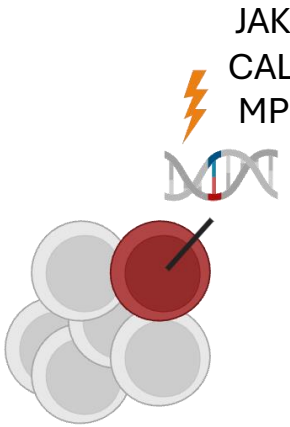
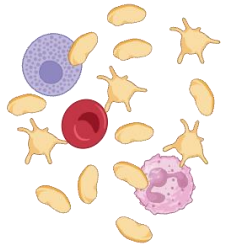
# What's New in MF Treatment

Dr Ashlyn Chee

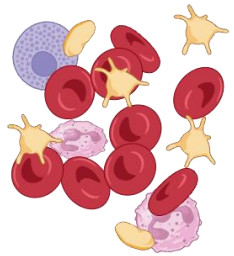
# MPN and evolution to MF



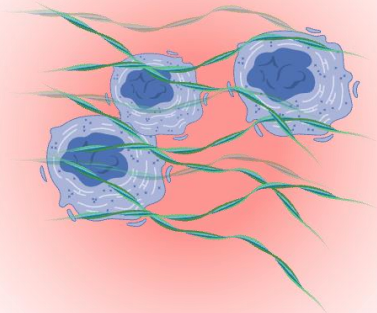

Mutation in blood stem cell



**Essential Thrombocythaemia**
Excess platelets

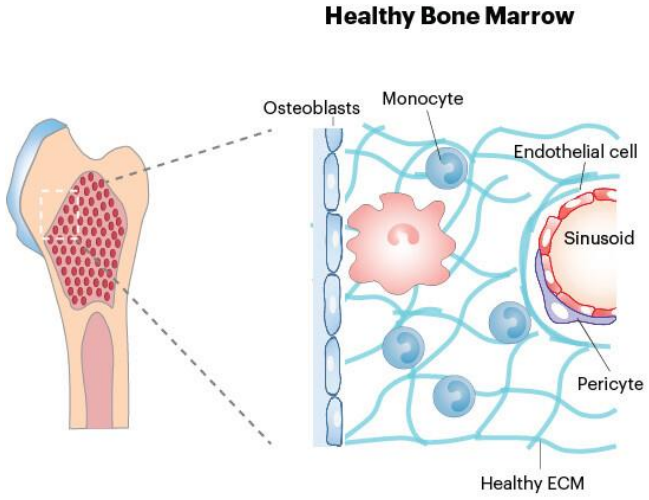


**Polycythaemia Vera**
Excess red cells



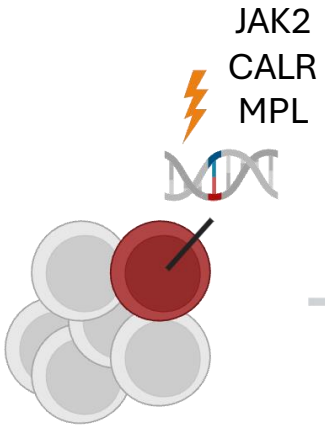
Megakaryocyte-driven inflammation
Fibrosis

Myelofibrosis

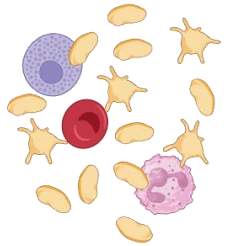



(Images: Beth and Wyss Institute at Harvard University)

# MPN and evolution to MF




Mutation in blood stem cell



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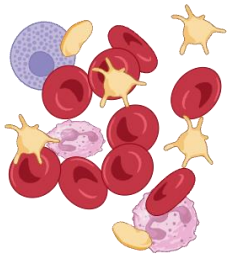

**Polycythaemia Vera**
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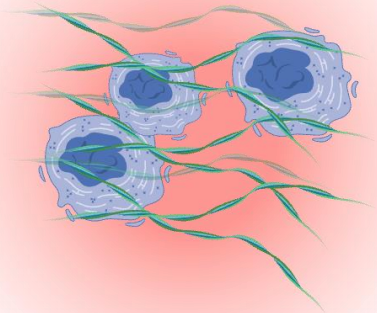


Megakaryocyte-driven inflammation
Fibrosis

Myelofibrosis

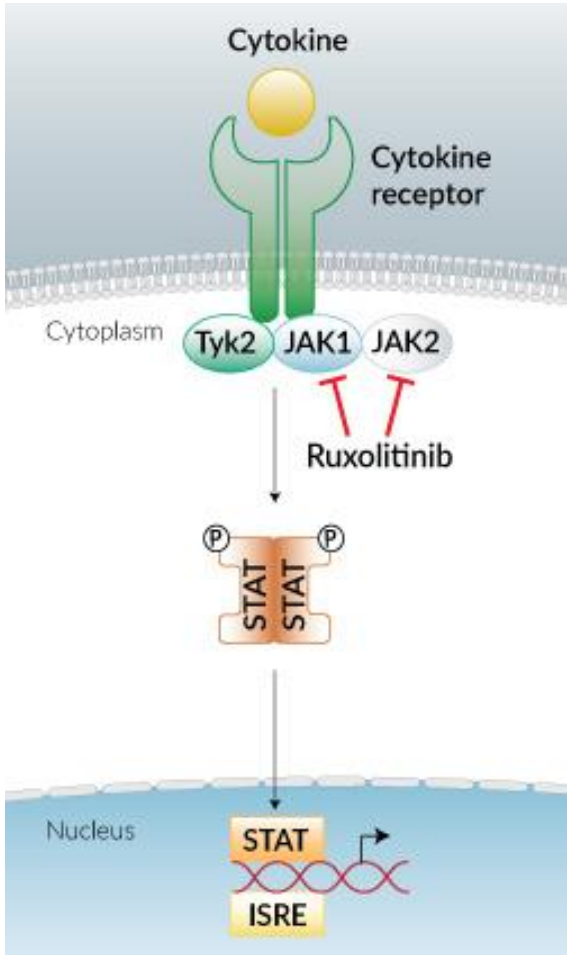
# Content

Current standard of care treatment

- JAK inhibitors
  - Ruxolitinib, Momelotinib, (Fedratinib, Pacritinib)
- Allogeneic stem cell transplant
- (Supportive care)

- JAK inhibitors + Add on therapies
  - BETi, MDM2i, XPO1
  - (PegIFN, BCL2-BCL-XL inhibition, LSD1i, telomerase inhibitor)
- Anti-clonal therapies

# JAK inhibitors – Mainstay of MF treatment




## Ruxolitinib (JAK1/2i)

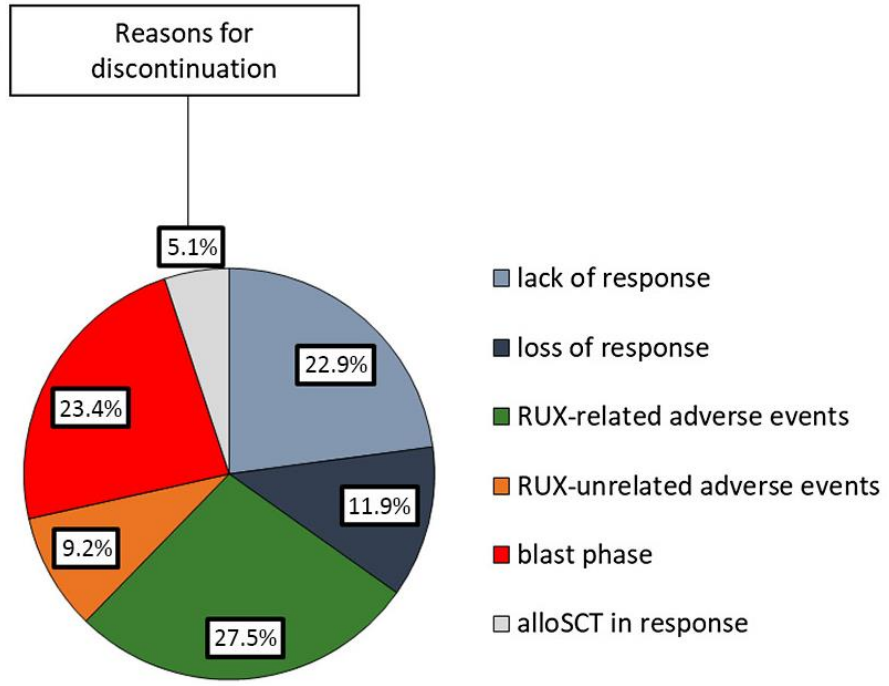
- Works on the JAK signaling pathway, irrespective of driver mutation status
- Effective in reducing splenomegaly, symptoms and QOL
- 5 year follow up confirms improved OS

Listed on PBS Australia since 2016 and only available therapy until April 2025

Harrison et al, 2012 NEJM
Verstovsek et al, 2017 J Haematol Oncol

# JAK inhibitors – Mainstay of MF treatment

- 40% of patients discontinued ruxolitinib after 3 years
- Discontinuation associated with acquisition of additional mutations e.g. RAS pathway
- Risk of non-melanomatous skin cancers
- Dose dependent anaemia and thrombocytopenia occurs frequently




Palendri et al. 2019. Cancer

## Momelotinib

JAK1+2i and ACVR1/ALK2

## Fedratinib

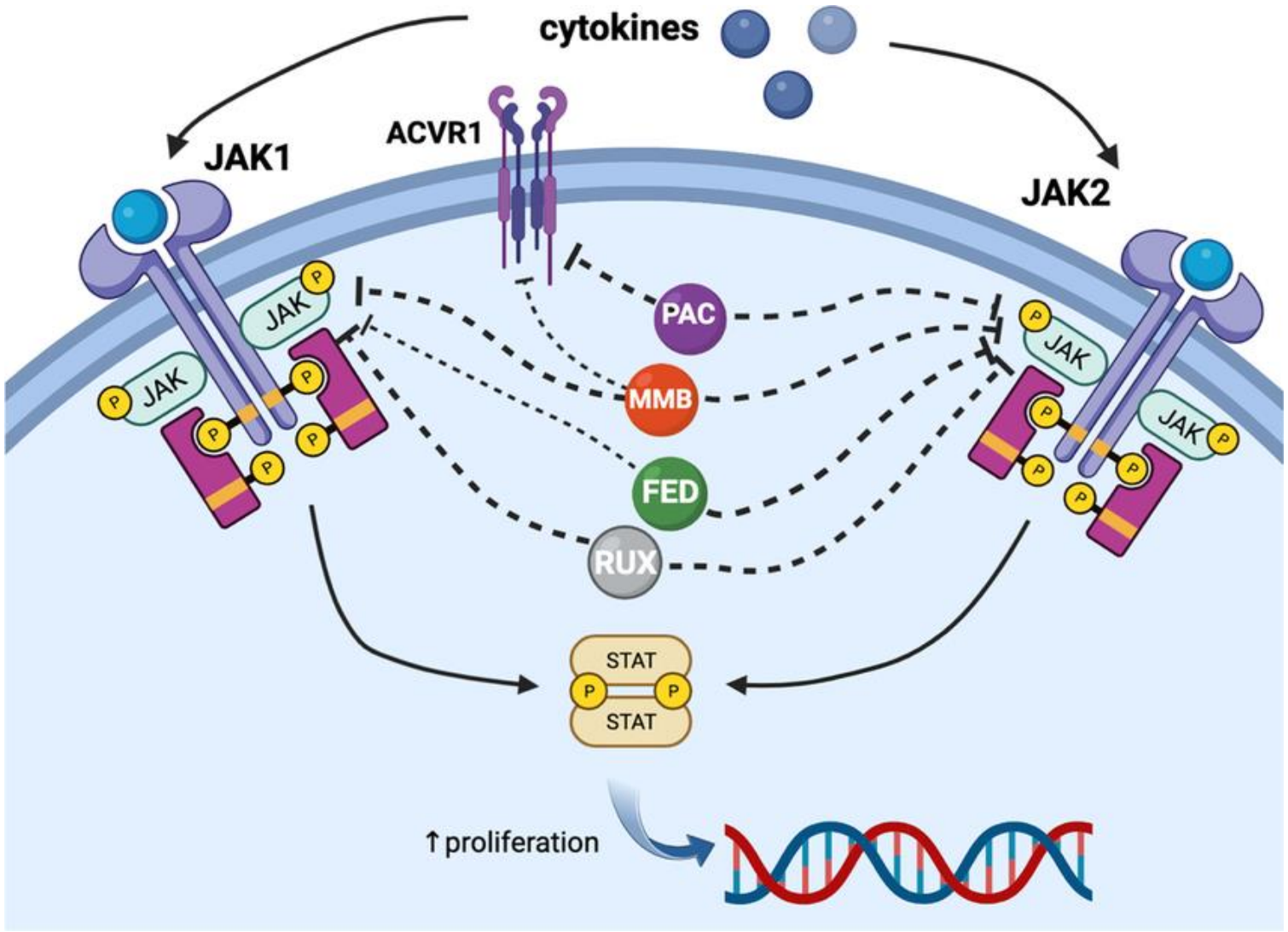
>300x more selective for JAK2, FLT3i

*not licensed in Aust

## Pacritinib

JAK2i, ACVR1i, FLT3i, IRAK1i

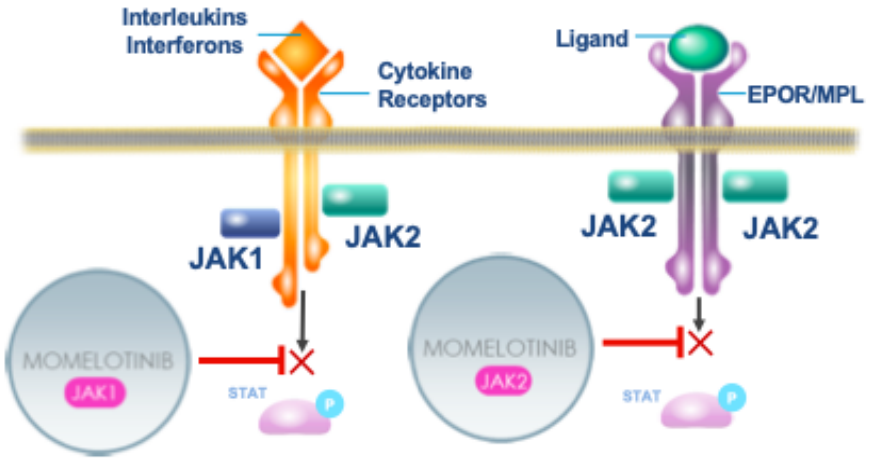
*not licensed in Aust

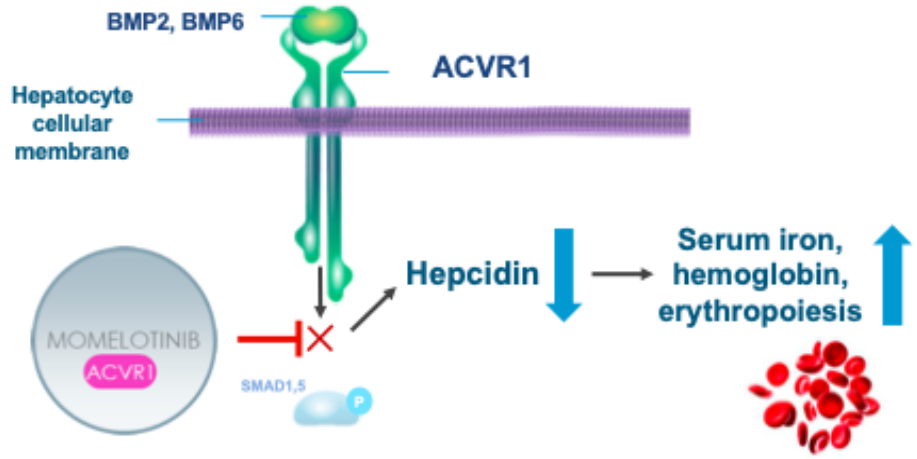



Schematic graphical representation of the therapeutic targets of the JAK inhibitors.
Duminico et al. A journey through JAK inhibitors for the treatment of MPN. Current haematologic malignancy reports. 2023.

# Momelotinib: On PBS as 1st/2nd line treatment for patients with MF & anaemia <100g/L (since 1 April 2025)

## Inhibits JAK1, JAK2, and ACVR1 to address symptoms, spleen & anemia




Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF

# Momelotinib: 3 Large phase 3 trials

## SIMPLIFY-1

Phase 3 trial, MMB vs RUX (N = 432)

**Eligibility:**

- MF **untreated** with JAK inhibitors

**Results:**

- SVR35: **noninferior to RUX** (27% vs 29%; *P* = .011)
- TSS50: **inferior to RUX** (28% vs 42%; *P* = .98)
- **RBC-TI: 67% (vs 49% with RUX; *P* < .001)**

Mesa RA, et al. J Clin Oncol. 2017;35:3844-3850;

## SIMPLIFY-2

Phase 3 trial, MMB vs BAT (N = 156)

**Eligibility:**

- MF **pretreated** with RUX

**Results:**

- SVR35: **not superior to BAT** (7% vs 6%; *P* = .89)
- TSS50: **superior to BAT** (26% vs 6%; *P* = .0006)
- RBC-TI: **43%** (vs 21% with BAT; *P* = .0012)

Harrison CN, et al. Lancet Haematol. 2018;5:e73-e81;

## MOMENTUM

Phase 3 trial, MMB vs DAN (N = 195)

**Eligibility:**

- MF **pretreated** with JAK inhibitors

**Results:**

- SVR35: **23%** (vs 3% DAN; *P* = .0006)
- TSS50: **25%** (vs 9% DAN; *P* = .0095)
- RBC-TI: **31%** (vs 20% DAN; 1-sided *P* = .0064)

Verstovsek S, et al. Lancet. 2023;401:269-280.

Slide adapted from Beth Psaila

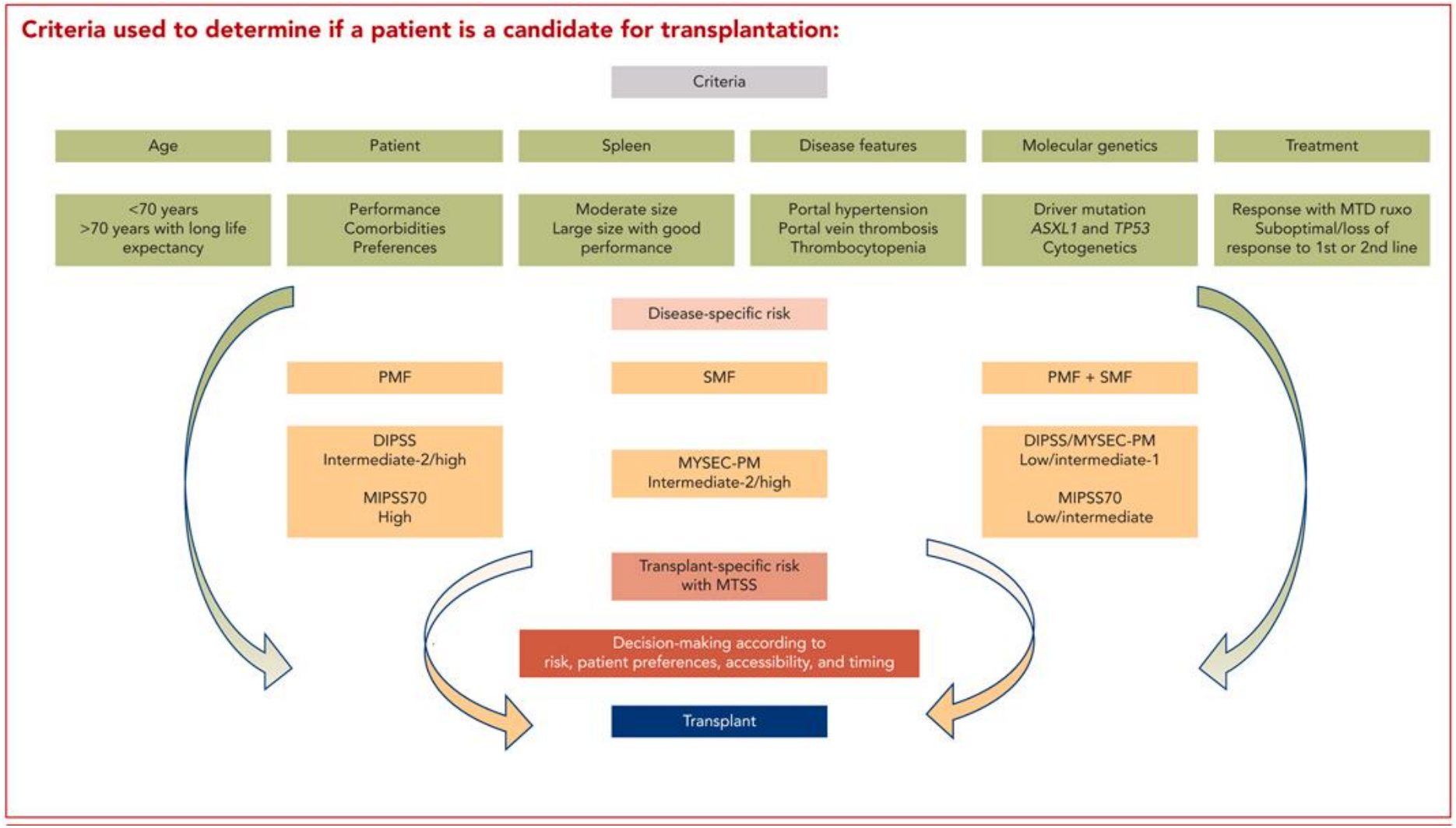
# Momelotinib: Practicalities

- How to choose?
  - Anaemic
  - Symptomatic with sweats, massive spleen
- How to switch?
  - No need to taper from ruxolitinib to momelotinib
- Remember!
  - Don't stop abruptly

**Side effects**

- Neutropenia and thrombocytopenia
- Neurological (neuropathy, hypotension, dizziness)
- GI
- Infections

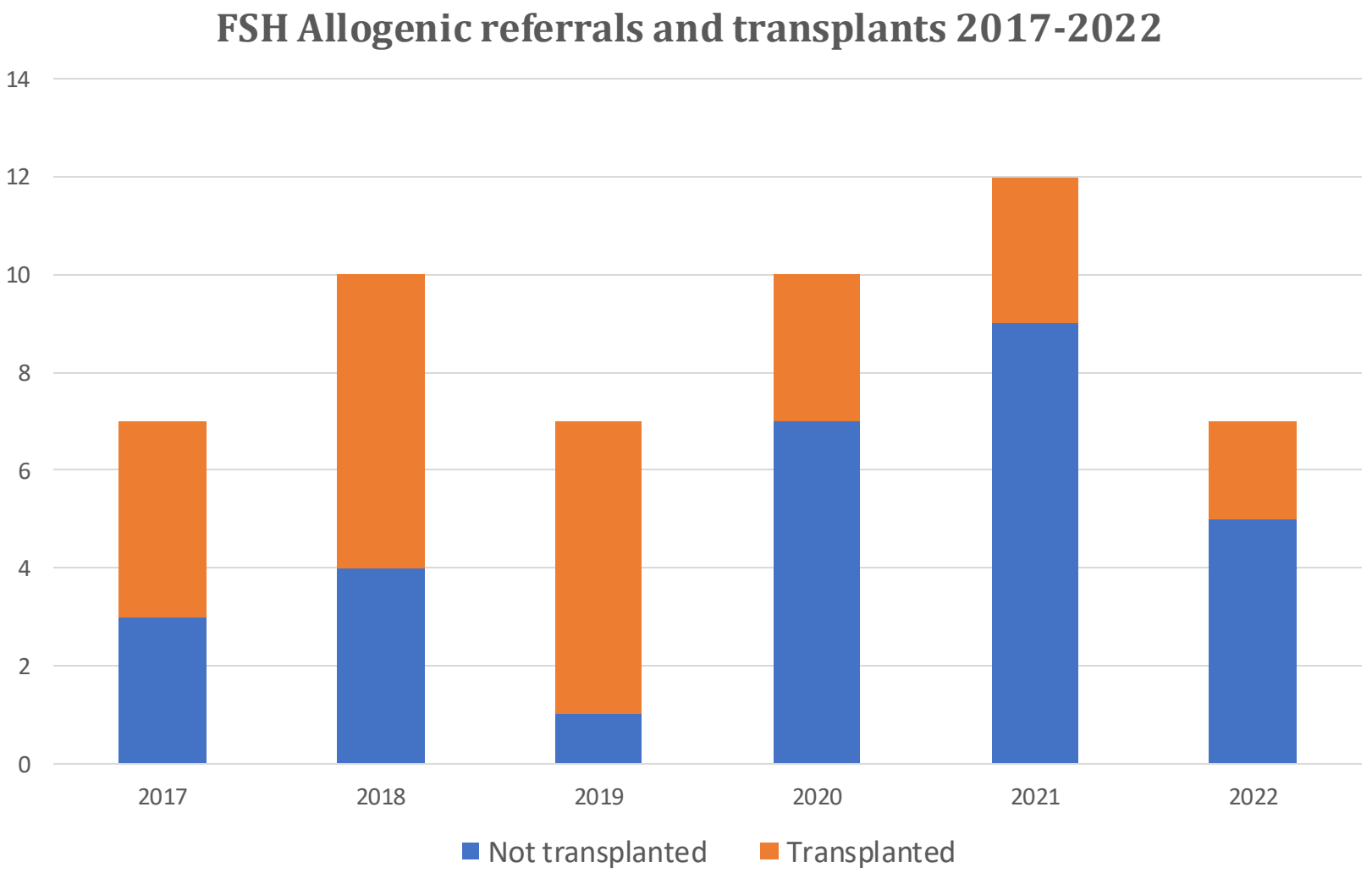
# Allogeneic stem cell transplant




Kroger et al, blood

- Only curative treatment
- Decision to transplant is a complex one

# Allogeneic stem cell transplant



# JAK + add on therapies

JAK inhibitors have limited ability to lower driver mutation allele burden, bone marrow fibrosis, or prevent disease progression.

# JAK + add on therapies

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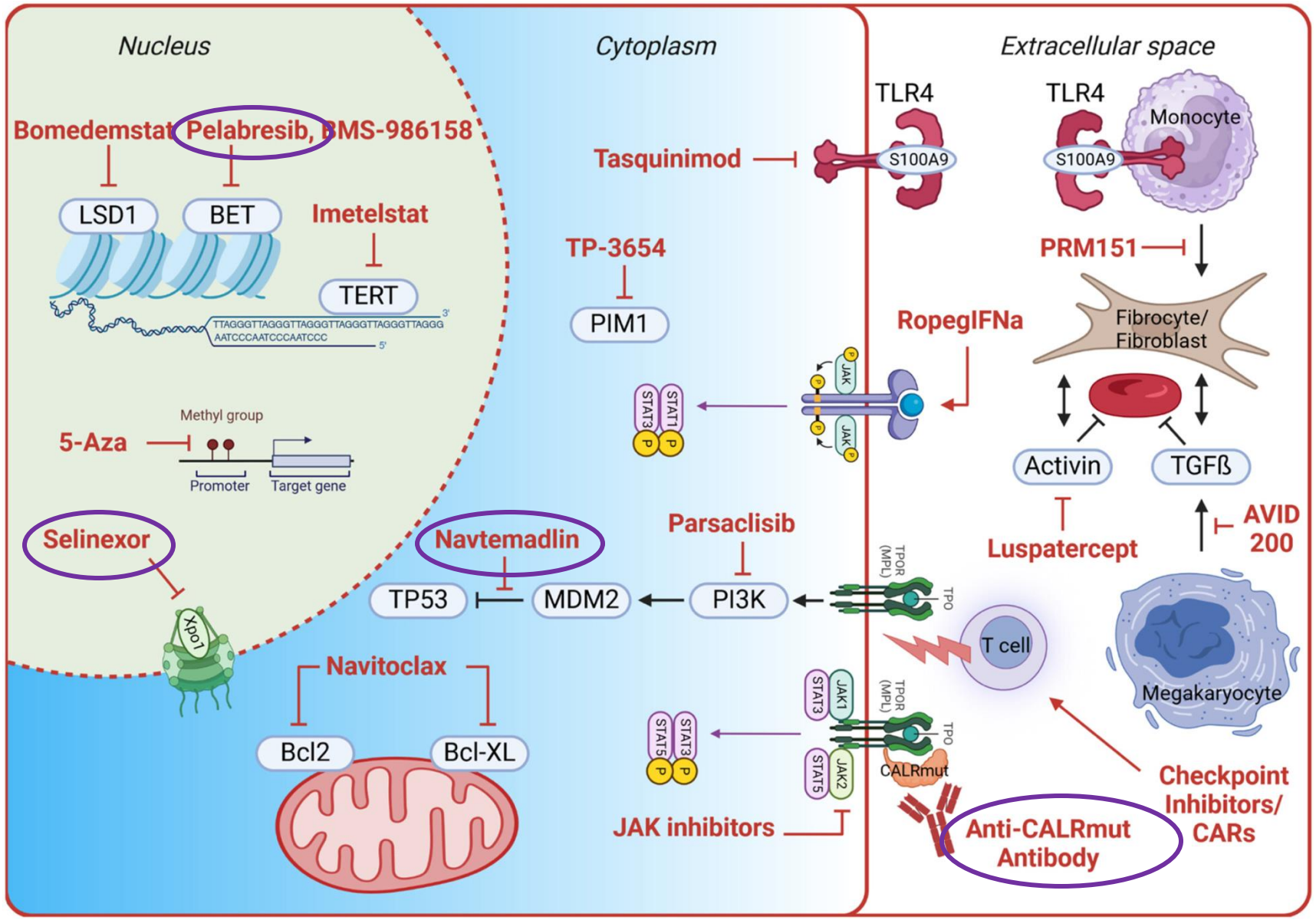
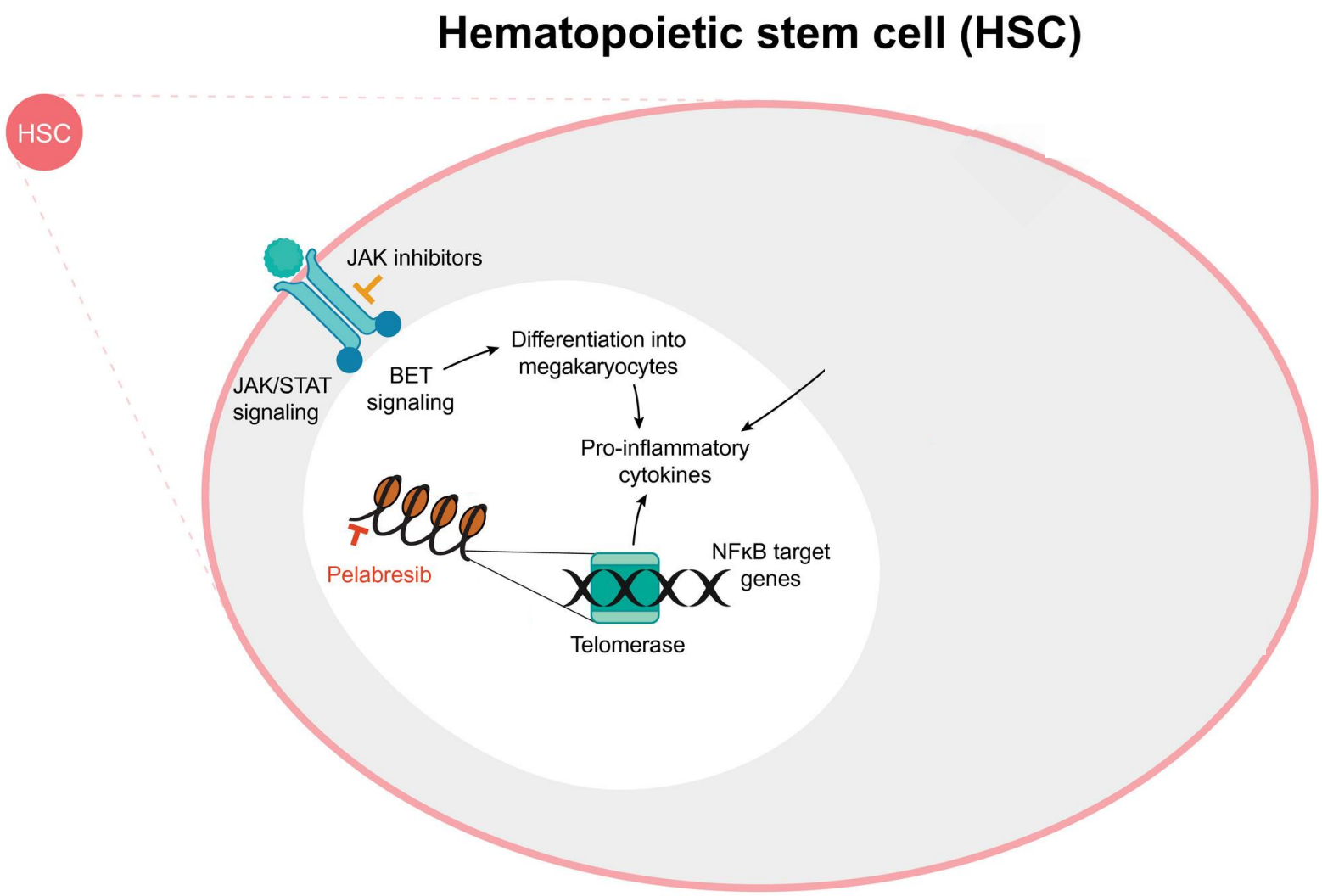



Novel approaches in myelofibrosis, Hemasphere Koschmeider 2024

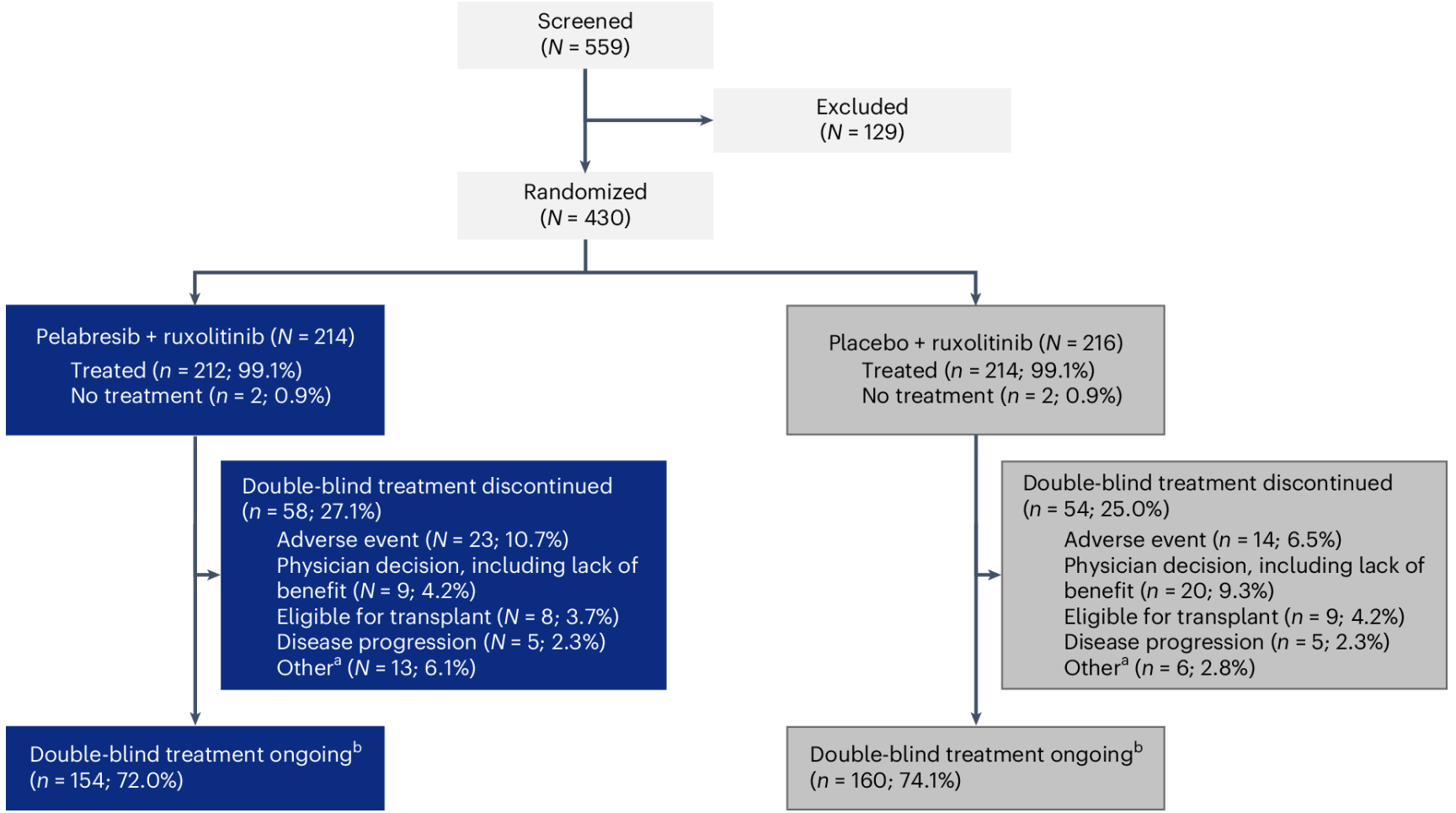
# JAK + add on therapies (BETi)

- BET inhibitor (Pelabresib)
- NF-κB-mediated inflammation



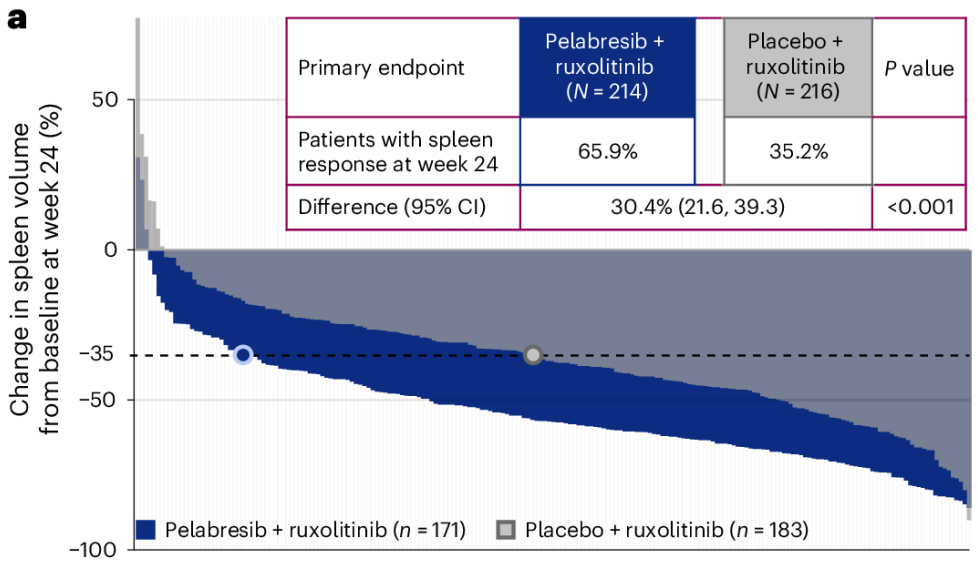
# JAK + add on therapies (BETi)

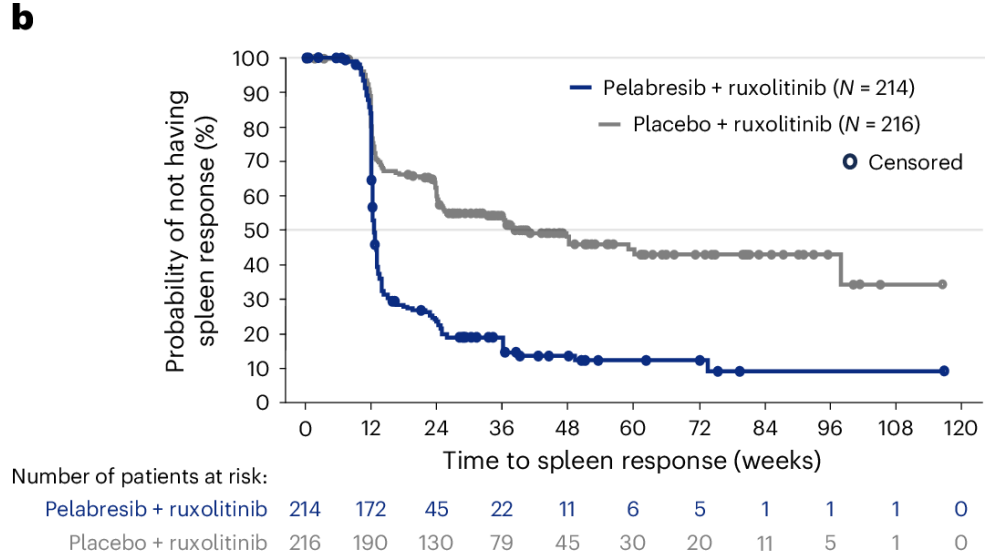
- MANIFEST-2 phase 3 study
- Pelabresib + ruxolitinib vs placebo + ruxolitinib in JAK inhibitor-naive patients with myelofibrosis
- Key eligibility – DIPSS≥ Int-1, peripheral blast <5%, plt >100
- Similar baseline characteristics



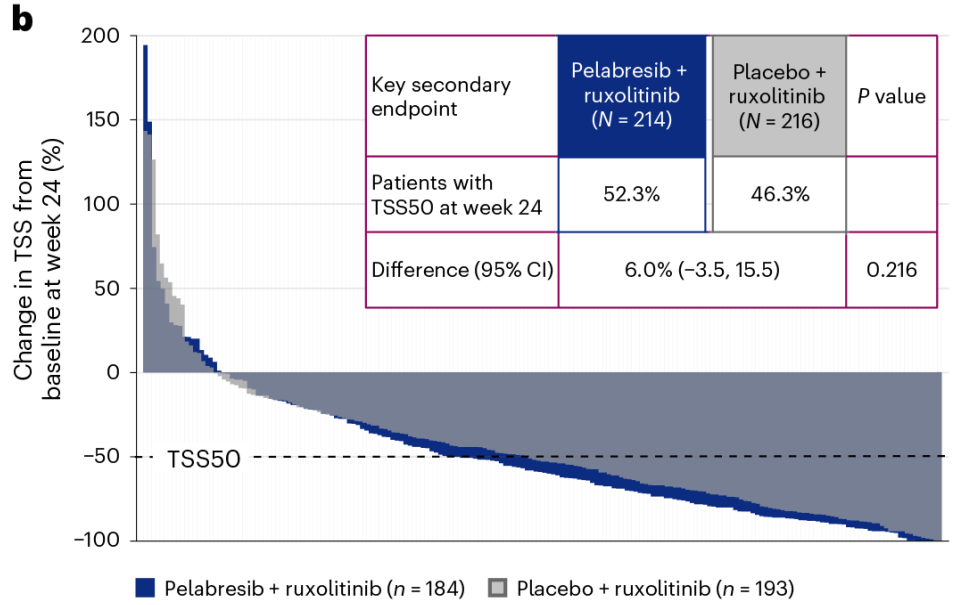

Rampal et al, 2025, Nature

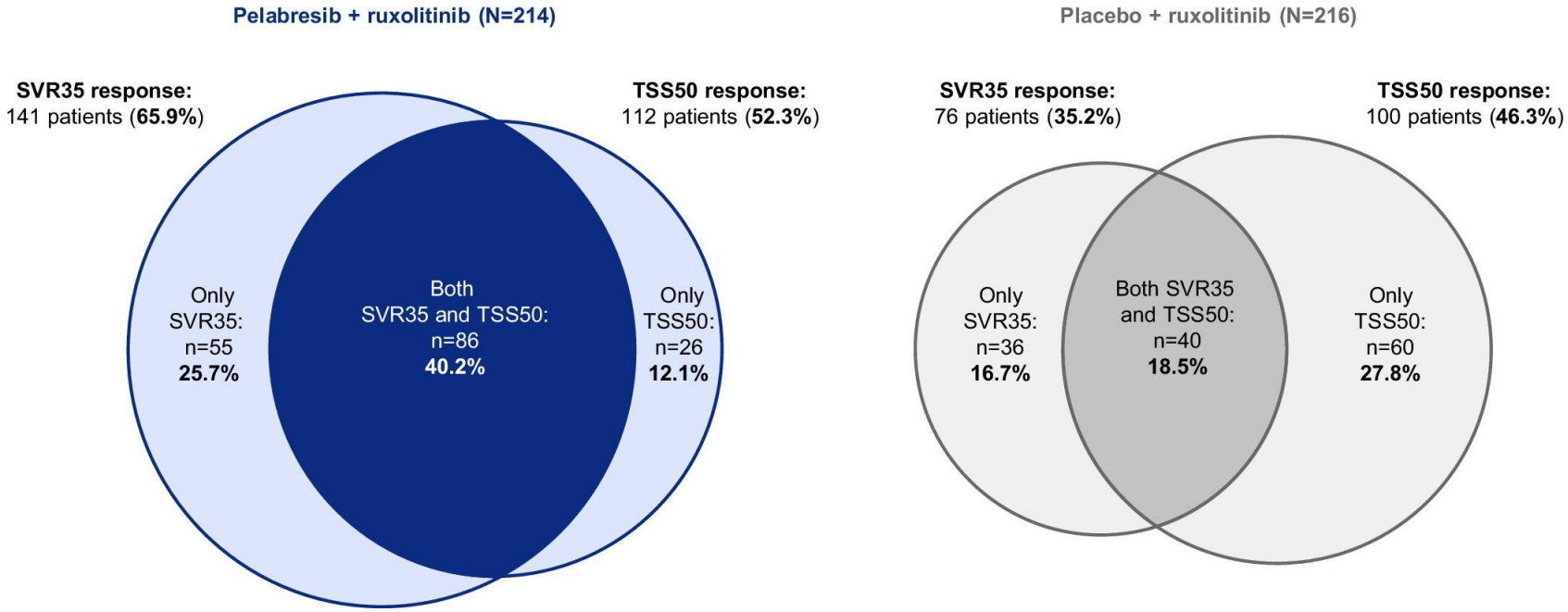
## Splenic response




## Symptom response



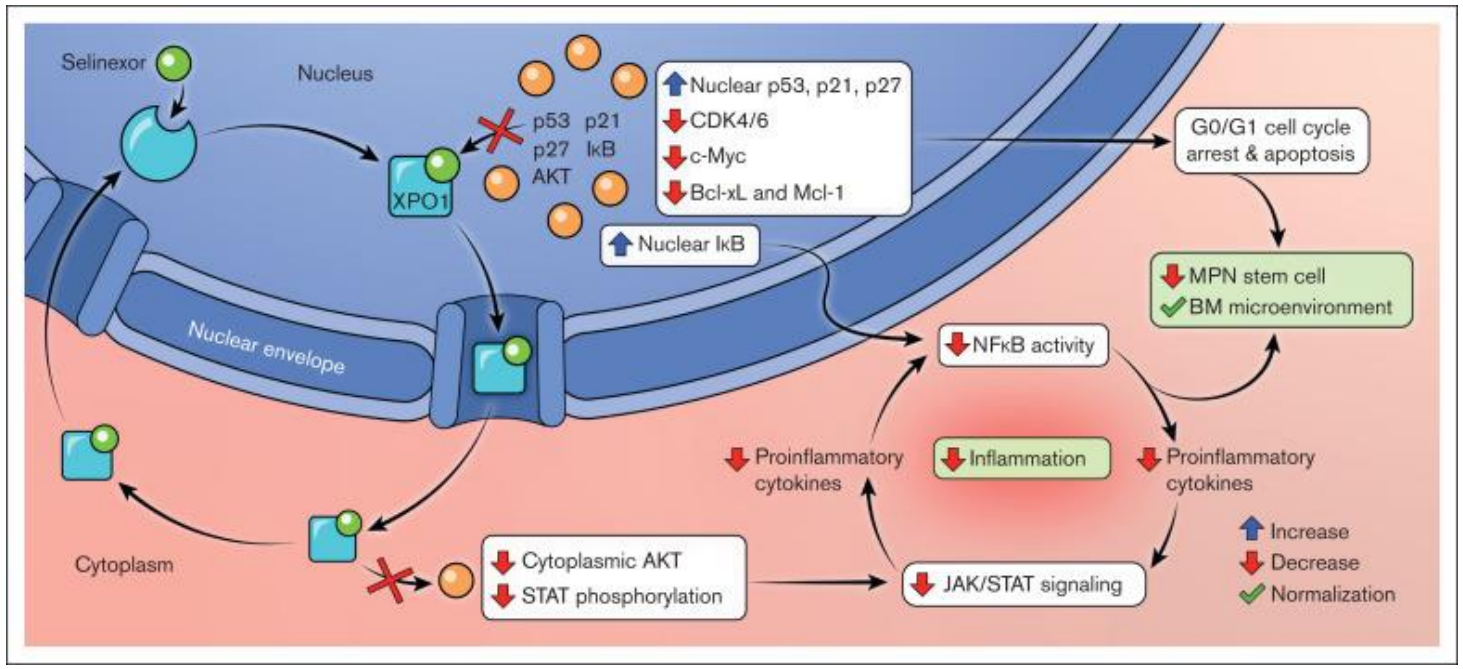



Safety

- Most frequent serious adverse events were pneumonia (3.3% vs 2.8%)
- Most frequent haematological AE was anaemia and thrombocytopenia
- Most frequent non-haematological AE was diarrhoea, altered sense of taste (tx) and constipation (placebo)
- Grade ≥3 TEAEs were lower for pelabresib-treated patients (49.1% vs 57.0%)

Greater reduction in fibrosis 18.8% vs 11.2% and inflammatory cytokines. Longer term data needed to assess JAK2 V617F VAF

# JAK + add on therapies (XPO1 inhibitor)




•Selinexor is an inhibitor of XPO1

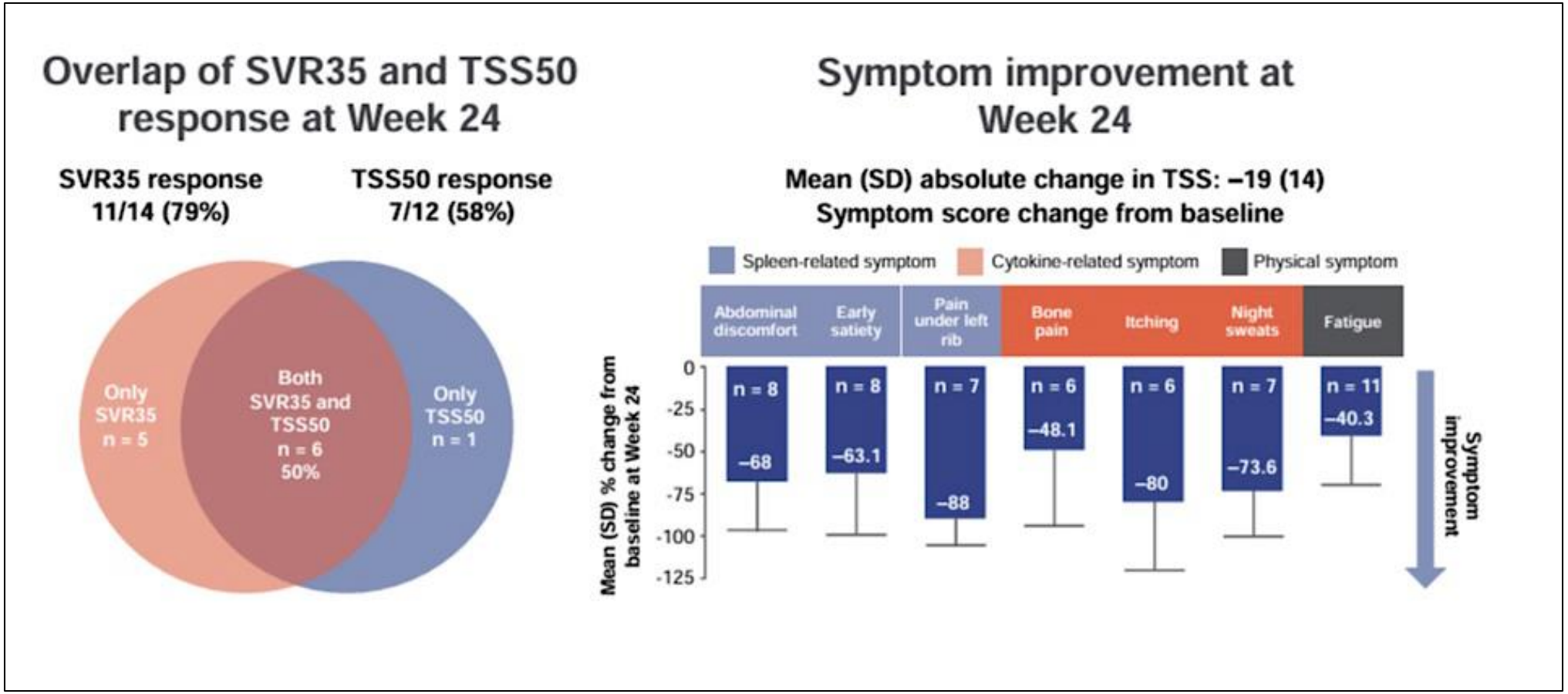
1. Results in cell-cycle arrest
2. Decreased NF-κB signalling
3. Decreased activation of STAT pathway

•Broad use in MM and other tumours

•Evaluated as monotherapy in JAK refractory/intolerance in previously treated MF (ESSENTIAL) and in treatment naïve MF (XPORT-MF-044)

# JAK + add on therapies (XPO1 inhibitor)

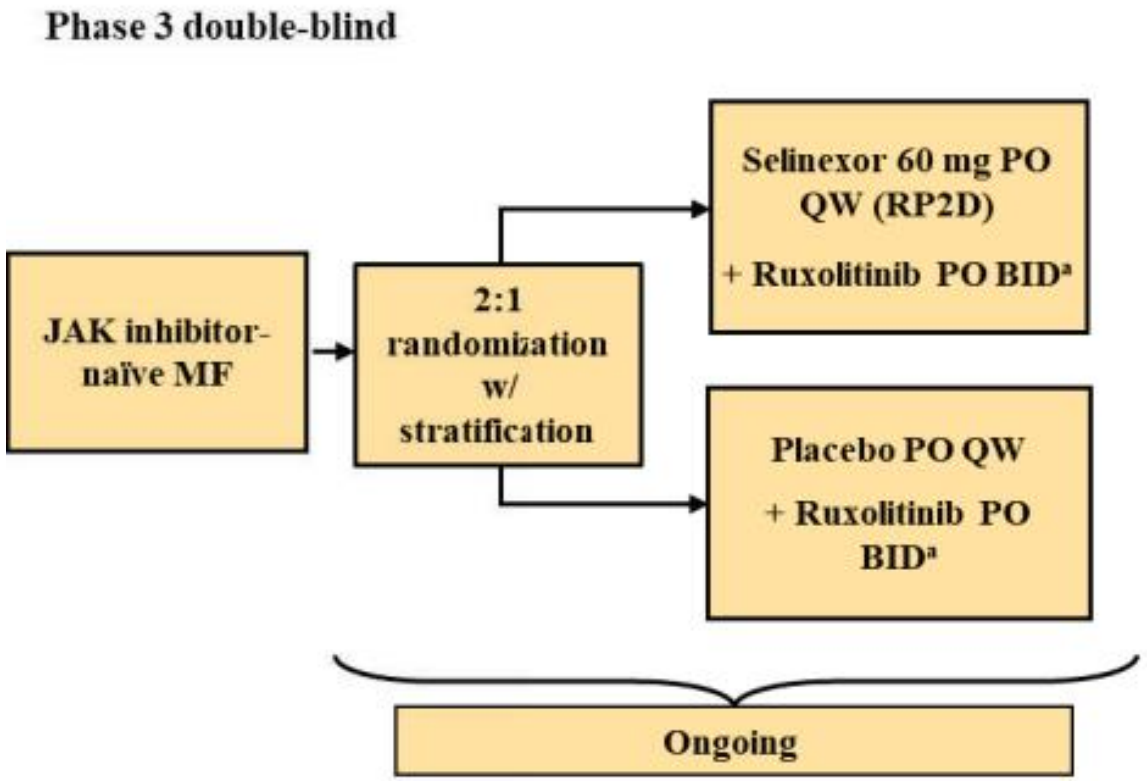
•Phase 1 (XPORT-MF-034) – Selinexor and ruxolitinib in treatment naïve Myelofibrosis
• Favourable impact on spleen and symptoms




•At week 24, 5 patients (38%) had a VAF reduction ≥20%
•Reduction in cytokines were also seen and corresponded to spleen and symptom response

Ali H, et al. AACR 2023; Abstract CT261
Ali H, et al. ASCO 2023; Abstract 7063

# XPORT-MF-034 (XPO1 inhibitor)




**Stratification Factors:**

- Dynamic International Prognostic Scoring System risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 $cm^3$ vs. ≥1800 $cm^3$ by MRI/CT scan
- Baseline platelet counts 100-200 × $10^9$/L vs. >200 × $10^9$/L

**XPORT-MF-034:** A Phase 3 study to evaluate selinexor + ruxolitinib vs placebo + ruxolitinib in treatment-naïve patients with myelofibrosis

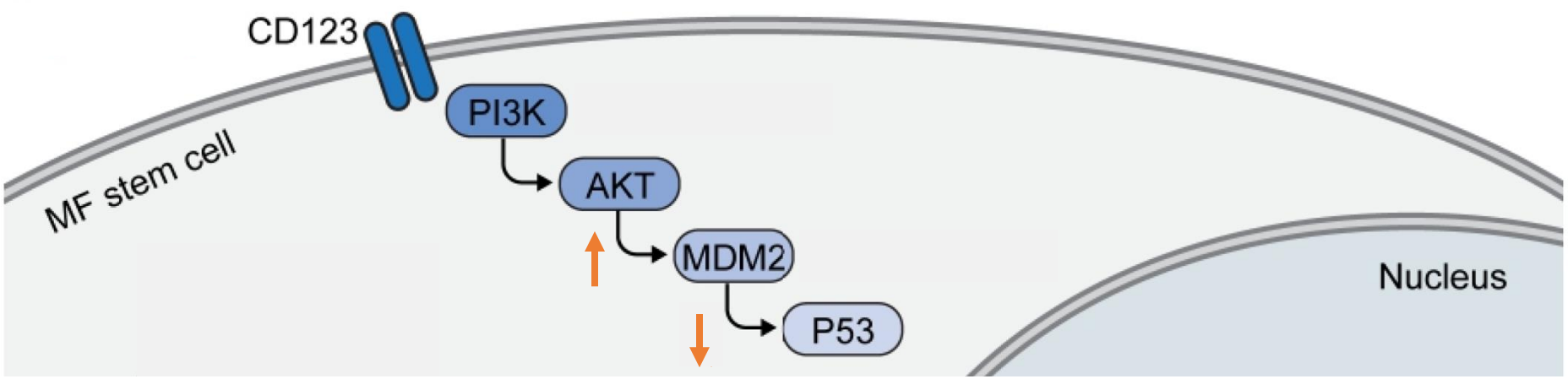
Key eligibility:

Inclusion: Splenomegaly >450cm3; platelet count >100

Exclusion: >10% blasts in blood or marrow; prior JAKi

Trial enrollment closed at OCR

# JAK + add on therapies (Navtemadlin)




- Navtemadlin (MDM2 inhibitor)
  - MDM2 is increased in MF, which is a negative regulator of P53
  - Inhibiting MDM2 restores P53 function allowing it to kill cancer cells

# JAK + add on therapies (Navtemadlin)

• BOREAS (Phase III) - Navtemadlin monotherapy vs best available therapy in patients with relapsed/refractory MF with prior JAKi therapy

  • Patients on navtemadlin (n = 123) - 15% achieved an SVR35 at week 24 compared with 5% (n = 60).

  • TSS50 rates at week 24 were 24% and 12%.

  • Patients remained on navtemadlin for 1.5 years vs 6 months.

  • At week 24, patients on navtemadlin (n = 82) achieved a reduction of driver gene VAF of at least 50% at a rate of 21% compared with 12% (n = 33)

Mascarenhas et al, 2024, ASH abstract

# JAK + add on therapies (Navtemadlin)

• KRT-232-109 (Phase Ib/II) study - Addition of navtemadlin to ruxolitinib in patients who have a suboptimal response to ruxolitinib

• Patients who received navtemadlin (n = 19)

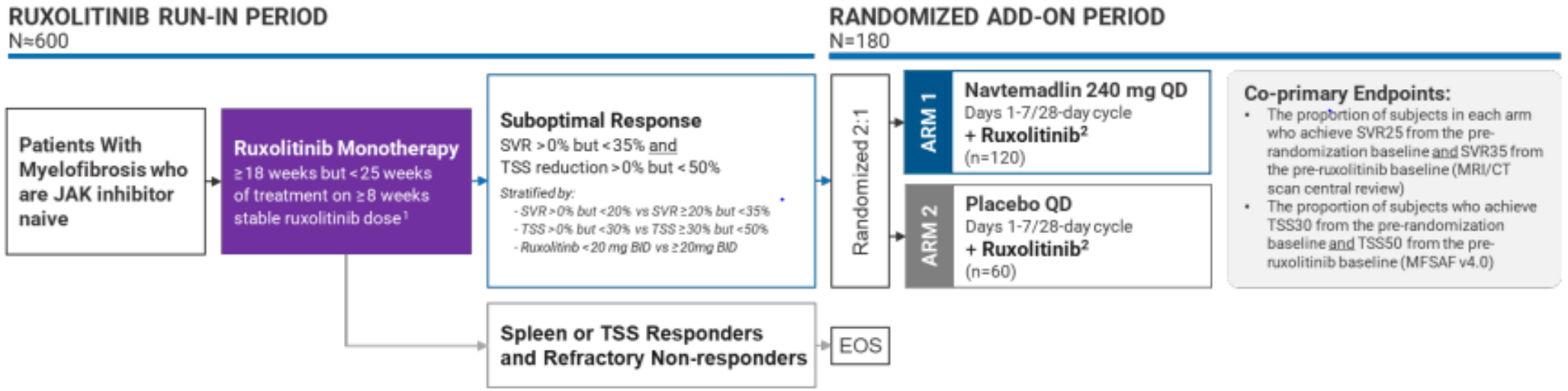
  • Spleen volume reduction of 25% at week 24 achieved in 42% of patients and spleen volume reduction of 35% at week 24 achieved in 32%.

  • TSS50 at week 24 was 32%.

•These findings formed the basis of the following trial…

Mascarenhas et al, 2023, EHA abstract

# JAK + add on therapies (Navtemadlin) - POIESIS study

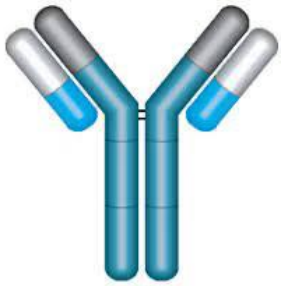



- Key eligibility
  - IPSS intermediate-1, intermediate-2 or high
  - Spleen >450
  - Plt >100, WCC <50, ANC >1.5
- Key exclusion
  - Blasts >10%

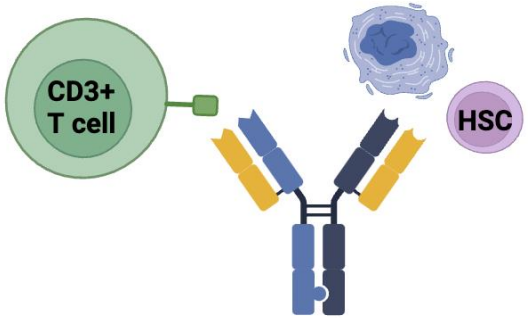
*Currently recruiting at RPH and SGCH

# Immunotherapy trials in MPN - a new horizon

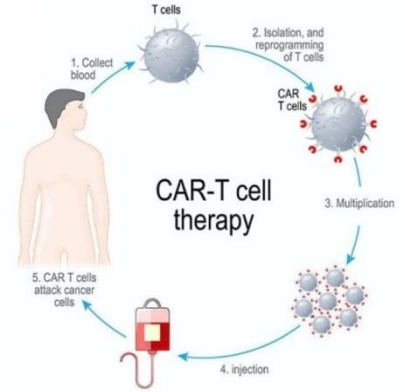
Inhibitory mut-CALR antibody



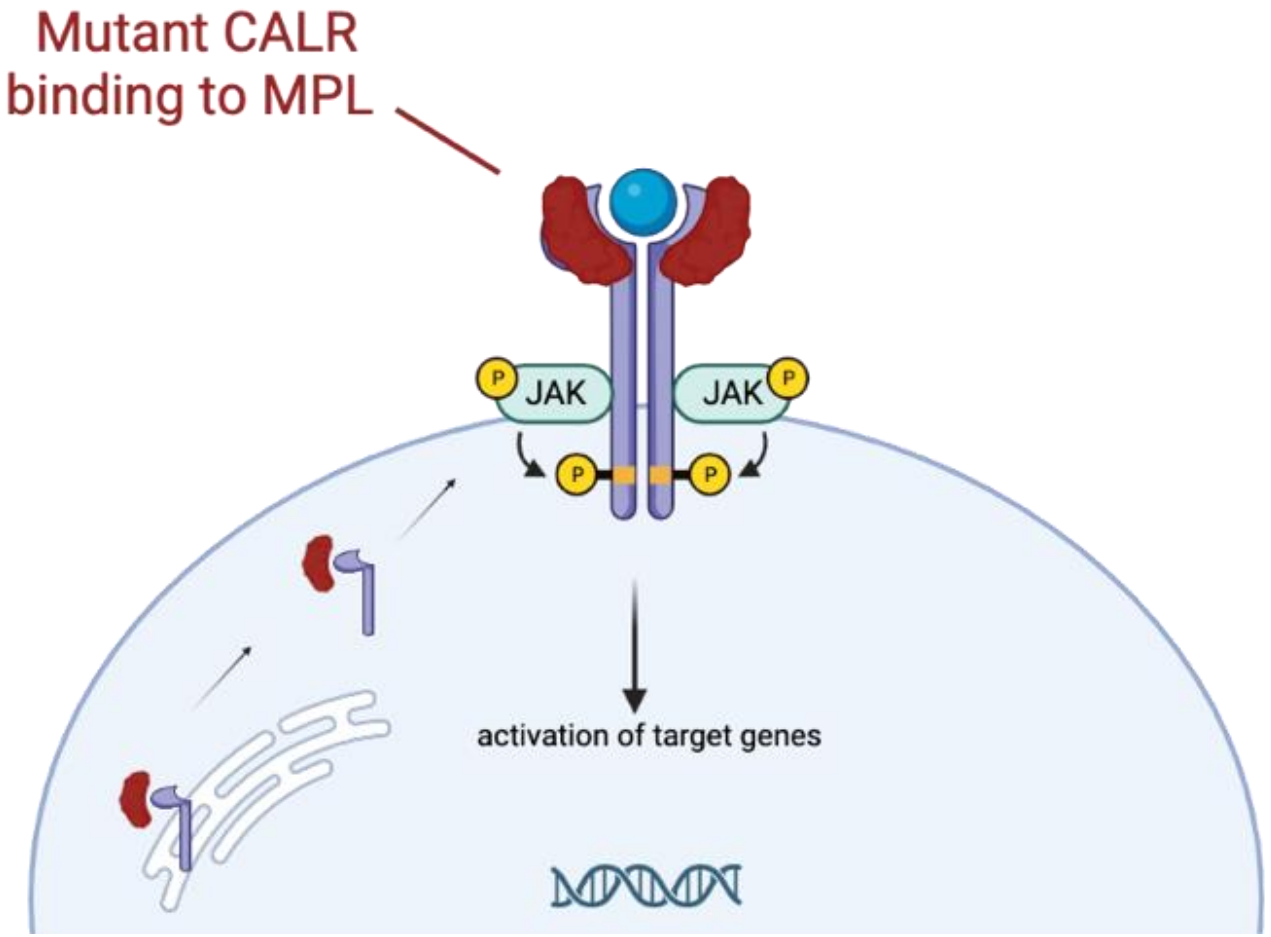
Anti-mutCALR bispecific antibodies

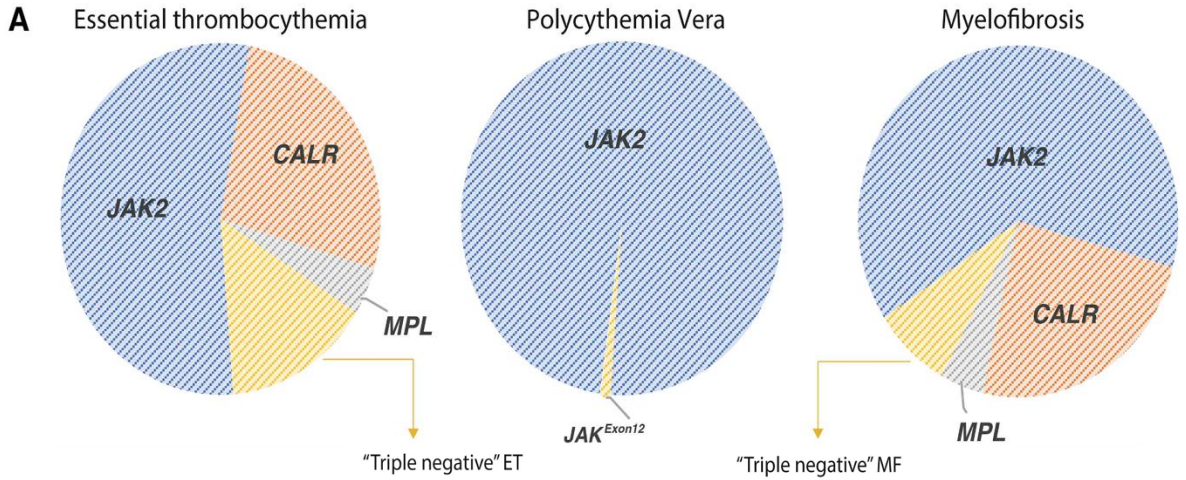



CAR-T cell therapies
(pre-clinical phase)



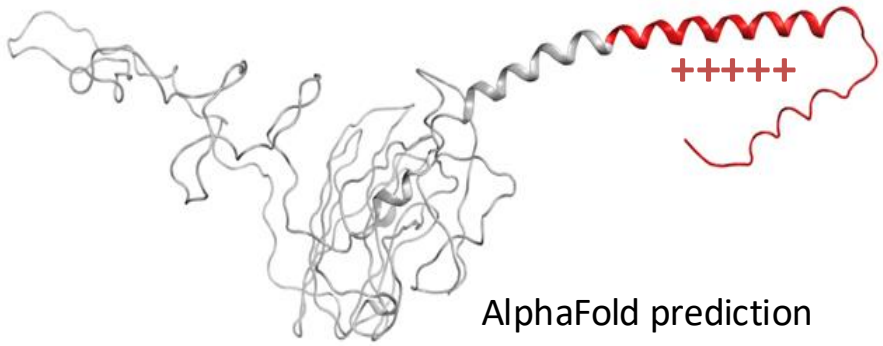
# Discovery of the CALR mutation in 2013



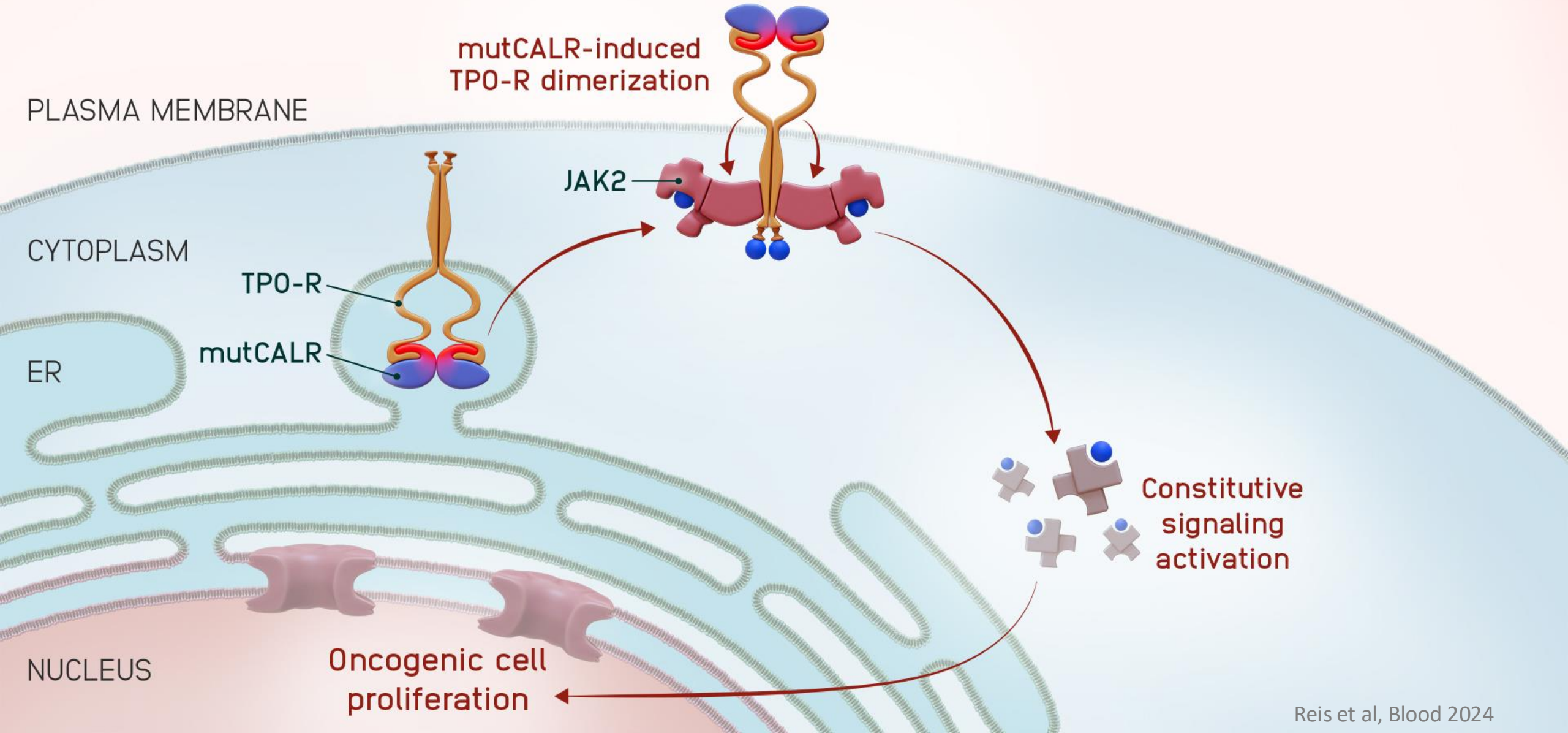




**52-bp deletion (Type 1) or 5 bp-insertion (Type 2) in *CALR* exon 9**

Mutant-specific C-terminus

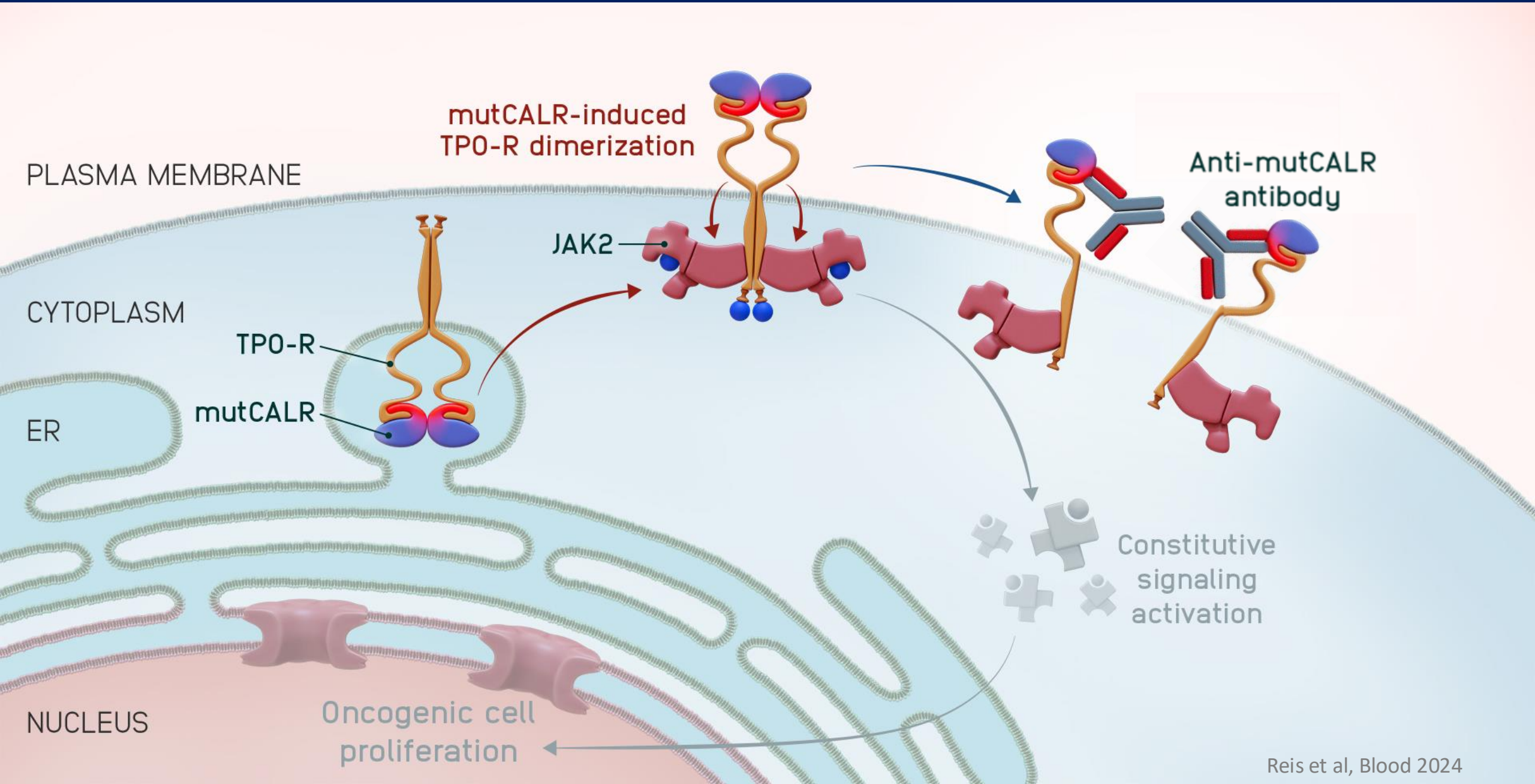



AlphaFold prediction



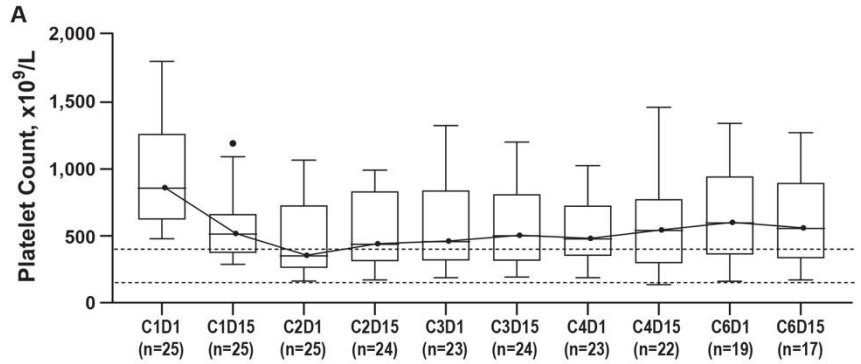

Reis et al, Blood 2024

# INCA033989 inhibits TPO-R dimerization and signaling

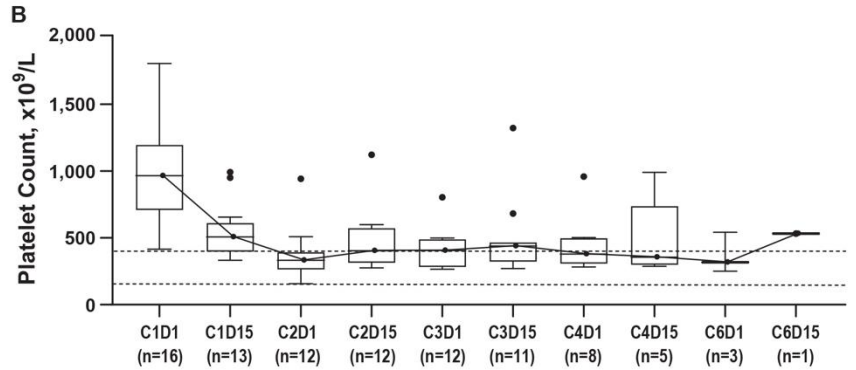



Reis et al, Blood 2024

# INCA33989 - Phase I CALR antibody trial

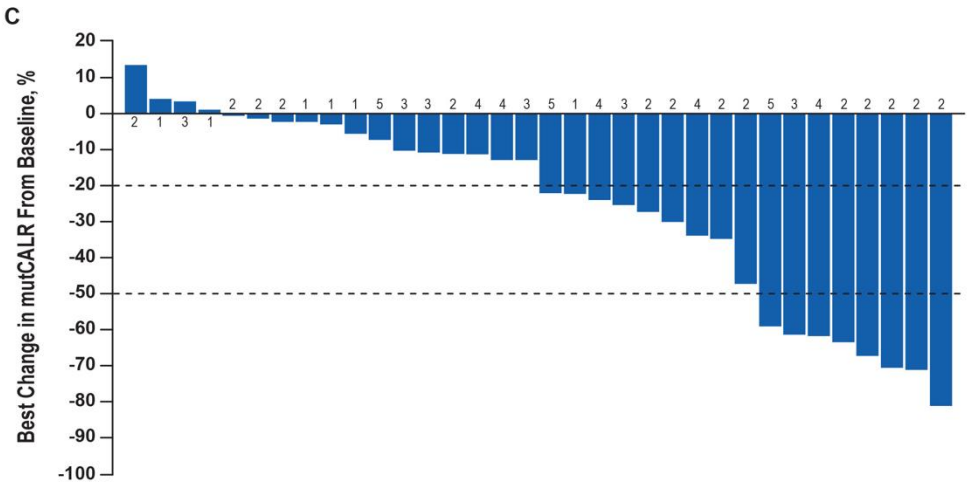



24 to 250 mg




≥400mg

Early data for the INCA33989 ESSENTIAL THROMBOCYTHEMIA (ET) cohort



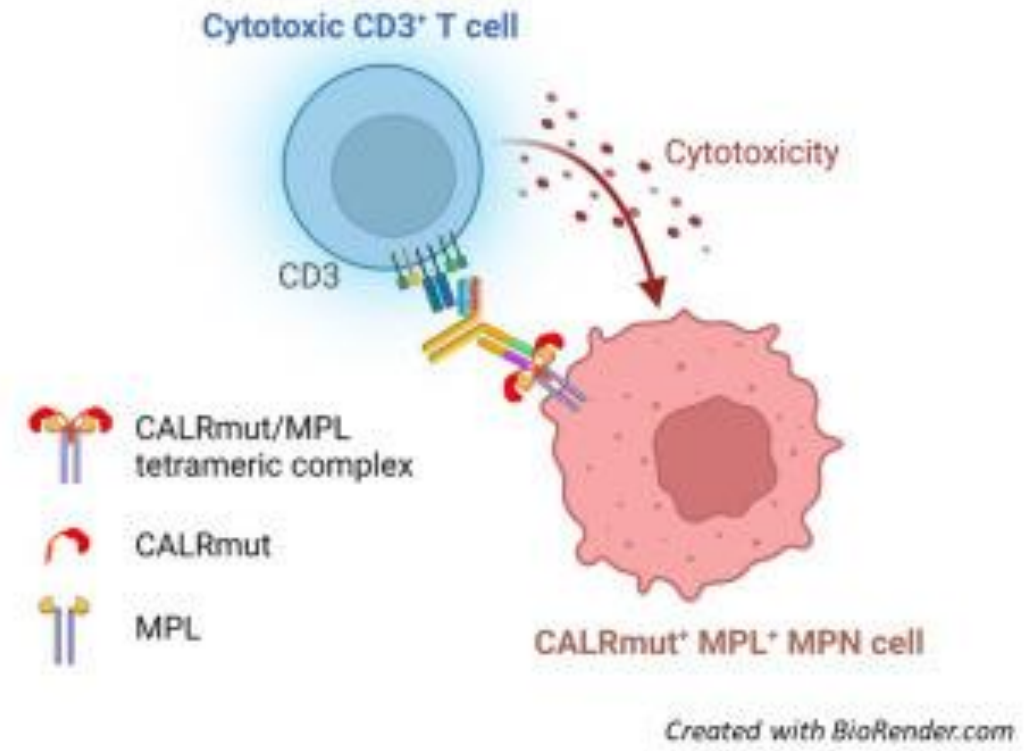

Change in CALR VAF

Mascarenhas et al, EHA abstracts, 2025

# Phase I CALR bispecific antibody trial

- JNJ88549968 (Johnson & Johnson)
- INCA035784 (Incyte)

Schematic explaining mechanism of action: JNJ-88549968 is a T-cell redirecting bispecific antibody that recognizes the CD3 antigen on T lymphocytes and CALRmut on an MPN clone.




Kuchnio et al, Blood abstract 2023

# Phase I CALR bispecific antibody trial

**INCA035784 (Incyte)**

- Drug – 30 min infusion, every 2 weeks
- Potential side effects – Cytokine release syndrome, ICANS, cytopenias
- Key eligibility
  - MF – int2 or high risk DIPPS, prev JAKi ≥12 weeks, <20% blasts (marrow), splenomegaly
  - ET - High risk (>60 y.o or hx of thrombosis/major bleeding or plt >1500/1000 with evidence of VWB)
  - At least 1 prior line of treatment for MF or 2 prior lines for ET.
- Exclusion
  - Plt <50 , ANC <1
  - Requires stopping current treatment for 5 half lives or 4 weeks

*Currently recruiting at SGCH/linear

# Take home messages

- JAK inhibitors and allogeneic stem cell transplant remain standard of care
- Limited options for JAKi refractory patients
- Combination therapies show promise for improving symptom control and spleen reduction, ?disease modification
- CALR immunotherapies are a novel treatment for MPN