POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

Essential Thrombocytemia Polycythemia Vera

Francesca Palandri
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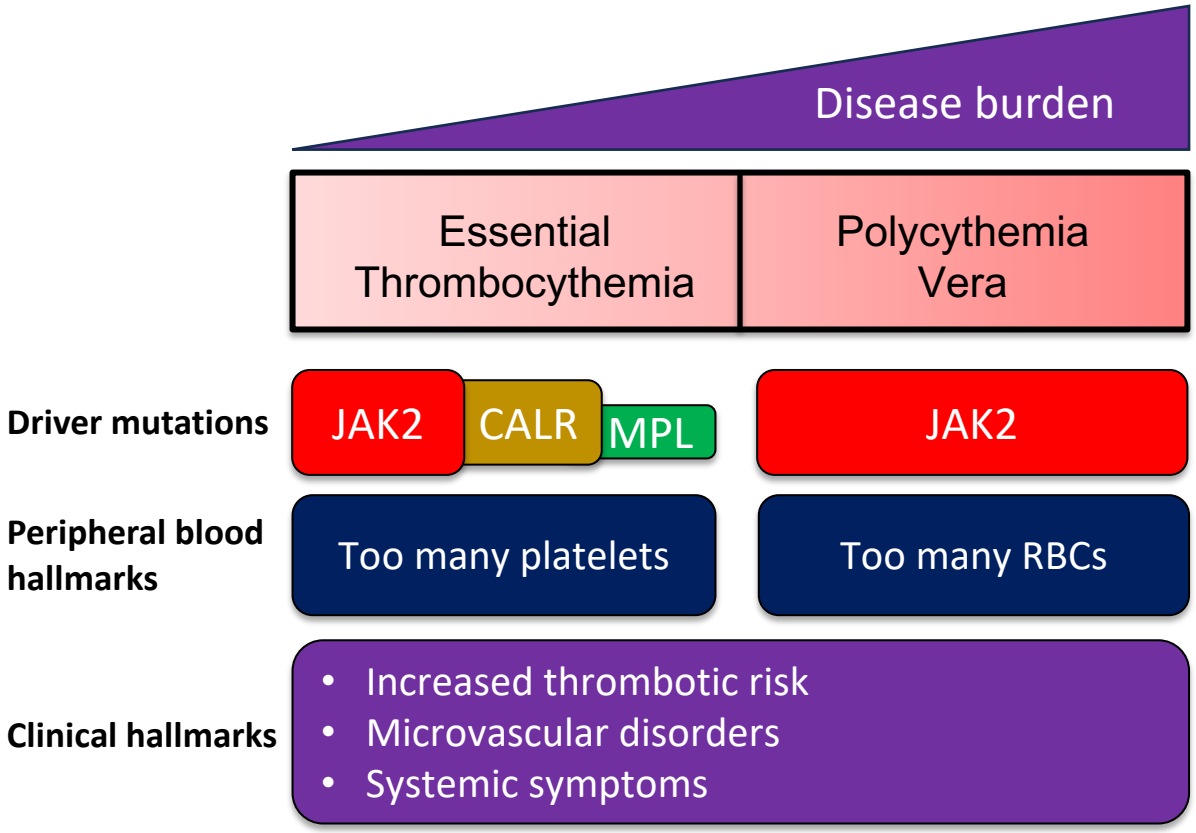
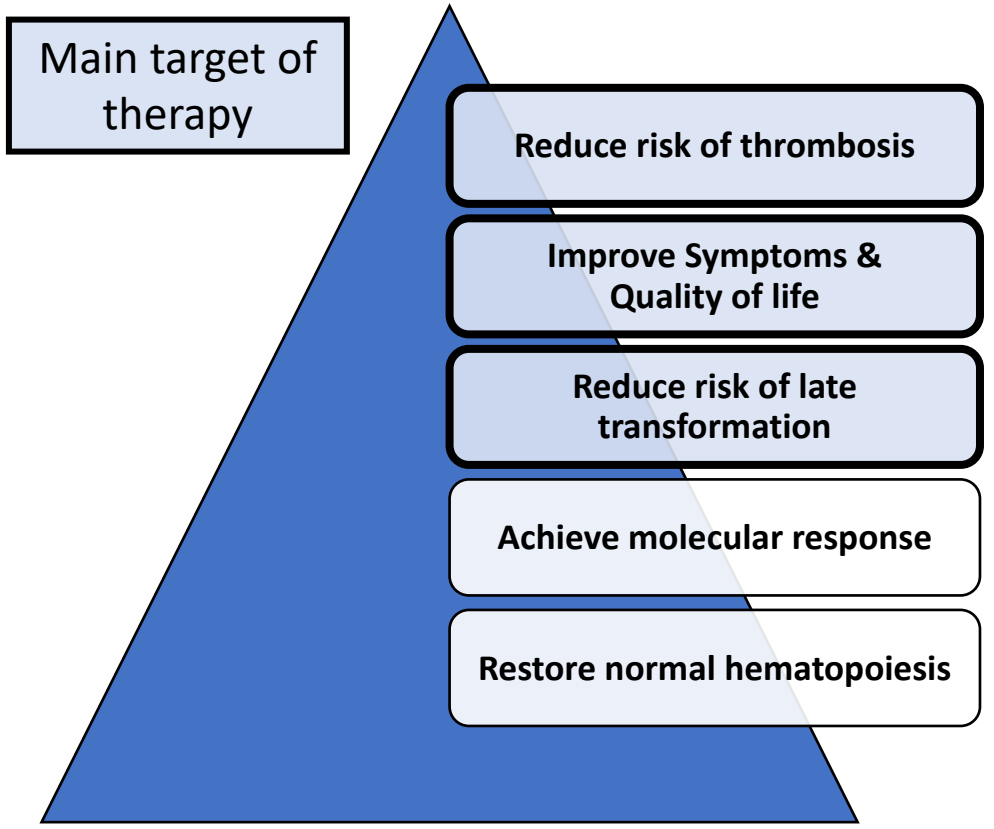
Disclosures of Francesca Palandri

acted as consultant and received honoraria from

- AbbVie
- Amgen
- AOP
- BMS Celgene
- Constellation/Moprhosys
- CTI
- GlaxoSmithKline
- Grifols
- Karyopharm/Telios
- Novartis
- Sierra Oncology
- Sobi

Essential thrombocythemia & polycythemia vera





1. Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311. 2. Vannucchi AM, Leukemia. 2007; 21: 1952-1959. 3. Guglielmelli P, Blood Cancer J. 2021 Dec; 11(12): 199. 4. Carobbio A, Blood Cancer J. 2022; 12: 28.

Conventional approaches and open issues in ET *addressed @ASH2023*

IPSET SCORE*

Very-low-risk	• Age ≤ 60 • No *JAK2* mutation • No h/o thrombosis	No therapy Consider anti-PLT therapy if CVRF
Low-risk	• Age ≤ 60 • **+ *JAK2* mutation** • No h/o thrombosis	Anti-platelet therapy
Intermediate-risk	• **Age > 60** • No *JAK2* mutation • No h/o thrombosis	**Anti-platelet therapy and cytoreduction** ***Hydroxyurea*** ***Interferons*** ***Anagrelide*** ***Busulfan***
High-risk	• **Age > 60 AND** • ***JAK2* mutation AND/OR** • **h/o thrombosis**	

The choice between cytoreductive agents is mainly based on patient preferences or regulatory limitations

Q1.May Interferons achieve better responses, and more prolonged, than HU in the 1L?

*Barbui T, Blood 2012; 120: 5128–5133

Final Analysis of the Daliah Trial: A Randomized Phase III Trial of Interferon-α Versus Hydroxyurea in Patients with MPN (abstract #746)

Trine Alma Knudsen[1], Dennis Lund Hansen[2,3], Lukas Frans Ocias[2], Ole Weis Bjerrum[4], Mette Brabrand[2], Sarah F. Christensen[1], Christina Schjellerup E. Eickhardt-Dalbøge[1], Christina Ellervik[5,6,7,8,9], Daniel el Fassi[4], Mikael Frederiksen[10], Lasse Kjær[1], Thomas Kielsgaard Kristensen[11], Torben A. Kruse[12], Morten Kranker Larsen[1], Torben Mourits-Andersen[13], Sören Möller[14], Ulrik Malthe Overgaard[4], Marianne Tang Severinsen[15], Vibe Skov[1], Anders Lindholm Sørensen[1], Jesper Stentoft[16], Jørn Starklint[17], Karin de Stricker[11], Mads Thomassen[12], Thomas Stauffer Larsen[2,3] and Hans Carl Hasselbalch[1]

[1]Dept. of Hematology, Zealand University Hospital, Roskilde, Denmark; [2]Dept. of Hematology, Odense University Hospital, Odense, Denmark; [3]Dept. of Clinical Research, University of Southern Denmark, Odense, Denmark; [4]Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [5]Dept. of Pathology, Harvard Medical School, Boston, MA; [6]Dept. of Laboratory Medicine, Boston, Children's Hospital, Boston, MA; [7]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [8]Dept. of Production, Research, and Innovation, Region Zealand, Soroe, Denmark; [9]Dept. of Data and Data Support, Region Zealand, Soroe, Denmark; [10]Dept. of Hematology, Hospital of Southern Denmark, Aabenraa, Denmark; [11]Dept. of Pathology, Odense University Hospital, Odense, Denmark; [12]Dept. of Clinical Genetics, Odense University Hospital, Odense, Denmark; [13]Dept. of Hematology, Hospital of South West Jutland, Esbjerg, Denmark; [14]Reserach Unit OPEN – Open Data patient Explorative Network, Odense University Hospital and University of Southern Denmark, Odense; Denmark; [15]Dept. of Hematology, Clinical Cancer Research, Aalborg, Denmark; [16]Dept. of Hematology, Aarhus University Hospital, Aarhus, Denmark; [17]Dept. of Hematology, Hospital of West Jutland, Holstebro, Denmark

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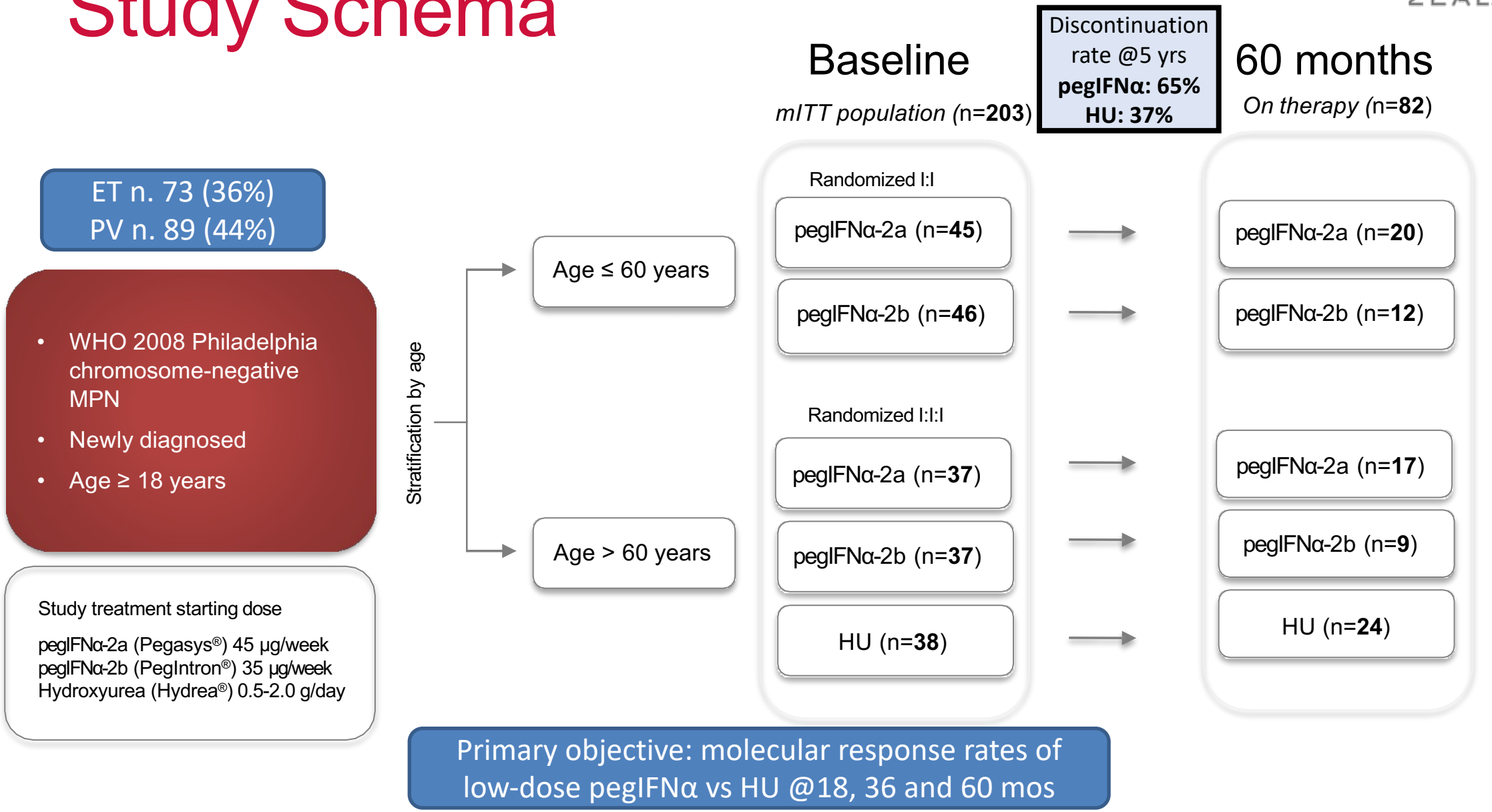
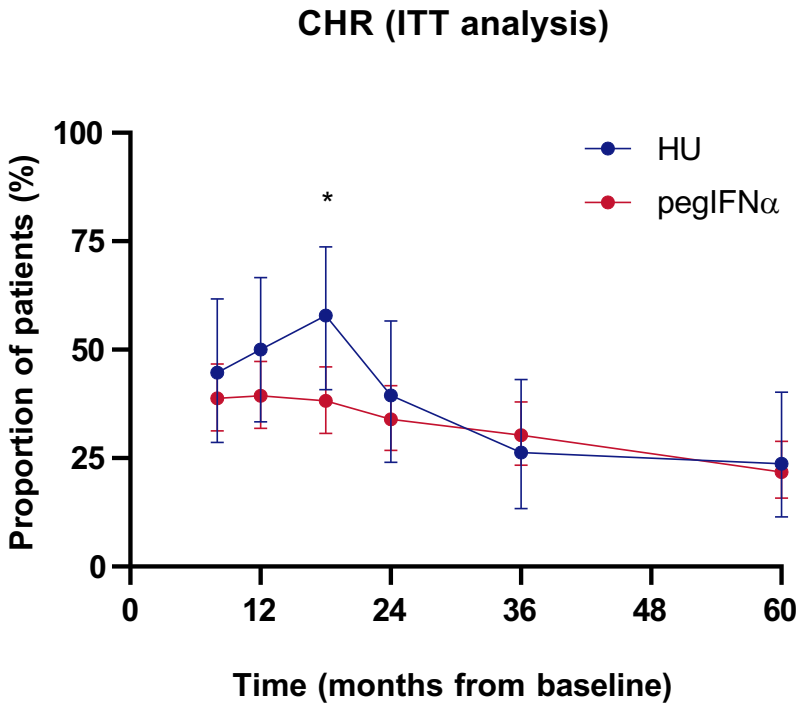
Knudsen TA et al, abstract #746, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 746.

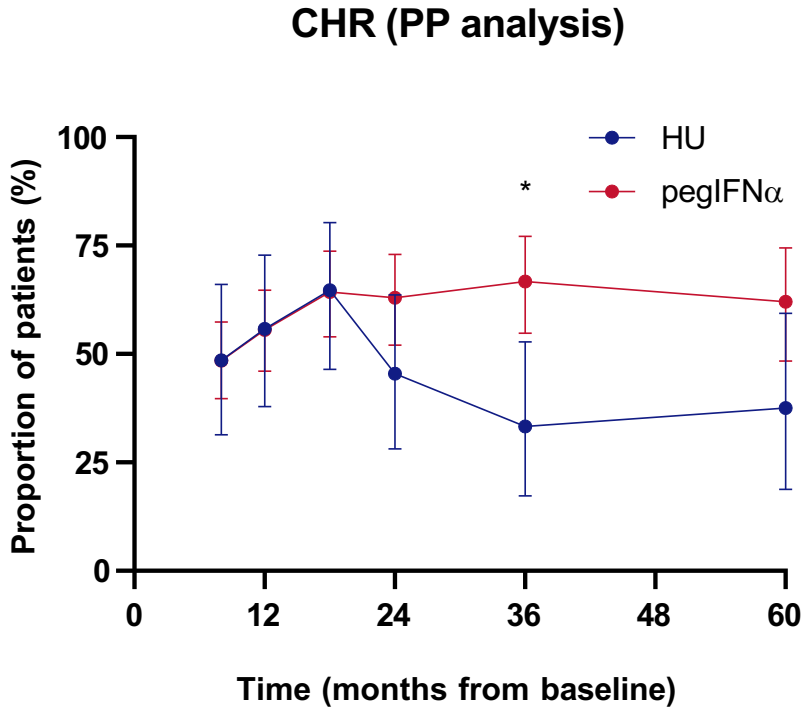
Study Schema



Knudsen TA et al, abstract #746, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 746.

Clinicohematologic Response





CHR outcome n/N (%)	HU	pegIFNα	*P* value*
Mo 12	19/38 (50)	65/165 (39)	0.27
Mo 60	9/38 (24)	36/165 (22)	0.83

* indicate p<0.05 by Fisher's exact test. Error bars indicate 95%CI

CHR outcome n/N (%)	HU	pegIFNα	*P* value*
Mo 12	19/34 (56)	65/117 (56)	1.00
Mo 60	9/24 (38)	36/58 (62)	0.05

* indicate p<0.05 by Fisher's exact test. Error bars indicate 95%CI

Knudsen TA et al, abstract #746, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 746.

Summary and Conclusions

- No difference in the MR or CHR rates between HU or pegIFNα by ITT- analysis with long-term treatment (60 months)
- PegIFNα more effectively reduced the *JAK2V617F* allele burden at month 36 and beyond
- HU was associated with greater histopathologic response rate at 60 months (HU: 18% vs pegIFNα: 5%, p=0.0096)
- The pegIFNα discontinuation rate was high despite a low-dose approach (HU: 37% vs pegIFNα: 65%, p=0.002)
- Patients with good pegIFNα tolerability had superior efficacy (MR and CHR) as compared to HU beyond 36 months (PP-analysis)

Practical take-home messages

Benefits of IFN therapy are achieved over a prolonged administration – younger patients are the ideal target population

High rates of early discontinuation with pegIFN: RopegIFNa2b perhaps better tolerated?

Rop-ET Trial in ET starting soon!

ROP-ET: A Phase III, **single arm,** multicentre study to evaluate the efficacy and safety of **ropeginterferon alfa-2b in ET patients who are intolerant or refractory to or not eligible for other cytoreductive treatments**

Knudsen TA et al, abstract #746, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 746.

Conventional approaches and open issues in ET *addressed @ASH2023*

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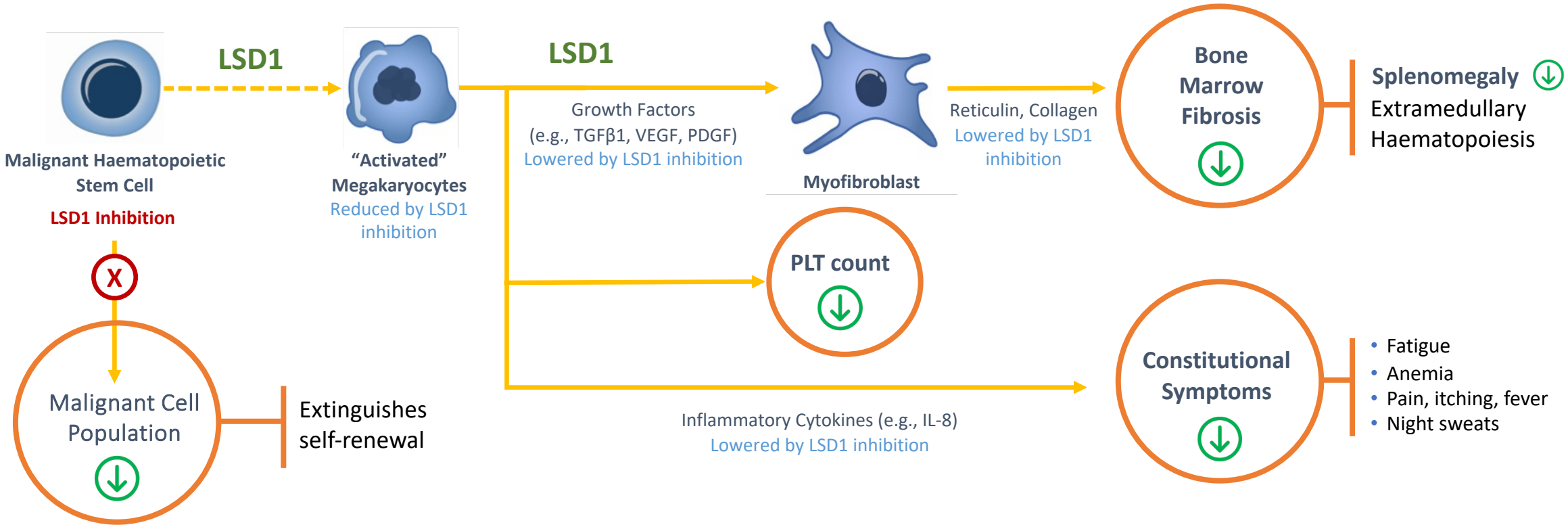
Many patients do not achieve PLT response or are intolerant to HU/IFN therapy

Q2. Do we have alternative cytoreductive therapies?

*Barbui T, Blood 2012; 120: 5128–5133

Bomedemstat: an LSD1 Inhibitor in ET (and MF)



LSD1 (lysine-specific demethylase 1) is an enzyme that regulates the proliferation of blood stem cells; LSD1 is essential for their differentiation into mature megakaryocytes and granulocytes[1,2]

1. Sprussel et a. 2021 2, Jutzi et al. 2018 and Pettit et al. 2019

Study Design (NCT04254978)

Key Eligibility Criteria

- Age ≥18 years
- Diagnosis of ET per WHO diagnostic criteria[1]
- Required cytoreduction based on age (>60 years) or history of thrombosis
- Inadequate response or intolerant to ≥1 standard therapy
- Platelet count >450 × 10^9/L
- Hemoglobin ≥100 g/L
- ECOG performance status 0-2
- No prior splenectomy

Initial 24-Week Treatment Period

Bomedemstat
Starting dose: 0.6 mg/kg/day PO

Titrated to a target platelet count of 200-400 × 10^9/L

Additional 24-Week Treatment Periods[a]

Bomedemstat
0.6 mg/kg/day PO

Titrated to a target platelet count of 200-400 × 10^9/L

Primary End Points

- Safety and tolerability
- Response, defined as platelet count ≤400 × 10^9/L without new thromboembolic events

Exploratory End Points

- Hematologic effects
- Durable reduction in platelets (≤400 × 10^9/L for ≥12 weeks)
- Durable reduction in WBCs (<10 × 10^9/L for ≥12 weeks)
- Patient reported symptom burden (MPN-SAF and PGIC)
- Thrombotic and hemorrhagic events
- Mutant allele burden[b]
- Transformation to AML

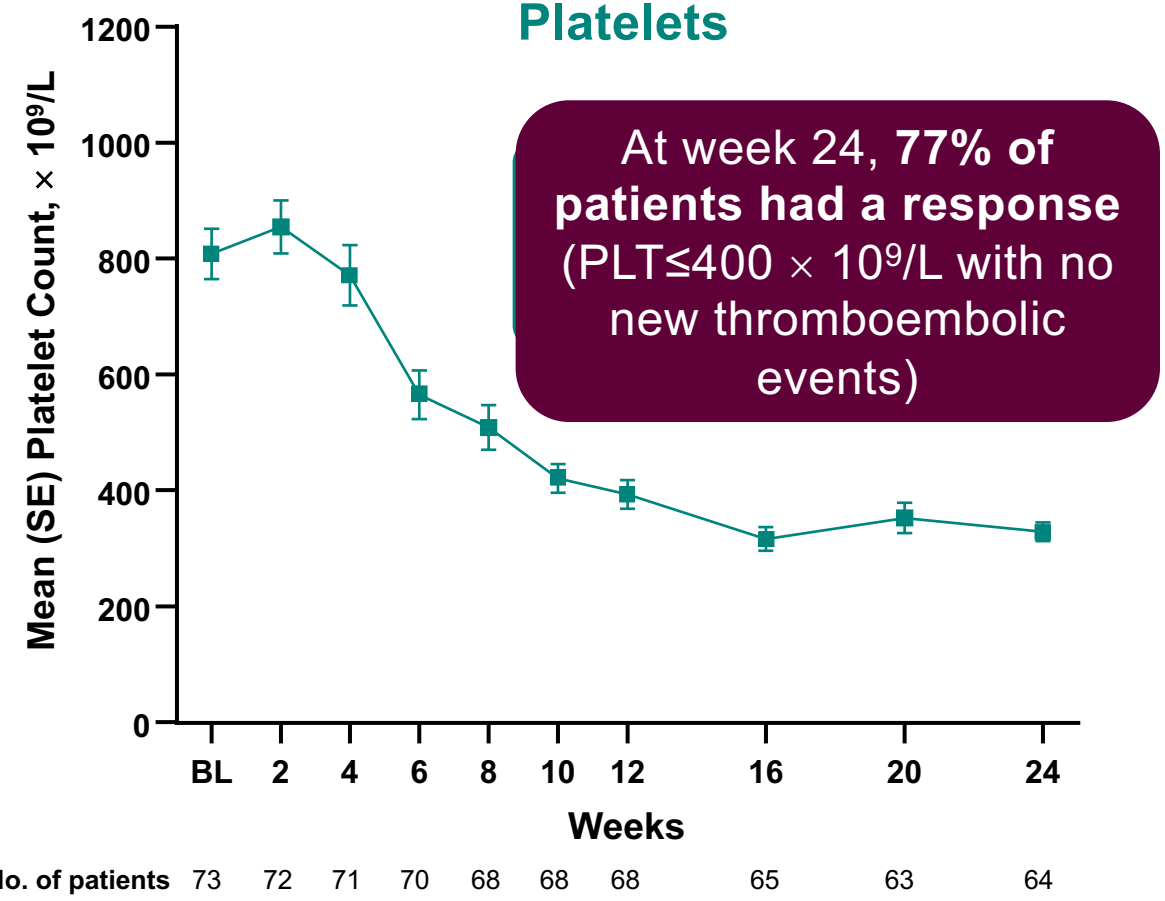
[a]Patient responses were reviewed every 24 weeks and those considered by the investigator to be deriving clinical benefit could remain on study. [b]Assessed by deep sequencing (median exonic depth of 1784 reads) of 261 genes of germline and somatic DNA. Homozygosity of mutant alleles was imputed when variant allele frequency was >50% and/or loss of heterozygosity was detected based on the difference between the minor allele frequency of flanking single nucleotide polymorphisms in germline versus granulocyte DNA. Single cell genotypes were determined in stem/progenitor (CD34+) and monocyte (CD14+) cells in patients with loss of heterozygosity using the Tapestri® system.

1. Arber DA et al. *Blood.* 2016;127:2391-2405.

Goethert JR et al, abstract #0747, ASH2023 oral presentation

Effect on Platelets and White Blood Cells

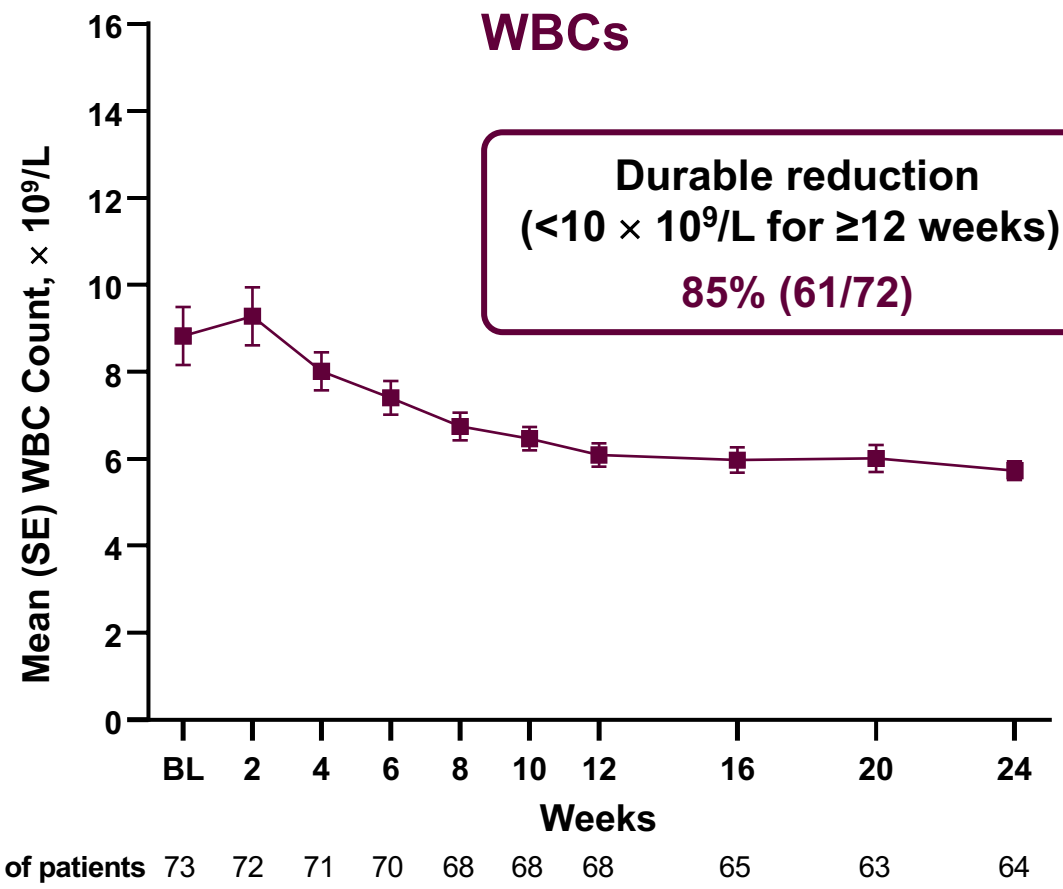
Platelets



At week 24, **77% of patients had a response** (PLT≤400 × 10^9/L with no new thromboembolic events)

No. of patients	73	72	71	70	68	68	68	65	63	64

WBCs



Durable reduction (<10 × 10^9/L for ≥12 weeks): 85% (61/72)

No. of patients	73	72	71	70	68	68	68	65	63	64

- Hemoglobin levels remained stable throughout the initial 24-week treatment period

Data cutoff date: May 03, 2023.

Goethert JR et al, abstract #0747, ASH2023 oral presentation

Summary and Conclusions

- Bomedemstat had clinically relevant activity in patients with ET who had an inadequate response to or were intolerant of ≥1 standard-of-care therapy
  - 77% of patients had a response at week 24; most achieved a response by week 12
  - Most patients had a durable reduction in platelet and white blood cell counts
  - No significant change in symptom burden (MPN-SAF TSS) and 72% reported a favorable response (PGIC)
- At week 24, 85% of evaluable patients had a decrease in the VAF of *JAK2*, *CALR*, or *MPL*
  - Some of the largest decreases in VAF occurred in patients with cells homozygous for these driver mutations
- Bomedemstat was generally well tolerated, with few thrombotic events
- Daily oral bomedemstat resulted in most patients with ET having a clinically relevant hematologic response

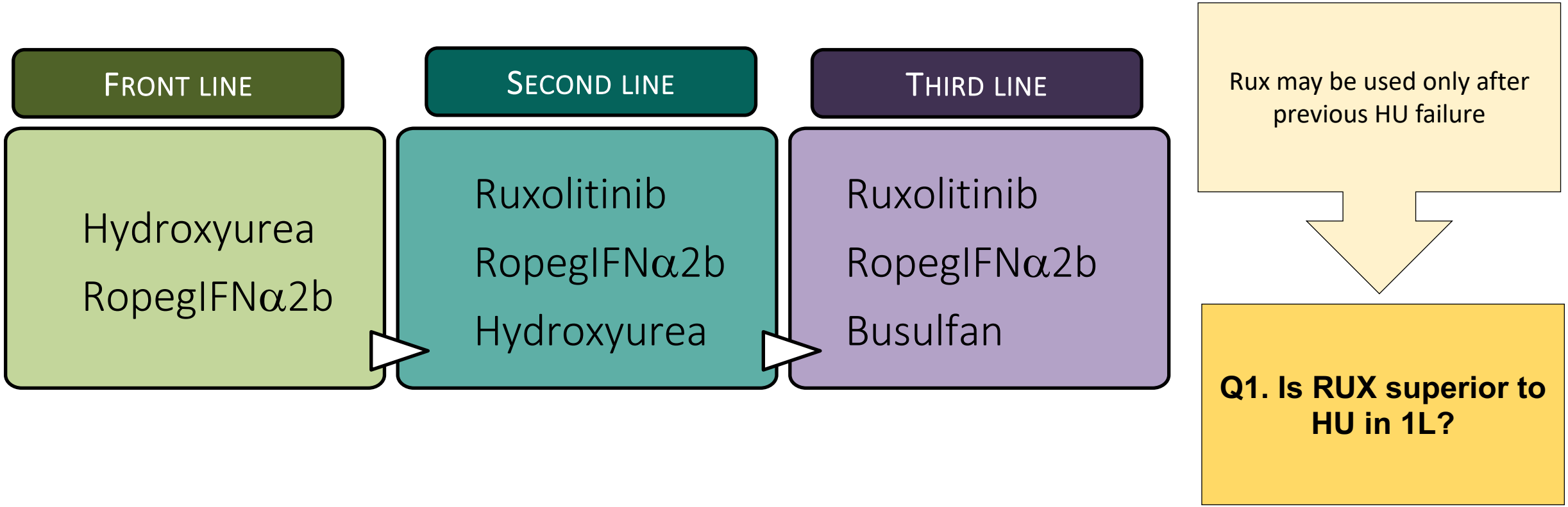
Practical take-home messages

BOMEDEMSTAT is a promising option in ET after HU failure

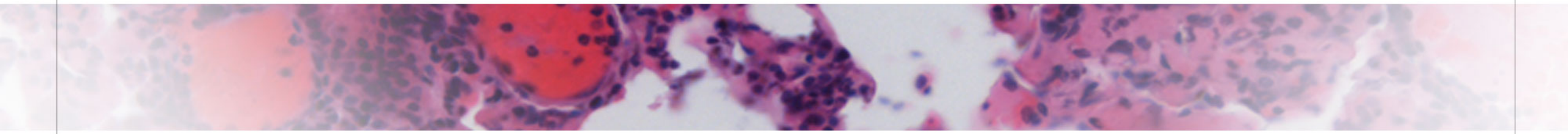
MK-3543-006
A phase 3 study evaluating **bomedemstat versus BAT** in patients with ET who had an **inadequate response to or were intolerant of hydroxyurea** (NCT06079879)

Goethert JR et al, abstract #0747, ASH2023 oral presentation

Conventional approaches and open issues in PV *addressed @ASH2023*



Vannucchi AM, Haematologica. 2017 Jan;102(1):18-29 ;Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311. McMullin MF, Br J Haematol. 2019 Jan;184(2):176-191. Spivak JL, Blood. 2019 Jul 25;134(4):341-352; Tefferi A, Am J Hematol. 2023;98:1465–1487.

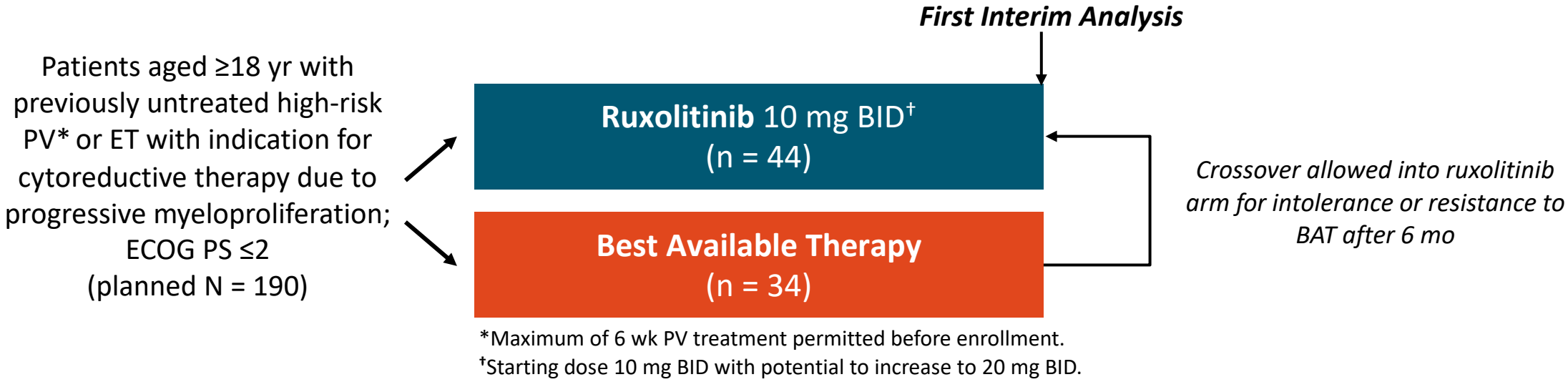


Firstline Treatment with Ruxolitinib Versus Best Available Therapy in Patients with Polycythemia Vera: Pre-Specified Interim Analysis of the Randomized Phase 2b **Ruxobeat** Clinical Trial of the German Study Group for Myeloproliferative Neoplasms (**GSG-MPN**)

Presenter: Steffen Koschmieder, MD

RuxoBEAT Interim Results: Study Design

- Multicenter, open-label phase IIb trial
  - Prespecified interim analysis conducted when study enrolled 78 patients



- **Primary endpoint:** rate of complete CHR at 6 mo (per European LeukemiaNet Criteria)
- **Secondary endpoints:** ORR (CR + PR), blood count, spleen reduction, PROMs

Koschmieder et al, abstract #619, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 619.

RuxoBEAT Interim Results: CR and ORR at 6 months

Outcome at Mo 6, %	Ruxolitinib (n = 44)	BAT (n = 34)	*P* Value
CR	2.3	2.9	1.0
ORR (CR + PR)	77.3	58.8	.09

- **No significant difference between ruxolitinib or BAT in CR or ORR**
- No difference in white blood cell counts or hematocrit at 6 mo (*P* >.05); trend for moderately higher platelet counts with ruxolitinib vs BAT (*P* =.0116)
- Number of patients with phlebotomy requirement was comparable between arms (14.3% vs 16.0%)
- **Spleen size reduction (*P* <.0001), fatigue scores (*P* <.05), and pruritus scores (*P* <.1) favored ruxolitinib vs BAT**

Koschmieder et al, abstract #619, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 619.

RuxoBEAT Interim Results: conclusions

- At first interim analysis of RuxoBEAT, ruxolitinib did not meet criteria for superiority vs BAT at 6 mo in previously untreated patients with high-risk PV
  - Patients receiving ruxolitinib vs BAT derived greater reduction in spleen size (*P* <.0001) and experienced less PV-associated patient-reported pruritus (*P* = .002)
- Trend favoring ruxolitinib vs BAT was observed with higher ORR (*P* = .09), and less fatigue vs baseline (*P* = .058)

Practical take-home messages

RUX 1L is not superior to HU in achieving a CHR @ 6 mos

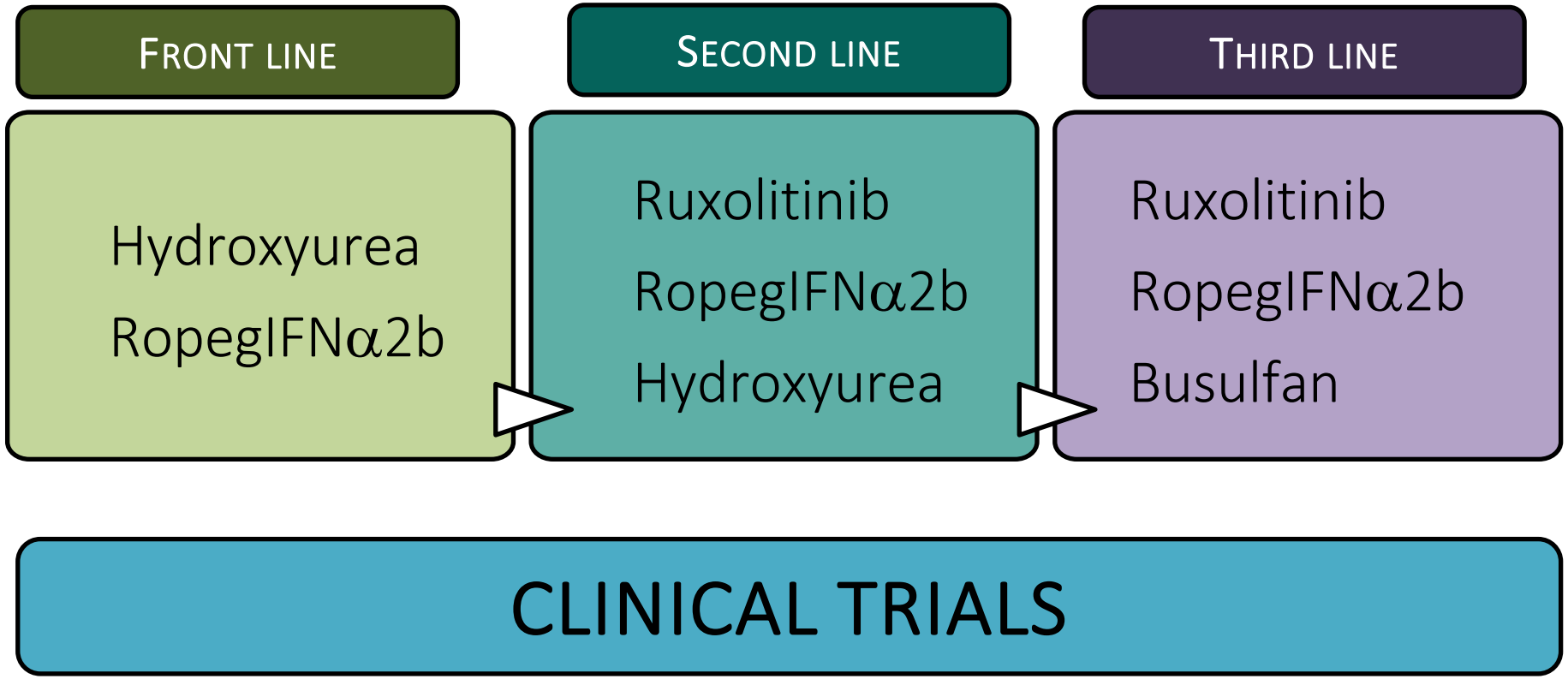
Change of our current clinical management is unlikely

RUX 1L is superior to HU in reducing spleen size and symptoms

RuxoBEAT study is ongoing (NCT02577926)

Koschmieder et al, abstract #619, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 619.

Conventional approaches and open issues in PV
addressed @ASH2023



In case of failure of conventional therapies, most patients continue the same drug[1]

Q2. What is the role of iron metabolism modifiers in PV?

1. Palandri F et al, Cancers 2023, 15(14), 3706

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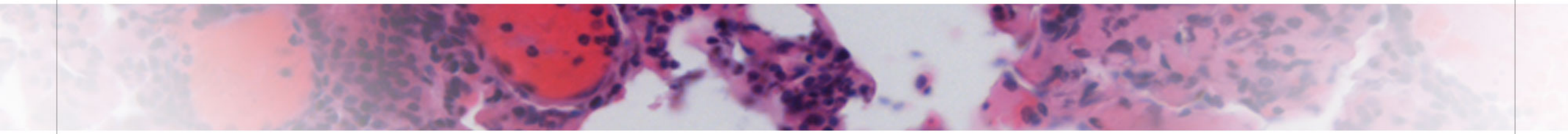


Durability of Hematocrit Control in Polycythemia Vera With the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results From the REVIVE Study

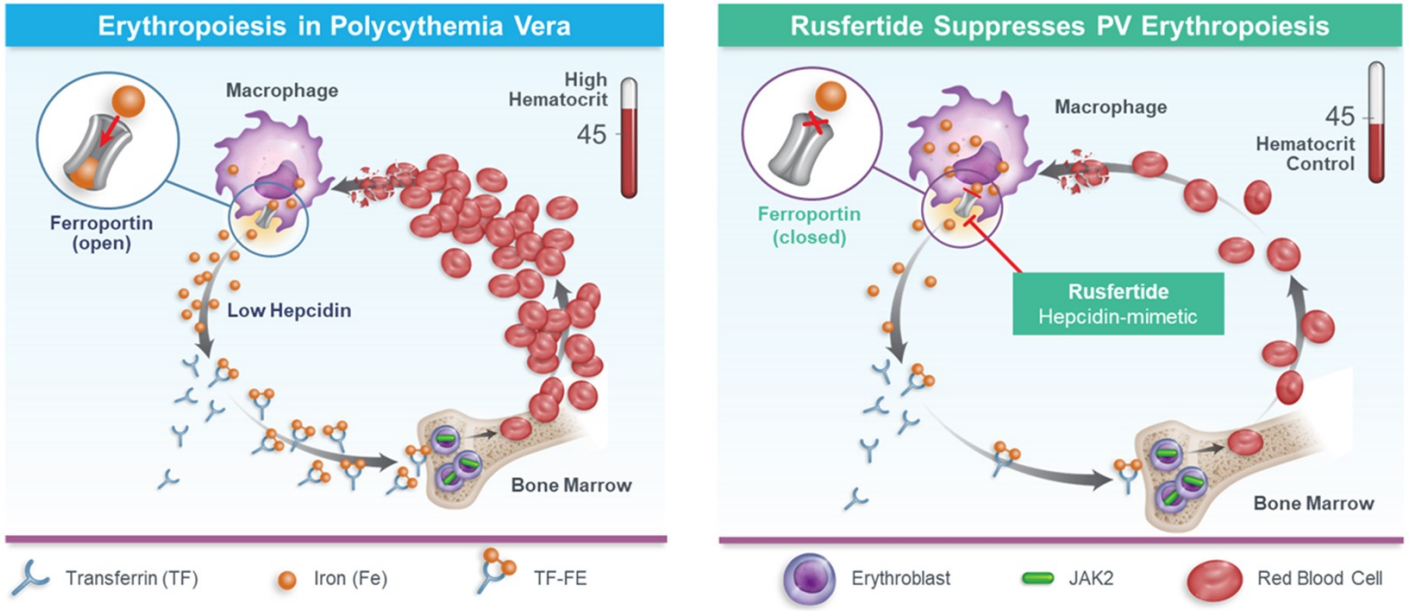
Presenter: Ellen K Ritchie, MD

Ellen K Ritchie, MD[1]; Kristin Marie Pettit, MD[2]; Andrew T. Kuykendall, MD[3]; Marina Kremyanskaya, MD, PhD[4]; Naveen Pemmaraju, MD[5]; Sarita Khanna, PhD[6] Arturo Molina, MD, MS, FACP[6]; and Suneel Gupta, PhD[6]

[1]Weill Cornell Medical College, Cornell University, New York, NY; [2]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; [3]Moffitt Cancer Center, Tampa, FL; [4]Division of Hematology & Medical Oncology, Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai, New York, NY; [5]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Protagonist Therapeutics, Inc., Newark, California

Background: Polycythemia Vera and Rusfertide

- PV is an MPN associated with uncontrolled erythrocytosis, systemic symptoms, and an increased risk of thromboembolic and cardiovascular complications[1,2]
  - These characteristics are largely driven by uncontrolled HCT levels
- Rusfertide is a hepcidin mimetic that controls red blood cell production in PV patients by limiting iron availability[3]



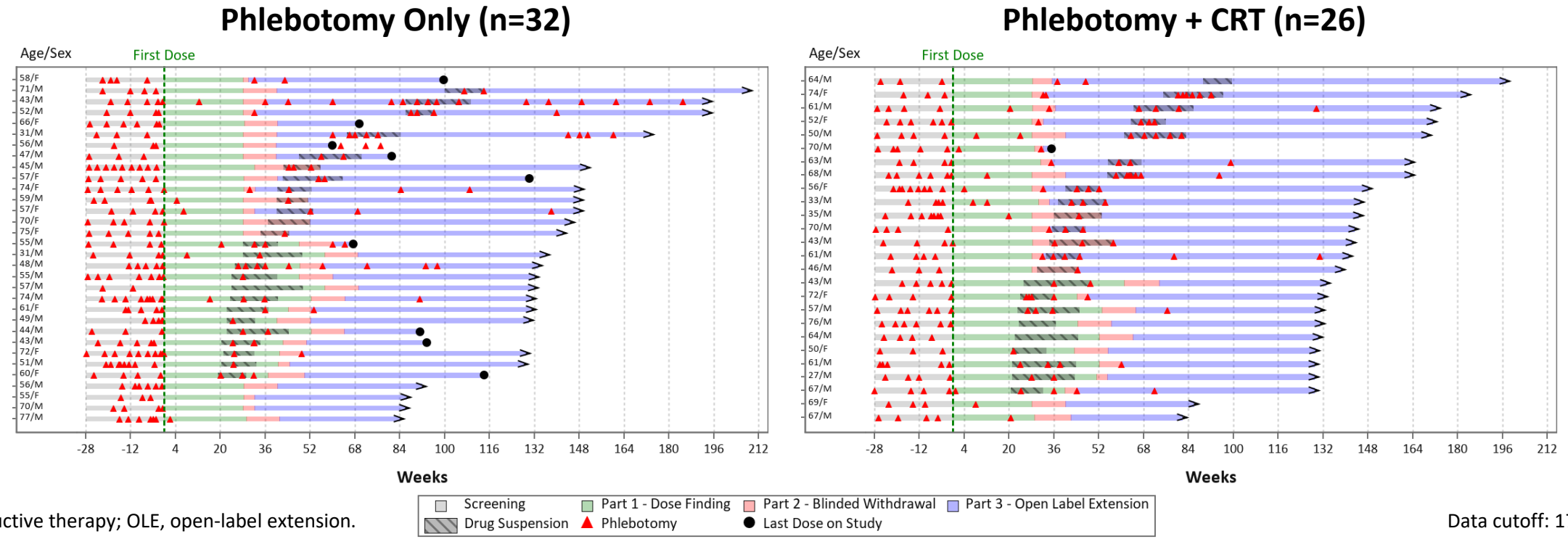
HCT, hematocrit; JAK2, Janus Kinase 2; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

1. Kuykendall AT. Ann Hematol. 2023. 2. Mora B, Passamonti F. Clin Lymphoma Myeloma Leuk. 2023;23(2):79-85. 3. Kremyanskaya M, et al. EHA2023. (Abstract LB2710).

Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

Rusfertide Decreased the Frequency of Therapeutic Phlebotomy
With or Without Concurrent Cytoreductive Therapy

- In patients who continued onto Part 3, 32 (55.2%) and 26 (44.8%) patients were treated with phlebotomy alone or phlebotomy with CRT, respectively
  - Of those patients receiving phlebotomy with CRT, 13 (22.4%) received hydroxyurea, 7 (12.1%) received interferon, 5 (8.6%) received a JAK inhibitor, and 1 patient (1.7%) received hydroxyurea and interferon

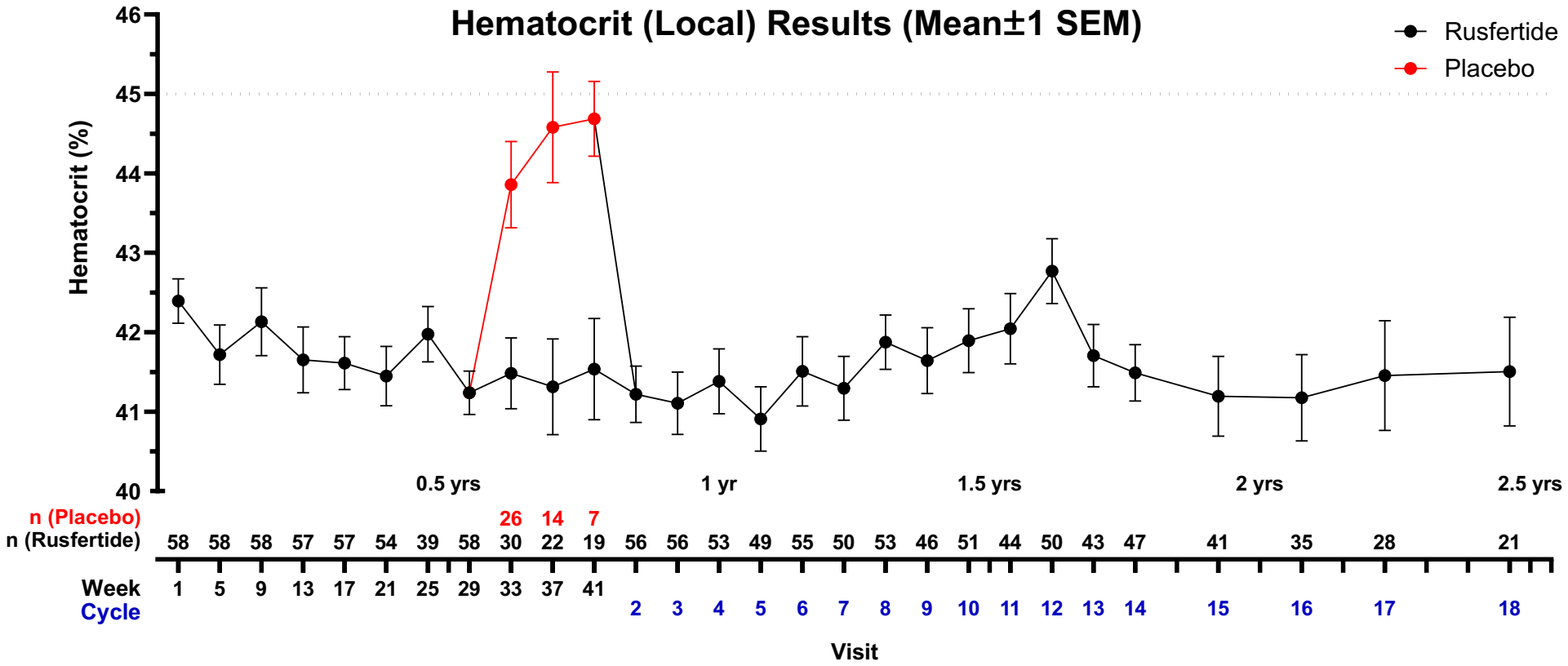


CRT, cytoreductive therapy; OLE, open-label extension.

Data cutoff: 17 October 2023

Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

Rusfertide Provided Durable Control of Hematocrit Through 2.5 Years



- Rusfertide treatment resulted in consistent maintenance of hematocrit <45%

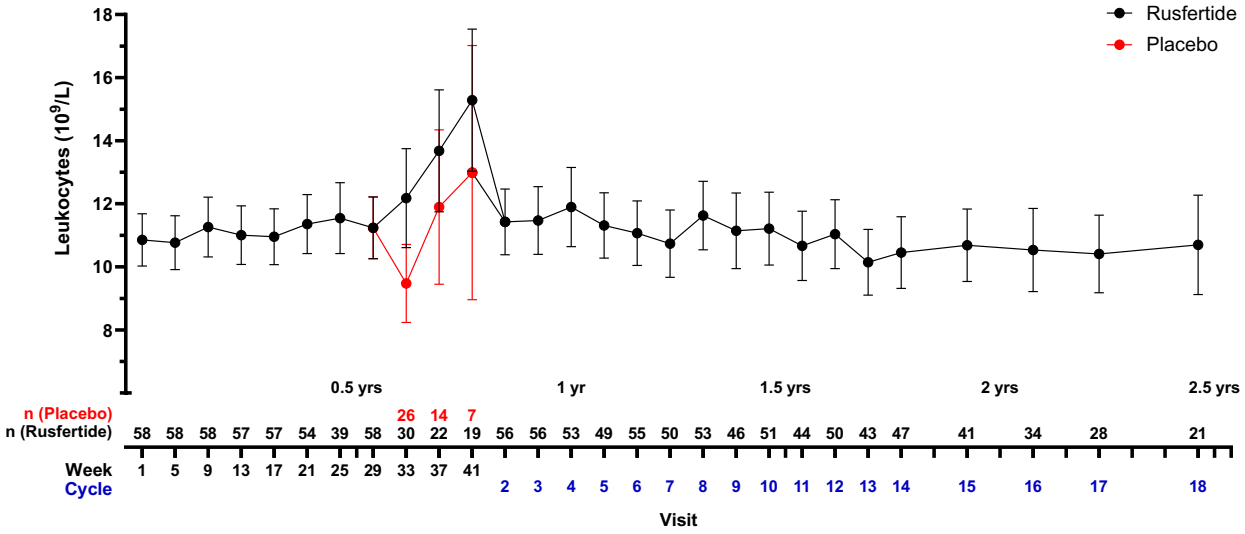
Dotted horizontal line, hematocrit <45%.
SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

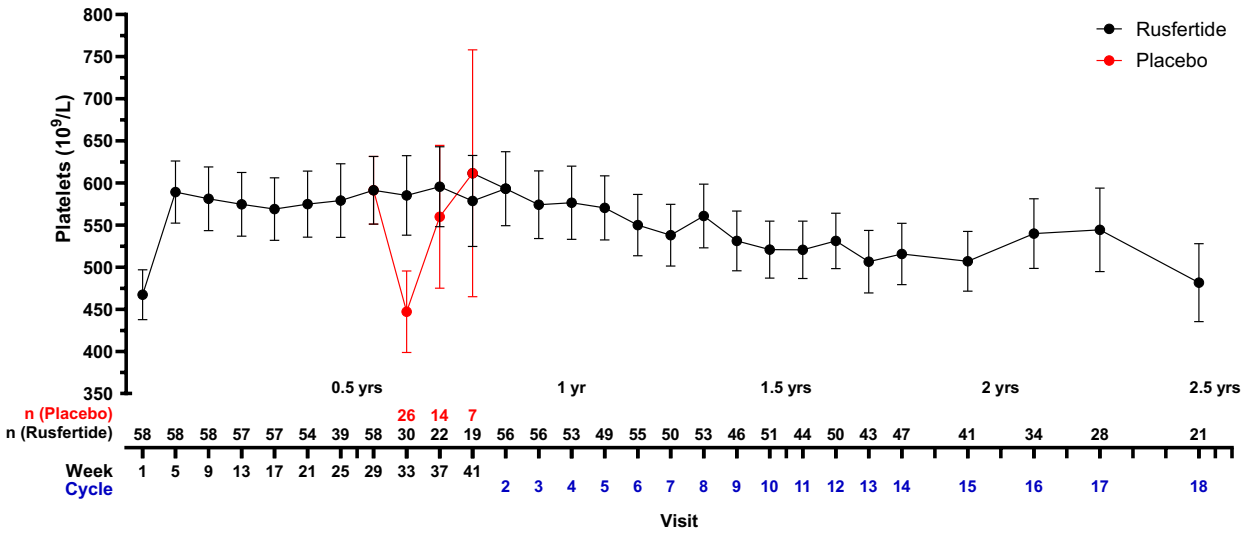
Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

Leukocytes Were Stable; Platelet Counts Increased During Initial Treatment and Remain Stable Over Time

Leukocytes (Local) Results (Mean±1 SEM)



Platelets (Local) Results (Mean±1 SEM)



- Mean leukocyte counts remained stable and did not change meaningfully over the duration of the trial

- After increasing by approximately 30% post-baseline, mean platelet counts stabilized over time

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

Data cutoff: 17 October 2023

Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

Conclusions

- Rusfertide added to therapeutic phlebotomy with or without cytoreductive therapy provided long-term durable control of hematocrit and decreased phlebotomy use
- Rusfertide resulted in improved and normalized serum ferritin levels through 2.5 years
- After rising by ≈30%, platelets remained stable over time with continued rusfertide therapy
- Rusfertide is well-tolerated and has a safety profile consisting mostly of Grade 1 or 2 injection site reactions
  - Approximately 75% of TEAEs were grade 1 or 2; fewer than 25% of patients had a grade 3 AE
  - Second malignancies were reported in 8 patients on study
    - Prior malignancies, prior lesions, and/or the patient's medical history may have contributed to the etiology of these second malignancies
  - TEs were reported in 5 patients
    - Most patients (85.7%; 12 of 14) who experienced a TE prior to study entry did not have a recurrent TE on study (all TEs occurred in high-risk patients – none occurred in low-risk patients)

Practical take-home messages

Rusfertide may be useful in achieving Hct control in pts with high phlebotomy need or phlebotomy intolerance

Rusfertide does not modify platelet and leukocyte count
→ It must be combined with cytoreduction when needed!

Phase 3 Study VERIFY (NCT05210790): Rusfertide vs Placebo in Patients With PV

POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

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Grazie!

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