Clinical trials and new therapies: ET and PV

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Thrombosis Risk-adapted Management of PV

Category	Characteristics
Low-risk	Age < 60 years and no history of thrombosis
High-risk	Age ≥ 60 years or history of thrombosis

Phlebotomy and low-dose ASA for all

ELN indications for cytoreduction

- High-risk PV, but also in low-risk PV in the following specific situations
  - Frequent PHL requirement
  - Severe disease-related symptoms
  - PLT count > 1,500 x 10^9/L (risk of bleeding!)
  - Progressive leukocytosis

Options for first-line cytoreduction include HU and IFN (and busulfan for very elderly patients)

ELN, European LeukemiaNet; HU, hydroxyurea; IFN, interferon; PHL, phlebotomy.

Barbui T, et al. J Clin Oncol. 2011;29:761-70.

ELN Consensus Criteria for Hydroxyurea Resistance and Intolerance in PV

Intolerance / resistance

- Need for PHL (Hct < 45%)
- PLT count > 400 x 10^9/L and WBC count > 10 x 10^9/L
- No reduction of spleen by 50%
- No reduction of spleen symptoms

→ After > 3 months at MTD or 2 g/day

- Cytopenias (any)
  - ANC < 1.0 x 10^9/L
  - Hb < 10^9/L
  - PLT count < 100 x 10^9/L

→ At lowest dose to achieve either a PR or CR by ELN criteria

- GI toxicity
- Fever
- Mucocutaneous toxicity
- Skin cancer

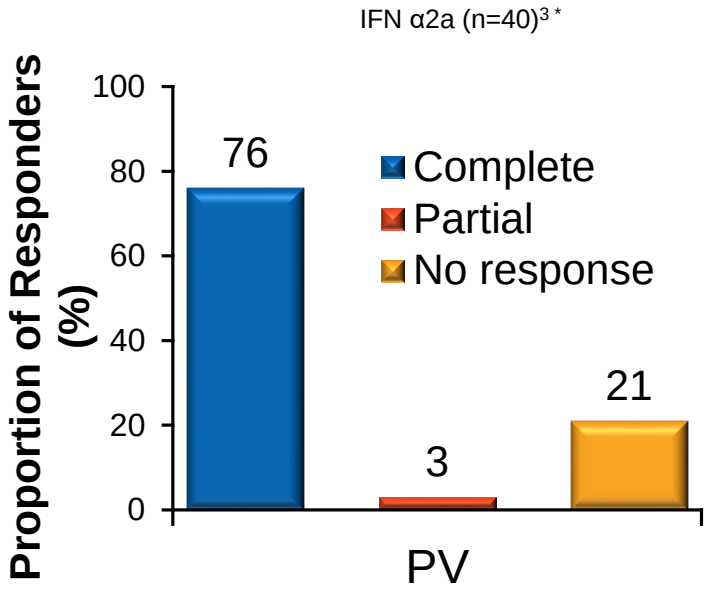
→ At any dose

GI, gastrointestinal; Hb, hemoglobin; MTD, maximum tolerated dose.

Barosi G, et al. *Br J Haematol*. 2010;148:961-3.

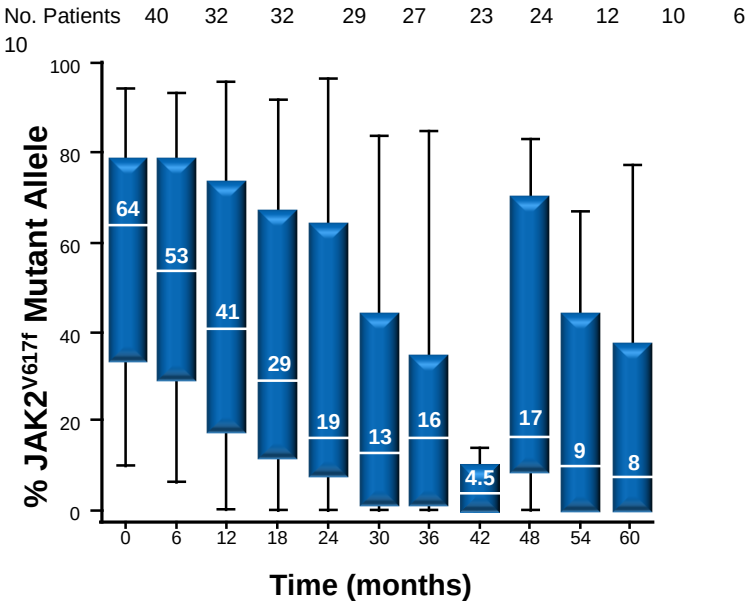
Pegylated Interferon-alpha 2a Is an Acceptable Alternative to HU in PV

<u>Phase II studies</u>: Treatment with PEG-IFN- α2a or α2b resulted in high rates of complete hematologic and molecular response (CMR), and low rates of thrombosis.[1-3]



*Complete response included absence of thrombosis

Median follow-up 42 months



1. Kiladjian JJ, et al. *Blood.* 2008;112:3065-72; 2. Quintas-Cardama A et al. *J Clin Oncol*. 2009;27:5418-24; 3. Quintas-Cardama A et al. *Blood.* 2013;122:893-901; 4. Masarova L, et al. *Lancet Haematol*. 2017;4:e165-e175.

PEG-IFN in Advanced PV: 7-Year Median Follow-Up

- Effective therapy

HR 80%, CHR 76%
- Response duration 66 months

>60% MR
- Duration 53 months
- Only CMR durable

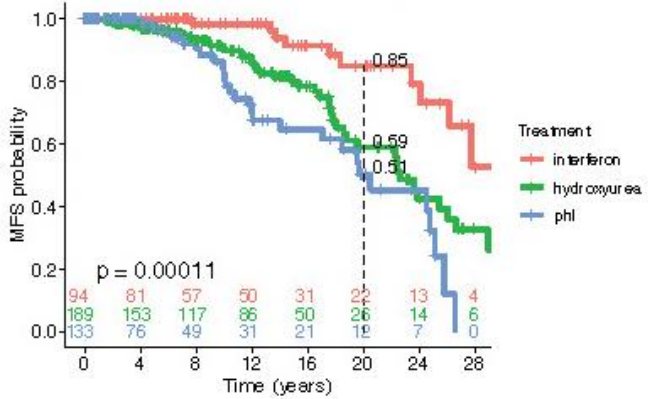
- Toxicity continues over time (~5%-10% per year)
- Discontinuation ~61% (35% for overt toxicity)
- Therapy failures occur (vascular events and progression)

Masarova L, et al. *Lancet Haematol*. 2017;4:e165-e175.

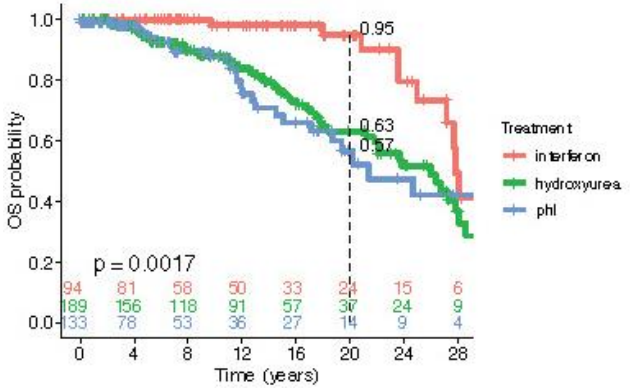
Effects of Recombinant Interferon-α Treatment in PV

- Retrospective study of 470 patients with PV treated with rIFN-α, HU (hydroxyurea), or PHL-O (phlebotomy)
- Myelofibrosis-free survival (MFS) and overall survival (OS) were better with interferon treatment
- Treatment with PHL-O was associated with a higher risk of MF than either rIFN-a or HU

MFS of patients by treatment group



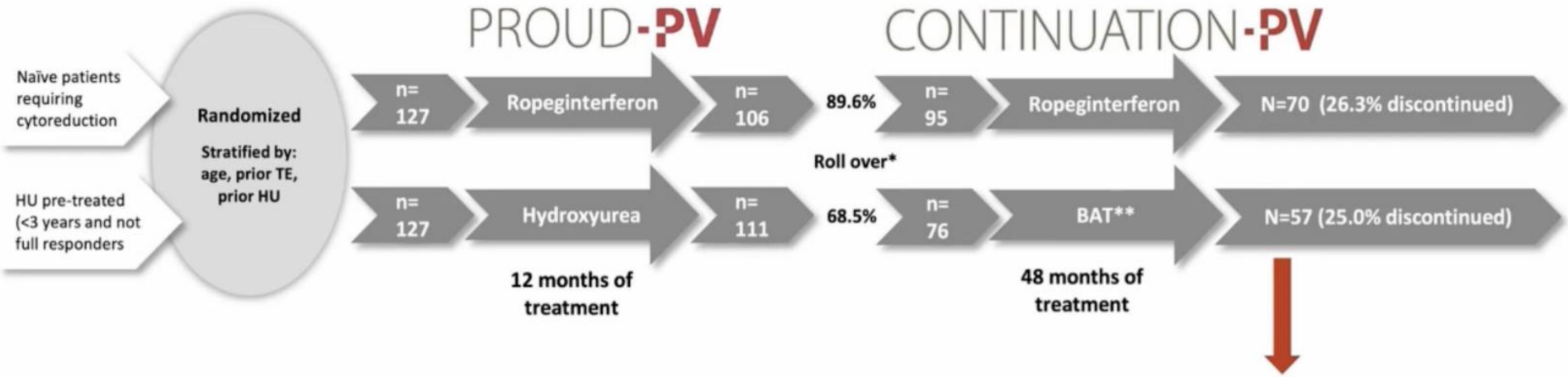
OS of patients by treatment group



Abu-Zeinah G, et al. *Blood*. 2020;136(Supplement 1):31-32.

Ropeginterferon alfa-2b: PROUD-PV and CONTINUATION-PV Design

- **CONTI-PV was initially planned as a single-arm extension of PROUD-PV to evaluate long-term safety and efficacy of ropeginterferon alfa-2b[1]**
- **A second arm (HU/BAT) was added later for comparison.[1]**



* There were no significant differences between patients who entered CONTINUATION-PV study and those who did not roll-over.
** Control group received best available treatment (BAT); 88% of patients received HU as of last available assessment)

60 MONTH INTERIM ANALYSIS:
Efficacy data up to month 60
All safety data up to database lock on 29.05.2020
(up to 6.3 years of treatment overall)

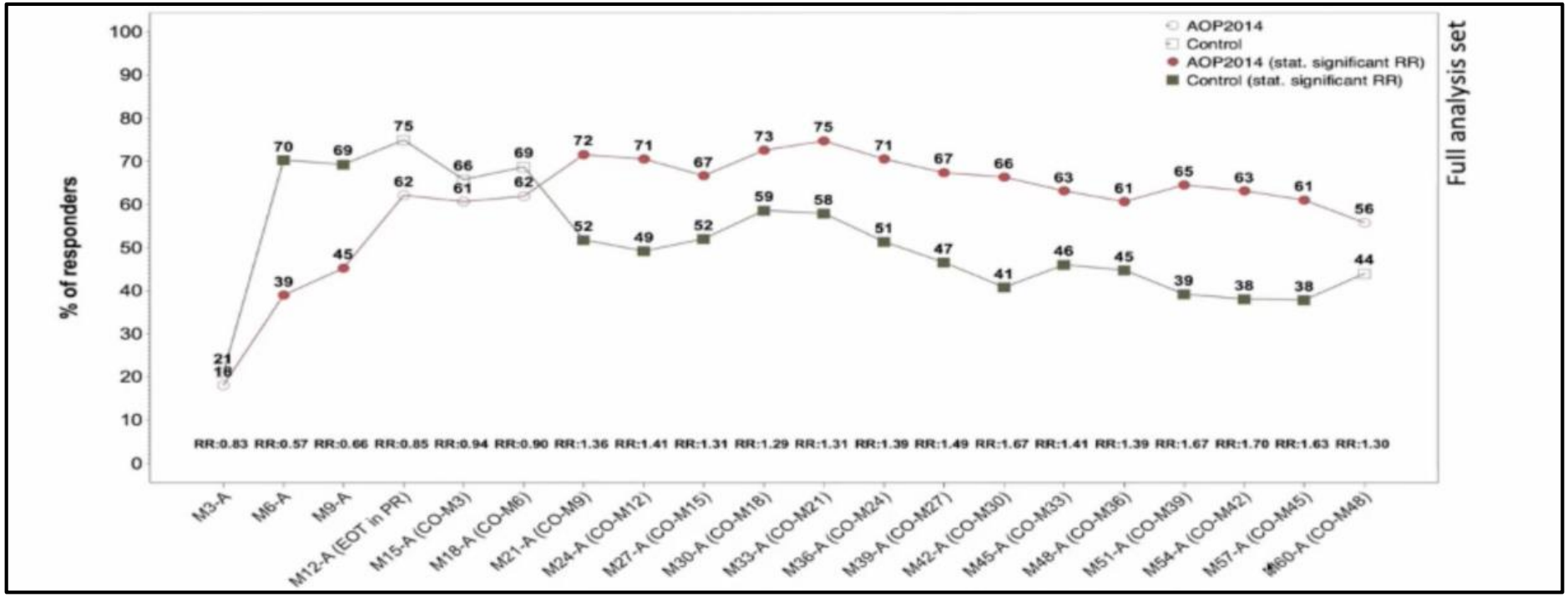
1. Gissingler et al., (2020). Long-term use of Ropeginterferon alpha-2b in PV: 5-year Results from a Randomized controlled Study and Its Extension. ASH 2020 Presentation.

Complete Hematological Response (CHR)

Definition of CHR:

- Hct<45% and no phlebotomy for at least 3 months
- PLTs<400 x 10^9/L
- WBCs<10 x 10^9/L

Discontinued patients were counted as non-responders



1. Gissingler et al., (2020). Long-term use of Ropeginterferon alpha-2b in PV: 5-year results from a randomized controlled study and Its extension. ASH 2020

Adverse Drug Reactions of Special Interest to IFN Therapy*

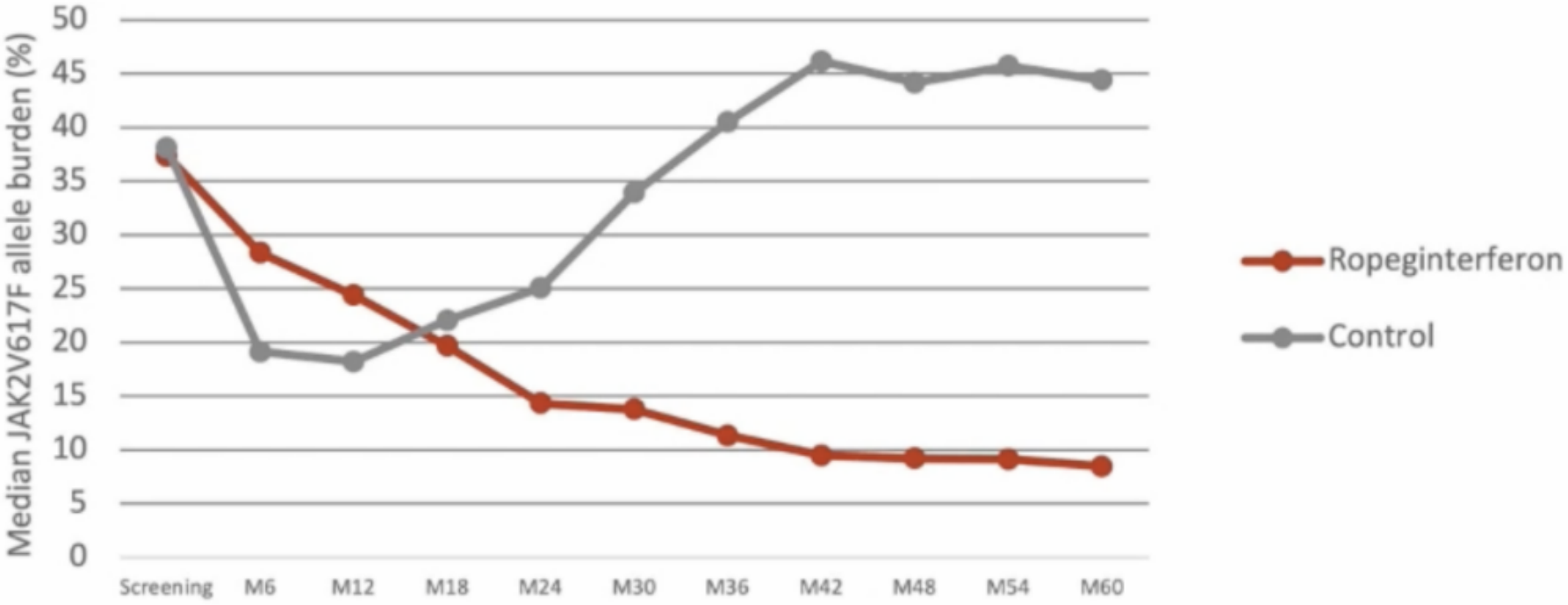
In Ropeginterferon-treated patients (N=127)

**Treatment related AEs of special interest to IFN therapy as assessed by investigator.*

Disorders by system organ class	N (%) in ropegIFN arm
Endocrine	**6 (4.7%)**
Autoimmune thyroiditis Hypothyroidism Hyperthyroidism	2 (1.6%) 4 (3.1%) 1 (0.8%)
Psychiatric	**1 (0.8%)**
Depression, anxiety, altered mood, nervousness	1 (0.8%)
Musculoskeletal / connective tissue	**2 (1.6%)**
Rheumatoid arthritis Sjögren syndrome	1 (0.8%) 1 (0.8%)
Skin / subcutaneous tissue	**2 (1.6%)**
Psoriasis Increased antinuclear antibody	1 (0.8%) 1 (0.8%)
Immune system / blood and lymphatic system	**1 (0.8%)**
Sarcoidosis	1 (0.8%)

1. Gissingler et al., (2020). Long-term use of Ropeginterferon alfa-2b in PV: 5-year Results from a Randomized controlled Study and Its Extension. ASH 2020

Median *JAK2* V617F Allele Burden



1. Gissingler et al., (2020). Long-term use of Ropeginterferon Alpha-2b in PV: 5-year Results from a Randomized controlled Study and Its Extension. ASH 2020.

Feasibility of Interferon Discontinuation in MPNs

- 381 patients treated with interferon-alpha (IFN) therapy
- Median driver variant allele frequency (VAF) at time of IFN therapy initiation was 34%
- Complete hematological remission (CHR) in 77.2%
- After a median follow-up of 72.4 months from IFN initiation:
  - 250 patients had discontinued therapy

- IFN discontinuation is a safe strategy in MPN patients who achieved CHR and driver VAF <10% at time of discontinuation

- VAF ≥ 10% at time of IFN discontinuation was independently associated with
  - higher cumulative incidence of relapse after IFN discontinuation
  - lower long-term CHR without therapy

De Oliveira R, et al. *Blood*. 2020;136(Supplement 1):35-36.

Ruxolitinib in PV: RESPONSE Study

- Resistance to or intolerance of HU[a]
- PHL requirement
- Splenomegaly[b]

Pre-randomization (Day −28 to Day −1) Hct 40–45%

Randomized 1:1

Ruxolitinib 10 mg X2/day

n = 110

Week 32 (primary endpoint)

Week 48 (primary data cut-off)

Extended treatment phase

Week 80 (planned analysis)

Week 256

BAT

n = 112

Crossover to ruxolitinib

Week 256

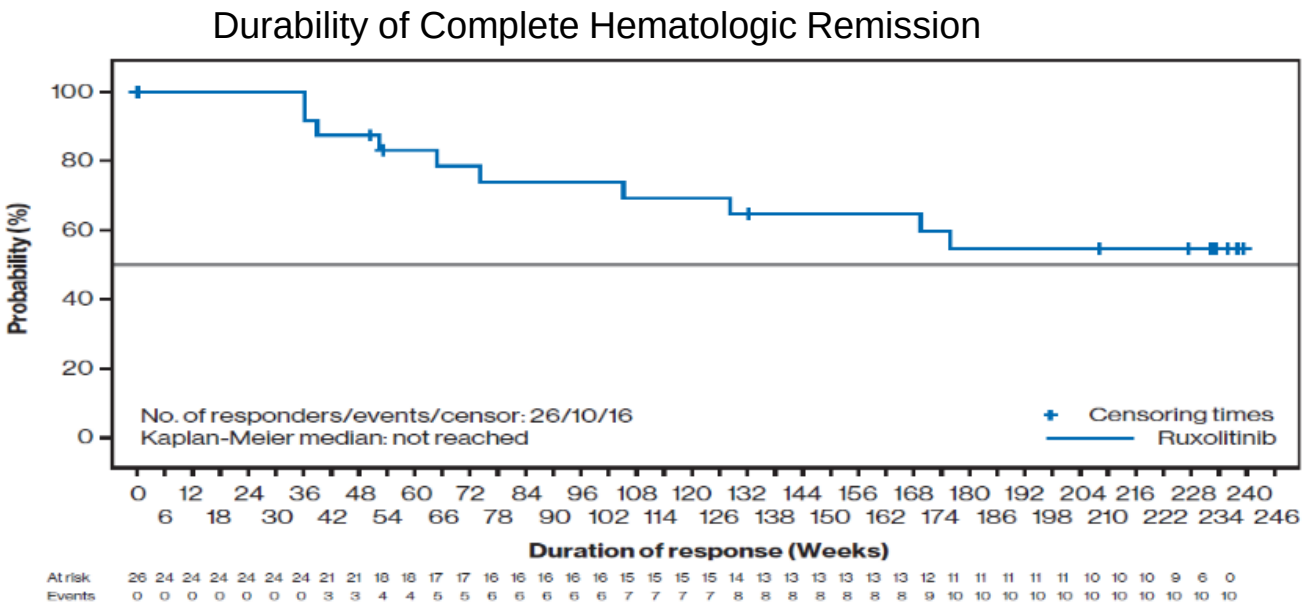
Compared with BAT, results showed that ruxolitinib led to

- Superior control of Hct
- Superior control of CBC (including WBCs and PLTs)
- Superior reduction in splenomegaly
- Superior reduction in PV-related symptoms
- Fewer TEs

[a] Modified ELN criteria.
[b] Spleen volume ≥ 450 cm^3.
BAT, best available therapy;
CBC, complete blood count.

Vannucchi AM, et al. *N Engl J Med.* 2015;372:426-35.

Long-term RESPONSE Study Results



- The K-M estimate of duration of **maintaining CHR** (HCT control, platelet count ≤ 400 × 109/L, and WBC count ≤ 10 × 109/L) for 224 weeks (starting from week 32) was **0.55** (95% CI: 0.32, 0.73)

Kiladjian; abstract 1753, ASH 2018

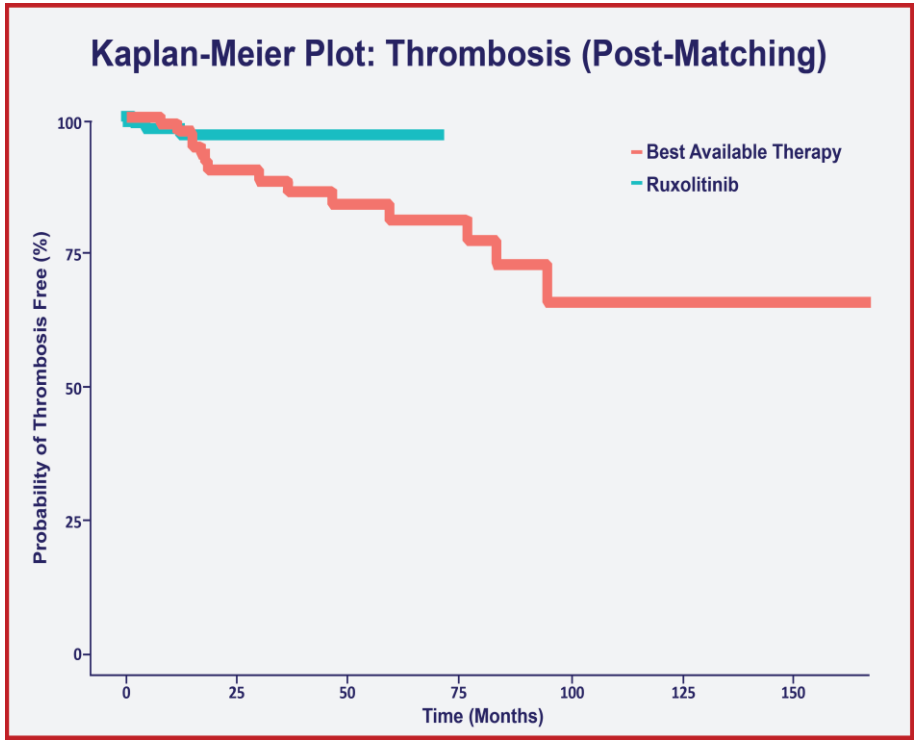
Exposure-adjusted Rates (per 100 patient-year) of Thromboembolic Events

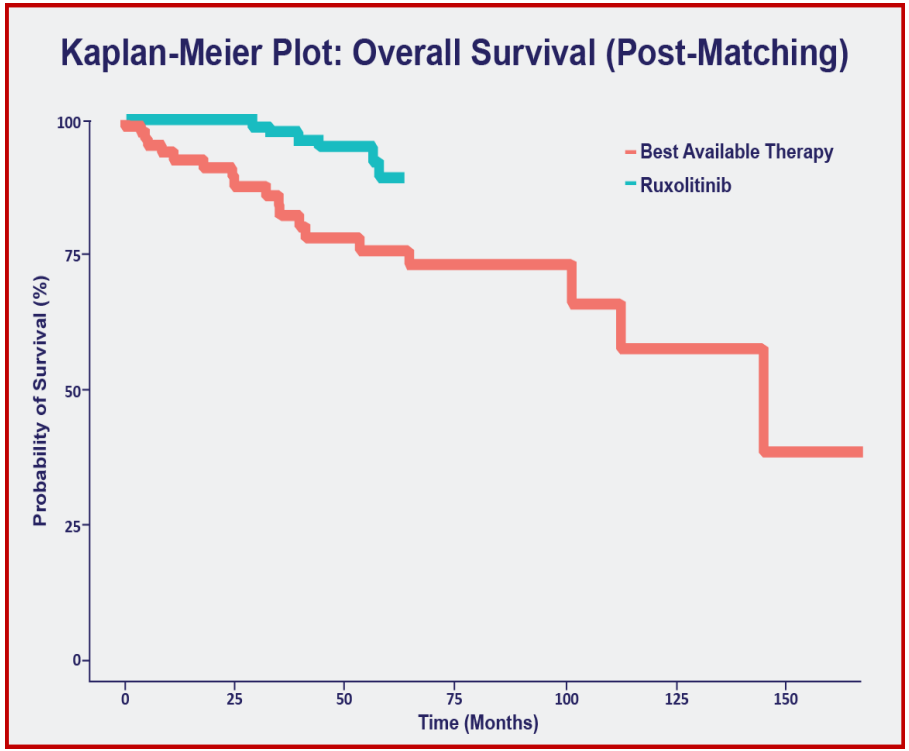
Event[a,b]	Ruxolitinib Rate per 100 Patient-Year of Exposure N = 110 Exposure = 428.4 Patient-Year		BAT Rate per 100 Patient-Year of Exposure N = 111 Exposure = 73.6 Patient-Year		Crossover Rate per 100 Patient-Year of Exposure N = 98 Exposure = 329.9 Patient-Year	
Number of Patients (Rate[b])	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
All thromboembolic events	5 (1.2)	3 (0.7)	6 (8.2)	2 (2.7)	9 (2.7)	5 (1.5)
Cerebral infarction	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic stroke	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)
Portal vein thrombosis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.2)	1 (0.2)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Retinal vascular thrombosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)
Acute Myocardial Infarction	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.4)	1 (0.3)	0 (0.0)
Thrombophlebitis	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)
Thrombosis	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)
Bone infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Coronary artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Disseminated intravascular coagulation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Splenic infarction	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Events occurring in ≥ 0.2% of patients in any group. MedDRA version 19.1 was used to code the events.

[b] Adjusted rates were calculated as the number of patients with events per 100 patient-year of exposure.

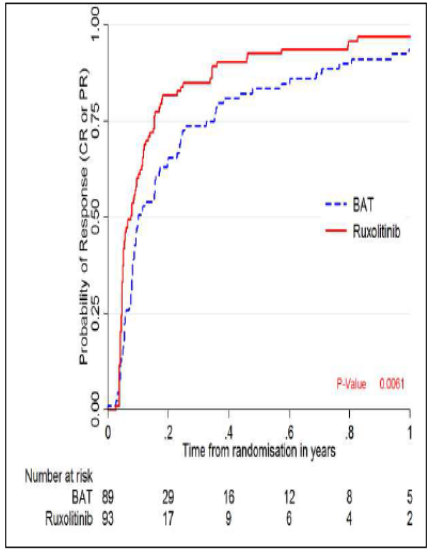
Comparison of Ruxolitinib Response and Real-world BAT (Spanish Registry) regarding OS and Thrombosis in Patients with PV Who Are Resistant or Intolerant to Hydroxyurea (EHA, Larran et al., 2018)



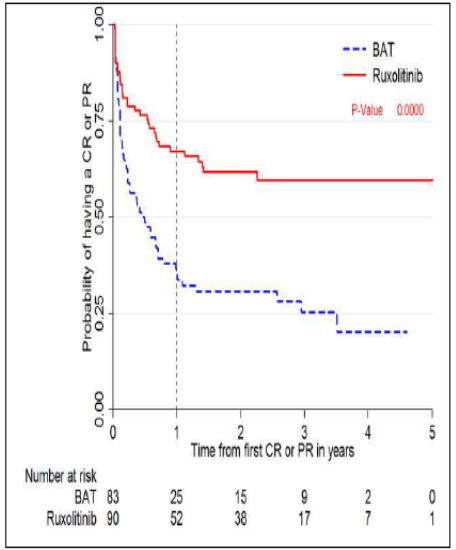


MAJIC STUDY

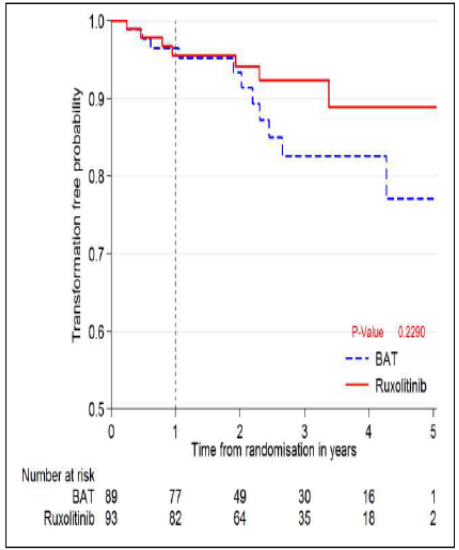
Speed of attaining response



Duration of overall response



Transformation free survival



- MAJIC PV is a UK randomised phase II study, in 190 PV patients resistant/intolerant to HU.
- The primary objective is to evaluate the activity (CHR at 1 year) of RUX compared to BAT (mainly, HU and IFN)
- The secondary objective is to evaluate the molecular response by *JAK2*V617F allele burden quantification

Curto-Garcia N. Jun 16, 2019; 267361; S1607

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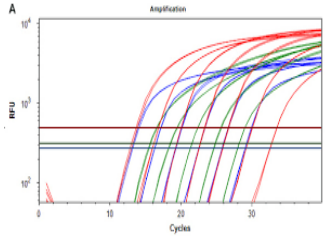
What about molecular response?

190 PV PATIENTS RANDOMIZED 1:1 RUX AND BAT

BASELINE & 1 YEAR WHOLE BLOOD OR GRANULOCYTE SAMPLES

JAK2 *V617F* by qPCR *



Analysis results according to ELN guidelines and correlation with clinical endpoints

**Bench A.J et al, Methods in Molecular Biology, 2013*

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Correlation between molecular and clinical endpoints

NO SIGNIFICANT CORRELATION

- Best haematological response within 1 year (p= 0.22)
- Haemorrhagic events (p= 0.83)

SIGNIFICANT CORRELATION

<u>Thrombosis</u>

- No thrombotic event for patients in PR
- No response 18/94 patients NR at least 1 thrombotic event (p=0.01)
- PROG +/++ & thrombotic event (p=0.07)

<u>PFS</u>

- PR better PFS (p=0.039)

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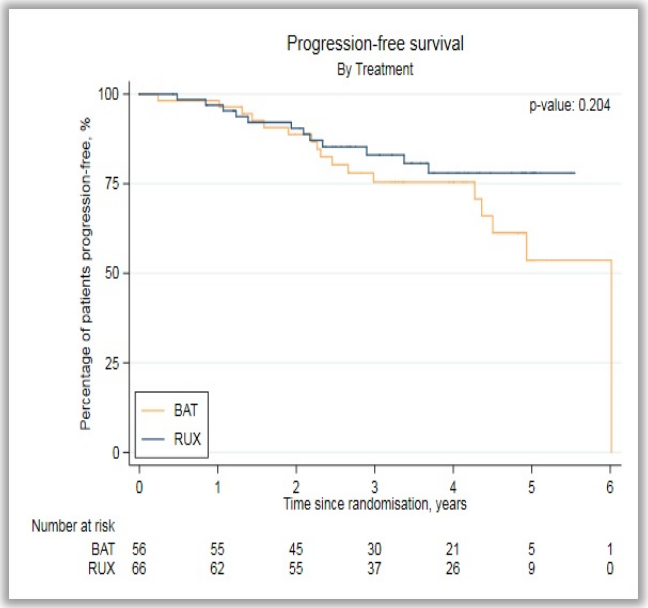
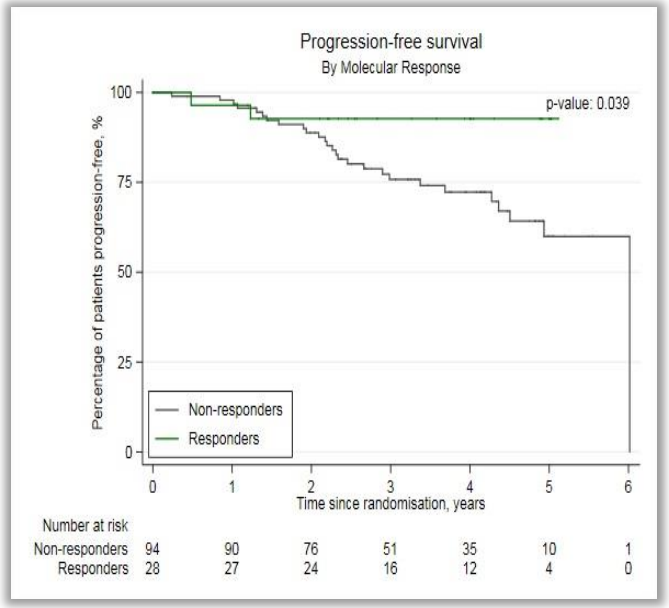
Curto-Garcia N. Jun 16, 2019; 267361; S1607

Progression-free survival





Curto-Garcia N. Jun 16, 2019; 267361; S1607

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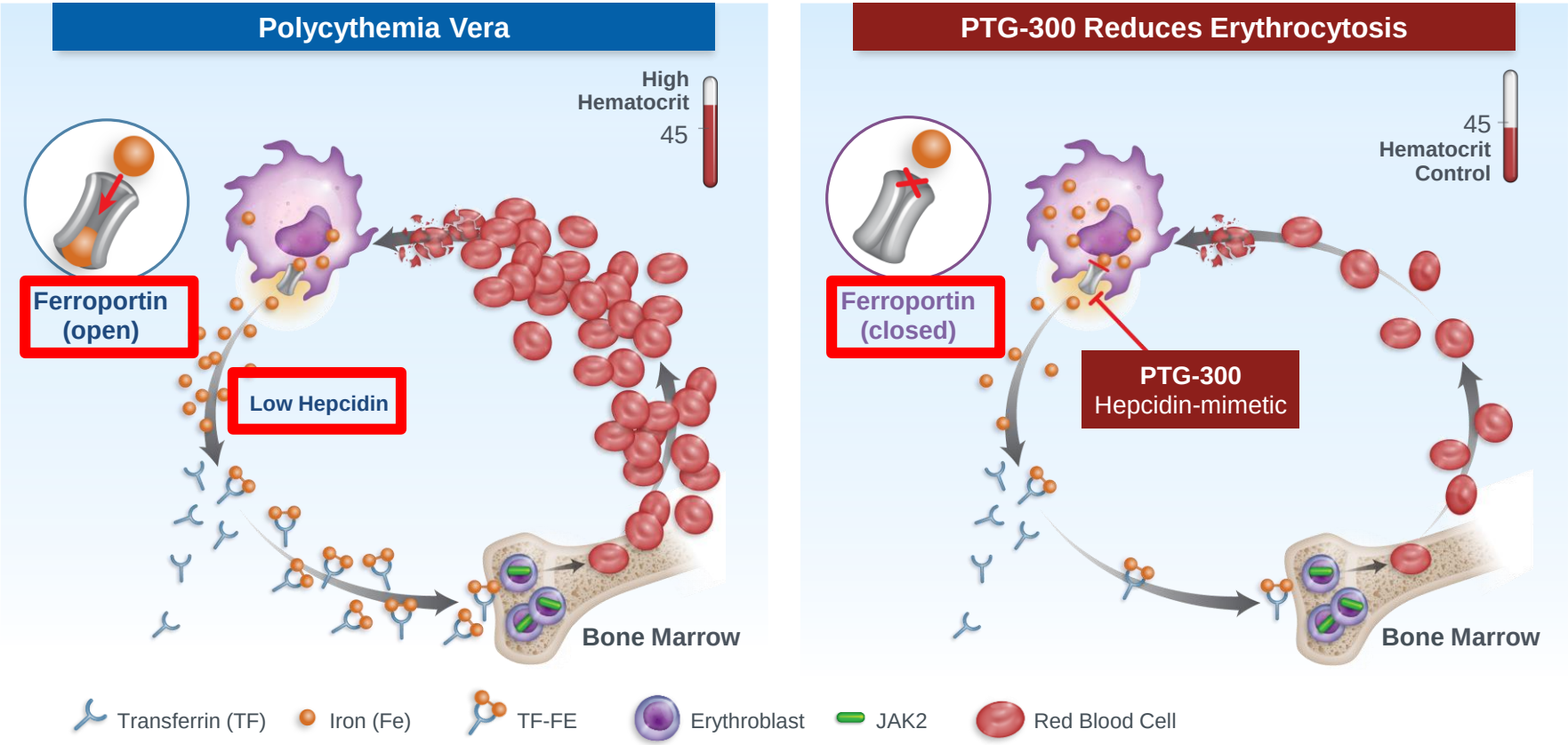
A question for the future?

A phase III, randomised, open-label, Multicenter International Trial comparing ruxolitinib with either HydRoxycarbamIDe or interferon Alpha as **first line** ThErapy for high risk polycythemia vera

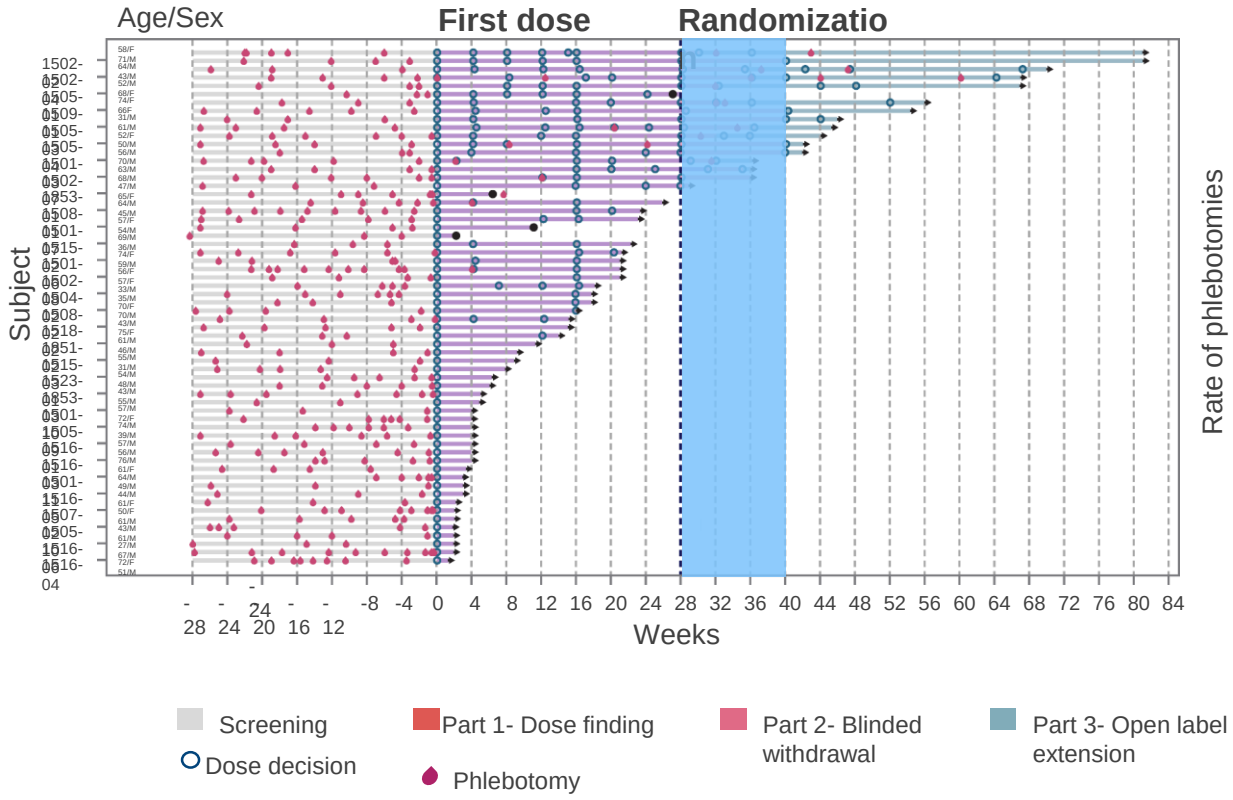
Primary end point:
Composite of thrombosis, haemorrhage or transformation
Will prospectively validate benefit of reduction of JAK2 allele burden

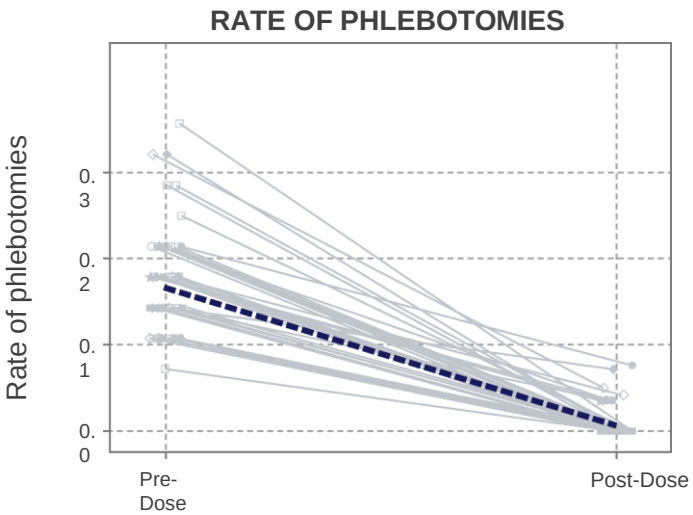
Eligibility:
Diagnosed <10 years, treated <5 years, High risk PV with WBC ≥11 (at any time)

PTG-300 (Rusfertide) Mechanism of Action

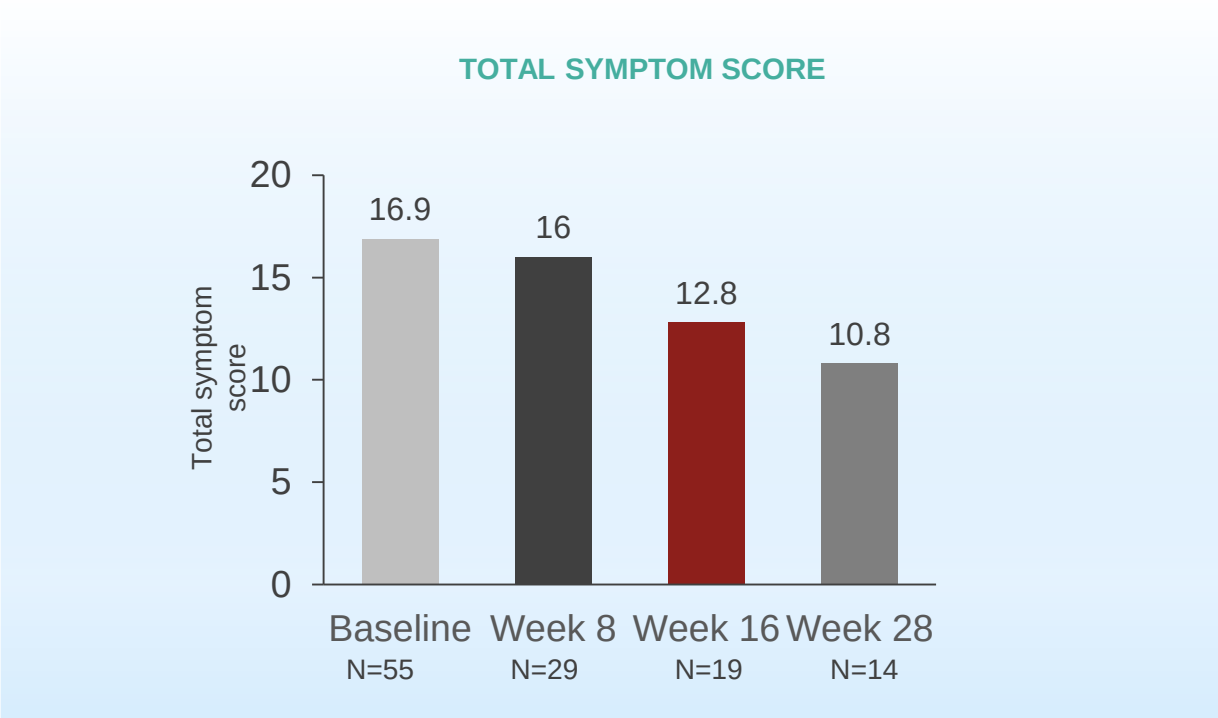


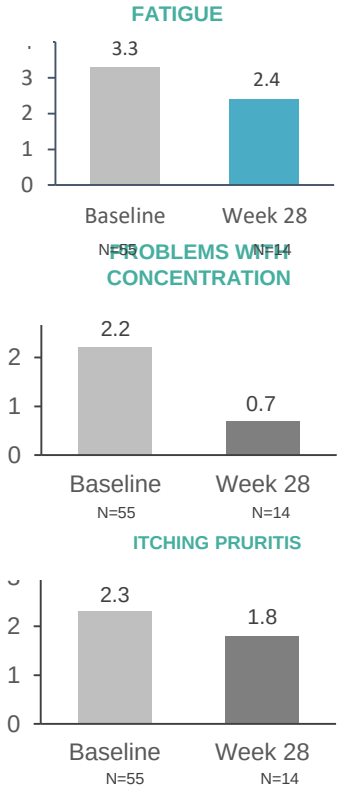
Therapeutic Phlebotomies Prior to and on PTG-300





Improvement in MPN-TSS Scores following PTG-300

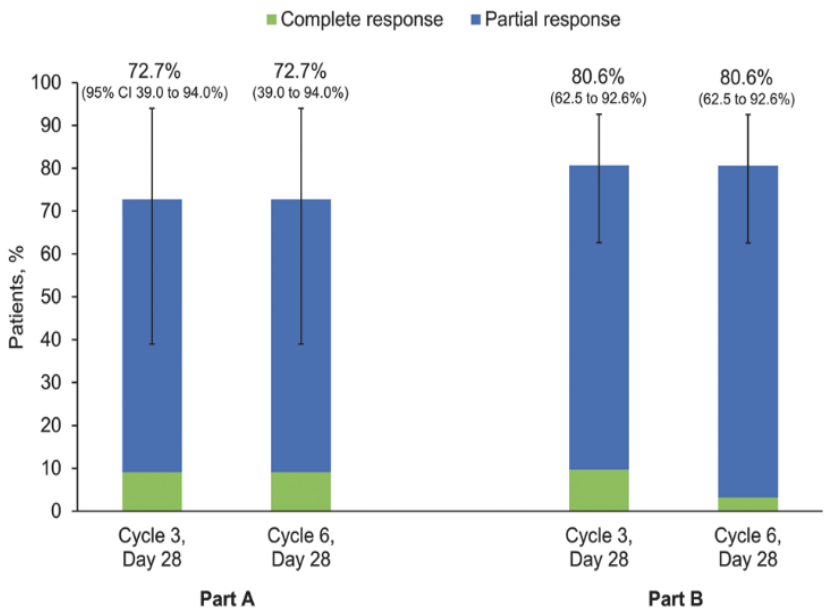




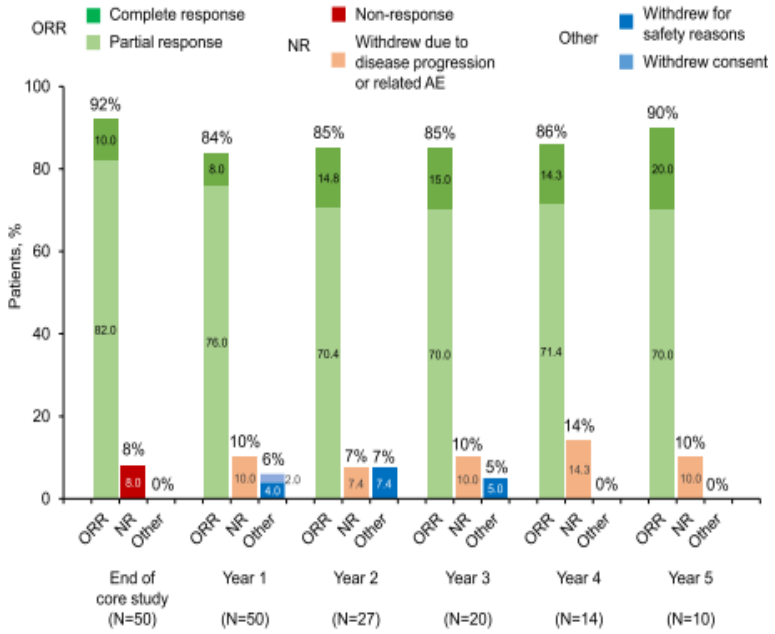
Givinostat Is a Well Tolerated HDACi That Induces Clinical Responses in PV Patients

- Givinostat is a histone-deacetylase inhibitor (HDACi)

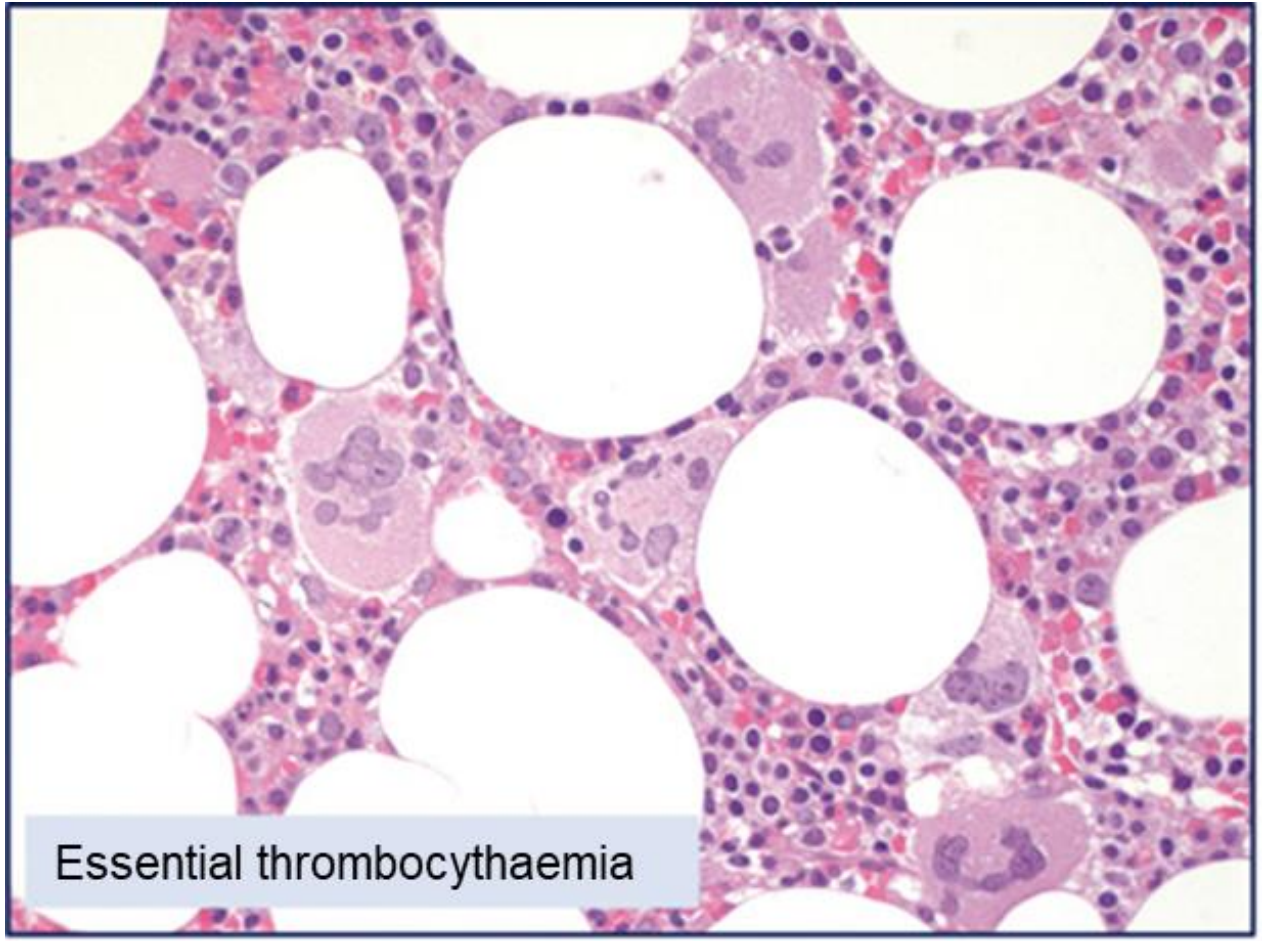
Phase 1b/2 Study[1]



3 Studies, 4-Year Mean Follow-Up[2]



1. Rambaldi A et al. *Leukemia.* 2020;34(8):2234-2237; 2. Rambaldi A et al. *Blood Cancer J.* 2021;11(3):53 (long-term follow up of an open-label, long-term study of 51 PV patients who received clinical benefit from givinostat in previous studies or on compassionate use)


Essential thrombocythaemia

On-going issues in ET?

Normal platelet count?

<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

Uncertain long-term benefit

Recent consensus publication CALR positive ET

Alvarez-Larran Lancet Haematology 2021

Key recommendations included

- careful observation for asymptomatic patients with classical, low-risk, CALR-mutated ET without cardiovascular risk factors

- caution in the use of antiplatelet therapy for symptomatic patients at low risk with platelet counts of 1000-1500 × 10^9 platelets per L, in such cases cytoreduction is an adequate option, especially if adquired Von Willebrand disease is present

- cytoreduction is recommended for extreme thrombocytosis (platelet count >1500 × 10^9 platelets per L) with pegylated interferon alfa being the preferred option for younger patients; both hydroxycarbamide and anagrelide might be given to patients ineligible for pegylated interferon alfa

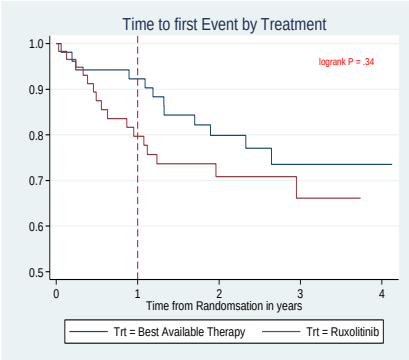
- treatment algorithms for patients with high-risk pregnancies should not be changed according to genotype.

Ruxolitinib in ET

MAJIC

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

- No difference in CHR at 1 yr
  - 46.5% Rux, 44.2% BAT
- No difference in survival
- No difference in transformation, thrombosis or haemorrhage



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Harrison et al, Blood 2017

A Phase 2 Study of the LSD1 Inhibitor IMG-7289 (Bomedemstat) in Patients with Essential Thrombocythemia

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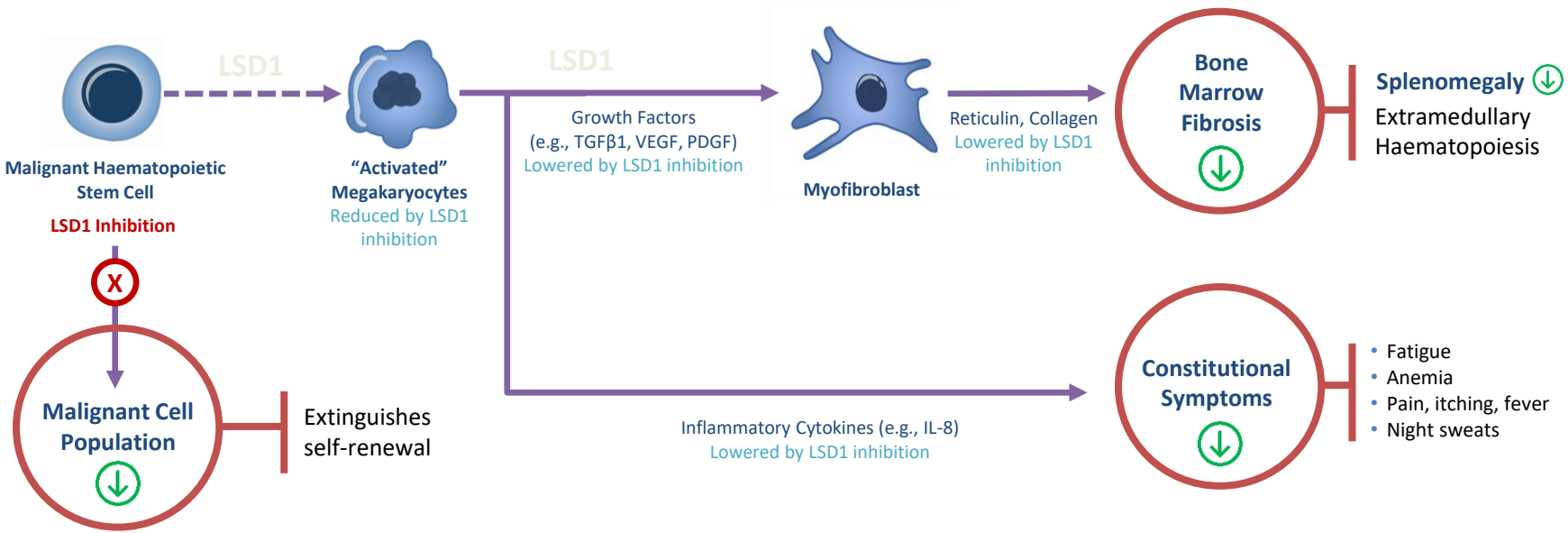
Strong Rationale for LSD1 Inhibition in MPNs

- Regulates the proliferation of haematopoietic stem cells and is essential for the differentiation of megakaryocytes and granulocytes
- Inhibiting LSD1 can reduce the hallmark symptoms of MPNs as well as lower the number of cells with the mutations that drive these diseases



Study Design

- **Phase 2 Study of IMG-7289 in Patients with Essential Thrombocythemia *(Multicentre, International Study)***

Primary Endpoints:

- Safety and tolerability
- Platelet count reduction (≤400 x 10^9/L) in the absence of thromboembolic events

Exploratory Endpoints:

- Durability of platelet and WBC count reduction
- Changes in cytokine profiles
- Symptom reduction (MPN-SAF TSS)
- Changes in mutant allele frequencies (MAF)

Key Eligibility Criteria:

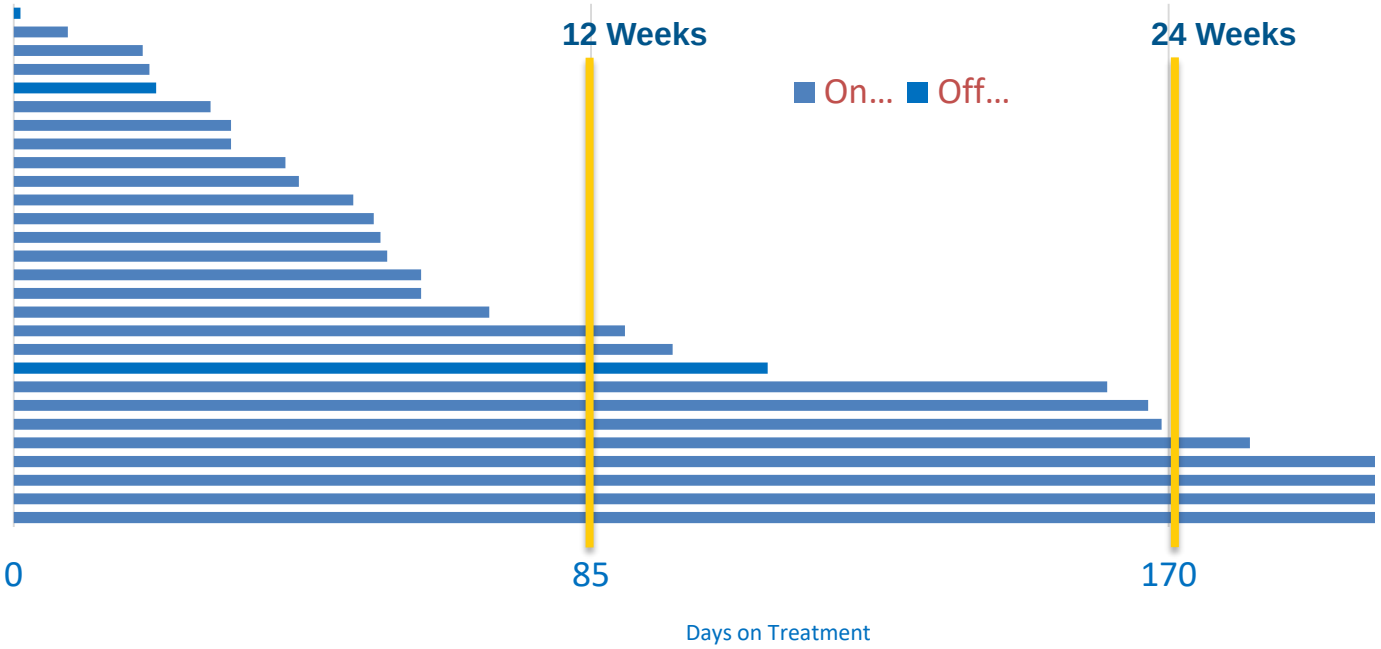
- Dx of ET
- High-risk classification
- Failed at least one standard therapy
- **Platelets >450 x 10^9/L**
- Peripheral blasts <1%
- Fibrosis Score <2 per protocol criteria
  - (Arber et al., 2016)
- Haemoglobin >10 g/dL

- Source: Imago interim and unaudited Phase 2 data

Enrollment and Treatment Duration

N=28 with 89% on study

Median Duration of Treatment: 58 days



- Source: Imago interim and unaudited Phase 2 data

IMAGO BIOSCIENCES

Safety and Tolerability Profile of Bomedemstat

Cumulative Safety Experience

- No dose limiting toxicities at 6 mg/kg/d
- No safety signals in >4 years with IMG-7289
- No genotoxicity

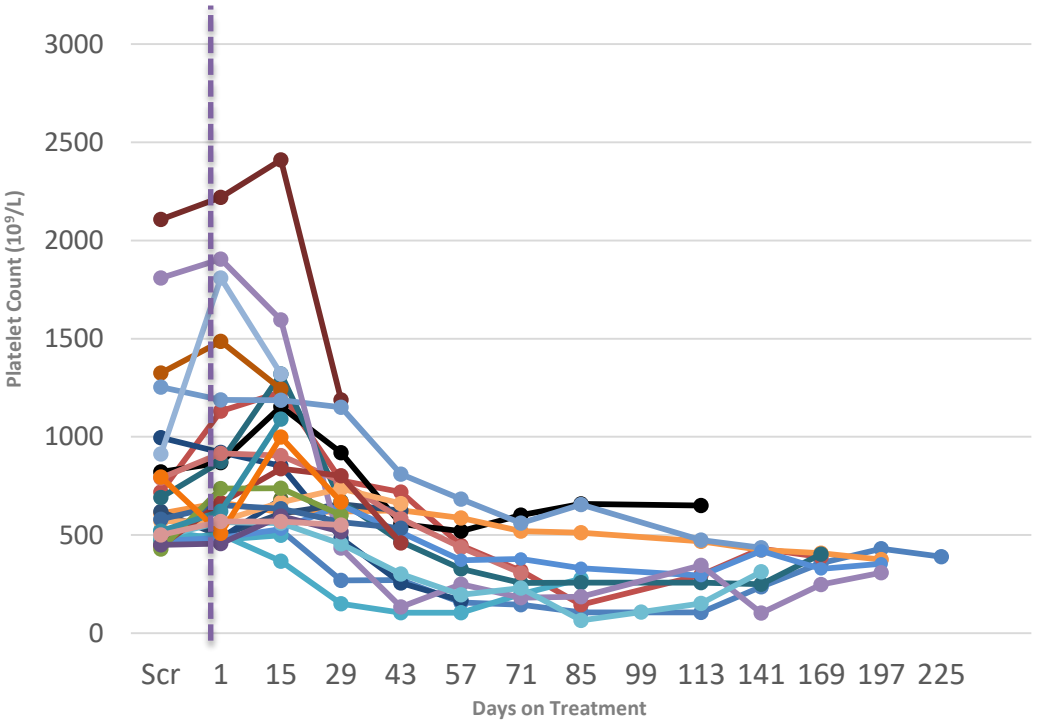
CTP-201 ET Study

- 19 patients reported 160 AEs, 78 attributed to IMG-7289 by the Investigator
- The most common non-hematologic AEs related to IMG-7289 were dysgeusia and diarrhea (Each n=4, 14% of patients)
- 1 SAE attributed by Investigators as unrelated to IMG-7289

Source: Imago interim and unaudited Phase 2 data

Bomedemstat in ET: Patients Achieve Normal Platelet Counts

- **Phase 2: Platelet Counts**



- At Week 12, 100% (10/10) patients showed reduction in platelets
  - Mean reduction of 547 x 10^9/L
- 91% of patients dosed for ≥6 weeks will have achieved a platelet count of <400 x 10^9/L

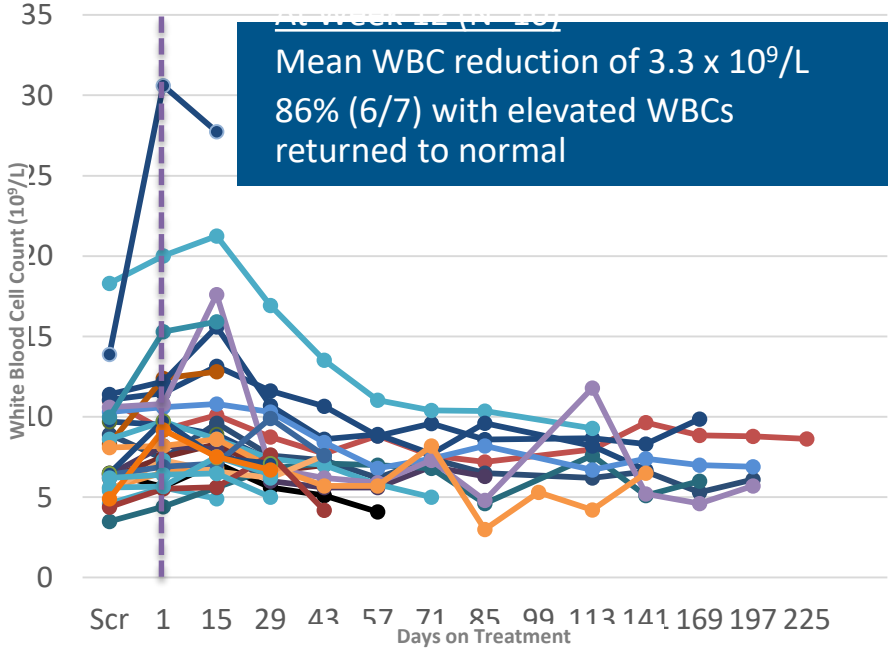
- Scr = Screening

Source: Imago interim and unaudited Phase 2 data

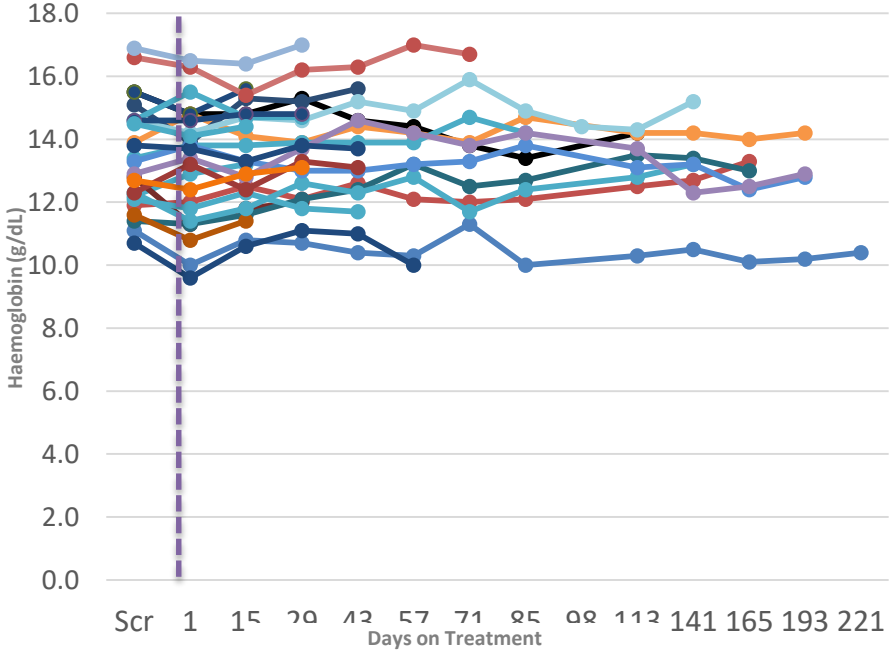
IMAGO BIOSCIENCES

Bomedemstat in ET: Controls WBCs and Maintains Hb levels

- **White Blood Cells (WBC)**



Hemoglobin (Hb)



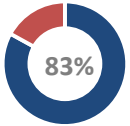
- *Pt removed due to in/exclusion violation

Source: Imago interim and unaudited Phase 2 data

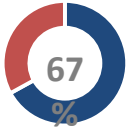
IMAGO BioSciences

Bomedemstat in ET: Total Symptom Score (TSS)

OVERVIEW:
TSS Change at 12 weeks
(Patients with scores >10 at Day 1)



5/6 **(83%)** had a decrease in TSS

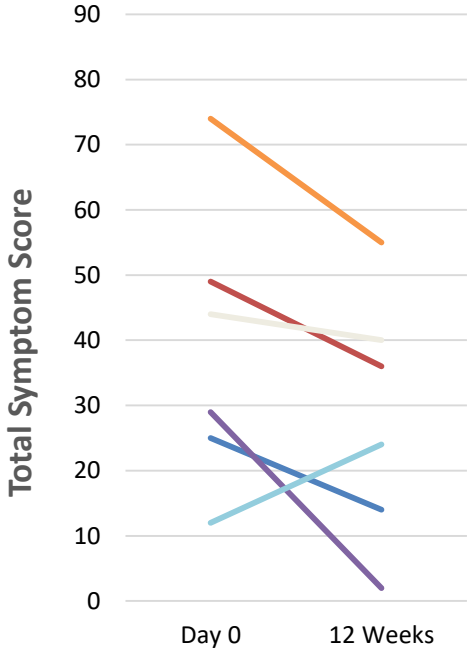


4/6 **(67%)** had a decrease of >10 points

No patient had splenomegaly

Change in MPN-SAF TSS

Absolute Change @ 12 ± 2 weeks



Source: Imago interim and unaudited Phase 2 data

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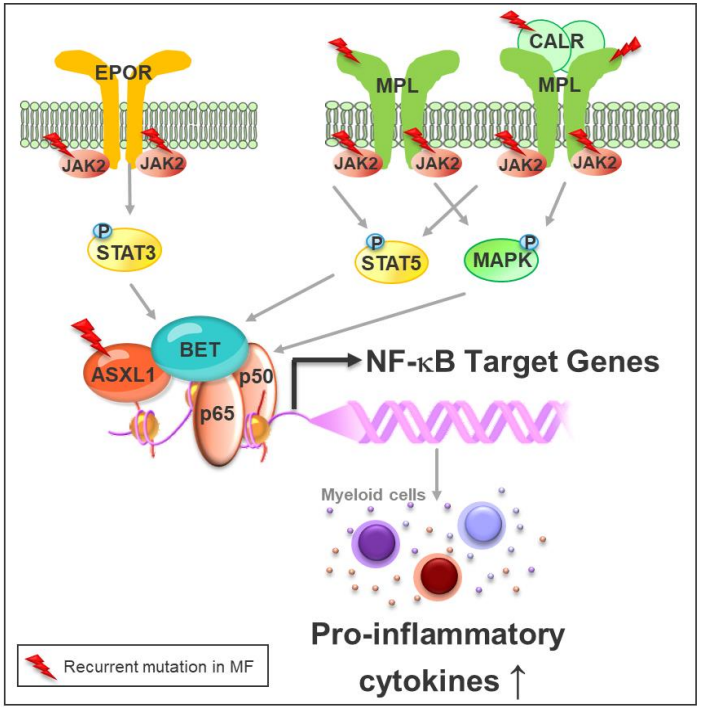
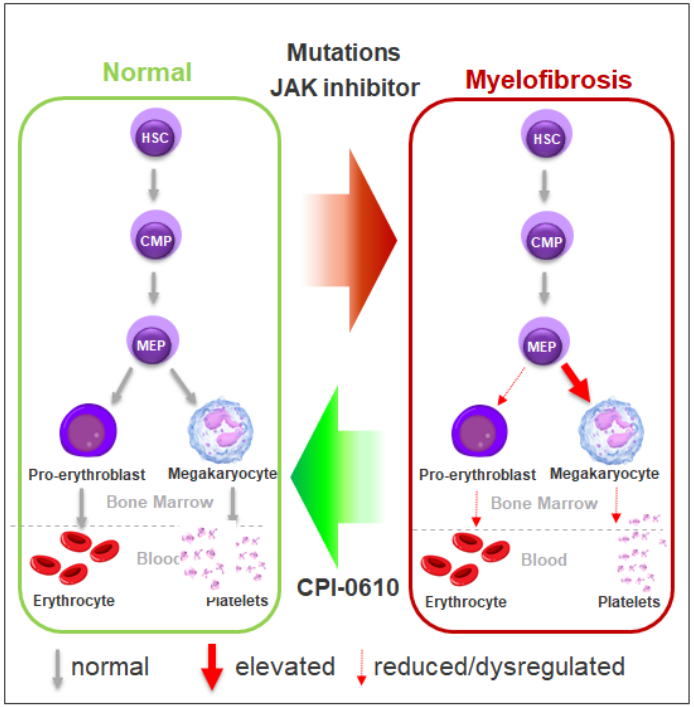
Mechanism of potential disease modification in MPN – BET inhibition

CPI-0610 reduces inflammatory cytokines



CPI-0610 affects megakaryocyte differentiation



- Reduce inflammation and suppress cells in the bone marrow that drive myelofibrosis

Adapted from Verstovsek S *et al.* EHA 2020. Poster Presentation EP1083; Mascarenhas J *et al.* EHA 2020. Poster presentation EP1084; Talpaz M *et al.* EHA 2020. Poster presentation EP1091.

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MANIFEST study design overview

	Study population	Treatment	Arm/Cohort	Primary endpoint
Arm 1	**Second line:** No longer on ruxolitinib Refractory or intolerant to ruxolitinib or ineligible for JAKi	CPI-0610 Mono	Cohort 1A: TD n=up to 60 patients	TD → TI
			Cohort 1B: Non-TD n=up to 25 patients	SVR35
Arm 2	**Second line:** "Add-on" to ruxolitinib Suboptimal response or MF progression	CPI-0610 + Ruxolitinib	Cohort 2A: TD n=up to 60 patients	TD → TI
			Cohort 2B: Non-TD n=up to 25 patients	SVR35
Arm 3	**First line:** No prior JAK inhibitor use	CPI-0610 + Ruxolitinib	JAKi naïve n=64 patients enrolled	SVR35

Also being tested in ET

JAKi, JAK inhibitor; TD, transfusion-dependent; TI, transfusion-independent; SVR35, ≥35% spleen volume reduction from baseline.
TD→TI: TD to TI conversion.
Verstovsek S et al. EHA 2020. Poster Presentation EP1080; Mascarenhas J et al. EHA 2020. Poster presentation EP1084; Talpaz M et al. EHA 2020. Poster presentation EP1081.

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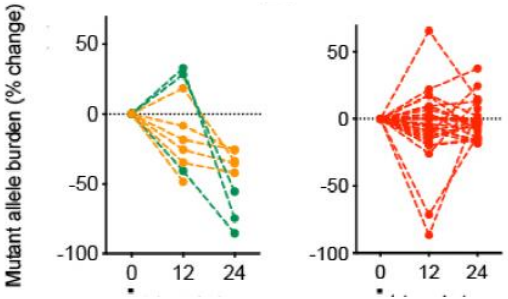
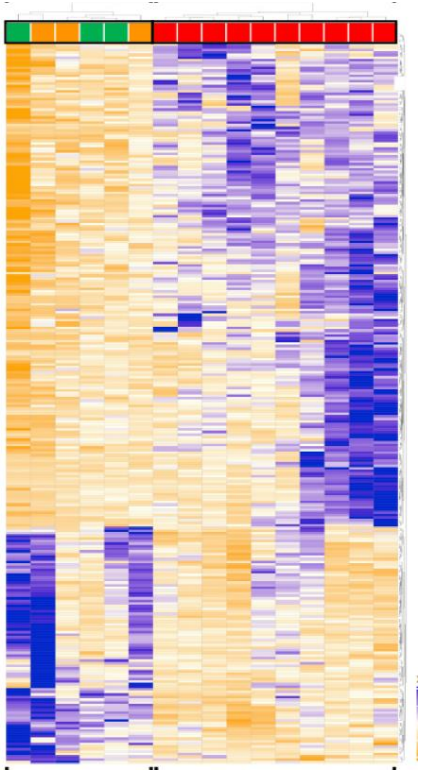
Repurposing of Tamoxifen

Mendes-Ferrer/Harrison/ UK ASH 2020

42 MPN patients with stable disease treated with Tamoxifen

Aims:
Molecular response
Safety & tolerability





Met endpoint for achieving molecular response

Not brilliantly tolerated

Interesting data regarding prediction of responders

Treatment options in ET and PV

ET

PV

1st line

Hydroxycarbamide

Standard 1st-line
Very long-term risks uncertain

Interferon-alfa

Off-label; option in pregnancy or if uncertain risks of HC undesirable

2nd line

Anagrelide

Monitor BM for fibrosis

Hydroxycarbamid

Interferon-alfa

Ruxolitinib

HC-refractory / intolerant

Busulphan, pipobroman, ^{32}P

Patients without long life expectancy

Experimental therapy

- HDACi (givinostat)
- Telomerase inhibition (imetelstat)……X
- MDM2 antagonist (idasanutlin)……X
- Tamoxifen
- CPI0610 Pelabresib
- IMG7289 Bomedemstat

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