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MD Anderson Cancer Center
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Myeloproliferative Neoplasms

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2025 UNMC Post-ASH Highlights: A Post-ASH Review
Omaha, NE, Feb 1, 2025

Disclosures

Consultant/Honoraria: AbbVie, Inc.; Blueprint Medicines Corporation; Bristol Meyers Squibb Company; Cogent Biosciences, Inc.; Disc Medicine; Geron; GlaxoSmithKline LLC; Incyte Corporation; Ionis Pharmaceuticals, Inc.; Jubilant Pharma Limited; Karyopharm; Keros Therapeutics; Morphic (Eli Lilly and Company); MorphoSys (Novartis Pharmaceuticals Corporation); Novartis Pharmaceuticals Corporation; Ono Pharma USA, Inc.; PharmaEssentia Corporation; Raythera; Sobi, Inc.; Sumimoto Pharma Co., Ltd.

Contracted Research: Ajax Therapeutics; Blueprint Medicines Corporation; Bristol Meyers Squibb Company; Cogent Biosciences, Inc.; Disc Medicine; Geron; Incyte Corporation; Ionis Pharmaceuticals, Inc.; Janssen Pharmaceuticals, Inc.; Kartos Therapeutics, Inc.; Karyopharm; MorphoSys (Novartis Pharmaceuticals Corporation); Sobi, Inc.; Sumitomo Pharma Co., Ltd.; Telios Pharmaceuticals, Inc.

INVESTIGATIONAL/OFF-LABEL USE OF DRUGS DISCLOSURE:
Off-label drug discussion of bezuclastinib for systemic mastocytosis.
Off-label drug discussion of CK0804, DISC-0974, elritercept, flonoltinib, imetelstat, INCB057643, luspatercept, navtemadlin, nuvisertib, and selinexor for myelofibrosis.

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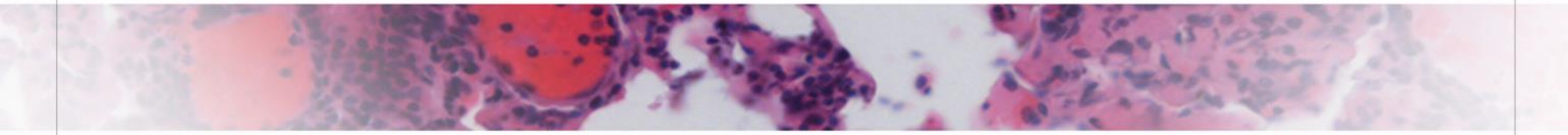


Dynamics of *CALR* Variant Allele Frequency with Therapy in Myeloproliferative Neoplasms

Zi Yun Ng[1], Laurane Cottin[2], Damien Luque Paz[2], Corentin Orvain[2], Kamel Laribi[3], Jean-Christophe Ianotto[4],

Eric Lippert[5], Alesia Khan[6], Daniel Lock[6], Valérie Ugo[2], Claire Harrison[1], Jennifer O'Sullivan[1,7]

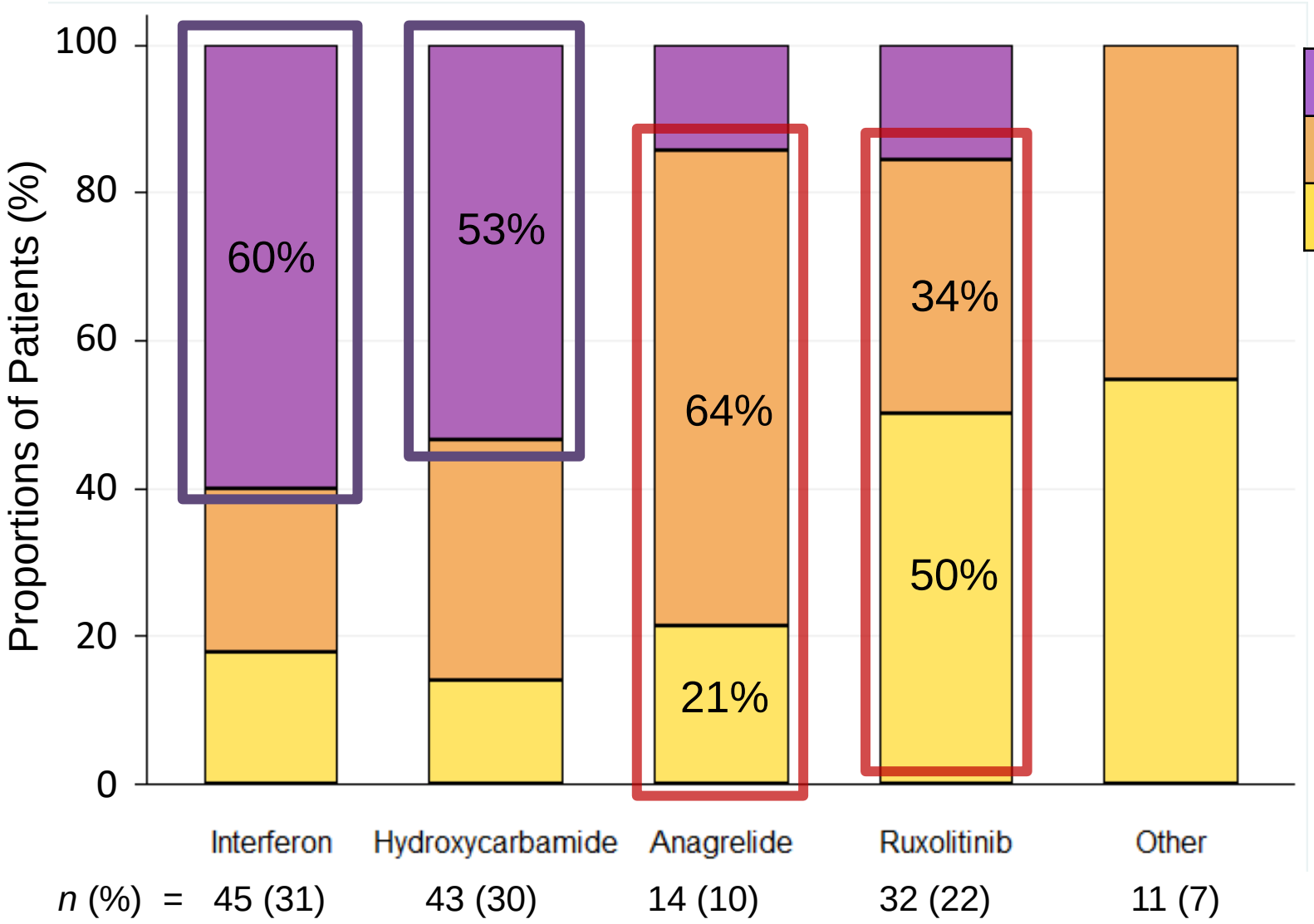
[1] Dept of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[2] Univ Angers, Nantes Université, CHU Angers, Inserm, CNRS, CRCI2NA, F-49000, Angers, France
[3] Hématologie Clinique, CH Le Mans, Le Mans, France
[4] Service d'Hématologie et d'Hémostase clinique, Institut de Cancérologie et Hématologie, CHU de Brest, Brest, France
[5] Service d'Hématologie biologique, Hôpital de la Cavale Blanche, CHU de Brest, Brest, France
[6] Haematological Malignancy Diagnostic Service, Leeds Teaching Hospital NHS Trust, United Kingdom
[7] Medical Research Council (MRC) Weatherall Institute of Molecular Medicine (WIMM) and NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

Baseline Characteristics, *n* = 145

Clinical parameter	***n* (%)**
Age at diagnosis, years (median, range)	56 (9 – 91)
Male Female	77 (53) 68 (47)
MPN subtype • ET • Pre-fibrotic MF • PMF + post-ET MF • MPN-U	 82 (57) 14 (10) 46 (31) 3 (2)

Molecular characteristics	***n* (%)**
CALR type • 1/like • 2/like • Atypical	 78 (54) 48 (33) 19 (13)
Median baseline VAF, % (range) • 14 (9.7%) had VAF <20%	38 (7-65)
Presence of additional mutations • 65% were in the MF group • High molecular risk	26/61 (43) 10/61 (16)

Treatment Characteristics



Median treatment time: 45 months (range 4-180)

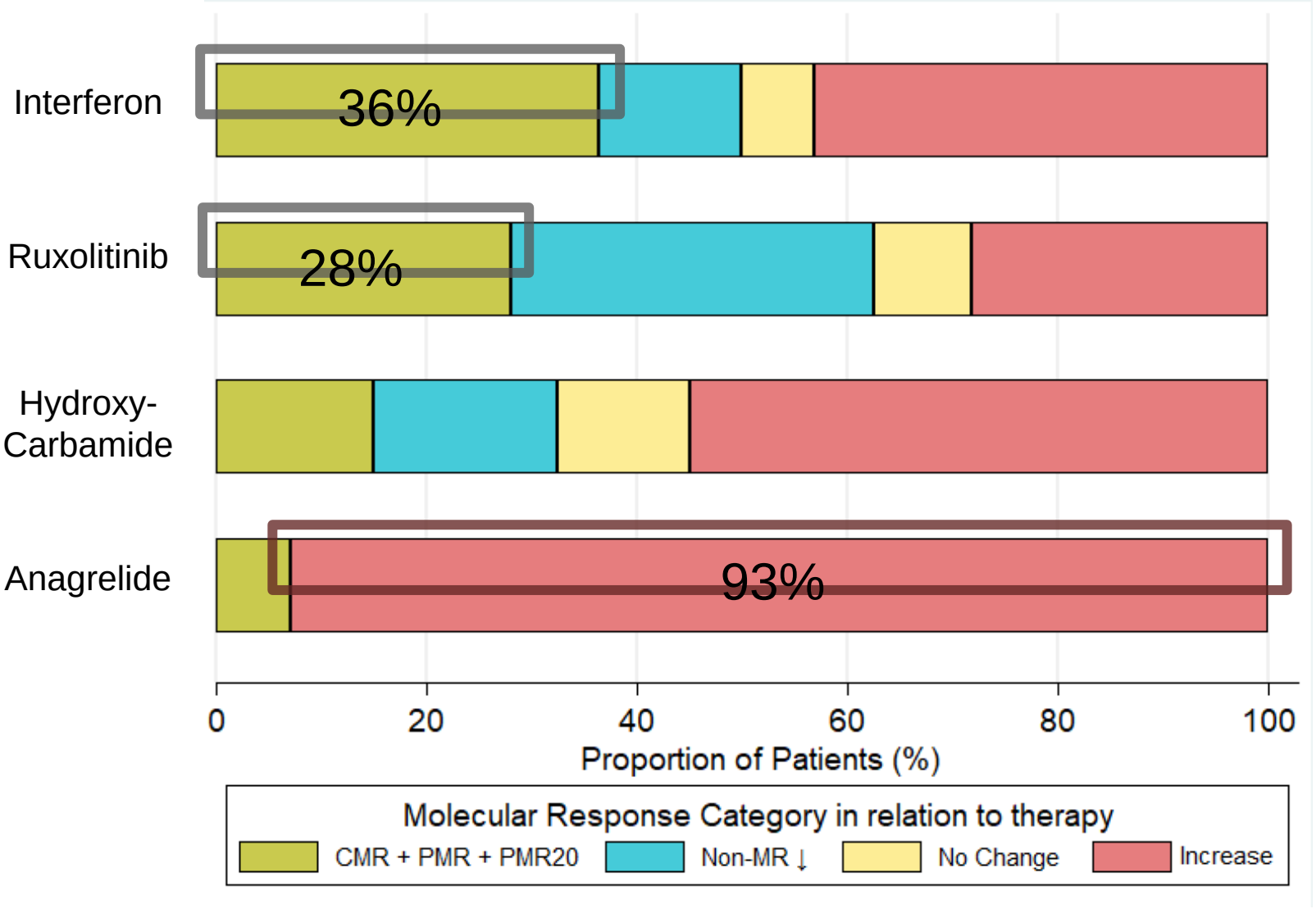
>50% had interferon or hydroxycarbamide as 1st line

>80% had ruxolitinib or anagrelide as ≥2nd line

p = <0.0001

Median treatment duration not different between treatment arms (p = 0.07)

CALR Molecular Response to Therapy



More molecular responses with interferon & ruxolitinib

Anagrelide associated with ↑ VAF

Median *CALR* VAF change for anagrelide group was +40%

***p* = 0.003**

↑*CALR* VAF with anagrelide and its link with fibrosis?

PT1 study: 809 ET patients	Anagrelide ↑ 3x MF transformation vs hydroxycarbamide
EXELS study: 3649 ET patients	Anagrelide ↑ 2-3x of MF transformation
Mayo Clinic: 1076 ET patients	↑ fibrotic progression, ↓ survival after 1997
48 young patients on >10 years of anagrelide	7 patients (15%) developed new reticulin fibrosis • 5 *CALR*-mutated

Harrison et al. *NEJM.* July 2005.
Birgegard et al. *Haematologica*. Jan 2018.
Tefferi et al. *AJH.* Sep 2018.
Bieniaszewska et al. *Leukaemia Research*. Dec 2022.

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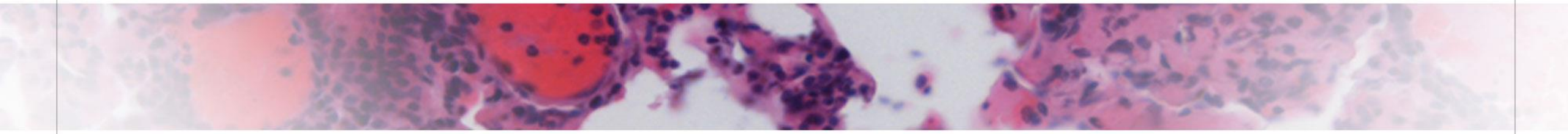
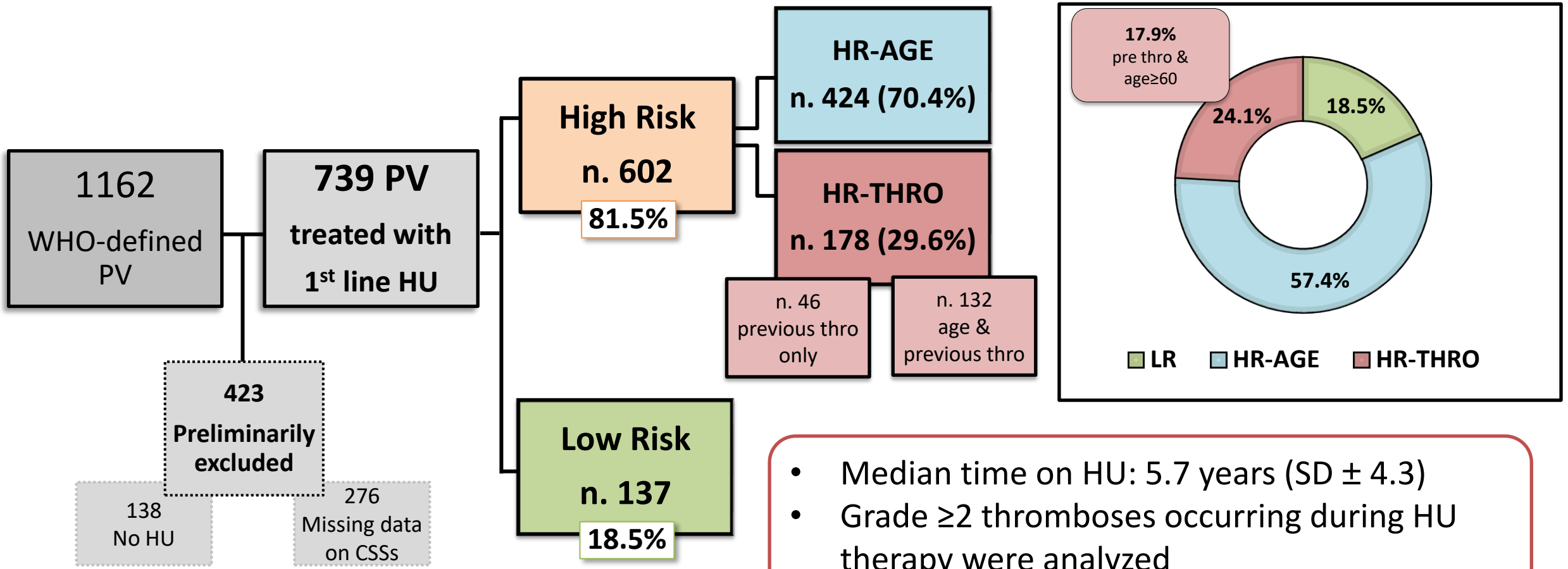


Revised ELN Criteria in Polycythemia Vera Identify an Increased Risk Phenotype for Thrombotic Events Beyond Conventional Risk Stratification. A Multicenter Cooperative Study

Francesca Palandri
IRCCS S. Orsola-Malpighi, Bologna

On behalf of the «PV-ARC» investigators
E. M. Elli, G. Benevolo, A. Dedola, R. Latagliata, E. Morsia, M. Tiribelli, F. Cavazzini, A. Tieghi, M. Farina, A. D'Addio, E. Abruzzese, F. Cavalca, R. Mullai, A. Cuneo, B. Martino, F.H. Heidel, GA. Palumbo, E. Rossi, M. Breccia*, **V. De Stefano* & F. Branzanti***

Patients and Methods

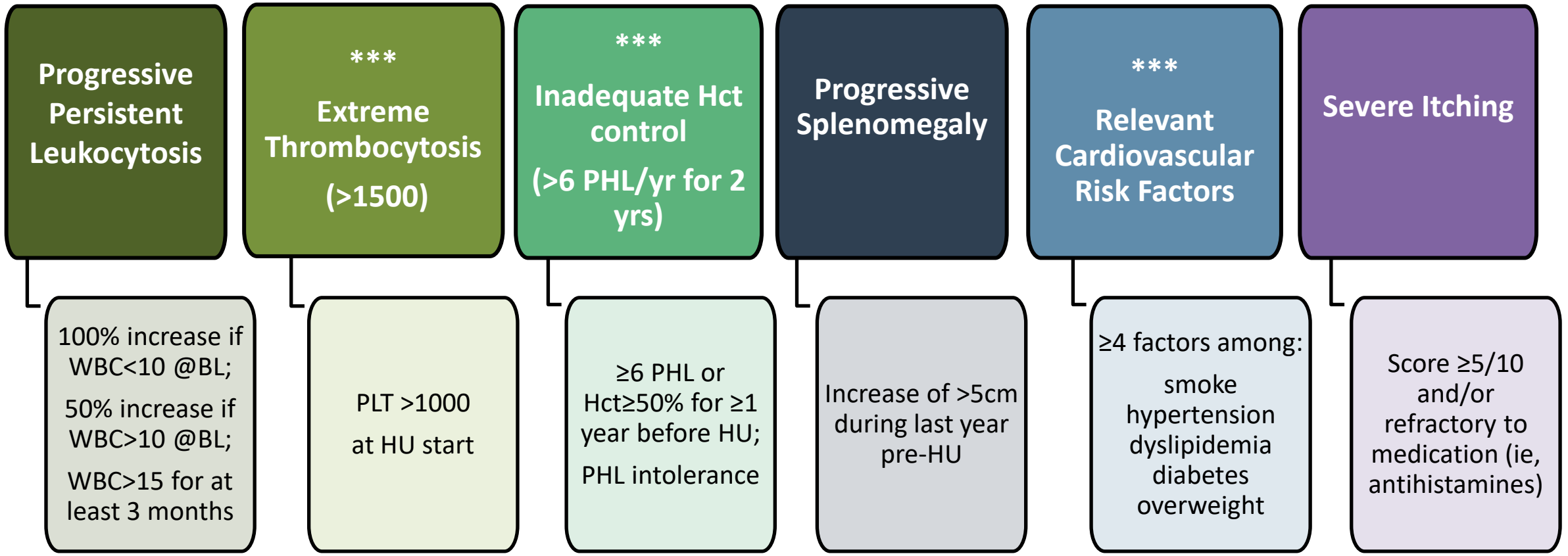


- Median time on HU: 5.7 years (SD ± 4.3)
- Grade ≥2 thromboses occurring during HU therapy were analyzed

The PV-ARC* Italian retrospective multicenter study started data collection in 2018

*clinicaltrials.gov identifier: #NCT06134102

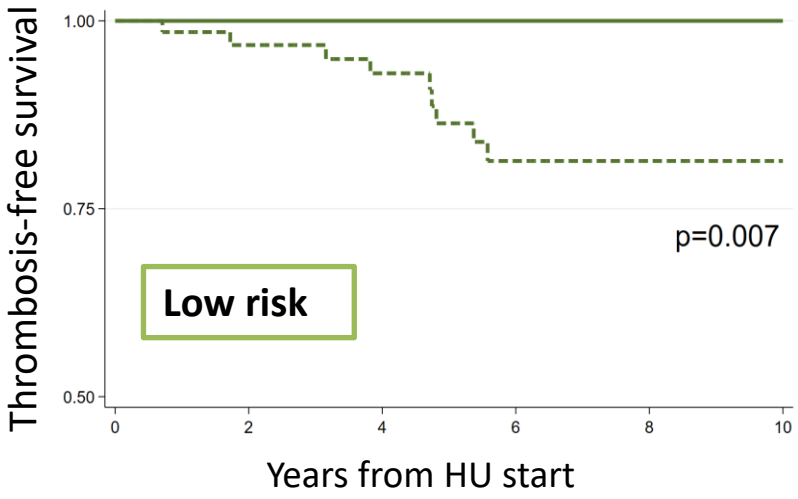
ELN Clinical Signs and Symptoms[1]

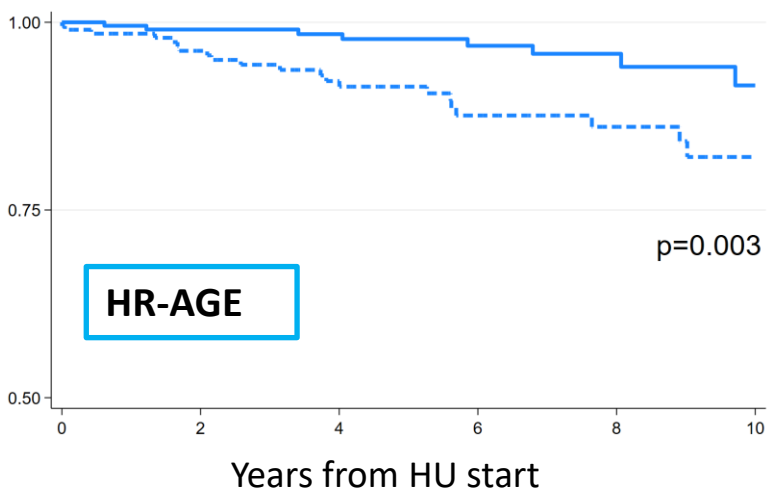


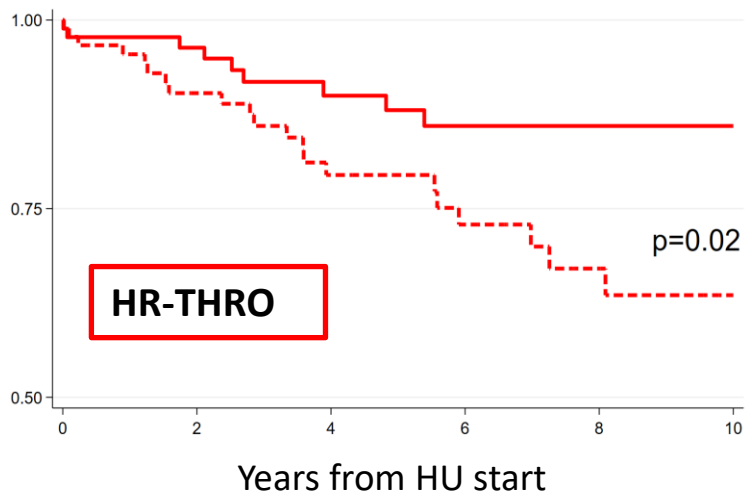
Three ELN Clinical Sign and Symptoms have been adapted based on real-life clinical experience***

1. Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311
**Revised CSS criteria based on real-life experience

CSSs are associated with worse TFS (each risk group)







Overall: 86.4% vs 100%

Arterial: 95.4% vs 100%
Venous: 93.7% vs 100%

Overall: 91.4% vs 97.8%

Arterial: 95.5% vs 99.5%
Venous: 96.7% vs 98.4%

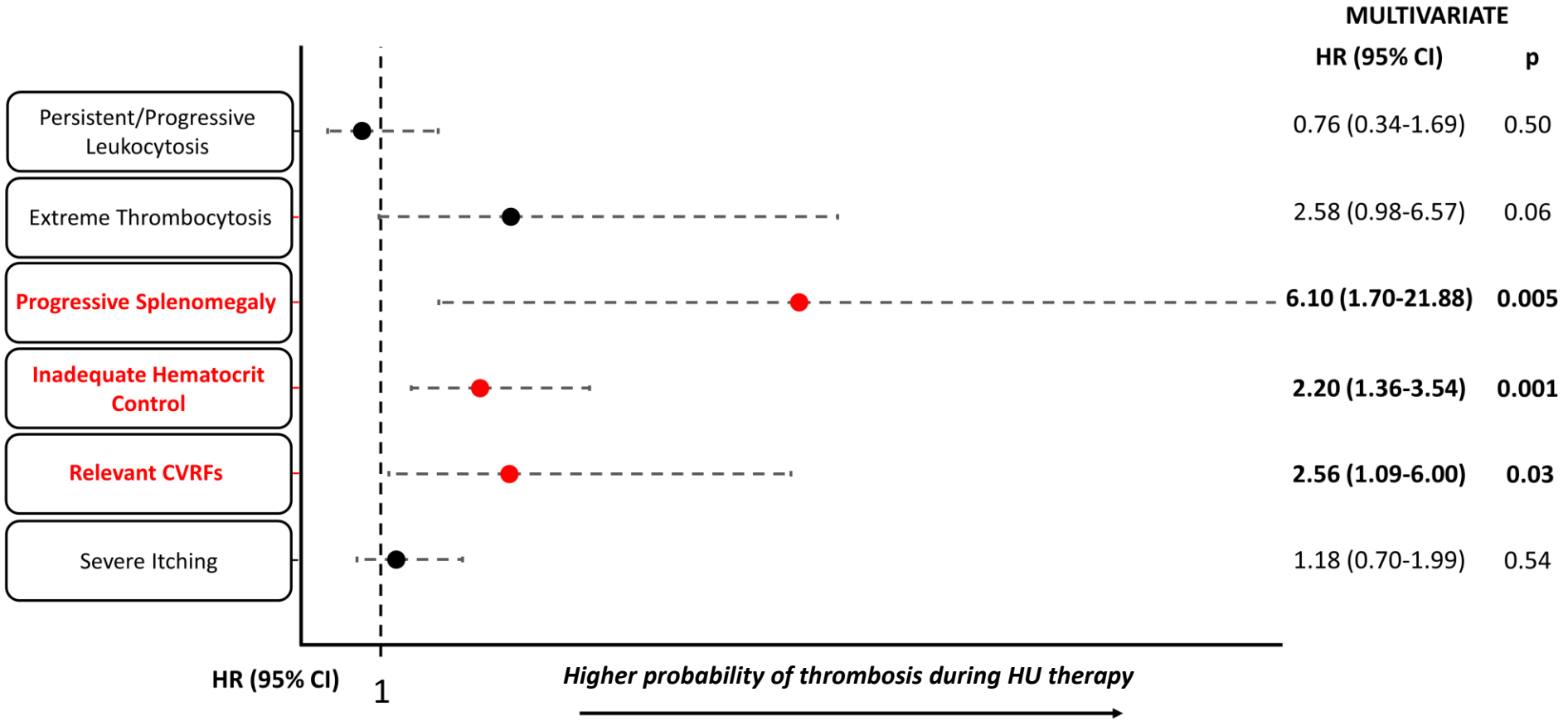
Overall: 79.5% vs 88.1%

Arterial: 92.7% vs 96.3%
Venous: 90.0% vs 93.2%

continuous line: patients without CSS

dashed line: patients with CSS

Differential impact of individual CSSs on thrombotic risk



In a MVA Cox analysis including all ELN Clinical Signs and Symptoms, progressive splenomegaly, inadequate hematocrit control and relevant CVRFs were the most significant predictors of thrombotic risk.

TP53 Alterations Confer Increased Risk of Leukemic Transformation & Worse Survival As Compared to High Molecular Risk Mutations in Patients with Myeloproliferative Neoplasms

Shivani Handa, Yosef Joseph Rene Amel Riazat-Kesh, Richard J Butterfield, Ganesh Sivakumar, Sangeetha Venugopal, Erin McGovern, Jonathan Feld, Douglas Tremblay, , Sebastian Elghaity-Beckley, Marina Kremyanskaya, John O. Mascarenhas, Blake Langlais, Gina L. Mazza, Daniel I. Nathan, Joseph Tripodi, Vesna Najfeld, Amylou C Dueck, Raajit Rampal, Ronald Hoffman, Bridget Kelly Marcellino

Conclusions

- Multi-hit *TP53* alterations are associated with a significantly increased risk of evolution to MPN-AP/BP as compared to previously validated HMR mutations
- Both single-hit & multi-hit *TP53* mutations confer worse OS compared to other HMR mutations
- Incidence of progression to MPN-AP/BP significantly increases with *TP53*^{mut} VAF >36%
- Results need to be further confirmed in a larger cohort
- Prospective evaluation of *TP53* mutations at defined clinical timepoints would be ideal for confirmatory studies

Efficacy and safety of fedratinib in patients with myelofibrosis and low baseline platelet counts in the phase 3 randomized FREEDOM2 trial

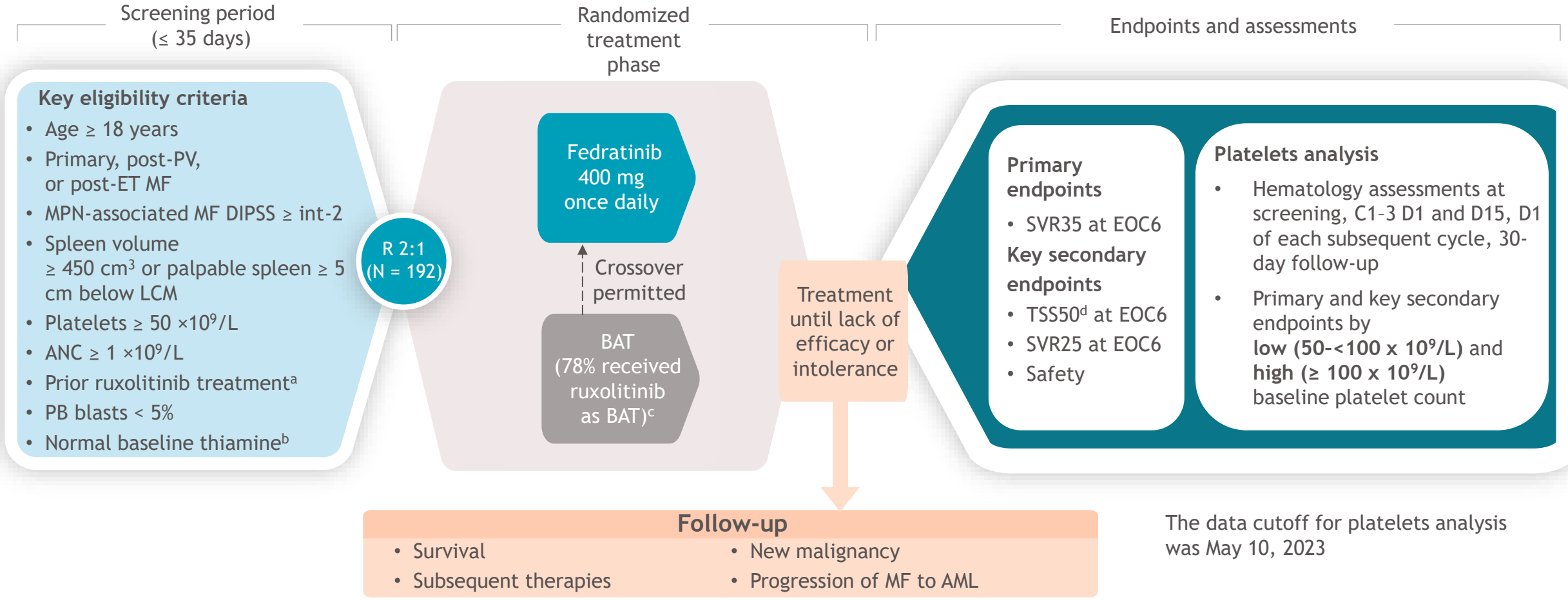
Haifa Kathrin Al-Ali,[1] Claire Harrison,[2] Ruben Mesa,[3] Moshe Talpaz,[4] Blanca Xicoy,[5] Francesco Passamonti,[6] Alessandro Vannucchi,[7] Patrick Brown,[8] Christopher Hernandez,[8] Jia Wang,[8*] Jun He,[9] Jean-Jacques Kiladjian[10]

[1]Universitätsklinikum Halle, Saale, Germany; [2]Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [4]University of Michigan Cancer Center, Ann Arbor, MI, USA; [5]Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol (HUGTP) - Josep Carreras Leukemia Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; [6]Università degli Studi di Milano; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [7]A.O.U. Careggi, Università di Firenze, Florence, Italy; [8]Bristol Myers Squibb, Princeton, NJ, USA; [9]Bristol Myers Squibb, Giralda Farms, NJ, USA; [10]Hospital Saint Louis and University Paris Cité, Paris, France

*Affiliation at the time of the trial

FREEDOM2 trial design

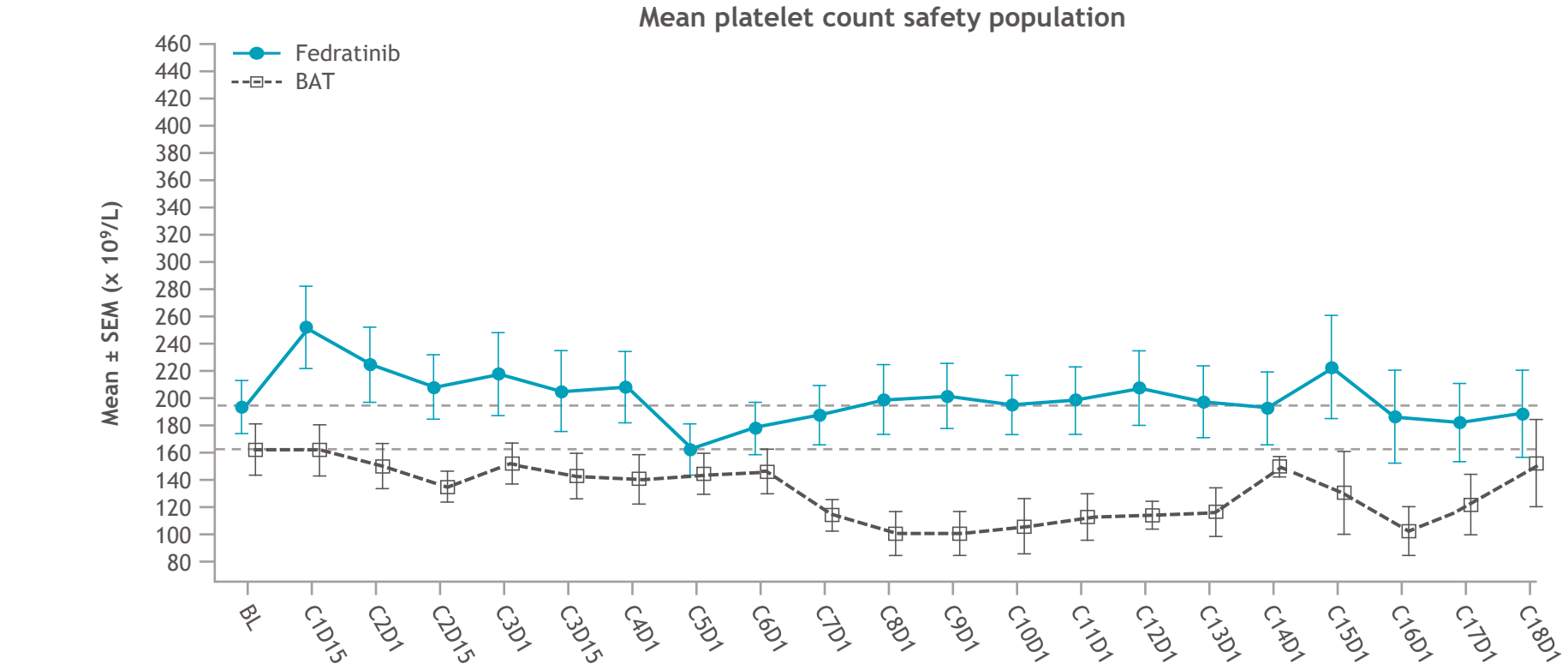
FREEDOM2 (NCT03952039) was a phase 3, multicenter, open-label randomized trial



The data cutoff for platelets analysis was May 10, 2023

[a]Patients must have received ruxolitinib for ≥ 3 months with < 10% SVR by MRI or < 30% decrease from baseline in spleen size by palpation or regrowth to these parameters (relapsed/refractory), or for ≥ 28 days with development of RBC transfusion requirement (≥ 2 units/month for 2 months) or grade ≥ 3 thrombocytopenia, anemia, hematoma, or hemorrhage (intolerant); [b]Thiamine lower limit of normal: 70 nmol/L, upper limit of normal: 180 nmol/L; [c]Other treatments in the BAT group were RBC transfusion (28%), hydroxyurea (19%), danazol (1%), mercaptopurine (1%), methylprednisolone (1%), interferon (1%), prednisone (1%), and thalidomide (1%); [d]≥ 50% reduction in MFSAF TSS.
AML, acute myeloid leukemia; BAT, best available therapy; C, cycle; D, day; DIPSS, Dynamic International Prognostic Scoring System; LCM, left costal margin; MFSAF, Myelofibrosis Symptom Assessment Form; PB, peripheral blood; TSS, total symptom score.

Mean platelet count per cycle (safety population)

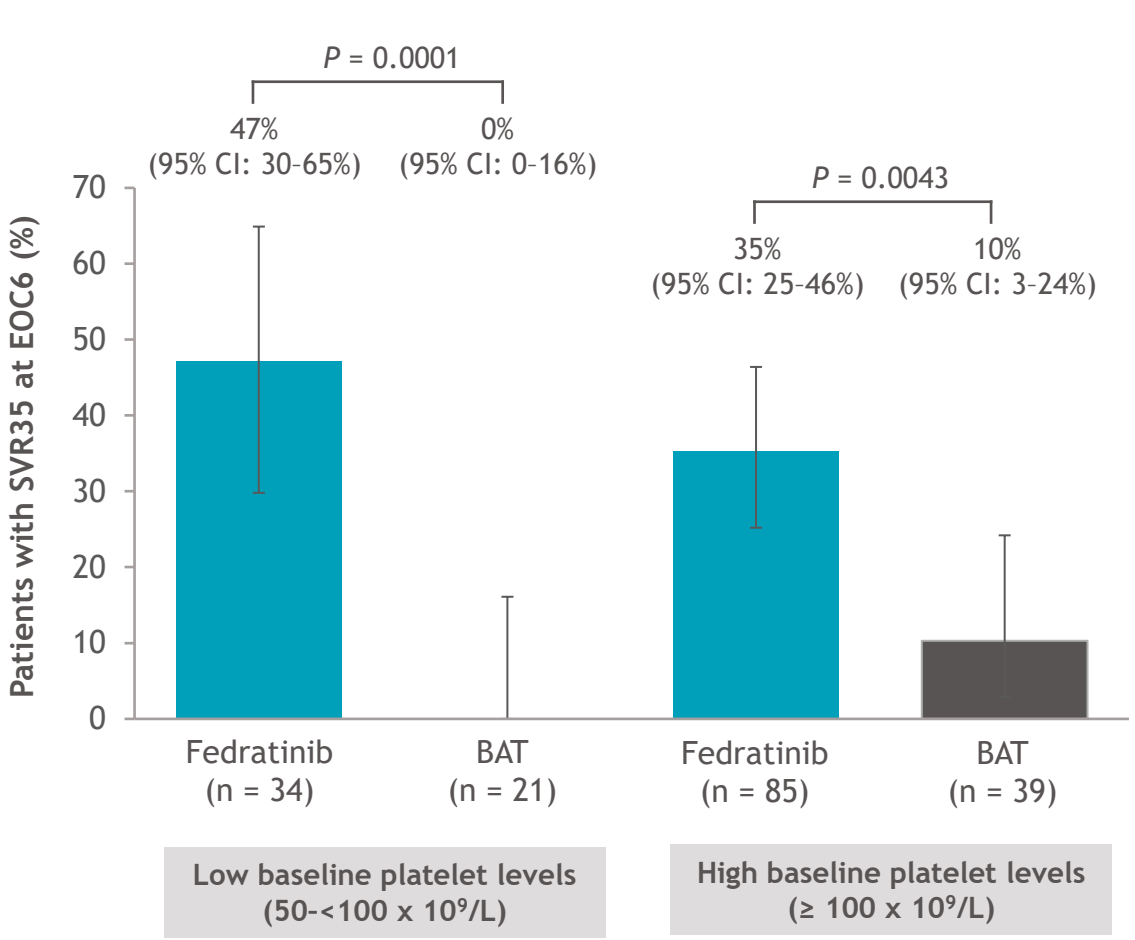


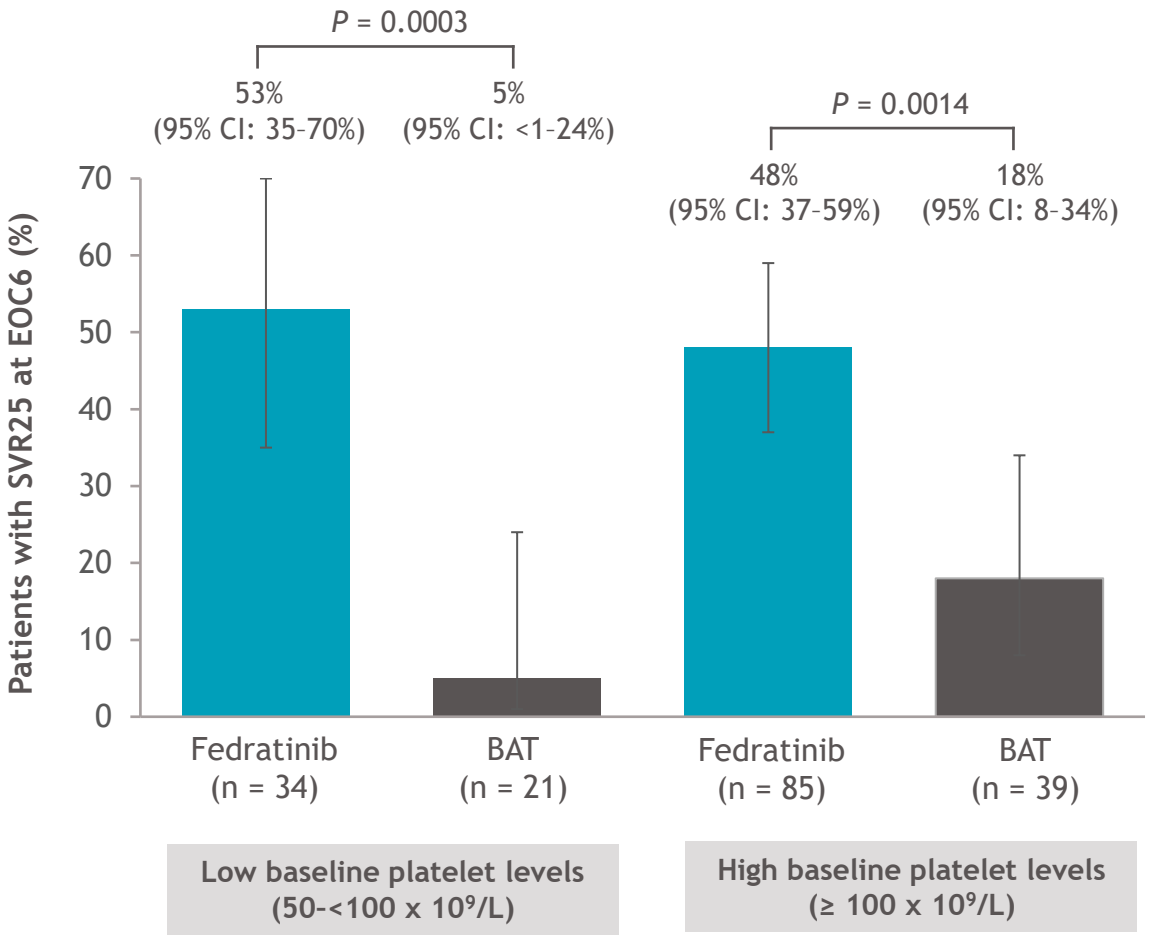
Number of patients	BL	C1D15	C2D1	C2D15	C3D1	C3D15	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1	C16D1	C17D1	C18D1
Fedratinib	129	100	99	90	91	82	92	82	78	75	70	69	59	55	55	51	43	42	32	33	31
BAT	64	53	52	48	52	45	48	48	46	28	10	7	6	6	6	5	2	3	3	4	3

Patients treated with fedratinib had higher mean platelet counts versus BAT, particularly in early treatment cycles

Data cutoff: Dec 27, 2022
Plot shows mean +/- SEM platelet count in the safety population.
SEM, standard error of the mean.

SVR35 at EOC6 by baseline platelet count



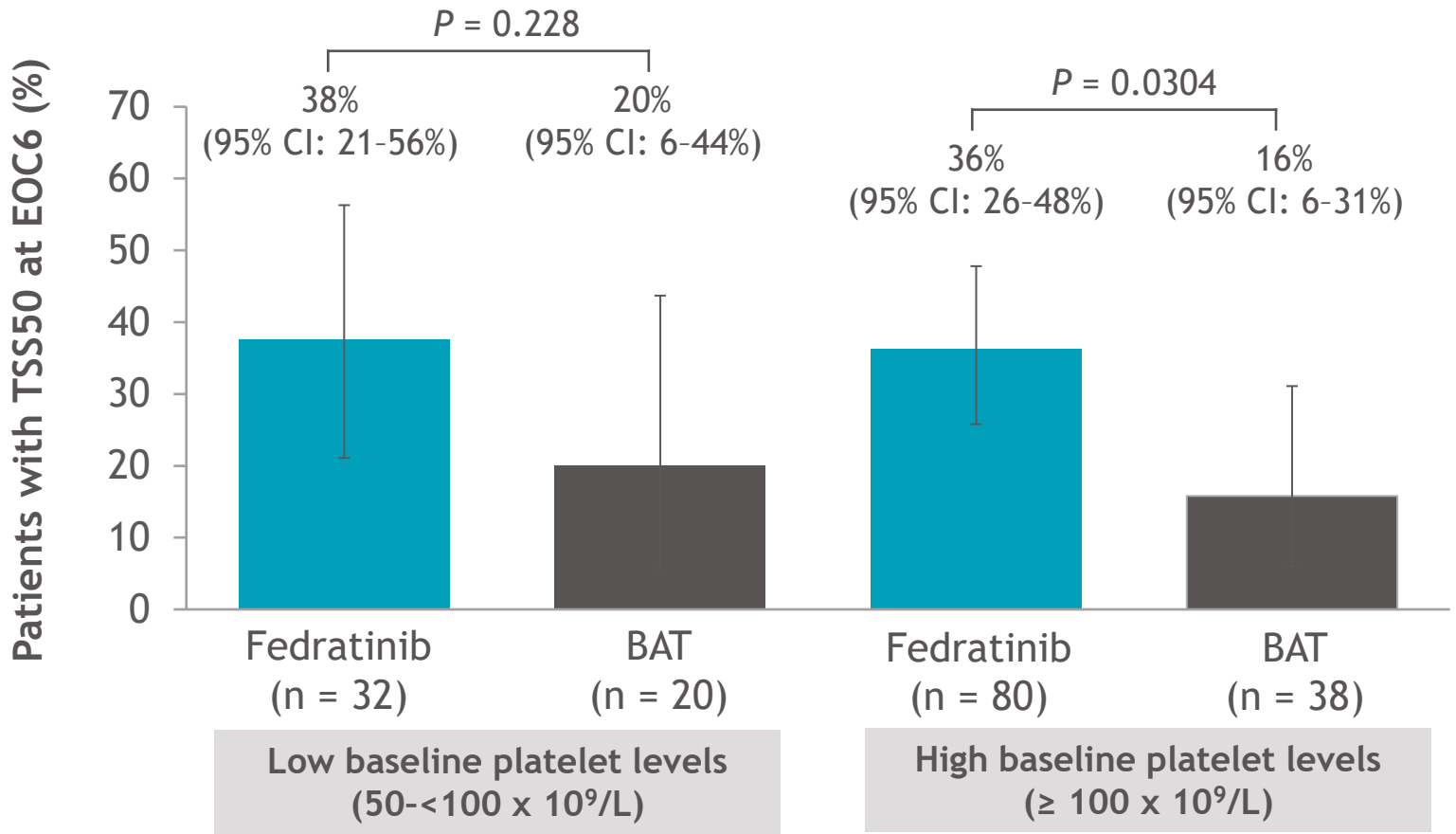


Patients with low and high baseline platelet count showed significant benefit of fedratinib versus BAT in SVR35 and SVR25 at EOC6, with a trend towards greater magnitude of benefit in the low versus high baseline platelet group

Data cutoff: Dec 27, 2022

Plot shows proportion of patients with SVR35 at EOC6 in the ITT population and 2-sided 95% CI based on the Clopper Pearson method; *P* value based on Fisher's exact test.

Symptom response at EOC6 by baseline platelet count



Among evaluable patients, both those with low and high baseline platelet levels had numerically higher rates of symptom response at EOC6 with fedratinib treatment vs BAT

Data cutoff: Dec 27, 2022
Plot shows proportion of patients with ≥ 50% reduction in TSS at EOC6 in the ITT population with non-zero baseline TSS and 2-sided 95% CI based on the Clopper Pearson method; *P* value based on Fisher's exact test.

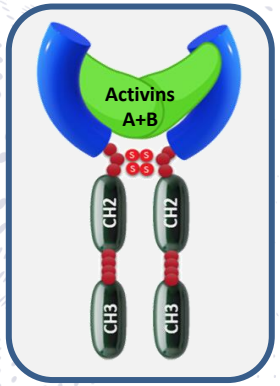
Hematological Improvement and Other Clinical Benefits of Elritercept as Monotherapy and in Combination with Ruxolitinib in Participants with Myelofibrosis from the Ongoing Phase 2 RESTORE Trial

Claire Harrison, MD, FRCP, FRCPath

Professor of Myeloproliferative Neoplasms and Deputy Chief Medical Officer (Research, Data, and Analytics) of the Guy's and St. Thomas' NHS Foundation Trust, UK

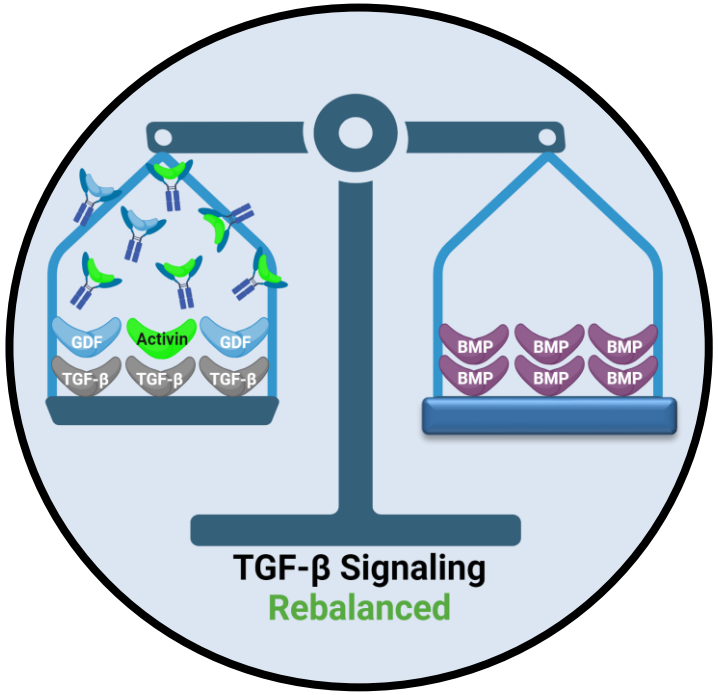
RESTORE

Elritercept (KER-050) is Designed to Target Disorders of Ineffective Hematopoiesis Including MF



Elritercept

- Designed to inhibit select TGF-beta superfamily ligands, including **activin A,** which has been associated with **ineffective hematopoiesis, inflammation, disease pathogenesis, and progression**[1,2,3]



Preclinical data showed that the research form of **elritercept** (RKER-050):

- induced erythropoiesis in mouse model of MF[4]
- reversed ruxolitinib-associated reductions in hemoglobin, hematocrit, and red blood cell (RBC) count[5]
- increased platelet counts[6]

Updated results from the ongoing open-label Phase 2 RESTORE trial evaluating elritercept in participants with MF and anemia will be presented

[1]Verma A, et al. *J Clin Inv.* 2020; [2]Portale F, et al. *Haematologica*. 2019; [3] Phillips D, et al. *Cytokine Growth Factor Rev.* 2009; [4]Moses B, et al. *EHA.* 2023; [5]Nathan R, et al. *ASH.* 2021; [6]Moses B, et al. *GRC: Cell Biology of Megakaryocytes and Platelets.* 2023.
TGF-β = transforming growth factor-β.

RESTORE

Conclusions

- The ongoing Phase 2 RESTORE trial of elritercept in MF has enrolled a broad population of patients with high disease burden
- Elritercept was generally well tolerated in participants with MF, both as monotherapy and in combination with ruxolitinib
- Potential for elritercept to address ineffective hematopoiesis in MF both as monotherapy and in combination with ruxolitinib is supported by observed increases in Hgb, transfusion independence or reduction, and preservation or improvement of platelet counts
- Observed reductions in spleen volume support potential for elritercept to improve splenomegaly, particularly in combination with ruxolitinib
- Potential for elritercept to improve symptoms is supported by observed reductions in total symptom scores as well as broad improvements across individual symptom domains both as monotherapy and in combination with ruxolitinib
- Enrollment in Part 2 of the RESTORE trial is ongoing at the RP2D of 3.75 mg/kg with titration to 5 mg/kg to further study effects of elritercept in participants with MF

Improvements in Hgb, transfusion burden, spleen volume, and symptom scores were observed in both monotherapy and combination arms, supporting potential for elritercept to provide broad, clinically meaningful benefits to patients with MF

RESTORE

Data as of 30Aug2024

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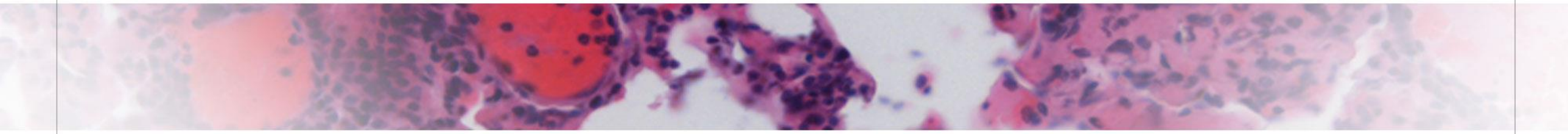


A Phase 1b Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia

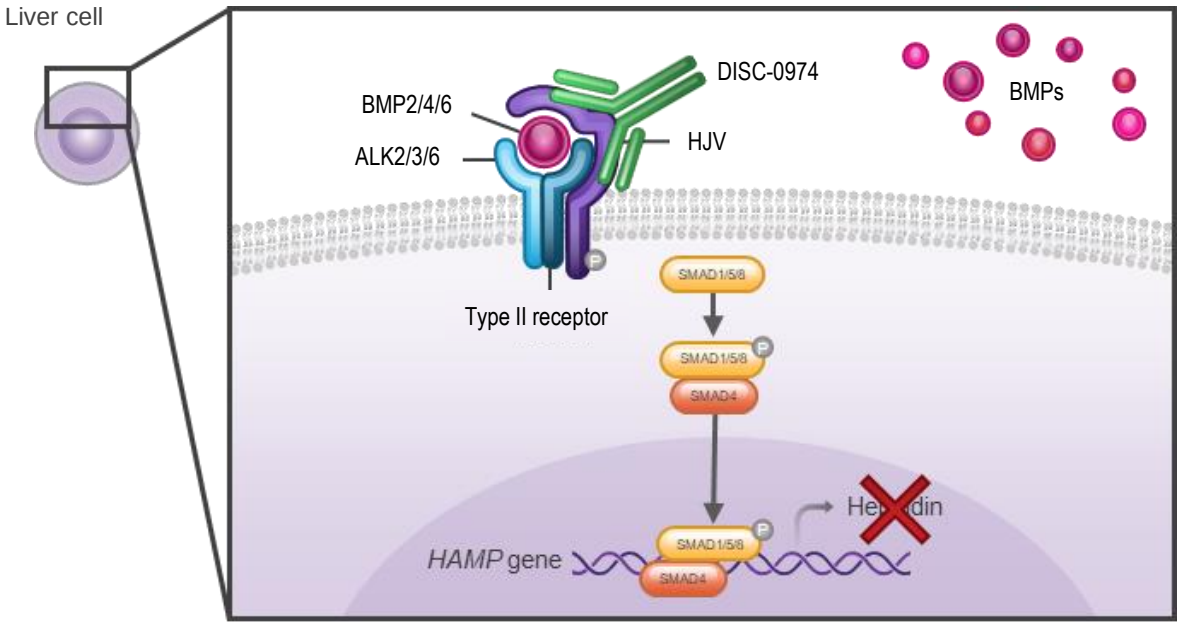
Naseema Gangat[1], James Foran[2], Anna Halpern[3,4], Raajit Rampal[5], Prithviraj Bose[6], Elizabeth Hexner[7], Moshe Talpaz[8], Laura Michaelis[9], Prioty Islam[5], Ronan Swords[10], Sima Bhatt[11], Akshay Buch[11], Olivia Pelletier[11], William Savage[11], Ayalew Tefferi[1]

1. Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN
2. Division of Hematology, Department of Medicine, Mayo Clinic, Jacksonville, FL
3. Department of Medicine, University of Washington, Seattle, WA
4. Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA
5. Memorial Sloan Kettering Cancer Center, New York, NY
6. MD Anderson Cancer Center, Houston, TX
7. University of Pennsylvania, Philadelphia, PA
8. University of Michigan, Ann Arbor, MI
9. Medical College of Wisconsin, Milwaukee, WI
10. Oregon Health and Science University, Portland, OR
11. Disc Medicine, Watertown, MA

DISC-0974 Targets Hemojuvelin (HJV) to Suppress Hepcidin

Inhibiting HJV Prevents Hepcidin Expression and Increases Iron

- **DISC-0974** is a first-in-class monoclonal antibody that binds to HJV and blocks BMP signaling
  - ↓ Hepcidin production
  - ↑ Iron absorption
  - ↑ Mobilization of stored iron into circulation
  - ↑ Hgb levels



Conclusions

- DISC-0974 was **safe and well tolerated** at all evaluated dose levels
- DISC-0974 resulted in **sustained ↓hepcidin and ↑serum iron** for several weeks after each dose
- Among participants treated at 28 mg to 100 mg:
  - ✓ 50% of nTD participants with durable Hgb increases of ≥1.5 g/dL
  - ✓ nTD participants have clinically meaningful improvement in FACIT-fatigue
  - ✓ 80% of TD-low participants achieved TI-16 weeks
  - ✓ 40% of TD-high participants achieved TI-12 weeks
  - ✓ 60% of TD-high participants achieved a 50% reduction in transfusions over a rolling 12-week window
  - ✓ 54% of participants (n=13) receiving concomitant JAKi therapy achieved durable hematologic responses
- **Phase 2 enrollment is ongoing with a 50 mg starting dose**
  - Study will include additional correlatives including cytokine levels and NGS testing

Abstract #483

8 December 2024

Disease-Modifying Activity of Navtemadlin Correlates With Clinical Responses in a Randomized, Multicenter, Global Phase 3 Study (BOREAS) in JAK-Inhibitor Relapsed/Refractory Myelofibrosis

John O. Mascarenhas, MD[1]; Prithviraj Bose, MD[2]; Hsin-An Hou, MD, PhD, MSc[3]; Wojciech Homenda, MD, PhD[4]; David Ross, MD[5]; Sanjay R Mohan, MD, MSc[6]; Jean-Jacques Kiladjian, MD, PhD[7]; Haifa Kathrin Al-Ali[8]; Andrew Charles Perkins, MBBS, PhD[9]; Yulia Khalina, BSc[10]; Tracy Clevenger, PhD[10]; Zhuying Huang, PhD[10]; Jesse McGreivy, MD[10]; Wayne Rothbaum, MA[10]; Srdan Verstovsek, MD, PhD[10]; and Alessandro M. Vannucchi, MD[11]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Department of Hematology and Bone Marrow Transplantation, Pomeranian University, Slupsk, Poland; [5]Royal Adelaide Hospital and SA Pathology, Adelaide, Australia; [6]The Vanderbilt Clinic, Nashville, TN; [7]Hopital Saint-Louis, Paris, France; [8]University Hospital Halle, Halle (Saale), Germany; [9]The Alfred Hospital and Monash University, Melbourne, Australia; [10]Kartos Therapeutics, Inc., Redwood City, CA; [11]University of Florence, Florence, Italy

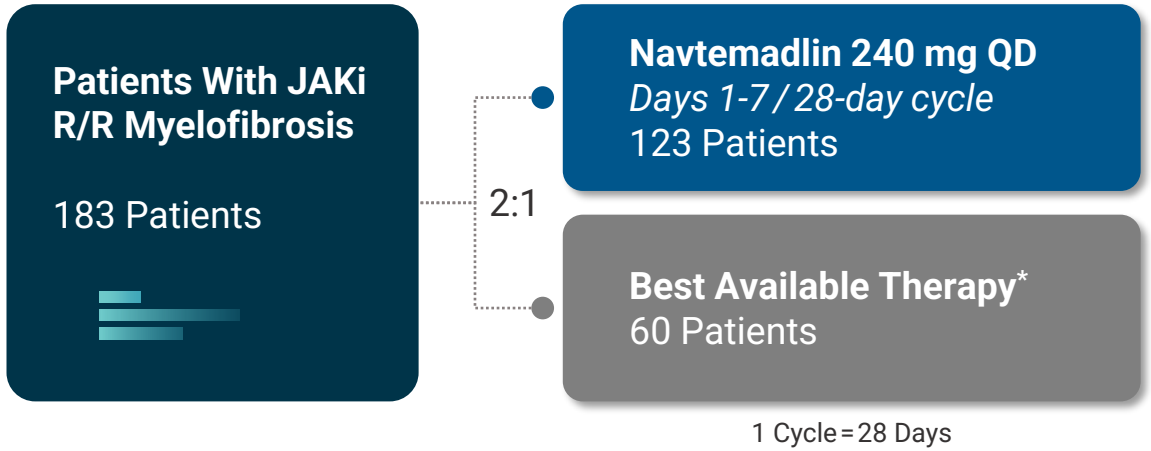
Phase 3 Study Design

A Randomized Open-Label Phase 3 Study of Navtemadlin in *TP53*^{WT} Subjects With Myelofibrosis Who Are Relapsed or Refractory to JAK Inhibitor Treatment

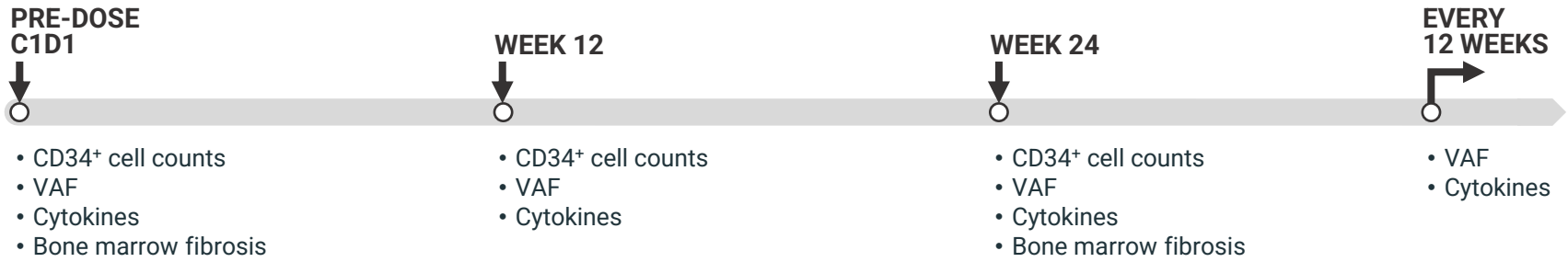
BOREAS
Blocking MDM2 to reactivate p53 in myelofibrosis

Stratification Factors:
- Primary MF vs Secondary MF
- Baseline TSS (≤10 vs >10)

Physician's Choice (BAT):
- Hydroxyurea
- Chemotherapy
- Peg Interferon
- IMiDs



EXPLORATORY ENDPOINTS
- CD34⁺ cell count in peripheral blood
- Variant allele frequency (VAF)
- Cytokines
- Bone marrow fibrosis

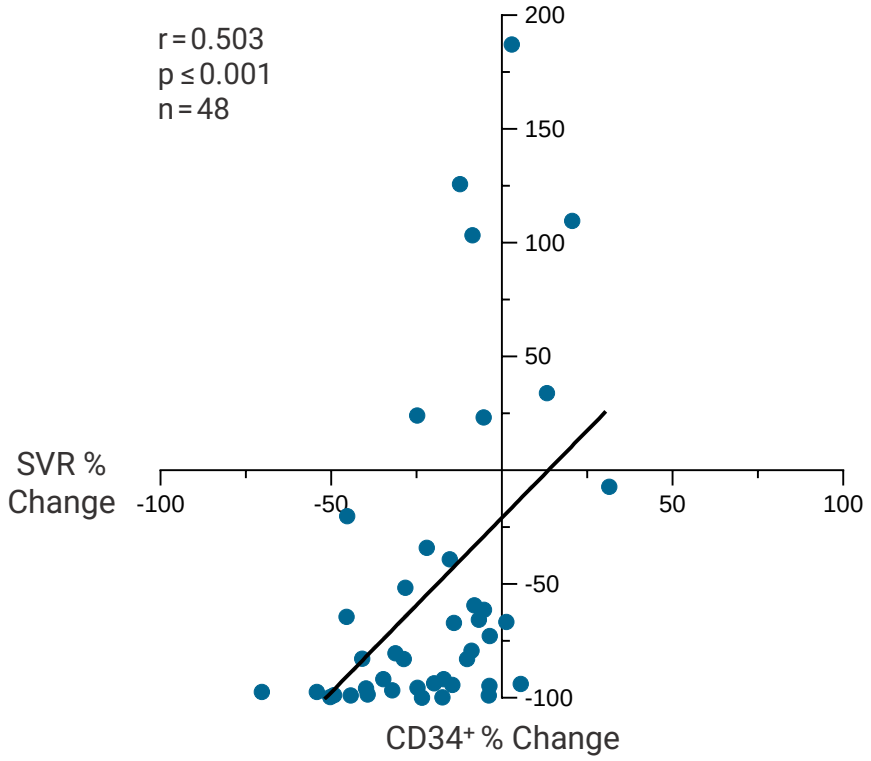


Note: BOREAS enrollment was closed at 183 patients.
*Crossover permitted in the BAT arm after disease progression or at Week 24.
Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1; IMiDs, immunomodulatory imide drugs (lenalidomide, pomalidomide); JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; QD, once daily; R/R, relapsed/refractory; TSS, total symptom score; VAF, variant allele frequency; WT, wild-type.

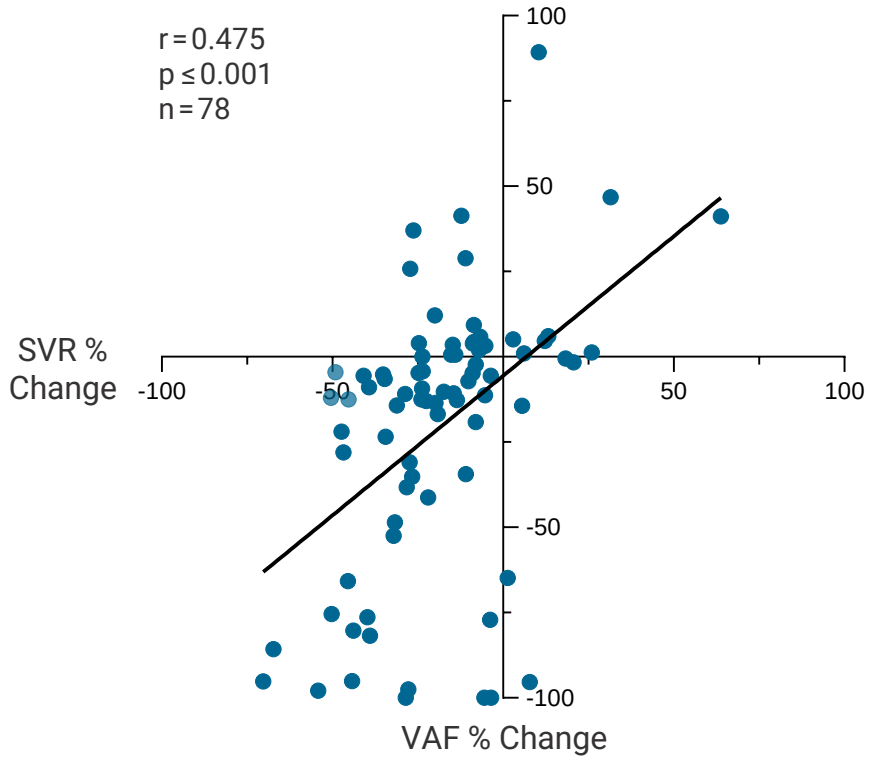
CD34+ and VAF Changes Correlate with SVR

Navtemadlin Reduces Circulating CD34+ and Driver Gene VAF – Baseline to Week 24

Circulating CD34+ Cells at Week 24



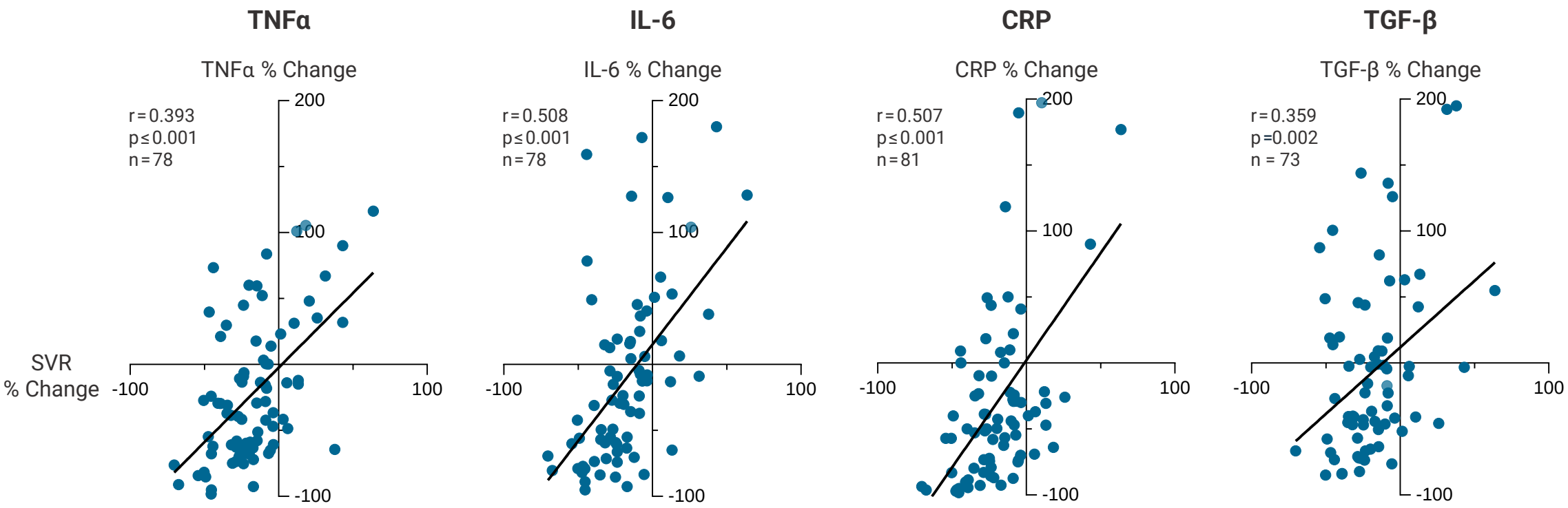
Driver Gene VAF at Week 24



Data cut-off: 30 Sep 2024.
Note: BAT Correlations - CD34+ r = 0.521, p = 0.027; VAF r = 0.337, p = 0.069. Baseline to Week 24.
Abbreviations: BAT, best available therapy; SVR, spleen volume reduction; VAF, variant allele frequency.

Reductions in Inflammatory Markers Correlate With SVR

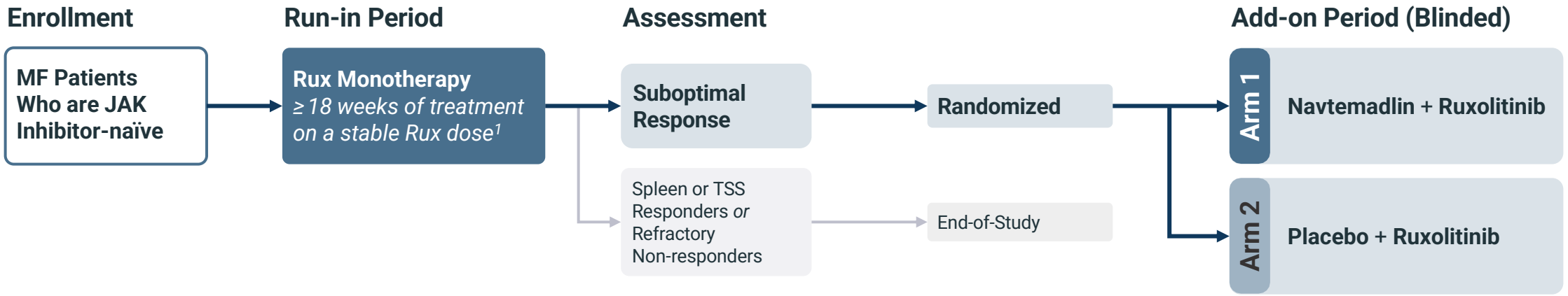
Navtemadlin Reduces Pro-Inflammatory Markers – Baseline to Week 24



Data cut-off: 30 Sep 2024.
Note: BAT Correlations: TNFα r=0.372, p=0.051; IL-6 r=0.579, p=0.001; CRP r=0.556, p=0.003.
Abbreviations: BAT, best available therapy; CRP, C-reactive protein; IL, interleukin; SVR, spleen volume reduction; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

Navtemadlin in Suboptimal Responders to Ruxolitinib

A Phase 3 Randomized, Double-Blind, Add-On Study Evaluating the Safety and Efficacy of Navtemadlin and Ruxolitinib vs Placebo and Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib Treatment



Run-in Period

Key Inclusion Criteria

- Primary or secondary MF by WHO criteria
- Int-1, Int-2, or High-risk disease by IPSS
- Spleen volume ≥450 cm^3
- Platelet count ≥100 x 10^9/L

Add-on Period

Key Inclusion Criteria

- *TP53*^{WT} by central testing
- Treatment with a stable dose of Rux
- Suboptimal response to Rux run-in

Endpoints

Co-primary Endpoints

- Targeted SVR and TSS reduction 24 weeks after randomization

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle).
[1]Stable ruxolitinib is ≥5 mg BID that does not require treatment hold or dose adjustment during the eight weeks prior to add-on navtemadlin or placebo.
Abbreviations: BID, twice daily; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; Rux, ruxolitinib; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

Thank you

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