Myeloproliferative Neoplasms: What's New In 2023?

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Disclosures

- **Steering Committee/Scientific Advisory Board/Consulting**: AbbVie, BMS, Genentech, Servier, Sanofi

- **Trial Support**: AbbVie, Astra Zeneca, Genentech, New Wave, Pfizer

Outline – MPN at ASH 2023

1. Polycythemia Vera / Essential Thrombocythemia

- **Abstract 748 (Ianotto JC):** Impact of cytoreductive drugs upon outcomes in a contemporary cohort of adolescent and young adults with essential thrombocythemia and polycythemia vera
- **Abstract 746 (Knudsen TA):** Final Analysis of the **DALIAH Trial**: A Randomized Phase III Trial of Interferon-α Versus Hydroxyurea in Patients with MPN
- **Abstract 745 (Ritchie EK):** Durability of Hematocrit Control in Polycythemia Vera With the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results From the **REVIVE Study**

2. Myelofibrosis

- **Abstract 628 (Rampal R):** Pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve patients with myelofibrosis: results of the **MANIFEST-2** randomized, double-blind, Phase 3 study
- **Abstract 620: (Pemmaraju N): TRANSFORM-1**: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Phase 3 Study of Navitoclax in Combination With Ruxolitinib Versus Ruxolitinib Plus Placebo in Patients With Untreated Myelofibrosis

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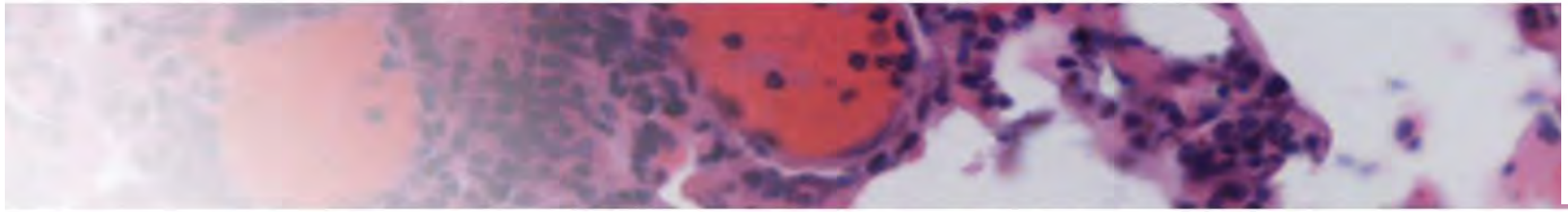
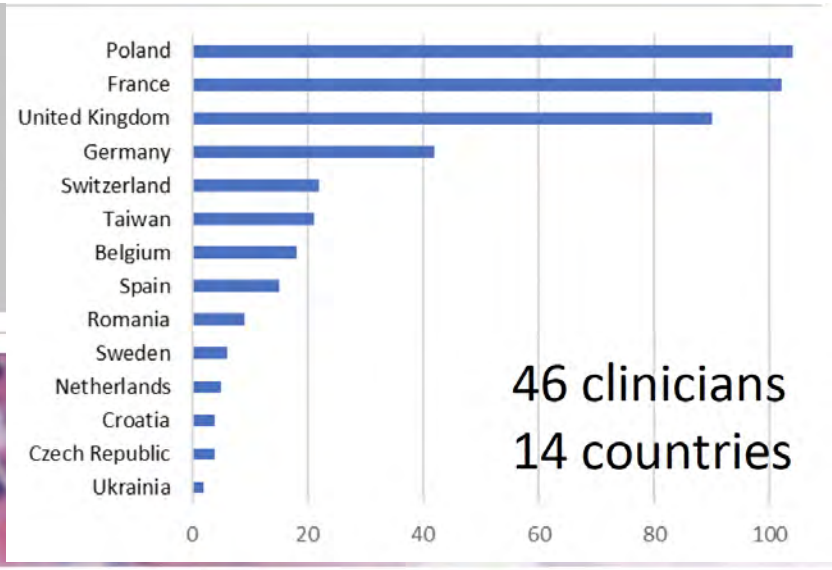
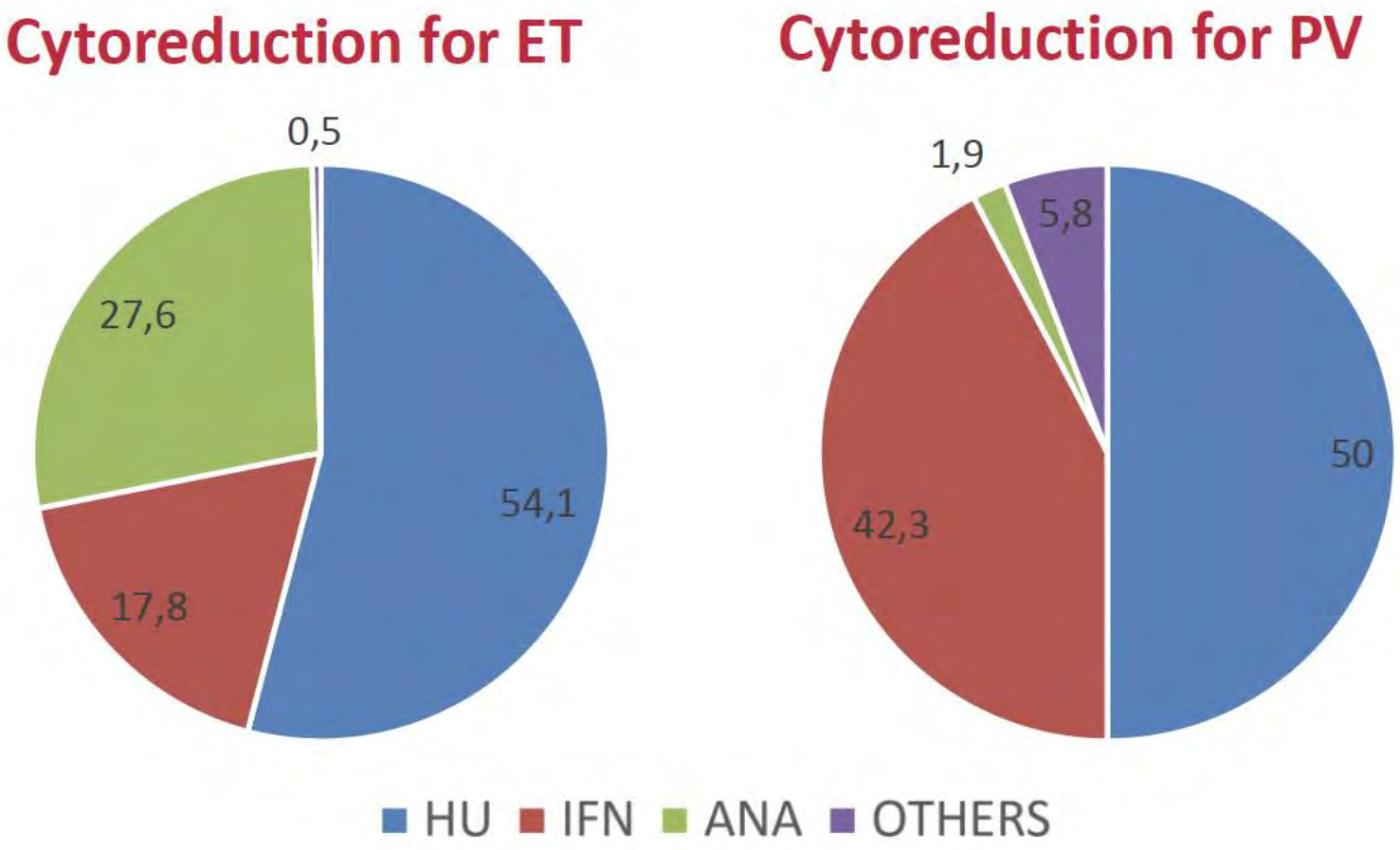




Impact of cytoreductive drugs upon outcomes in a contemporary cohort of adolescent and young adults with essential thrombocythemia and polycythemia vera

Y. Beauverd, **JC. Ianotto**, H. Thaw, M. Sobas, P. Sadjadian, N. Curto-Garcia, L. Yung Shih, T. Devos, D. Krochmalczyk, S. Galli, M. Bieniaszewska, I. Seferynska, MF. McMullin, A. Armatys, A. Spalek, J. Waclaw, M. Zdrenghea, L. Legros, F. Girodon, K. Lewandowski, A. Angona Figueras, J. Samuelsson, A. Abuin Blanco, P. Cony-Makhoul, A. Collins, C. James, R. Kusec, M. Lauermannova, M. Sol Noya, M. Skowronek, L. Szukalski, A. Szmigielska-Kaplon, M. Wondergem, I. Dudchenko, J. Gora Tybor, K. Laribi, A. Kulikowska de Nalecz, JL. Demory, K. Le Du, S. Zweegman, C. Besses Raebel, R. Skoda, S. Giraudier, M. Griesshammer, JJ. Kiladjian, C.N. Harrison

Various indications for frontline therapy in ET and PV among children AYA cohort



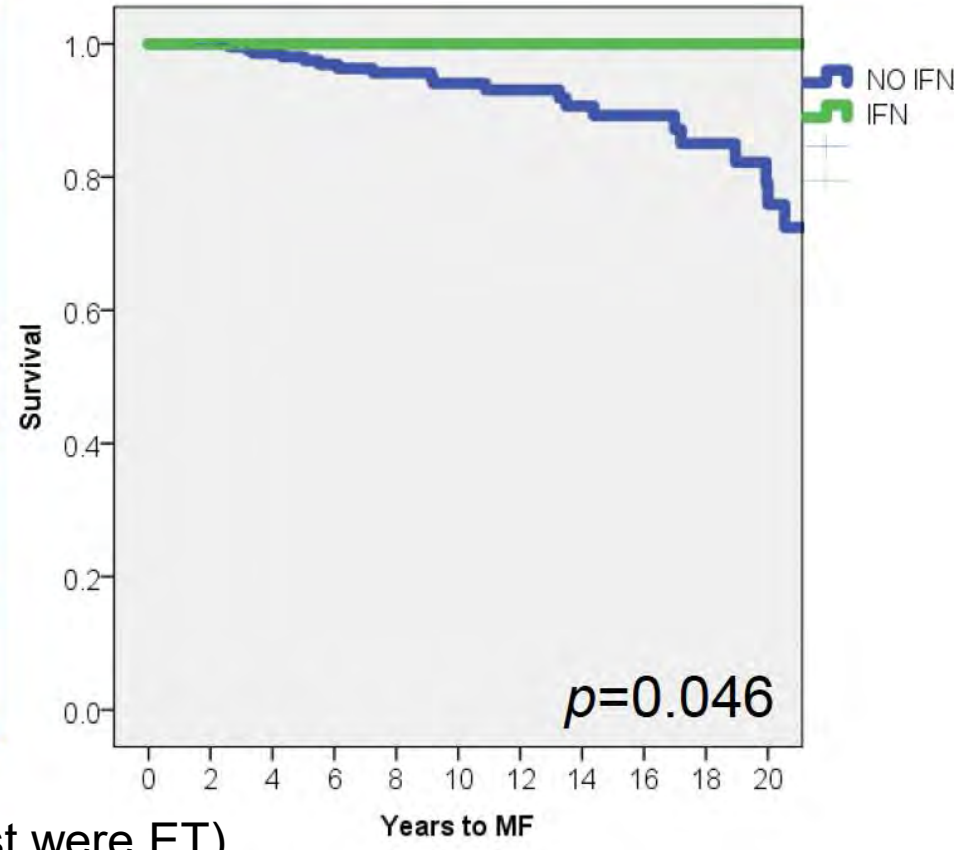
Cytoreductive drugs	All
None (%)	31.9
1 line (%)	27.9
2 lines (%)	23.6
≥3 lines (%)	16.6

Indication for Cytoreduction :

1) Platelet count (40%)
2) Thrombotic event (14%)
3) Symptoms (5%)
4) Others (3%)
5) Unknown (38%)

Cytoreductive Therapy For ET or PV Impacts Myelofibrosis Free Survival

All (n=348), first line	10 yrs MFS	20 yrs MFS
Interferon	100%	100%
Hydroxyurea	93% (86-99%)	74% (57-92%)
Anagrelide	92% (82-100%)	73% (40%-100%)
No cytoreduction	94% (88-100%)	74% (47-100%)



- 20% of children-AYA with ET/PV progress to sMF by 20 years (most were ET)
- IFN significantly reduces risk of progression to sMF
- CALR mutation presence is a risk factor for progression to sMF

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

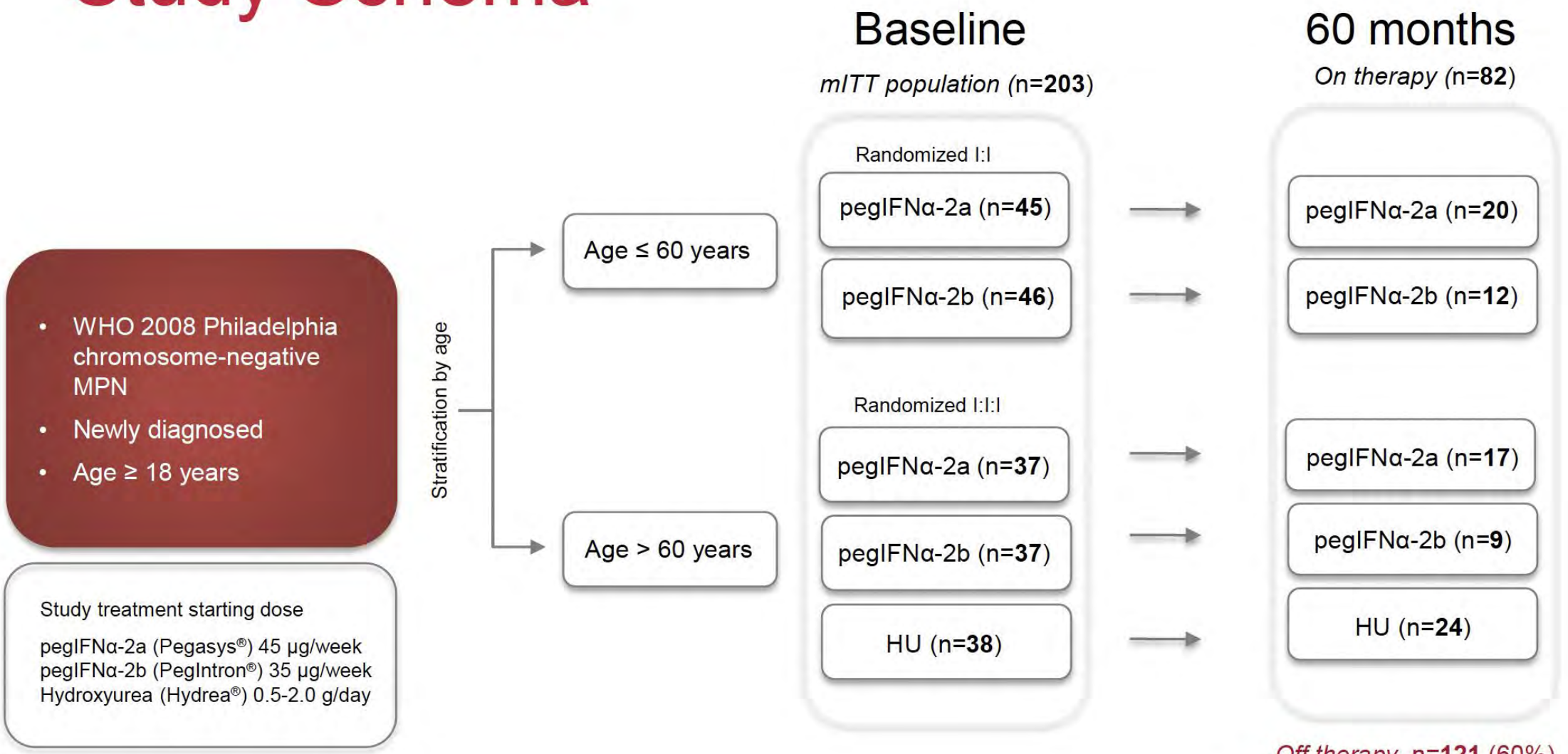
Daliah: Trial Objectives and Study Design

- **Primary Objectives:** To compare the **molecular response rates** of **low-dose pegIFNα vs HU** in patients with MPN by ELN criteria at 18, 36, and 60 months

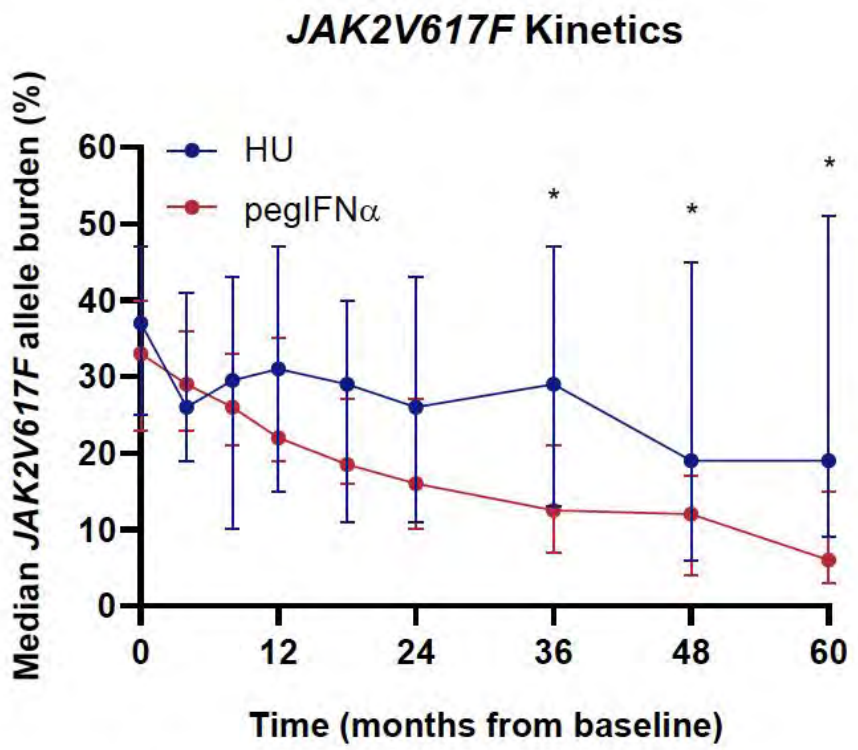
- **Secondary Objectives:** Complete clinicohematologic response rate (by ELN 2009 or EUMNET 2005 criteria at 12 months), histopathologic bone marrow response rate (by ELN 2009 or IWG-MRT 2006 criteria at 36 and 60 months), and treatment discontinuation rate (at 18 months)

- **Population**: Ph-Neg Newly Diagnosed MPN

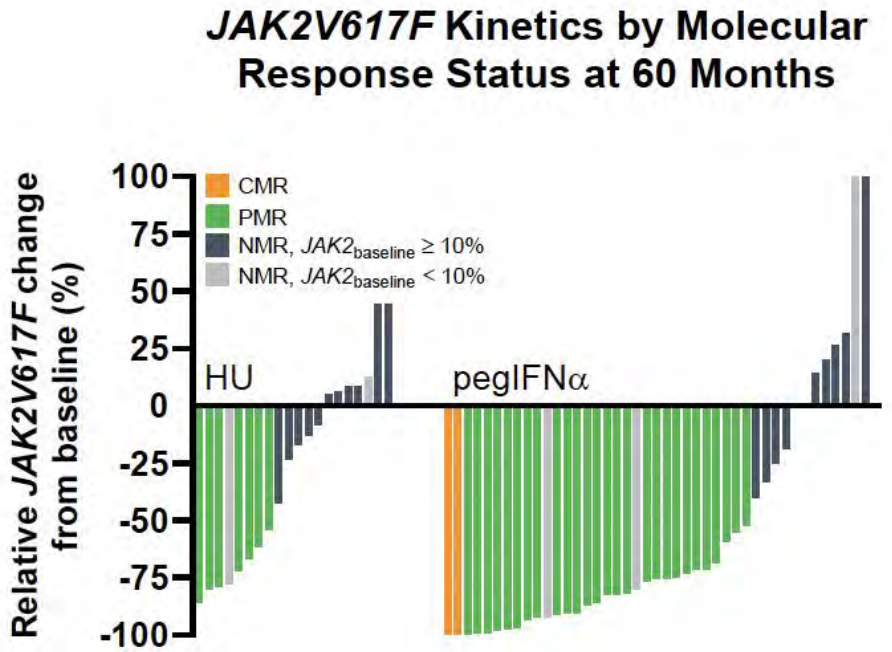
Study Schema



PegIFNα more effectively reduced JAK2V617F molecular burden at 36 months and beyond



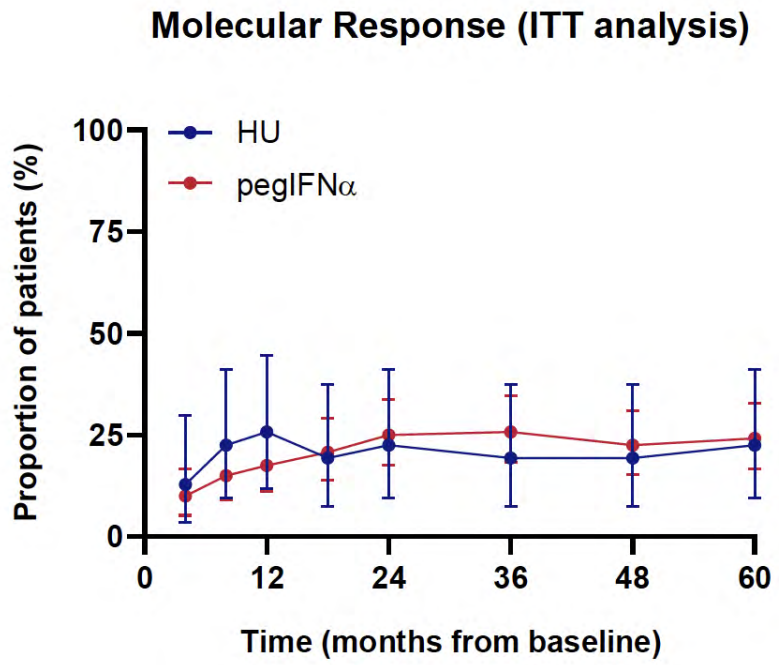
* indicate p<0.05 by Wilcoxon rank-sum test
Error bars indicate IQR intervals

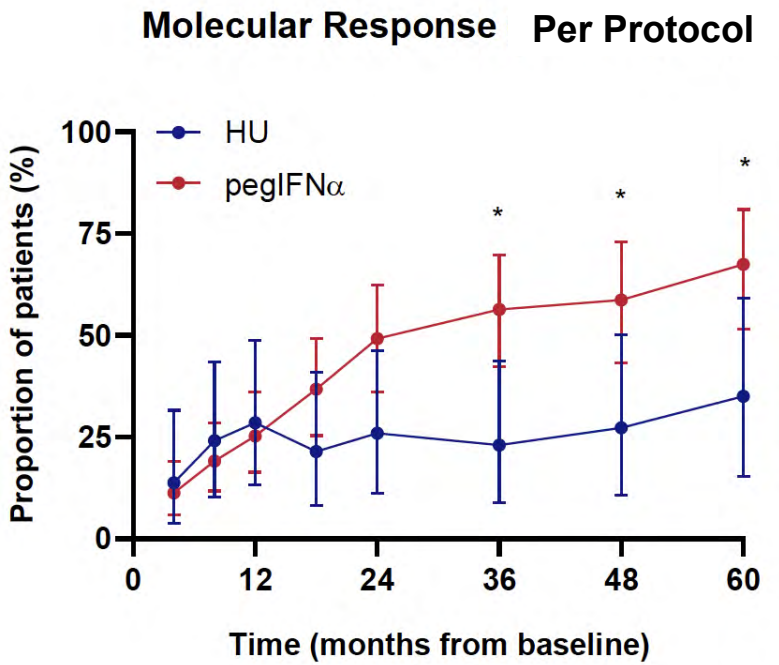


The absolute (IQR) change in *JAK2V617F* from baseline	HU	pegIFNα	*P* value*
Mo 60	-7% (3;-15)	-20% (-9;-49)	0.005

* indicate p<0.05 by Wilcoxon rank-sum test

No difference in Molecular Response by ITT-analysis with long-term treatment but observed in those that stay on pegIFN





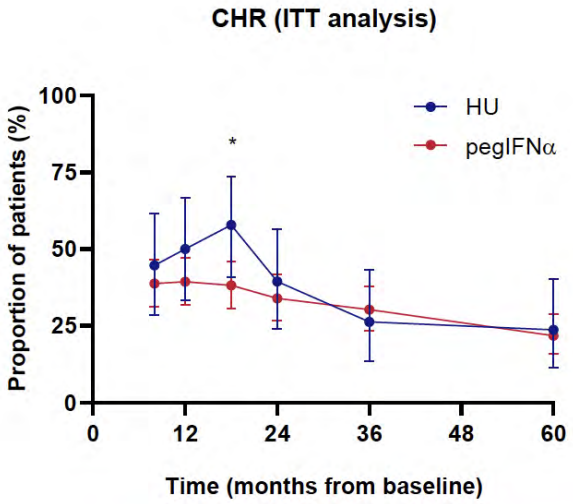
MR outcome n/N (%)	HU	pegIFNα	*P* value*
Mo 18	6/31 (19)	25/120 (21)	1.00
Mo 36	6/31 (19)	31/120 (26)	0.64
Mo 60	7/31 (23)	29/120 (24)	1.00

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

MR outcome n/N (%)	HU	pegIFNα	*P* value*
Mo 18	6/28 (21)	25/68 (37)	0.16
Mo 36	6/26 (23)	31/55 (56)	**0.01**
Mo 60	7/20 (35)	29/43 (67)	**0.03**

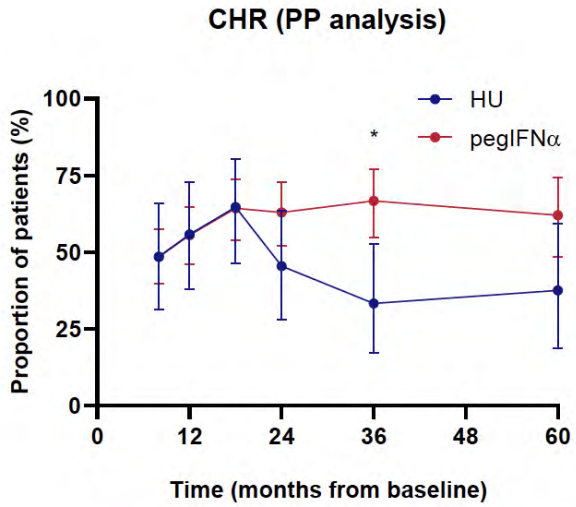
* indicate *P* value <0.05 by Fisher's exact test. Error bars indicate 95%CI

No difference in clinicohematologic response by ITT and worse fibrosis for those on pegIFNalpha



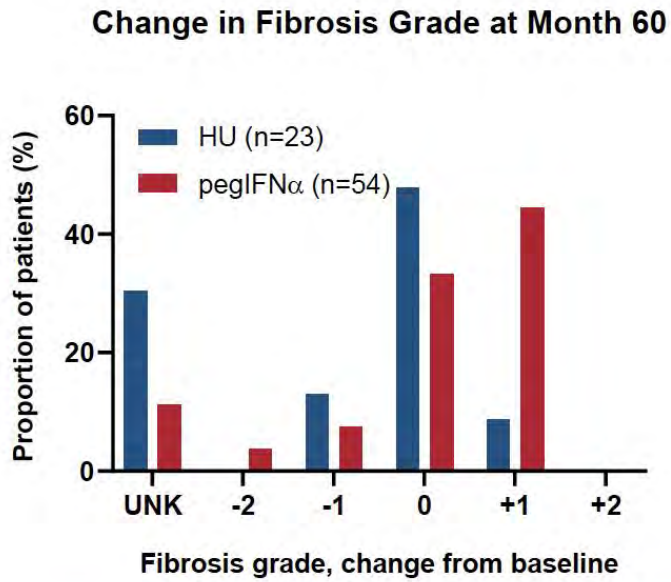
CHR outcome n/N (%)	HU	pegIFNα	*P* value*
Mo 12	19/38 (50)	65/165 (39)	0.27
Mo 60	9/38 (24)	36/165 (22)	0.83

* 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

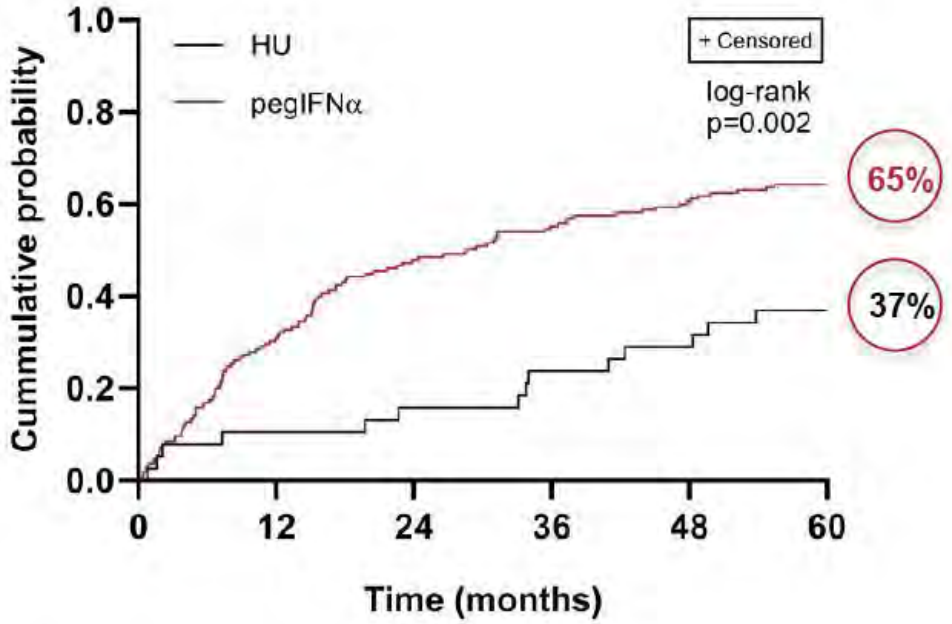
* indicate p<0.05 by Fisher's exact test. Error bars indicate 95%CI



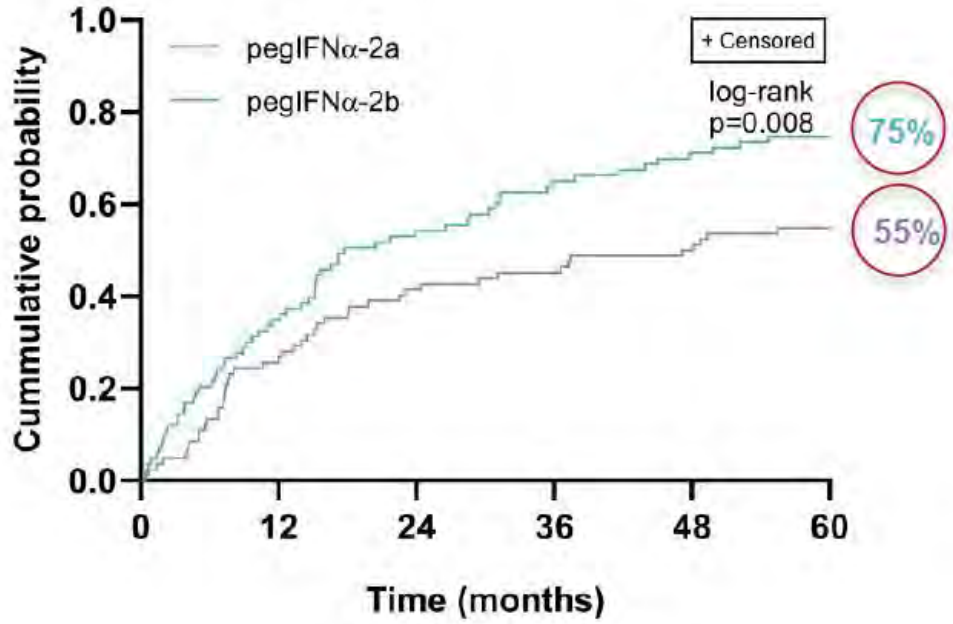
Change in fibrosis grade n/N (%)	HU	pegIFNα	*P* value*
Stationary or improved	14/23 (61)	24/54 (44)	0.12
Worsened	2/23 (9)	24/54 (44)	0.003

* Fisher's exact test

Rate of pegIFNα discontinuation was high despite a low-dose approach (65% pegIFNα vs 37% HU, p=0.002)



No at risk						
HU:	38	34	33	30	26	24
pegIFNα:	165	117	89	75	65	59



No at risk						
pegIFNα-2a:	82	61	50	45	40	37
pegIFNα-2b:	83	56	39	30	25	21

Toxicities not so different with HU vs pegIFN

MedDRA term, n (%)	HU n=38	pegIFNα > 60 years n=74	pegIFNα ≤ 60 years n=91	P*
Embolic and thrombotic events (SMQ term)	4 (11) 4 events	10 (14) 12 events	2 (2) 3 events	0.77
Malignant tumors (SMQ term)	7 (18) 7 events	6 (8) 7 events	2 (2) 2 events	0.13
Psychiatric disorders (SOC term)	19 (50)	39 (53)	62 (68)	0.84
Depression (SMQ term)	3 (8)	10 (14)	13 (14)	0.54
Alanine aminotransferase increased (PT term)	1 (3)	3 (4)	11 (12)	1.00
Thyroid dysfunction (SMQ term)	1 (3)	5 (7)	5 (5)	0.66

* p-value by Fishers' exact test comparing HU with pegIFNα group > 60 years
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; Standardized MedDRA Queries; SOC: System Organ Class; PT: Preferred Term
Events of "special interest" were defined retrospectively. Events were registered until 28 days after the last administration of study therapy.

None of the patients transformed to sMF, MDS, or sAML
Five patients died during follow-up (HU: n=2; pegIFNα > 60 years: n=2; pegIFNα ≤ 60 years: n=1)

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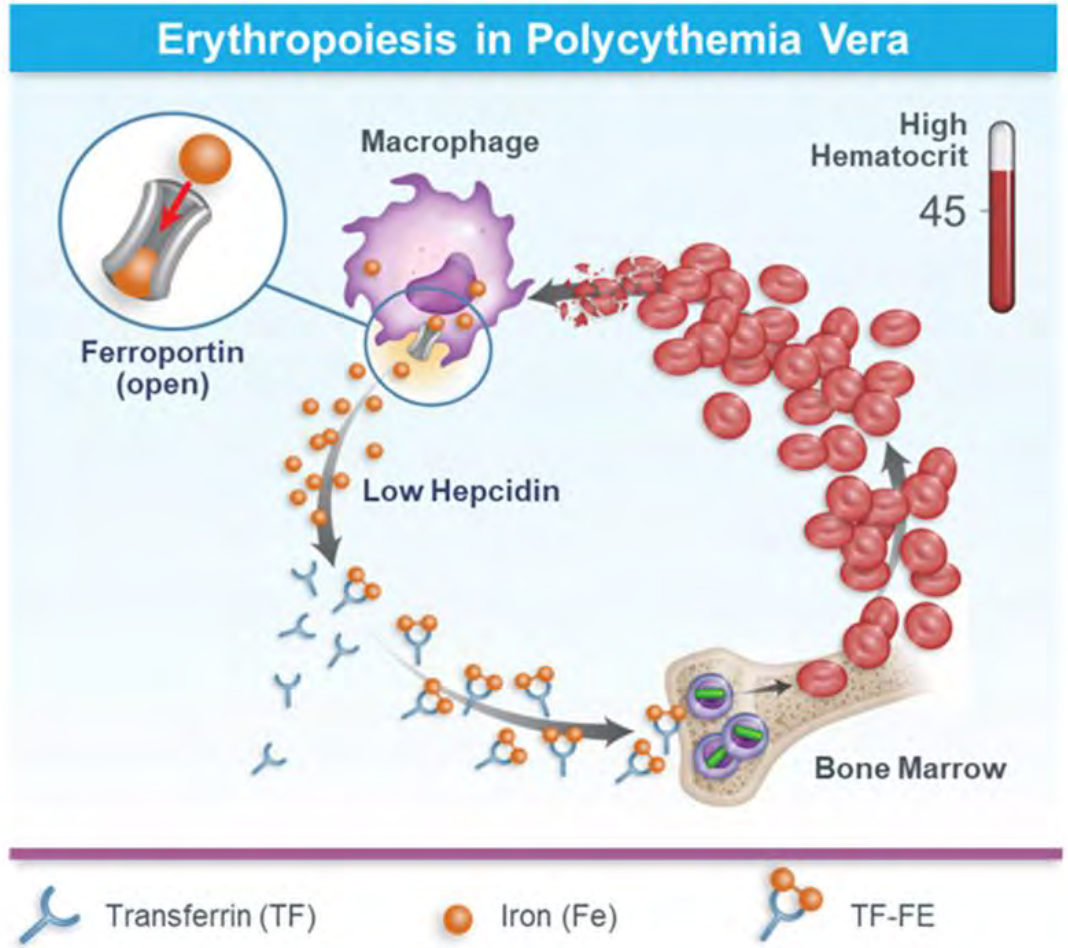
Durability of Hematocrit Control in Polycythemia Vera With the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results From the REVIVE Study

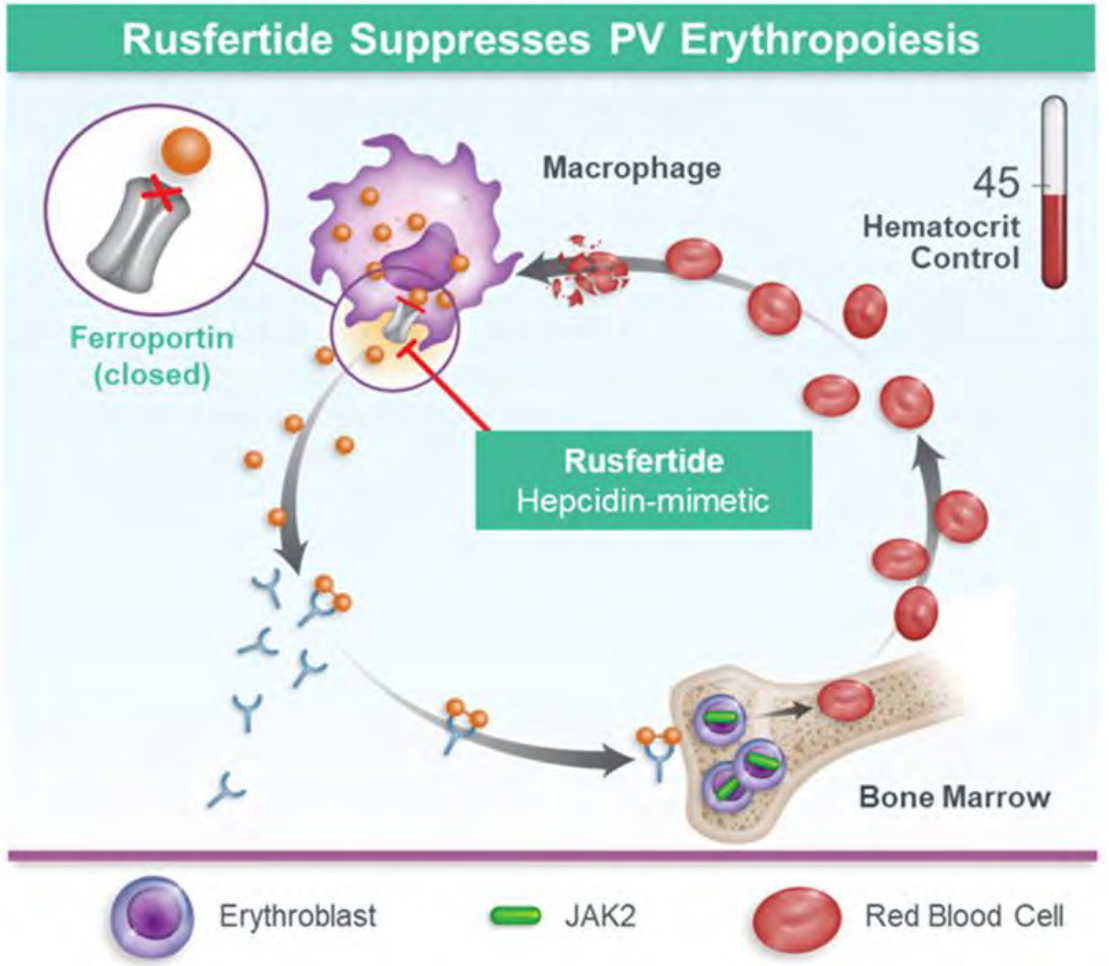
Presenter: Ellen K Ritchie, MD

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

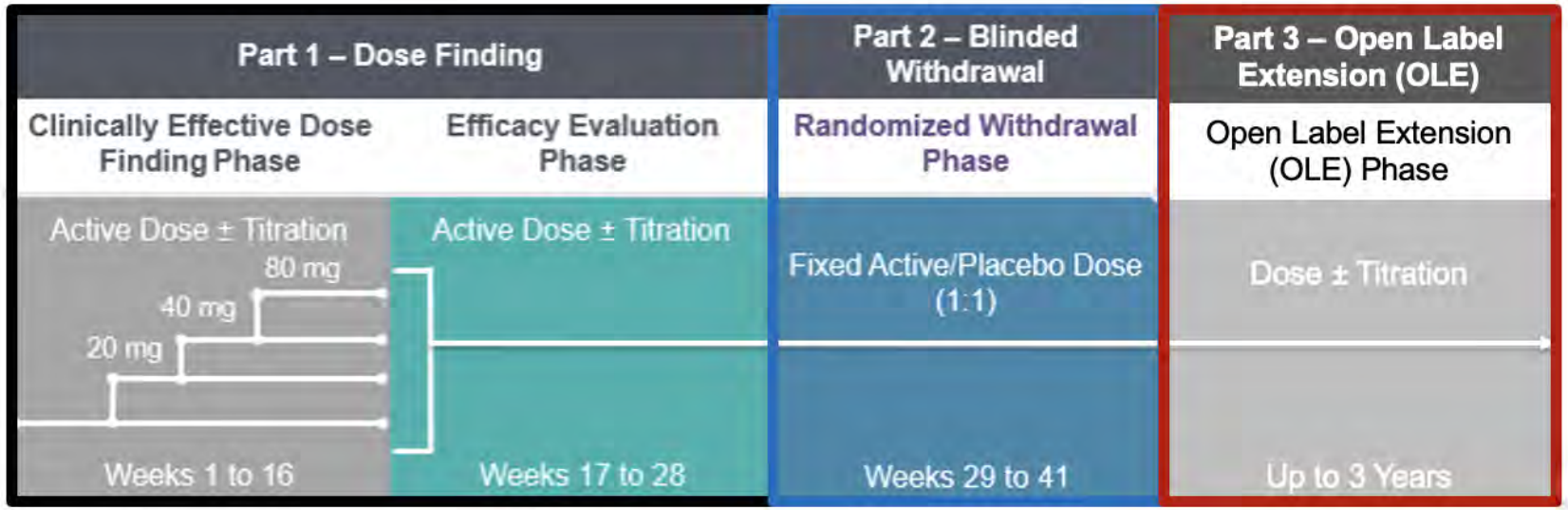
Rusfertide (PTG-300) is a hepcidin-mimetic that limits iron availability thereby controlling red blood cell production



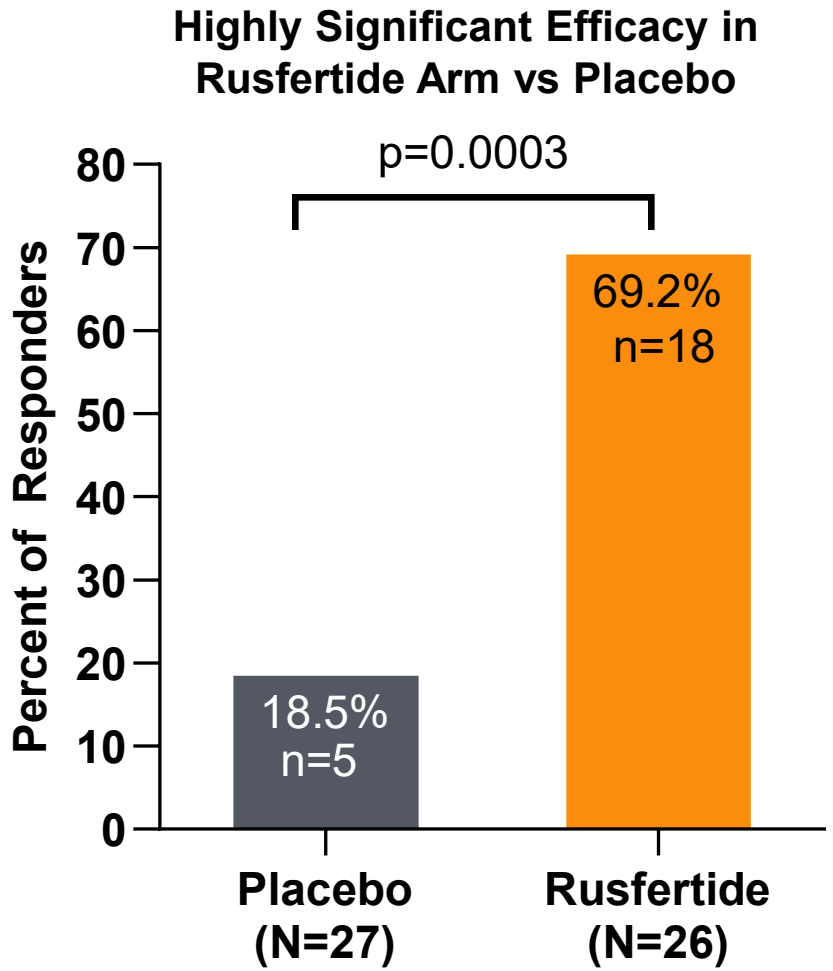


Kremyanskaya M, et al. EHA2023. (Abstract LB2710).

REVIVE: Primary objective was to provide long-term follow up of Part 3

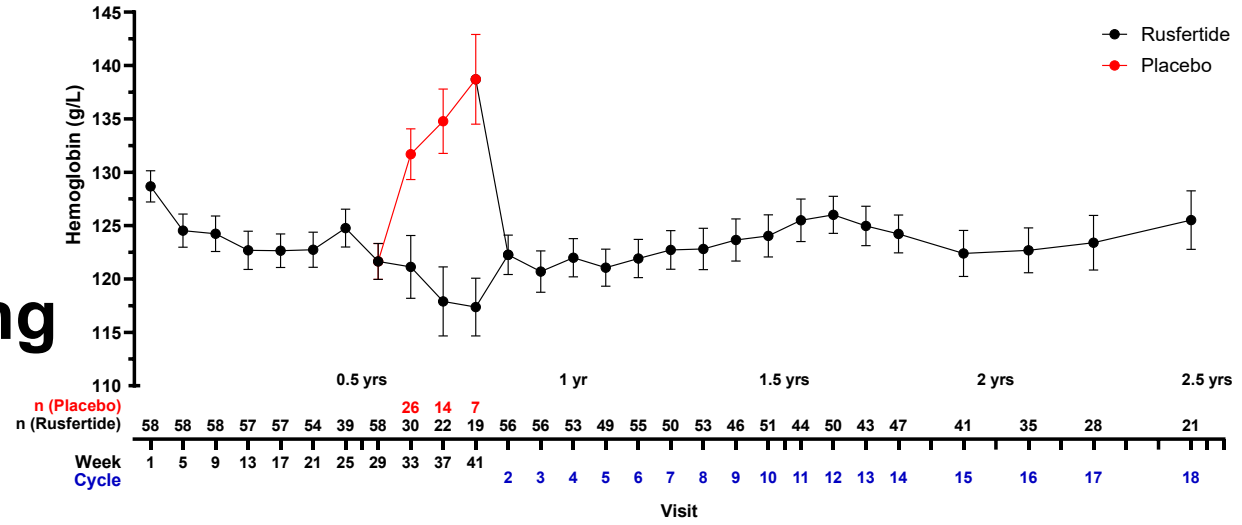


Eligible: PV and ≥3 phleb in 28 wks prior to enrollment with or without cytoreductive therapies

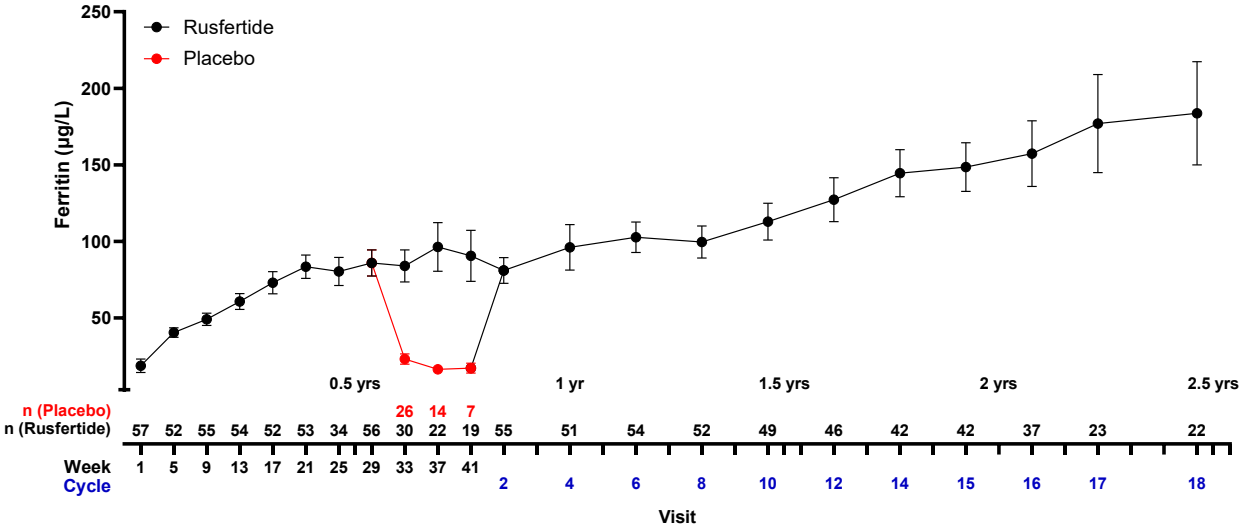


Rusfertide provides durable control of hematocrit, decreases phlebotomy use and normalizes serum ferritin levels through 2.5 years (reversing "iron deficiency"

Hemoglobin (Local) Results (Mean ± 1 SEM)



Serum Ferritin (Central) Data (Mean ± 1 SEM)



NEXT STEP

- Phase 3 Study VERIFY (NCT05210790): Rusfertide vs Placebo in Patients With PV
  ≈250 Patients with PV Are Being Randomized Globally
- 1° Endpoint: Proportion of patients achieving response, defined as absence of phlebotomy eligibility (Weeks 20-32); and comparing mean number of phlebotomies (Weeks 0-32)

Cancer History and Second Malignancies Reported on Study

Case	Age/Sex	Race	Malignancy	Grade	Relation	Day	Medical History	Prior PV treatment	Patient Status
Patients With Prior History of Skin Cancer									
1	72/F	White	• SCC in situ	2	• Not related	50	• Melanoma and multiple SCC	• HU ongoing for 5 years prior to event onset	• Ongoing (128+ weeks on study)
2	64/M	White	• BCC • Malignant melanoma Stage I	2 2	• Not related • Not related	171 171	• Multiple BCC • Multiple BCC	• Ruxolitinib ongoing for 15 months prior to onset of first event	• Ongoing (128+ weeks on study)
3	64/M	White	• SCC in situ • AML	1 3	• Not related • Unlikely related	226 253	• Melanoma and BCC • Radioiodine treatment for thyroid cancer (2015)	• HU ongoing for ≈5 years prior to onset of events	• Discontinued (Day 259)
4	70/F	American Indian/Alaska Native	• SCC in situ • BCC	2 2	• Unlikely related • Unlikely related	307 814	• Multiple BCC and SCC	• Ruxolitinib for 11 months, stopped ≈1 year before event onset	• Ongoing (144+ weeks on study)
5	68/M	White	• BCC	2	• Unlikely related	798	• BCC	• HU ongoing for 6 years prior to event onset	• Ongoing (160+ weeks on study)
Patients With Preexisting Lesions Prior to Rusfertide Exposure									
6	55/M	White	• BCC	2	• Unlikely related	234	• Preexisting lesion (captured in medical history; diagnosed only after initiation of rusfertide)	• None	• Discontinued (Day 498)
7	51/M	White	• Malignant melanoma Stage Ia	2	• Possibly related	562	• Undiagnosed lesion in the same area present prior to rusfertide exposure; history of atypical moles	• None	• Ongoing (128+ weeks on study)
Patients with Prior History of Cancer									
8	57/F	White	• Lung cancer	3	• Not related	226	• Cervix carcinoma, COPD, history of tobacco use	• Ruxolitinib, HU	• Discontinued (Day 988)

- In REVIVE, 19 of 70 patients (27.1%) had a history of cancer prior to enrolling on study
  - Of these patients, 10 (14.3%) had a history of skin cancer

*Day, time from first dose of rusfertide to diagnosis of malignancy on study.
AML, acute myeloid leukemia; BCC, basal cell carcinoma; HU, hydroxyurea; [illegible]cinoma.

Data cutoff: 17 October 2023

Remaining questions

- For patients warranting cytoreduction – in which patients should interferon be used as frontline therapy for PV/ET?
- Which genetic subsets?
- Why is there discrepancy between disease modification and clinical outcome?

Pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve patients with myelofibrosis: results of the MANIFEST-2 randomized, double-blind, Phase 3 study

Raajit Rampal,[1] Sebastian Grosicki, Dominik Chraniuk, Elisabetta Abruzzese, Prithviraj Bose, Aaron T Gerds, Alessandro M Vannucchi, Francesca Palandri, Sung-Eun Lee, Vikas Gupta, Alessandro Lucchesi, Stephen Oh, Andrew T Kuykendall, Andrea Patriarca, Alberto Álvarez-Larrán, Ruben Mesa, Jean-Jacques Kiladjian, Moshe Talpaz, Morgan Harris, Sarah-Katharina Kays, Anna Maria Jegg, Qing Li, Barbara Brown, Claire Harrison*, John Mascarenhas*

*Both authors contributed equally

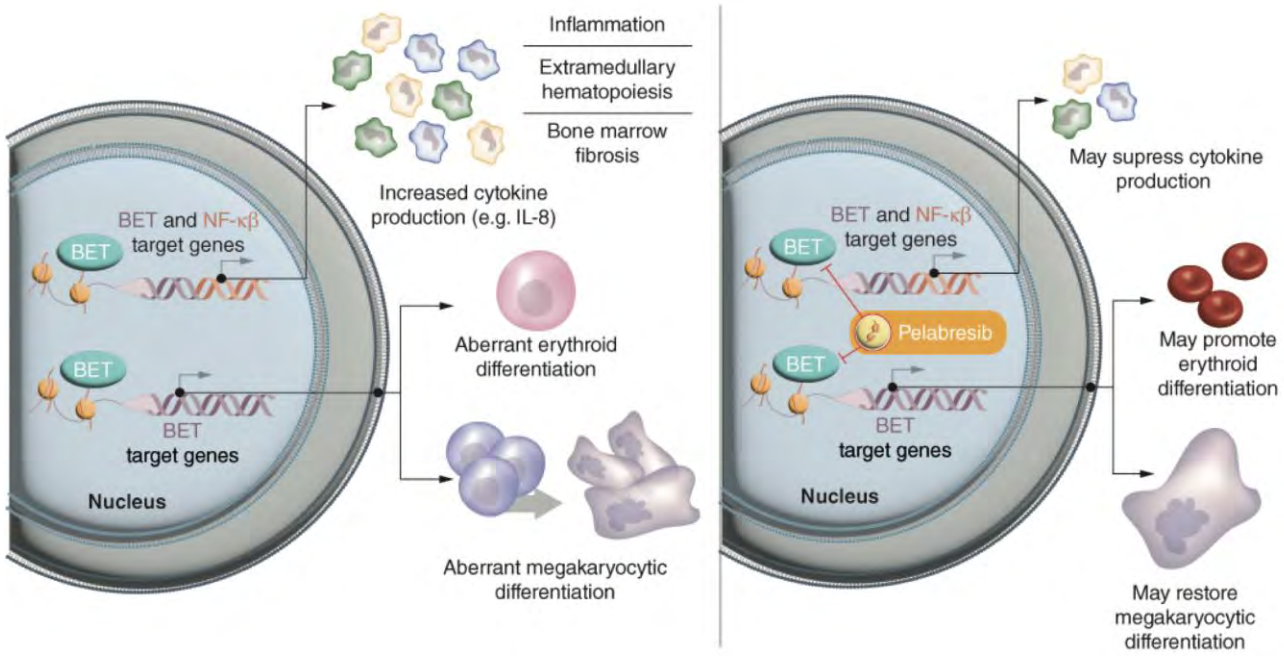
[1]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

Abstract 628 (Rampal R)

Courtesy of Dr. R Rampal

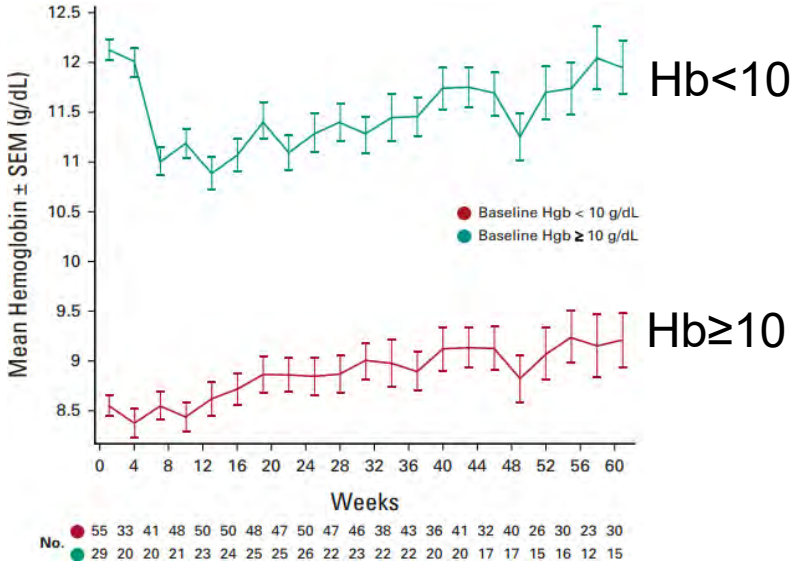
Pelabresib (CPI-0610) inhibits BET proteins and decreases BET-mediated gene expression



Harrison CN et al., Future Oncology, 2022

<u>MANIFEST (Phase 2):</u> Pelabresib+Rux in Treatment Naïve MF

- TSS50 was 56% at week 24 and 83% at anytime
- BM fibrosis improved in 28%
- Mean Hb increase in ≥1.5 g/dL from baseline over 12-week period in 24%

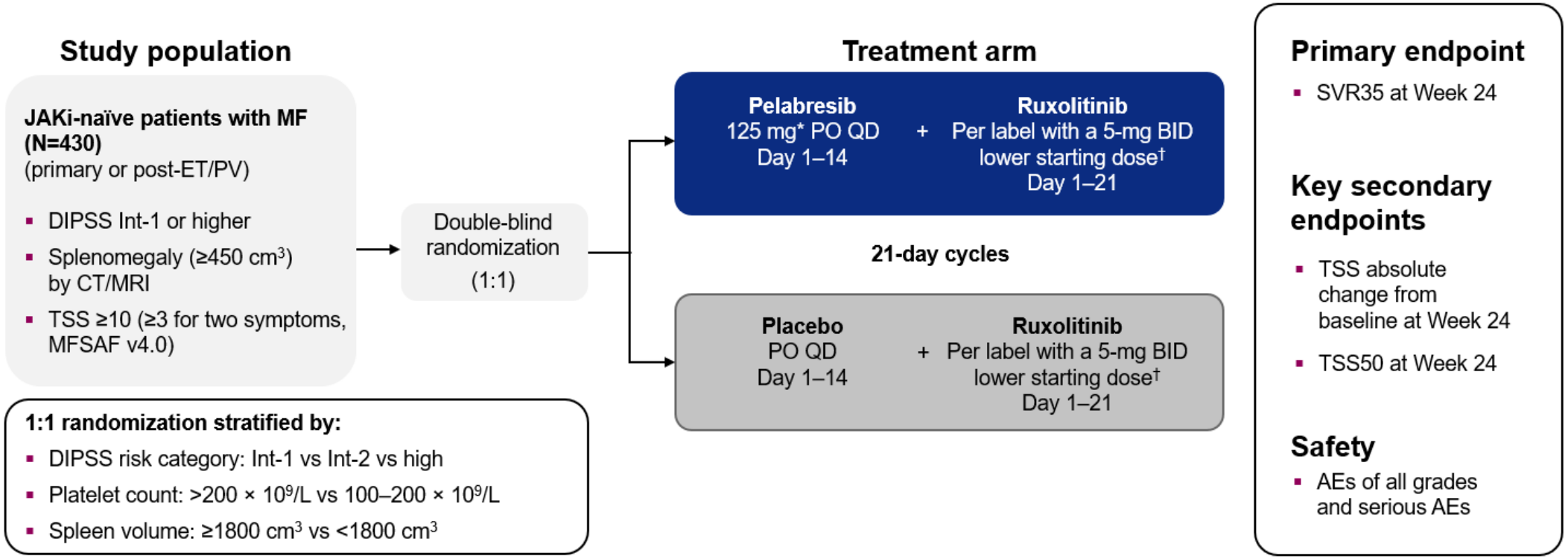


Hb<10

Hb≥10

Mascarenhas J et al., J Clin Oncol, 2023

Global, randomized, double-blind, active-control, Phase 3 study



AE, adverse event; BID, twice daily; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imagining; PO, orally; PV, polycythemia vera; QD, once daily; SVR35, ≥35% reduction in spleen volume; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score. *The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD; †Ruxolitinib was started at 10 mg BID (baseline platelet count 100–200 × 10⁹/L) or 15 mg BID (baseline platelet count >200 × 10⁹/L) with a mandatory dose increase by 5 mg BID after one cycle and a maximum dose of 25 mg BID per label. Harrison CN, et al. *Future Oncol.* 2022;18(27):2987-29977.

Rampal R, et al. ASH 2023. Oral 628

Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

Baseline disease characteristics

Characteristic		Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Age — years	Median (min, max)	66 (19, 84)	66 (26, 88)
Sex — n (%)	Female / male	85 (39.7) / 129 (60.3)	94 (43.5) / 122 (56.5)
Race — n (%)	White / Asian / Black American Indian or Alaska Native Not reported / Unknown	160 (74.8) / 35 (16.4) / 2 (0.9) 1 (0.5) 15 (7.0) / 1 (0.5)	163 (75.5) / 42 (19.4) / 0 0 11 (5.1) / 0
Myelofibrosis subtype — n (%)	Primary myelofibrosis Post-polycythemia vera myelofibrosis Post-essential thrombocytopenia myelofibrosis	107 (50) 45 (21) 62 (29)	110 (50.9) 53 (24.5) 53 (24.5)
Dynamic International Prognostic Scoring System — n (%)	Intermediate-1 Intermediate-2 High-risk	128 (59.8) 75 (35) 11 (5.1)	127 (58.8) 74 (34.3) 15 (6.9)
Mutations — n (%)*	*JAK2* V617F *CALR* *MPL* Triple negative High-molecular risk mutations Missing	125 (67.2) 45 (24.2) 11 (5.9) 8 (4.3) 72 (38.7) 28 (13.1)	122 (64.6) 50 (26.5) 13 (6.9) 5 (2.6) 88 (46.6) 27 (12.5)
Hemoglobin — g/dL	Median (range) ≤10 — n (%)	10.9 (5.8–18.0) 70 (32.7)	11.0 (6.7–17.9) 76 (35.2)
Platelets — × 10^9/L	Median (min, max) >200 × 10^9/L — n (%)	285 (99, 1303) 154 (72)	287 (66, 1084) 157 (72.7)
Peripheral blasts	Mean (SD)	0.8 (1.18)†	0.8 (1.25)‡
RBC transfusions — patient n (%)	Requiring RBC transfusion at baseline	35 (16)	25 (12)
ECOG performance status — n (%)	0 1 ≥2 Missing	107 (50) 97 (45.3) 10 (4.7) 0	109 (50.5) 95 (44.0) 10 (4.6) 2 (0.9)
Spleen volume (central read)§	Median spleen volume (range) — cc	1308.89 (200.24–7117.03)	1382.97 (277.87–5540.45)
Total symptom score¶	Median total symptom score (range)	26.6 (7.3–66.4)	24.7 (9.0–68.4)

Data cut off: August 31, 2023. *CALR*, calreticulin; ECOG, Eastern Cooperative Oncology Group; *JAK*, Janus kinase; max, maximum; min, minimum; *MPL*, MPL proto-oncogene, thrombopoietin receptor; RBC red blood cell; SD, standard deviation. *Results do not originate from a validated programming environment. †n=208. ‡n=207. §Randomization of patients was based on local read. ¶Patients with baseline TSS values of <10 have at least 2 individual symptoms score ≥ 3 at baseline.

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Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

5

Note: DIPSS Intermediate-1: 59.8%

Patient disposition

	Pelabresib + ruxolitinib	Placebo + ruxolitinib
Randomized	214 (100%)	216 (100%)
Treated	212 (99.1%)	214 (99.1%)
Discontinued double-blind treatment	58 (27.1%)	54 (25.0%)
Adverse event	23 (10.7%)	14 (6.5%)
Physician decision (including lack of benefit)	9 (4.2%)	20 (9.3%)
Disease progression	5 (2.3%)	5 (2.3%)
Eligible for transplant	8 (3.7%)	9 (4.2%)
Other*	13 (6.0%)	6 (2.8%)
Ongoing on double-blind treatment	154 (72.0%)	160 (74.1%)

	Pelabresib + ruxolitinib	Placebo + ruxolitinib
Mean daily dose for pelabresib (14 days per 21-day cycle)	108 mg	N/A
Mean daily dose for ruxolitinib (daily)	29.3 mg	31.3 mg
Median follow-up on study (weeks)	45.4	

Data cut off: August 31, 2023. N/A, not applicable. *Other: non-compliance, withdrawal of consent. The study opened for enrollment in November 2020; the first patient received their initial treatment on April 22, 2021, and the last patient received their first treatment on March 2, 2023. Percentages reported are based on the number of patients randomized (intent-to-treat set).

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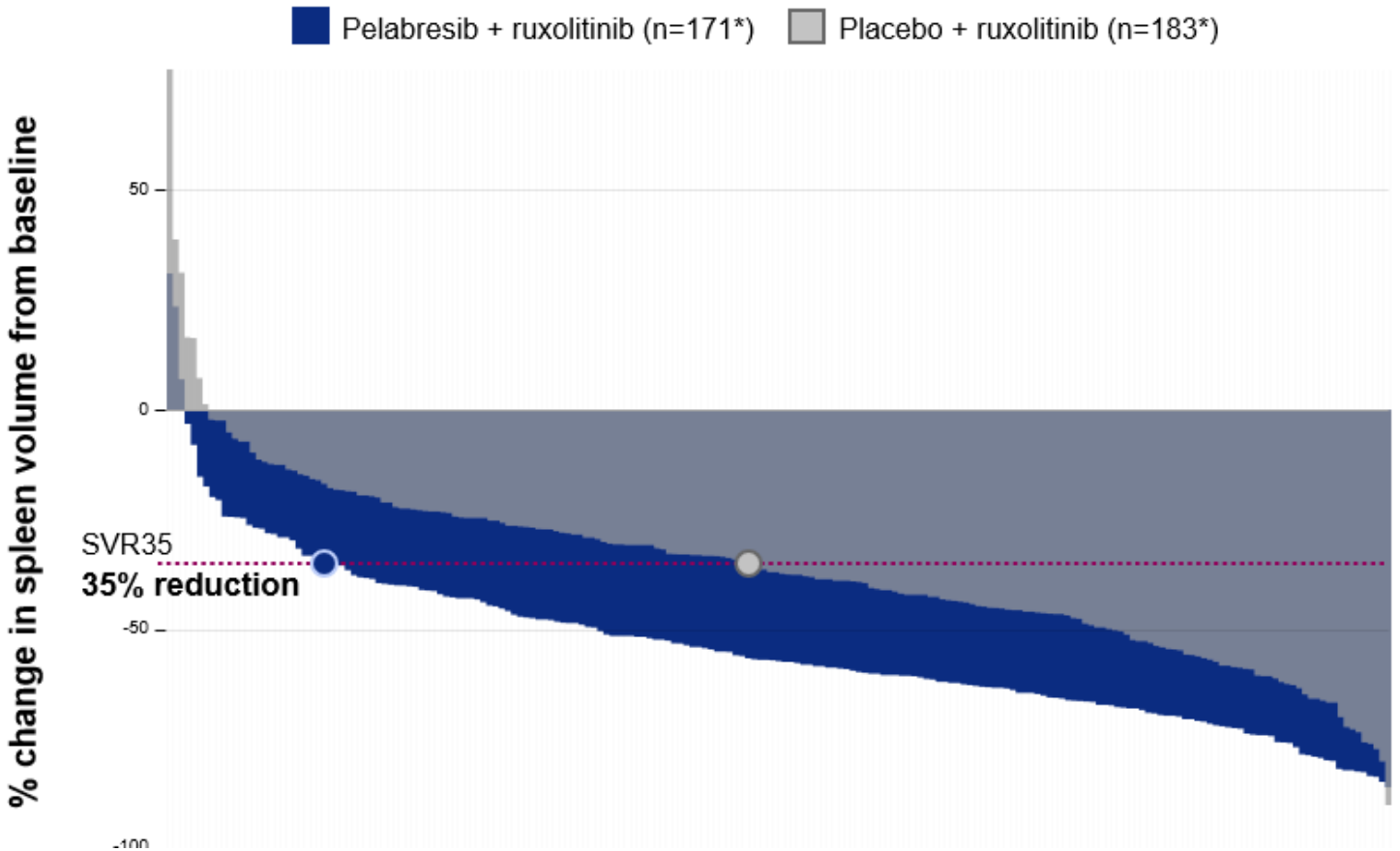
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

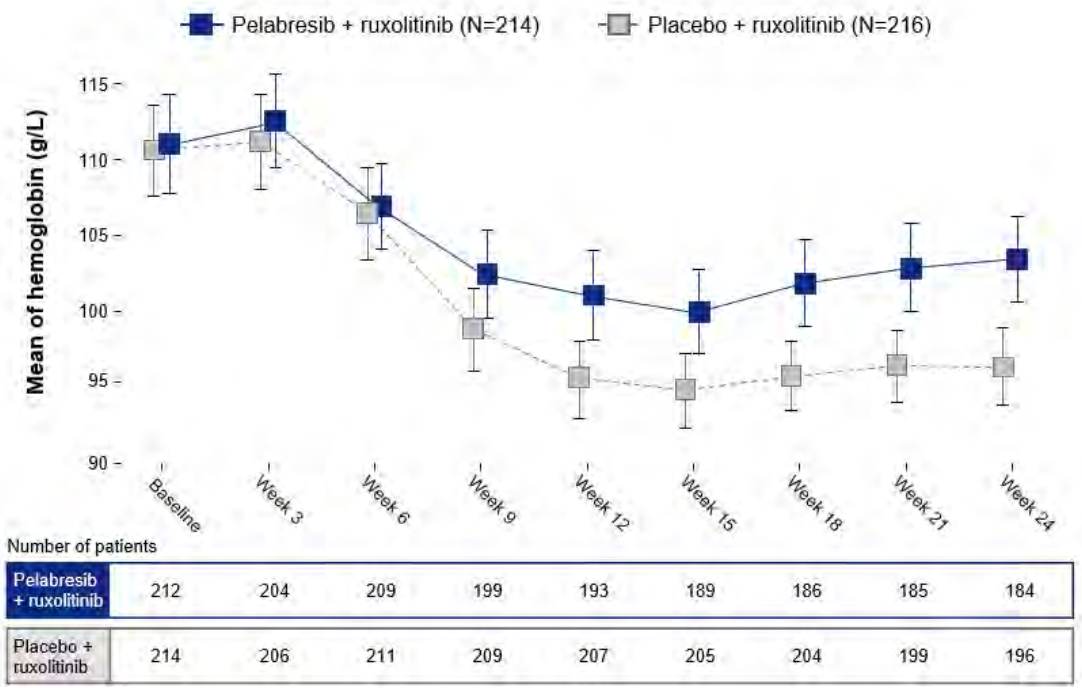
MANIFEST-2: Primary endpoint achieved SVR35 at week 24 (65.9% vs 35.2%)



ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
SVR35 at Week 24	65.9%	35.2%	
Difference† (95% CI)	30.4 (21.6, 39.3)		<0.001
Mean % change in spleen volume at Week 24‡	-50.6 (n=171)	-30.6 (n=183)	
95% CI	-53.2, -48	-33.7, -27.5	

MANIFEST-2: Longer term follow up needed to understand anemia responses



Follow up is short - only 45 weeks

ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Hemoglobin response* ≥1.5 g/dL mean increase (95% CI)	9.3% (5.45, 13.25)	5.6% (2.50, 8.61)
Patients requiring RBC transfusion during screening, n (%)	35 (16.4)	25 (11.6)
Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)	66 (30.8)	89 (41.2)

SECONDARY ENDPOINTS

Pela/Rux vs Pbo/Rux

- Absolute TSS at Week 24: ns
- TSS50 at Week 24: ns
- TSS domains at Week 24: ns
- Safety profile SAME
- Dual SVR35/TSS50: 40.2% vs 18.5%

TRANSFORM-1: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Phase 3 Study of Navitoclax in Combination With Ruxolitinib Versus Ruxolitinib Plus Placebo in Patients With Untreated Myelofibrosis

Naveen Pemmaraju[1], Adam J. Mead[2], Tim CP Somervaille[3], James McCloskey[4], Francesca Palandri[5], Steffen Koschmieder[6], David Lavie[7], Brian Leber[8], Su-Peng Yeh[9], Maria Teresa Gomez Casares[10], Emanuele Ammatuna[11], Ho-Jin Shin[12], Keita Kirito[13], Eric Jourdan[14], Timothy Devos[15], Hun S. Chuah[16], Atanas Radinoff[17], Andrija Bogdanovic[18], Rastislav Moskal[19], Qi Jiang[19], Avijeet S Chopra[19], Elektra J Papadopoulos[19], Jalaja Potluri[19], Francesco Passamonti[20]

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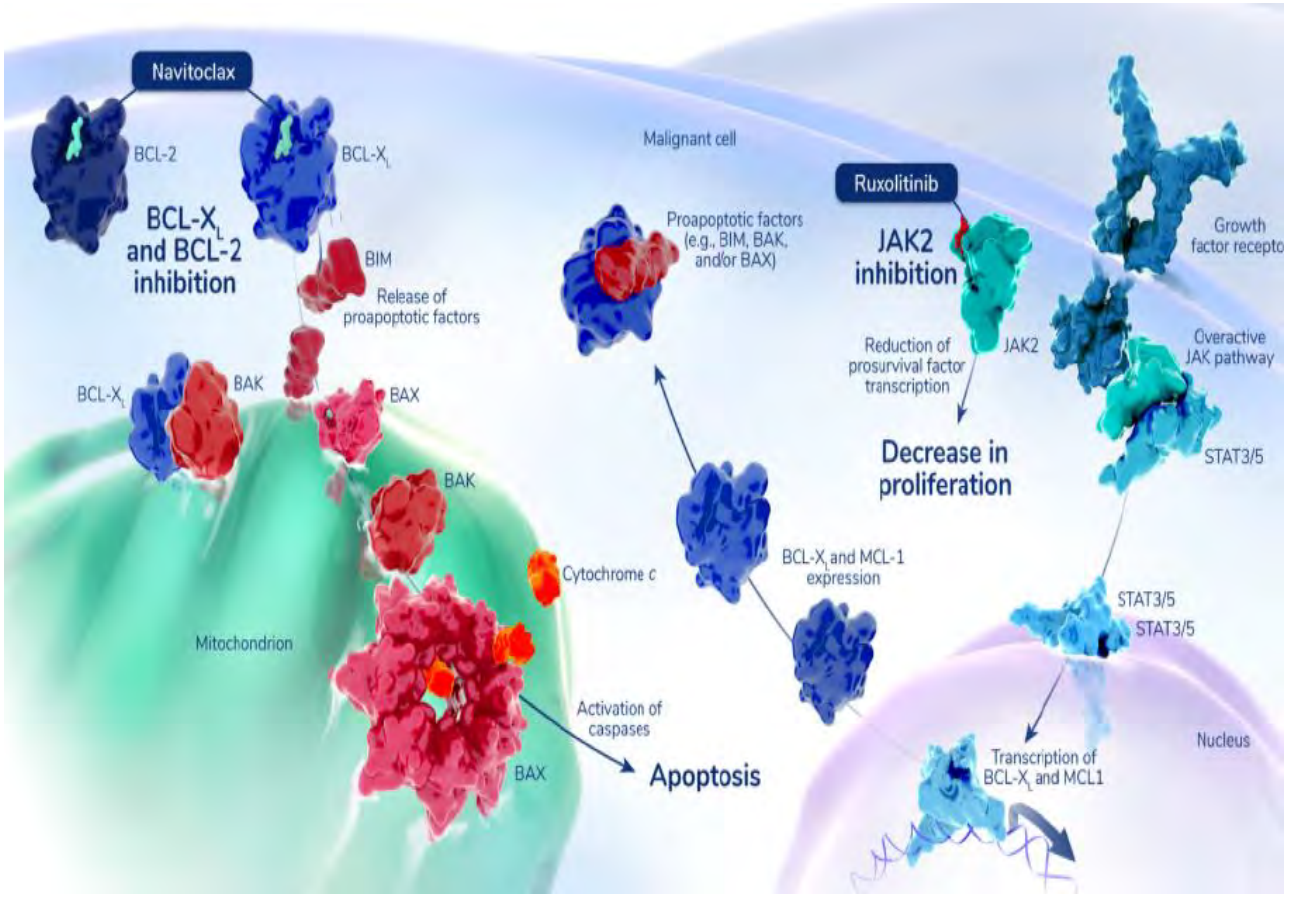
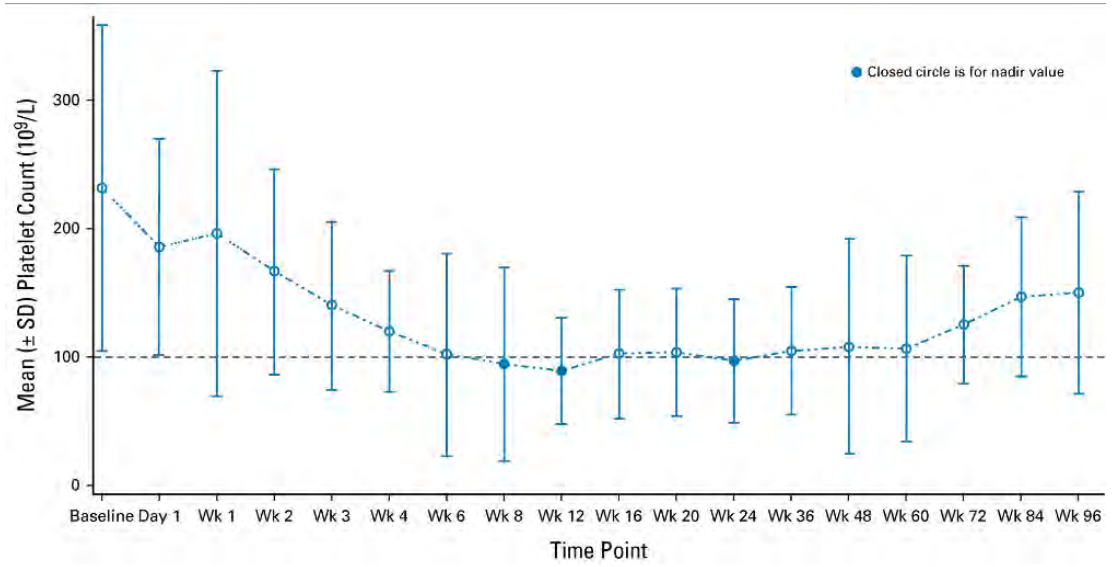
TRANSFORM-1: Navitoclax inhibits BCL-XL and BCL-2



REFINE: Addition of navitoclax to ongoing ruxolitinib in suboptimal or R/R MF

- Thrombocytopenia expected but uncomplicated and manageable with dose reductions
- BM fibrosis reduction in 38% and this modification is associated with survival benefit



Harrison CN et al., *J Clin Oncol*, 2022.
Pemmaraju N et al., *Lancet Haematol*, 2022.

Demographics and Disease Characteristics Were Similar Between Groups

	NAV + RUX (N=125)	PBO + RUX (N=127)
Age, median (range), years	70 (42–87)	69 (37–85)
Sex, male	63 (50)	81 (64)
Time from last MF diagnosis to study entry, median (range), months	8 (0.3–181.6)	6 (0.3–198.8)
Type of MF		
Primary	63 (50)	72 (57)
Post-PV-MF or Post-ET-MF	62 (50)	55 (43)
Number of prior lines of therapy, median (range)	1 (1–3)	1 (1–4)
Spleen volume, median (range), cm^3	1441 (419–8020)	1639 (219–5664)
TSS score, median (range)	21 (0.1–60.6)	24 (6.7–61.6)
Transfusion dependent at BL	5 (4)	4 (3)
Calculated DIPSS+ risk at study entry[a]		
Intermediate-1	8 (6)	5 (4)
Intermediate-2	104 (83)	110 (87)
High	13 (10)	12 (9)
Driver mutations		
JAK2 V617F	81 (65)	79 (62)
CALR	22 (18)	26 (20)
MPL W515	14 (11)	10 (8)
HMR mutations, n/N (%)	57/120 (48)	50/117 (43)

- Median (range) follow-up was 14.9 (0.0–29.5) months

Data cutoff: 13 Apr 2023. Data are n (%) unless otherwise stated. [a]DIPSS+ risk was calculated based on all available screening data.
BL, baseline; CALR, calreticulin; DIPSS+, Dynamic International Prognostic Scoring System Plus; ET, essential thrombocythemia; HMR, high molecular risk; JAK2, Janus kinase 2; MF, myelofibrosis; MPL, gene encoding the thrombopoietin receptor; NAV, navitoclax; PBO, placebo; PV, polycythemia vera; RUX, ruxolitinib.

Discontinuation of Study Treatment Was Similar Between Groups

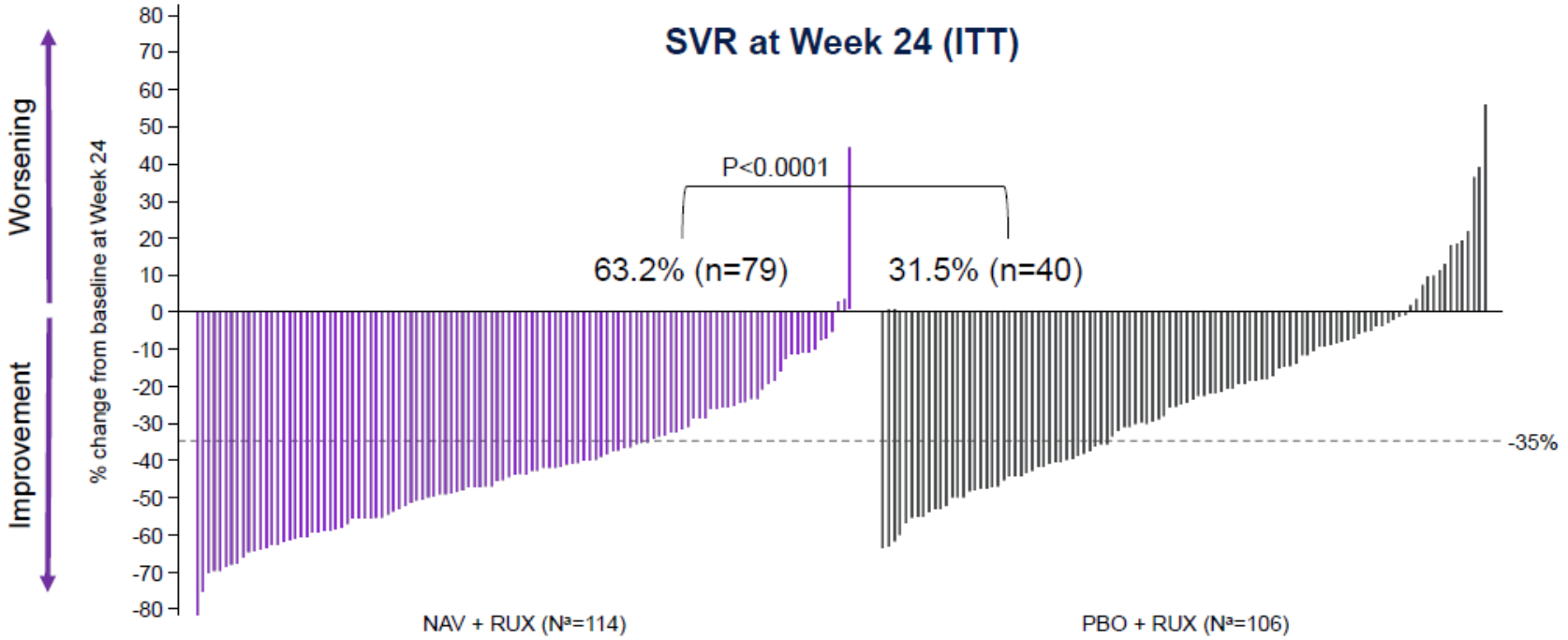
- Of all enrolled patients, 83 (33%) discontinued study treatment (30% NAV + RUX vs 35% PBO + RUX)
  - Most common primary reason in both arms was due to AEs (14% NAV + RUX and 11% PBO + RUX)

	NAV + RUX (N=125)	PBO + RUX (N=127)
Discontinue study for any reason	20 (16)	23 (18)
Discontinue NAV/PBO treatment for any reason	38 (30)	45 (35)
Discontinue NAV/PBO treatment[a]		
AE	18 (14)	14 (11)
Physician decision	6 (5)	8 (6)
Withdrawal of consent	6 (5)	4 (3)
MF disease progression	2 (2)	10 (8)
Leukemia transformation	3 (2)	3 (2)
Disease relapse	1 (1)	2 (2)
Discontinued study[a]		
Death	13 (10)	13 (10)
Withdrawal of consent	7 (6)	10 (8)

TRANSFORM-1: Primary endpoint achieved SVR35 at week 24 (63.2% vs 31.5%)

NAV + RUX Led to an SVR_{35W24} Rate That Was Twice as High as PBO + RUX

- A significantly higher number of patients achieved SVR_{35W24} in NAV + RUX arm compared with PBO + RUX [79 (63.2%) vs 40 (31.5%); P<0.0001]



[a]Number of patients with available percent change in SVR_{35W24}.
ITT, intention-to-treat; NAV, navitoclax; PBO, placebo; RUX, ruxolitinib; SVR, spleen volume reduction; SVR_{35W24}, SVR of ≥35% at Week 24.

SECONDARY ENDPOINTS

Nav/Rux vs Pbo/Rux

- SVR at any time: 76.8% vs 41.7% (P<0.0001)
- TSS50 at Week 24: ns (same)
- 12-month duration of SVR35 rate: ns (same)

Follow up is short - 14.8 months

TRANSFORM-1: Cytopenias are common but manageable

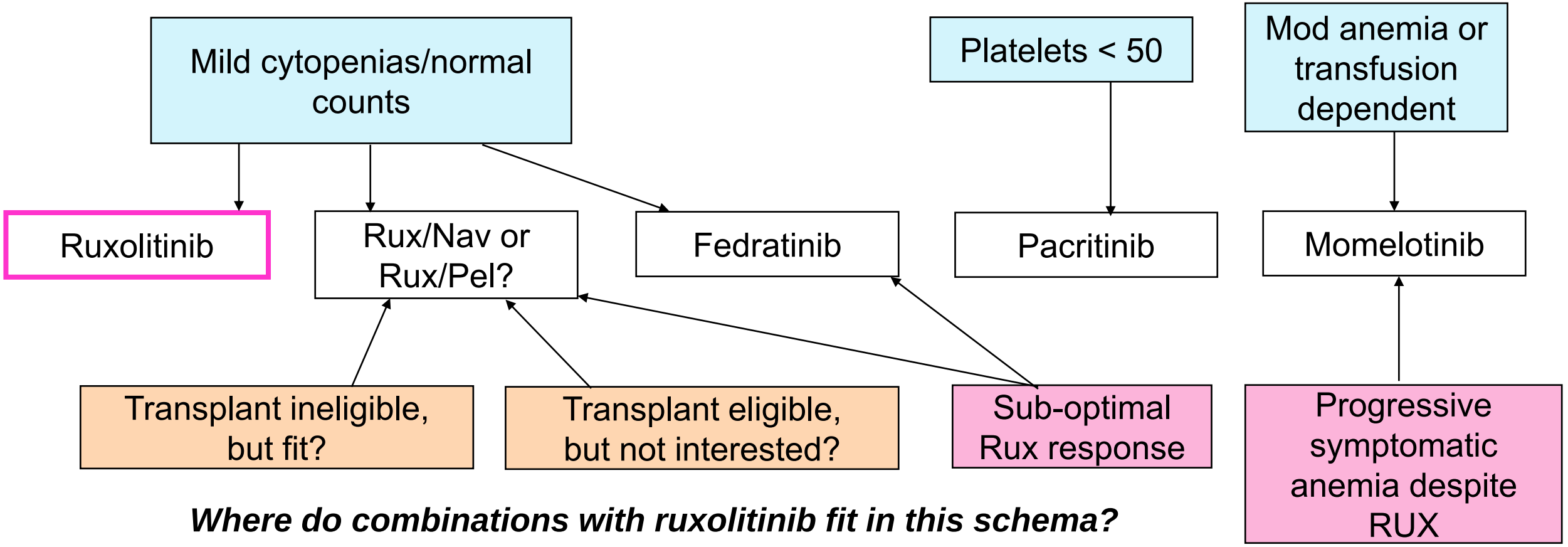
	NAV + RUX (N=124)[a] N (%)		PBO + RUX (N=125)[a] N (%)	
Any AE	124 (100)		121 (97)	
Any AE grade ≥3	105 (85)		87 (70)	
Most common AEs (>30% patients receiving NAV)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Thrombocytopenia	112 (90)	63 (51)	62 (50)	19 (15)
Anemia	74 (60)	57 (46)	61 (49)	49 (39)
Neutropenia	56 (45)	47 (38)	7 (6)	5 (4)
Diarrhea	42 (34)	6 (5)	17 (14)	0
Bleeding/hemorrhagic events	30 (24)	2 (2)	27 (22)	7 (6)
COVID-19	26 (21)	1 (1)	23 (18)	7 (6)
Contusion	13 (10)	0	7 (6)	0
Abdominal pain	11 (9)	1 (1)	8 (6)	1 (1)
Abdominal pain upper	9 (7)	1 (1)	10 (8)	1 (1)
Bone pain	9 (7)	0	6 (5)	0
Any serious AE	32 (26)		40 (32)	
AEs leading to dose reduction				
Navitoclax/placebo	101 (81)		39 (31)	
Ruxolitinib	112 (90)		76 (61)	
AE leading to dose interruption				
Navitoclax/placebo	87 (70)		44 (35)	
Ruxolitinib	78 (63)		41 (33)	
All deaths	13 (10)		13 (10)	
Deaths ≤30 days following last dose of study drug	6 (5)		5 (4)	

[a]All AEs are presented as n (%).
AEs, adverse events, NAV, navitoclax; PBO, placebo; RUX, ruxolitinib.

Remaining questions

- Is 24-week SVR35 achievement enough for approval or importantly to change current practice?
- Which MF patients warrant combination?
- What long term benefits would we want to see with combination compared to monotherapy?
- How do we evaluate Rux-combinations when standard of care options are evolving?

How I use JAKi for higher risk myelofibrosis with symptoms and splenomegaly in 2024



Where do combinations with ruxolitinib fit in this schema?

TRANSFORM-2 (Rux/Navitoclax vs BAT) pending

Conclusions

- Polycythemia Vera and Essential Thrombocythemia
  - Molecular response was not improved with IFN compared to HU in the randomized setting
  - However, IFN may still be a good option for high-risk patients warranting cytoreductive therapy IF they can tolerate IFN long enough to achieve benefit
  - Preliminary data suggest rusfertide may mitigate phlebotomy need and is well tolerated

- Myelofibrosis
  - Ruxolitinib-combinations (more treatment) reduced spleen volume more than rux alone
  - Longer follow up of MANIFEST-2 and TRANSFORM-1 are needed to assess for additional benefits and durability of response in the frontline setting (anemia, fibrosis, TSS, and survival)

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