New Treatments for Polycythemia Vera

Marina Kremyanskaya MD PhD

Icahn School of Medicine at Mount Sinai

What are the Goals of Treatment for PV?

Improve	Prevent	Decrease	Alleviate
Improve survival!	Prevent disease progression to myelofibrosis and MPN blast phase	Decrease the incidence of thrombotic and hemorrhagic events •Hematocrit control	Alleviate systemic symptoms

Current Drugs:

- IFN
- Ruxolitinib

New Drugs in Development

Rusfertide (Protagonist Therapeutics)

Divesiran (Silence Therapeutics)

Sapablursen (Ionis)

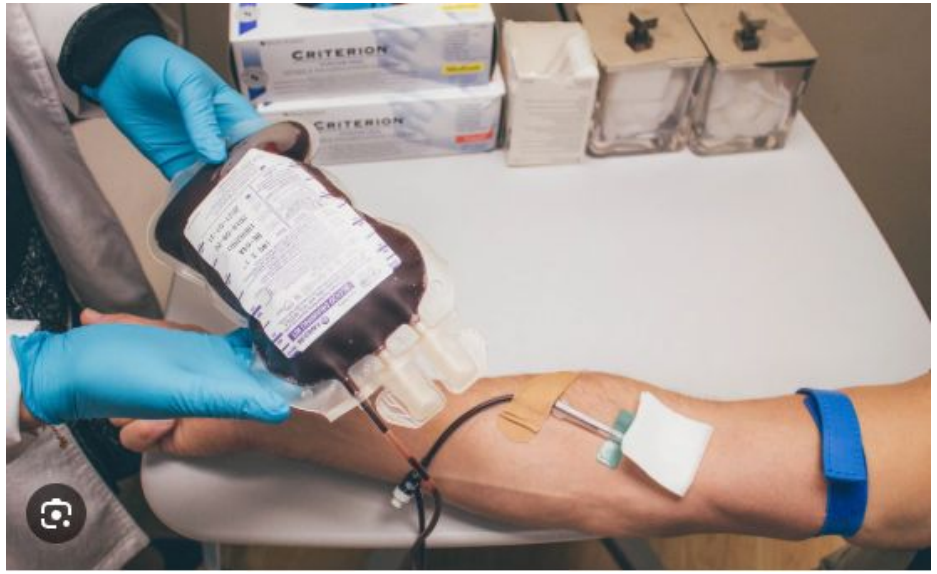
Givinostat (Italfarmaco)

Polycythemia Vera Treatment

- What is the main problem in PV?

  Too much blood is being produced by the bone marrow

- What is the main form of treatment in PV?



What are the potential problems with phlebotomies?

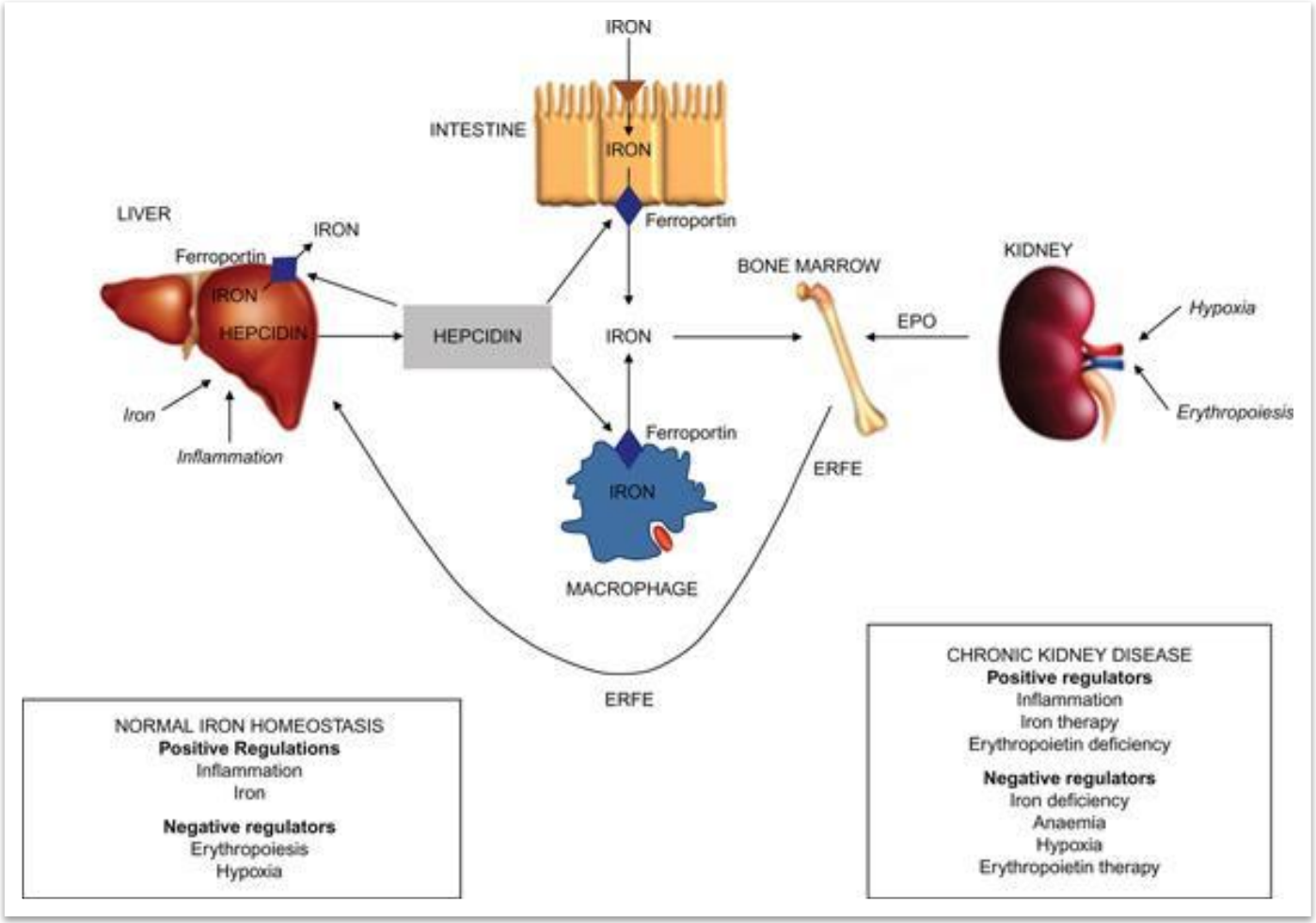
- Hematocrit level is not maintained at goal, but goes up and down
- Phlebotomies can worsen iron deficiency and result in worsening symptoms
  - Difficulties concentrating (brain fog)
  - Itching
  - Fatigue
- Some people physically or emotionally do not tolerate phlebotomies
  - Anxiety
  - Poor venous access
  - Fainting

Can we avoid phlebotomies for some patients?

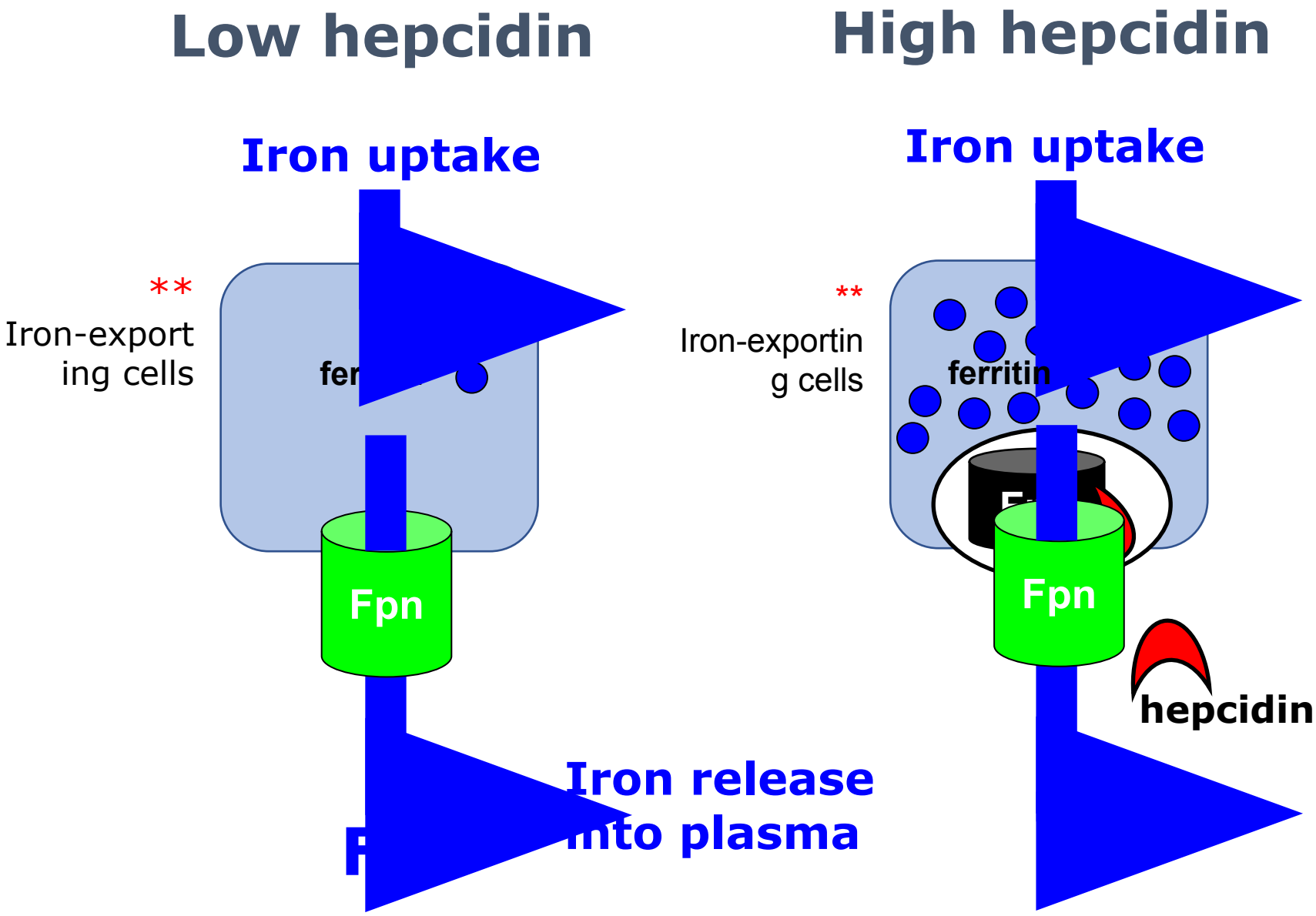
Yes. Cytoreductive Therapies

And new drugs affecting the hepcidin pathway

Hepcid/Iron Pathway and Regulation of RBC Production in the Bone Marrow

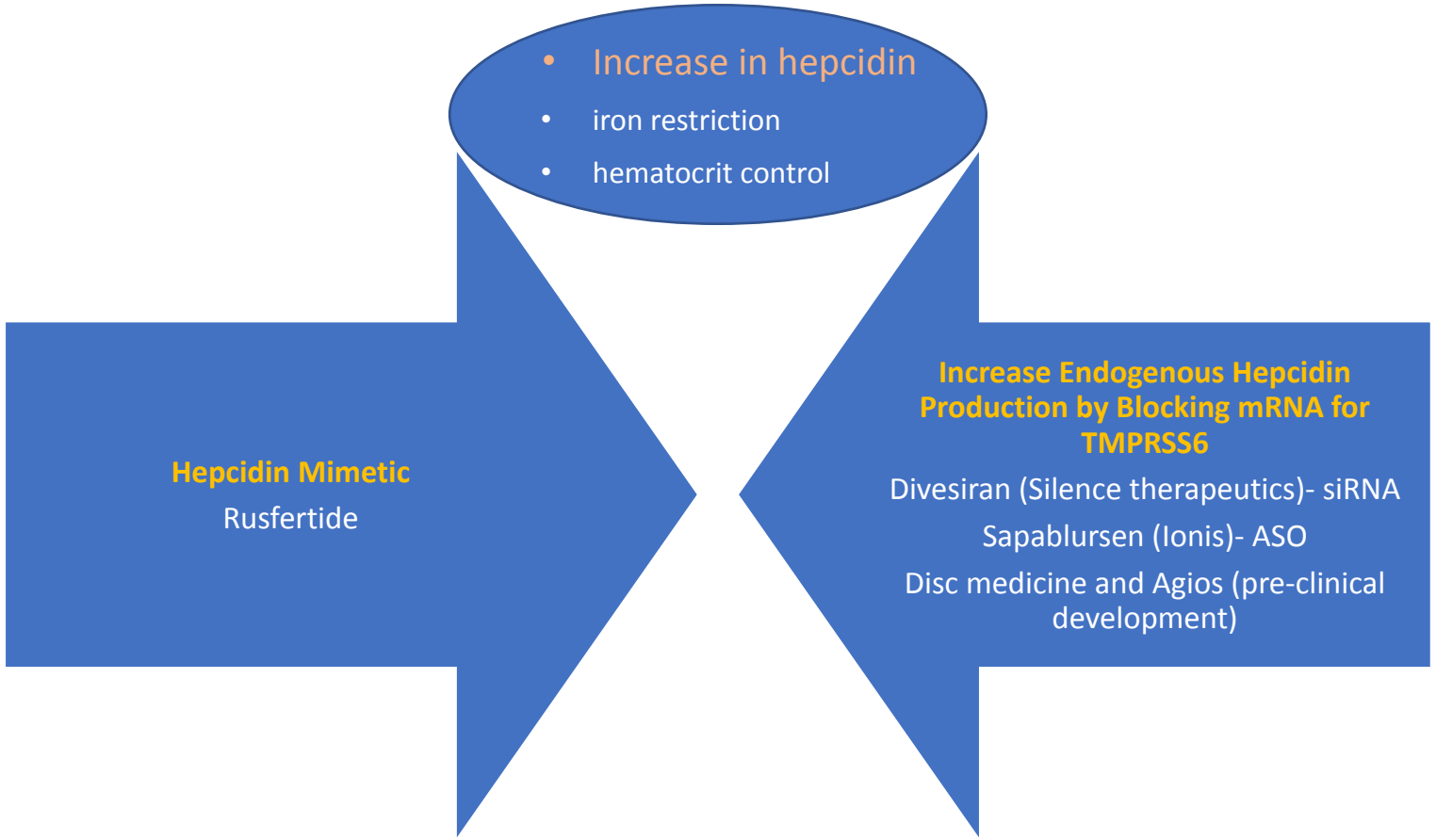


Hepcidin is produced by the liver and regulates uptake of iron from the gut and release of iron from iron storing cells

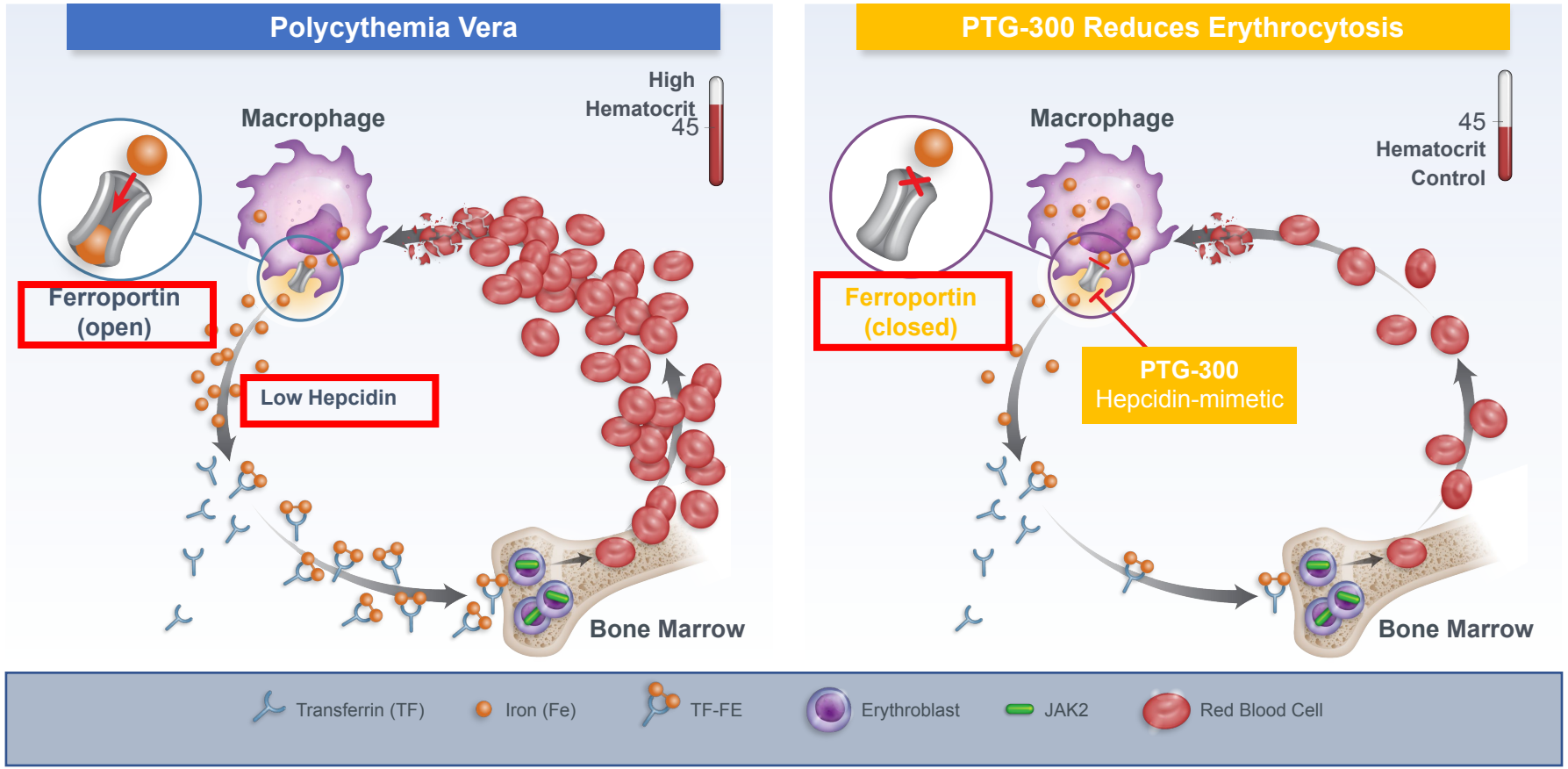


** e.g. duodenal enterocytes, macrophages, hepatocytes

Current Approaches to Target Hepcidin Pathway in Polycythemia Vera

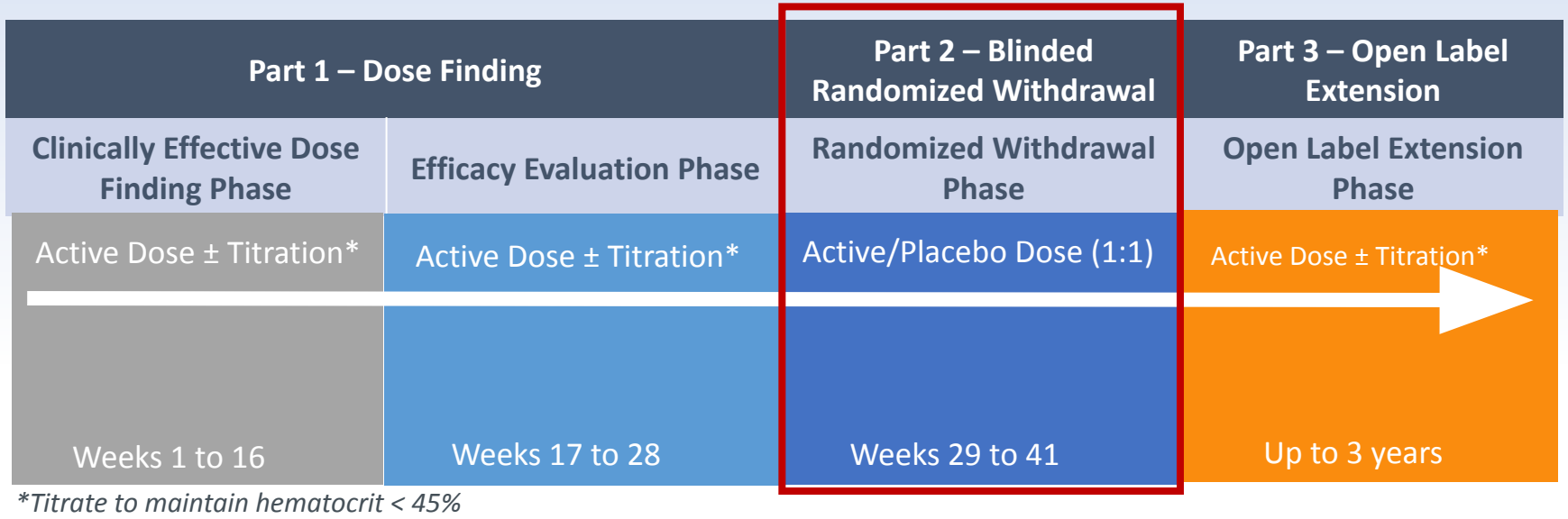


Hepcidin-mimetic Rusfertide Mechanism of Action in PV



Phase 2 Study of Rusfertide in PV Patients (REVIVE)

Clinical Proof-of-Concept Study with Add-On Rusfertide



**Titrate to maintain hematocrit < 45%*

STUDY ELIGIBILITY:

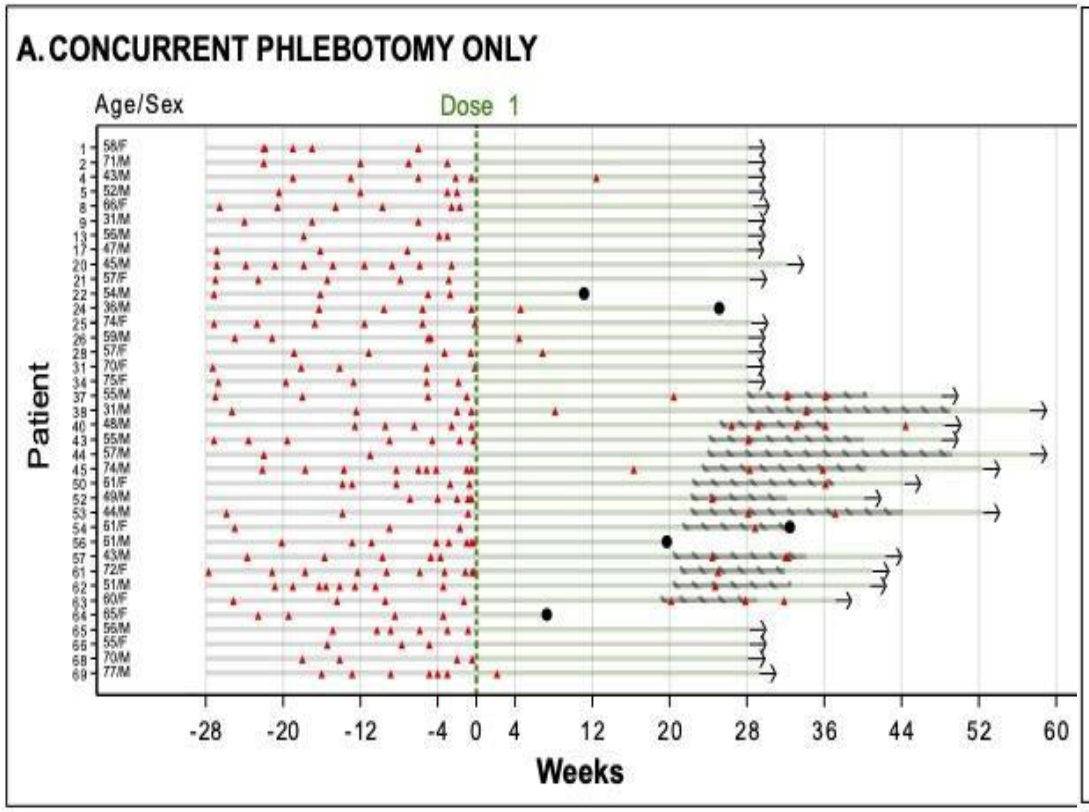
- Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria
- ≥3 phlebotomies in 28 weeks with or without concurrent cytoreductive therapy
- All patients prior to first rusfertide dose were phlebotomized to HCT <45% to standardize the starting HCT
- **Rusfertide (PTG-300) doses of 10-120 mg administered subcutaneously weekly added to prior standard therapy**

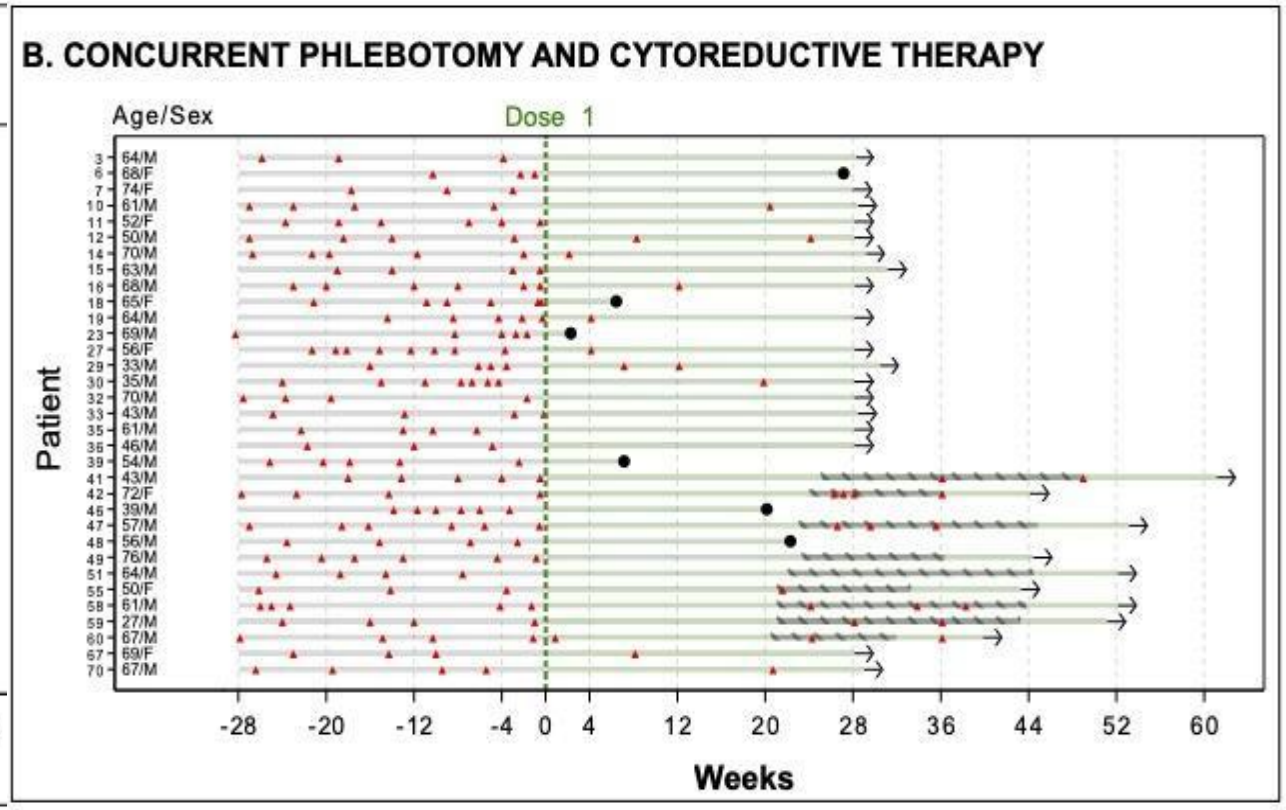
KEY ENDPOINTS:

- Safety
- **Efficacy**
  - Proportion of Responders in Part 2
    - Maintain Hematocrit <45%
    - Reduction in Phlebotomies
  - Number and rate of phlebotomies compared to historic experience
  - Patient Outcomes: MPN-SAF TSS

Phlebotomy Events before and after Starting Rusfertide

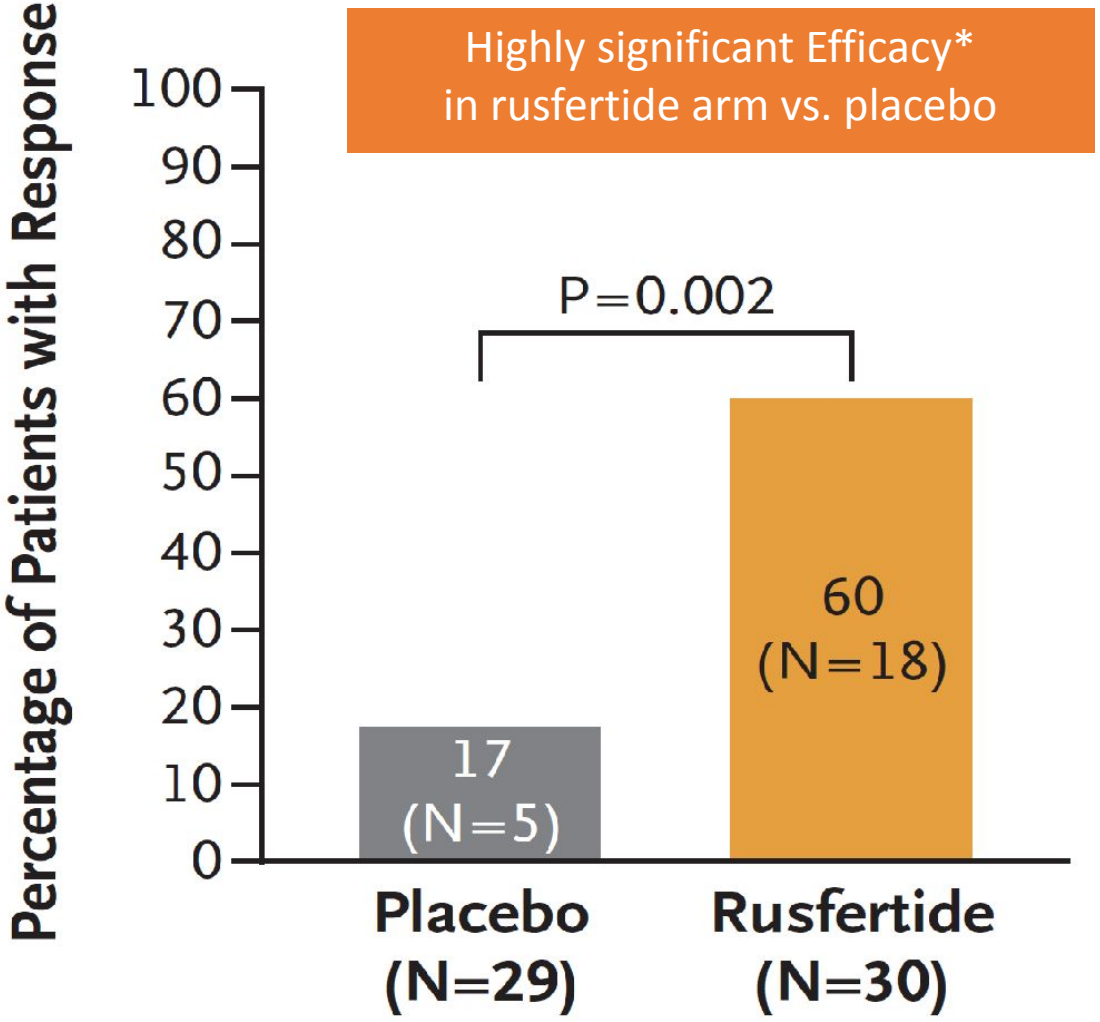
Dramatic decrease in the number of therapeutic phlebotomies is observed after starting rusfertide





M Kremyanskaya et al. N Engl J Med 2024;390:723-735.

Efficacy as Demonstrated by Responders in Rusfertide vs Placebo in Part 2

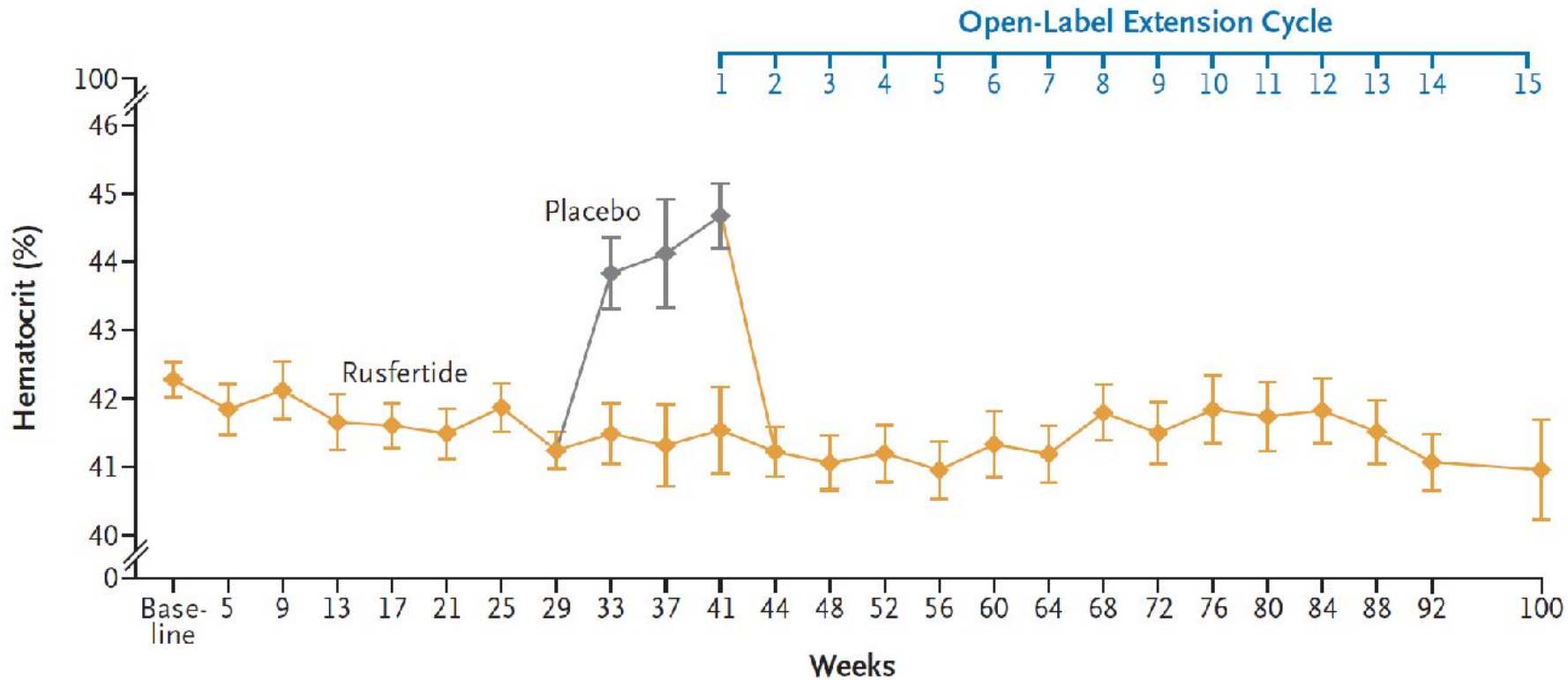


Responder definition as per protocol

- Did not receive a phlebotomy
- Completed 12 weeks of treatment
- Hematocrit control maintained without phlebotomy eligibility, which is defined as

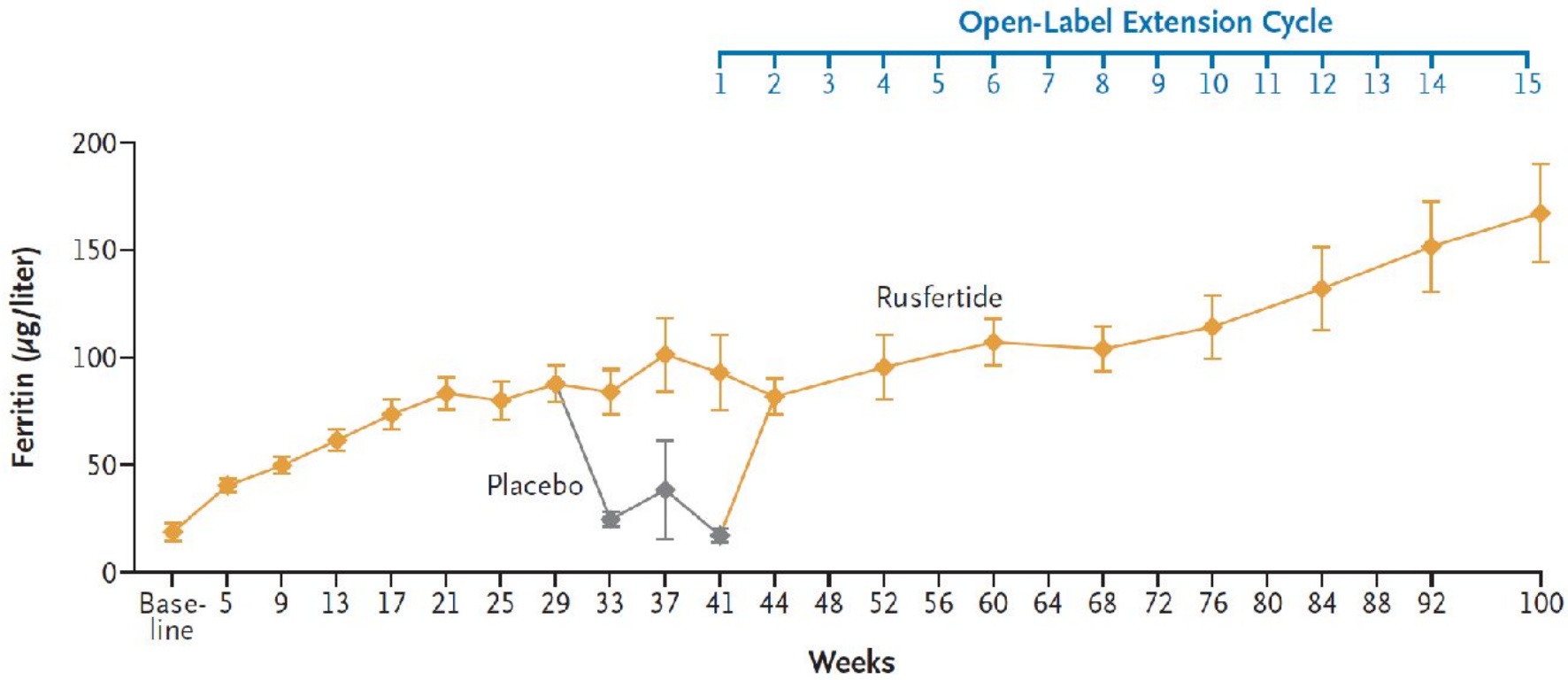
  Hematocrit ≥45% that was ≥3% higher than Week 29 pre-randomization hematocrit value
  or
  Hematocrit >48% **or**
  An increase of ≥5% in hematocrit compared to Week 29 pre-randomization hematocrit value

Rusfertide Treatment Results in Sustained Hematocrit Control over time



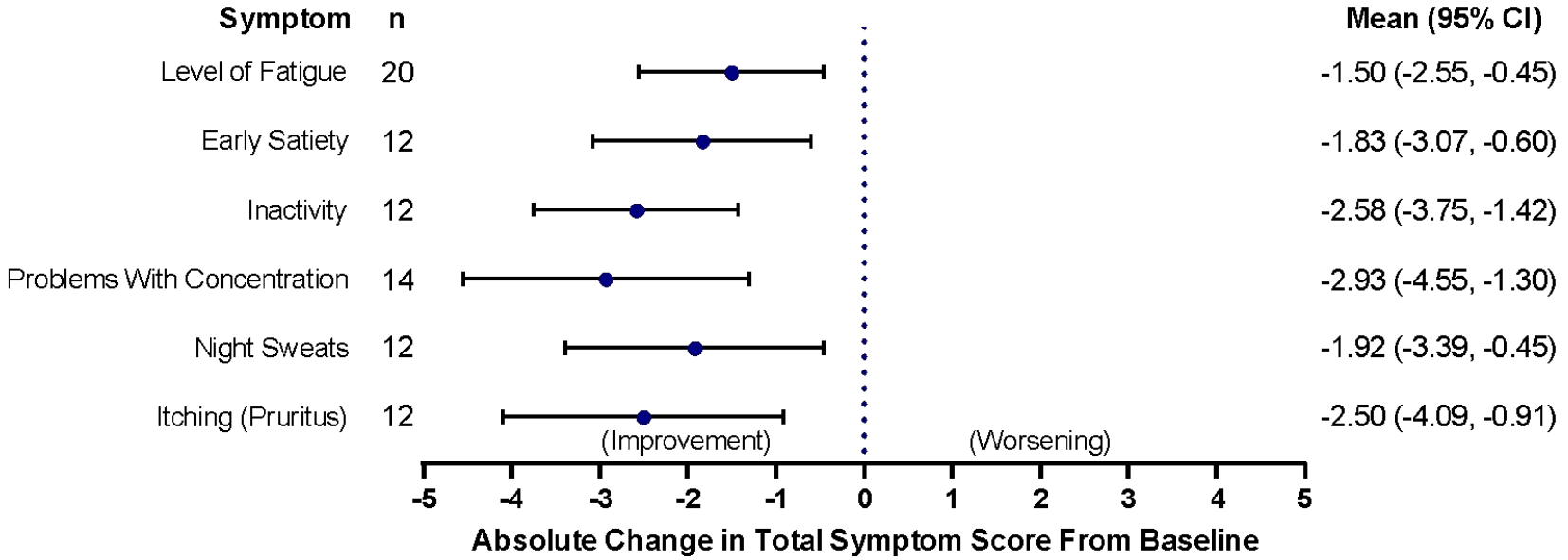
No. of Patients																								
Rusfertide	58	60	59	58	58	55	41	59	30	22	19	56	55	49	47	49	47	43	39	38	32	28	25	24	16
Placebo									27	15	7													

Rusfertide Treatment Results in Increase in Serum Ferritin Levels



REVIVE Part 1: Rusfertide Improved Patient-Reported Outcomes

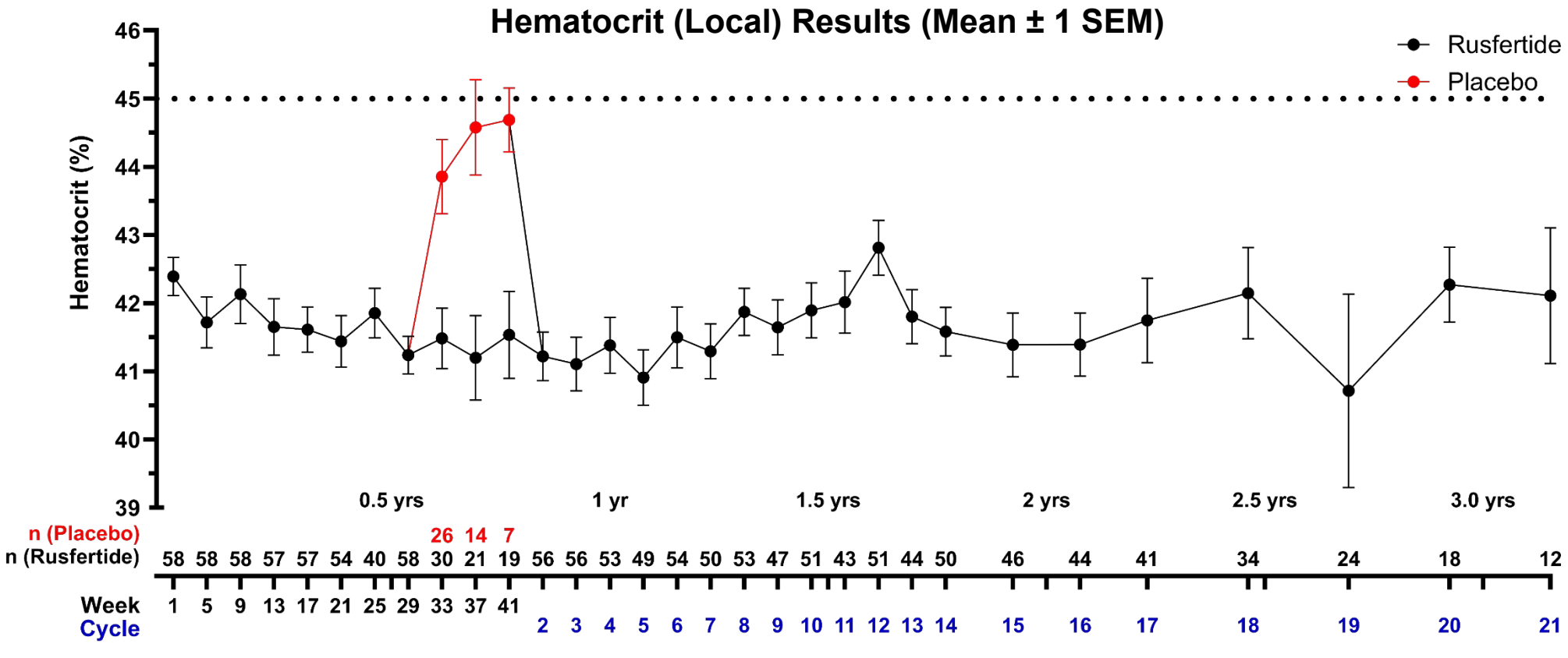
- In Part 1, PROs were assessed using the MPN-SAF TSS
  - Mean change from Baseline (Week 1) to Week 29 of ISSs from the MPN-SAF for patients with moderate (score, 4-6 out of 10) to severe symptoms (score, 7-10 out of 10) at Baseline
  - In patients with moderate or severe ISSs at Baseline (≥4 out of 10), rusfertide significantly decreased symptoms in **fatigue, early satiety, night sweats, problems with concentration, inactivity, and itching**



Error bars represent 95% CIs around the mean change from baseline. No multiplicity adjustments were made for analyses for all the supportive efficacy endpoints. Symptoms presented are limited to those with at least 10 patients.

CI, confidence interval; ISS, individual symptom score; MPN-SAF, myeloproliferative neoplasm symptom assessment form; PROs, patient-reported outcomes.

Rusfertide Provided Durable Control of Hematocrit Through 3 Years



Dotted horizontal line, hematocrit <45%.
Hct, hematocrit; SEM, standard error of the mean; yr, year.

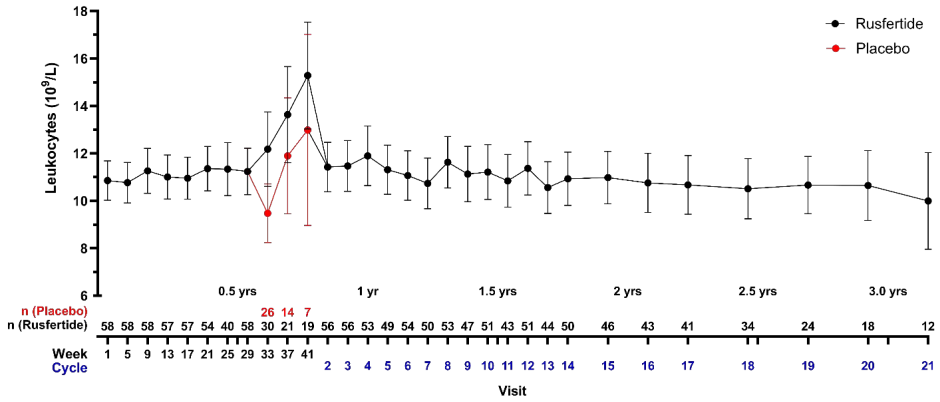
Data cutoff: 9 April 2024

- Starting within 4 weeks of treatment initiation, rusfertide consistently maintained Hct <45%, including in patients who were on therapy for 3+ years

Pettit et al EHA 2024

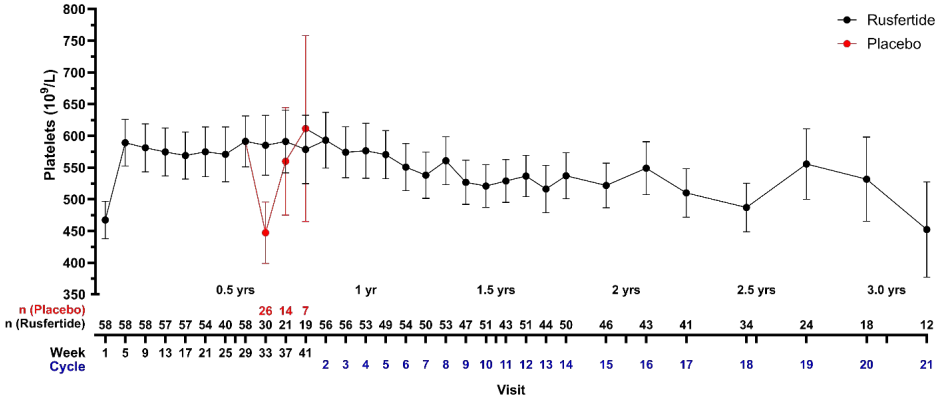
Leukocytes and Platelet Values Stabilized Over Time

Leukocyte (Local) Results (Mean±1 SEM)



- Mean leukocyte counts remained stable throughout the study

Platelet (Local) Results (Mean±1 SEM)



- Platelets increased post-baseline without significant clinical sequelae and stabilized over time

SEM, standard error of the mean; yr, year.

Data cutoff: 9 April 2024

Pettit et al EHA 2024

REVIVE: Long-Term Safety Profile of Rusfertide

- The most common (≥20%) Treatment Emergent Adverse Events (TEAEs) were injection site reactions, fatigue, COVID-19, pruritus, arthralgia, dizziness, nausea, anemia, and headache
  - Grade 3 TEAEs occurred in 25.7% of patients
  - There were no Grade 4 or 5 TEAEs

Reported TEAEs (Any Grade) in ≥10 Patients	Overall, n (%)
Patients with at least 1 TEAE	70 (100.0)
Injection site erythema	**46 (65.7)**
Injection site pain	30 (42.9)
Injection site pruritus	27 (38.6)
Fatigue	25 (35.7)
COVID-19	22 (31.4)
Injection site mass	21 (30.0)
Pruritus	21 (30.0)
Arthralgia	19 (27.1)
Dizziness	19 (27.1)
Injection site swelling	17 (24.3)
Nausea	17 (24.3)
Anemia	16 (22.9)
Headache	16 (22.9)
Injection site irritation	14 (20.0)
Diarrhea	12 (17.1)
Injection site bruising	11 (15.7)
Dyspnea	10 (14.3)
Hyperhidrosis	10 (14.3)
Injection site warmth	10 (14.3)
Myalgia	10 (14.3)
Paresthesia	10 (14.3)
Upper respiratory tract infection	10 (14.3)

Data cutoff: 9 April 2024

COVID-19, coronavirus disease; MI, myocardial infarction; PV, polycythemia vera; TE, thromboembolic event; TEAE, treatment-emergent adverse event.

Phase 3 Study VERIFY (NCT05210790): Rusfertide vs Placebo in Patients With PV[1,2]

250 Patients with PV Are Being Randomized Globally[1]

Key Eligibility:[1-3]

- Age ≥18 years
- Meet revised 2016 WHO criteria for diagnosis of PV
- ≥3 phlebotomies due to inadequate HCT control in 28 weeks[a] before randomization
  OR
  ≥5 phlebotomies due to inadequate HCT control within 1 year prior to randomization

N=250

Part 1A: Double-Blind[1,2]

32 weeks (Weeks 0-32)

R 1:1

- **Placebo + ongoing therapy**
- **Rusfertide + ongoing therapy**
  Starting dose: 20 mg SC Q1W

CRT may be decreased or stopped but not increased

Part 1B: Open-Label[1,2]

20 weeks (Weeks 32-52)

Goal: Assess durability of responses through Week 52

Rusfertide + ongoing therapy

CRT may be decreased or stopped but not increased

Part 2: Open-Label[1,2]

104 weeks (Weeks 52-156)[c]

Goal: Assess long-term safety

Rusfertide + PV therapy

Dose of CRT may be changed or new CRT may be initiated

Key Endpoints:[1,4,5]

- Proportion of patients achieving response, defined as absence of phlebotomy eligibility[b] (Weeks 20-32)
- Mean number of phlebotomies (Weeks 0-32)

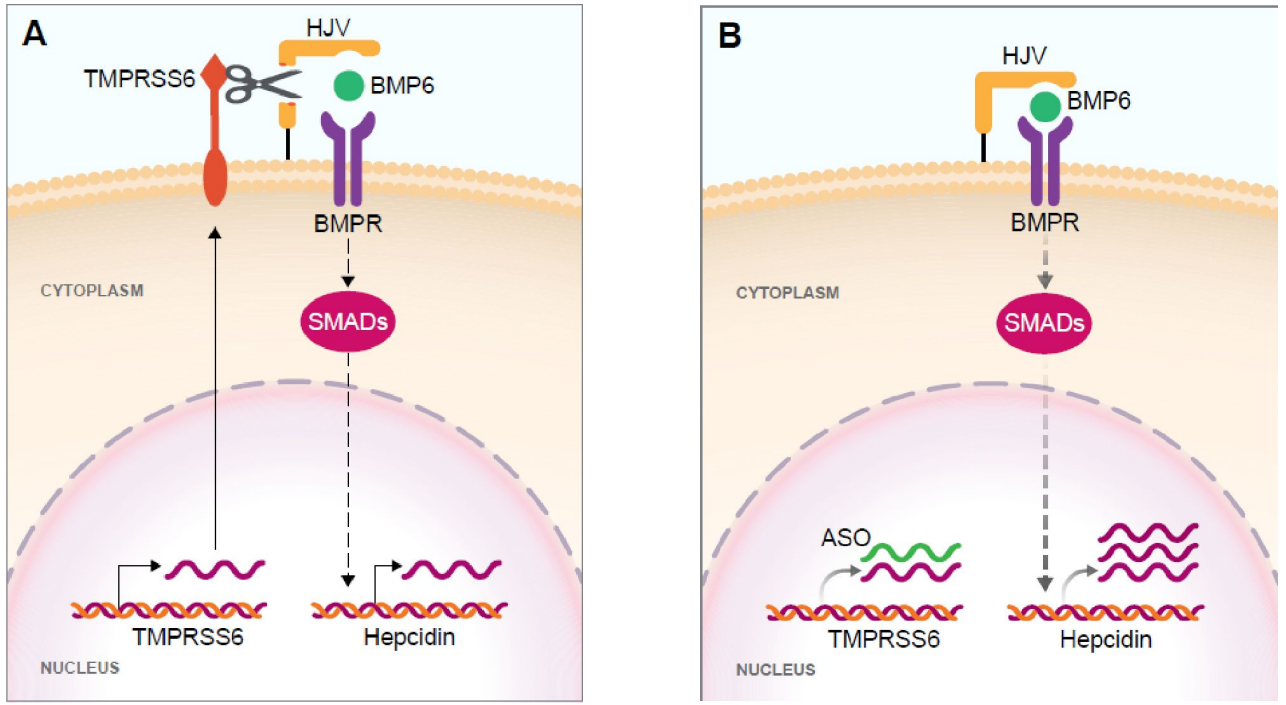
[a]Defined as 28 weeks in protocol amendment 3.1, but previously published as 6 months.[2,3] [b]Phlebotomy eligibility defined as confirmed HCT ≥45% that is ≥3% higher than baseline, or HCT ≥48%.[1]

CRT, cytoreductive therapy; **HCT**, hematocrit; **PV**, polycythemia vera; **Q1W**, once a week; **R**, randomized; **SC**, subcutaneous; **WHO**, World Health Organization.

1. ClinicalTrials.gov. NCT05210790. https://clinicaltrials.gov/ct2/show/NCT05210790 **2.** Verstovsek S, et al. 64th American Society of Hematology (ASH) Annual Meeting; December 2022. TiP poster presentation. **3.** Protagonist Therapeutics. Protocol Number: PTG-300-11, Protocol Amendment 3.1. July 25, 2023. **4.** Protagonist Therapeutics. Press release. Published March 22, 2021. https://feeds.issuerdirect.com/news-release.html?newsid=653501200562085 8 **5.** EU Clinical Trials Register. 2021-004732-29. https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-004732-29/HU.

Using RNA Technology to Manipulate Hepcidin Production by the Liver

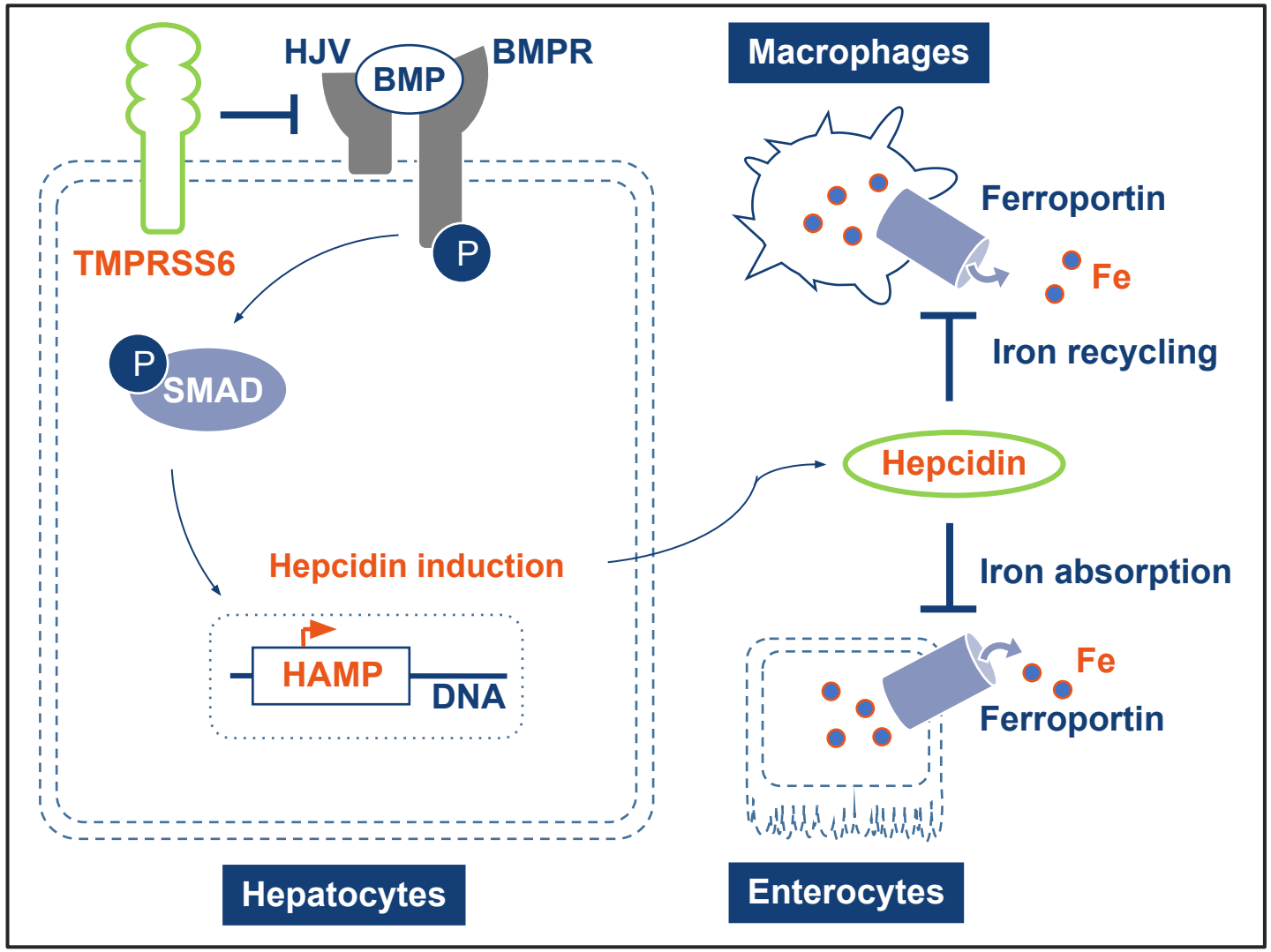
Decrease the amount of negative regulator (TMPRSS6) of hepcidin production in the liver by
-ASO (sapablursen)
-si RNA (divesiran)



Adapted from Finberg. Journal of Clinical Investigations 2013; 123 (4), 1424.

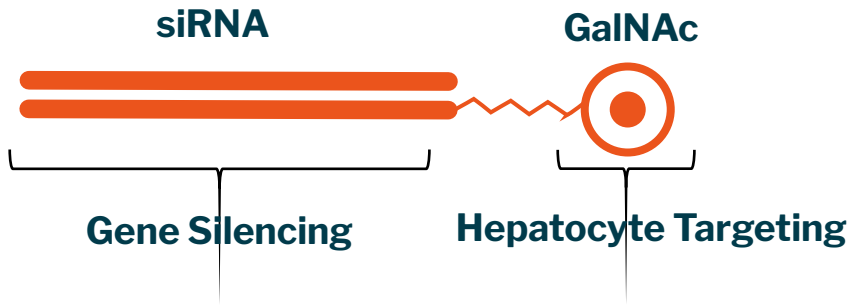
Silence Therapeutics.

Divesiran (SLN124) Enhances Hepcidin Expression via TMPRSS6 Inhibition by siRNA

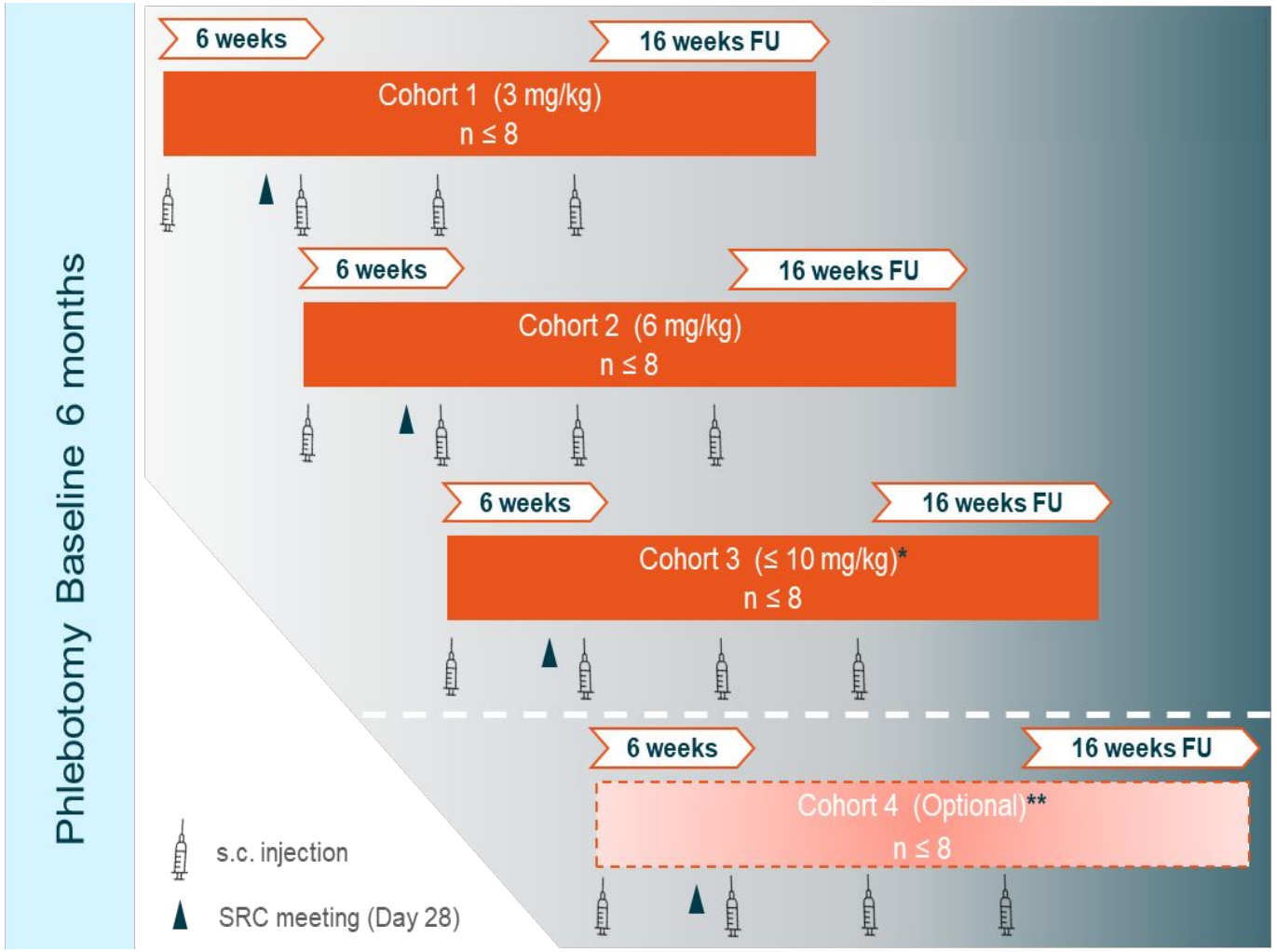


> **TMPRSS6** is a negative regulator of the BMP/SMAD signaling pathway; activation of the pathway induces hepcidin expression

> **GalNAc siRNA approach** for gene silencing in the liver



Phase 1 Study Design



Study stopped enrolment in June 2024 (n=21)

Divesiran was administered SC Q6W X four doses, followed by 16 week observation

Cohort 1 – 3 mg/kg, 6 participants

Cohort 2 – 6 mg/kg, 8 participants

Cohort 3 – 9 mg/kg, 7 participants

Eligibility Criteria

PV diagnosis according to WHO 2016

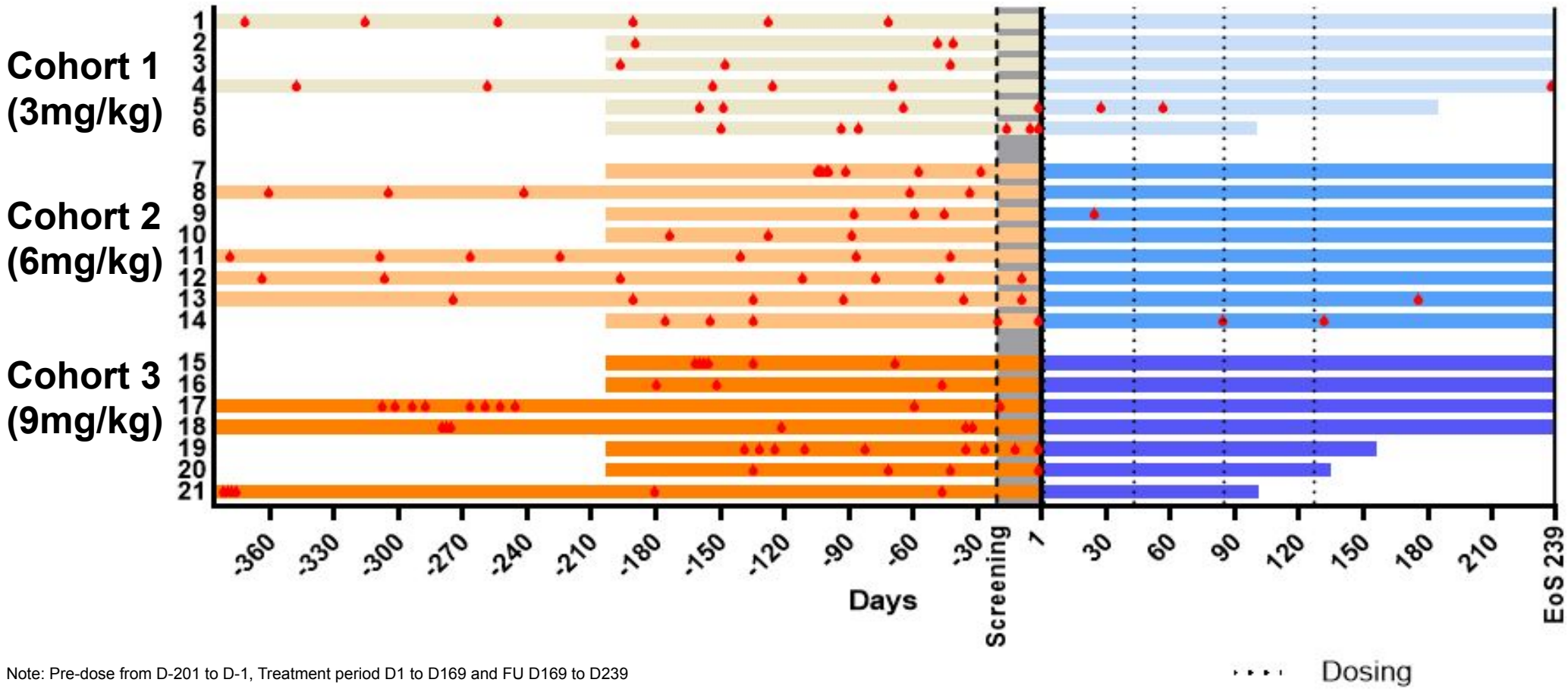
At least 3 phlebotomies in previous 6 months or 5 in previous 12 month to screening.

Cytoreductives allowed if patient on stable dose for 12 weeks prior to screening and no planned dose changes.

Platelets ≤ 1,000,000/uL, WBC ≤ 25,000/uL

Kremyanskaya et al ASH 2024

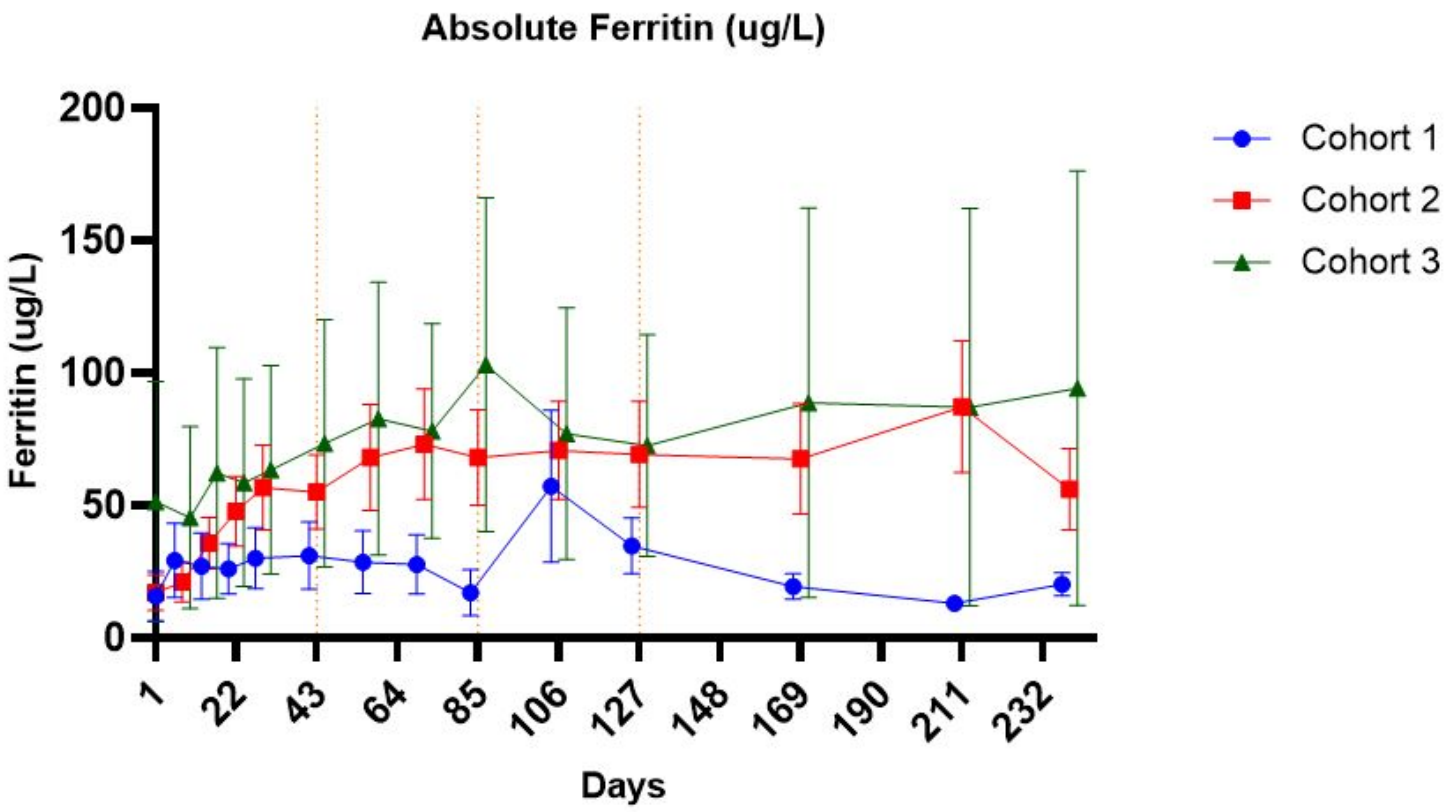
Divesiran Reduces Phlebotomy Frequency in PV Patients



Note: Pre-dose from D-201 to D-1, Treatment period D1 to D169 and FU D169 to D239

79 phlebotomies prior to dosing, 5 in treatment period and 2 in Follow-up.
No well-controlled patients (HCT<45% at baseline) required a phlebotomy

Divesiran Treatment Results in Elevated Ferritin



Most patients were iron deficient (≤25 ug/L ferritin, n= 18) at baseline.

3/21 patients had ferritin >25 ug/L (range 62 to 324 ug/L at baseline).

Divesiran treatment increases ferritin

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

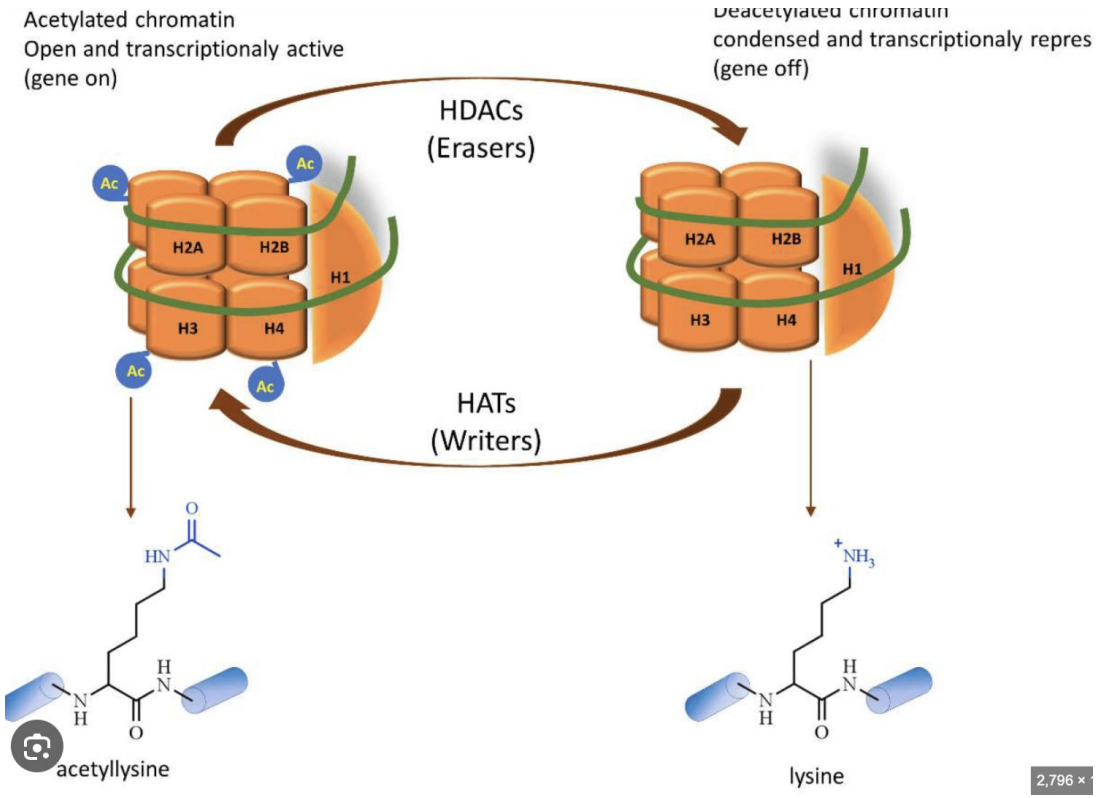
Divesiran is Safe and Well Tolerated

- Divesiran is well tolerated without dose-limiting toxicities.
- Treatment emergent adverse events (TEAEs) were recorded in 19/21 participants.
- Majority of TEAEs (84%) were grade 1
- No TEAEs grade > 2.
- 52 mild self-limiting injection site reactions were observed in 13/21 participants.
- No treatment-related serious adverse events or TEAEs leading to discontinuation.

Summary of Hepcidin Targeting Agents

- Iron/hepcidin pathway is an attractive tool to control erythrocytosis in patients with PV
- Rusfertide has been shown to be effective in controlling phlebotomy requirements in PV patients as well as increasing ferritin
- Results of phase III VERIFY study are eagerly awaited
- Long term extension THRIVE study will continue to provide long term experience with rusfertide
- Approaches to increase endogenous hepcidin via inhibition of TMPRSS6 mRNA are currently being explored in phase I/II studies by Silence Therapeutics and Ionis Pharmaceuticals. Both agents allow less frequent dosing compared to rusfertide
- Phase 1 study of diveserin shows promising early activity. Phase 2 is enrolling outside of US and hopefully soon in the US
- Additional agents are being explored in pre-clinical or early clinical development

Givinostat in PV



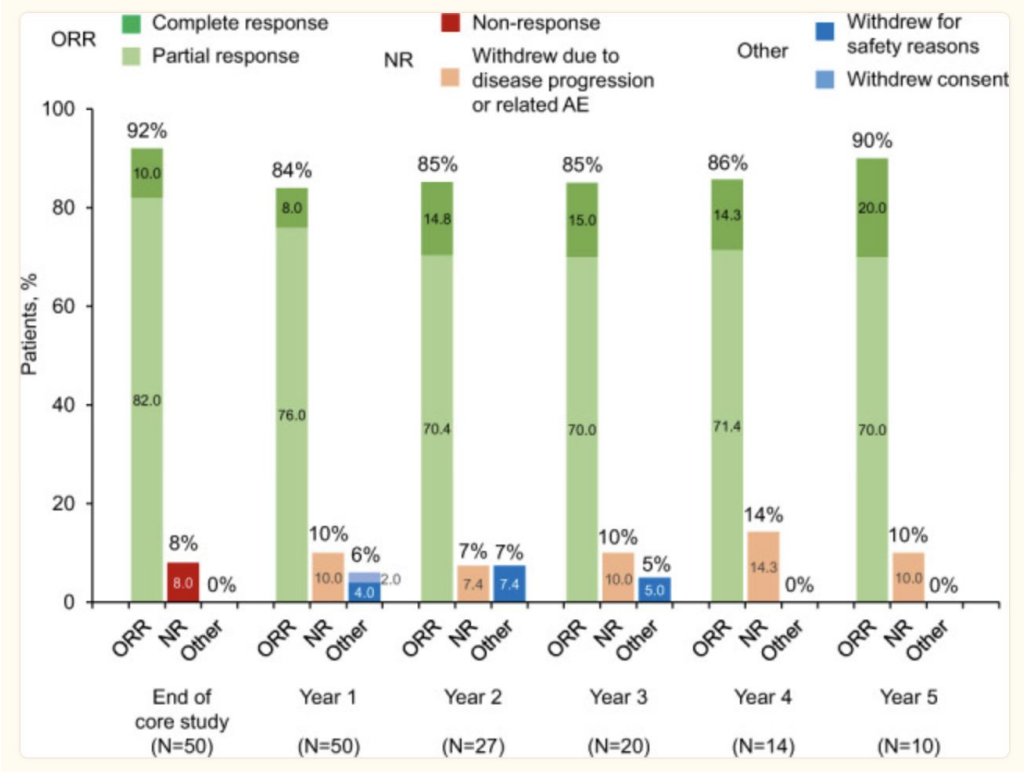
- Synthetic orally bioavailable potent HDAC inhibitor
- Histone are proteins that associate with DNA and help condense it into chromatin
- HDAC activity results in compact chromatin and suppressed gene expression-silencing of tumor suppressor gene/pro-apoptotic genes
- Increased expression of HDACs has been reported in MPNs (and many other tumors)

Givinostat in PV

Givinostat

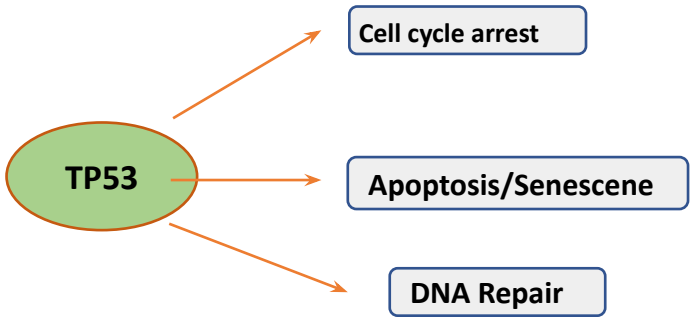
- Demonstrated good safety and efficacy in 3 phase I/II studies in patients with PV
- Eligible pts with JAK2+ MPN who tolerated givinostat treatment and had achieved clinical benefit at the end of core protocol continued treatment in long term, multicenter, international study (NCT01761968)
- 51 pts with PV
- 4 year mean (2.8 median) follow up. Range 3 months to 11 years
- The overall response rate for the duration of follow up was >80%
- Well tolerated
- **Phase III is enrolling-GIV-IN PV trial of givinostat vs HU in high risk PV patients**

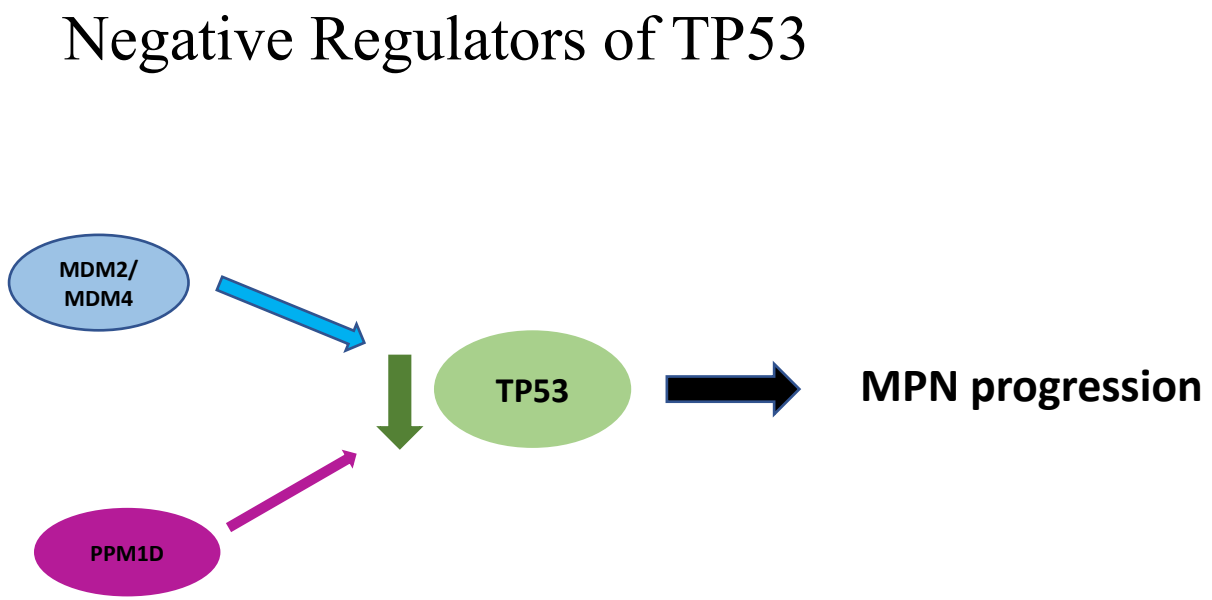
Rambaldi et al Blood Cancer J 2021



TP53 in MPNs

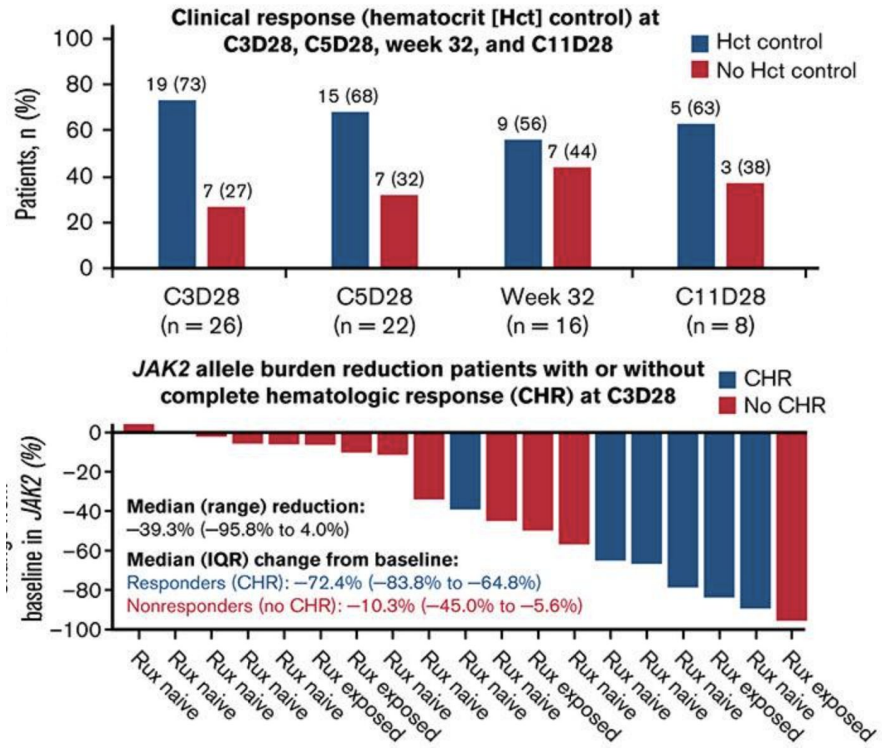
- TP53 regulates cell cycle, apoptosis, DNA repair, and senescence
- Low allele burden *TP53* mutations in ~15% of chronic MPN patients, unclear clinical significance
- *TP53* loss of heterozygosity and rapid expansion of *TP53* mutant clones is associated with transformation to blast phase
- Inactivating *TP53* mutations are observed in up to 20% of MPN-BP





Nakatake M et al. *Oncogene*. 2012;31(10):1323-1333.
Shangary S and Wang S. *Clin Cancer Res*. 2008;14(17):5318-5324.

Idasanutlin (MDM2 inhibitor) Showed Clinical Activity in Patients With PV in a Multicenter Phase 2 Study



Mascarenhas et al Blood Adv 2022

- Idasanutlin is effective in achieving hematologic and molecular responses
- Not well tolerated due to GI toxicity
- Development of idasanutlin in PV was halted
- Oral HDM2 inhibitor KRT 232 (navtemadlin) is currently under clinical investigation in MF

Summary

Agents targeting iron/hepcidin pathway are being developed to control hematocrit and reduce the need for phlebotomies

May improve symptoms and hopefully reduce the risk of thrombosis long term

Other agents such as givinostat are being investigated for potentially first line therapy in patients with PV

MPNs are hot area of clinical investigation and hopefully more drugs are on the horizon

Thank you for your attention

- Questions?