Liang[13], Adam Mead[14], Monia Marchetti[15], Alessandro Vannucchi[16], Andrew Wilson[17], Joachim R. Göthert[18], Merit Hanna[19], Francesco Passamonti[20], William S. Stevenson[21], Claire N. Harrison[22], Moshe Talpaz[23], Nicola Vianelli[24], Hugh Young Rienhoff Jr.[25]

[1]Department of Medicine, University of Hong Kong, Hong Kong, China; [2]Institute of Hematology "L. & A. Seràgnoli", Sant'Orsola-Malpighi University Hospital, Bologna, Italy; [3]Department of Haematology, Royal Adelaide Hospital and SA Pathology, Adelaide; [4]Department of Haematology, Gold Coast University Hospital, Southport; [5]Department of Haematology, Gold Coast University Hospital, Southport, Australia; [6]QIMR Berghofer Medical Research Institute, Brisbane, Australia; [7]University of Sydney, Sydney, NSW, Australia; [8]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [9]Department of Medicine, Division of Hematology, University of Washington, Seattle, WA; [10]Monash Haematology, Monash Health, Clayton, Australia; [11]UPMC Hillman Cancer Center, Pittsburgh, PA; [12]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; [13]Middlemore Hospital, Auckland, New Zealand; [14]MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; [15]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [16]University of Florence, AOU Careggi, CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Florence, Italy, [17]University College London Hospitals NHS Foundation Trust, London, United Kingdom; [18]Department of Hematology, West German Cancer Center (WTZ), University Hospital Essen, Essen, Germany, [19]North Shore Hospital. Waitemata District Health Board, Auckland, New Zealand; [20]Haematology, University of Insubria, Varese, Italy, [21]Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, Australia; [22]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [23]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [24]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology L.e A. Seragnoli, Hematology, Bologna, Italy, [25]Imago BioSciences, Inc., San Carlos, CA

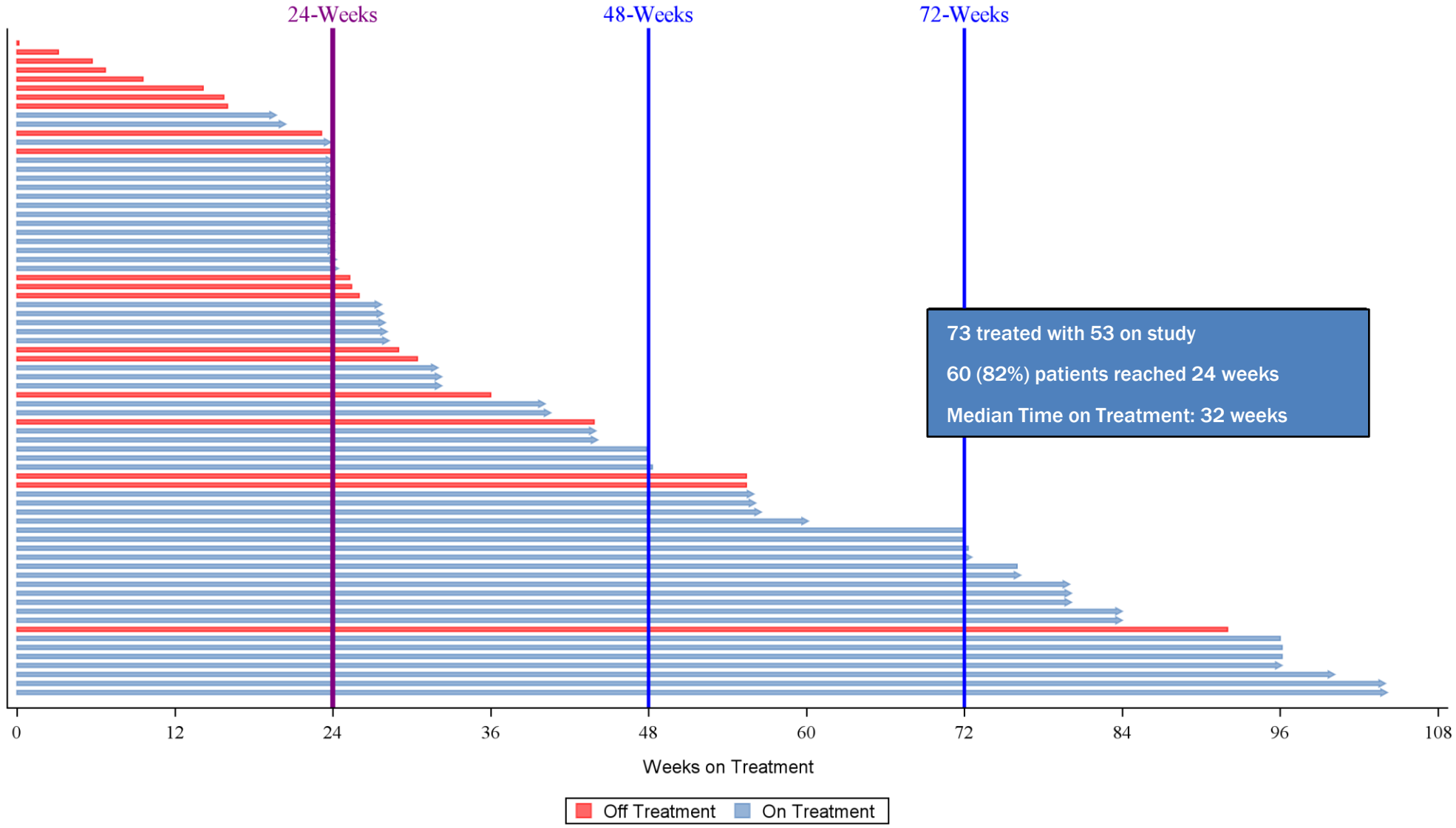
Rationale for Targeting LSD1 in MPNs

- Lysine Specific Demethylase 1 (LSD1) = Epigenetic enzyme
  - Demethylates histone H3K4 and other chromatin-associated proteins, *e.g.*, p53
- LSD1 is required for the differentiation of megakaryocyte-erythroid progenitors to mature megakaryocytes
- LSD1 is overexpressed in MPNs



Gill et al. ASH oral abstract 2022; Harris *et al.* 2012; Sprussel *et al.* 2012; Neibel *et al.* 2014; Lara-Astiaso *et al.* 2014

Enrollment and Treatment Status



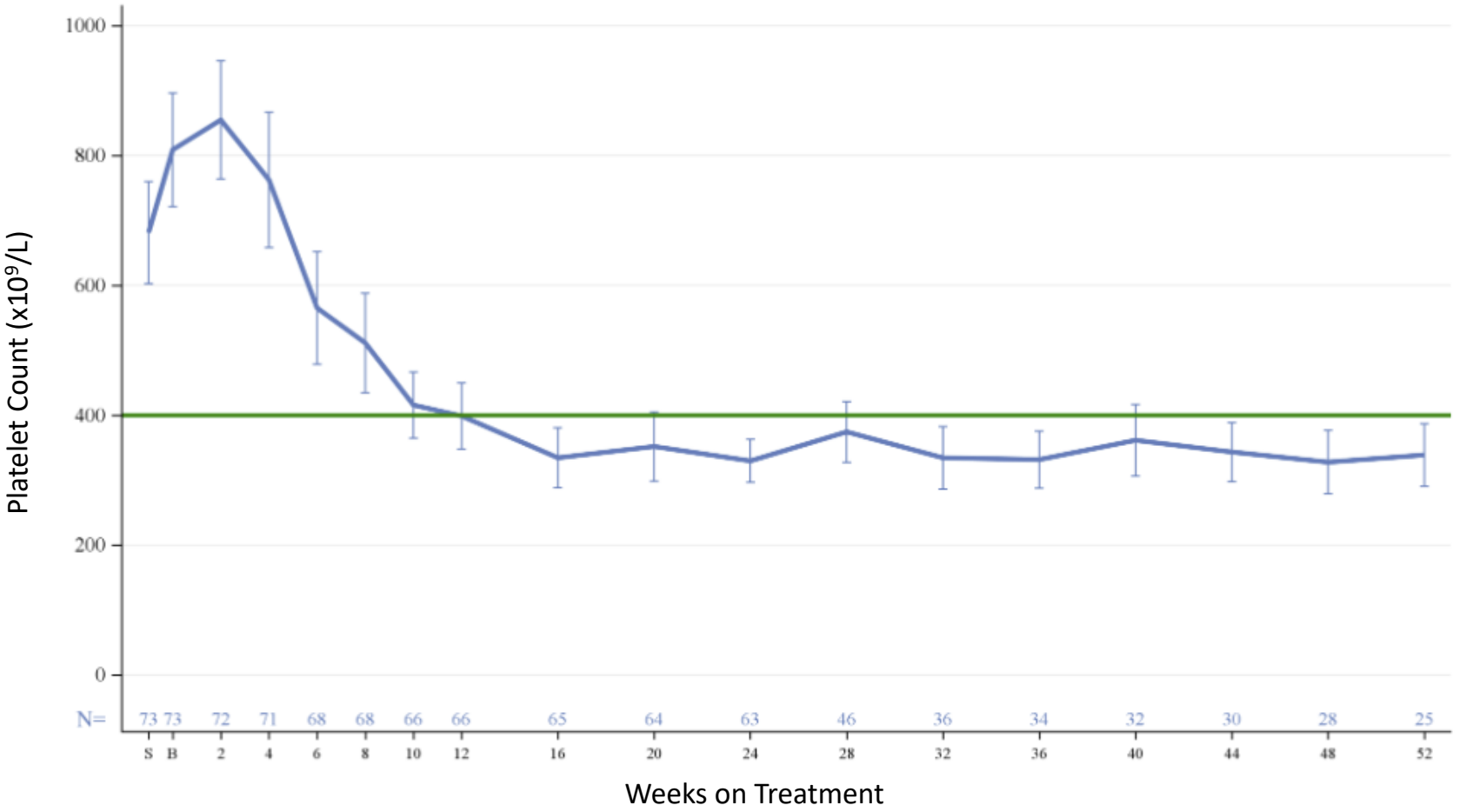
Abbreviations: EOT used for last dose date if available, otherwise last dose date in exposure dataset.

- Source: Imago interim, unaudited and ongoing Phase 2 data of Investigational Product; Data cut-off: 18Oct2022

IMAGO BIOSCIENCES

Primary Objective: Reduction in Platelet Count

- **Mean Platelet Count (±95% CI) N=73**



S=Screening, B = Last non-missing value closest to Day 1

Of 62 patients treated for **≥24 weeks:**

- **100%** achieved a platelet count of ≤400 x 10^9/L
- **95%** achieved a platelet count of ≤400 x 10^9/L in the absence of thromboembolic events
- Median time to ≤400 x 10^9/L is 10 weeks

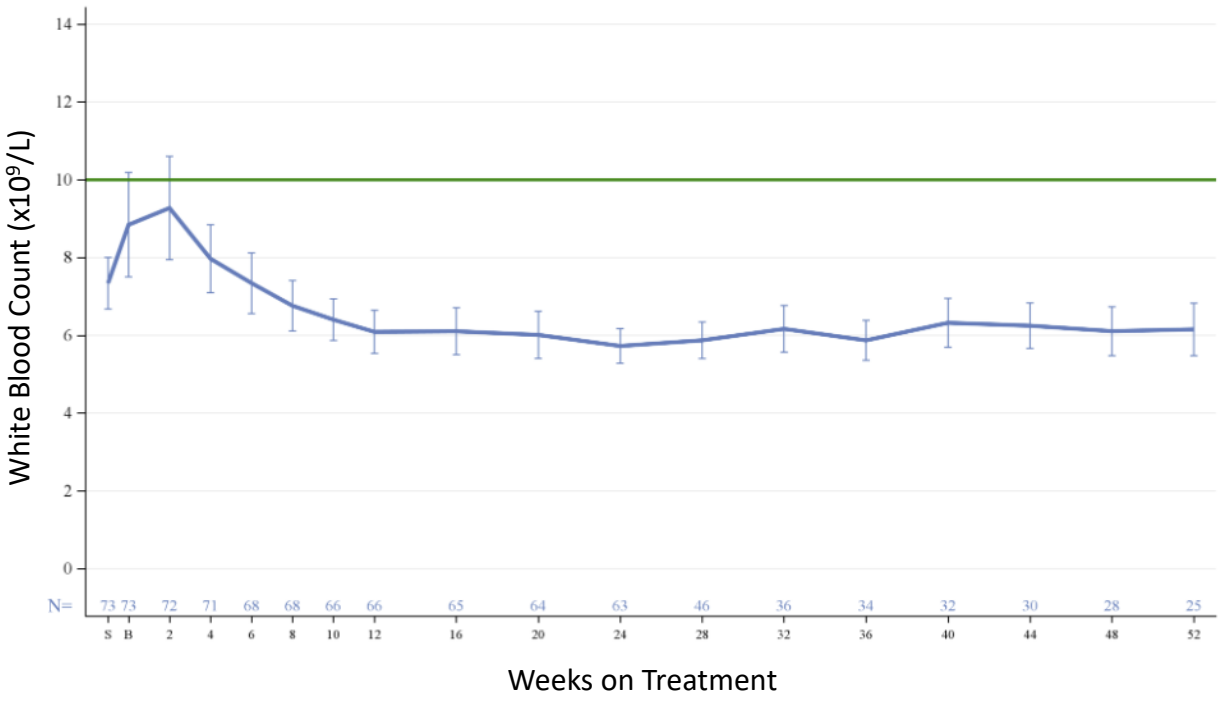
Of 28 patients treated for **48 weeks:**

- **89%** achieved a durable (≥12 weeks) platelet count of ≤400 x 10^9/L by week 48

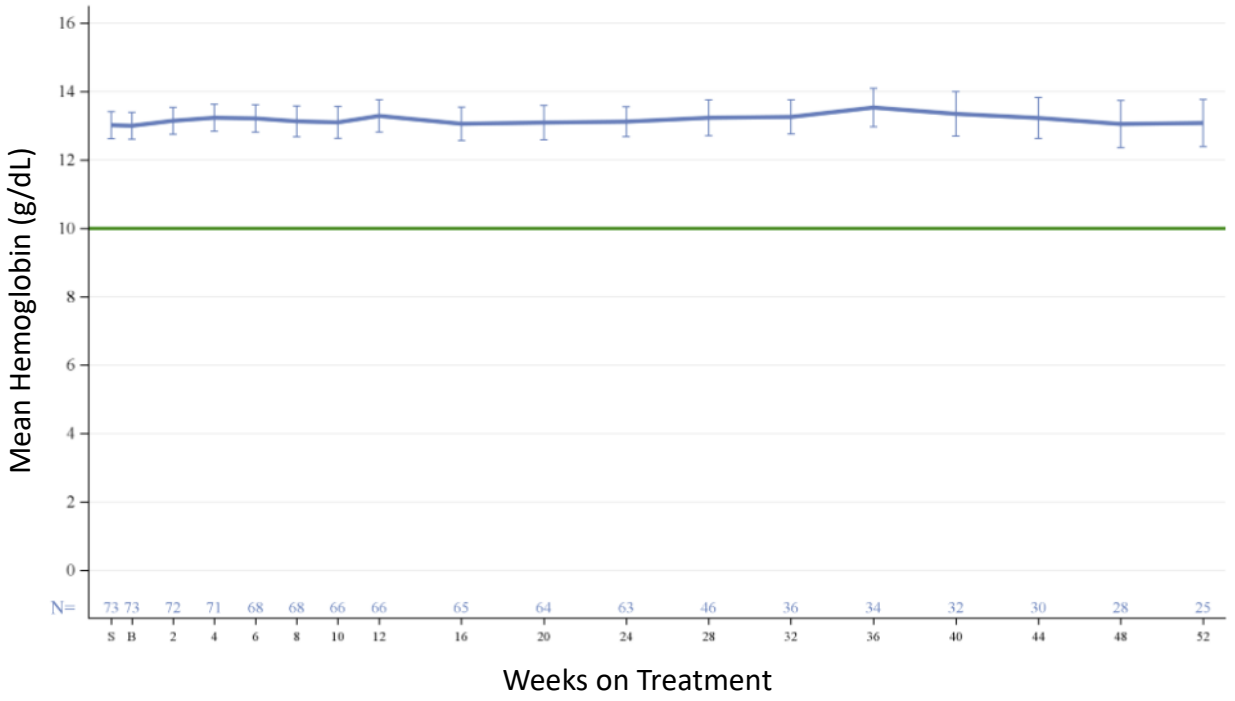
Source: Imago interim, unaudited and ongoing Phase 2 data of Investigational Product; Data cut-off: 18Oct2022

Lowers WBCs and Maintains Hemoglobin (Hb) levels

• Mean WBC (±95% CI) N=73



Mean Hb (±95% CI) N=73



S=Screening, B = Last non-missing value closest to Day 1

Source: Imago interim, unaudited and ongoing Phase 2 data of Investigational Product; Data cut-off: 18Oct2022

IMAGO BIOSCIENCES

Platelet Responses by Driver Mutation (or absence thereof)

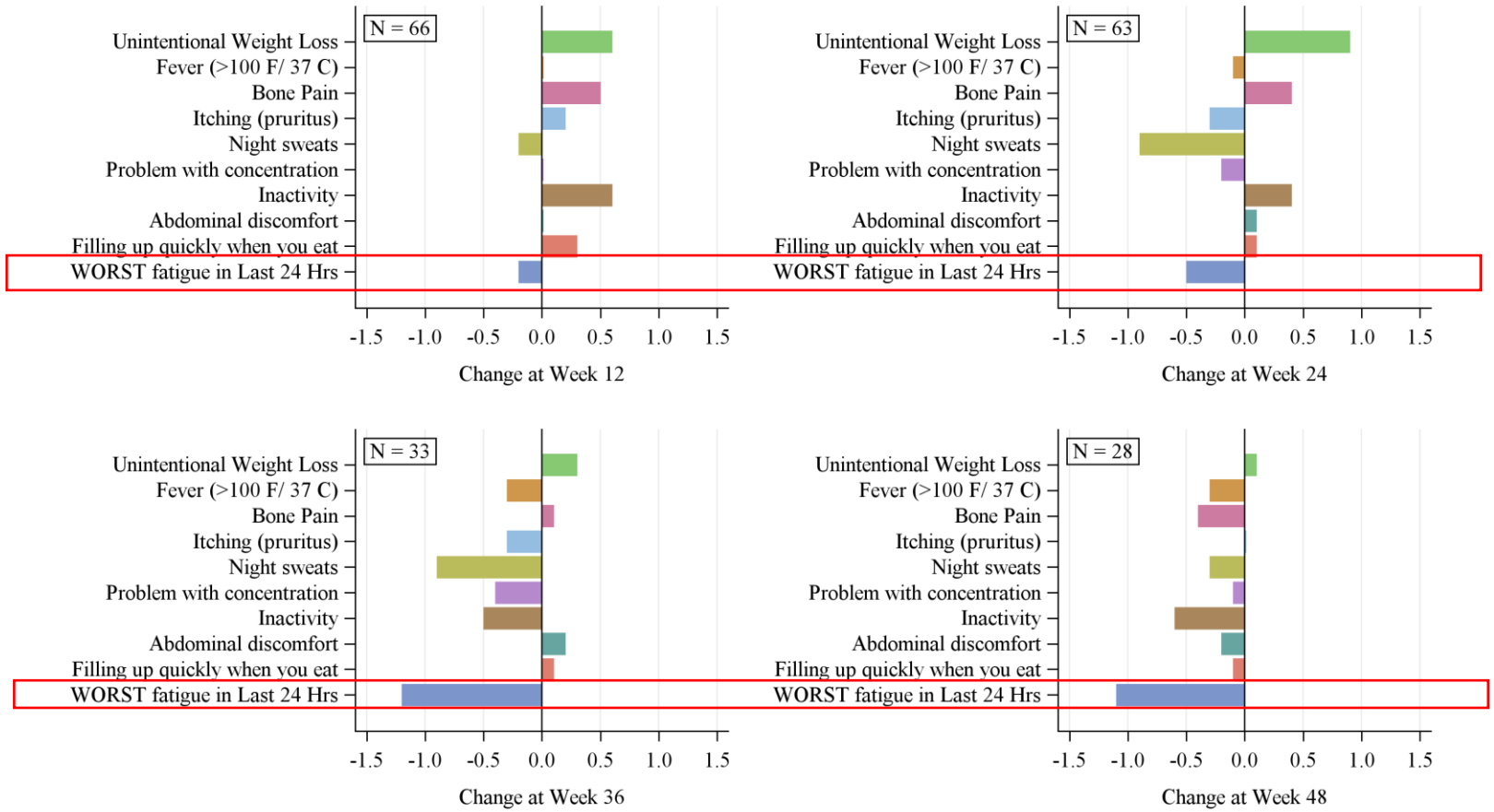
Mutation	No. of Patients*	Mean Baseline Platelet Count (x10^9/L)	Platelet Count Response# (%)
All Pts	**73**	**809**	**100%**
JAK2^{V617F}	34	730	100%
CALR	27	955	100%
MPL	3	881	100%
Triple Negative	6	493	100%

*3 patients did not have mutation status available.
#**Any** post baseline platelet count ≤400 x10^9/L; ≥24 weeks treatment; N=62

Patients with *CALR* mutations respond similarly to patients with *JAK2* mutations

Source: Imago interim, unaudited and ongoing Phase 2 data of Investigational Product; Data cut-off: 18Oct2022

Changes in Individual Components of the MPN-SAF TSS



For patients with a baseline TSS>20 (N=12),

75% had any decrease in TSS

67% had a reduction of ≥10 points

- Fatigue is the most severe symptom in CTP-201 and the most improved along with associated symptoms of inactivity and impaired concentration

Source: Imago interim, unaudited and ongoing Phase 2 data of Investigational Product; Data cut-off: 18Oct2022

IMAGO BIOSCIENCES

Safety and Tolerability Profile

Preferred Term (N=73)	Any Grade AEs	Grade 3/4 AEs
Dysgeusia	40 (55%)	N/A
Constipation	25 (34%)	1 (1%)
Thrombocytopenia	20 (27%)	6 (8%)
Arthralgia	20 (27%)	4 (6%)
Fatigue	17 (23%)	0
Contusion	15 (21%)	1 (1%)
Diarrhoea	15 (21%)	1 (1%)
Pruritus	13 (18%)	0
Anaemia	12 (16%)	5 (7%)
COVID-19	12 (16%)	0
Headache	11 (15%)	1 (1%)
Peripheral oedema	11 (15%)	1 (1%)

Any grade of AE occurring at a frequency of ≥15% of patients included regardless of relatedness; N/A = Gr 3/4 events do not exist per CTCAE criteria

Discontinued from Study (N=20)	
AE	10
Withdrawal of consent/Subject decision	7
Investigator decision	1
Disease progression to MF	1
Death*	1

** Unrelated death due to aspiration pneumonia*

- Bomedemstat is generally well-tolerated
- Most common AE was dysgeusia, (CHANGE IN TASTE) **majority were Grade 1**; only 3/73 leading to treatment discontinuation
- 22/73 (30%) of patients reported 38 SAEs
- 7 SAEs deemed related to bomedemstat (N=4 pts)
- One patient experienced thrombotic event – pulmonary embolism - unrelated to bomedemstat

- Source: Imago interim, unaudited and ongoing Phase 2 data of Investigational Product; Data cut-off: 18Oct2022

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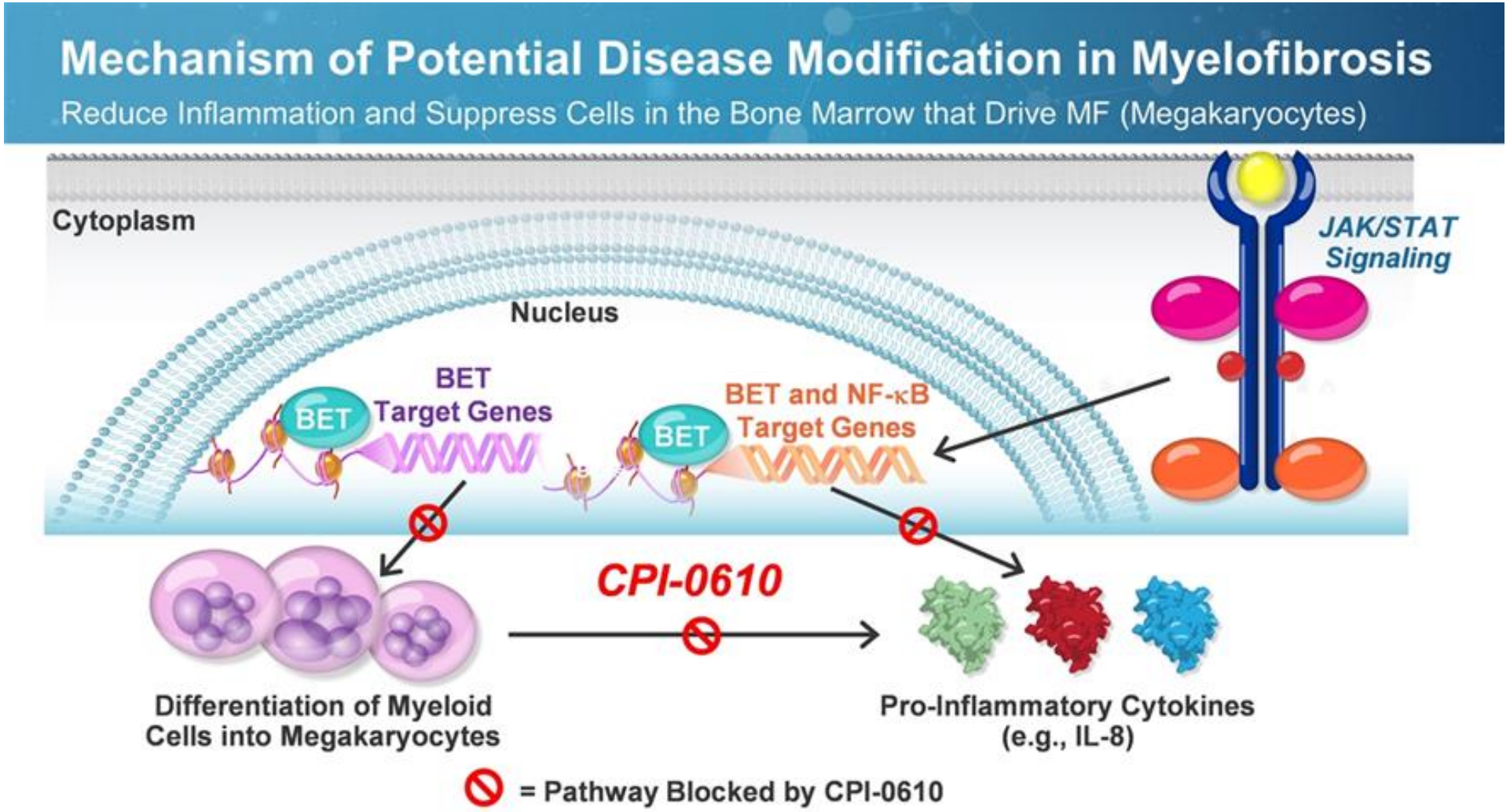
MANIFEST study - Pelabresib



MANIFEST Arm 4: Pelabresib monotherapy in patients with high-risk ET refractory or intolerant to hydroxyurea

Study Population

- High-risk ET
- Refractory or intolerant to hydroxyurea*[3]
- ≥ two symptoms (average score ≥3/TSS ≥15) per MPN-SAF in the prior 7 days
- Platelets >600 × 10^9/L

Pelabresib monotherapy 225 mg PO QD in 21-day cycles (14 days on, 7 days off) N=21

Endpoints

Primary Endpoint

Complete hematologic response at anytime (confirmed)
Normalization of platelet count (≤400 × 10^9/L) and WBC (≤10 × 10^9/L), confirmed 3 weeks later and a normal spleen size

Secondary Endpoints

Partial hematologic response at anytime (confirmed)
Platelets 400–600 × 10^9/L and WBC within normal range (≤10 × 10^9/L), confirmed 3 weeks later

Symptom improvement
The proportion of patients with ≥50% reduction from baseline in the MPN-SAF total score

Exploratory Endpoints

Translational assessment of *IL-8* expression change, cytokines and mutation status

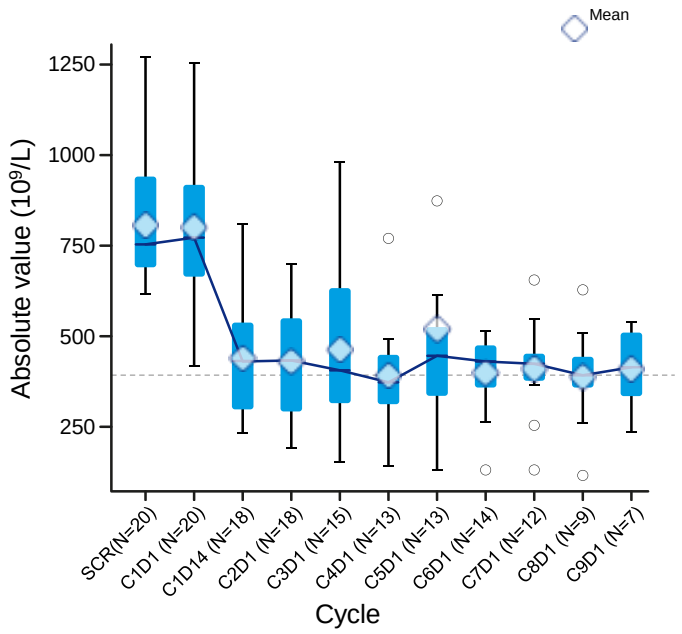
*Refractory or intolerant criteria, as per Barosi, et al. 2007.
ET, essential thrombocythemia; TSS, total symptom score; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; WBC, white blood cell.
1. ClinicalTrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed May 30, 2023; 2. Constellation. Data on file (CPI-0610); 3. Barosi G, et al. *Leukemia* 2007;21:277–280.

Passamonti F, et al. EHA 2023. S168

Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

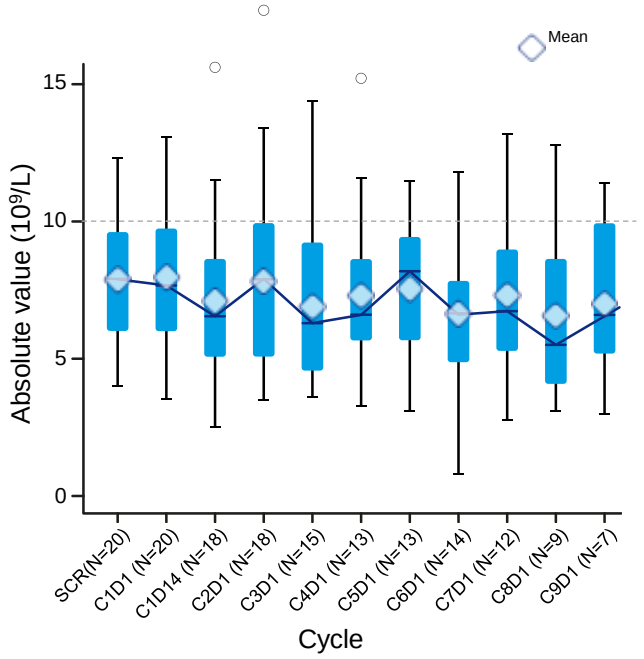
MANIFEST Arm 4: Platelet count, white blood cell count and hemoglobin

Platelets over time



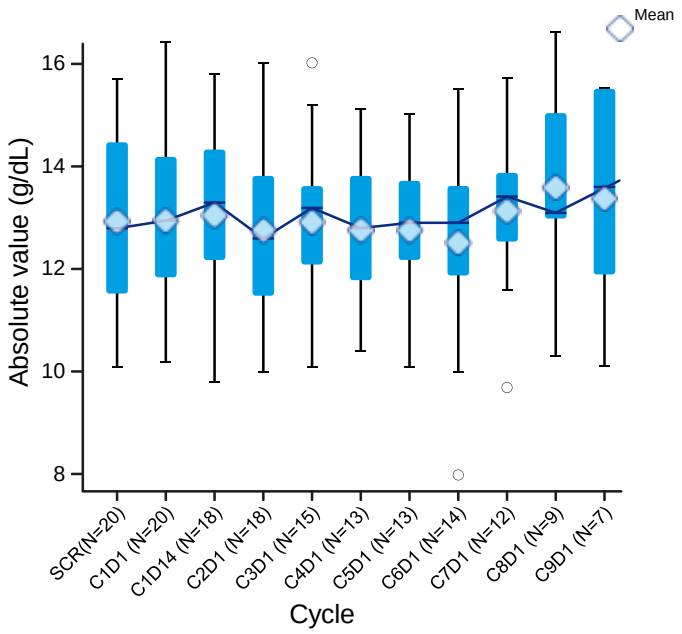
	Platelet count
≤400 × 10^9/L	60% (12/20)
Median at Wk 12	446 × 10^9/L
Median % change at Wk 12	–40%

WBC over time



	WBC count
≤10 × 10^9/L	95% (19/20)
Median at baseline	7.9 × 10^9/L
Median at Wk 12	8.2 × 10^9/L

Hemoglobin over time



Hemoglobin	Baseline	Week 12 (N=13)	Week 24 (N=7)
Mean (g/dL)	13.0	13.0	13.6
Median (g/dL)	13.0	13.0	13.4

CXDX, Cycle X Day X; SCR, screening.

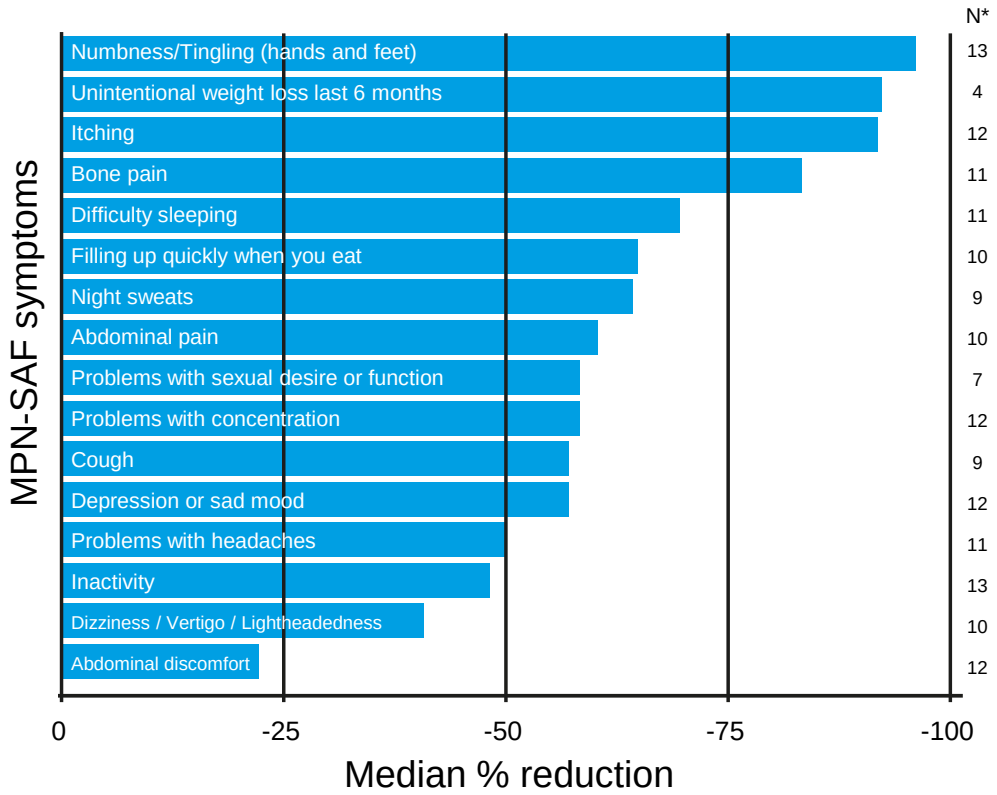
Data cutoff 29 July 2022

Passamonti F, et al. EHA 2023. S168

Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

MANIFEST Arm 4: Total symptom score

Best percentage reduction in MPN-SAF symptoms



N=14*	MPN-SAF symptoms
TSS50 at anytime	50% (7/14)
Median % TSS reduction at Week 12	–31%

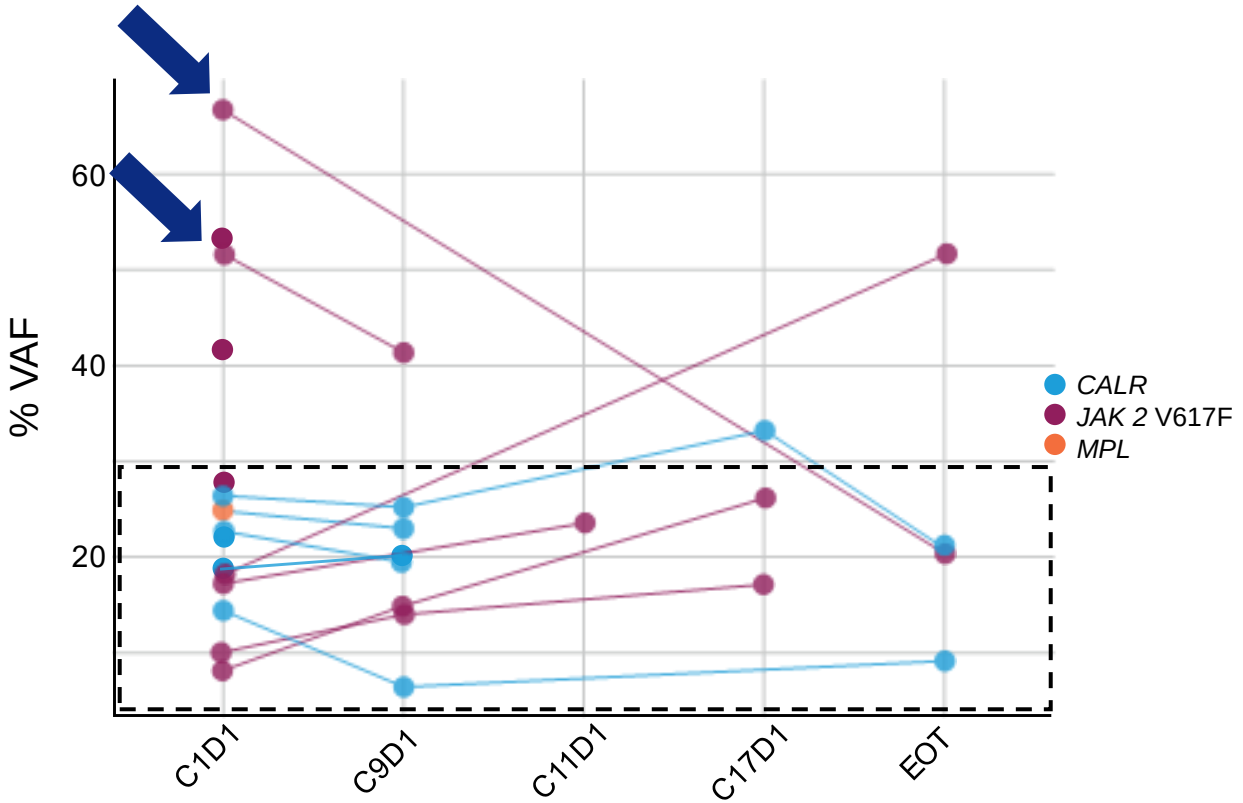
*Patients with nonmissing and nonzero baseline symptom score.

Fever not depicted in the figure due to zero baseline.
TSS, total symptom score assessed based on MPN-SAF; TSS50, ≥50% reduction in total symptom score from baseline.

Data cutoff 29 July 2022 Passamonti F, et al. EHA 2023. S168 **Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority**

MANIFEST Arm 4: VAF reduction in driver mutations

Driver mutation levels

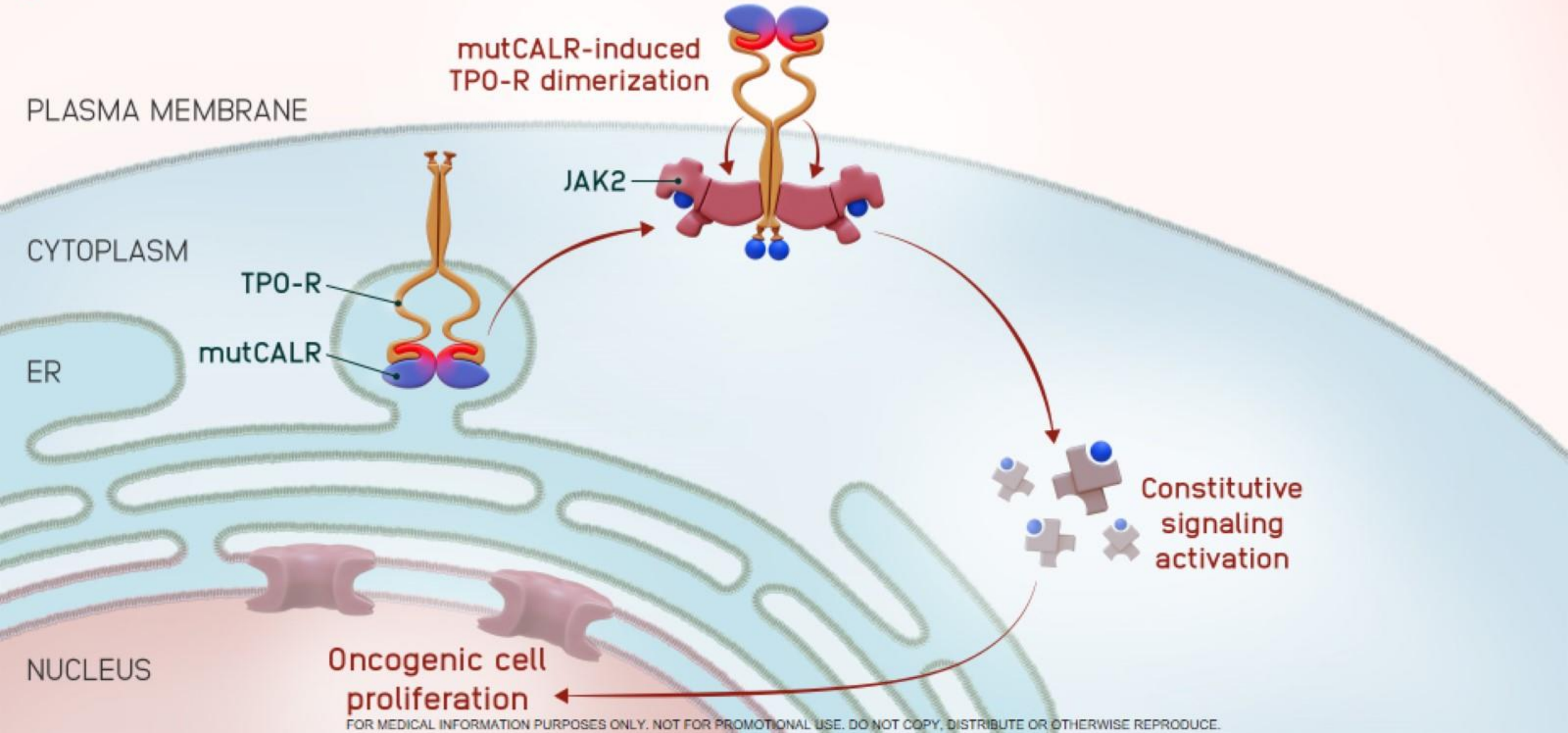


- 2 out of 6 patients with *JAK2* V617F mutation assessment post-baseline showed a meaningful VAF reduction (67% → 20% and 52% →40%)
- VAF levels were maintained in most patients with ≤30% driver mutations

Peripheral blood next-generation sequencing panel to quantify the frequency of allele mutations at baseline and on treatment.
One patient with the MPL mutation at baseline did not have a postbaseline assessment; therefore, they were not presented.
Mutation profile change analyzed in 18 patients. During pelabresib treatment, 11 patients were analyzed over 4 timepoints.
CXDX, Cycle X Day X; VAF, variant allele fraction.

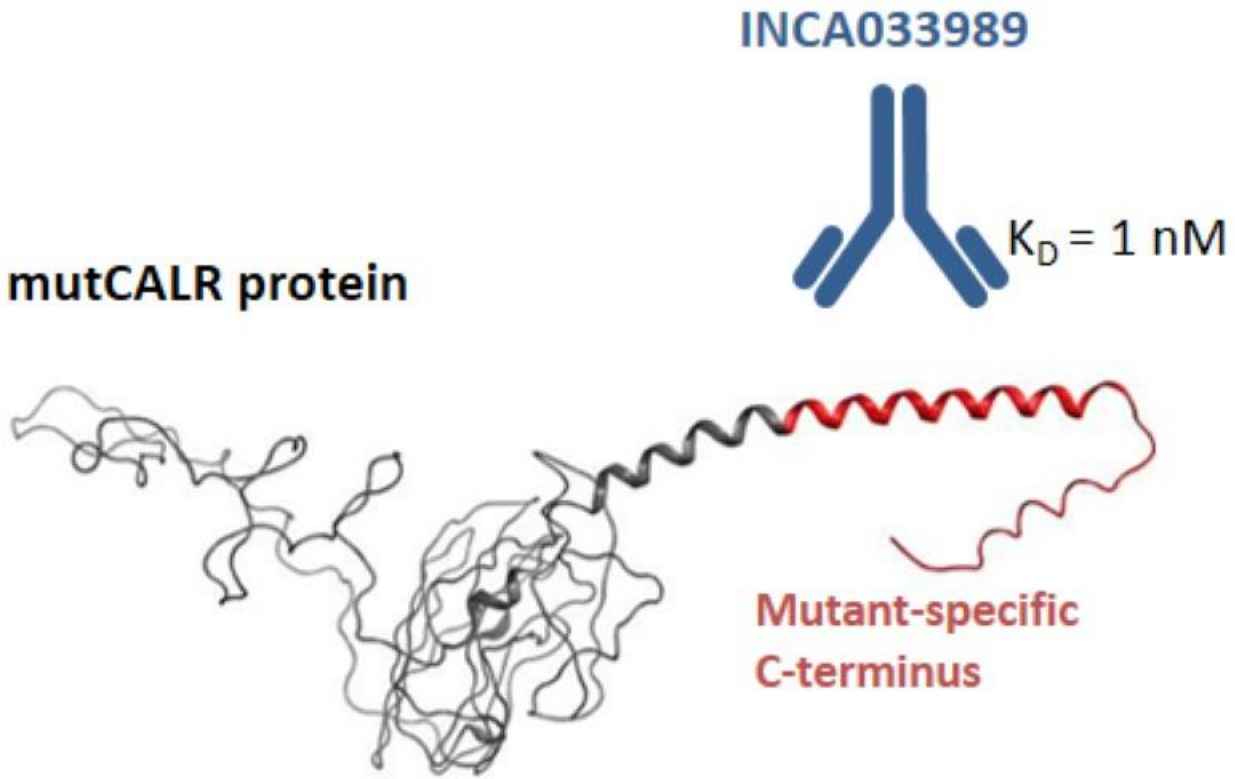
Data cutoff 29 July 2022 Passamonti F, et al. EHA 2023. S168 **Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority**

Mutant calreticulin (mutCALR) induces oncogenic cell proliferation



INCA033989: a mutCALR-specific monoclonal antibody

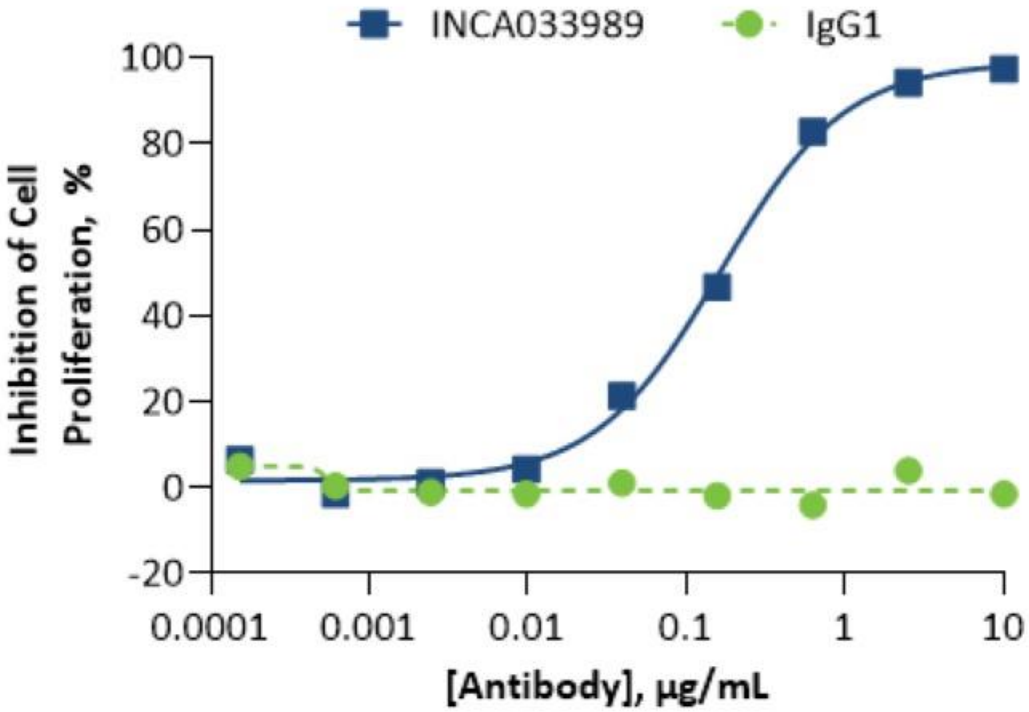
- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function

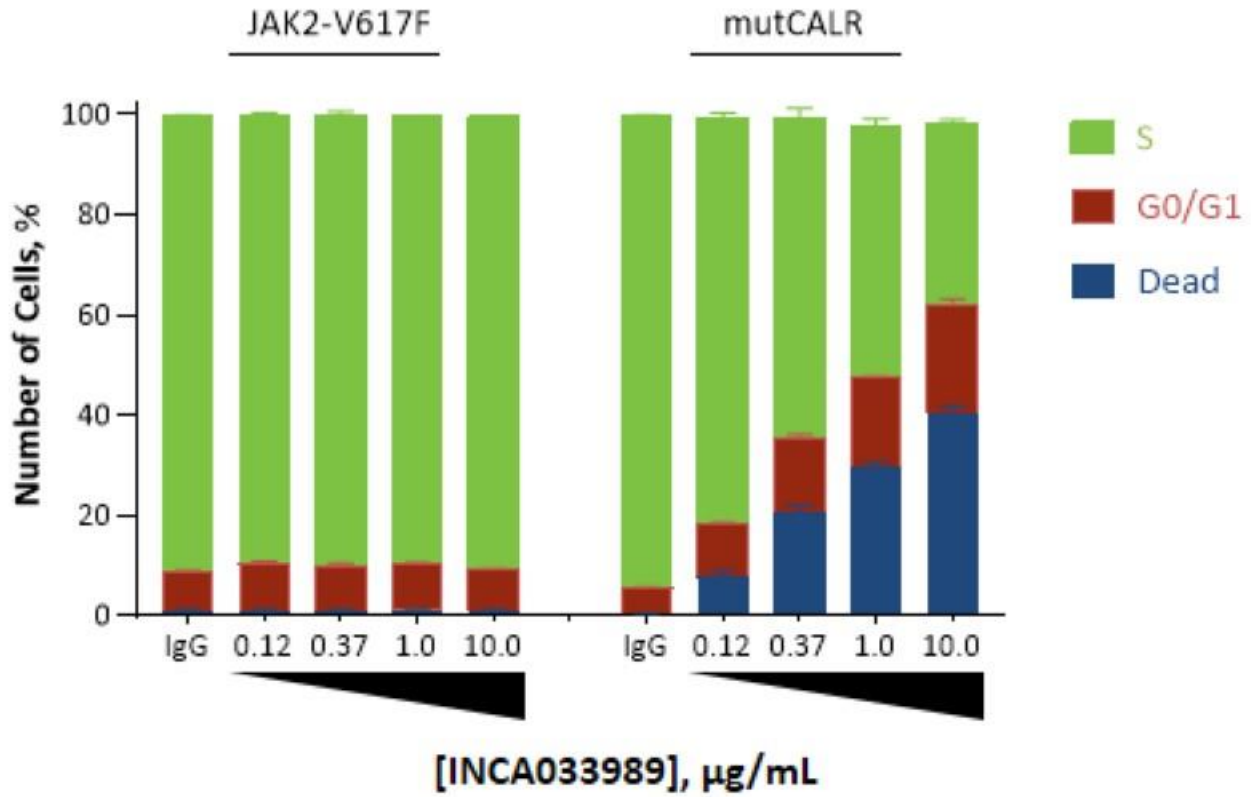


Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).

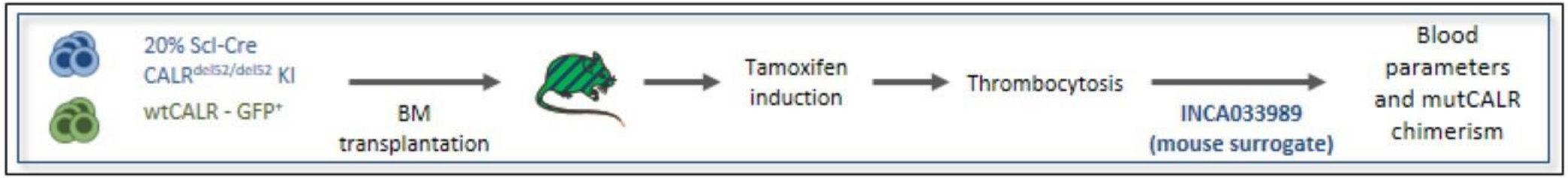
IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

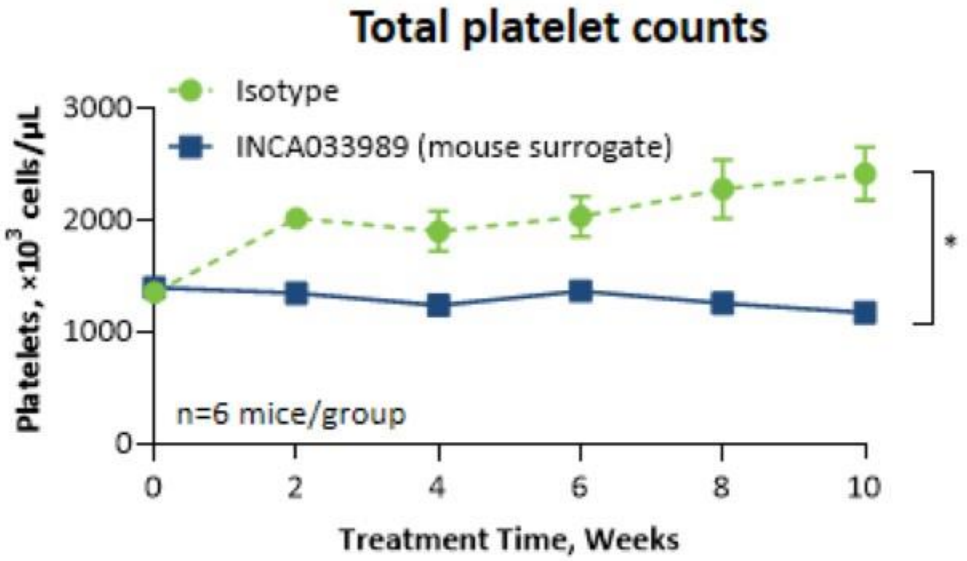
INCA033989 selectively inhibits cell proliferation and induces death of mutCALR^{+} cells

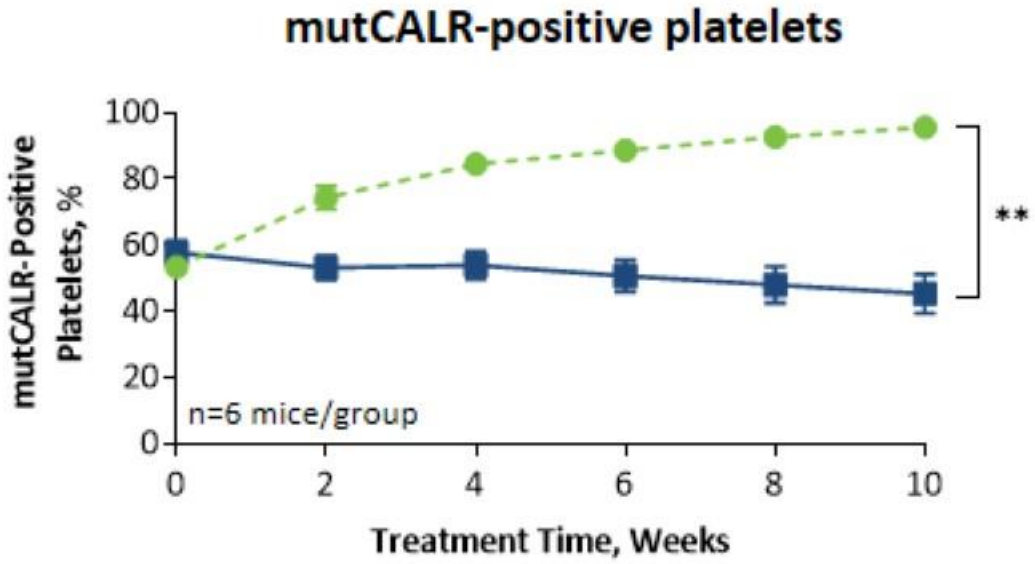




INCA033989 surrogate restores hematologic and molecular responses in a murine model of ET







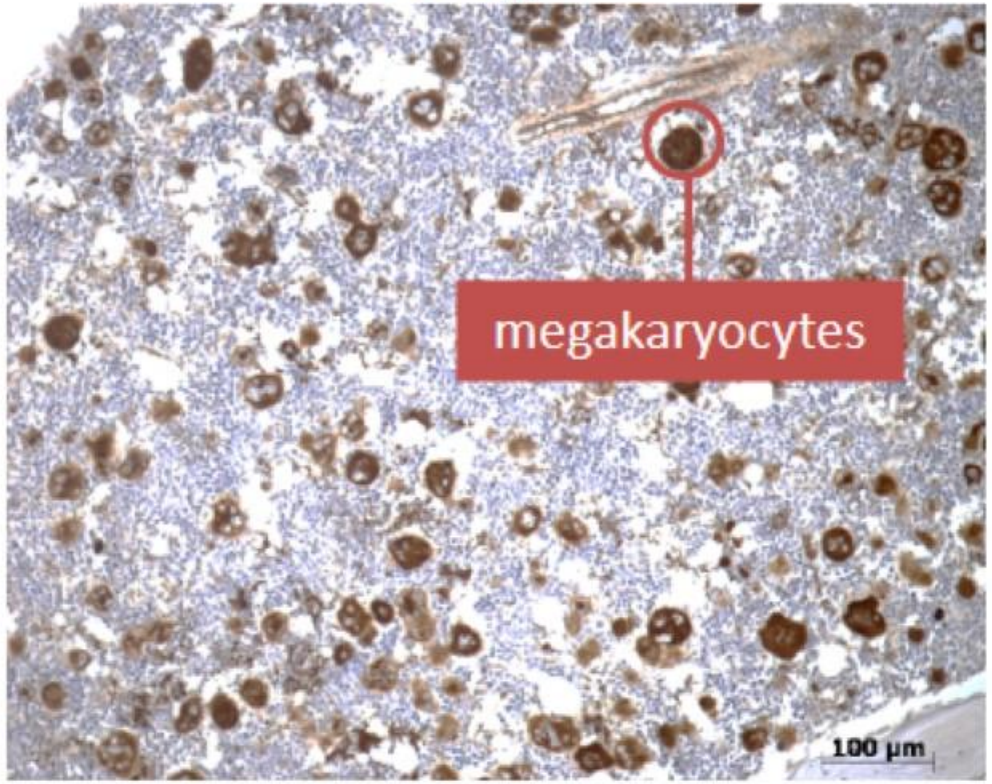
*P<0.001; **P<0.0001.

BM, bone marrow; ET, essential thrombocythemia.

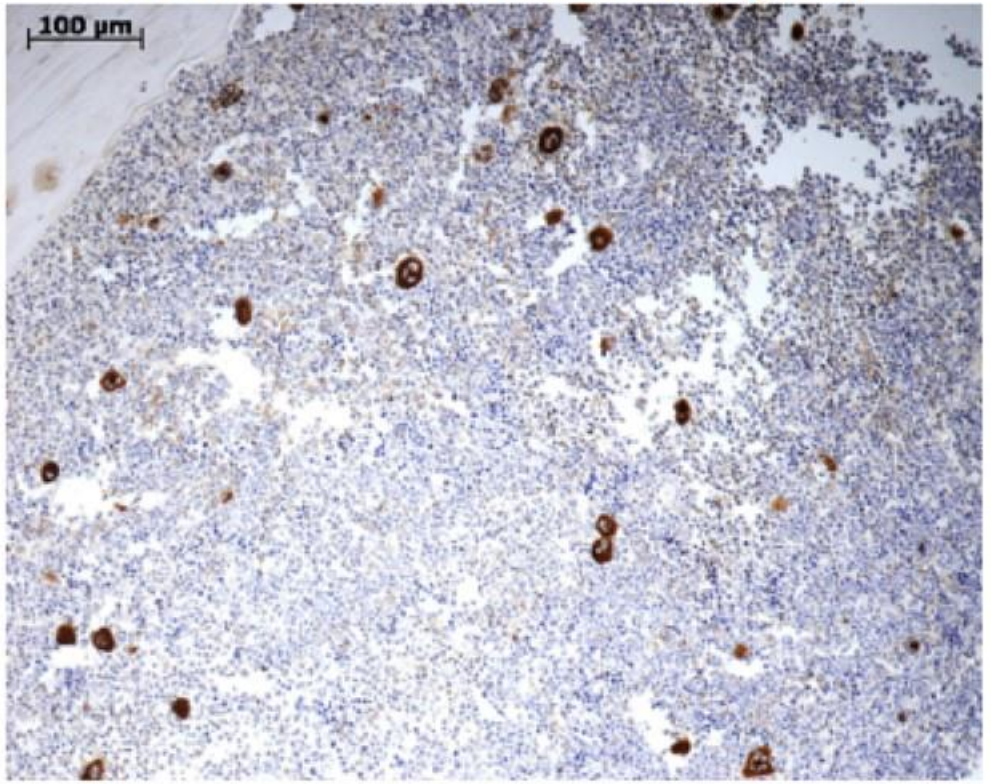
Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

INCA033989 surrogate treatment re-establishes normal megakaryopoiesis

Isotype



INCA033989 (mouse surrogate)



Megakaryocytes stained with anti–von Willebrand factor antibody.

Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

On-going issues in high-risk ET?

First and foremost is it ET? and
Is it High-risk? Might differ according to drive mutation
Don't forget basic cardiovascular risk assessment

Normal platelet count target?

<400 - high-risk PT1
<600 - Bergamo study

High platelet count correlates with haemorrhagic but not thrombotic risk

Haematological response?

- Standardised criteria from ELN (2009) and IWG-MRT (2013)
- Complete haem response:
  plts ≤400, normal spleen, WBC ≤10
- Complete remission:
  symptom improvement, histological remission, no vascular events
- Retrospective study showed no benefit of CR on thrombotic risk or survival

Barosi et al, Blood 2009, 2013;
Hernandez-Boulla et al, B J Haematol 2011

Molecular response?

Patients in molecular response still have thrombotic and transformation events

? Different responses for different molecular profile

Uncertain long-term benefit

Thanks to and acknowledgement of:

GSTT MPN team and patients

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

UK NCRN MPN Clinical Study Group

Global MPN friends and collaborators