What's New in ET and PV Treatment

MPN Education Symposium 2025

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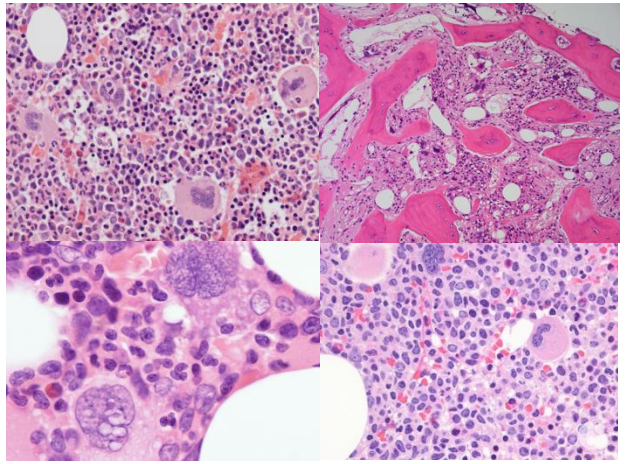
25th Oct 2025



Myeloproliferative Neoplasms (MPN)

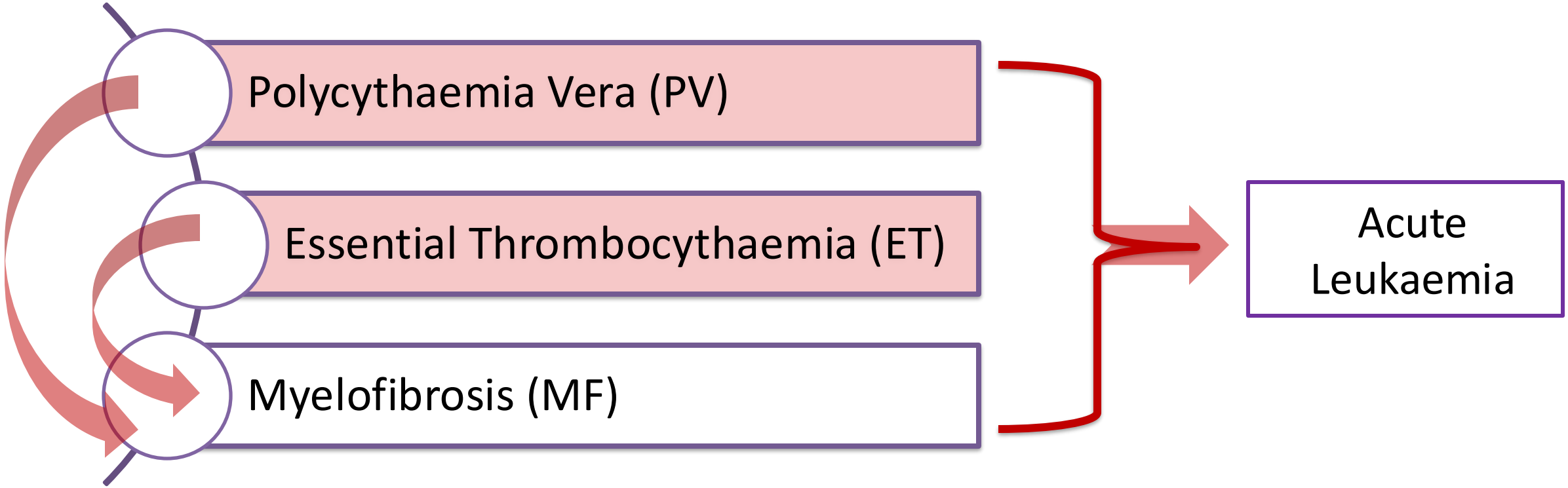
Thrombosis risk
Constitutional symptoms
Disease progression

- Polycythaemia Vera (PV)
- Essential Thrombocythaemia (ET)
- Myelofibrosis (MF)

→ Acute Leukaemia

Myeloproliferative Neoplasms (MPN)

Thrombosis risk
Constitutional symptoms
Disease progression

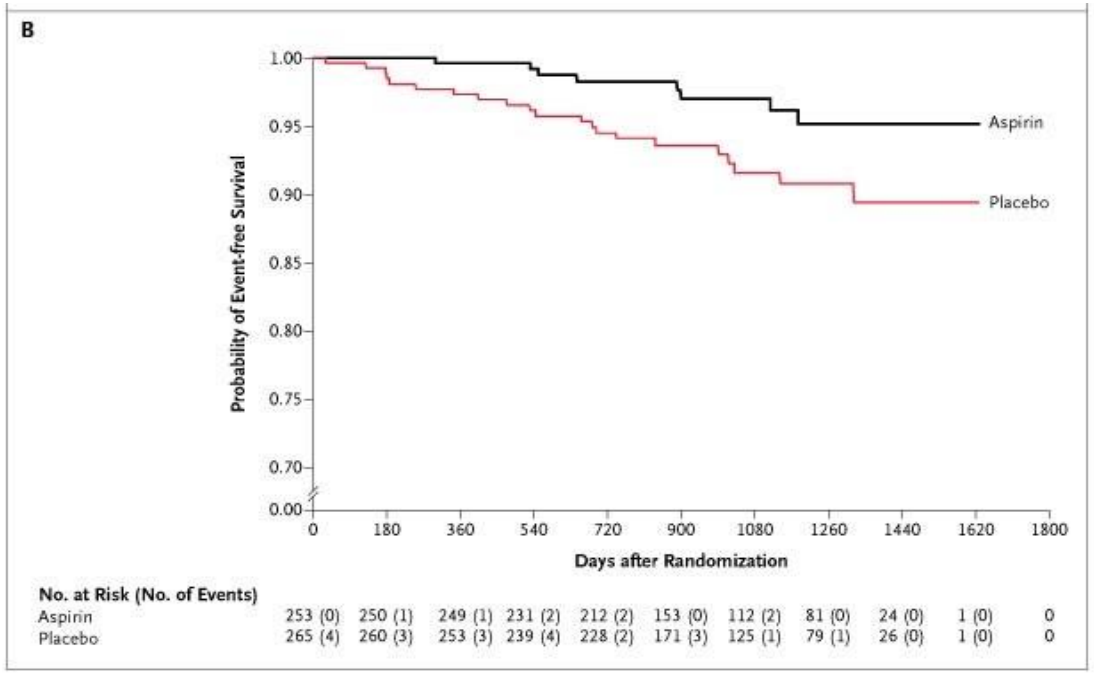


Aims of Treatment

- Reduce transformation risk
- Relief of symptoms
  - Microvascular
  - Disease related
- Minimise treatment related morbidity
- Manage emotional & psychological burden
- Prevent thrombosis and haemorrhage

Treatment Paradigm – PV and ET

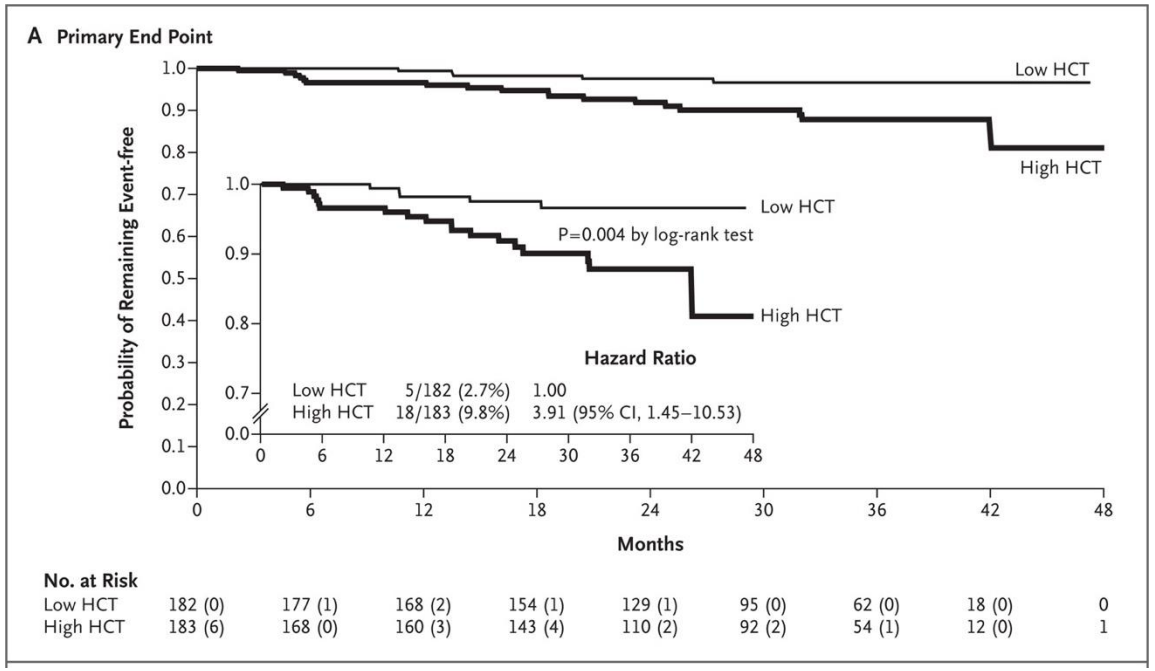
Antiplatelets



ECLAP study: Aspirin was effective in reducing from cardiovascular and thrombotic events.

Landolfi et al. *NEJM 2004.*

Controlling blood counts



CYTOPV study: Aiming for a HCT <0.45 superior to a HCT 0.45-0.50 in terms of death from cardiovascular & thrombotic events.

Machioli et al. *NEJM 2013.*

Treatment Paradigm – PV and ET

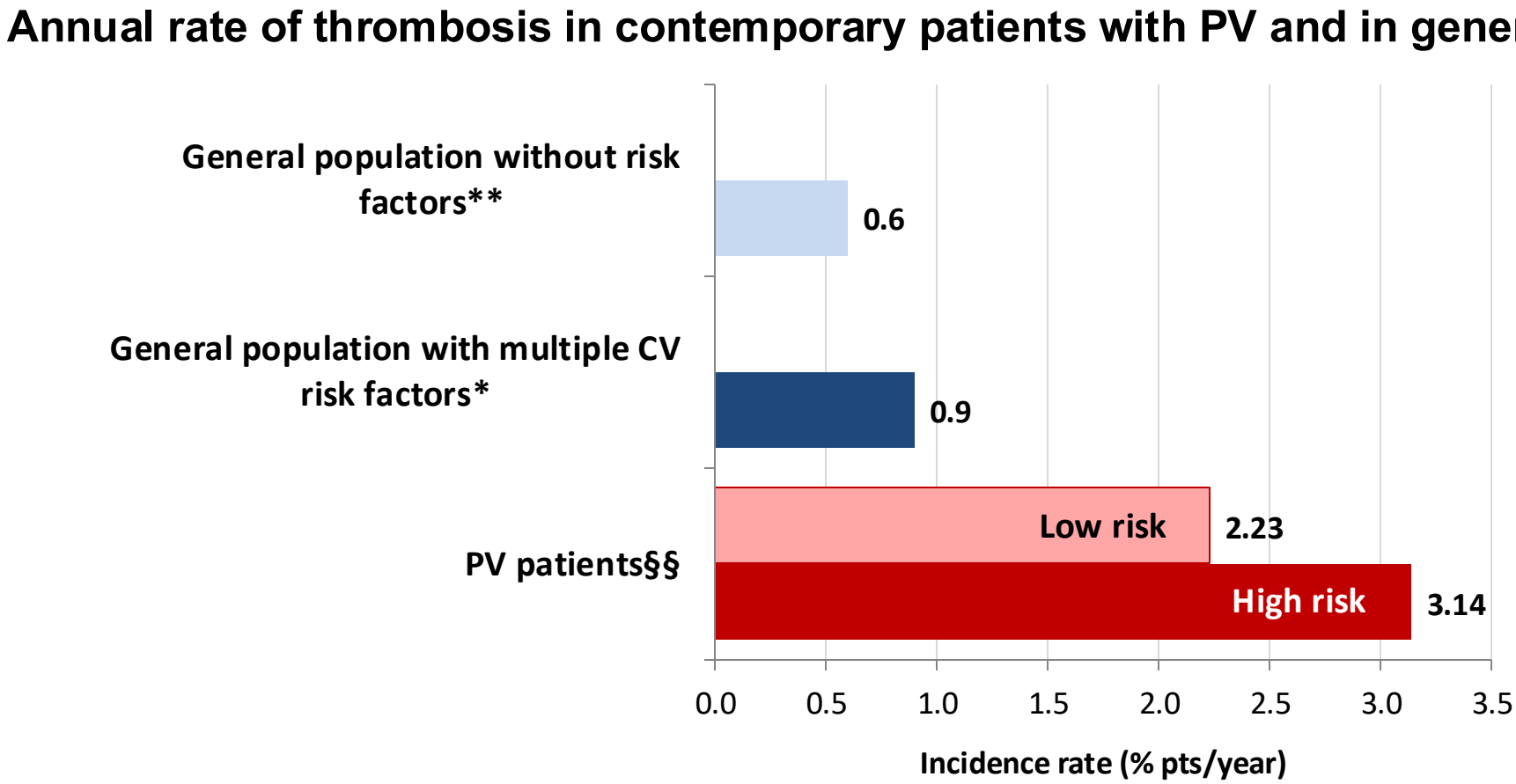
Traditionally, cytoreductive therapy only started for:

Age ≥ 60 years old

and/or

Thrombotic event

We might need to rethink PV treatment
As Low-Risk Polycythemia Vera is not NO RISK from PV



Slide courtesy of Claire Harrison

** Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual partecipant data from randomized trials, Lancet 2009; 373:1849-1860..* Yusef S et al Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease NEJM 2016

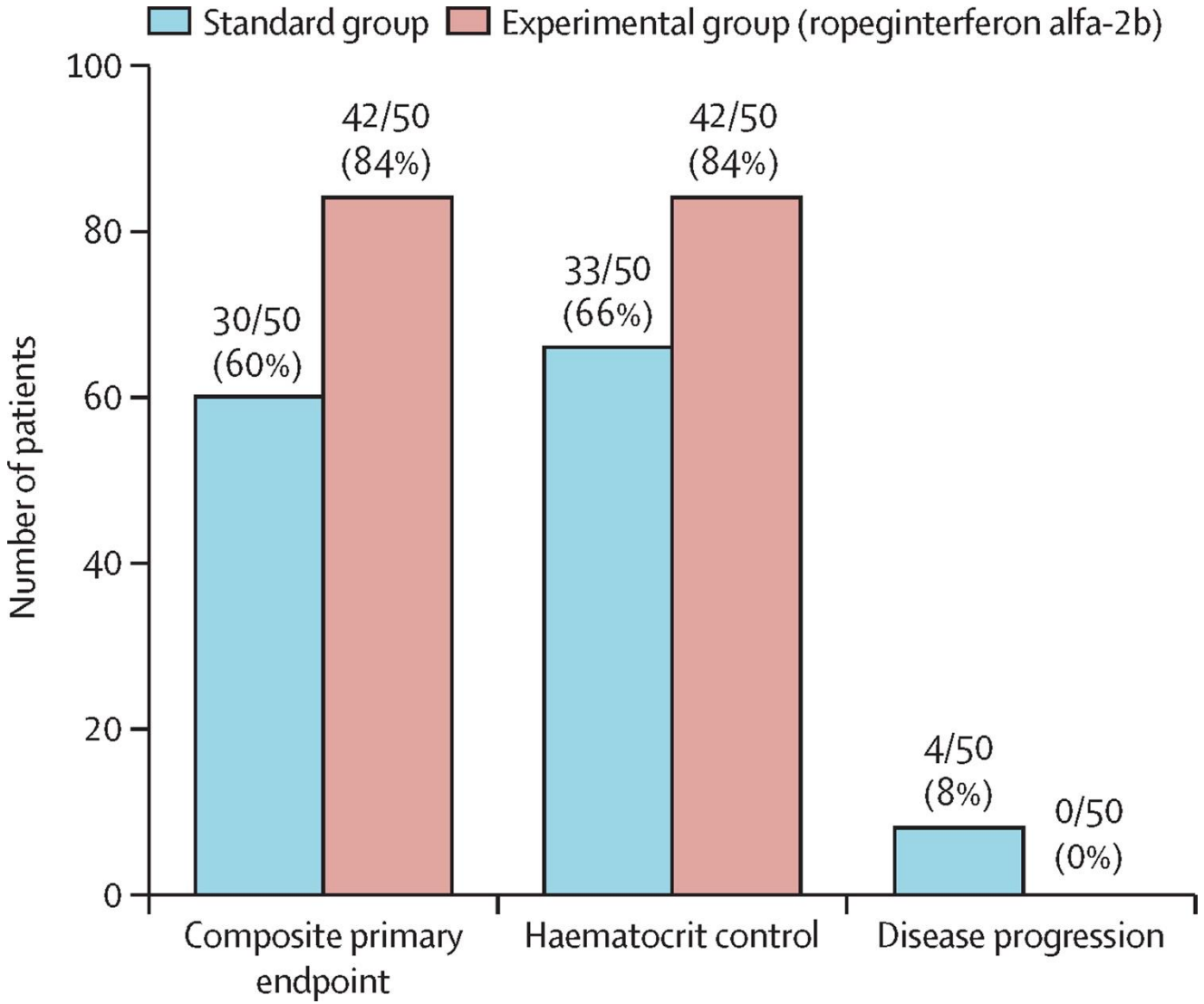
***The Risk and Prevention Study Collaborative Group. N–3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors N Engl J Med 2013;368:1800-8.*

§ Barbui T, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J. 2015 Nov 27;5(11):e369.

§§ Barbui T, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood 2014 124: 3021-3023

Low-PV study
↑ efficacy

- 127 low-risk PV pts randomised to either *phlebotomy and aspirin +/- ropeginterferon*
- Stopped early at 2 years due to superiority of experimental arm
- Composite primary endpoint = maintenance of hct <45%, no progressive disease, vascular or major bleeding complication



OR 3.5, **p=0.0075**

Barbui et al. *Lancet*. 2021.

Which low-risk PV patient should get cytoreductive therapy?

- Strictly defined intolerance to phlebotomy
- Inadequate haematocrit control requiring phlebotomies
- Symptomatic progressive splenomegaly
- Persistent leukocytosis, WCC >15 x 10^9/L
- Progressive leukocytosis
  - at least 100% ↑ if baseline count is <10 or at least 50% ↑ if baseline count is >10
- Extreme thrombocytosis, platelets >1500 x 10^9/L
- Persistently ↑ CVS risk
- Persistently ↑ symptom burden

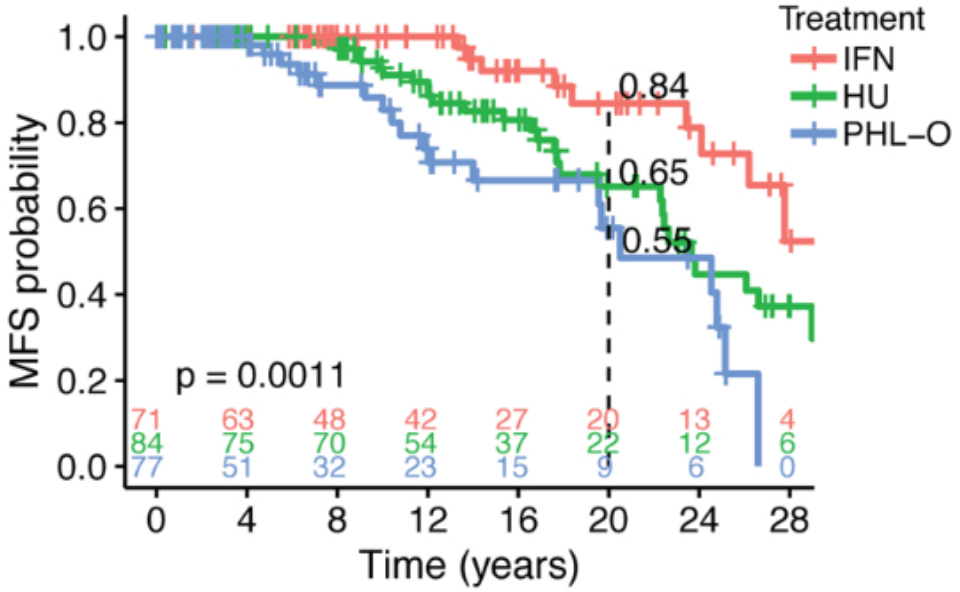
Treatment Paradigm – PV and ET

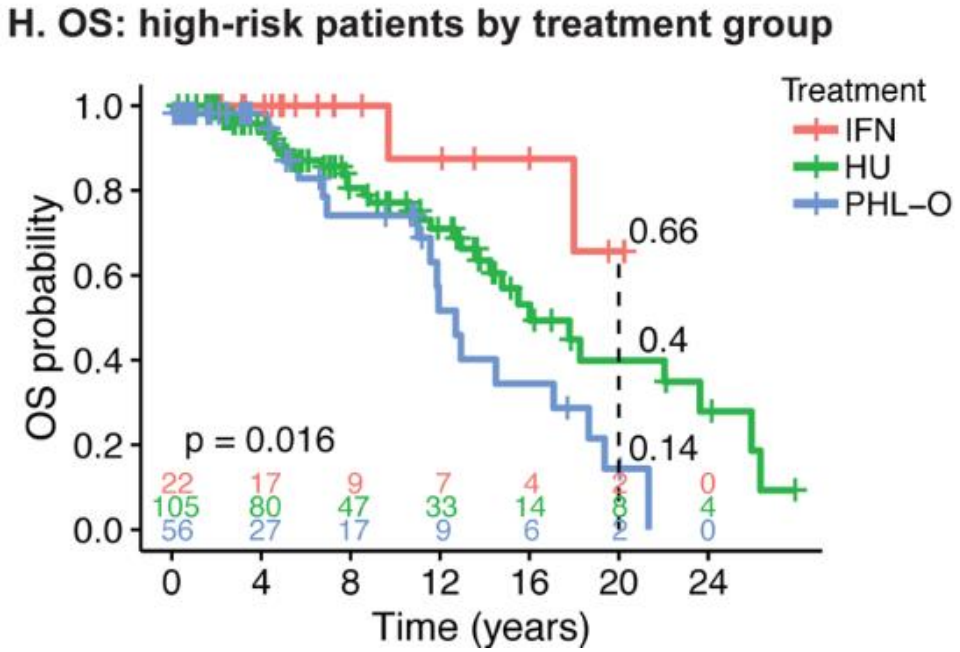
Controlling blood counts… but not modifying the disease

- Phlebotomy (PV)
- Hydroxycarbamide
- Anagrelide (ET)

- Pegylated interferon
- Ruxolitinib (PV)

Disease modifying?





Pegylated Interferon (PV)

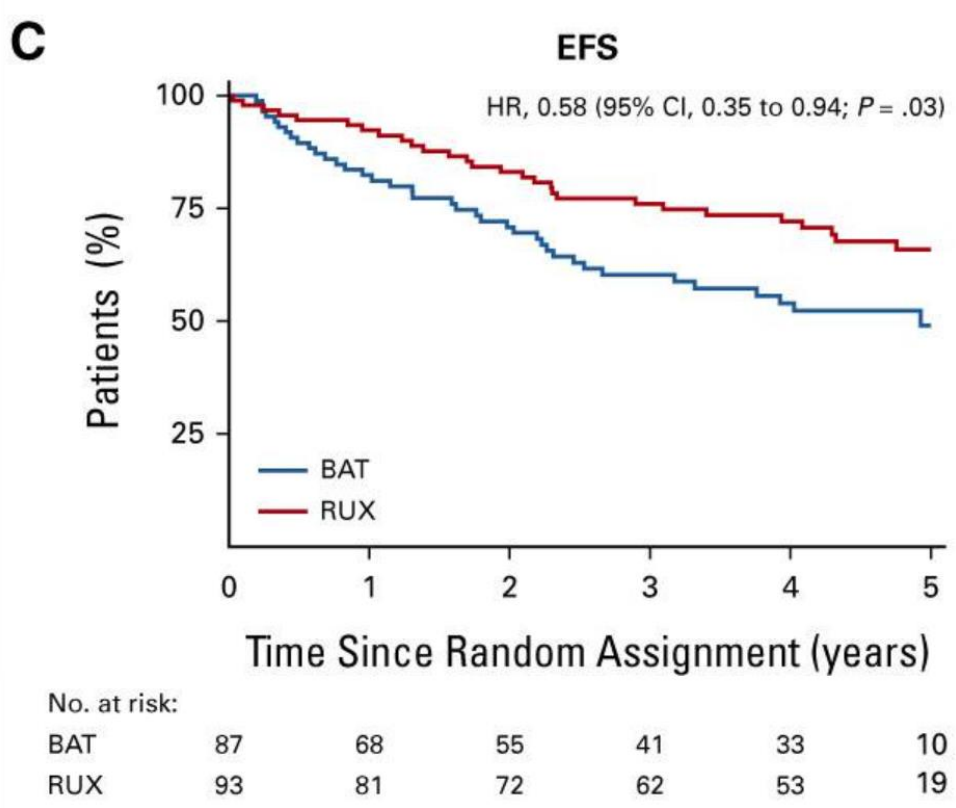
- Improves myelofibrosis-free survival in low-risk PV patients
- Improves overall survival in high-risk PV patients

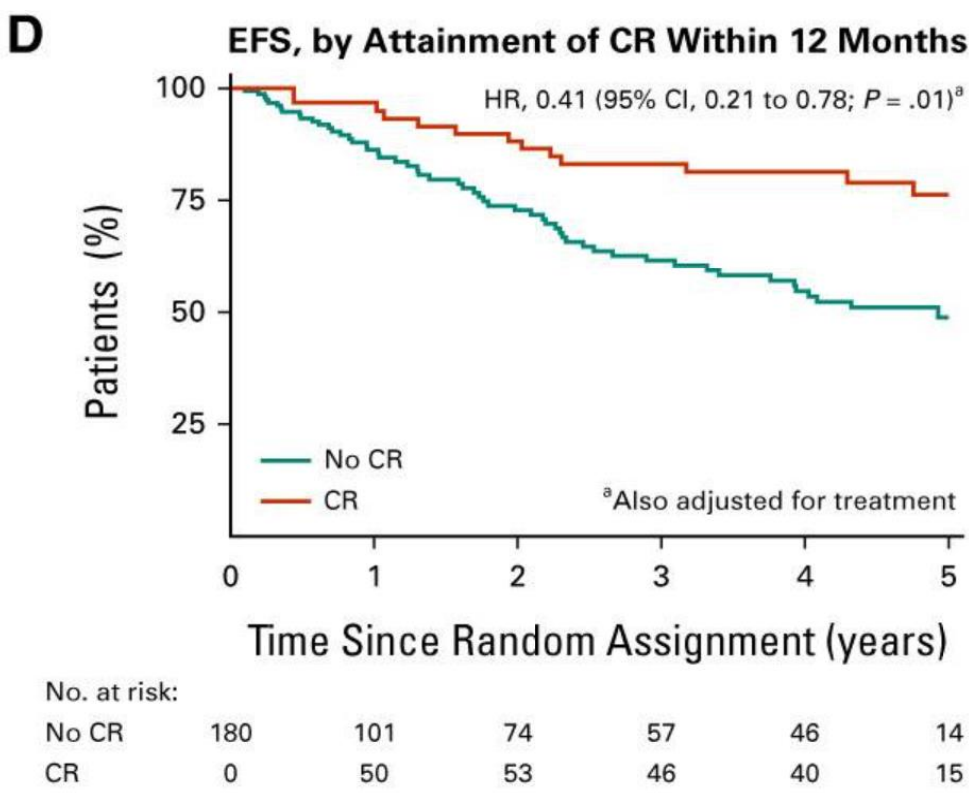
Abu-Zeinah et al. *Leukaemia 2022.*

MAJIC-PV Study (Ruxolitinib vs Best Available Therapy)

Ruxolitinib superior to BAT for event-free survival (EFS)

EFS superior if complete response attained, regardless of treatment arm





Harrison et al. *JCO*. 2023.

Ruxolitinib now available on PBS – Sep 2025

RUXOLITINIB

Source	General Schedule
Body System	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS > ANTINEOPLASTIC AGENTS > PROTEIN KINASE INHIBITORS

▸ Note

▾ ⚠ Authority Required

Polycythemia vera

Treatment Phase: Initial treatment

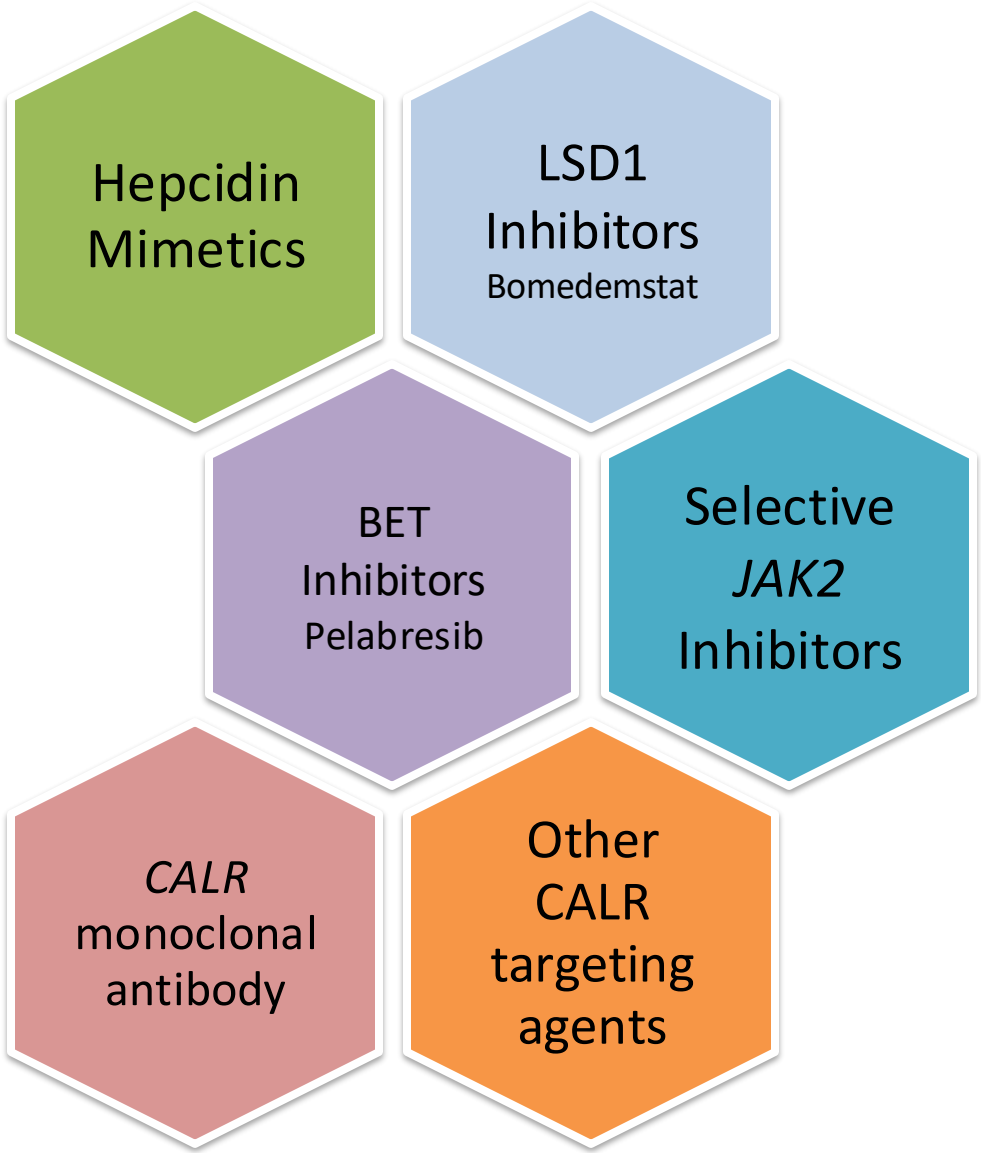
Clinical criteria:

- Patient must be resistant to hydroxycarbamide (hydroxyurea); OR
- Patient must have an intolerance to hydroxycarbamide (hydroxyurea) of a severity necessitating permanent treatment withdrawal; OR
- Patient must have developed a clinically important adverse event/contraindication to hydroxycarbamide (hydroxyurea) as defined in the TGA-approved Product Information necessitating permanent treatment withdrawal,

AND

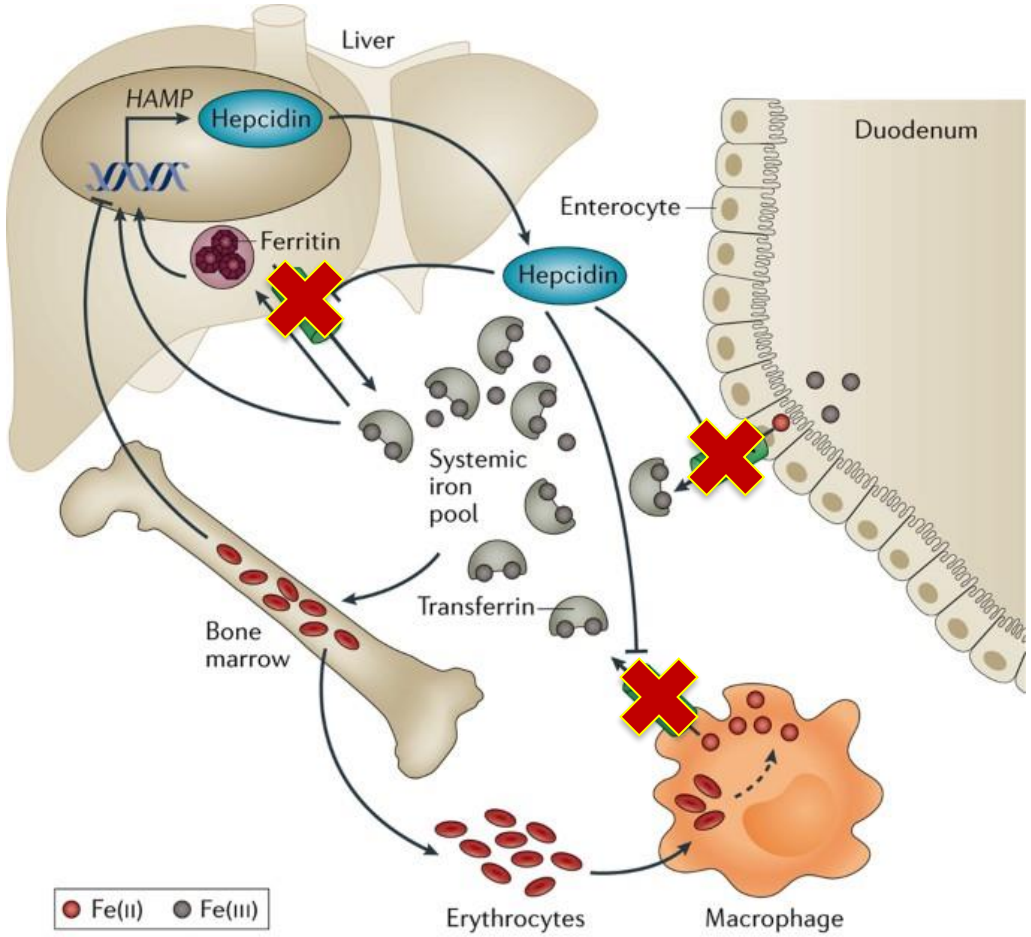
- Patient must not have previously received PBS-subsidised treatment with this drug for this condition.

New Treatments in ET and PV



Hepcidin Mimetics – PV only

- Rusfertide
  - Weekly subcut injection
  - FDA: breakthrough therapy Aug 2025

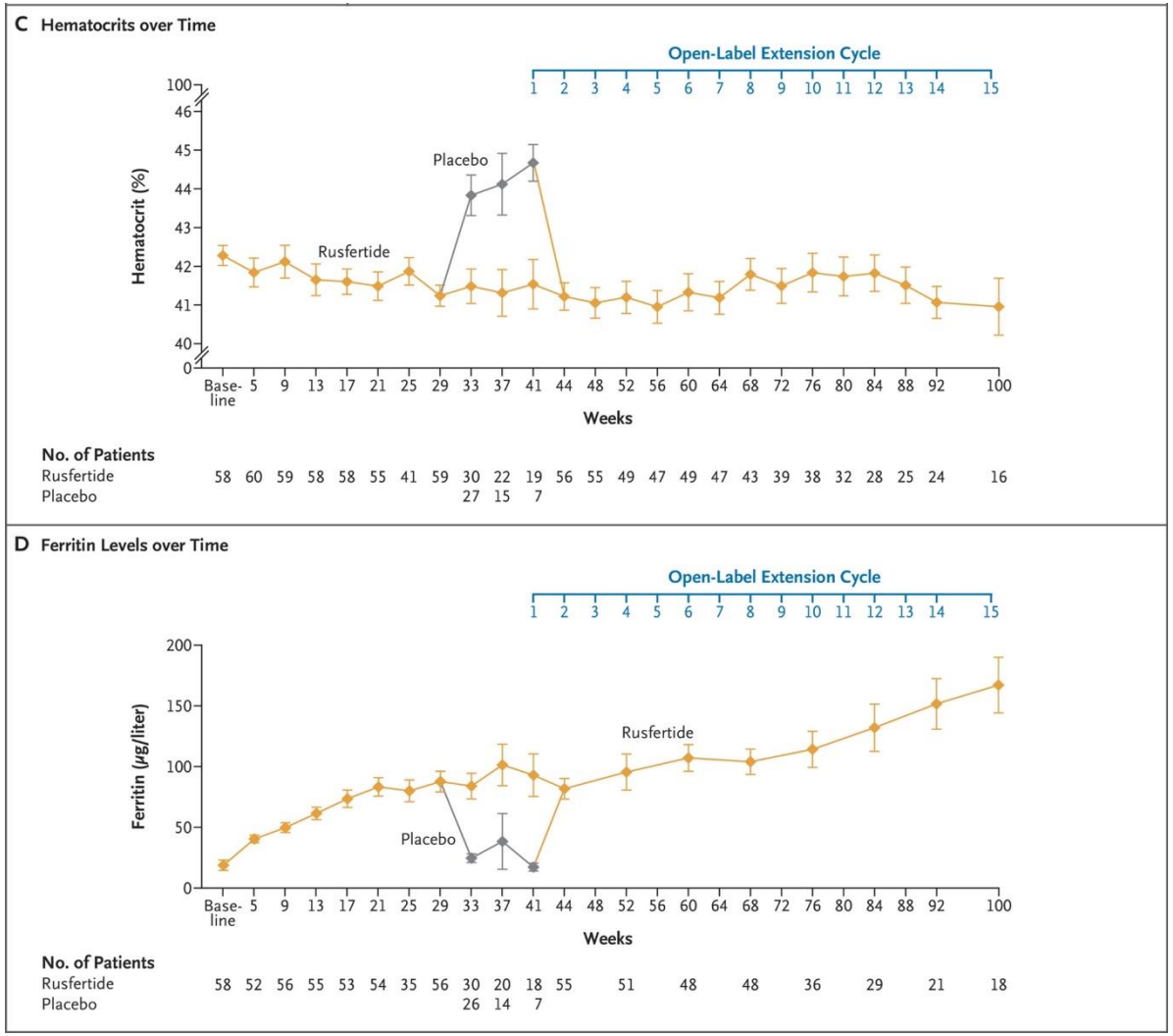


Nature Reviews | Drug Discovery

Hepcidin Mimetics – PV only

- Rusfertide
  - Weekly subcut injection
  - FDA: breakthrough therapy Aug 2025
  - Improvement of fatigue/symptoms

Kremyanskaya et al. *NEJM*. 2024.

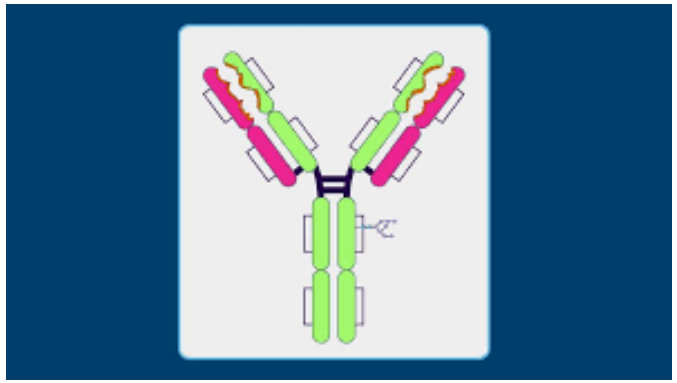


New substances: influencing iron metabolism

Sapablursen

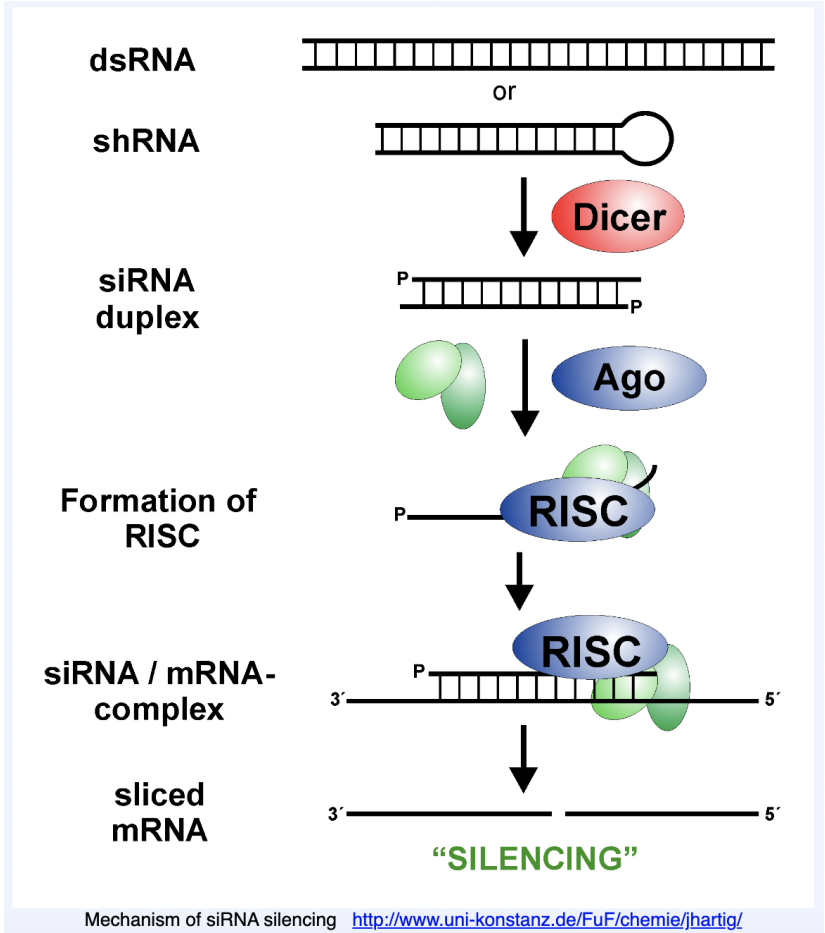
Sapablursen, formerly known as IONIS-TMPRSS6-L_{Rx}, is an investigational **L**igand **C**onjugated **A**ntisense (LICA) medicine designed to target the TMPRSS6 gene to [illegible] the production of hepcidin, which is the key regulator of iron homeostasis. By modulating hepcidin expression, sapablursen has the potential to positively impact blood diseases, such as polycythemia vera (PV).

ligand-conjugated antisense oligonucleotide



9MW3011/ DISC-3405

SLN124 / BEBT-507

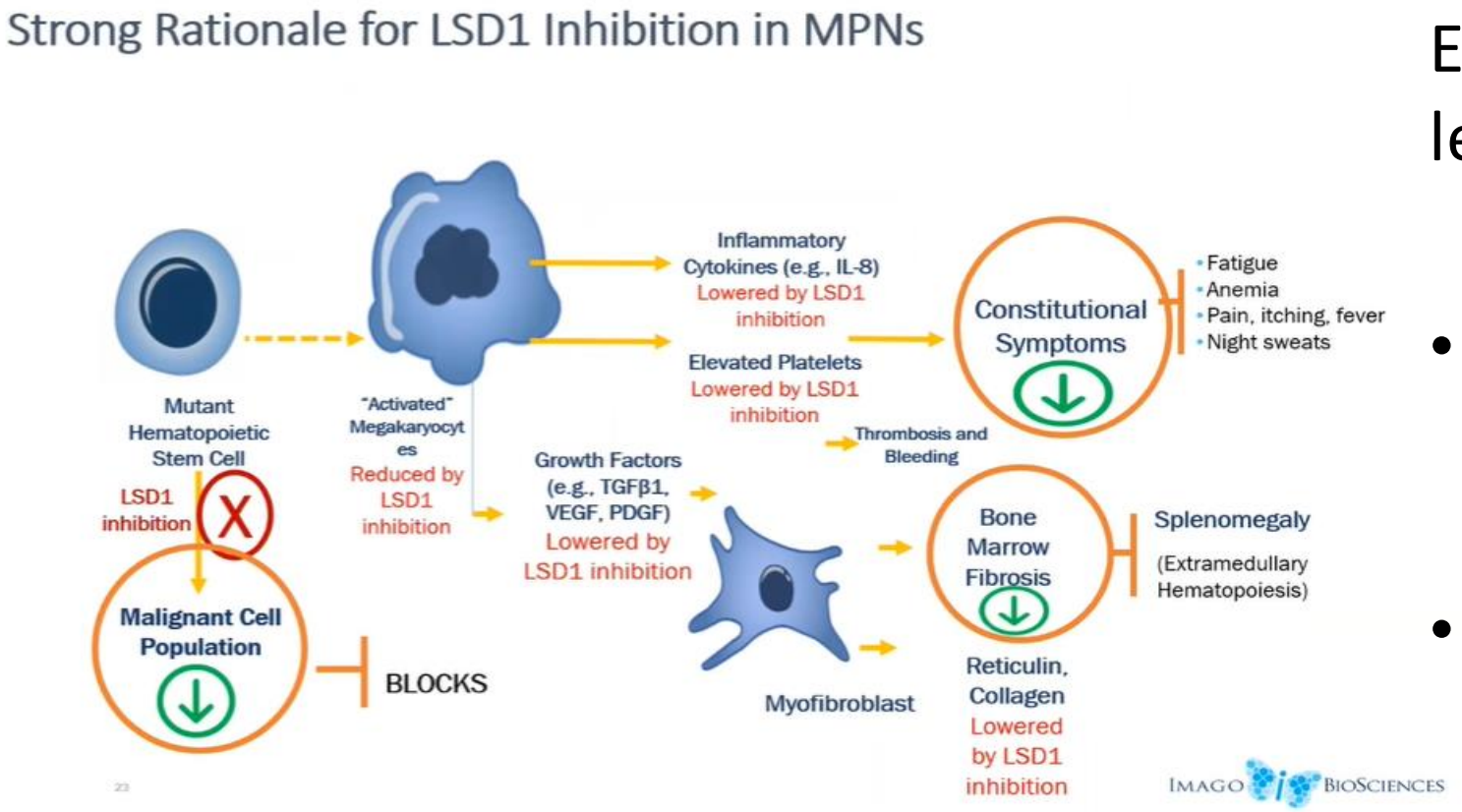


Mechanism of siRNA silencing http://www.uni-konstanz.de/FuF/chemie/jhartig/

Slide courtesy of Susanne Isfort

Source: https://www.gene-quantification.de/si-rna.html; https://www.ionis.com/medicines/sapablursen/

Bomedemstat (LSD1 Inhibitor)

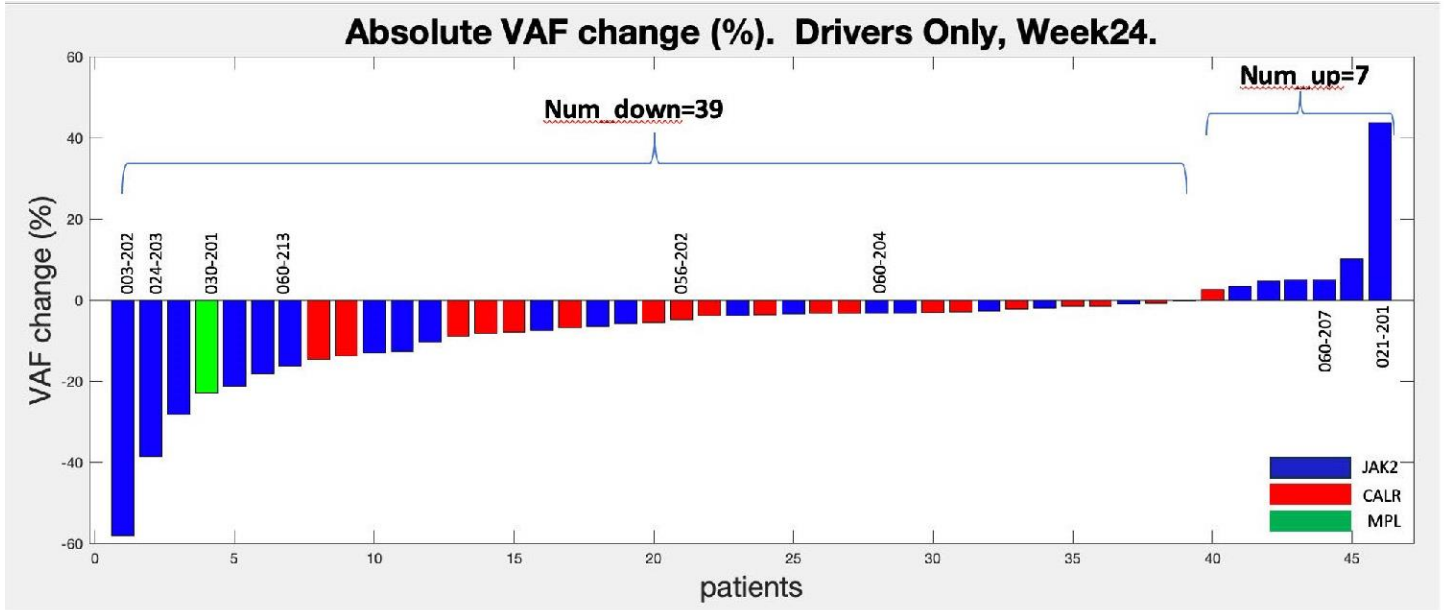


ET pts resistant/intolerant to at least 1 treatment (Week 24):

- 95% (61/64) achieved platelets ≤400 without new thrombosis
- 52% pts with baseline TSS score >20 had ↓ ≥10 points

Bomedemstat (LSD1 Inhibitor)

- Side effects: altered taste (55%), constipation (38%)
- ↓ platelets without anaemia or leucopenia
- 85% (39/46) patients had ↓ VAF



Goethert et al. *Blood supp*. 2023.

Pelabresib (BET inhibitor)

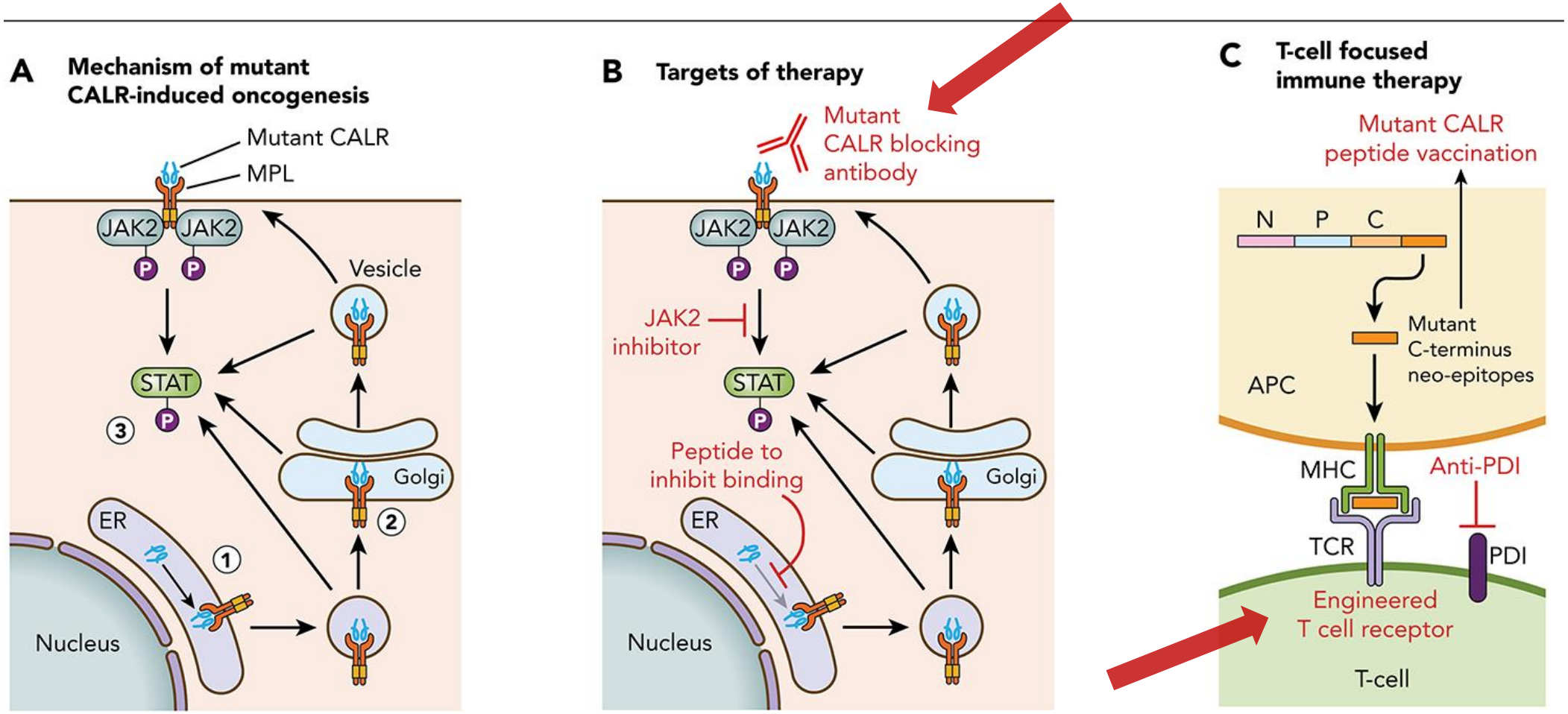
High-risk ET pts resistant/intolerant to hydroxyurea

- 40% (8/20) patients achieved platelets ≤400 and WCC ≤ 10
- TSS ↓ in 86% (12/14)
- Median TSS ↓ at week 12 was -31%

- Common side effects: nausea (60%), diarrhoea (35%), altered taste (35%)

Passamonti et al. *JCO*. 2023.

Molecularly Directed Therapy: The Future?

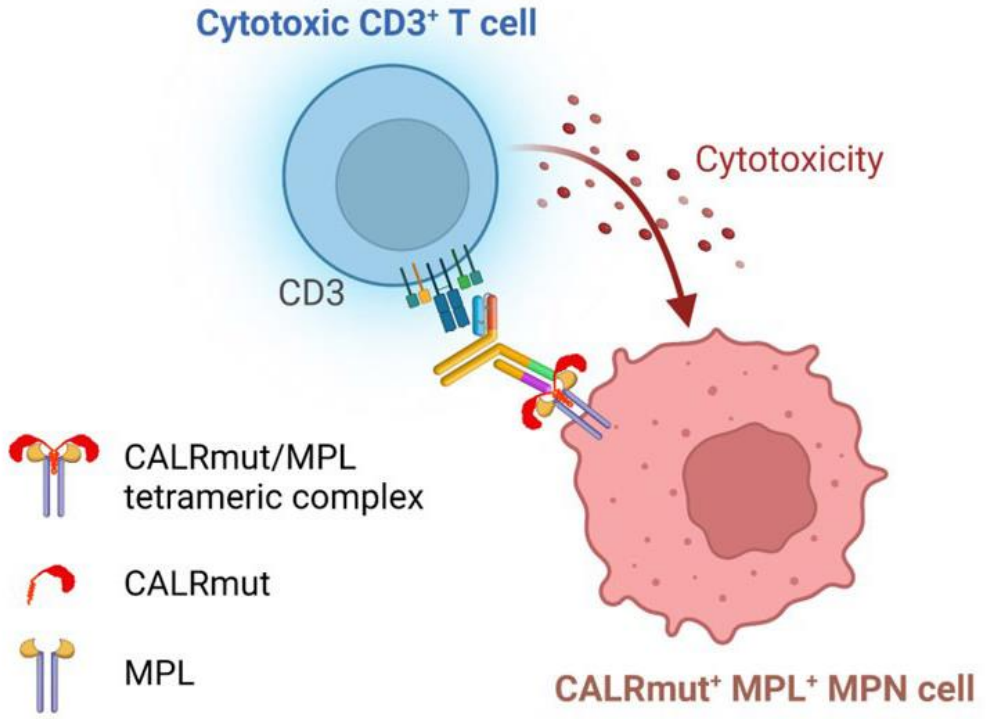


Joan How, Gabriela S. Hobbs, Ann Mullally. Blood, 2019

CALR Targeting Agents – ET only

- Bispecific antibody against CALR (J&J)
- CAR-T cells against CALR (pre-clinical)

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.

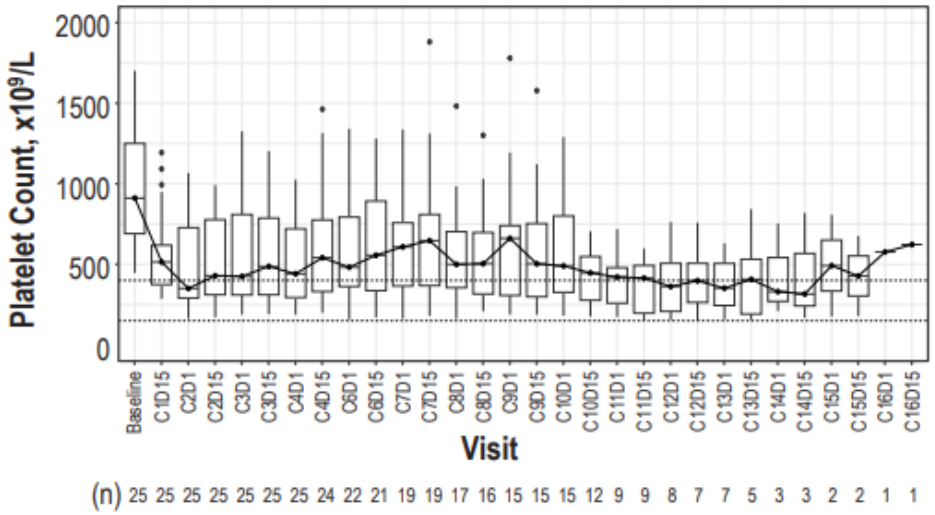


Created with BioRender.com

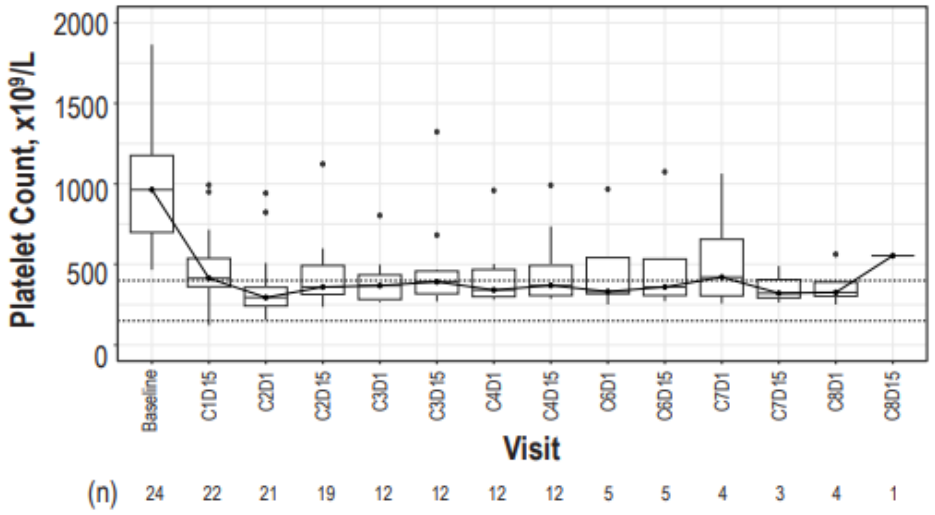
INCA33989 – monoclonal antibody targeting *CALR*

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.

Slide courtesy of Claire Harrison

Selective type 2 *JAK2* Inhibitors

- AJ1-11095
  - non-covalent TKI, binds both active and inactive conformations of JAK2 and prevents heterodimerization with JAK1 and TYK2
  - overcoming common mechanism of clonal persistence and drug resistance

- INCB160058
  - high-affinity pseudokinase (JH2) binding inhibitor of $JAK2^{V617F}$
  - blocks cytokine-independent activity of $JAK2^{V617F}$ while preserving cytokine-dependent signalling

Methotrexate… Old is new again?

NCT06541249 **MethoTRExATE in MyelOpRolifErative Neoplasms (TREATMORE) Trial**

- Low-dose MTX widely used, inexpensive, and safe.
- Identified as a type 2 JAK inhibitor.
- Being tested in a single centre (New York)

→ In cases of adequate responses, high potential in low income countries

Conclusions

- Low risk PV may not be "low risk" – consider treating certain patients earlier.
- Standard of care treatments:
  - ➢ if no contraindications, and disease modification is a goal, consider
    - Pegylated interferon as 1st line
    - Ruxolitinib as 2nd line (PV only)
- Enrol in a clinical trial if available
- More therapies are coming for ET and PV, including targeting the driver mutation
- Do not forget about vascular risk factors e.g. Diabetes, hypertension, dyslipidaemia, smoking

Thank You!

Questions?