Myeloproliferative neoplasm

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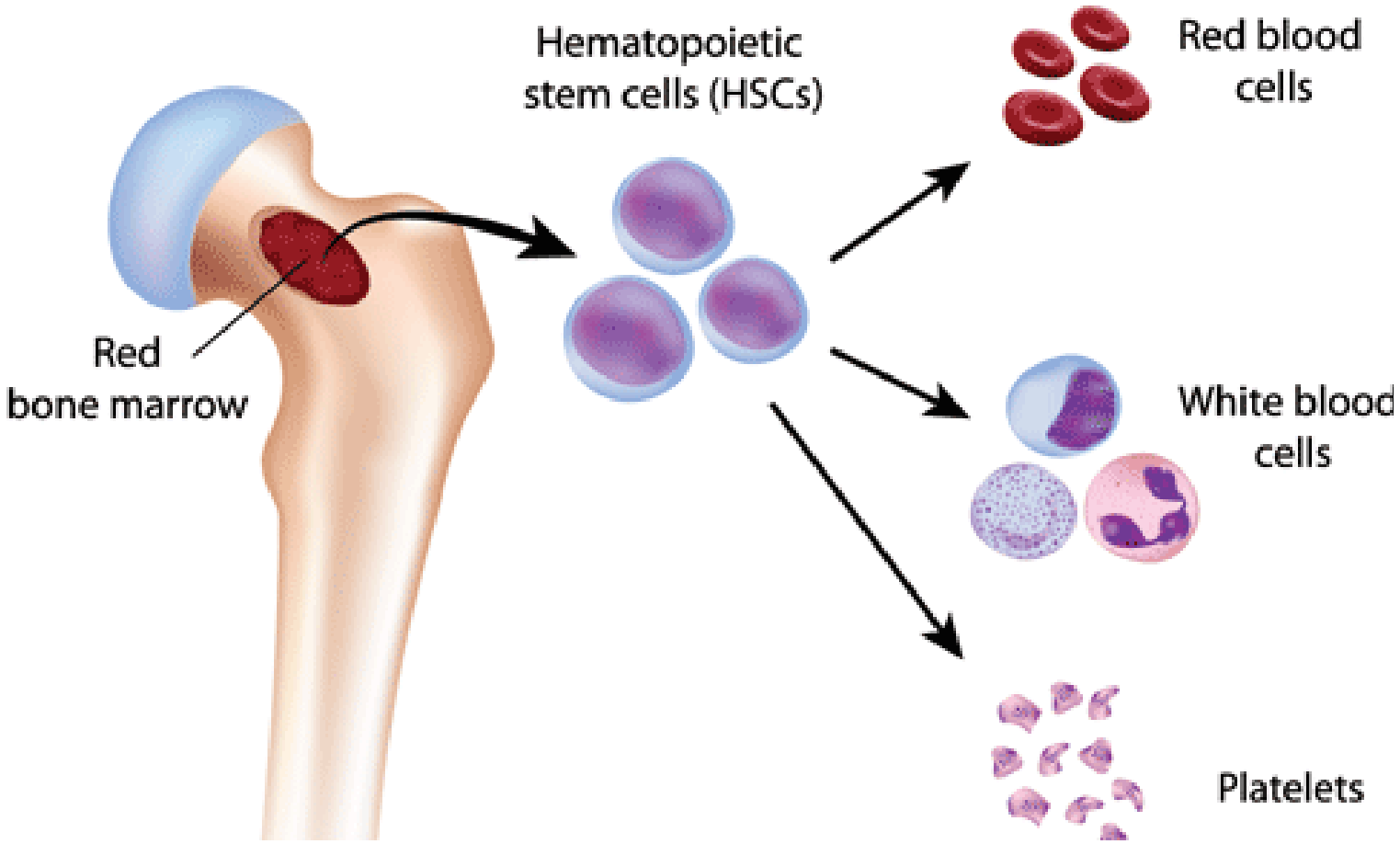
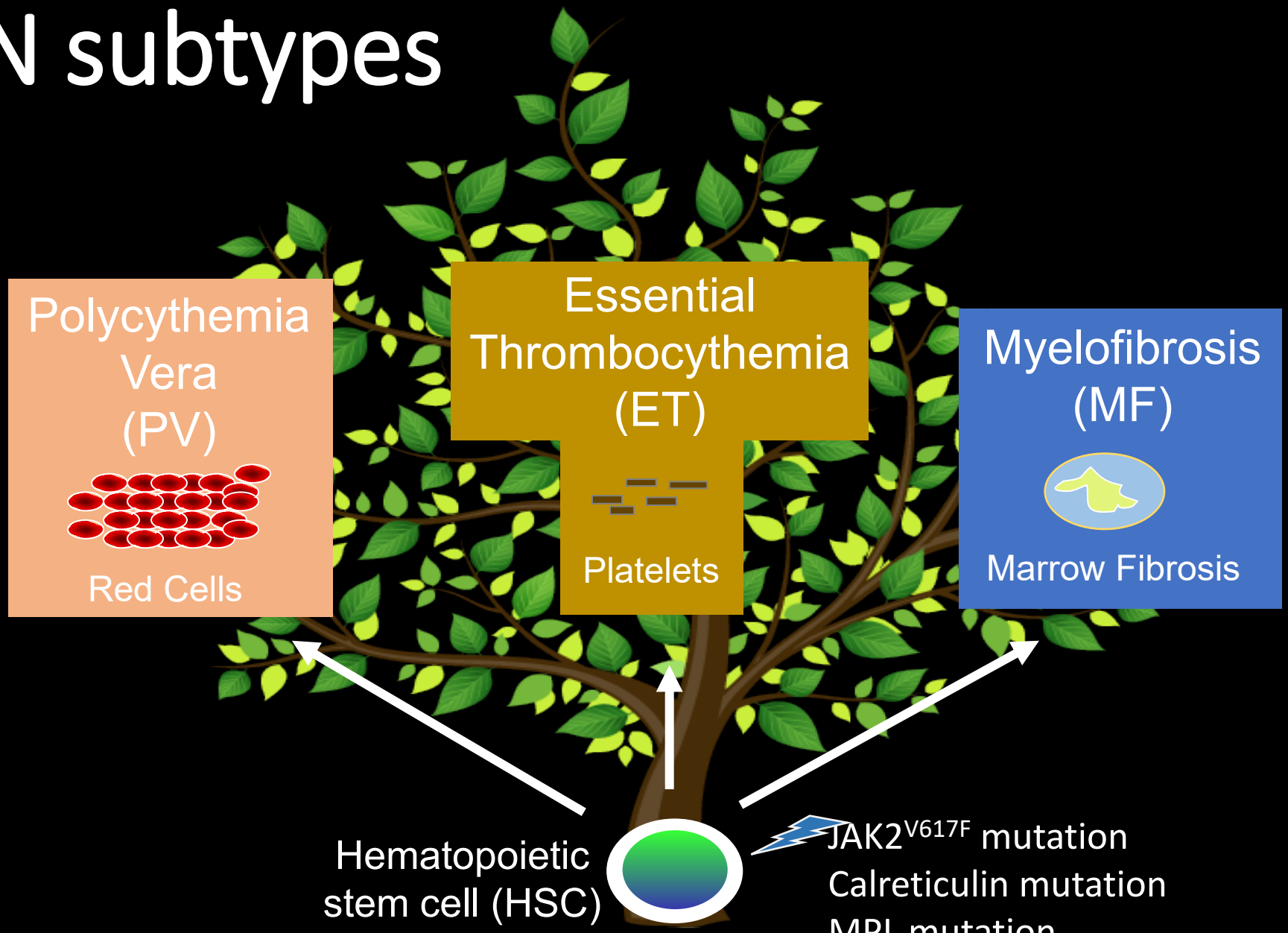
What we'll be covering tonight

- Differences/similarities between polycythemia vera, essential thrombocythemia, myelofibrosis
- Is a JAK inhibitor right for me, and if so which one?
- New treatments on the horizon for MPN

MPN is a disease of the bone marrow

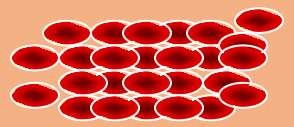


MPN subtypes



Polycythemia Vera

Polycythemia Vera (PV)

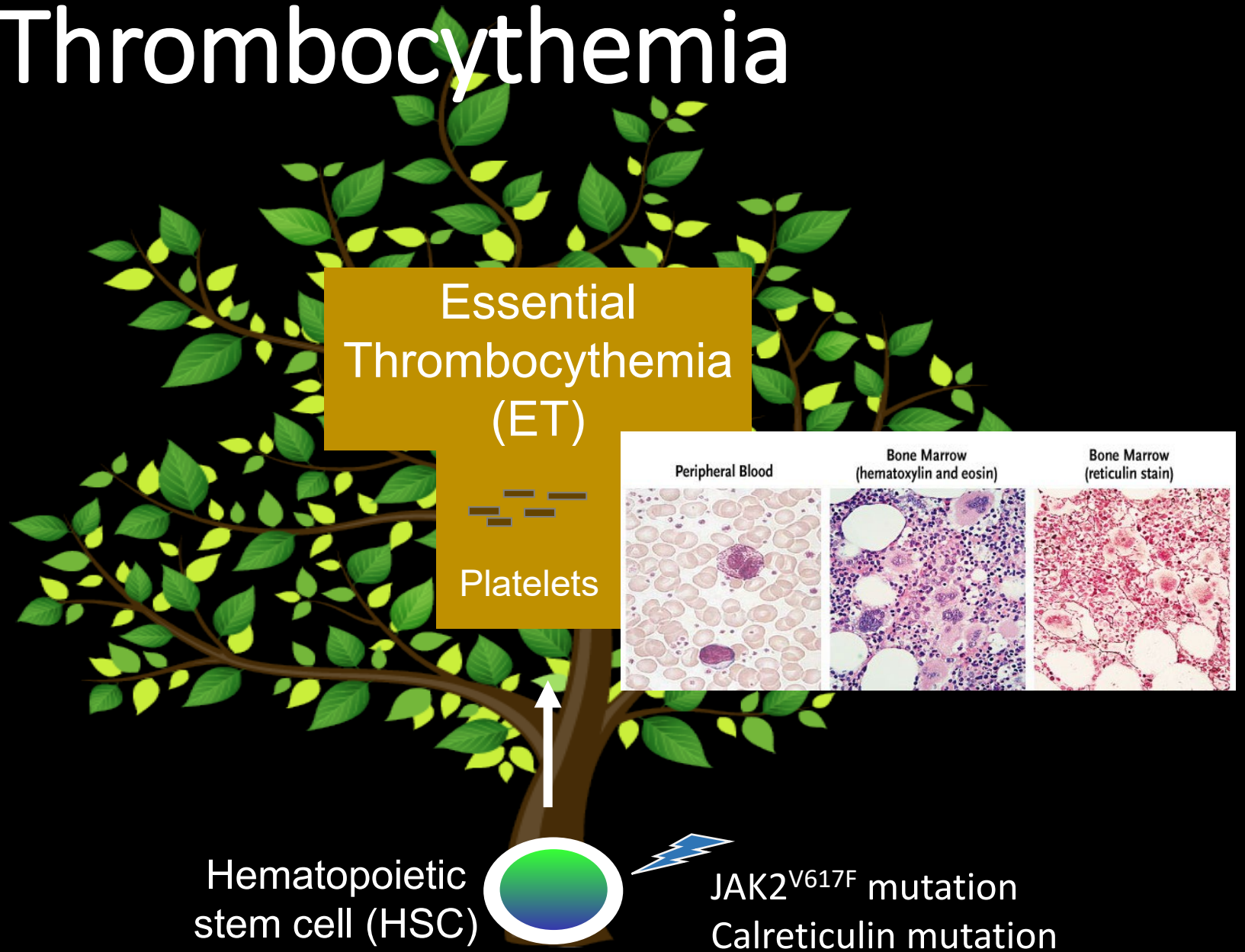


Red Cells

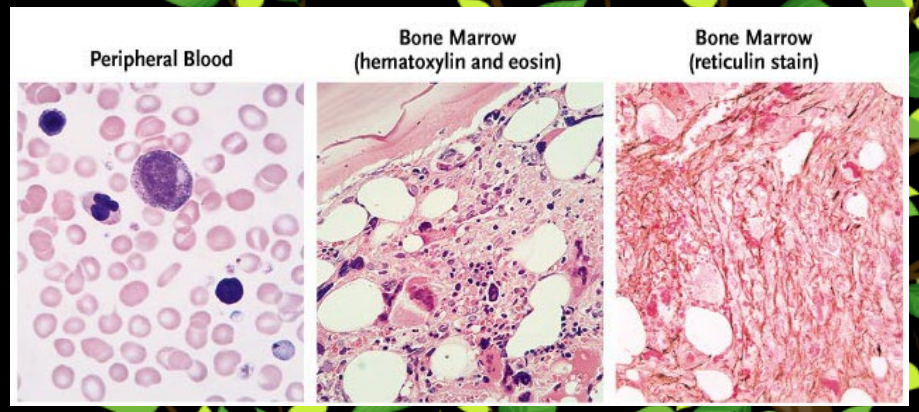
Hematopoietic stem cell (HSC)

JAK2^{V617F} mutation

Essential Thrombocythemia



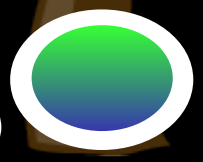
Myelofibrosis



Myelofibrosis (MF)

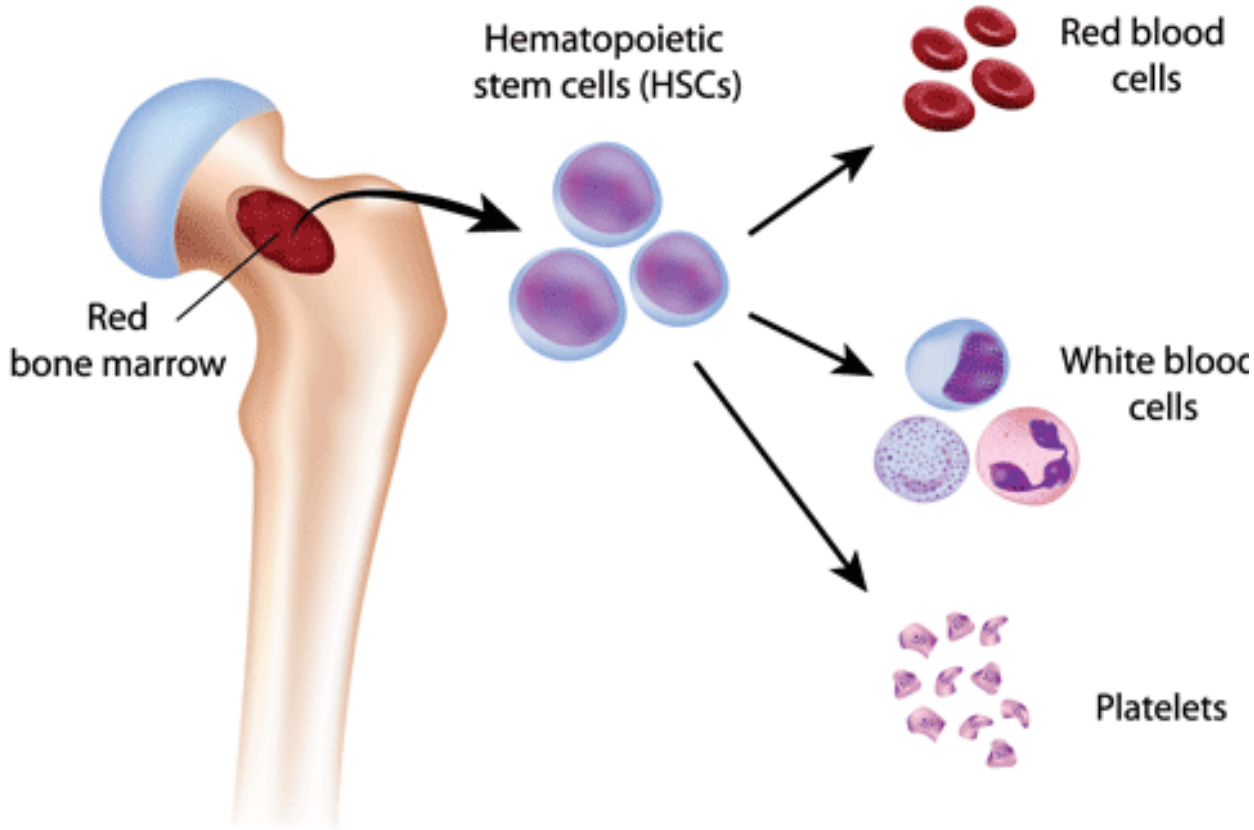
Marrow Fibrosis

Hematopoietic stem cell (HSC)



JAK2^{V617F} mutation
Calreticulin mutation
MPL mutation

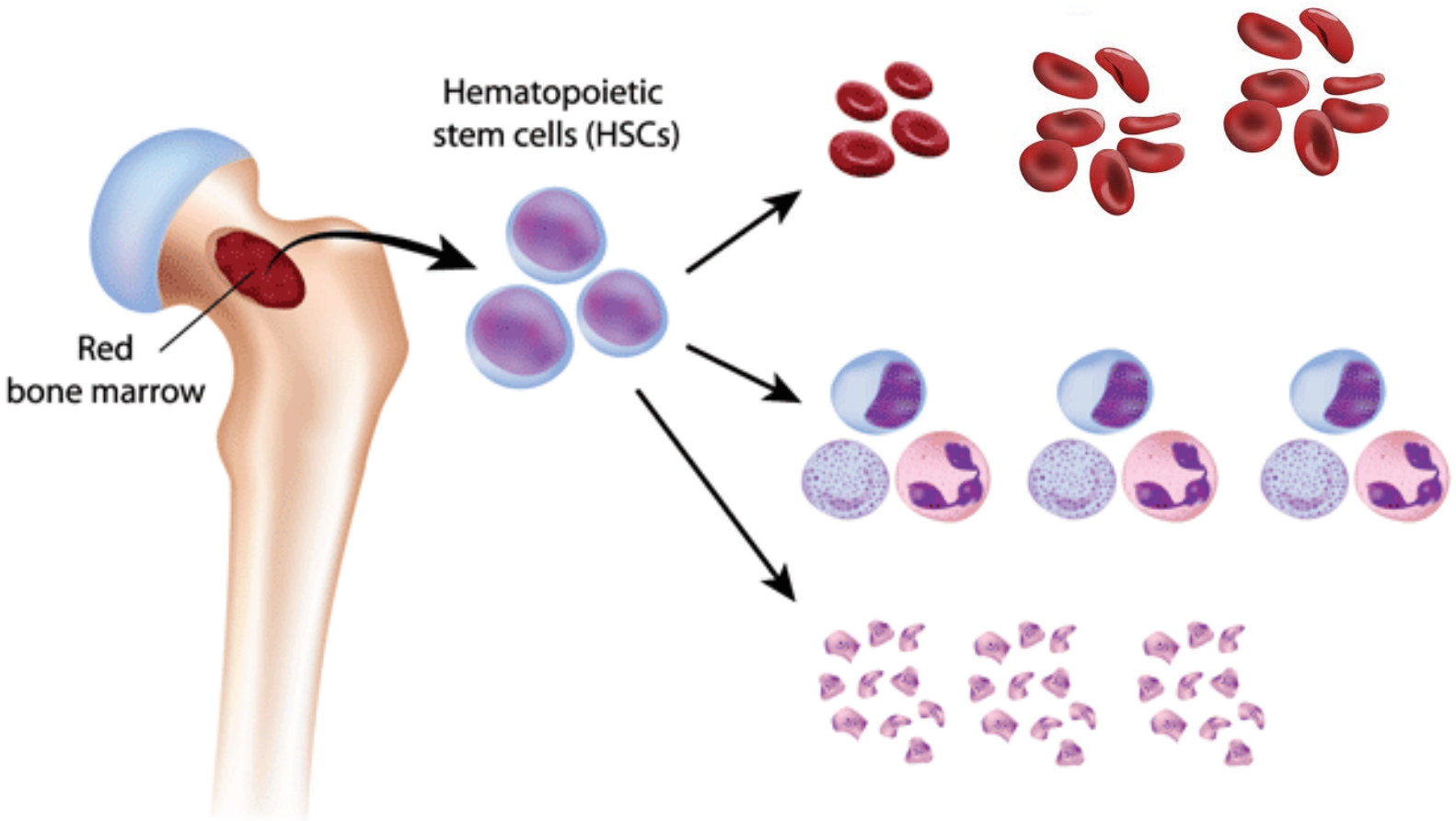
What do MPN “driver” mutations do?



Normal

The body knows when to produce blood cells based on its current needs

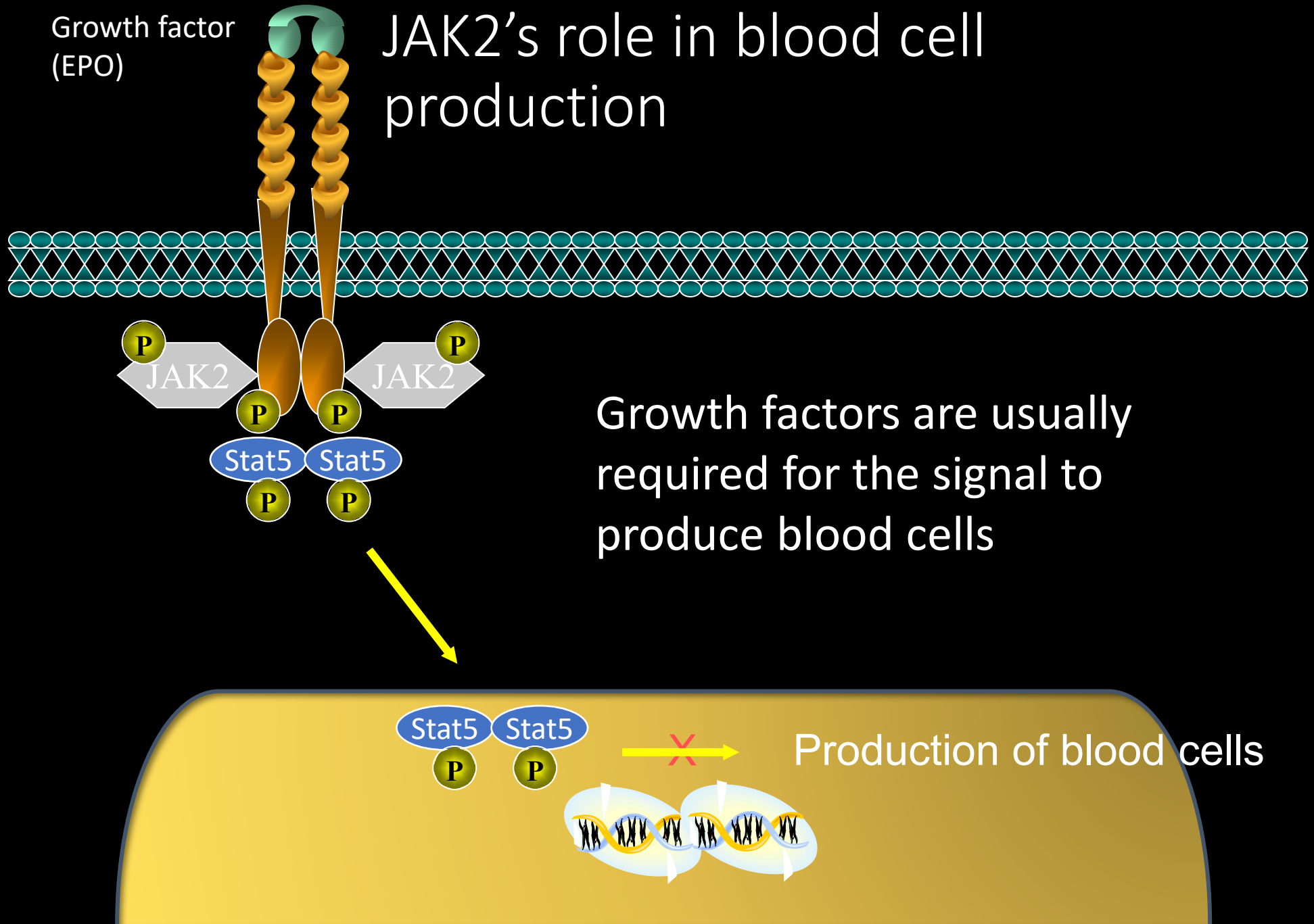
What do MPN “driver” mutations do?



MPN

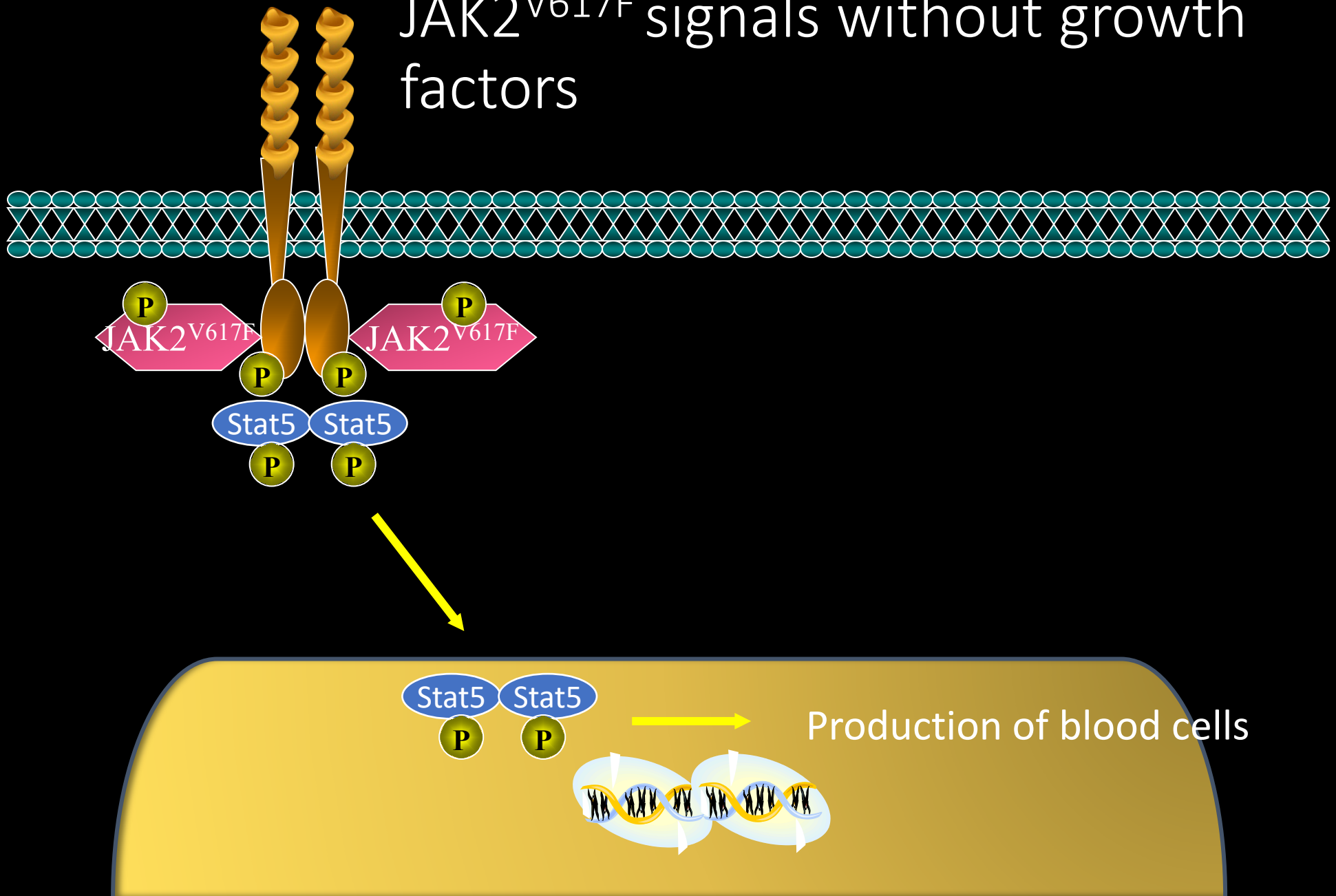
The body produces lots of blood cells even when it doesn’t need it

JAK2's role in blood cell production

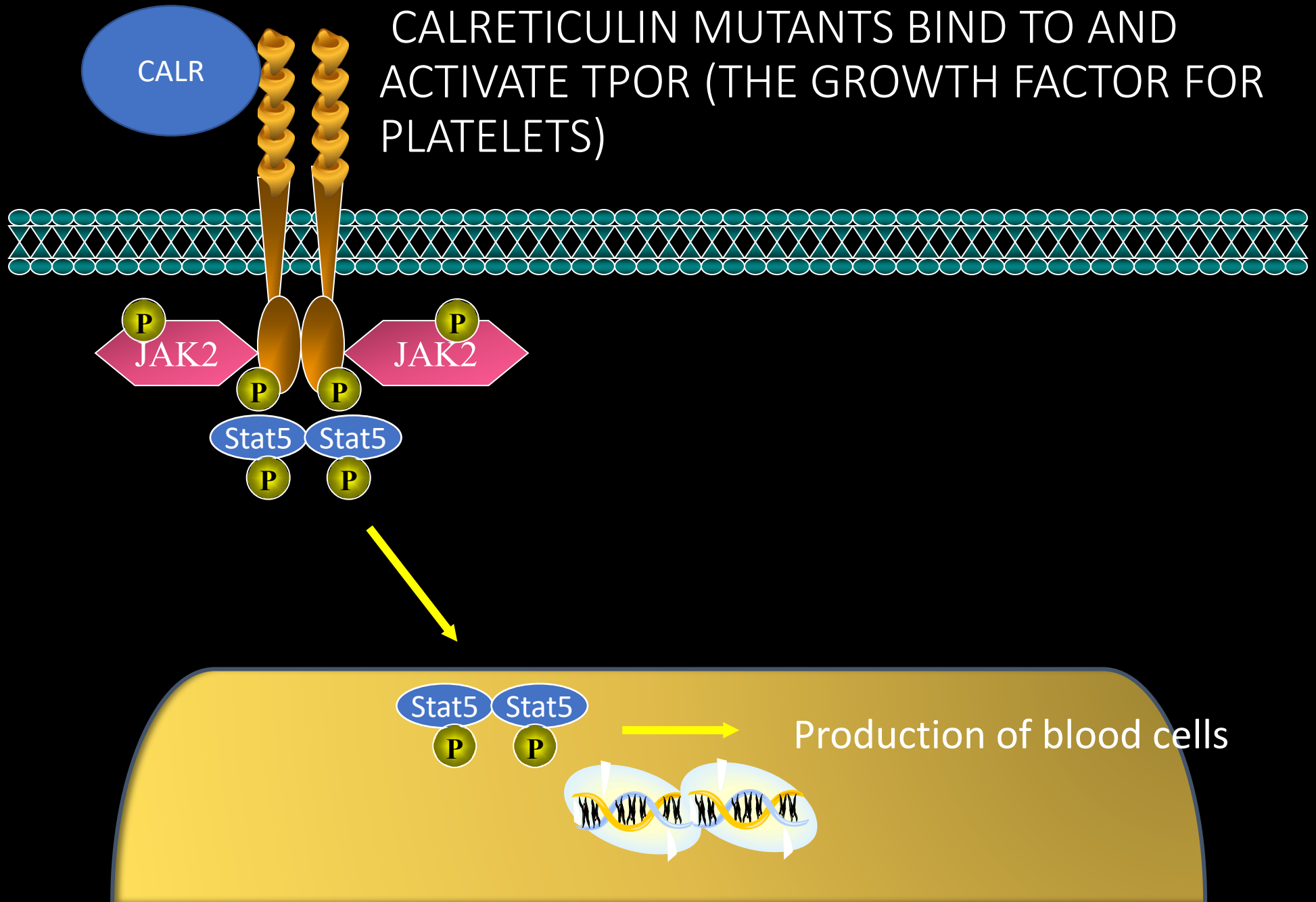


Growth factors are usually required for the signal to produce blood cells

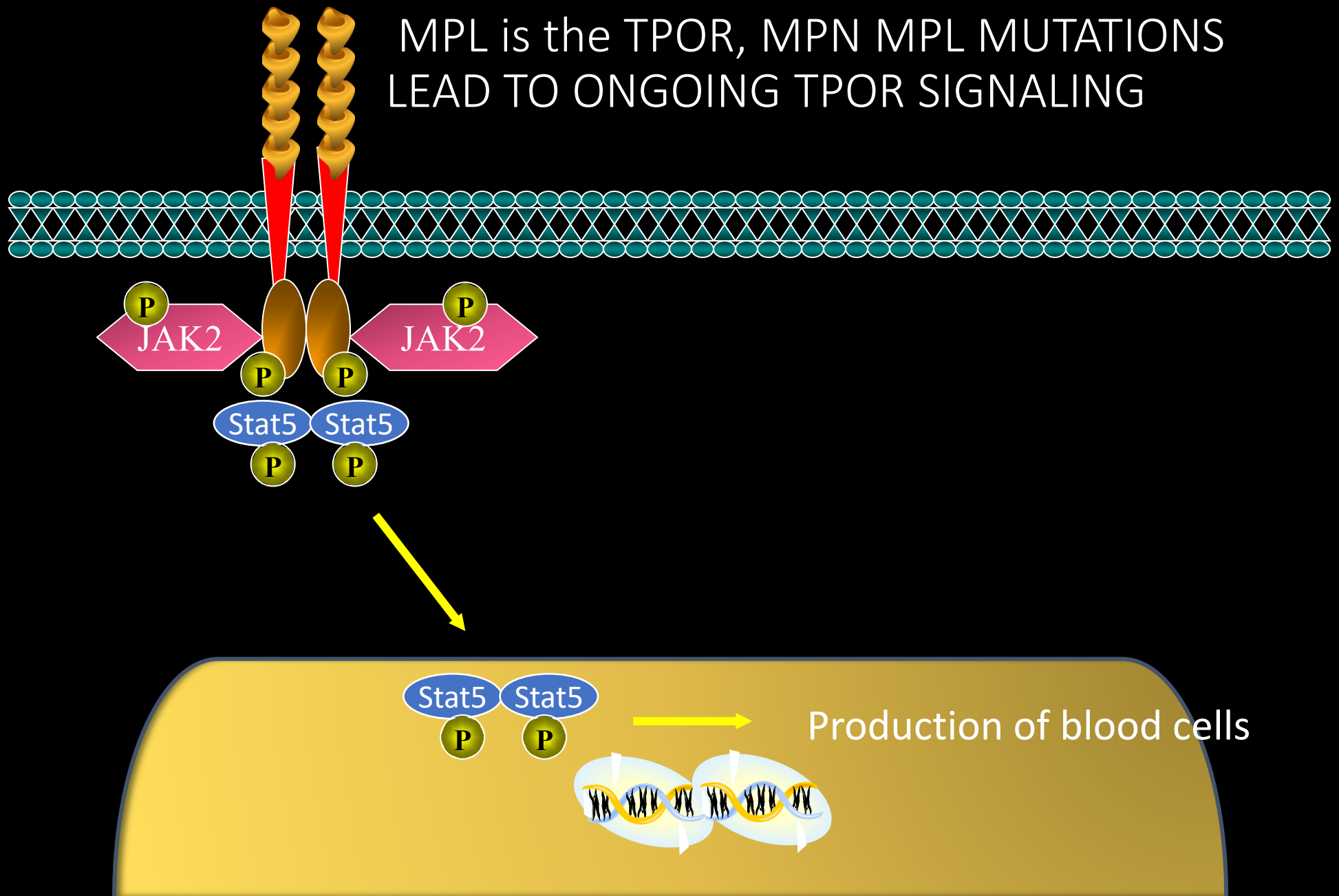
JAK2^{V617F} signals without growth factors



CALRETICULIN MUTANTS BIND TO AND ACTIVATE TPOR (THE GROWTH FACTOR FOR PLATELETS)



MPL is the TPOR, MPN MPL MUTATIONS LEAD TO ONGOING TPOR SIGNALING



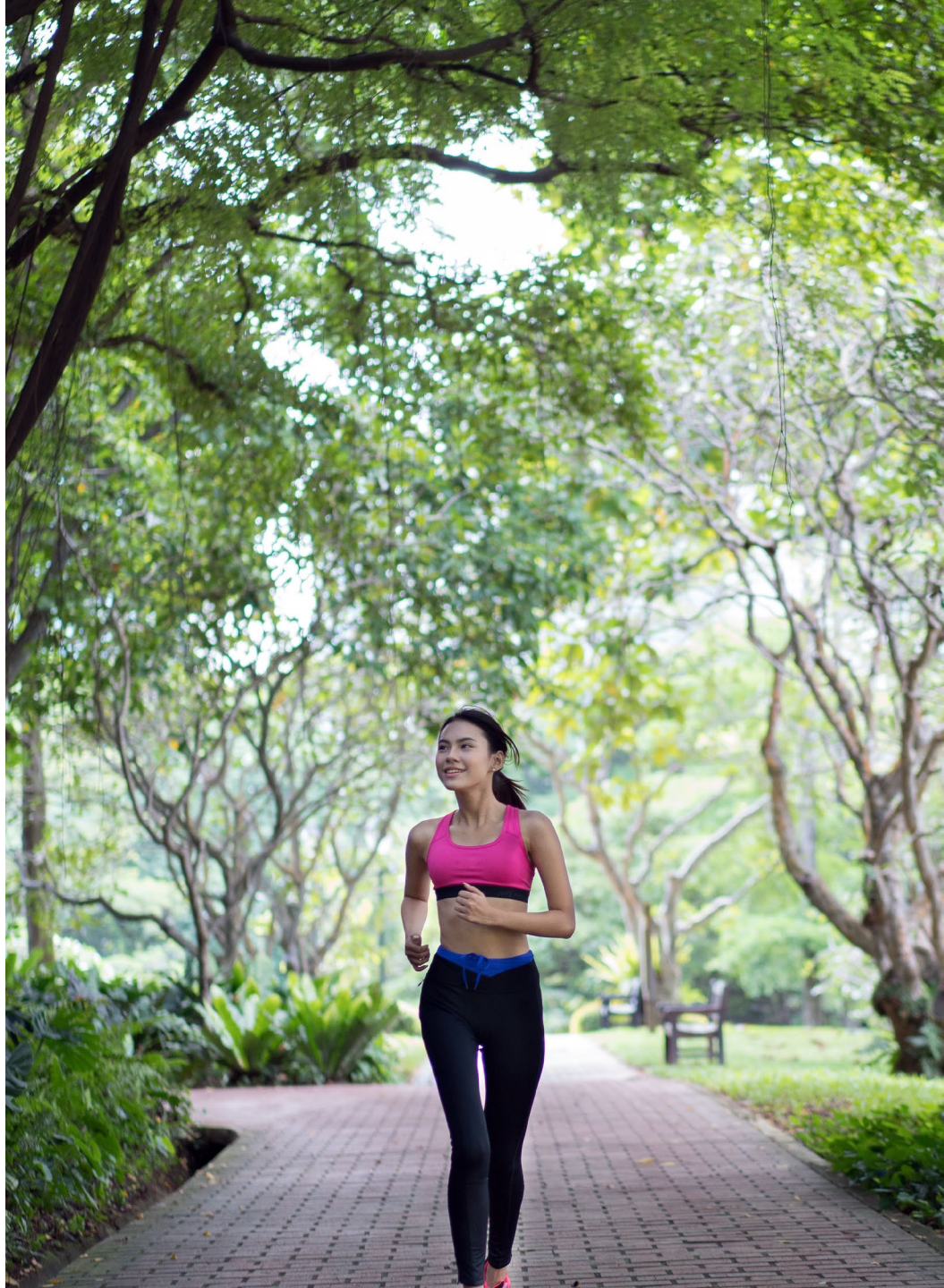
Treatment goals in MPN

- Reduce risk of blood clots
- Relieve symptoms

What every MPN patient should be doing:

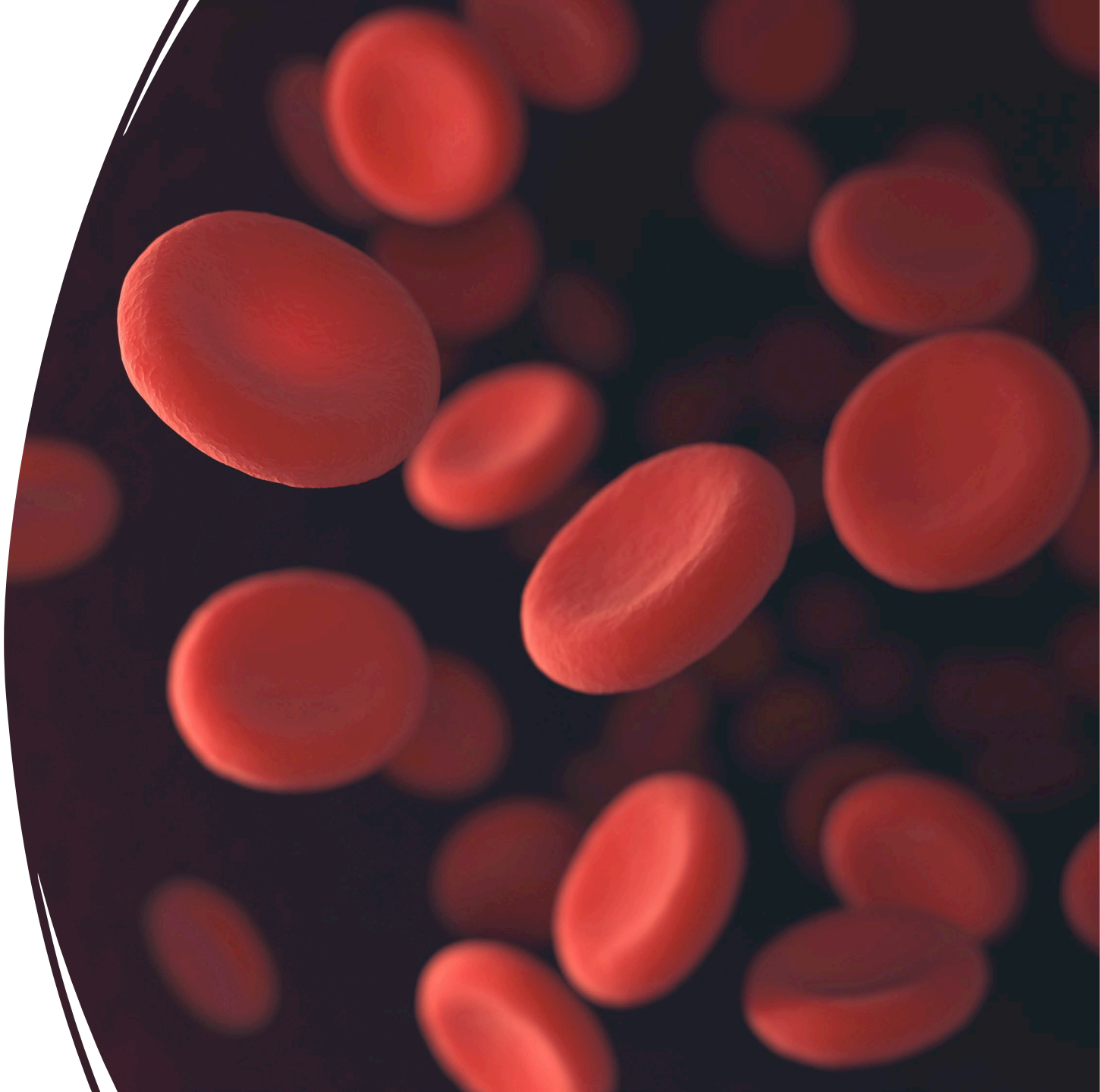
Optimize cardiovascular risk factors

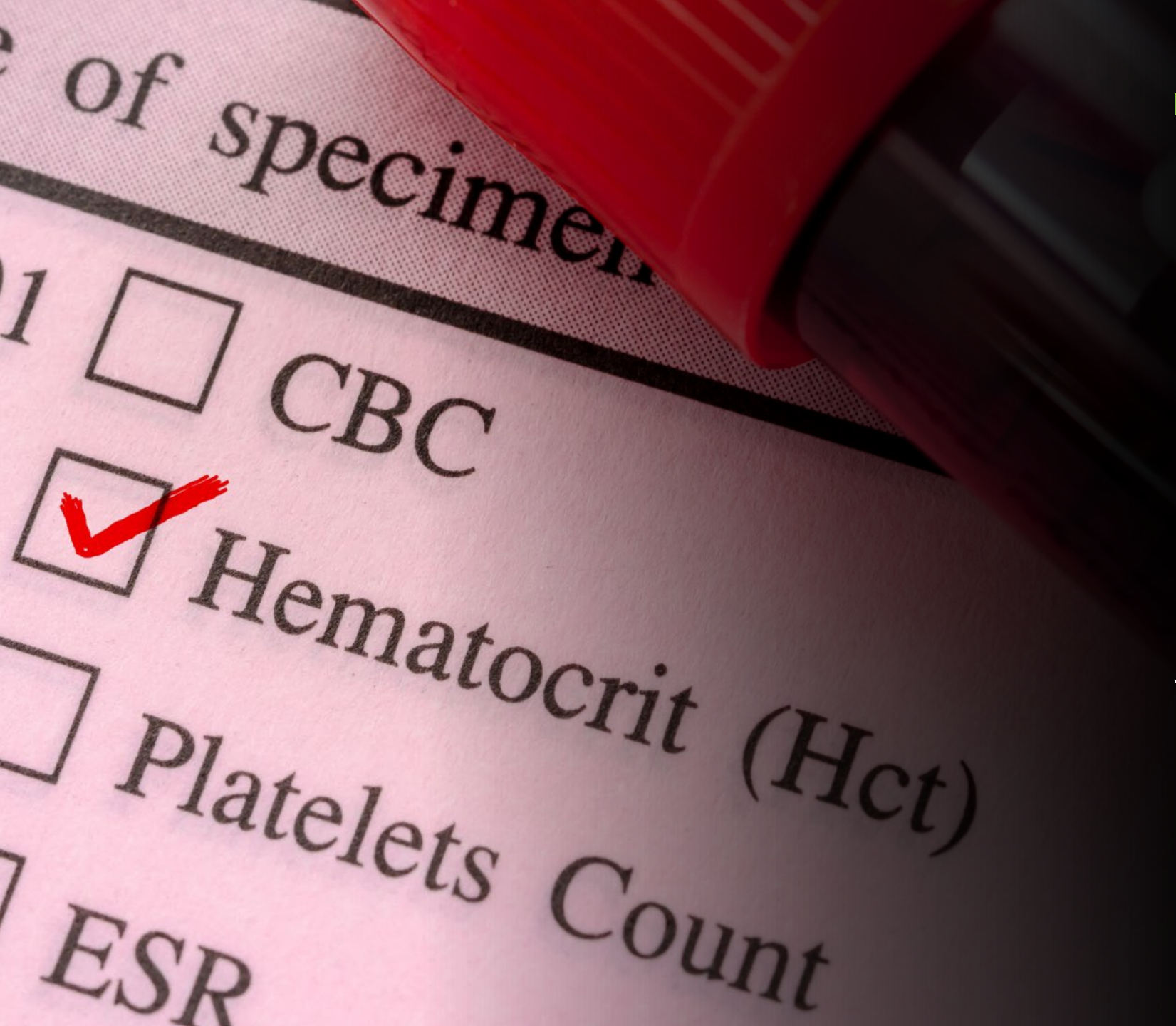
- Weight loss
- Lipid management
- BP management
- Healthy diet/exercise



Factors associated with increased risk of blood clots in MPN

- Age > 65
- JAK2V617F mutation
- Prior thrombosis
- WBC > 12K at diagnosis





Polycythemia Vera

Risk Factor Categories for PV

Low risk – age < AND no history of blood clot

High risk – age ≥ 60 OR history of blood clot

Treatment Recommendations for PV

Low Risk

- Manage Cardiovascular Risk Factors
- Keep Hct < 45%
- Aspirin

High Risk

- Manage Cardiovascular Risk Factors
- Keep Hct < 45%
- Aspirin
- “Cytoreductive” drug such as hydroxyurea, Interferon-alpha

Where does the hct goal of < 45% come from?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

Roberto Marchioli, M.D., Guido Finazzi, M.D., Giorgina Specchia, M.D., Rossella Cacciola, M.D., Ph.D., Riccardo Cavazzina, Sc.D., Daniela Cilloni, M.D., Ph.D., Valerio De Stefano, M.D., Elena Elli, M.D., Alessandra Iurlo, M.D., Ph.D., Roberto Latagliata, M.D., Francesca Lunghi, M.D., Monia Lunghi, M.D., et al., for the CYTO-PV Collaborative Group*

Marchioli et al, NEJM 2013

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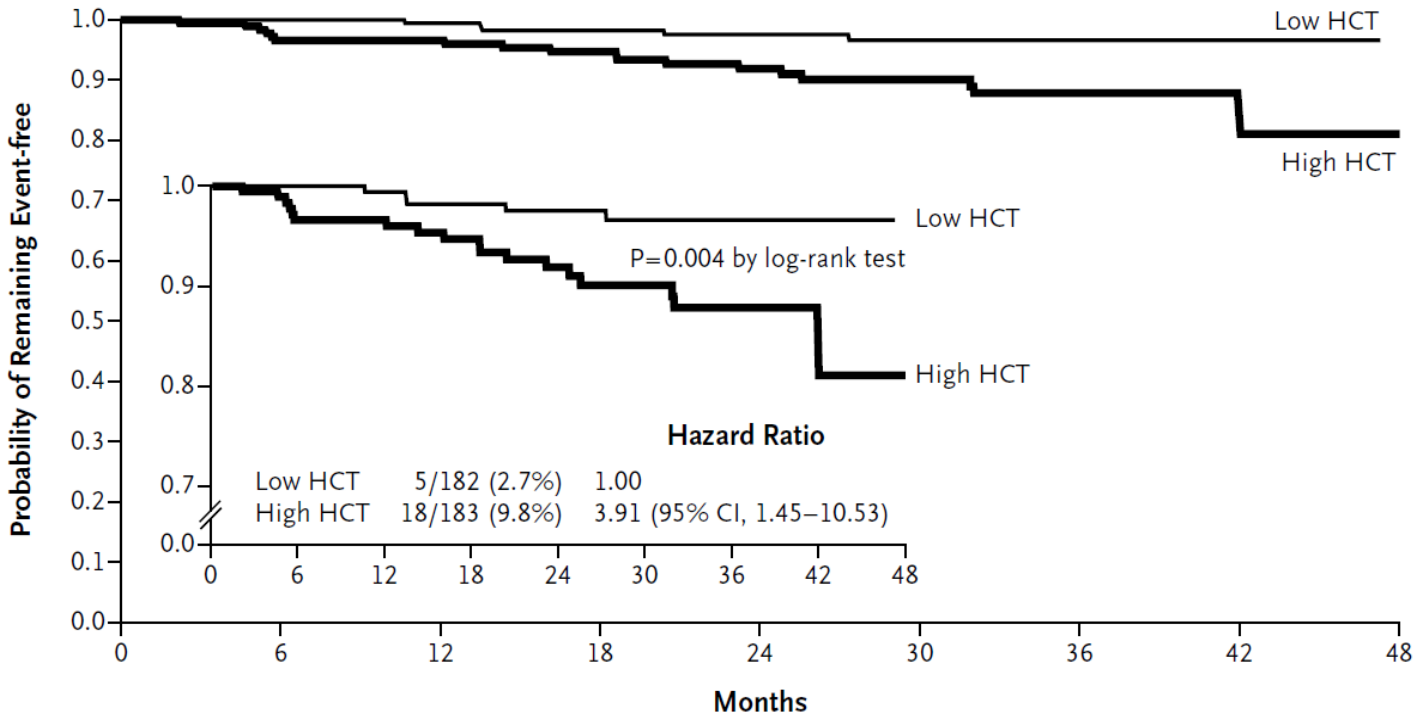
- **Randomly assigned 365 adults with JAK2-positive polycythemia vera treated with phlebotomy, hydroxyurea**

- **Intensive treatment** (target hematocrit, <45%)
- **Less intensive treatment** (target hematocrit, 45 to 50%)

- **Primary end point** - time until death from cardiovascular causes or major thrombotic events

- **Secondary end points** - cardiovascular events, cardiovascular hospitalizations, incidence of cancer, progression to myelofibrosis, myelodysplasia or leukemic, transformation, and hemorrhage

Keeping hematocrit below 45% in PV patients reduces risk of death from cardiovascular causes or major thrombotic event



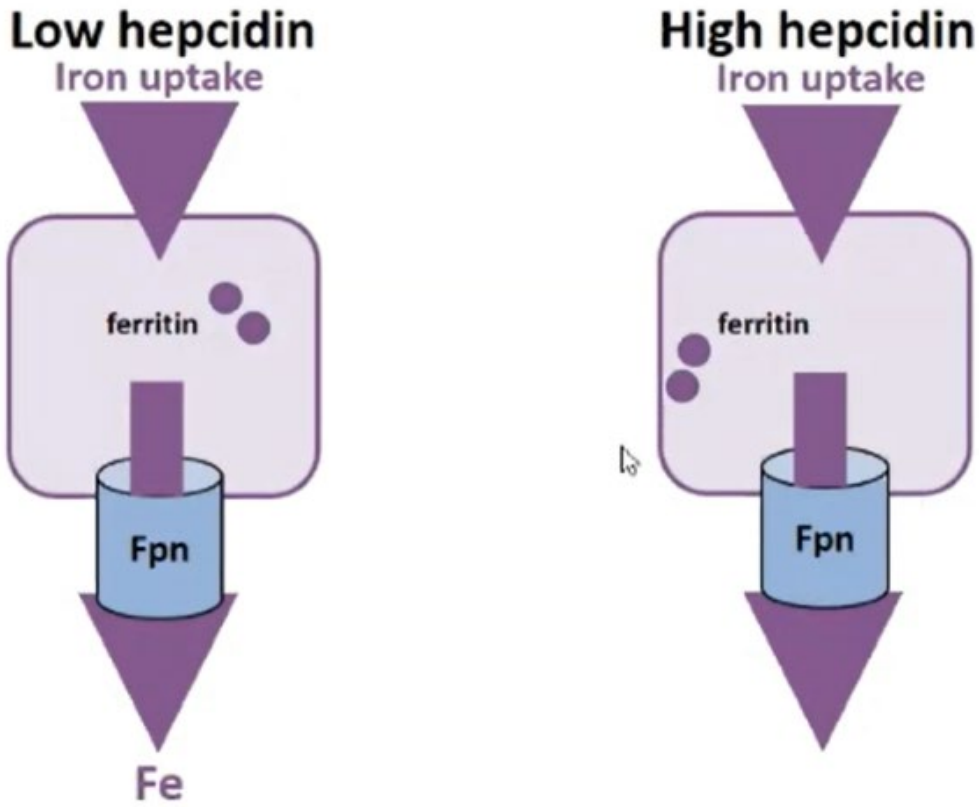
Marchioli et al, NEJM 2013

Downsides to therapeutic phlebotomy

- PV patients likely spend a significant amount of time with hematocrit > 45%, thereby potentially increasing their risk of thrombosis
- Symptomatic iron deficiency is a challenge in PV
- Some people may find it hard to tolerate

Hepcidin as a Negative Regulator of Iron Flux

- **Iron exporting cells:**
- Duodenal enterocytes, macrophages, hepatocytes



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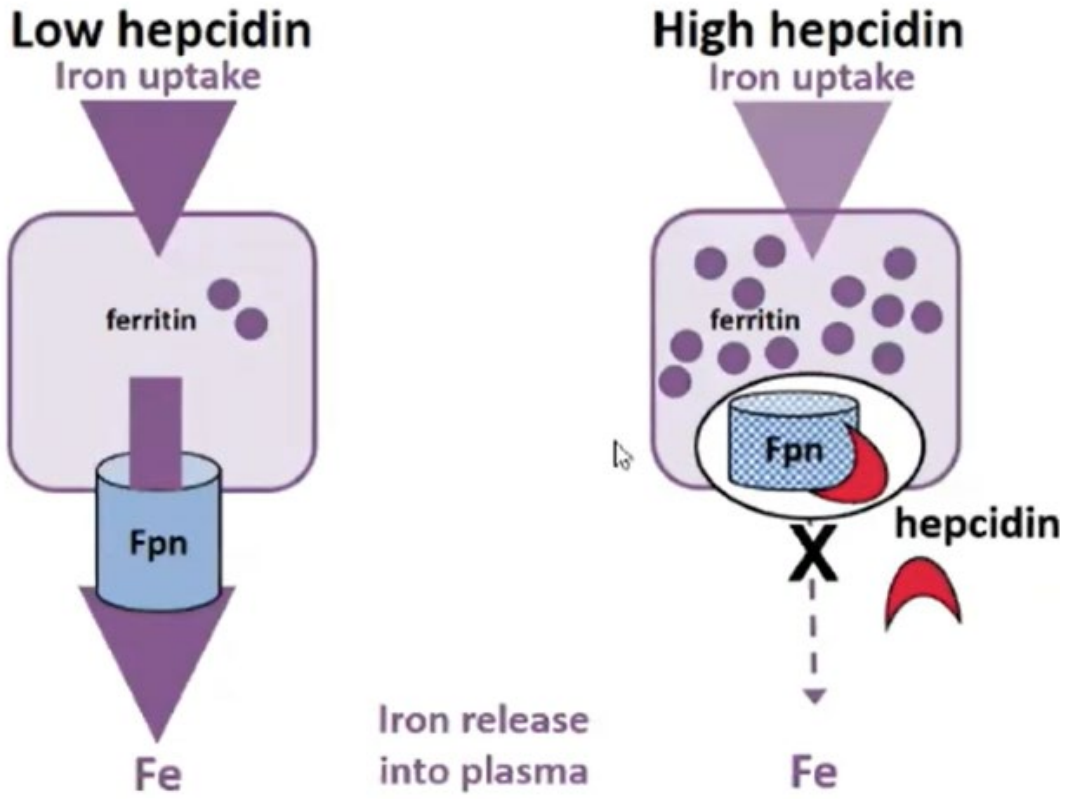
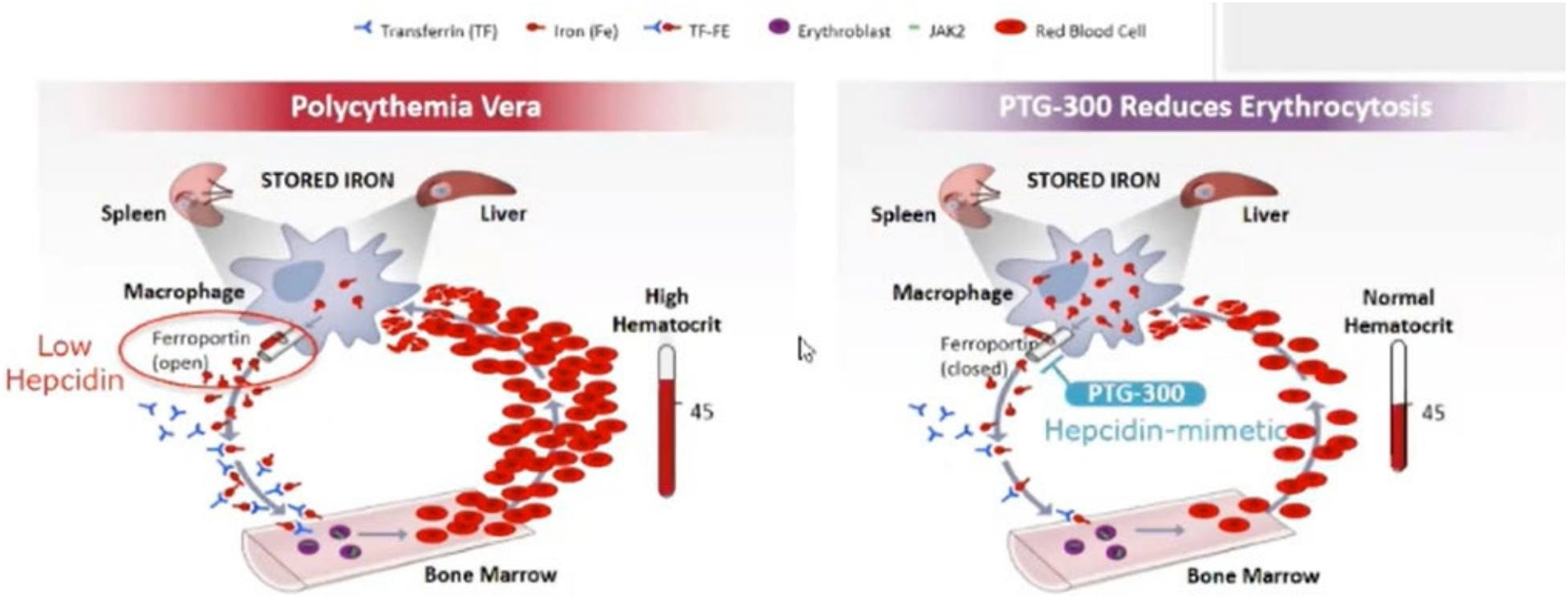


Mechanism of Action: Hepcidin mimetic Rusferitide (PTG-300)

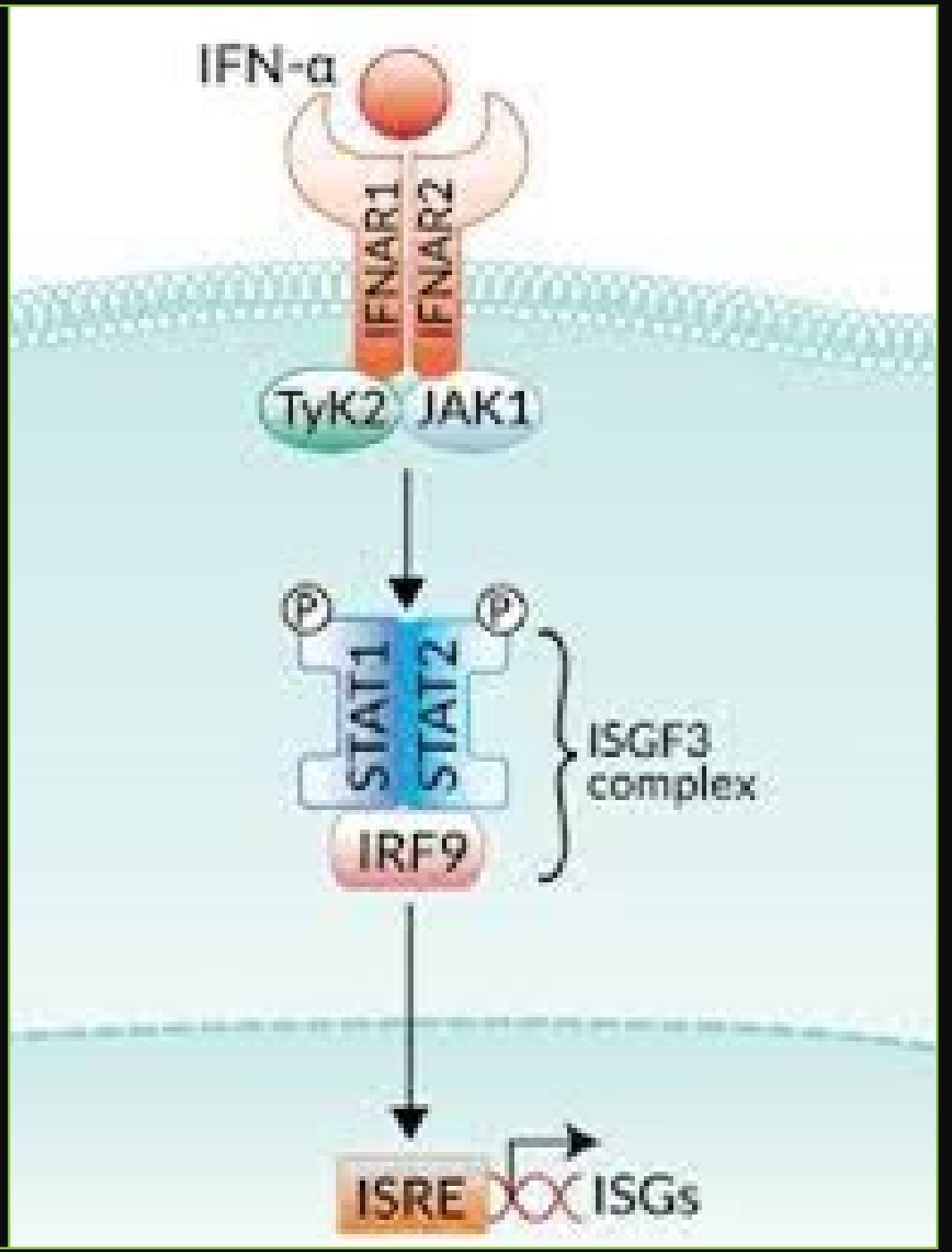


Protagonist Therapeutics

A second approach to increasing hepcidin to reduce Hct in PV

- **ISIS 702843-CS4**

Interferon-alpha in PV

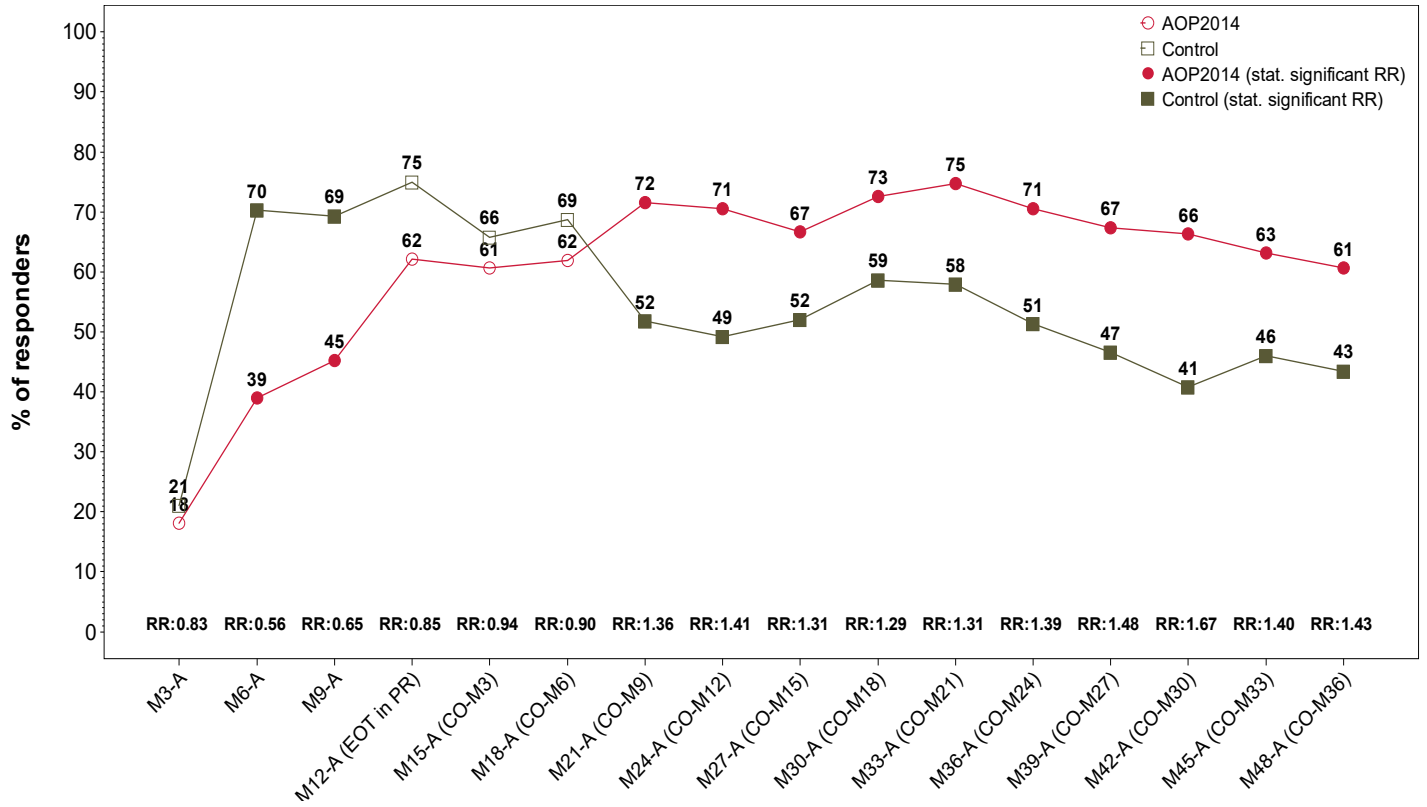


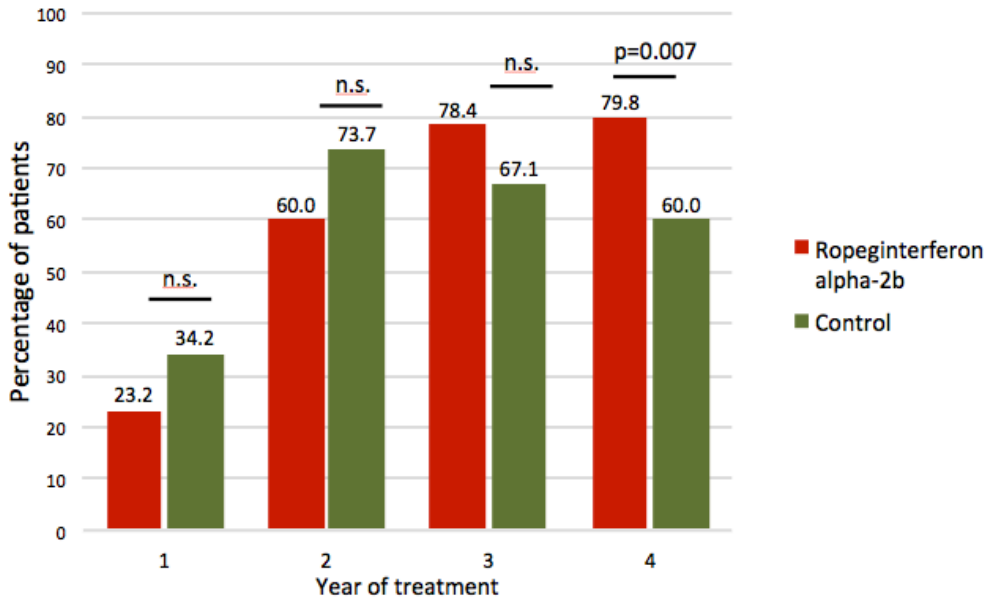
- Very long acting interferon-alpha
- Maintains efficacy of interferon-alpha but more easily tolerated
- Now FDA approved for PV

BESREMi
(ROPEGINTERFERON α-2B)

Complete Hematologic Response (CHR)

Full Analysis Set

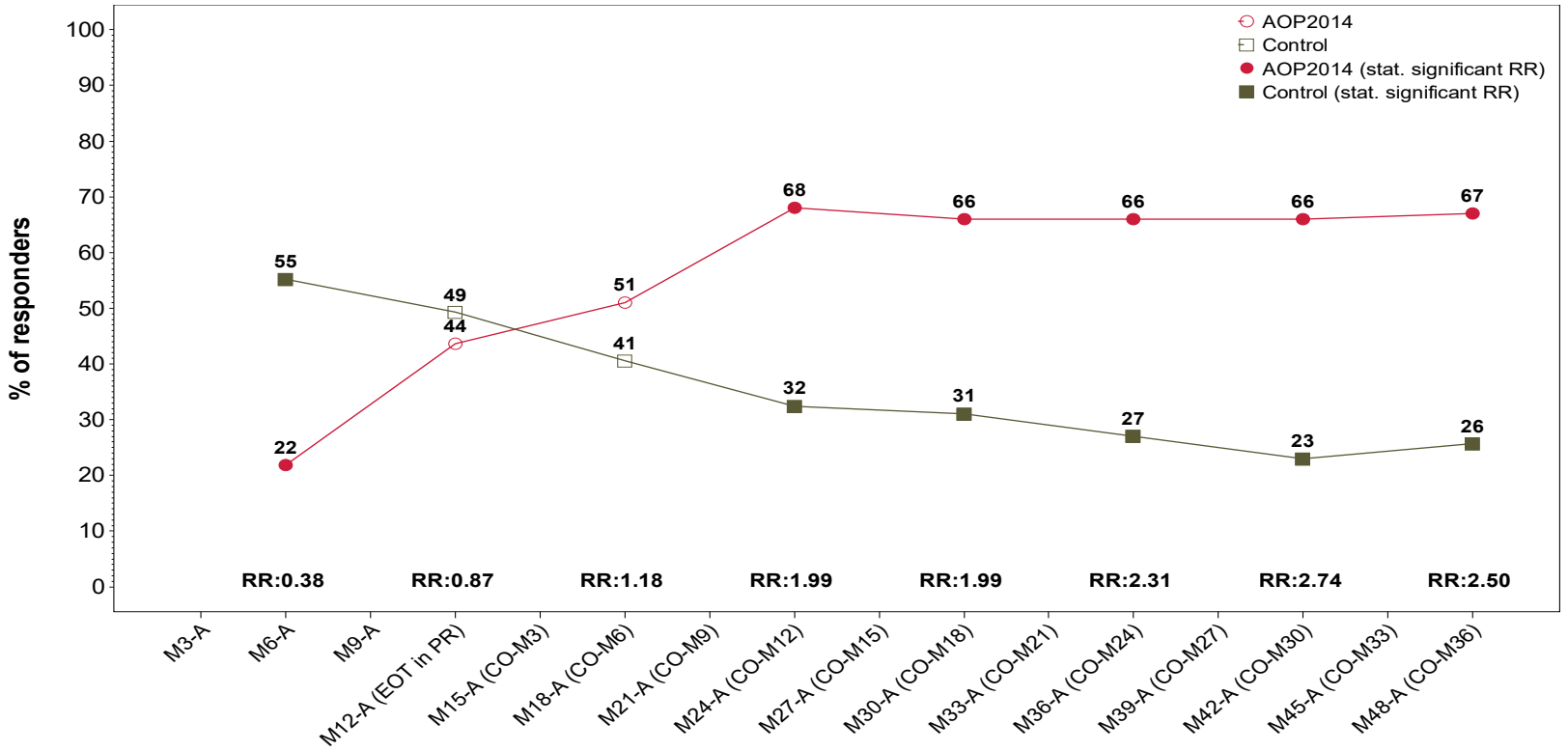




Phlebotomy-free Patients

Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeginterferon (N=95)		Control (N=76)			
Month 12 (End of PROUD-PV)	59/95	62.1	57/76	75.0	0.1211	0.85 [0.70-1.04]
Month 24	67/95	70.5	33/67	49.3	0.0117	1.41 [1.08-1.85]
Month 36	67/95	70.5	38/74	51.4	0.0108	1.39 [1.08-1.79]
Month 48	57/94	**60.6**	33/76	**43.4**	**0.0194**	**1.43 [1.06–1.93]**

Molecular Response – reduction in JAK2V617F cells



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	Ropeginterferon (N=95)		Control (N=76)			
Month 12 (End of PROUD)	41/94	43.6	36/73	49.3	0.3706	0.87 [0.63-1.19]
Month 24	64/94	68.1	24/74	32.4	<0.0001	1.99 [1.41-2.82]
Month 36	62/94	66.0	20/74	27.0	<0.0001	2.38 [1.56-3.42]
Month 48	63/94	**67.0**	19/74	**25.7**	**<0.0001**	**2.50 [1.68-3.72]**

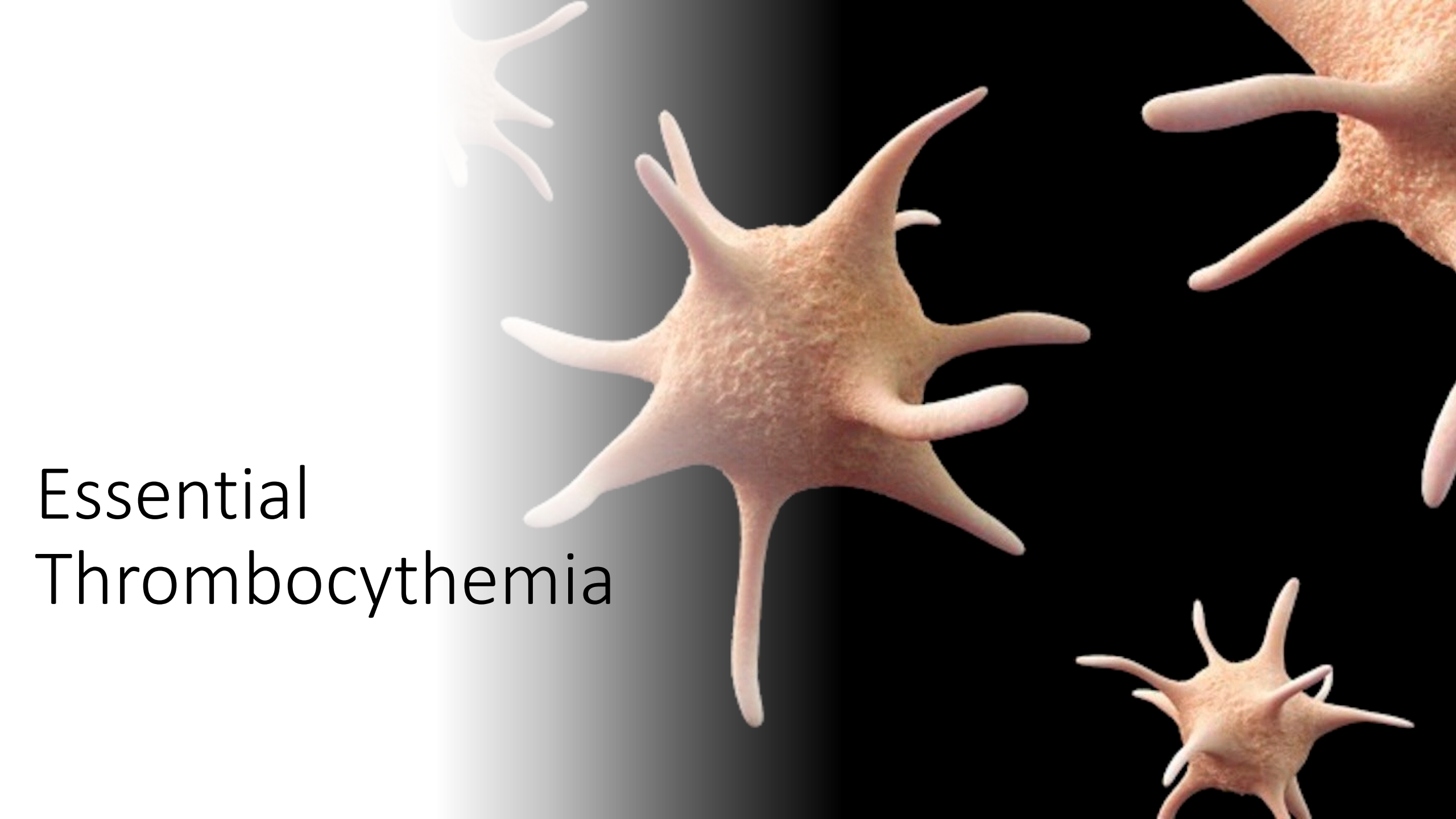
Ropeginterferon: Contraindications

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt
- Hepatic impairment (Child-Pugh B or C)
- History or presence of active serious or untreated autoimmune disease

Ropeginterferon: Monitoring

- Follow CBC every 2 weeks initially to assess blood counts
- Follow liver function tests
- Monitor thyroid function
- Eye exams

Essential Thrombocythemia



Risk Categories in ET

VERY LOW RISK
- < 60 years old
- Don’t have a JAK2 mutation
- No history of blood clot

LOW RISK
- < 60 years old
- Have a JAK2 mutation
- No history of blood clot

INTERMEDIATE RISK
- > 60 years old
- No history of blood clot

HIGH RISK
- Had a blood clot

OR
- > 60 years old AND have a JAK2 mutation

Treatment Recommendations for ET

Very Low, Low, and Intermediate Risk

- Manage cardiovascular risk factors
- Aspirin

High Risk

- Manage cardiovascular risk factors
- Aspirin
- Hydroxyurea, anagrelide, or interferon

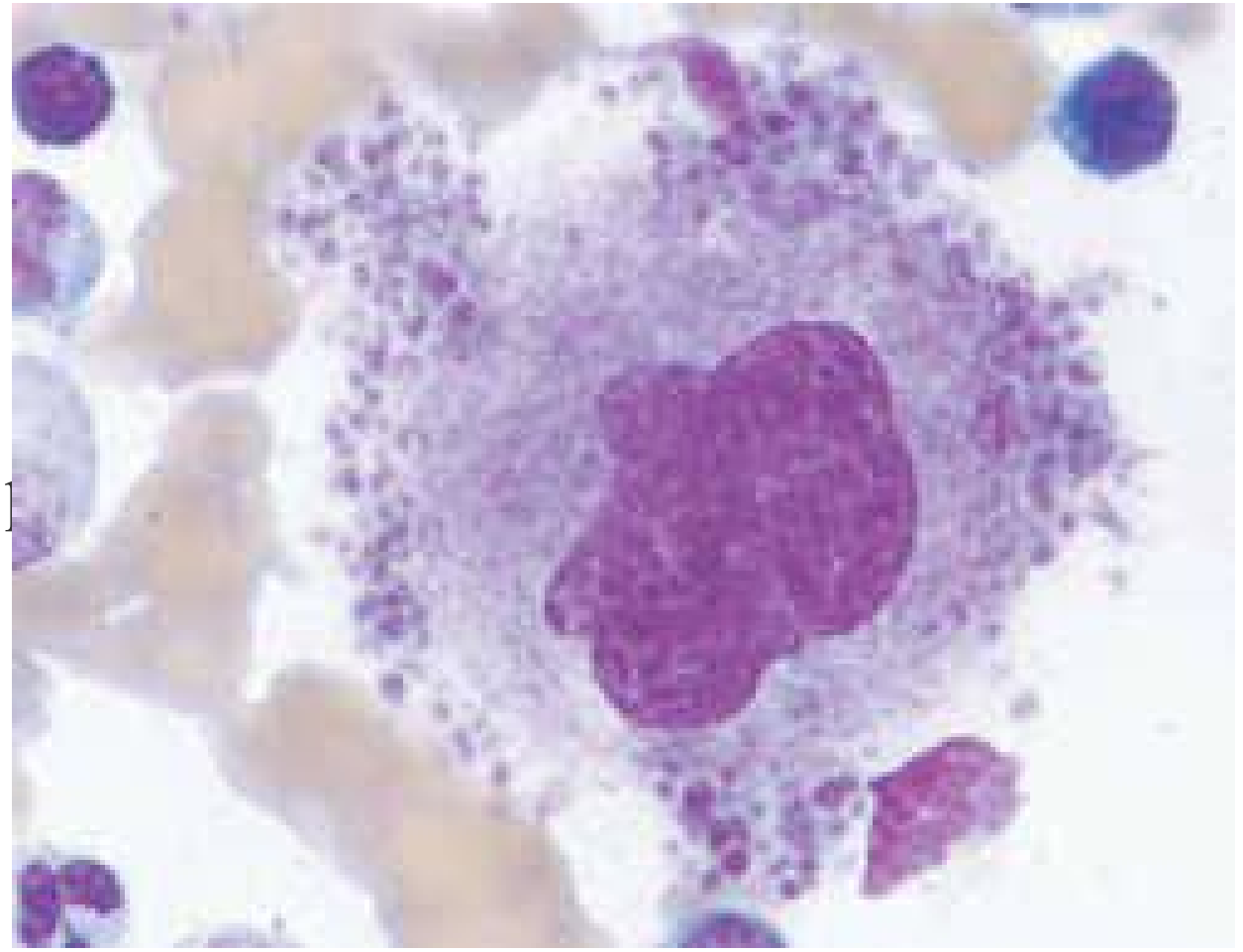
New Treatments for ET

IMAGO BIOSCIENCES

Bromedemstat in ET

Bromedemstat is an LSD1 inhibitor

Lysine-specific demethylase-1 (LSD1) is critical for the self-renewal malignant stem cells and maturation of megakaryocytes, the cells that make platelets



Bromedemstat in ET

A **treatment response** is when a participant has a **platelet** count of 400 X 10^9/L or less without a blood clot event.

94% of participants had a **treatment response**

Average hemoglobin levels were maintained

All mutation types responded similarly

24 participants had their frequency of mutations analysed.

67% of those participants had a reduction in the frequency of mutations

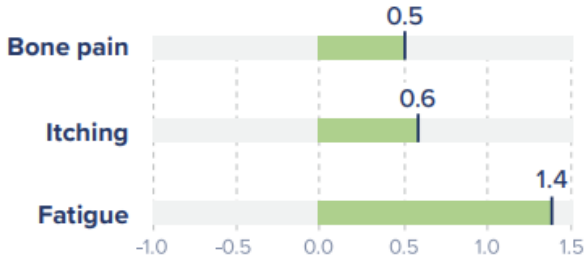
Participants rated their **symptoms** caused by their ET during the study. Key symptoms include fatigue, bone pain, and itching. The results after 24 weeks of treatment are given below.

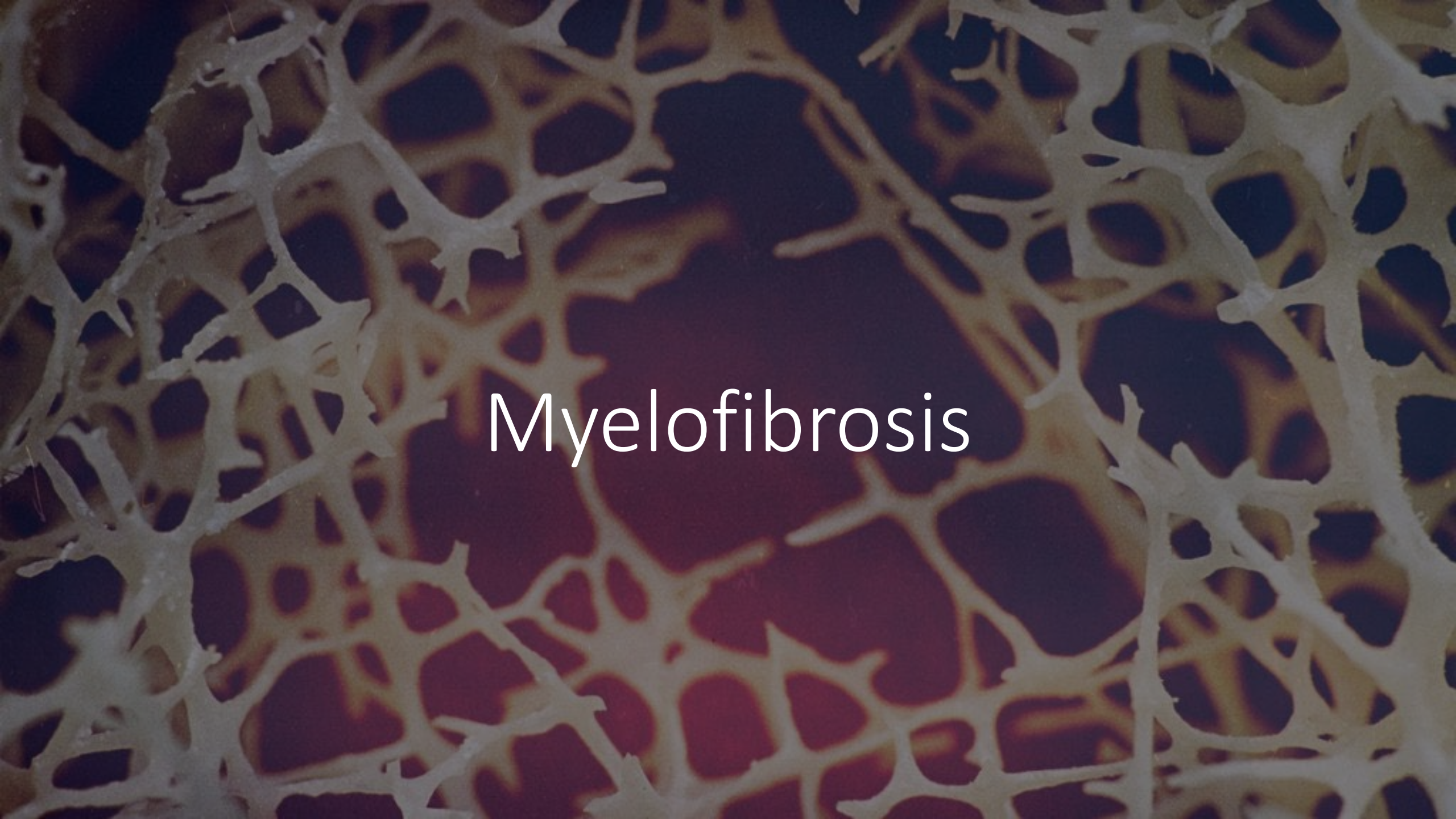
58% (out of 31) participants had an improvement in their symptom score

85% (out of 13) participants with severe symptoms improved*

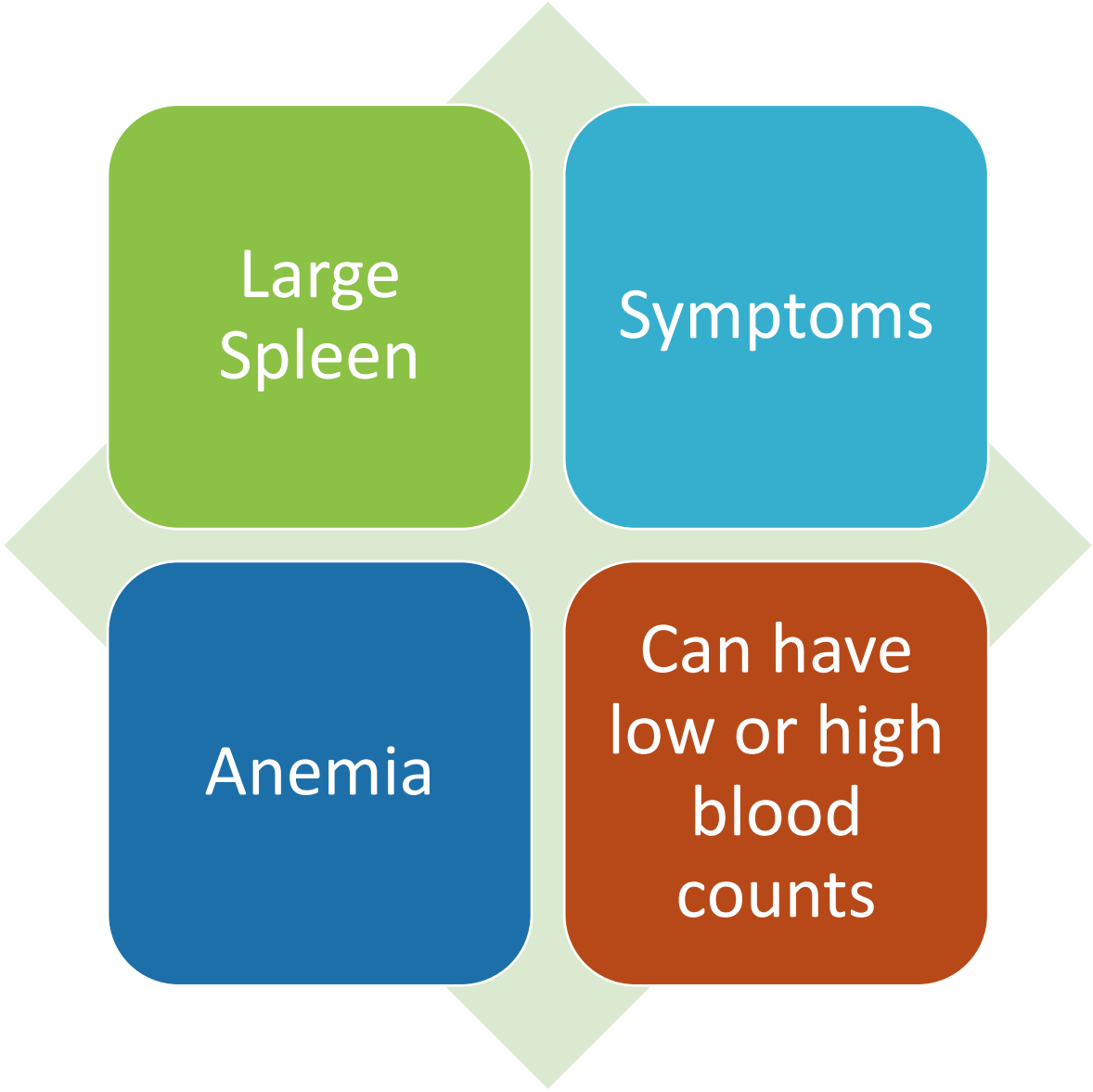
*Refers to participants with severe symptoms at the start of the study.

The graphs below show the **average symptom improvement** in bone pain, itching, and fatigue for participants at 48 weeks.




Myelofibrosis

Myelofibrosis is complex with many different clinical issues



3 JAK inhibitors currently approved for MF

JAK inhibitors

WHAT THEY CAN DO:

- Reduce spleen size
- Relieve symptoms

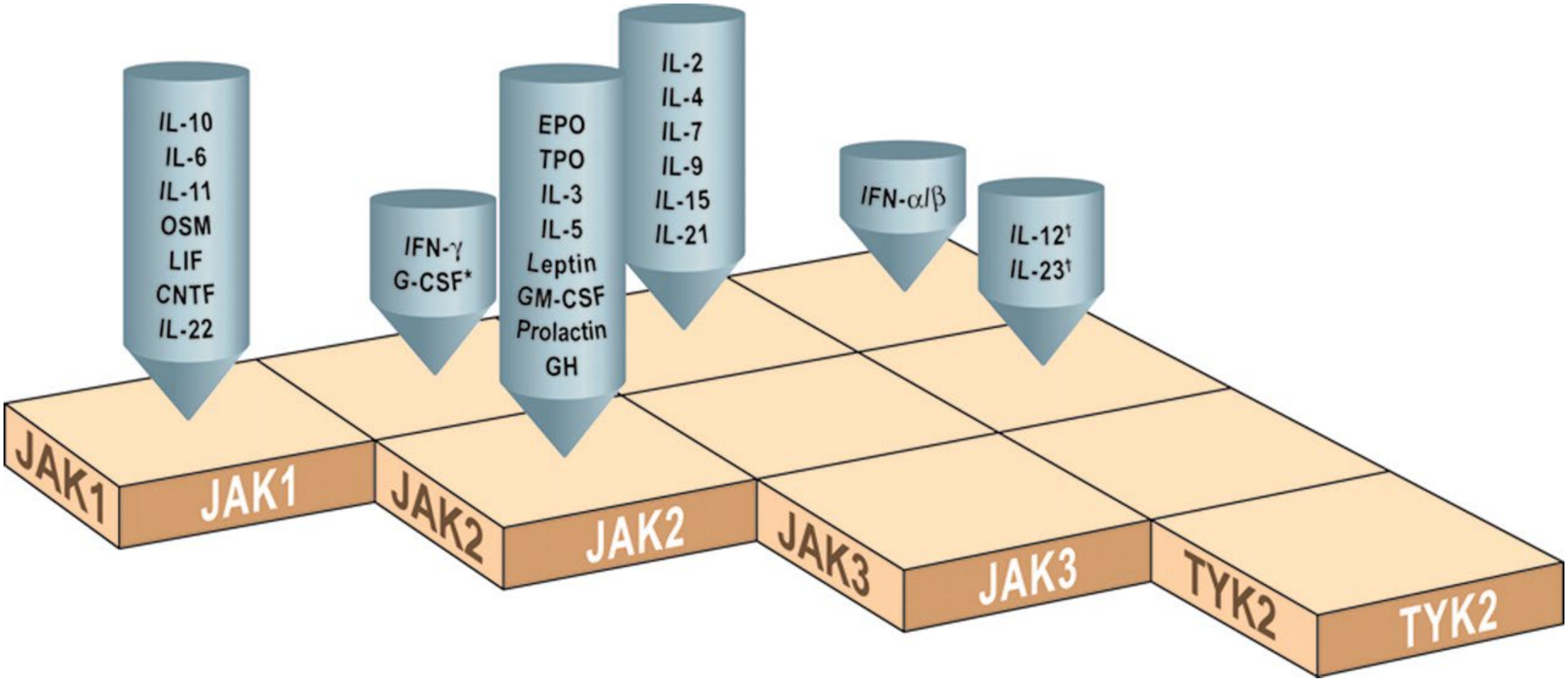
WHAT THEY DON'T DO:

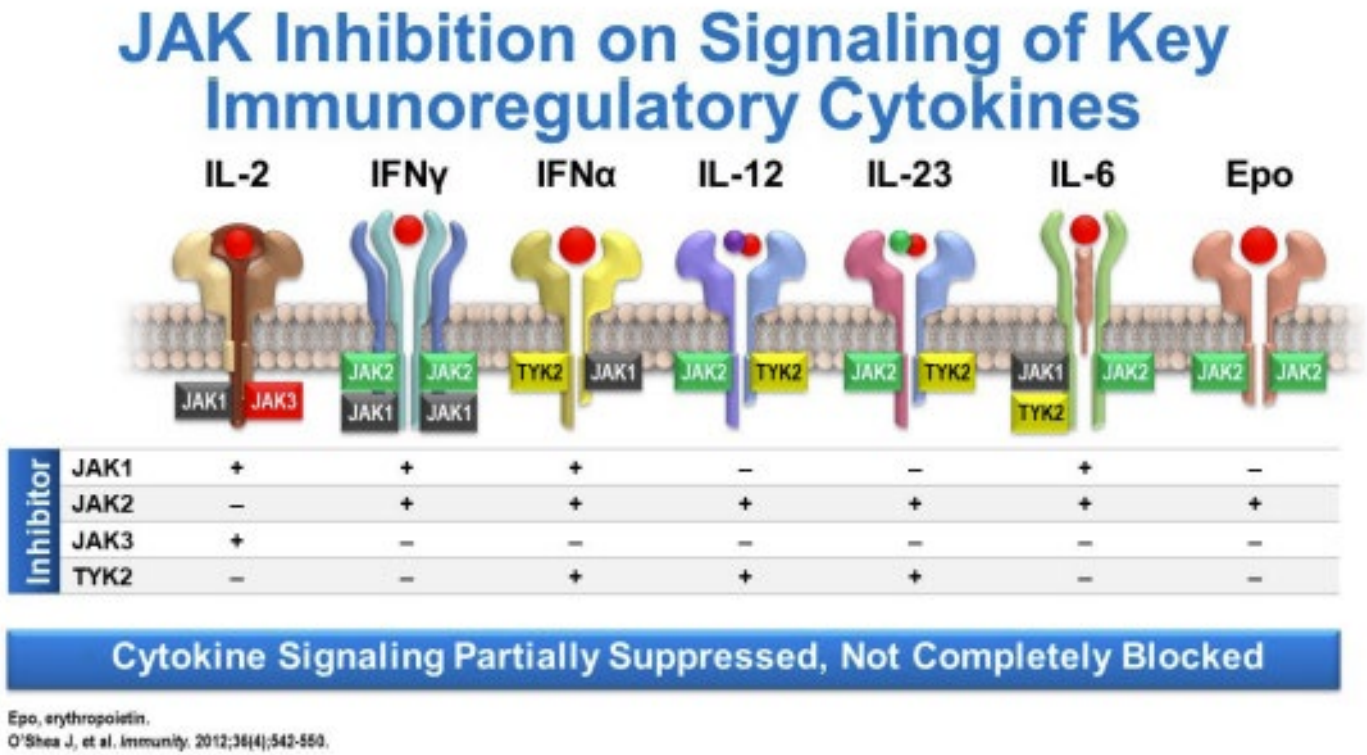
- Improve anemia
- Significantly reduce the $JAK2^{V617F}$ allele burden

WHAT THEY MAY DO:

- Retard progression of fibrosis
- Extend lifespan

Different JAKs are involved in production of different inflammatory proteins





Ruxolitinib – JAK1/2

Fedratinib – JAK2

Pacritinib - JAK2

Momelotinib – JAK1/2

Which JAK inhibitor do you chose?

“cytopenic” MF

Low blood counts,
Plts < 50
Low JAK2 allele burden

Pacritinib (Vonjo)

“proliferative” MF

High blood counts
High JAK2 allele burden

Ruxolitinib (Jakafi)
Fedratinib (Inrebic)

Clinical Trials for MF

- CPI-0610 (Pelabresib) – BET inhibitor
- Imetelstat – telomerase inhibitor
- Navitoclax – BCL-xL inhibitor

Thank you

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