New Drugs for Myelofibrosis

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New Drugs in MF

- New JAK inhibitors
- New non-JAK inhibitors
- JAK inhibitor based combinations

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New Drugs in MF

- **New JAK inhibitors**
  - **INCB160058 JAK2V617F selective inhibitor**
  - **AJ-11095 type 2 JAK2 inhibitor**

- New non-JAK inhibitors

- JAK inhibitor based combinations

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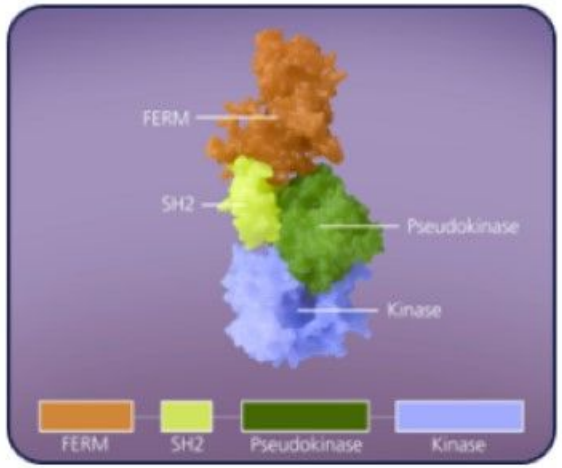
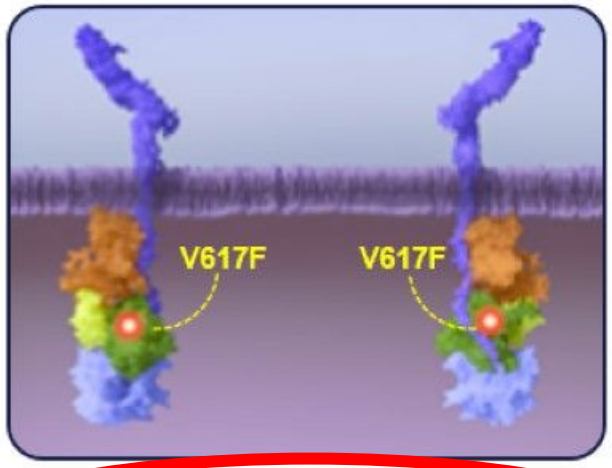
*JAK2*V617F is the Most Common Oncogenic Driver Mutation in the BCR::ABL1-Negative MPNs[1]

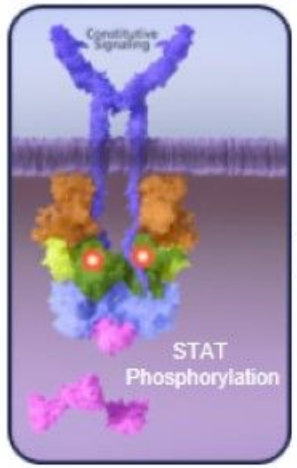
*JAK2*V617F occurs in ~65% of patients with PMF, ~96% of patients with PV and ~55% of patients with ET

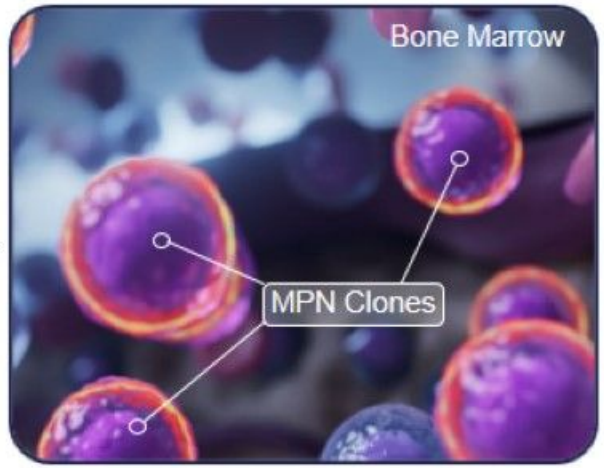


JAK2 has 4 domains: FERM and SH2 which interact with cytokines receptors, a **pseudokinase** domain, and a kinase domain[2]



The **V617F mutation** leads to cytokine-independent homodimerization through the **pseudokinase** domains[3,4]





Homodimerization leads to constitutive, cytokine-independent signaling which can lead to cellular proliferation and result in the development of myeloproliferative neoplasms[1,2,4]

Incyte is investigating **INCB160058**, a JAK2V617F-selective inhibitor

INCB160058 binds to the pseudokinase domain near the site of the V617F mutation which disrupts oncogenic homodimerization and blocks cytokine-independent activity[5-7]

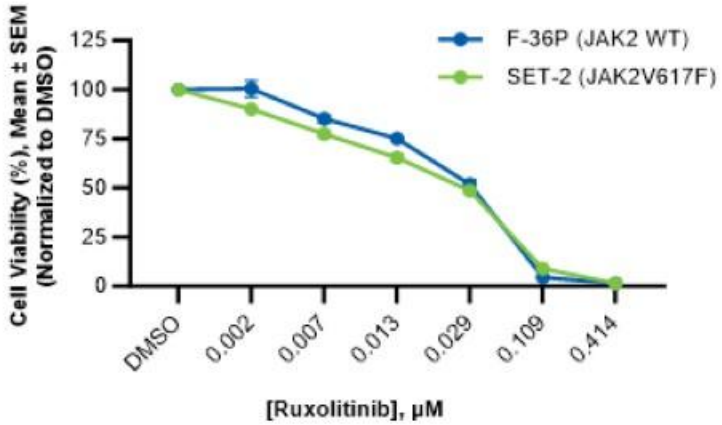
1. Tefferi A. *Am J Hematol*. 2021;96:145-162. 2. Shan Y, et al. *Nat Struct Mol Biol*. 2014;21:579-584. 3. Oh ST, Gotlib J. *Expert Rev Hematol*. 2010;3:323-337. 4. Abraham et al. *Sci Adv*. 2024;10(10):eadl2097. 5. Stubbs M et al. ASH 2023. Abstract 860. 6. Shide K, et al. Blood. 2011;117(25):6866-75. 7. Nakaya Y, et al. Blood Cancer J. 2014; 4(1): e174

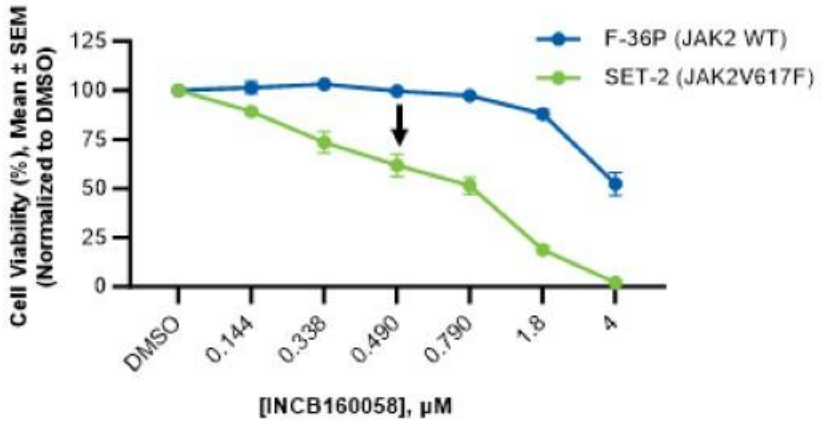
INCB160058 Selectively Inhibits Growth of JAK2V617F- Expressing Cells Across a Range of Concentrations

Ruxolitinib

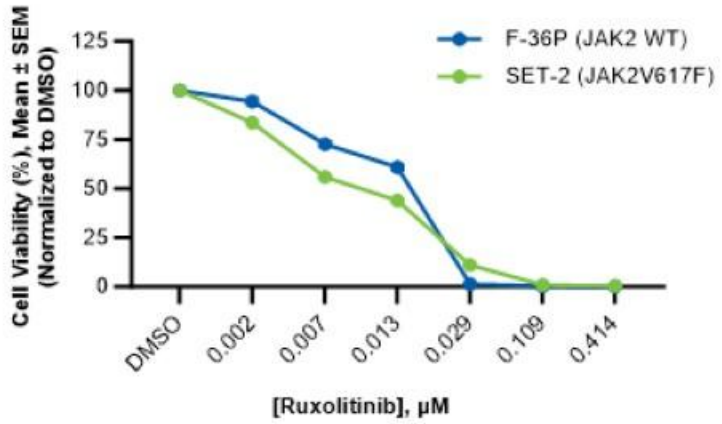
INCB160058

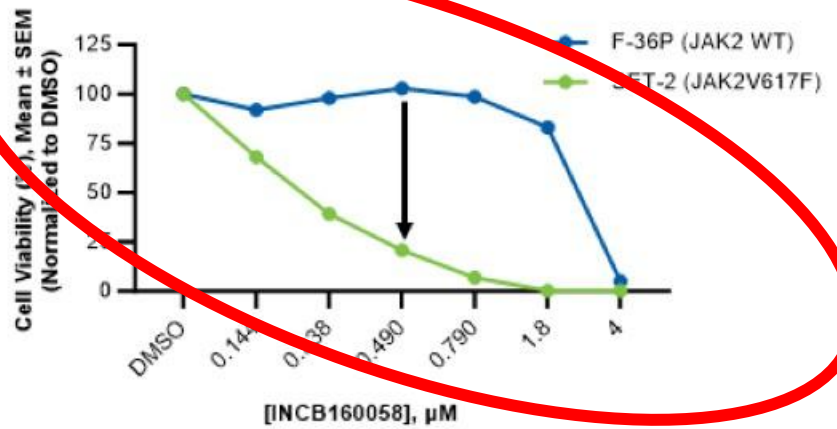
Day 6





Day 18





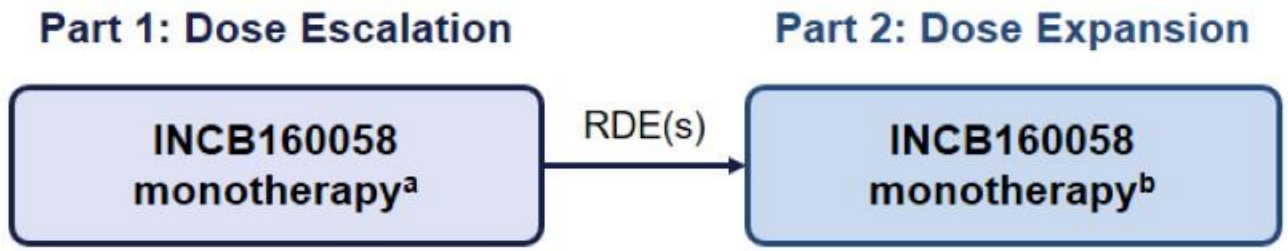
Stubbs M et al. ASH 2023. Abstract 860.

INCB160058-101: Study Design Overview[1,2]

Study design: Phase 1, open-label study (NCT06313593) to investigate the safety, tolerability, and DLTs of oral INCB160058 (JAK2V617F-selective inhibitor) in patients with myeloproliferative neoplasms to determine MTD and RDE(s).

Select Inclusion Criteria

- Age ≥18 years
- DIPPS INT-1 or higher PMF, post-PV MF, or post-ET MF
- Existing *JAK2*V617F mutation
- PLT ≥50 × 10^9/L
- Previous JAKi therapy ≥12 weeks and resistant, refractory, intolerant, or lost response to therapy



Primary Endpoints

- Occurrence of DLTs
- Incidence of TEAEs
- Incidence of TEAEs leading to drug modifications and discontinuations

Secondary Endpoints

- Safety
- PK measures
- Response per IWG-MRT and ELN response criteria
- SVR35 and SVR25 at week 12 and week 24
- TSS50 at week 24

Exploratory Endpoint

- Allele burden level of *JAK2*V617F mutation

Based on INCB160058 selectivity for the JAK2V617F mutation, potential for evaluation in PV and/or ET[3]

[a] Administered at protocol defined starting regimen to identify MTD and/or RDE(s).[b] Doses administered at RDE(s) identified in Part 1.
DIPPS, Dynamic International Prognostic Scoring System; DLT, dose-limiting toxicities; ELN, European LeukemiaNet; ET, essential thrombocythemia; IWG-MRT, International Working Group for Myeloproliferative Neoplasms Research and Treatment; MTD, maximum tolerated dose; PK, pharmacokinetics; PLT. platelet count; PV, polycythemia vera; RDE, recommended dose expansion; SVR, spleen volume reduction; TEAE, treatment emergent adverse event; TSS, total symptom score.

1. ClinicalTrials.gov. Accessed Aug 2024. https://www.clinicaltrials.gov/study/NCT06313593. 2. Data on file. Incyte Corporation. 3.Stubbs M et al. ASH 2023. Abstract 860.

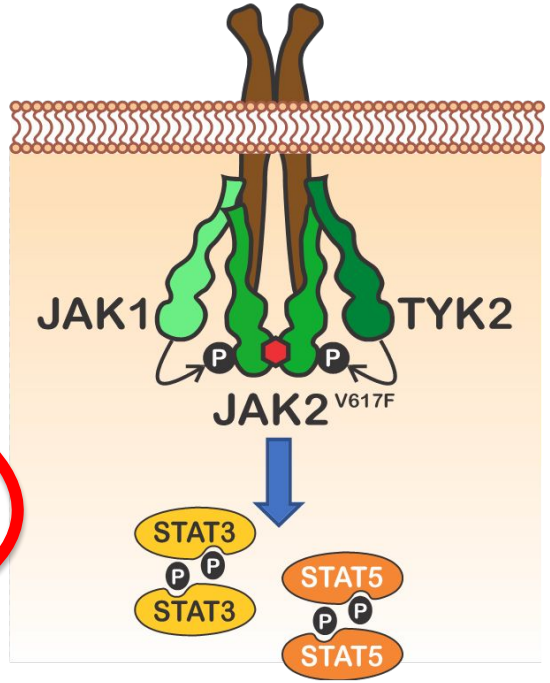
AJ-11095 Type II JAK2 Inhibitor Phase 1 multicenter trial

QR code with link to AJX-101 trial at ClinicalTrials.gov

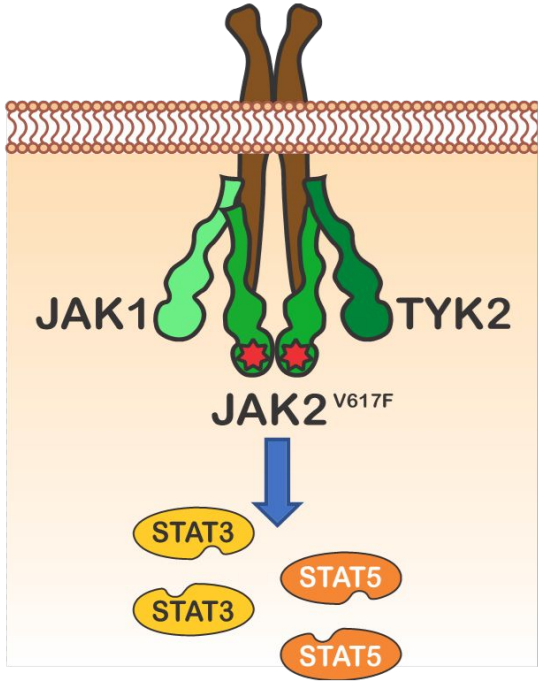
ClinicalTrials.gov ID: NCT06343805

- The JAK2 kinase has two conformations — active "DFG-in" (Type I) and inactive "DFG-out" (Type II)
- **All approved JAK2 inhibitors**, including ruxolitinib, fedratinib, momelotinib and pacritinib, **are Type I inhibitors that bind the *active* conformation only**
- **Type I JAK2 inhibitors' major limitation:** allow JAK2 to form complexes with other JAKs (e.g. JAK2/JAK1, JAK2/TYK2) resulting in "persistent" MPN cells that lose response to Type I therapy
- Previous work showed Type II JAK2 inhibition **overcomes ruxolitinib persistent MPN cells and induces disease modification** in MPN/JAK-mutant leukemia preclinical models

Chronic type I JAK Inhibition



Type II JAK Inhibition



Persistent JAK-STAT Activation

Reversal of Persistent Activation

New Drugs in MF

- New JAK inhibitors
- **New non-JAK inhibitors**
  - **Nuvisertib PIM1 kinase inhibitor**
  - **Reparaxin CXCR 1/2 antagonist**
  - **INCA033989 mCALR antibody**
- JAK inhibitor based combinations

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Nuvisertib (TP-3654), an Investigational Selective PIM1 Kinase Inhibitor, Showed Durable Clinical Response and Sustained Hematological Improvement in Patients With Relapsed/Refractory Myelofibrosis

Firas El Chaer, MD[1], Lindsay Rein, MD[2], Junichiro Yuda, MD, PhD[3], Kazuya Shimoda, MD, PhD[4], Akiyoshi Takami, MD, PhD[5], Michiko Ichii, MD, PhD[6], James McCloskey, MD[7], Joseph Scandura, MD, PhD[8], Allessandra Iurlo, MD, PhD[9], Prithviraj Bose, MD[10], Tamanna Haque, MD[11], Alessandro Lucchesi, MD, PhD[12], Shuichi Shirane, MD, PhD[13], Giulia Benevolo, MD[14], Idoroenyi Amanam, MD[15], Jean-Jacques Kiladjian, MD, PhD[16], Pankit Vachhani, MD[17], Srinivas Tantravahi, MBBS, MRCP[18], Yasushi Onishi, MD, PhD[19], Ciro Rinaldi, MD, PhD[20], Marcello Rotta, MD[21], Nikki Granacher, MD[22], Anand A. Patel, MD[23], Michael Loschi, MD, PhD[24], Samah Alimam, MD, PhD[25], Terrence Bradley, MD[26], Stanley Cheung, MD, PhD[27], Vincent Ribrag, MD[28], Sujan Kabir, MD[29], Karen Ansaldo, PharmD[29], Masataka Seki, MS[29], Vincent Loksa, PharmD[29], Zhonggai Li, PhD[29], Jason M Foulks, PhD[29], Jatin Shah, MD[29], Raajit Rampal, MD, PhD[11]

[1]University of Virginia Health System, VA; [2]Duke University Medical Center, NC; [3]National Cancer Center Hospital East, Japan; [4]University of Miyazaki, Japan; [5]Aichi Medical University School of Medicine, Japan; [6]Osaka University Graduate School of Medicine, Japan; [7]John Theurer Cancer Center at Hackensack Meridian Health, NJ; [8]Weill Cornell Medicine, NY; [9]Hematology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy; [10]MD Anderson Cancer Center, University of Texas, TX; [11]Memorial Sloan Kettering Cancer Center, NY; [12]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Italy; [13]Juntendo University School of Medicine, Japan; [14]Azienda Ospedaliero-Universitaria, Italy; [15]City of Hope, CA; [16]Hopital Saint-Louis, France; [17]University of Alabama at Birmingham, AL; [18]Huntsman Cancer Institute, UT; [19]Tohoku University Hospital, Japan; [20]United Lincolnshire Teaching Hospital and University of Lincoln, UK; [21]Colorado Blood Cancer Institute, CO; [22]ZNA Middelheim, Belgium; [23]University of Chicago, IL; [24]CHU de Nice Hôpital l'Archet 1, France; [25]University College London Hospitals, UK; [26]University of Miami Health System, FL; [27]ICON Cancer Care, Australia; [28]Institut Gustave Roussy, France; [29]Sumitomo Pharma America, Inc., MA

Ongoing Nuvisertib (TP-3654) Global Phase 1/2 Study in MF

Phase 1
Monotherapy (Arm 1)
Dose escalation
480 mg QD – 1440 mg BID
Bayesian Dose escalation

→ **MTD/ RP2D** → **Phase 2 Dose Expansion**

Study Population*

- Primary, Post-PV, Post-ET MF
- Relapsed, refractory, intolerant, or ineligible for JAK inhibitors
- DIPSS intermediate or high-risk
- Platelet count ≥ 25 x 10^9/L
- No Restriction on hemoglobin
- Spleen vol ≥ 450 cm^3 per CT/MRI
- ≥ 2 symptoms by MF-SAF v4.0

Endpoints*

Primary
- Safety and tolerability

Secondary
- Spleen volume reduction (SVR)
- Total symptom score (TSS) reduction
- Overall survival
- Bone marrow fibrosis change
- Pharmacokinetics

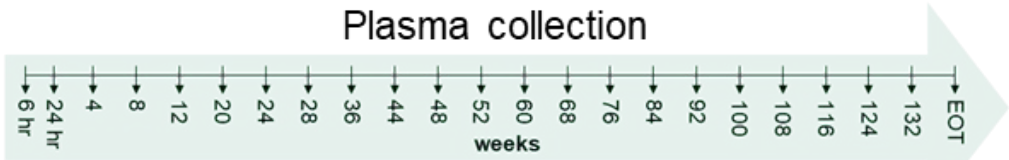
* Refer to ClinicalTrials.gov (NCT04176198, Arm 1) for further information

Comprehensive Cytokine Analysis Plan

Enrolled patients in TP-3654-102 trial (N=74)

↓

Plasma collection



↓

Measurement of a panel 64 cytokines
Following quality control, 42 cytokines were evaluable

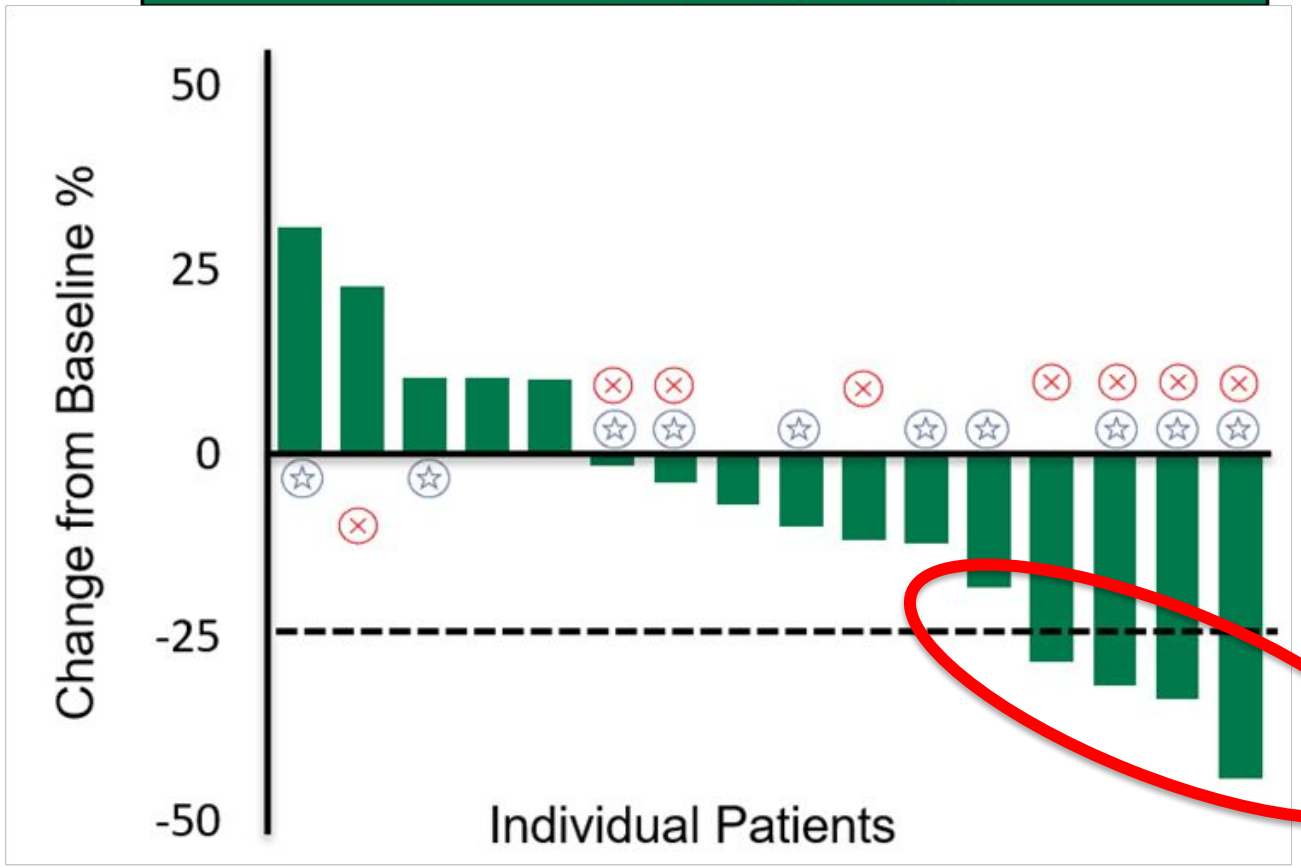
Longitudinal analysis → Patients with cytokine data n=63 (as of 04 July 2024)

Correlations with TSS and individual symptoms by Kaplan Meier → Patients with cytokine data n=63 (as of 04 July 2024)

Preliminary data as of 01 Oct 2024

Spleen Volume Response at 720 mg BID

Best Changes in Spleen Volume at Any Time
SVR25: 22.2% (4 of 18)



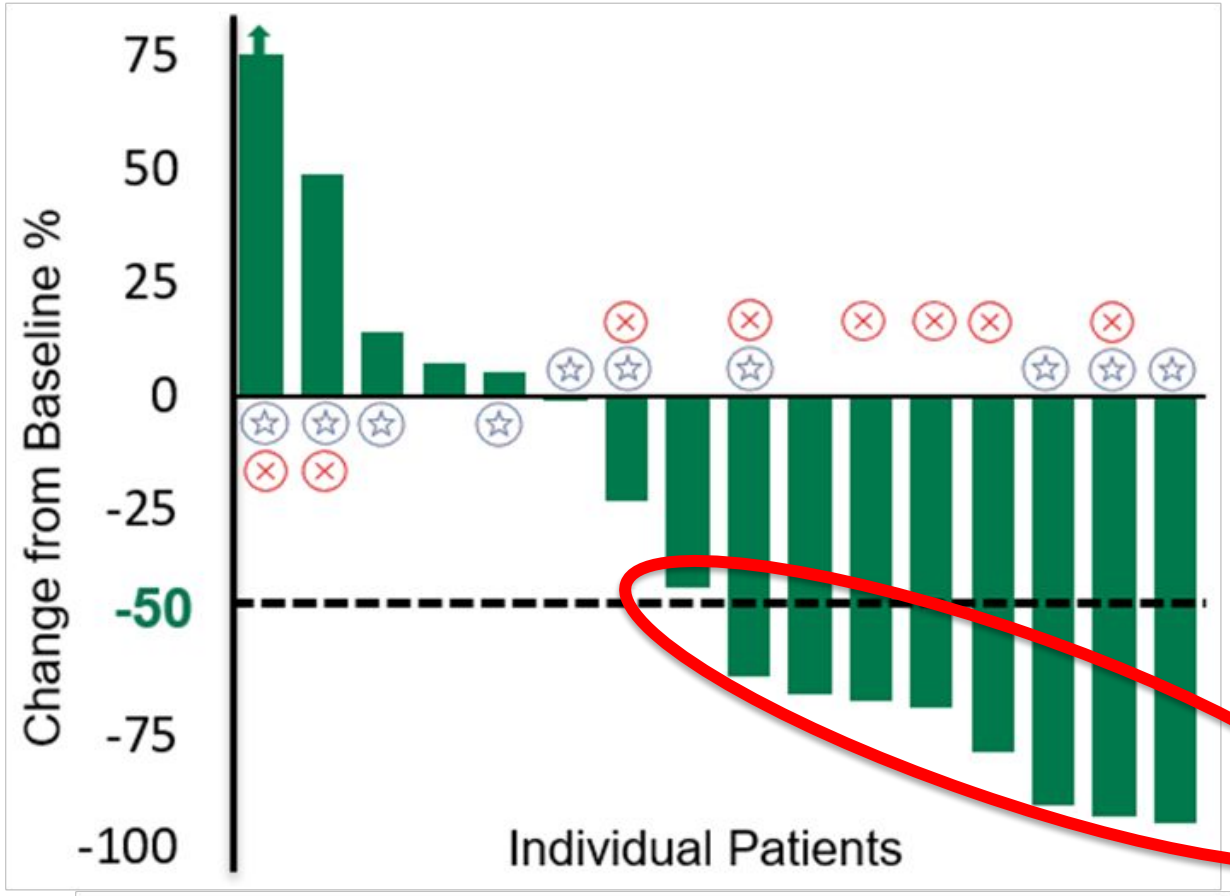
- 18 evaluable patients* at 720 mg BID dose regimen (projected RP2D)
- 11 of 18 (61%) patients have shown spleen volume reduction
  - 4 of 18 (22.2%) patients have shown 25% spleen volume reduction (SVR25)

* Evaluable patients = who completed ≥ 12 weeks of treatment or discontinued prior to week 12 for treatment-related AE or PD
Evaluable dose: 720 mg BID (projected RP2D)

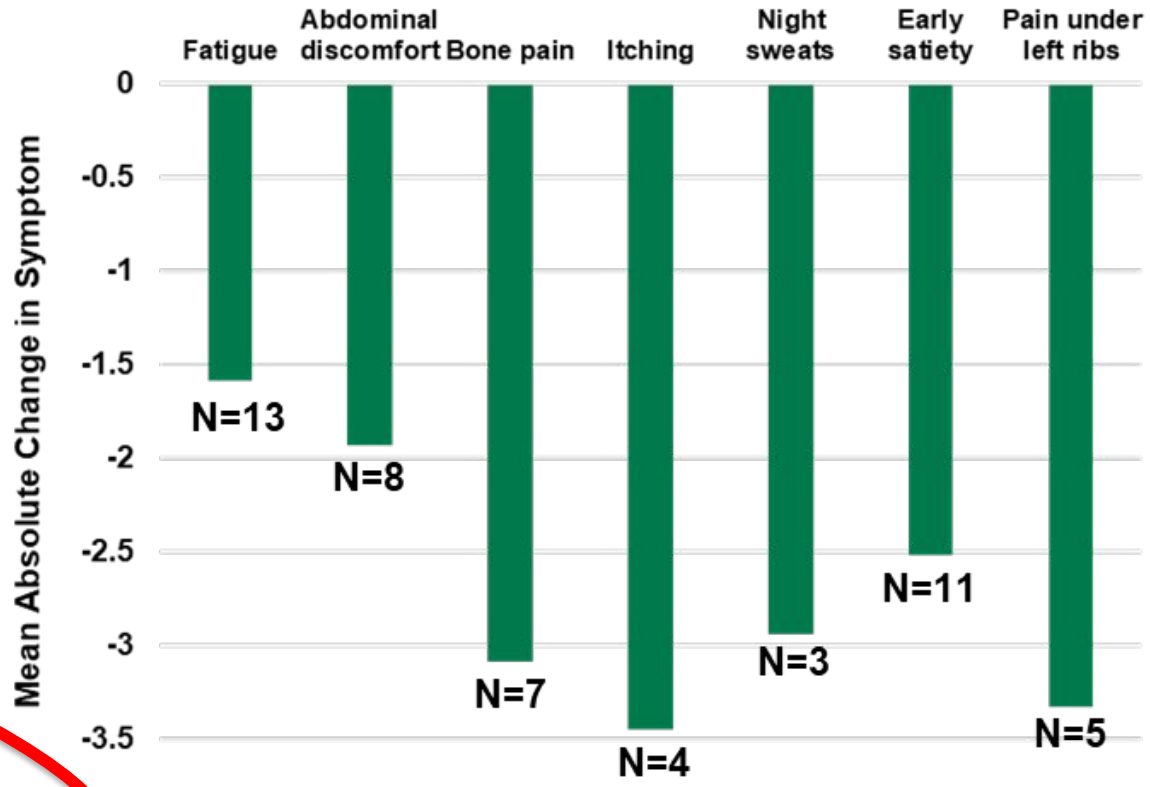
Preliminary data as of 01 Oct 2024

Symptom Response at 720 mg BID

Best Changes in TSS at Any Time (N=18)* TSS50: 44.4% (8 of 18)



Absolute Changes in Individual Symptoms (Baseline Individual Symptom Score ≥3)

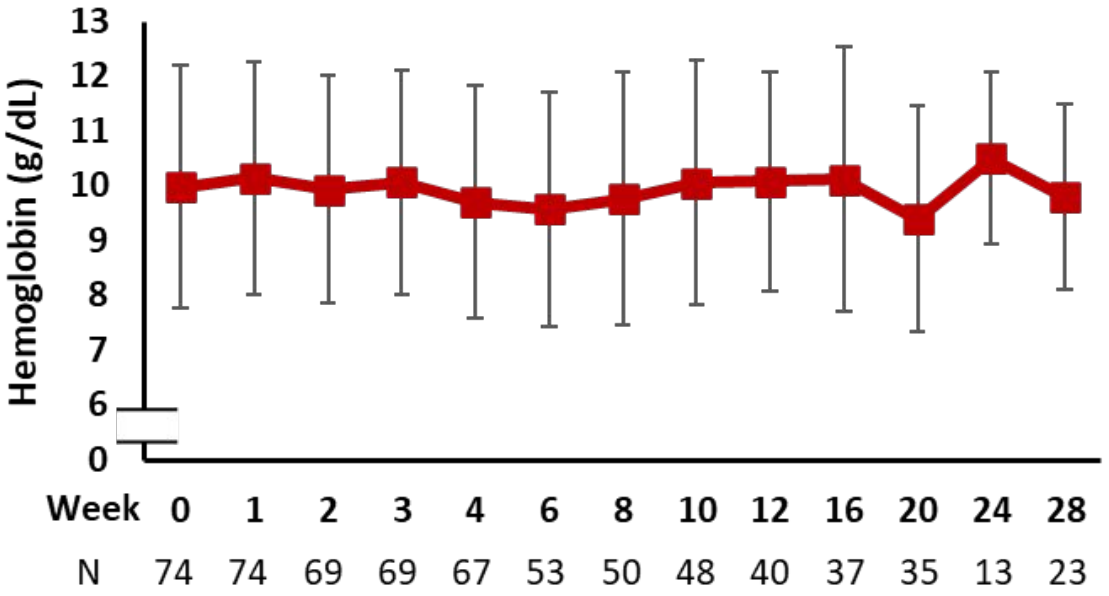


* Evaluable patients = who completed ≥ 12 weeks of treatment or discontinued prior to week 12 for treatment-related AE or PD
Evaluable dose: 720 mg BID (projected RP2D)

Preliminary data as of 01 Oct 2024

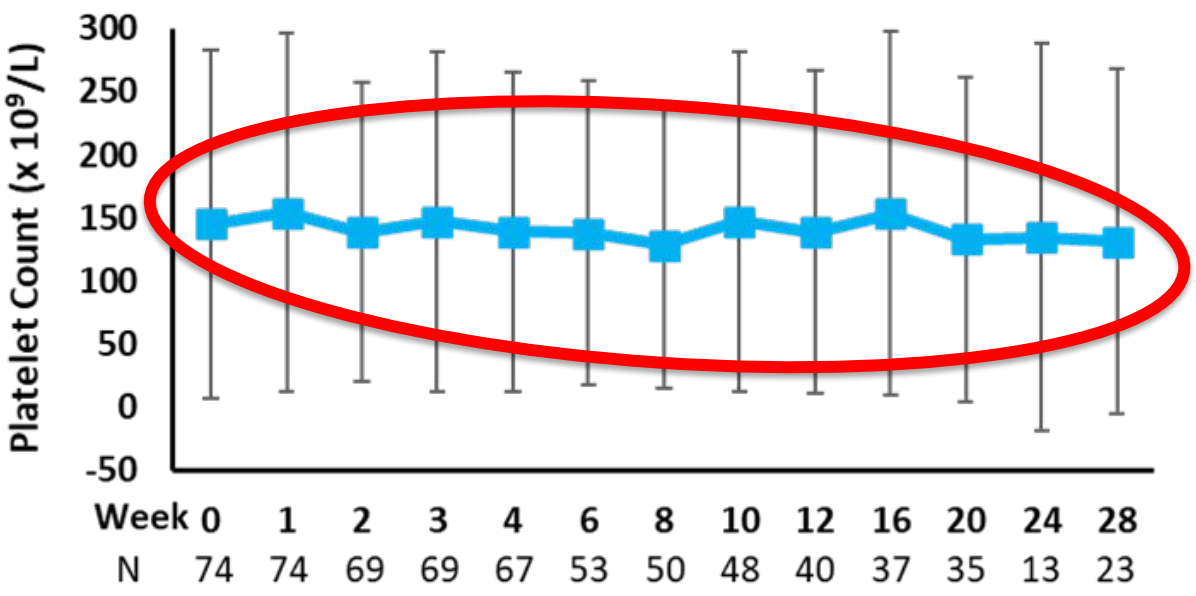
Preservation of hematopoiesis with nuvisertib

Hemoglobin Stability During Treatment N=74 (All Patients); Mean ± SD



- Hemoglobin remains stable in all patients during first 28 weeks of nuvisertib treatment

Platelet Stability During Treatment N=74 (All Patients); Mean ± SD



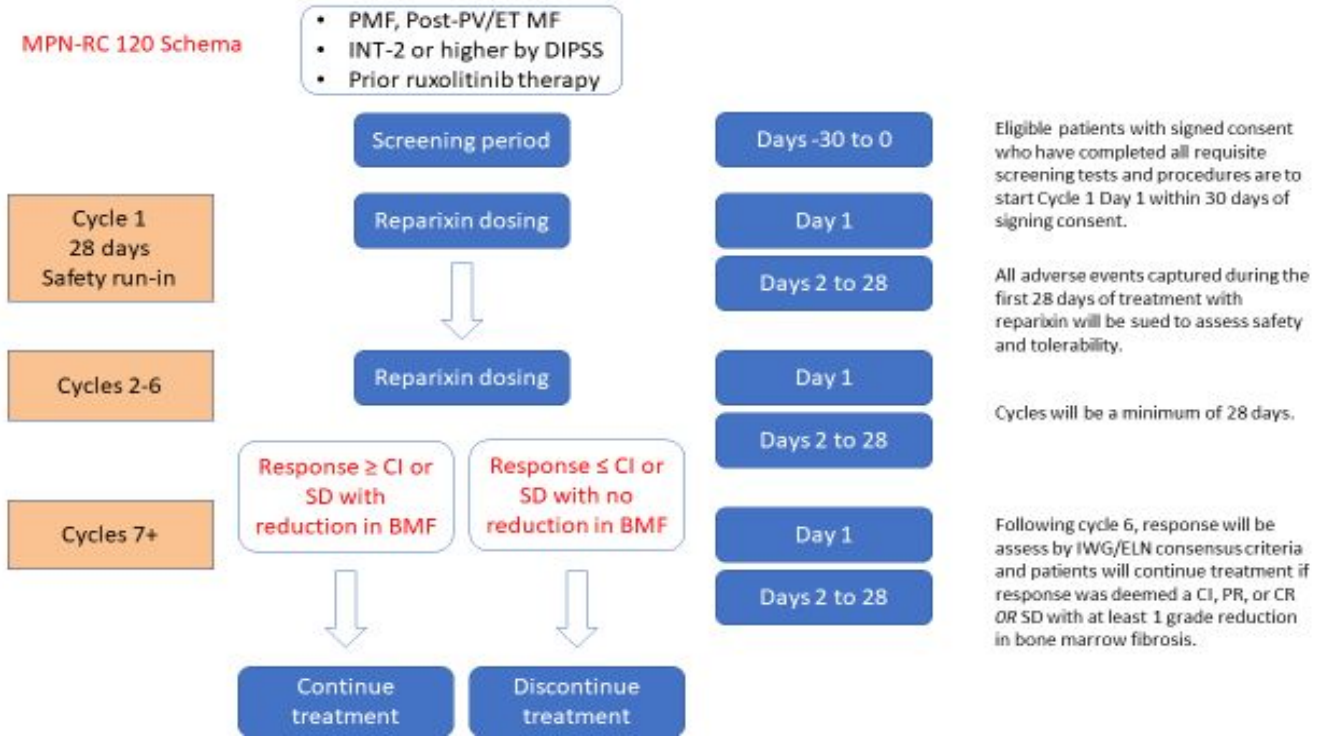
- Platelet count remains stable in all patients during first 28 weeks of nuvisertib treatment

Preliminary data as of 01 Oct 2024

MPN-RC 120: Targeting IL-8 in Myelofibrosis with Reparixin

NCT05835466

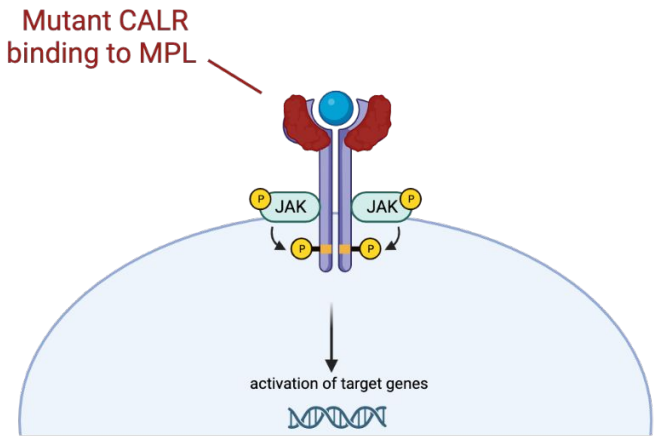
- IL-8 is elevated in MF and associated with adverse outcome
- IL-8 is secreted by the MF HSC and promotes proliferation and survival
- IL-8 pathway inhibition in culture reduced MF HSC engraftment and survival in mice



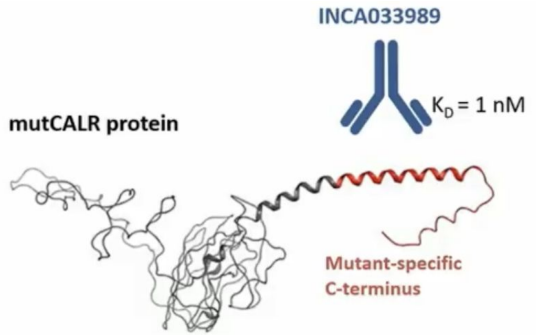
Study Chairs: Aaron Gerds, MD (Cleveland Clinic) Marina Kremyanskaya, MD (Mount Sinai)

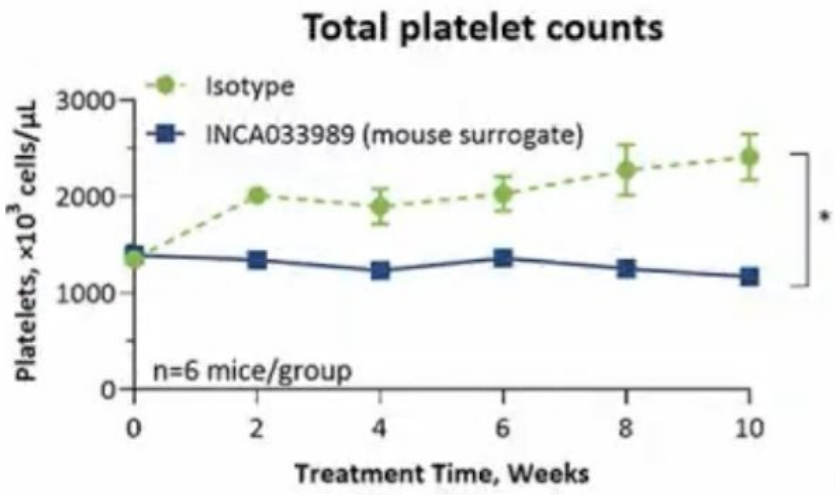
INCA033989, a mutant CALR specific monoclonal antibody
Phase 1 global trials

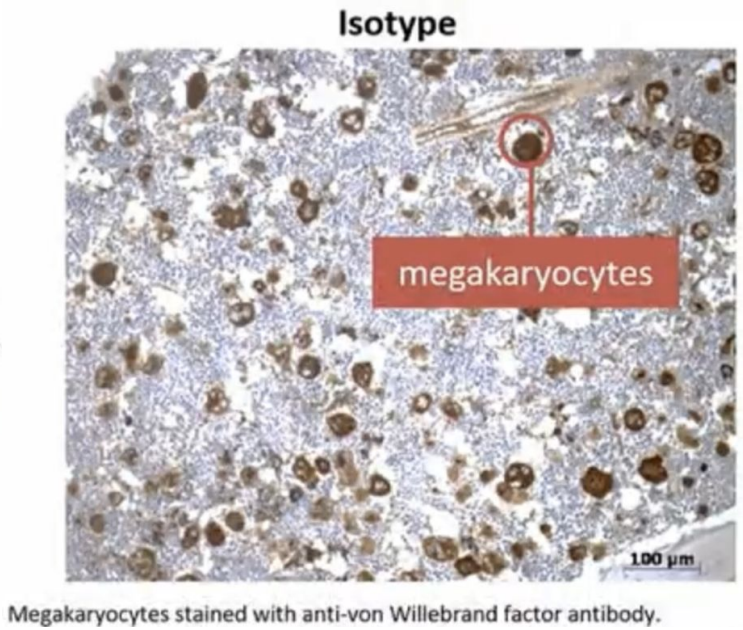
NCT05936359

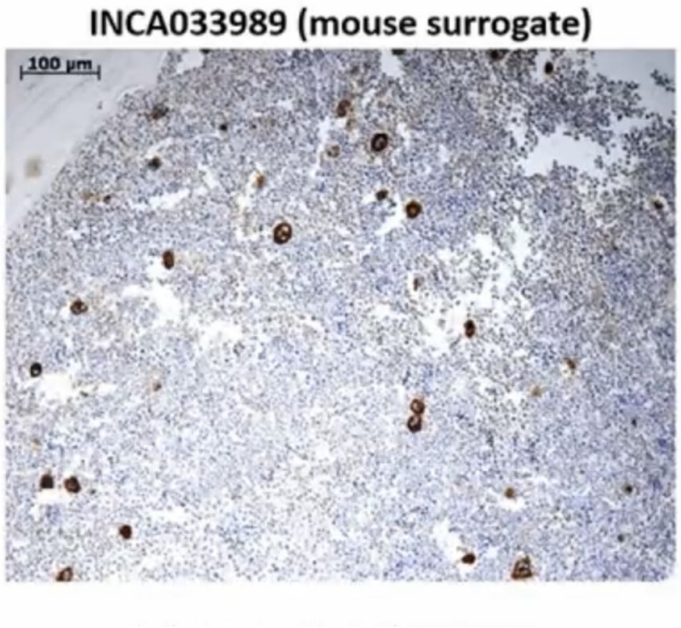


- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function









Megakaryocytes stained with anti-von Willebrand factor antibody.

Fc, fragment crystallizable; Ig, immunoglobulin.
Reis E, et al. ASH 2022. Plenary Session.

New Drugs in MF

- New JAK inhibitors
- New non-JAK inhibitors
- **JAK inhibitor based combinations**
  - **MANIFEST-2: Pelabresib**
  - **SENTRY: Selinexor**
  - **POIESIS: Navtemadlin**

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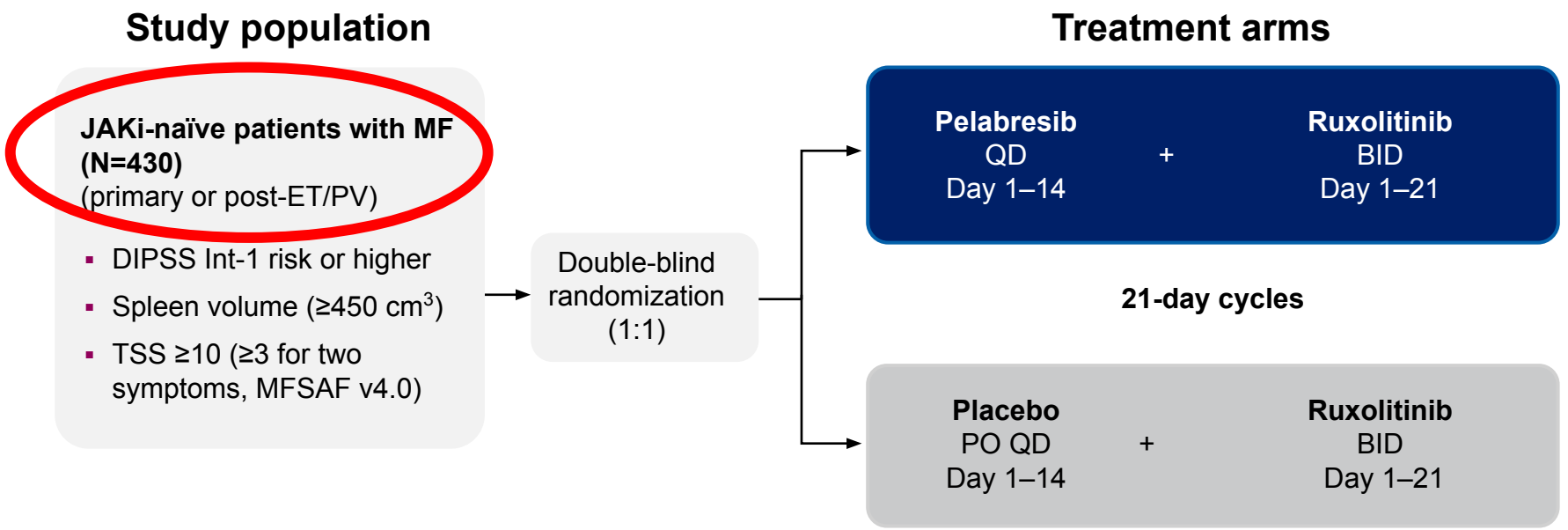
Updated Results From the Phase 3 MANIFEST-2 Study of Pelabresib in Combination With Ruxolitinib for Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis

John Mascarenhas,[1] Sebastian Grosicki,[2] Dominik Chraniuk,[3] Elisabetta Abruzzese,[4] Prithviraj Bose,[5] Aaron Gerds,[6] Alessandro M. Vannucchi,[7] Francesca Palandri,[8] Sung-Eun Lee,[9] Vikas Gupta,[10] Alessandro Lucchesi,[11] Stephen T. Oh,[12] Andrew T. Kuykendall,[13] Andrea Patriarca,[14] Alberto Álvarez-Larrán,[15] Ruben Mesa,[16] Jean-Jacques Kiladjian,[17] Moshe Talpaz,[18] Morgan Harris,[19] Sarah-Katharina Kays,[20] Tabea Kräft,[20] Qing Li,[21] Anna-Maria Jegg,[20] Claire Harrison,[22] Raajit K. Rampal[23]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Department of Cancer Prevention, Medical University of Silesia, Katowice, Poland; [3]Hematology Ward, Wojewódzki Szpital Zespolony im. L. Rydygiera, Torun, Poland; [4]Department of Hematology, S. Eugenio Hospital, Tor Vergata University, ASL Roma 2, Rome, Italy; [5]Leukemia Department, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [7]Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; [8]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli”, Bologna, Italy; [9]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [10]Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio e la Cura dei Tumori (IRST) “Dino Amadori”, Meldola (FC), Italy; [12]Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [13]Moffitt Cancer Center, Tampa, FL, USA; [14]Hematology Unit, AOU Maggiore della Carità and University of Eastern Piedmont, Novara, Italy; [15]Hematology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [16]Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC, USA; [17]Clinical Investigation Center, Hôpital Saint-Louis, Université de Paris, Paris, France; [18]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [19]Constellation Pharmaceuticals, a MorphoSys Company, Boston, MA, USA; [20]MorphoSys AG, Planegg, Germany; [21]MorphoSys US Inc, Boston, MA, USA; [22]Department of Haematology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK; [23]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

MANIFEST-2 Study: Global, Randomized, Double-Blind, Active-Controlled, Phase 3 Trial



- As of March 29, 2024, 58.9% (126/214) and 62.0% (134/216) of patients continued on double-blind treatment in the pelabresib + ruxolitinib and placebo + ruxolitinib arms, respectively
- Reasons for discontinuation in patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib include AE (15.9% vs 9.7%), physician decision (6.5% vs 12.5%), disease progression (4.2% vs 3.7%), eligible for transplant (4.7% vs 5.6%), and other reasons including non-compliance or withdrawal of consent (8.9% vs 5.6%)

Primary endpoint

- SVR35 at Week 24

Key secondary endpoints

- Absolute change in TSS from baseline at Week 24
- TSS50 at Week 24

Other prespecified* endpoints

- SVR35 response at Week 48
- Absolute change in TSS at Week 48
- TSS50 response at Week 48
- Hemoglobin response†
- Bone marrow fibrosis at Week 48

Exploratory* endpoints

- Changes in proinflammatory cytokine levels from baseline at Week 48
- Changes in mutant clone burden VAF from baseline at Week 48

Safety

- AEs of all grades and serious AEs

*Other prespecified and exploratory endpoints are presented descriptively. †Hemoglobin response defined as ≥1.5 g/dL mean increase from baseline without transfusions in the prior 12 weeks.

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 imaging; PO, orally; PV, polycythemia vera; QD, once daily; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline; VAF, variant allele fraction.

Harrison CN, et al. *Future Oncol.* 2022;18(27):2987-2997; Rampal R, et al. Presented at ASH 2023 [Oral 628].

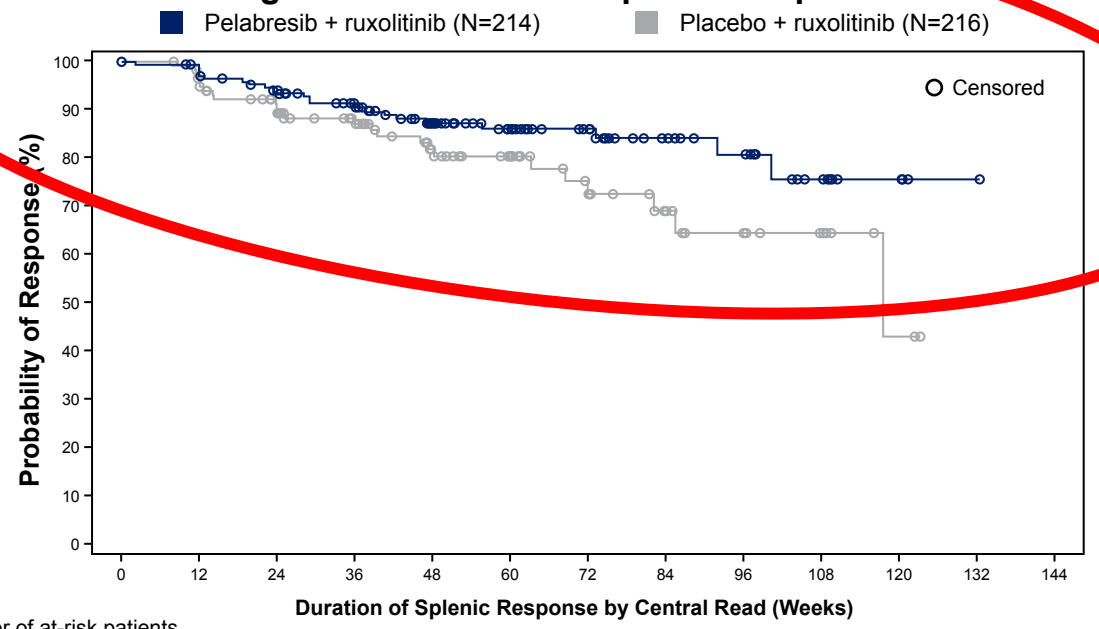
Splenic Response at Week 48

SVR35 response rates continued to be greater at Week 48 with pelabresib + ruxolitinib versus placebo + ruxolitinib (57.0% vs 37.5%, respectively)

Table 1. Splenic Response at Week 48 and Loss of Splenic Response

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
SVR35 response at Week 48, %	57.0	37.5
Difference* (95% CI)	19.1 (10.1, 28.0)	
Mean % change in spleen volume at Week 48†	−54.5 (n=138)	−33.5 (n=156)
95% CI	−58.1, −51.0	−36.9, −30.1
SVR35 response at anytime, % (n/N)	82.2 (176/214)	57.9 (125/216)
Loss of SVR35 response and >25% increase in spleen volume from nadir (main analysis), % (n/N)‡	13.1 (23/176)	20.0 (25/125)
Loss of SVR35 response (alternative definition), % (n/N)§	21.0 (37/176)	36.8 (46/125)

Figure 1b. Duration of Splenic Response



Number of at-risk patients

Pelabresib + ruxolitinib	176	166	152	126	92	70	51	35	24	11	4	1	0
Placebo + ruxolitinib	125	109	96	76	56	35	27	17	11	8	2	0	0

- Higher proportion of patients maintained SVR35 responses in the pelabresib + ruxolitinib arm versus the placebo + ruxolitinib arm

Data cutoff date: March 29, 2024. Spleen volume assessed by central read. *Calculated by stratified Cochran–Mantel–Haenszel test. †Patients without Week 48 assessment are considered non-responders. ‡Among anytime SVR35 responders. Duration of the splenic response is defined as the time from when the criterion for splenic response is first met (ie, a ≥35% reduction from baseline spleen volume) until the time at which there is a <35% reduction in spleen volume from baseline and also an increase of >25% from nadir as measured by MRI or CT is first documented. §Among anytime SVR35 responders. The alternative definition for duration of the splenic response is defined as the time from when the criterion for splenic response is first met (ie, a ≥35% reduction from baseline spleen volume) until the time at which there is a <35% reduction in spleen volume from baseline.

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; SVR35, ≥35% reduction in spleen volume from baseline.

Total Symptom Score at Week 48

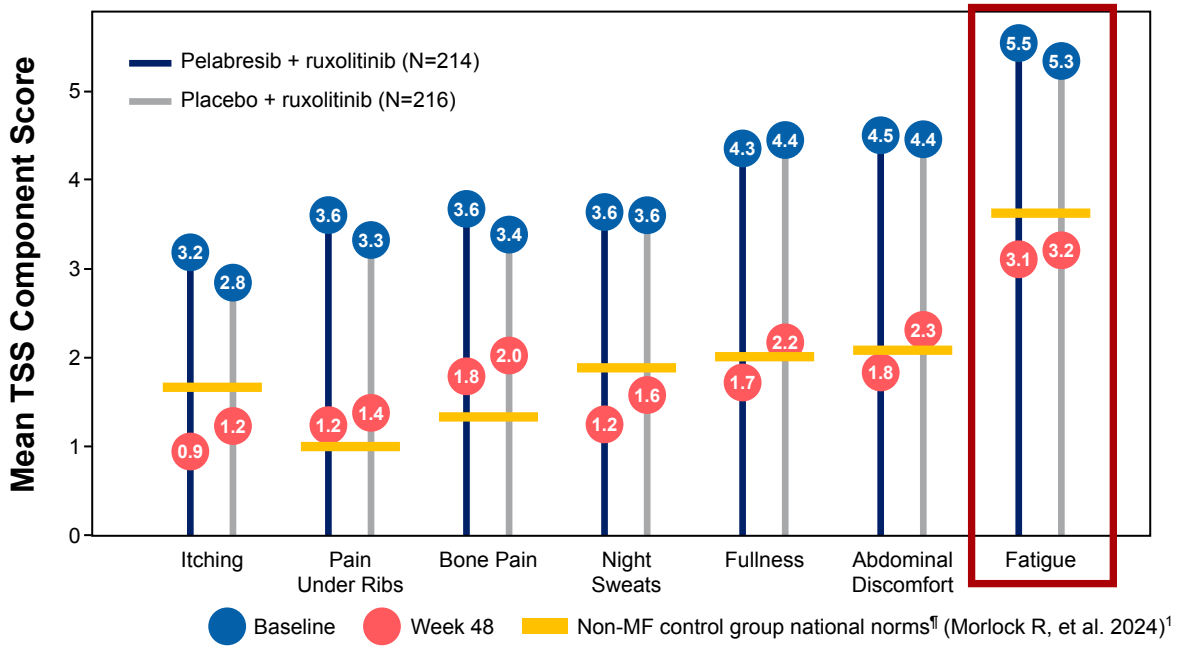
Numerically greater improvements for patients treated with pelabresib + ruxolitinib versus placebo + ruxolitinib, with large symptom reduction in both arms

Figure 2. Total Symptom Score at Week 48

2a. TSS at Week 48 (ITT Population)

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
TSS change* from baseline at Week 48	−16.24	−14.11
Mean difference† (95% CI) at Week 48	−2.13 (−4.25, −0.01)	
TSS50 response at Week 48, %	45.3	39.4
Difference‡ (95% CI) at Week 48	5.6 (−3.7, 14.9)	
mTSS§ equivalent on 70-point scale at Week 48	−16.19	−13.86
Mean difference (95% CI) at Week 48	−2.33 (−4.39, −0.28)	

2b. TSS Component Scores at Week 48



- TSS individual domain scores were similar between the two arms and similar to the national norms in people without MF[1]
- In the analysis of mTSS (MFSAF excluding fatigue) equivalent on 70-point scale, LSM change from baseline was −16.19 with pelabresib + ruxolitinib versus −13.86 with placebo + ruxolitinib (mean difference: −2.33; 95% CI −4.39, −0.28)
- At Week 48, 36% of patients in the pelabresib + ruxolitinib arm had both SVR35 and TSS50 responses versus 19% in the placebo + ruxolitinib arm

Data cutoff date: March 29, 2024. *Change from baseline determined by ANCOVA model using multiple imputation. †LSM difference from ANCOVA model using baseline DIPSS score, baseline platelet count, and baseline spleen volume as factors, and baseline TSS as covariate. ‡Difference in treatment groups analyzed by stratified Cochran–Mantel–Haenszel test (weighted 95% CI adjusted across strata). §Modified TSS (excludes fatigue domain). ¶Non-MF control group was of a similar age to patients in the MANIFEST-2 study.

ANCOVA, analysis of covariance; CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; LSM, least squares mean; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; mTSS, modified total symptom score; ITT, intent-to-treat; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

1. Morlock R, et al. Presented at ASH 2024 [Abstract 2419].

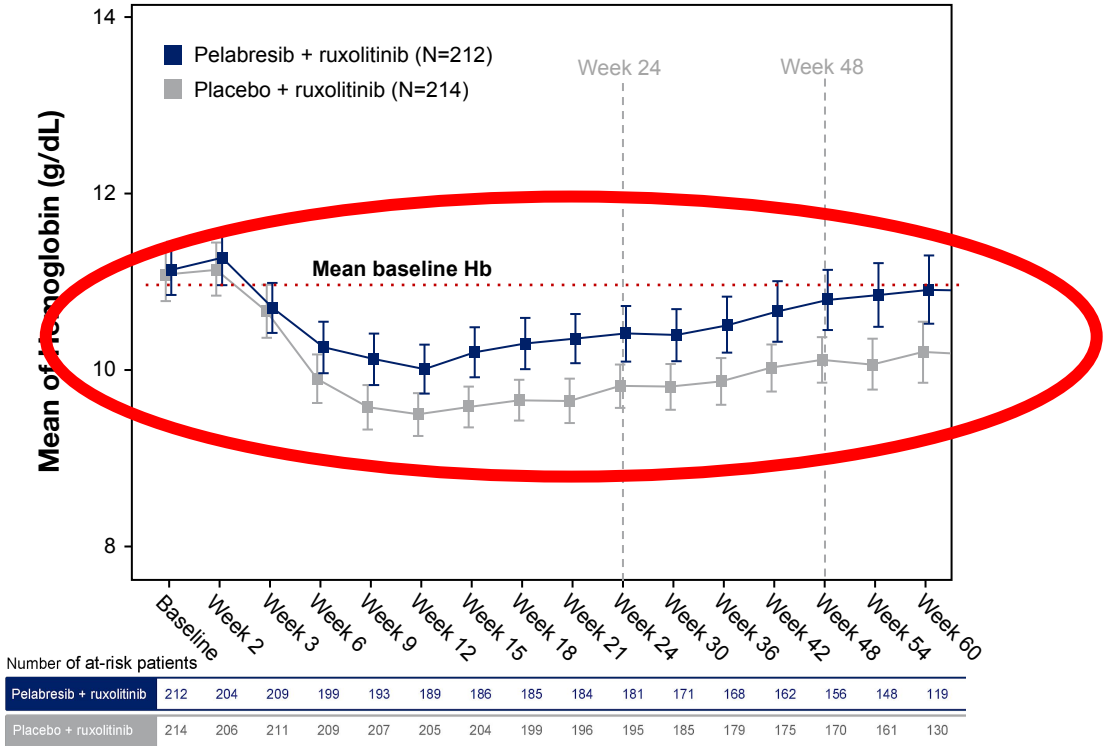
Overall, a numerically greater proportion of patients had a hemoglobin response with pelabresib + ruxolitinib versus placebo + ruxolitinib

Figure 4. Hemoglobin Response at Week 48

4a. Hemoglobin Response and RBC Transfusions at Week 48

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Hb response,*,† % (n/N) (95% CI)	13.1 (28/214) (8.57, 17.60)	7.9 (17/216) (4.28, 11.46)
Hb response*,† in patients with anemia (baseline <10 g/dL), % (n/n) (95% CI)	19.4 (13/67) (9.93, 28.87)	14.1 (10/71) (5.99, 22.18)
Patients requiring RBC transfusion‡,§ during screening, n (%)	18/170 (10.6)	18/184 (9.8)
Rate¶ (95% CI)	1.15 (0.81, 1.49)	1.11 (0.69, 1.54)
Patients requiring RBC transfusion‡, during first 24 weeks of study treatment, n/n (%)**	47/170 (27.6)	71/184 (38.6)
Rate¶ (95% CI)	1.15 (0.78, 1.52)	1.15 (0.78, 1.52)
Patients requiring RBC transfusion‡,†† during 25–48 weeks of study treatment, n/n (%)	37/170 (21.8)	61/184 (33.2)
Rate¶ (95% CI)	1.15 (0.77, 1.53)	1.19 (0.92, 1.47)

4b. Mean Hemoglobin Levels Over Time, Safety Population



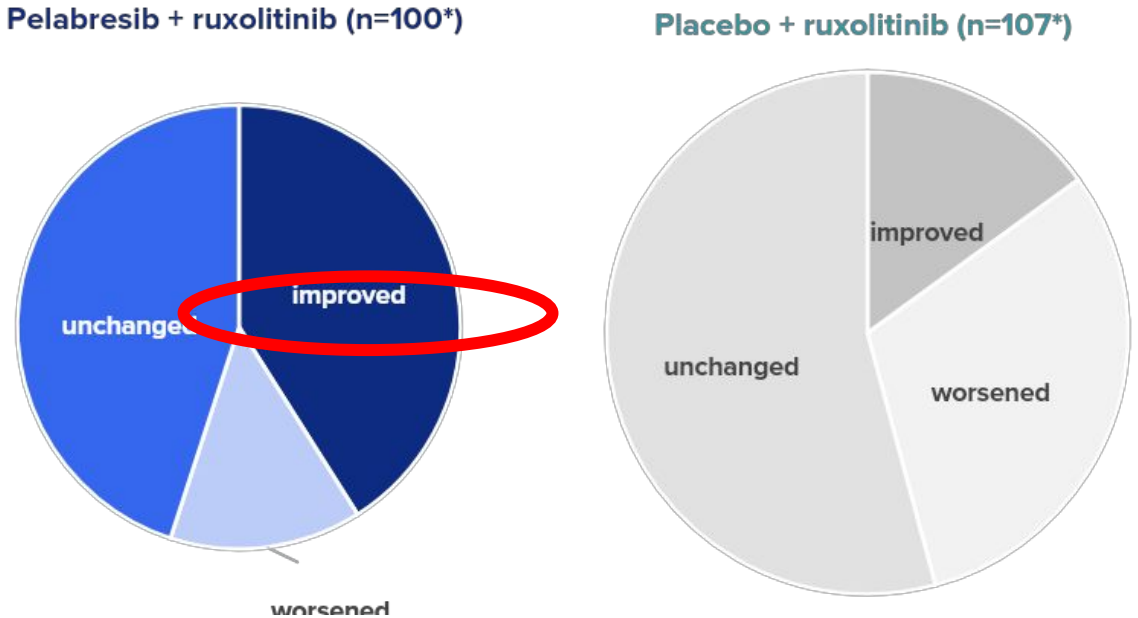
- Fewer patients required RBC transfusions during the first 48 weeks in the pelabresib + ruxolitinib arm versus placebo + ruxolitinib arm

Data cutoff date: March 29, 2024. *Hemoglobin response in the ITT population. †Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. A similar effect was seen across DIPSS categories. ‡RBC transfusion evaluable patients are patients who have been on the study for 48 weeks without starting new anti-MF treatment. §RBC transfusions refer to number of patients who received any RBC transfusion during the 12-week baseline period prior to dosing. ¶Rate is the average number of RBC units of transfusion per patient-months. **RBC transfusions refer to number of patients who received any RBC transfusion during the first 24 weeks after Cycle 1 Day 1. ††RBC transfusions refer to number of patients who received any RBC transfusion during the 25–48 weeks after Cycle 1 Day 1.

CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; ITT, intent-to-treat; MF, myelofibrosis; RBC, red blood cell.

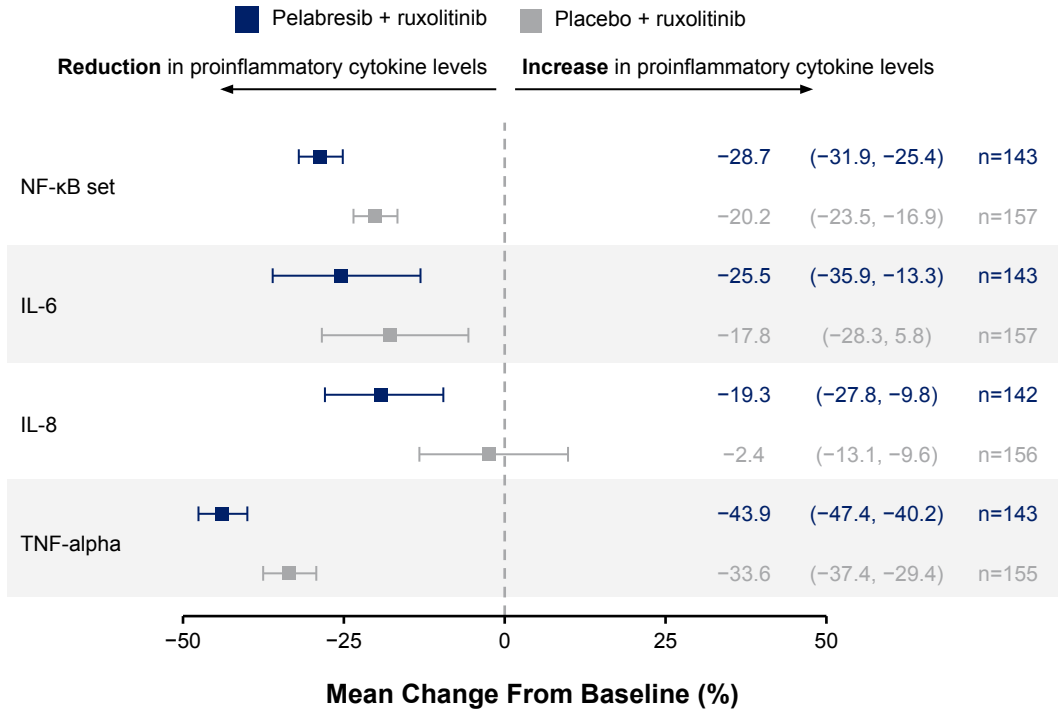
Bone Marrow Fibrosis and Proinflammatory Cytokines

Figure 5. Change in Bone Marrow Fibrosis Grade by Central Read at Week 48



- Bone marrow fibrosis improvement of ≥1 grade in evaluable patients was reported in 41.0% vs 15.0% of patients in the pelabresib + ruxolitinib vs placebo + ruxolitinib arms, respectively, at Week 48 (difference: 27.32%; 95% CI 15.52, 39.12)
- There was a larger difference between treatment arms in bone marrow fibrosis improvement of ≥1 grade at Week 48 compared with Week 24, in favor of the pelabresib + ruxolitinib arm

Figure 6. Percent Change in Proinflammatory Cytokines Levels From Baseline at Week 48



- Independent of treatment, lower levels of proinflammatory cytokines were observed in patients with SVR35 response compared with SVR35 non-responder at Week 48

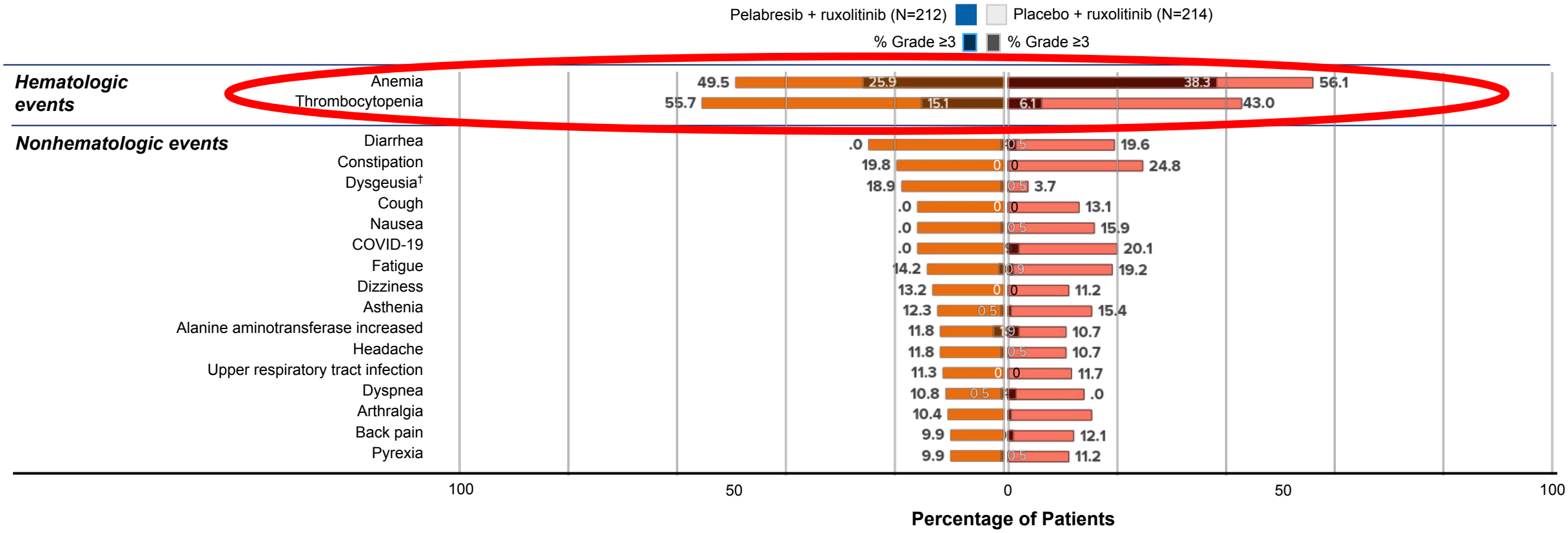
Data cutoff date: March 29, 2024. *n=207 evaluable patients (baseline and Cycle 17 Day 1); n=100 in the pelabresib + ruxolitinib arm and n=107 in the placebo + ruxolitinib arm. n=223 (52%) missing data.

Proinflammatory cytokine levels were measured by bead-based multiplex assay from plasma. NF-κB set includes B2M, CRP, CD40-L, hepcidin, IL-6, IL-12p40, MIP-1 beta, MPIF-1, RANTES, TNFR2, TNF alpha, VCAM-1.

B2M, beta-2 microglobulin; CD, cluster of differentiation; CI, confidence interval; CRP, C-reactive protein; IL, interleukin; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NF-κB, nuclear factor kappa B; RANTES, regulated upon activation, normal T cell expressed and secreted; SVR35, ≥35% reduction in spleen volume from baseline; TNF, tumor necrosis factor; TNFR, TNF receptor; VCAM, vascular cell adhesion protein.

Safety: Treatment-Emergent Adverse Events and Deaths at Week 48

Figure 8. TEAEs Reported in ≥10% of Patients in Either Arm*



- As of the data cutoff date of March 29, 2024, TEAEs resulting in death occurred in 5.2% (11/212) of patients in the pelabresib + ruxolitinib arm versus 3.3% (7/214) of patients in the placebo + ruxolitinib arm

Data cutoff date: March 29, 2024. *Safety population: received at least one dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blind treatment period is defined as an AE that has a start date on or after the first dose of pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first. †Dysgeusia was successfully managed in most patients by dose reductions of pelabresib.

AE, adverse event; COVID-19, coronavirus disease 2019; MF, myelofibrosis; TEAE, treatment-emergent adverse event.

Trial Update from IMproveMF, an Ongoing, Open-label, Dose-Escalation and -Expansion Phase 1/1b Trial to Evaluate the Safety, Pharmacokinetics, and Clinical Activity of the Novel Combination of Imetelstat with Ruxolitinib in Patients with Intermediate-1, Intermediate-2, or High-Risk Myelofibrosis

John O. Mascarenhas, MD,[1] Salman Otoukesh, MD,[2] Terrence Bradley, MD,[3] Bart L. Scott, MD,[4] Habte A. Yimer, MD,[5] Souria Dougherty, MBA,[6] Lixian Peng, PhD,[6] Fei Huang, PhD,[6] Ying Wan, MD, PhD,[6] Faye M. Feller, MD,[6] Vivian Rodolf, MD,[6] Judy Ho, BS,[6] Tymara Berry, MD,[6] Andrew T. Kuykendall, MD[7]

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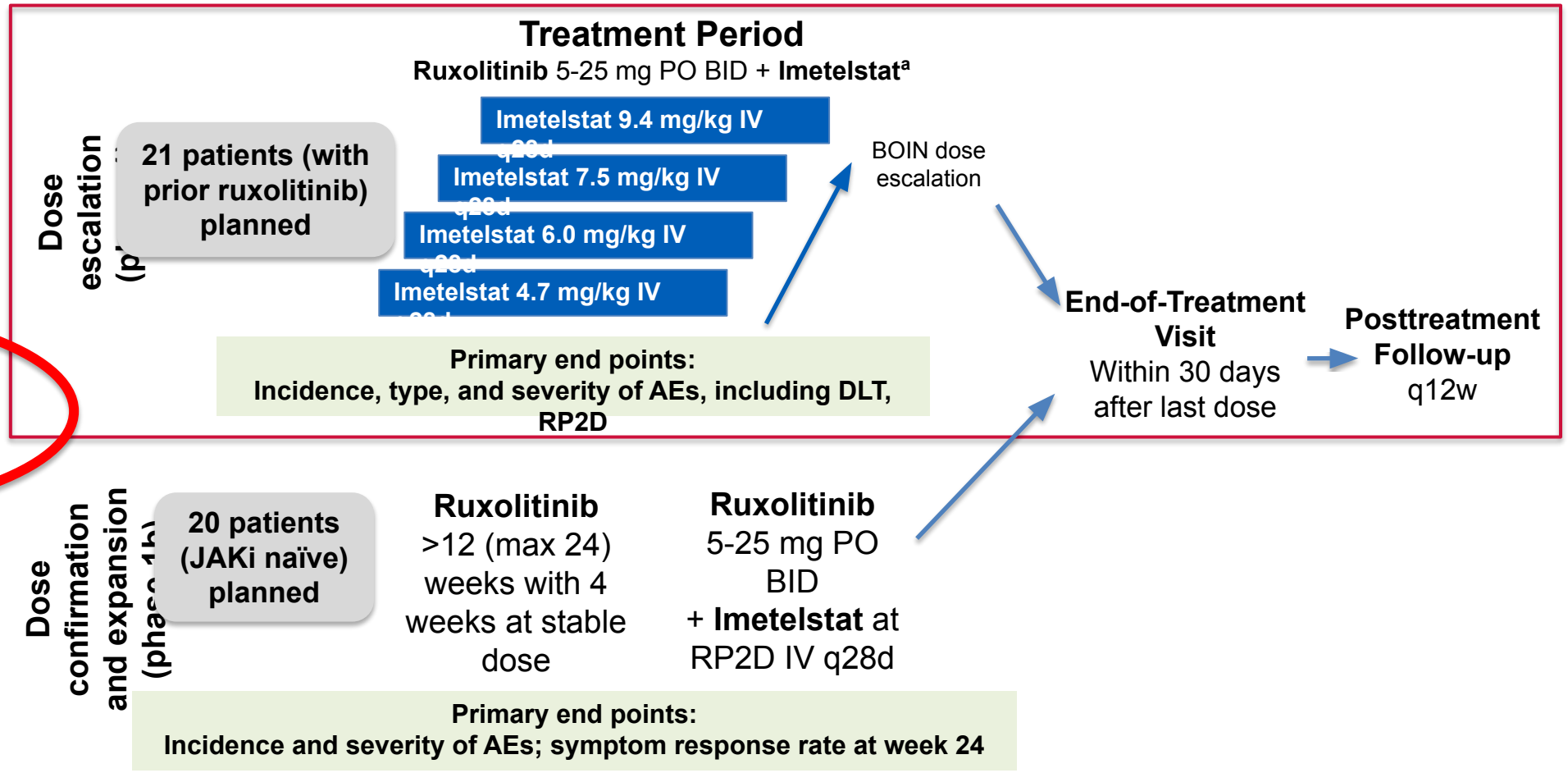
Presentation 998 | Presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA

IMproveMF: Ongoing Multicenter Phase 1/1b Trial

Inclusion Criteria

- ≥18 years of age
- DIPSS INT-1, INT-2, or HR MF
- ECOG PS ≤2
- Prior JAKi use:
  - Phase 1: ≥12 weeks ruxolitinib with ≥4 weeks immediately before enrollment at stable dose
  - Phase 1b: JAKi naïve
- Peripheral blood blast count ≤10%
- Bone marrow blast count ≤10%



AE, adverse event; BID, twice daily; BOIN, Bayesian Optimal Interval Design; DIPSS, Dynamic International Prognostic Scoring System; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, high risk; INT, intermediate; IV, intravenous; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PO, per oral; q12w, every 12 weeks; q28d, every 28 days; RP2D, recommended part 2 dose.
[a]Imetelstat sodium doses are listed, which are equivalent to 4.4, 5.6, 7.1, or 8.9 mg/kg active imetelstat doses, respectively.

Imetelstat Combined With Ruxolitinib Was Well Tolerated

- No DLTs[a] were reported at any imetelstat dose level within the first 28 days of cycle 1

Any-grade TEAEs in ≥15% of patients

Preferred term, n (%)	Total (N=17)
Patients with ≥1 TEAE	**15 (88)**
Pain in extremity	7 (41)
Nausea	6 (35)
ALT increased	5 (29)
Anemia	5 (29)
Thrombocytopenia[b]	4 (24)
Fatigue	4 (24)
AST increased	3 (18)
Neutropenia[c]	3 (18)

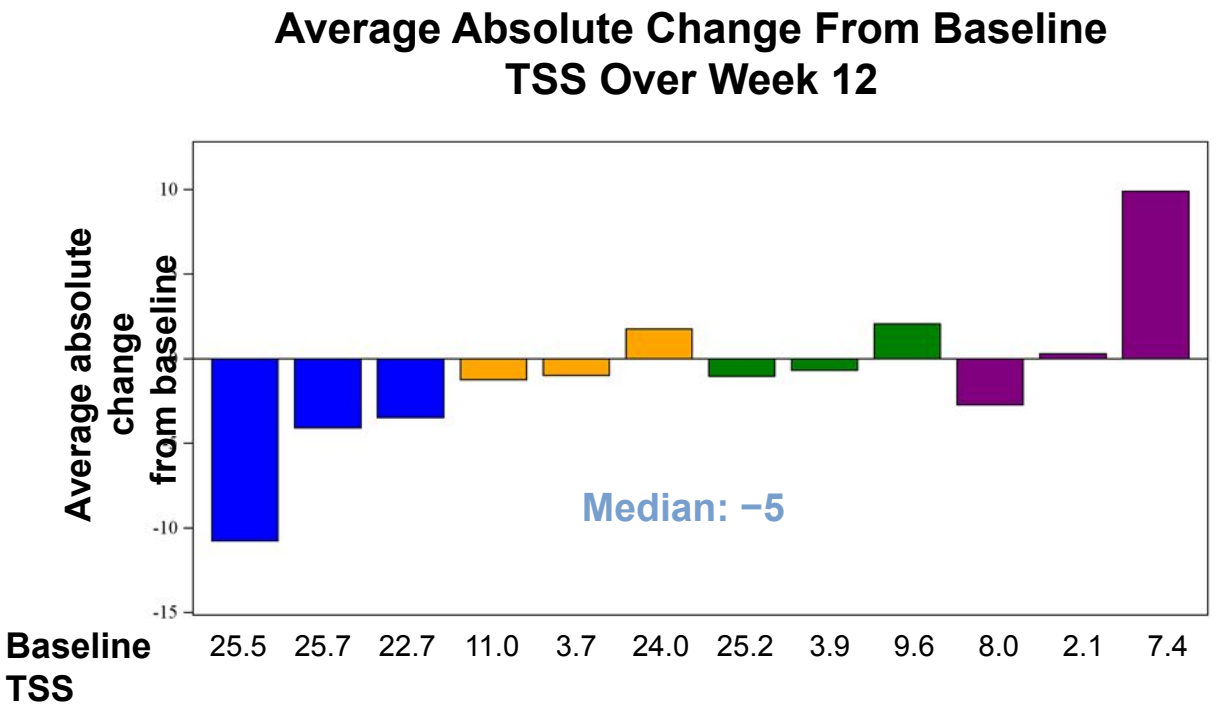
Grade 3 TEAEs

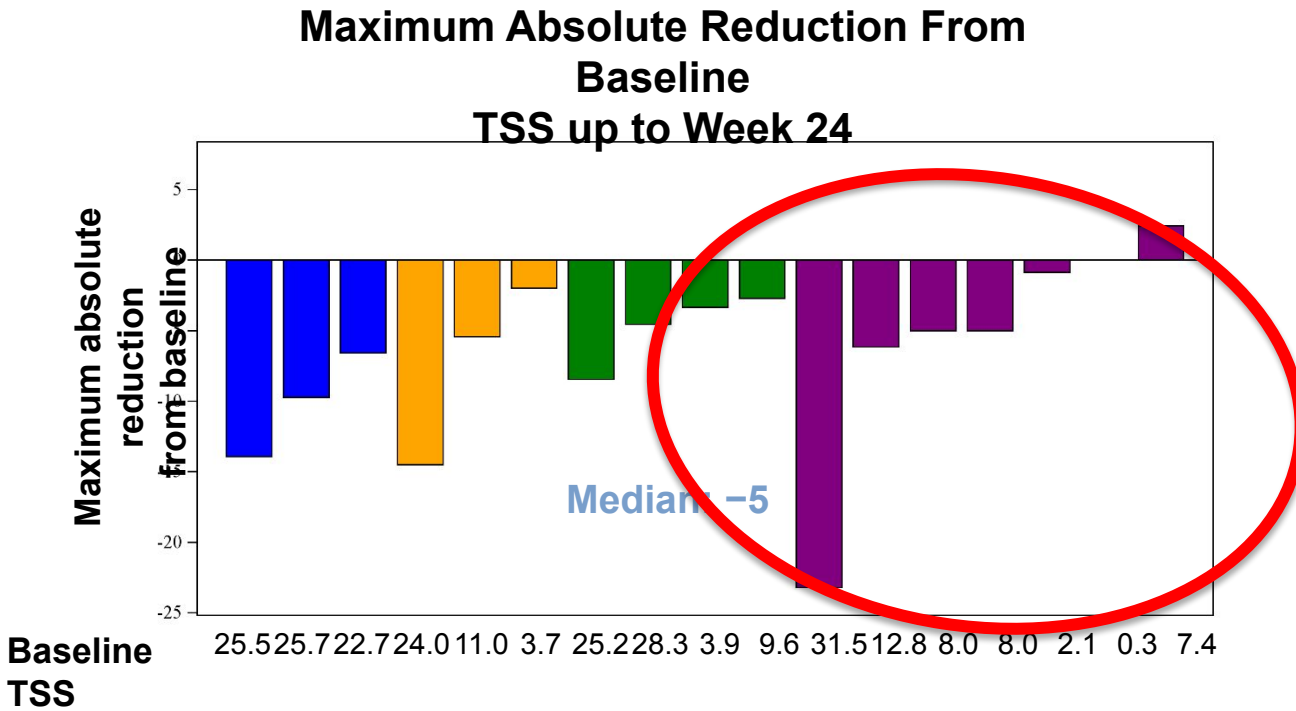
Preferred term, n (%)	Total (N=17)
Patients with ≥1 grade 3 TEAE	**8 (47)**
Anemia[d]	4 (24)
Neutropenia[c]	3 (18)
Leukopenia[e]	2 (12)
Abdominal pain	1 (6)
Fatigue	1 (6)
Pneumonia[f]	1 (6)
Epistaxis[f]	1 (6)

- No grade 4 or 5 events were reported

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Toxicities determined by the investigator to be possibly, probably, or definitely related to imetelstat treatment, and not attributable to the underlying disease, or toxicities with ruxolitinib increasing in grade and/or clinically significant from before imetelstat initiation. [b]Combined term includes decreased platelet count. [c]Combined term includes decreased neutrophil count. [d]One was a SAE considered related to study treatments and resulted in dose reduction to 6.0 mg/kg. [e]Combined term includes decreased white blood cell count. [f]SAE considered to be related to underlying disease and resolved without dose modification.

Change in TSS From Baseline by Patient

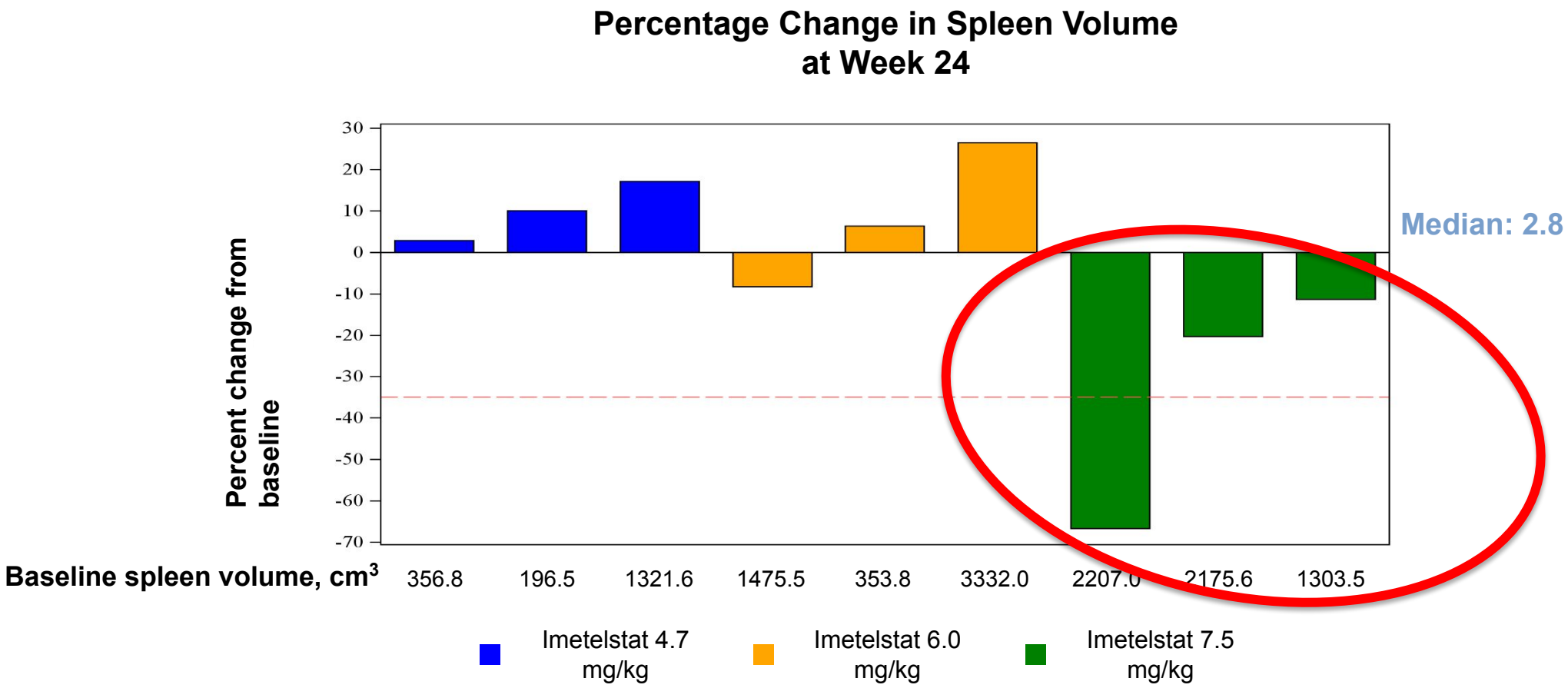




Imetelstat 4.7 mg/kg
Imetelstat 6.0 mg/kg
Imetelstat 7.5 mg/kg
Imetelstat9.4 mg/kg

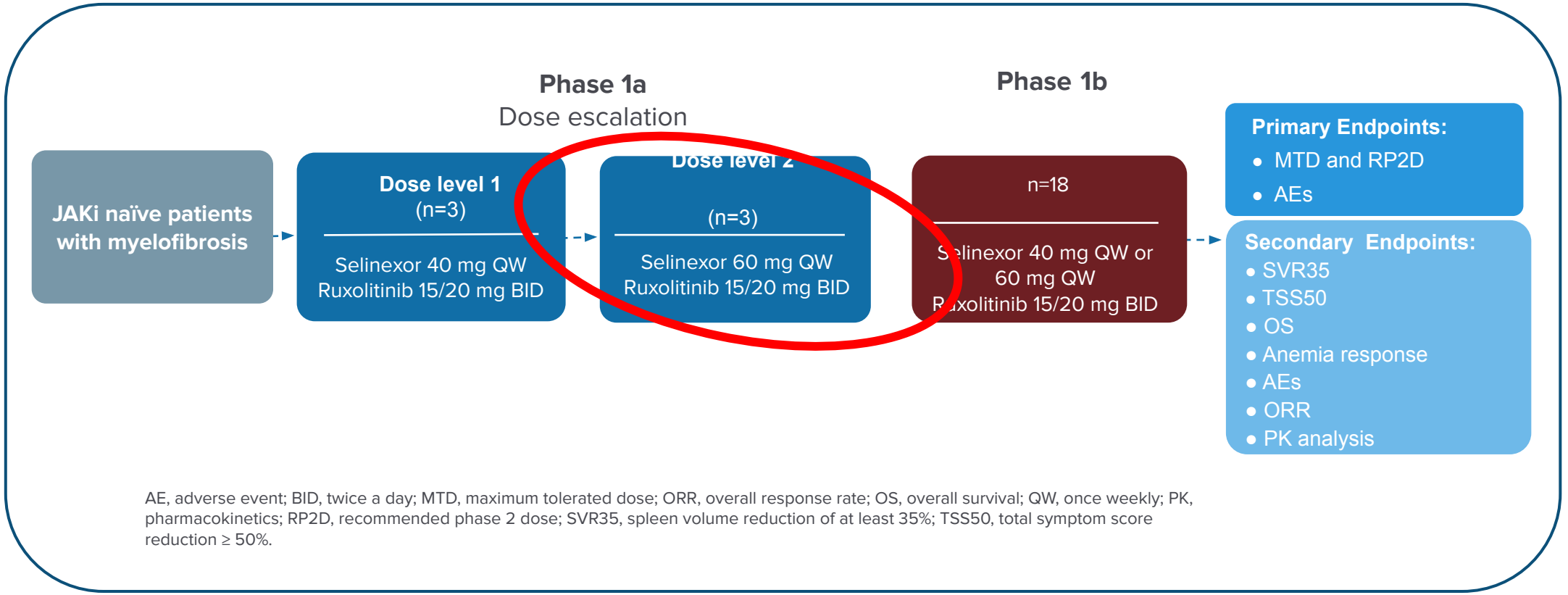
TSS, Total Symptom Score.

Spleen Volume Reduction by Patient at 24 Weeks



[a]The percent change for this patient is based on the spleen assessment at end of treatment due to the early discontinuation of treatment before week 24.

Phase 1 Study (XPORT-MF-034[1]) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis



AE, adverse event; BID, twice a day; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; QW, once weekly; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%.

* Enrollment completed; 24 patients had been assigned to either a 40 mg (n=10) or 60 mg (n=14) once weekly dose of selinexor, in combination with ruxolitinib 15/20 mg BID (twice daily)

1. NCT04562389

Rapid and Deep SVR35 Achieved with Selinexor 60 mg at Weeks 12 and 24

Population	Timepoint	Selinexor 40 mg +ruxolitinib n (%)	Selinexor 60 mg +ruxolitinib n (%)
Efficacy Evaluable	SVR35 at Week 12	3/10 (30.0)	10/12** (83.3)
	SVR35 at Week 24	**4/8* (50.0)**	**11/12 (91.7)**
	SVR35 at anytime	4/10 (40.0)	12/12 (100.0)
Intent-to-Treat	SVR35 at Week 12	3/10 (30.0)	10/14 (71.4)
	SVR35 at Week 24	**4/10 (40.0)**	**11/14 (78.6)**
	SVR35 at anytime	4/10 (40.0)	12/14 (85.7)

* Two patients discontinued prior to Week 24.
** One patient discontinued prior to week 12; one patient with missing data at week 12 who subsequently discontinued prior to week 24.

SVR35, spleen reduction volume ≥35%

Data cut February 24, 2023

Treatment-Emergent Adverse Events (TEAEs) of Selinexor 60 mg QW Cohort*

TEAEs	Selinexor 60 mg QW + ruxolitinib (N = 14)
Any grade (≥ 30% overall), n (%)	
Nausea	11 (78.6)
Anemia	9 (64.3)
Thrombocytopenia	9 (64.3)
Fatigue	8 (57.1)
Constipation	7 (50.0)
Vomiting	7 (50.0)
Dyspnea	5 (35.7)
Headache	5 (35.7)
Hyponatremia	5 (35.7)
Leukopenia	5 (35.7)
Neutropenia	5 (35.7)
Grade 3+ (> 5%), n (%)	
Anemia	6 (42.9)
Thrombocytopenia	4 (28.6)
Back pain	2 (14.3)
Neutropenia	1 (7.1)
Atrial fibrillation	1 (7.1)
Leukopenia	1 (7.1)
Treatment-related AEs leading to treatment discontinuations, n (%)	
Thrombocytopenia, Grade 3	1 (7.1)
Peripheral neuropathy, Grade 3	1 (7.1)

Prophylactic Antiemetic use Reduced the Incidence and Severity of Nausea

Nausea was transient in nature with a median duration ~2 cycles

64% Patients in the 60 mg cohort received one prophylactic antiemetic

67% Of these patients had nausea (Grade 1 only)

Versus

100% Patients without antiemetic prophylaxis had nausea (Grades 1–3)

2.5 kg Median weight gain at Week 24

Median Hemoglobin (Hgb) Levels and Platelet Counts Were Generally Stable

46% Transfusion-independent patients had stable Hb levels†

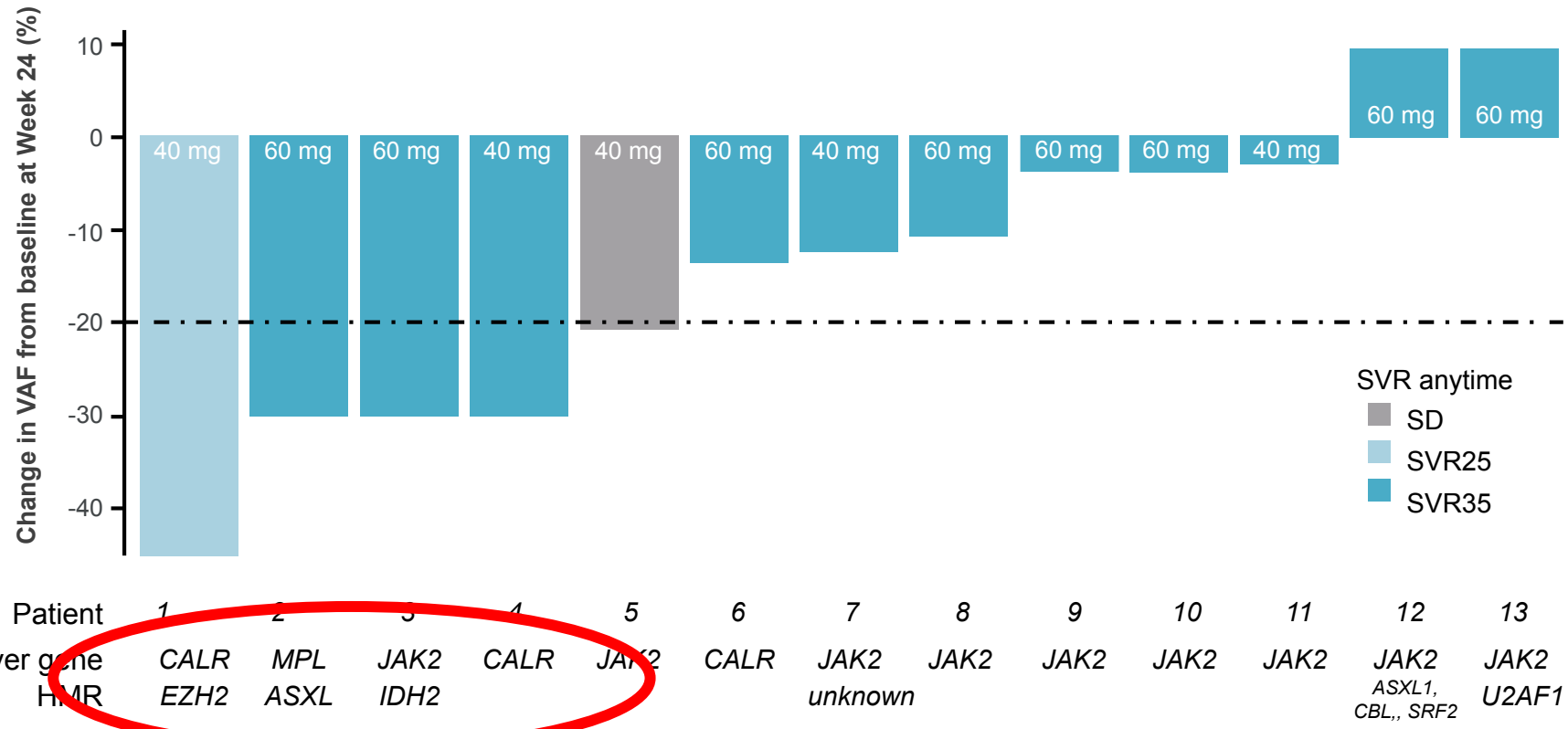
Median Hgb levels (g/dL): 9.9 Baseline → 8.8 Week 12 → 9.1 Week 24

Median platelet levels ($\times 10^9$/L): 220 Baseline → 135 Week 12 → 137 Week 24

AE, adverse event; Hb, hemoglobin; TEAE, treatment-emergent adverse event.

*Data cutoff date: August 01, 2023; †Patients who do not have Hb level decreased by > 2 g/dL from baseline over the entire treatment duration and who remained transfusion independent.

Variant Allele Frequency (VAF) at Week 24 With Selinexor (40 or 60 mg QW) Plus Ruxolitinib

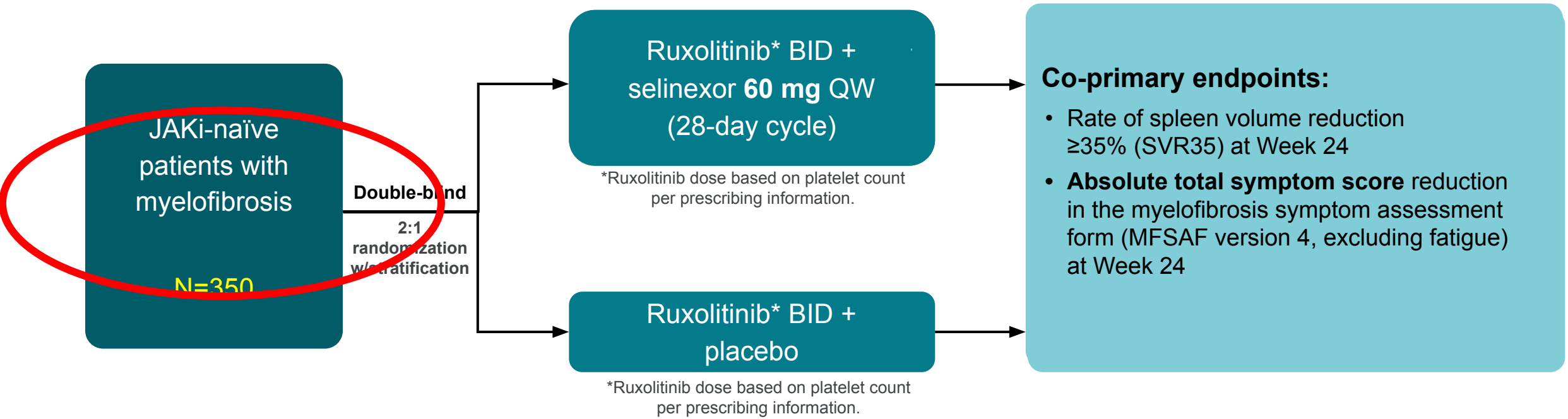


Reduced allele burden regardless of driver gene mutations were observed in 13 evaluable patients*

- ≥ 20% decreases in VAF were observed in five patients
  - Three of whom had ≥ 50% VAF at baseline and were high molecular risk (HMR)
- 13 of 24 patients had VAF values at baseline and Week 24; 11 of these 13 achieved SVR35 at any time

CALR, calreticulin; HMR, high molecular risk; MPL, myeloproliferative leukemia virus; SD, stable disease; SVR25, spleen volume reduction of 25% from baseline; VAF, variant allele frequency.
*Analysis includes all patients who had at least one dose of selinexor (40 mg or 60 mg) and had VAF values at baseline and Week 24.

SENTRY Phase 3: Trial design[1]



Randomization stratified by:

- DIPSS risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 cm^3 vs. >1800 cm^3 by MRI/CT scan
- Baseline platelet counts 100–200 x 10^9/L vs. >200 x 10^9/L

BID, twice a day; CT, computerized tomography; DIPSS, Dynamic International Prognostic Scoring System; MFSAF, myelofibrosis symptom assessment form; MRI, magnetic resonance imaging; QW, once weekly; SVR35, spleen volume reduction ≥35%; TSS, total symptom score.

1. ClinicalTrials.gov. Available at: Study Details | Study of Selinexor in Combination with Ruxolitinib in Myelofibrosis | ClinicalTrials.gov. Accessed: 01 October 2024.

Abstract #1000

9 December 2024

Results from the Randomized, Multicenter, Global Phase 3 Study BOREAS: Navtemadlin Versus Best Available Therapy in JAK Inhibitor Relapsed/Refractory Myelofibrosis

John O. Mascarenhas, MD[1]; Viola Maria Popov, MD, PhD, MSc[2]; Sanjay Mohan, MD[3]; Zübeyde Nur Özkurt, Prof.[4]; Jean-Jacques Kiladjian, MD, PhD[5]; Haifa Kathrin Al-Ali[6]; Andrew Charles Perkins, MBBS, PhD[7]; Zhuying Huang, PhD[8]; Hope Qamoos, NP[8]; Jesse McGreivy, MD[8]; Wayne Rothbaum, MA[8]; Srdan Verstovsek, MD, PhD[8] and Maciej Kaźmierczak, MD, PhD[9]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY. [2]Colentina Clinical Hospital Bucharest, Hematology Department, Pitesti, Arges, Romania. [3]The Vanderbilt Clinic, Nashville, TN. [4]Gazi University, Faculty of Medicine, Department of Hematology, Ankara, Turkey. [5]Hopital Saint-Louis, Paris, France. [6]University Hospital Halle, Halle (Saale), Germany. [7]The Alfred Hospital and Monash University, Melbourne, Australia. [8]Kartos Therapeutics, Inc., Redwood City, CA. [9]University of Medical Sciences, Poznan, Poland.

PRESENTED BY: John O. Mascarenhas, MD

American Society *of* Hematology

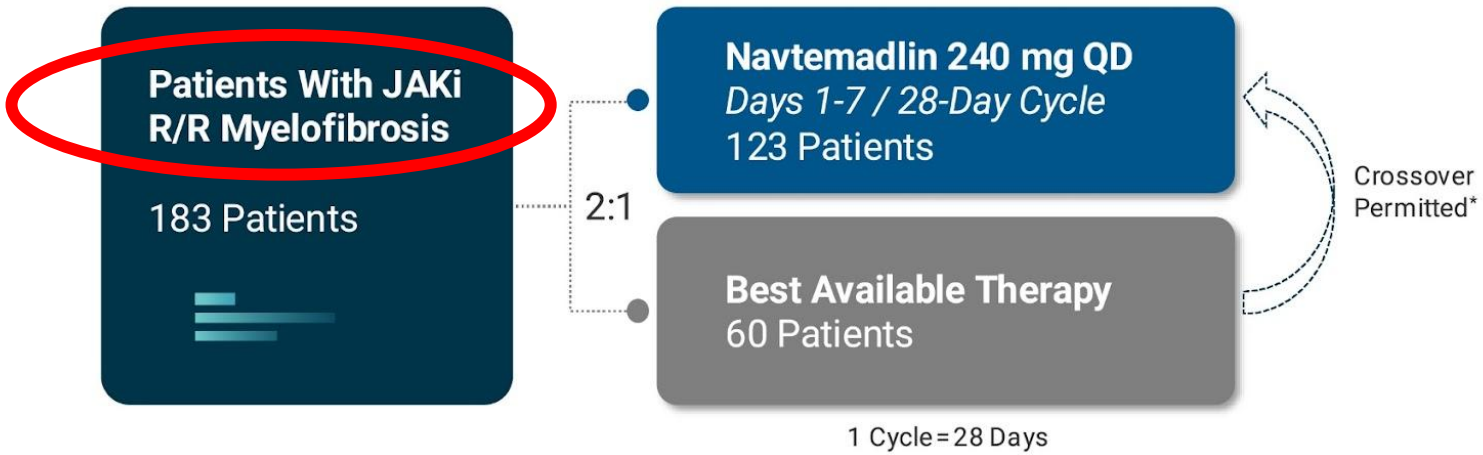
Phase 3 Study Design

A Randomized, Open-Label, Global Phase 3 Study of Navtemadlin in *TP53*^{WT} Patients 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
- Peginterferon
- IMiDs
- Supportive care



PRIMARY ENDPOINT	KEY SECONDARY ENDPOINT	KEY PHASE 3 STUDY NOTES
• SVR35 Week 24 by MRI/CT Central Review	• TSS50 Week 24 by MFSAF v4.0	• 28-day JAKi wash-out prior to C1D1 • JAKi excluded in BAT arm • C1D1 occurred within 7-days of baseline MRI/CT • Diarrhea prophylaxis for first two cycles

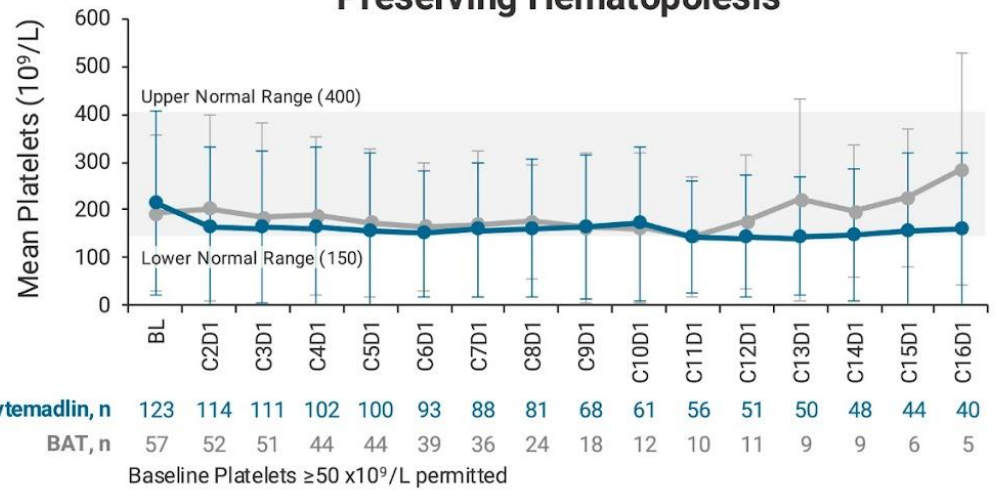
Note: BOREAS enrollment was closed at 183 subjects.
*Crossover in the BAT arm was permitted after disease progression or at Week 24.
Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1; CT, computed tomography; IMiDs, immunomodulatory imide drugs (lenalidomide, pomalidomide); JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, myelofibrosis symptoms assessment form; MRI, magnetic resonance imaging; QD, once daily; R/R, relapsed/refractory; SVR, spleen volume reduction; SVR35, spleen volume reduction ≥ 35%; TSS, total symptom score; TSS50, total symptom score reduction ≥ 50%; WT, wild-type.

Treatment-Emergent Adverse Events

	Navtemadlin n = 123[1]		Best Available Therapy n = 57[1,2]	
Preferred Term, n (%)	**All Grade**	**Grade 3/4**	**All Grade**	**Grade 3/4**
TEAE Occurring in ≥ 10%[1]				
Thrombocytopenia[3]	57 (46)	45 (37)	18 (32)	14 (25)
Nausea	52 (42)	5 (4)	3 (5)	–
Diarrhea	50 (41)	7 (6)	9 (16)	1 (2)
Anemia	44 (36)	35 (29)	16 (28)	16 (28)
Neutropenia[4]	37 (30)	31 (25)	10 (18)	7 (12)
Constipation	25 (20)	1 (1)	2 (4)	–
Vomiting	31 (25)	3 (2)	1 (2)	–
Decreased Appetite	22 (18)	–	4 (7)	1 (2)
Fatigue	19 (15)	4 (3)	7 (12)	2 (4)
Peripheral Edema	15 (12)	–	7 (12)	1 (2)
Asthenia	16 (13)	2 (2)	5 (9)	1 (2)
Abdominal Pain, Upper	13 (11)	2 (2)	1 (2)	–
Pruritus	7 (6)	–	6 (11)	–

Median time on study, months (range): Navtemadlin 15.6 (0.23, 39.9); BAT 6.5 (0.03, 30.5)

Preserving Hematopoiesis



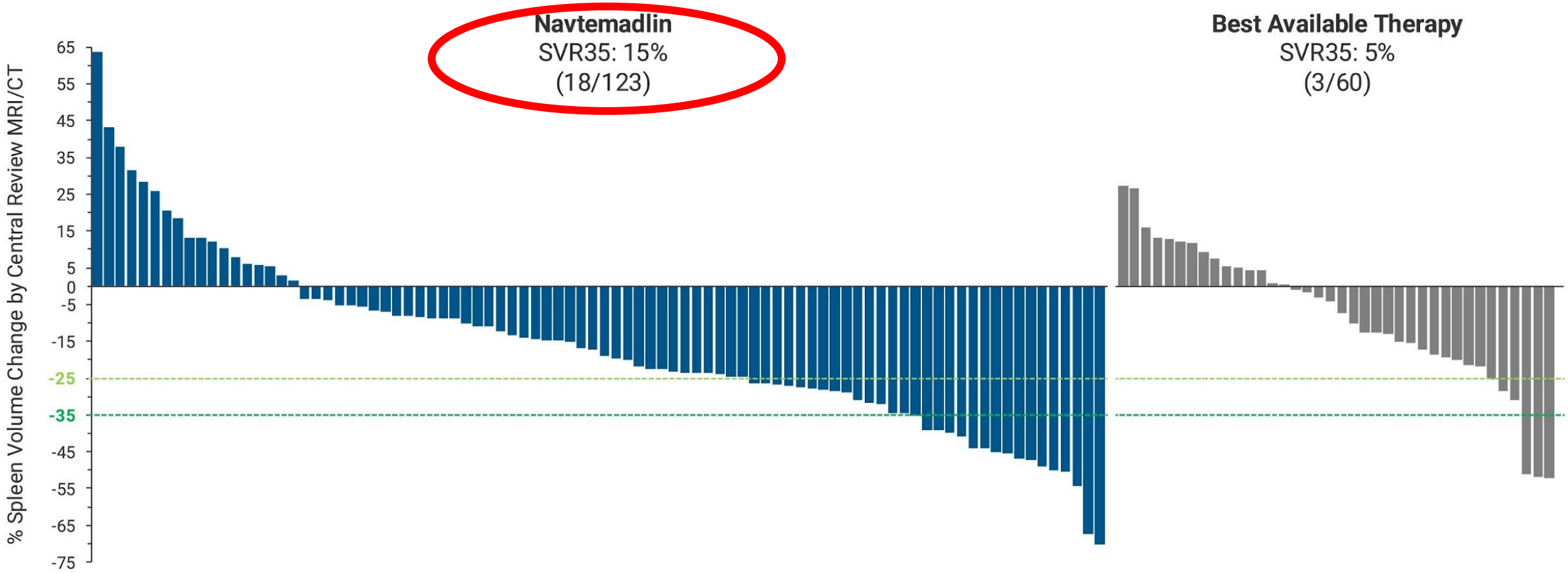
Data cut-off: 30 Sep 2024.

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle).

[1]Safety dataset is all subjects who received ≥1 dose of study treatment. [2]One subject randomized to BAT, first cycle was navtemadlin. [3]Combined terms: thrombocytopenia and platelet count decrease. [4]Combined terms: neutropenia and neutrophil count decrease. Abbreviations: BAT, best available therapy; BL, baseline; C, cycle; D, day; QD, once daily; TEAE, treatment-emergent adverse event.

SVR35 at Week 24 (ITT Population)

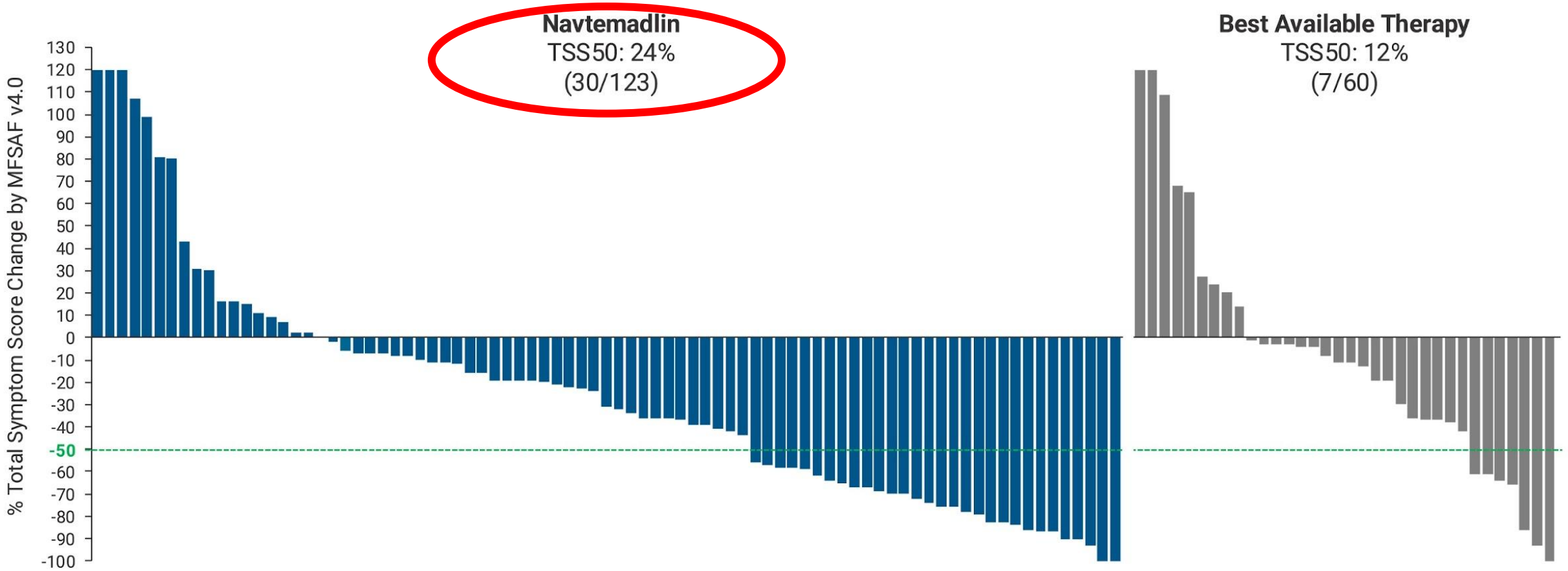
Spleen Volume Reduction by Central Review MRI/CT – Baseline to Week 24



Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). ITT is all randomized subjects. Figure represents subjects with baseline and Week 24 data.
Navtemadlin vs BAT, p=0.0815. SVR25: Navtemadlin, 27% (33/123); BAT, 10% (6/60). BAT SVR35 responders received hydroxyurea (2) and lenalidomide (1).
Abbreviations: BAT, best available therapy; CT, computed tomography; ITT, intention-to-treat; MRI, magnetic resonance imaging; SVR35, spleen volume reduction ≥35%.

TSS50 at Week 24 (ITT Population)

Total Symptom Score Reduction by MFSAF v4.0 – Baseline to Week 24

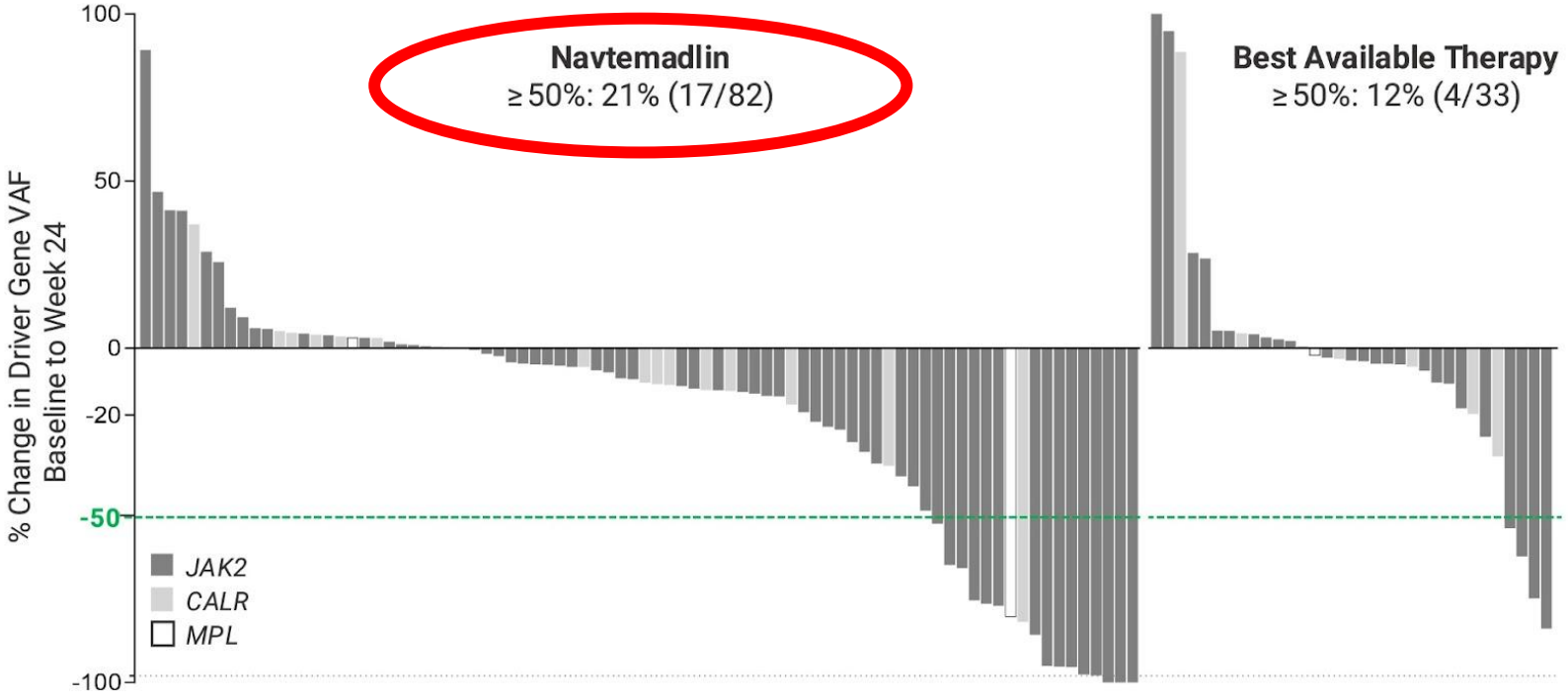


Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). ITT is all randomized subjects. Figure represents subjects with baseline and Week 24 data. Navtemadlin vs BAT, p=0.0507.
Week 24 TSS assessment includes Week 23 scores for subjects who stopped TSS at the start of Week 24 (n=2).
Abbreviations: BAT, best available therapy; ITT, intention-to-treat; MFSAF, myelofibrosis symptom assessment form; TSS, total symptom score; TSS50, total symptom score reduction ≥50%.

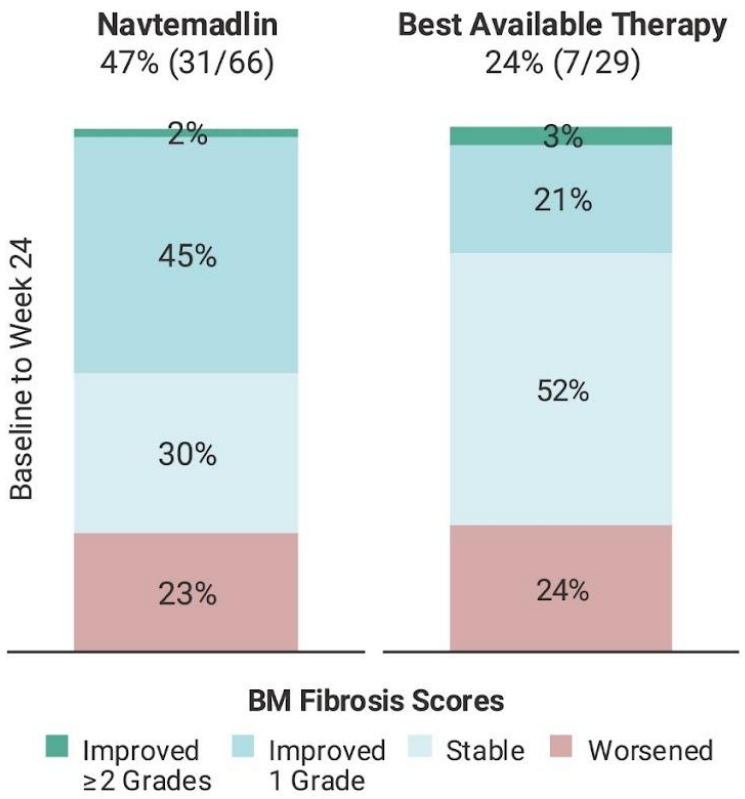
Potential for Disease Modification

Driver Gene VAF Reduction and Bone Marrow Fibrosis Improvement – Baseline to Week 24

Driver Gene VAF by Central Laboratory



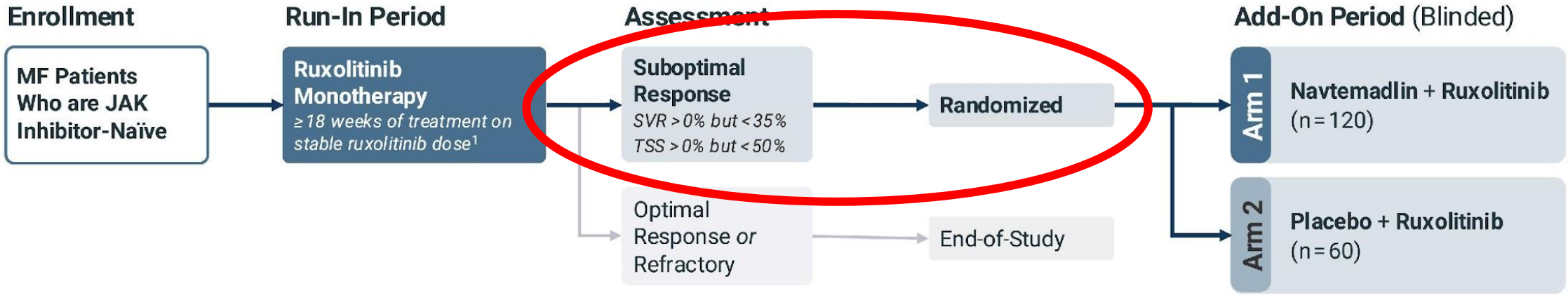
Bone Marrow Fibrosis by Central Pathology Review



Data cut-off: 30 Sep 2024.
Note: Week 24 evaluable subjects shown.
Abbreviations: BM, bone marrow; *CALR*, calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukemia virus oncogene; VAF, variant allele frequency.

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 (N = 600)

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 (N = 180)

Key Inclusion Criteria

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

Endpoints

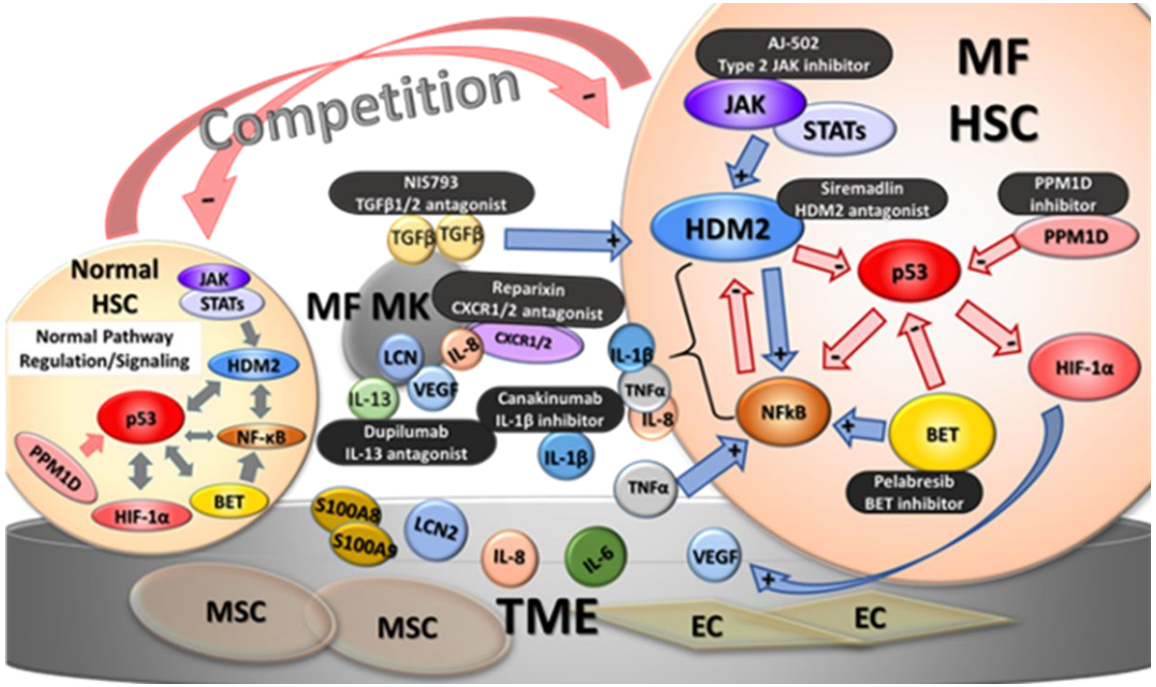
Co-Primary Endpoints

- Targeted SVR and TSS reduction 24 weeks after randomization

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Target enrollment from 220 sites across 19 countries.
[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; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

New Drugs in MF= Better Options for Our Patients

- New JAK inhibitors
  - AJ-11095 type 2 JAK2 inhibitor
  - INCB160058 JAK2V617F selective inhibitor
- New non-JAK inhibitors
  - Nuvisertib PIM1 kinase inhibitor
  - Reparaxin CXCR 1/2 antagonist
  - INCA033989 mCALR antibody
- JAK inhibitor based combinations
  - MANIFEST-2: Pelabresib
  - SENTRY: Selinexor
  - IMproveMF: Imetelstat
  - POIESIS: Navtemadlin



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