Mass General Brigham
Mass General Cancer Center

MPN Advocates Network

PV – Standard of Treatment in 2023

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Conflict of Interest

Research funding- Incyte, ASH-AMFDP, MGH PSDA
Advisory boards- BMS, Novartis, Pfizer, MorphSys, Abbvie, Pharmaxis, Pharmaessentia

Regeneron- spouse employment

Objectives

Background

Management

Upcoming therapy

2016 WHO Diagnostic Criteria
Polycythemia Vera

Major Criteria

- Hemoglobin >16.5 g/dL in men, >16 in women
- Hematocrit >49% in men, >48% in women
- Increased red cell mass

AND

- Bone marrow biopsy shows PV
- Presence of JAK2 mutation or exon 12

Minor Criteria

- Low EPO

NATURAL HISTORY OF PV

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Cumulative Proportion Surviving

— PV patients
- - reference cohort

p = 0.01

0 5 10 15 20 25 30 35 40 45 50 55 60 65

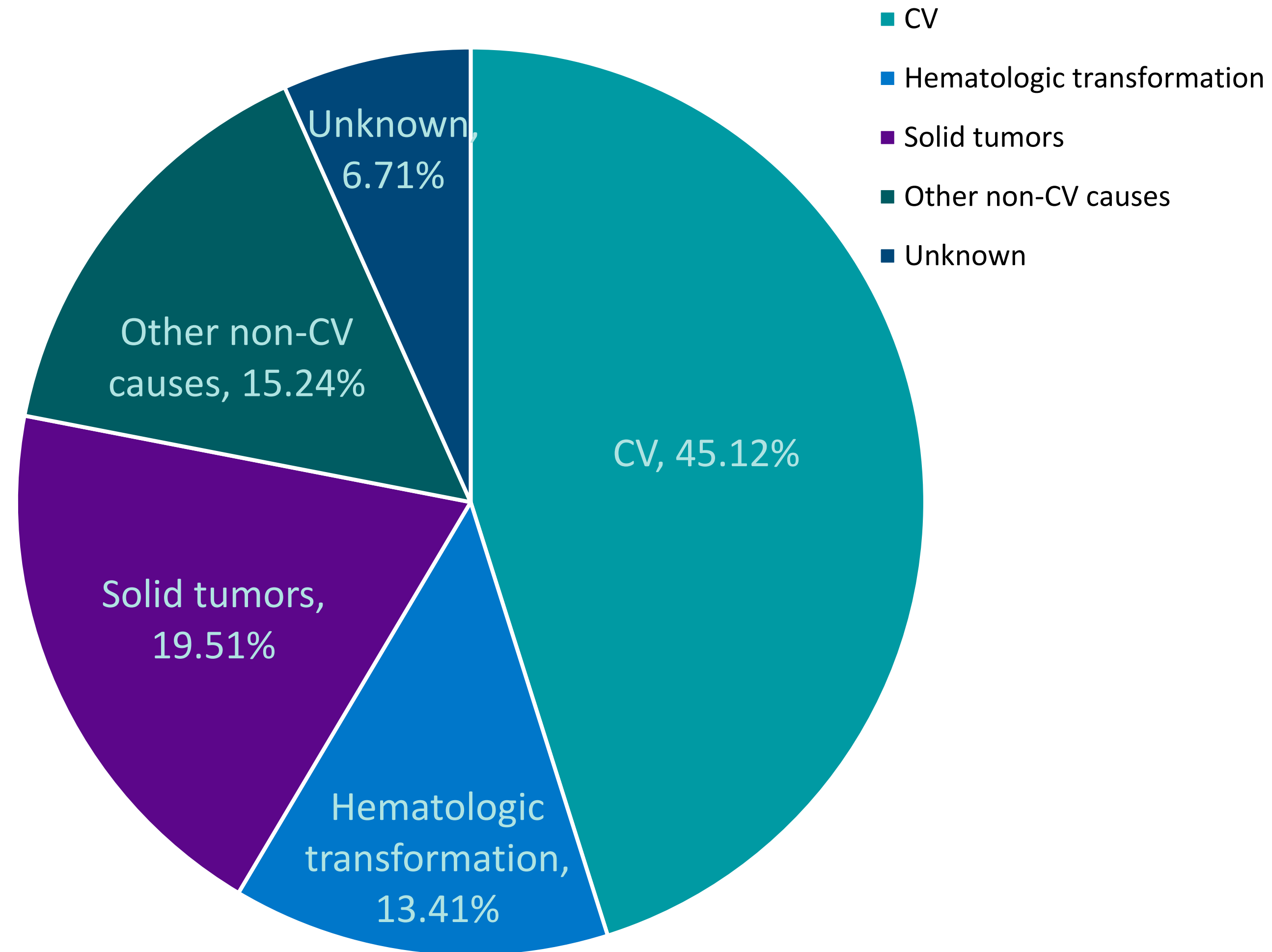
Time (years)

No. at risk: 396 282 186 104 52 8

- Median survival 20 years
- Survival is inferior to general population
- 15-year leukemia risk=5% (10% at 20 years)
- 15-year myelofibrosis risk=5-10%
- **15-year thrombosis risk=27%**

Passamonti *et al. Am J Med*. 2004
Tefferi *et al* Blood 2014

Mortality in PV



Marchioli R, et al. J Clin Oncol. 2005;23:2224-2232.

PV Treatment

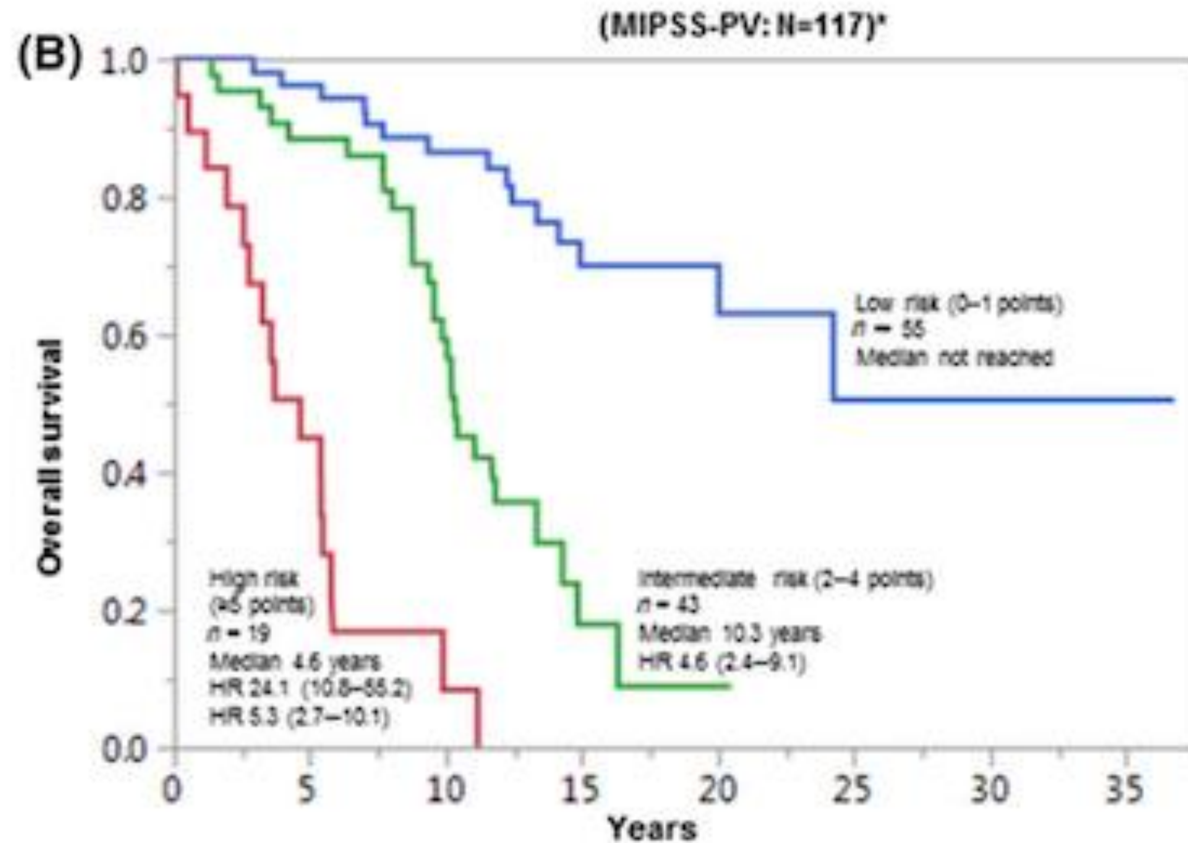
Risk Categories	
Low-risk (Age<60 and no thrombosis)	Aspirin + Phlebotomy Ropeginterferon
High-risk (age >60 OR thrombosis)	Aspirin + phlebotomy + cytoreduction
High-risk and refractory to hydroxyurea	Ruxolitinib or <65-interferon >65-busulfan

ASA BID considered for patients with refractory symptoms and arterial thrombosis

Marcholi NEJM 2013
Tefferi, 2013 Am J Hematol. 2013 Jun;88(6):507-16.

MIPSS-PV

Thrombosis
WBC >15
Age >67
SRSF2



	19	2	0
risk	43	22	2
	55	41	11

Tefferi Br J Haematol 2020; 189-291-302

Cytoreductive therapy

- Hydroxyurea
- Interferon
- Ruxolitinib

Phlebotomy

A Primary End Point

Probability of Remaining Event-free

1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0

Low HCT

High HCT

1.0 0.9 0.8 0.7 0.0

Low HCT

P=0.004 by log-rank test

High HCT

Hazard Ratio

Low HCT	5/182 (2.7%)	1.00
High HCT	18/183 (9.8%)	3.91 (95% CI, 1.45–10.53)

0 6 12 18 24 30 36 42 48

0 6 12 18 24 30 36 42 48

Months

No. at Risk									
Low HCT	182 (0)	177 (1)	168 (2)	154 (1)	129 (1)	95 (0)	62 (0)	18 (0)	0
High HCT	183 (6)	168 (0)	160 (3)	143 (4)	110 (2)	92 (2)	54 (1)	12 (0)	1

B Total Cardiovascular Events

Probability of Remaining Event-free

1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0

Low HCT

High HCT

1.0 0.9 0.8 0.7 0.0

Low HCT

P=0.01 by log-rank test

High HCT

Hazard Ratio

Low HCT	8/182 (4.4%)	1.00
High HCT	20/183 (10.9%)	2.69 (95% CI, 1.19–6.12)

0 6 12 18 24 30 36 42 48

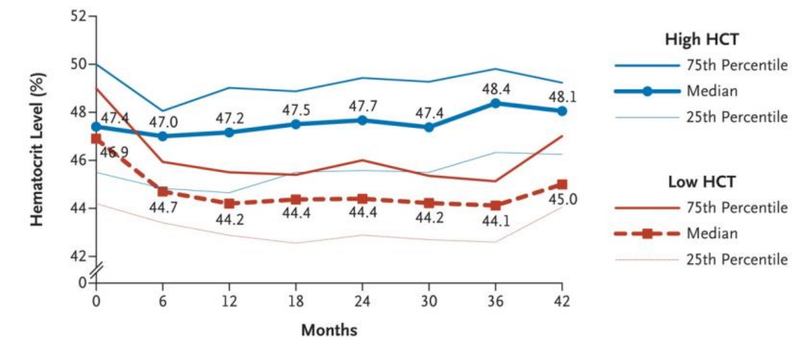
0 6 12 18 24 30 36 42 48

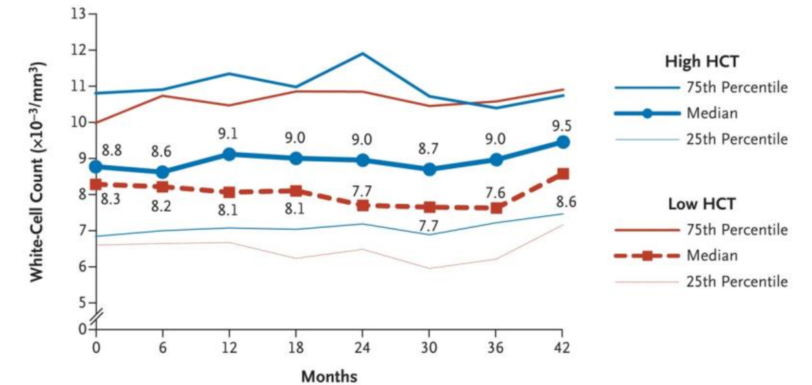
Months

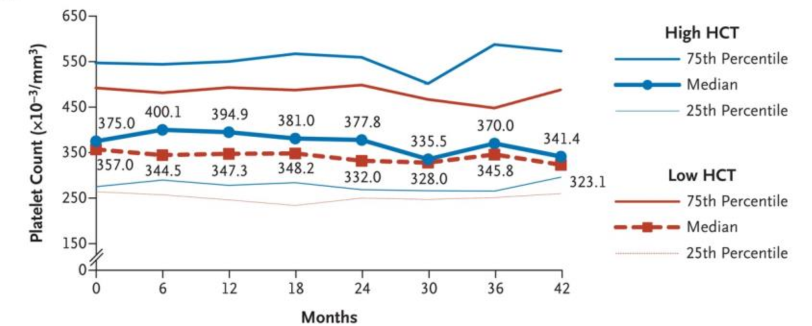
No. at Risk									
Low HCT	182 (1)	176 (3)	165 (2)	151 (1)	127 (0)	94 (1)	60 (0)	18 (0)	0
High HCT	183 (7)	167 (0)	159 (4)	141 (4)	108 (2)	91 (2)	53 (1)	11 (0)	0

Marchioli CYTO-PV NEJM 2013

Is it just the HCT that matters?







Marchioli CYTO-PV NEJM 2013

Is too much phlebotomy a problem?

100
80
60
40
20
0

%

0 12 24 36 48 60

Months of therapy

>3 Phleb/year + HU = Increased thrombotic risk

Alvarez-Larran Haematologica 2017

Hydroxyurea

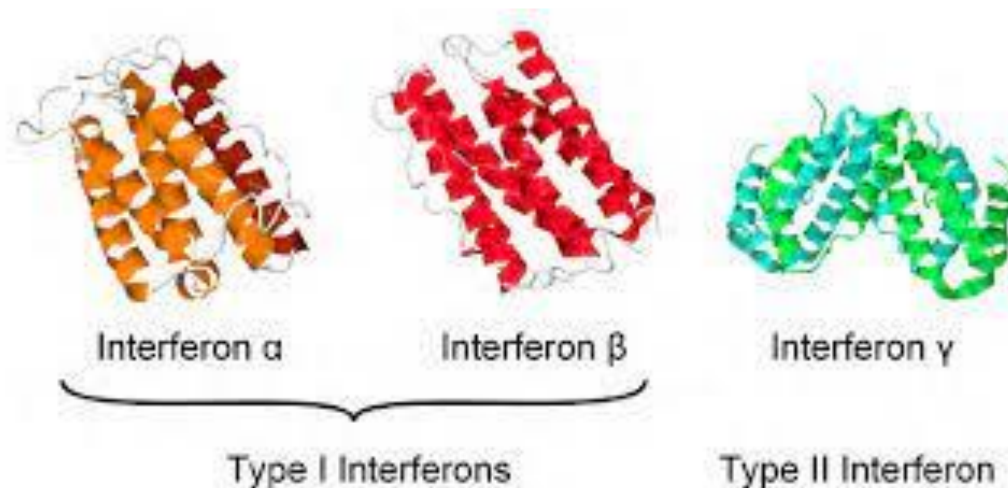
Well tolerated
Inexpensive
Some of the early studies were in ET more than PV (PT1)

Interferon

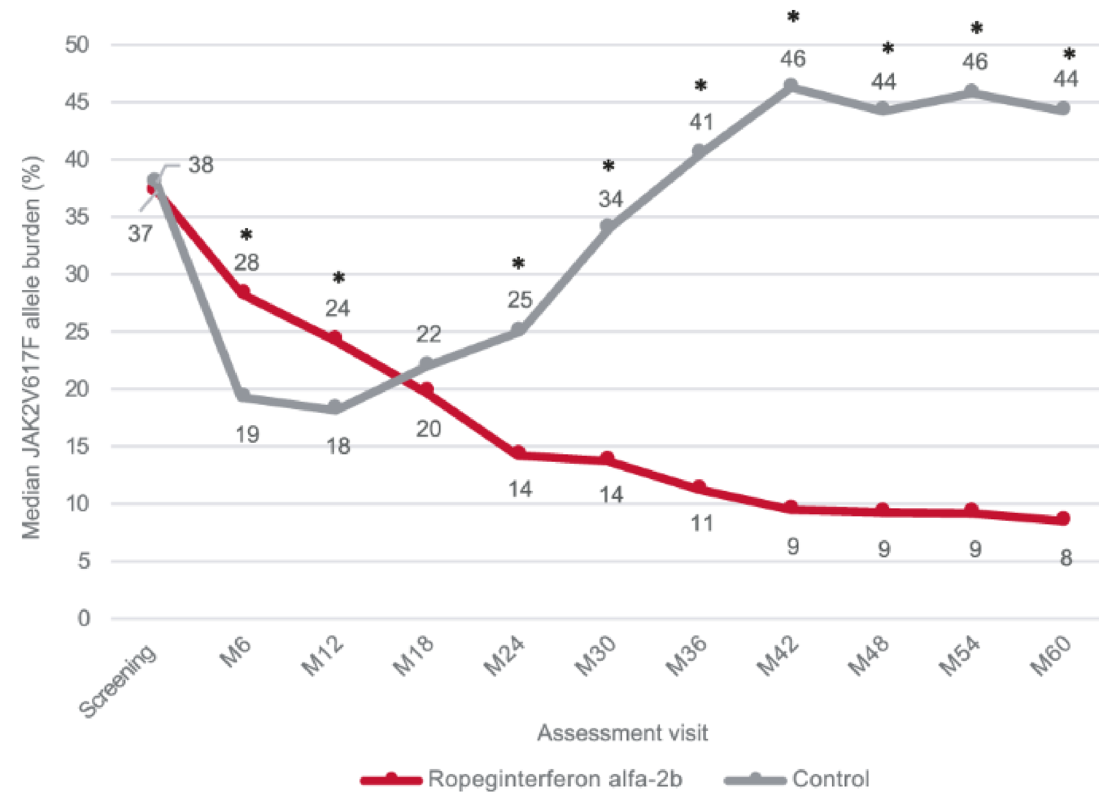
Recombinant INFα has been used for >3 decades in MPN

Type I Interferons in use:

- Intron A (standard INFα-2b)
- Pegylated INFα (Pegasys)
- Pegylated INFα-2b (PegIntron)
- Ropeginterferon α-2b (Besremi)



Median JAK2V617F burden (%)



Kiladjian *Leukemia* **v36**, 1408–1411 (2022)

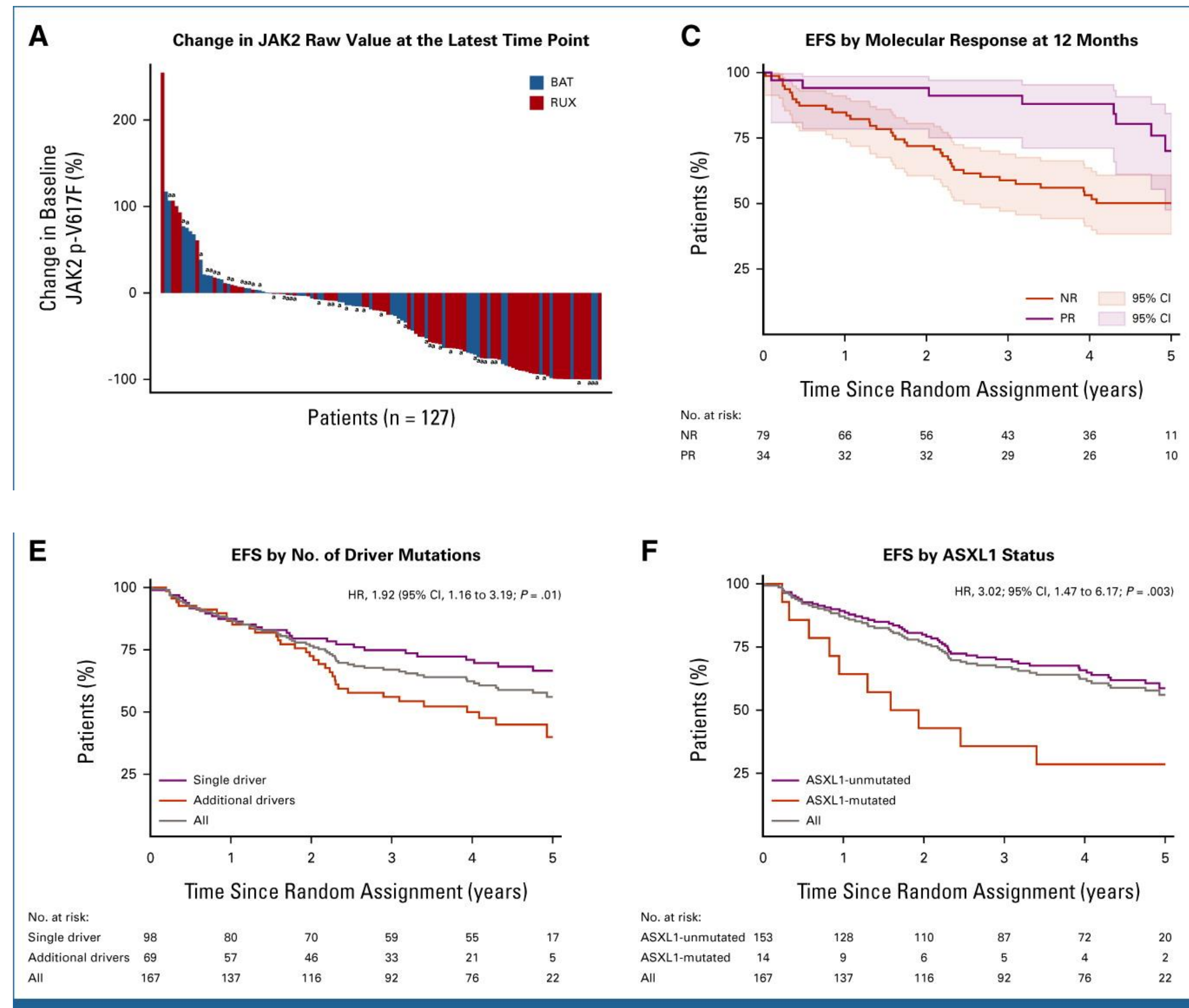
Ruxolitinib

- JAK inhibitor- Approved for MF and PV
  - Selectively inhibits JAK1 and JAK2 cell signaling
- Warnings/precautions
  - Thrombocytopenia, anemia, and neutropenia, infection, lipid elevation, major adverse cardiovascular (CV) events, thrombosis, skin cancer, symptom exacerbation following discontinuation or interruption

Baseline platelet counts	Initial ruxolitinib dose
> 200 x 10^9/L	20 mg twice daily
100 to 200 x 10^9/L	15 mg twice daily
50 to < 100 x 10^9/L	5 mg twice daily

Ruxolitinib [package insert]

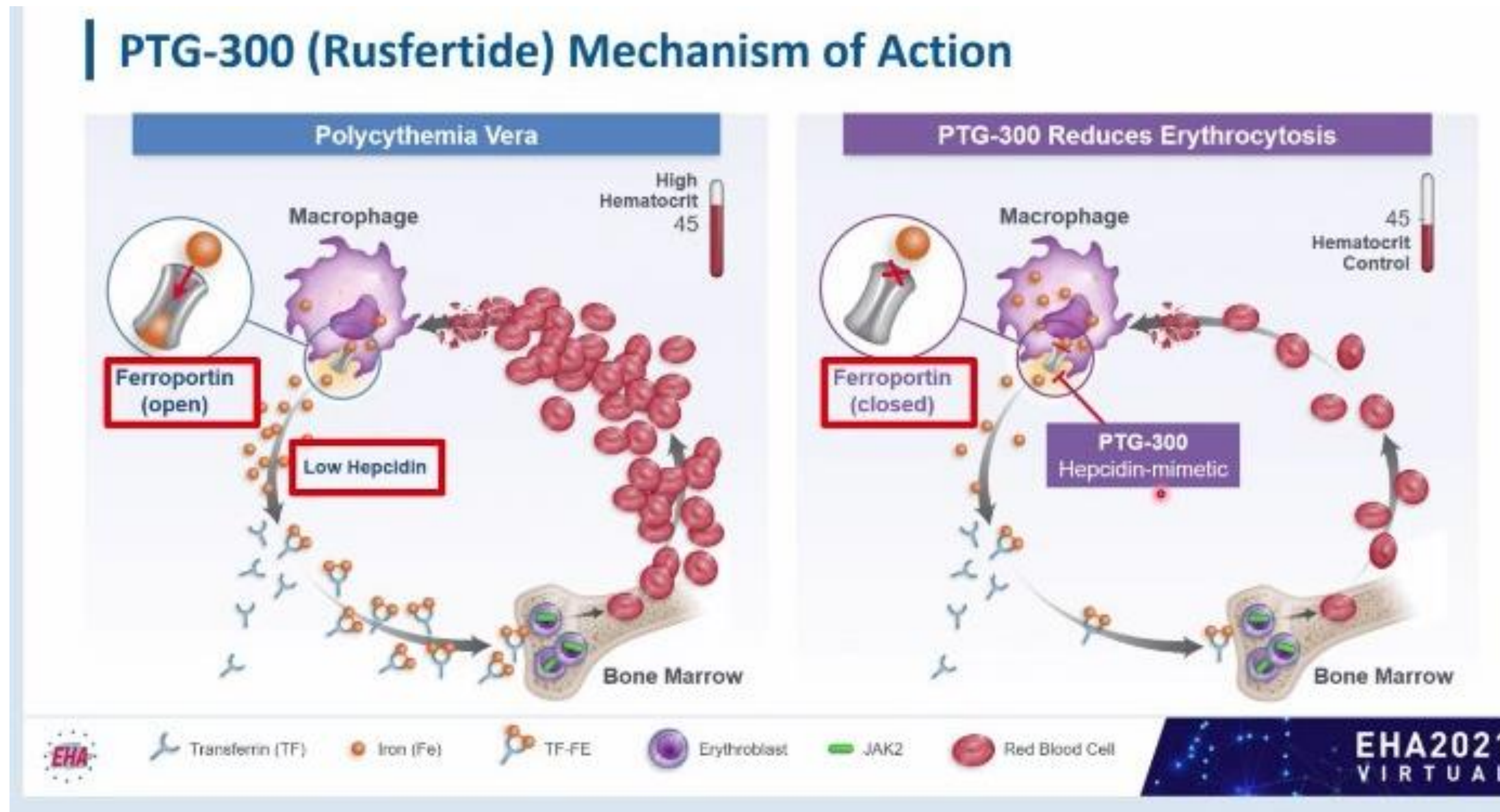
What about JAK2 allele burden in ruxolitinib treated patients?



Harrison, MAJIC-PV JCO 2023

Treatments under investigation

Rusferitide (PTG-300), hepcidin mimetic, PV



MGH trials for PV and ET

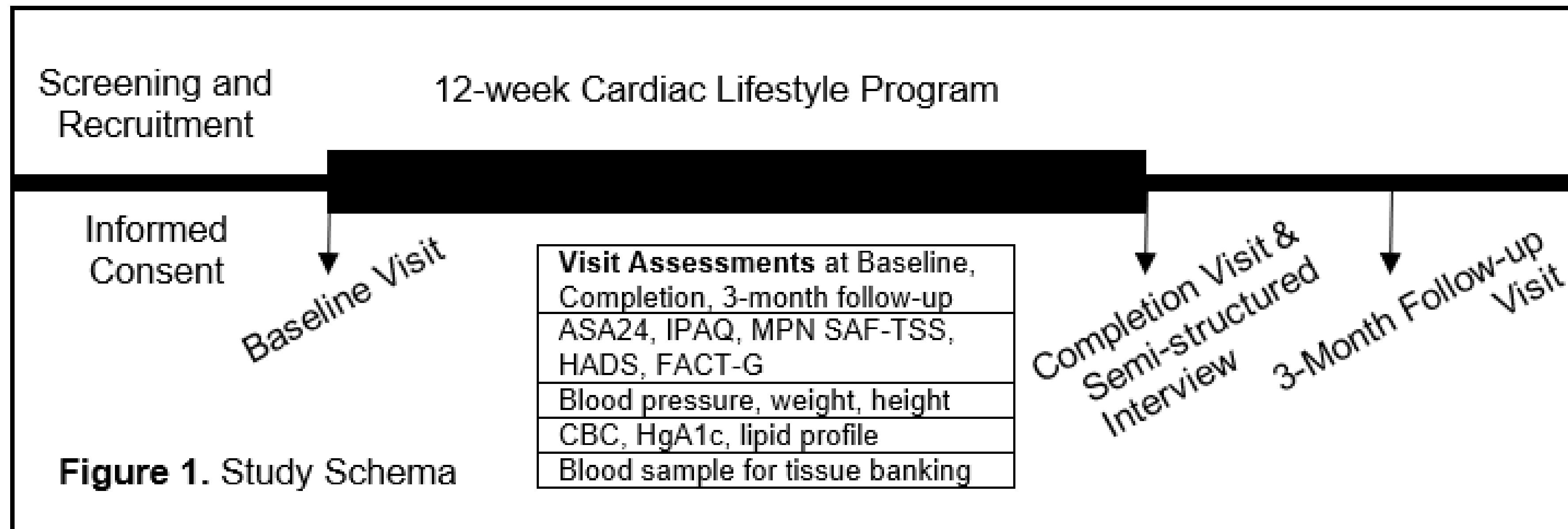
Ruxolitinib for low-risk PV and ET with significant symptoms

Lifestyle program for ET and PV patients

Ruxolitinib for low-risk and symptomoatic ET and PV patients

- (NCT04644211)
- Diagnosis of ET and PV with significant symptom burden measured by MPN-SAF
- Low-risk disease (no indication for cytoreduction for thrombosis prevention)
- Prior cytoreduction allowed if used for symptoms
- Minimal clinic burden
- Total accrual 60
- Thus far ~8 patients enrolled with adequate response and tolerability

Lifestyle intervention in ET/PV- I can **M**ove with **P**urpose **N**ow! (I can MPN!)



Visit Assessments at Baseline, Completion, 3-month follow-up
ASA24, IPAQ, MPN SAF-TSS, HADS, FACT-G
Blood pressure, weight, height
CBC, HgA1c, lipid profile
Blood sample for tissue banking

ASA24=Automated Self-Administered Dietary Assessment Tool; IPAQ=International Physical Activity Questionnaire; Myeloproliferative Neoplasm Symptom Assessment Form – Total Symptom Score; HADS=Hospital Anxiety and Depression Scale; FACT-G=Functional Assessment of Cancer Therapy – General; CBC=complete blood count; HgA1c=hemoglobin A1c; LDL=low density lipoprotein; VLDL=very low-density lipoprotein; HDL=high density lipoprotein; TAG=triglycerides

Thank you