Myeloproliferative Neoplasms: Updates and Next Questions in MPN

Presenter

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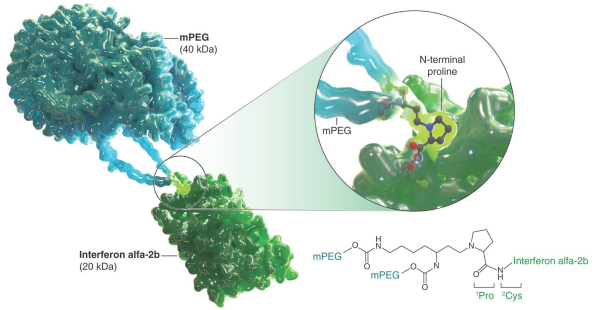
Ropeginterferon in SURPASS-ET



Entry criteria

- Eligible high-risk ET patients
- Resistant or intolerant to HU
- Platelet count >450 × 10^9/l
- WBC count of >10 × 10^9/l

Randomization
- 1:1

Stratification factors
- Platelet count ≥800 × 10^9/l (yes/no)
- TSS (<20, ≥20)
- Ethnicity (Asian/non-Asian)

Investigational arm: P1101, Q2W, sc. (n = 80)

Fixed dose
250 (W0) → **350** (W2) → **500** (W4)

Reference arm: Anagrelide, p.o. (n = 80)

Labelled dose
Maintain optimal blood counts control at acceptable toxicity

Dose escalation | **52W treatment** | **4W FU**

Baseline — 4W — Primary analysis 39W and 52W

Verstovsek S et al. *Future Oncol*. 2022.

Phase 3 SURPASS-ET: Positive Topline Results

- Primary endpoint: durable clinical response as per modified ELN criteria
  - 42.9% (39/91) of participants in the ropeg arm achieved end point at months 9 and 12, compared to 6.0% (5/83) in the anagrelide; *P*=0.0001
- Secondary endpoint: various endpoints
  - The *JAK2* V617F allelic burden was assessed at baseline and 12 months, showing a decrease from 33.7% to 25.3% (-8.4% change) in the ropeg arm, compared to a reduction from 39.7% to 37.3% (-2.4% change) in the anagrelide arm.
- Lower rate of serious TRAEs with ropeg (2.2%) vs anagrelide (10%), underscoring the manageability of its safety profile.

Phase 2 REVIVE Study Design[1]

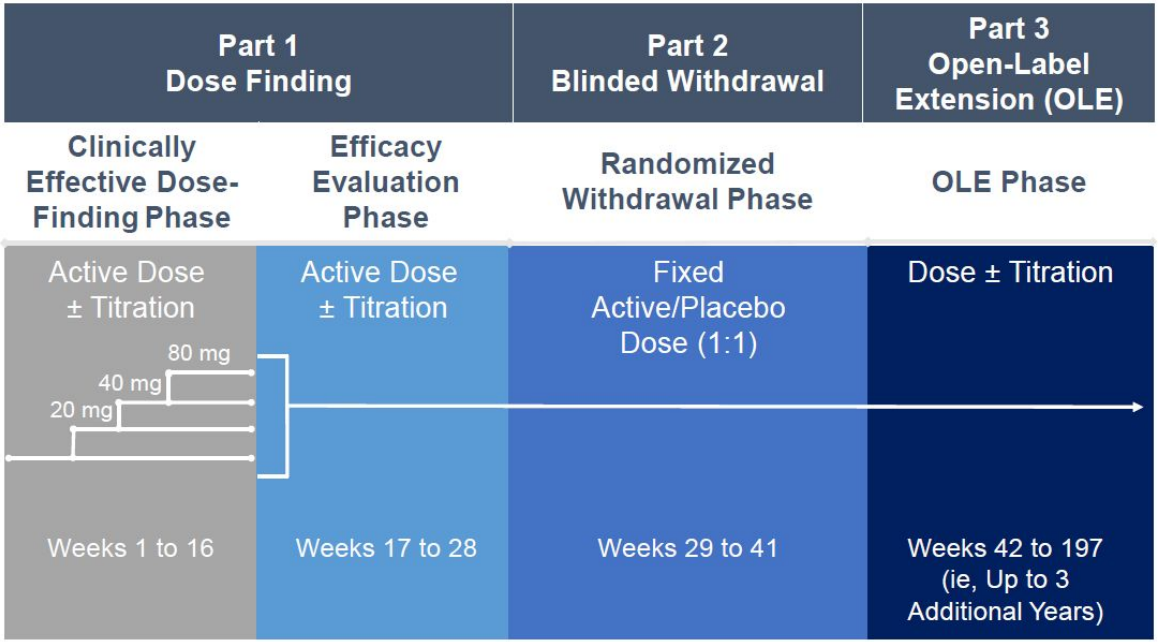
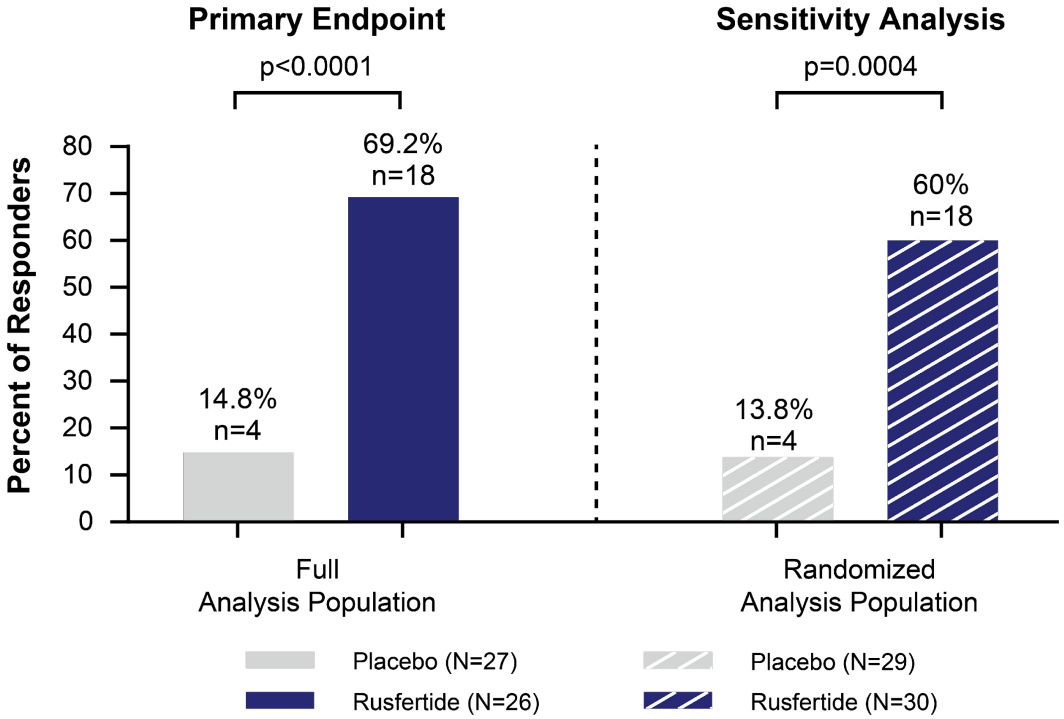


Figure adapted from Pettit K et al. Presented at EHA 2024; June 13-16, 2024; Madrid Spain.[1]

- Response was defined as not meeting any of the "phlebotomy eligibility" criteria including:
  1) hematocrit ≥45% that was ≥3% higher than their week 29 pre-randomization hematocrit value, or
  2) hematocrit >48%, or
  3) an increase of ≥5% in hematocrit compared to their week 29 pre-randomization value

REVIVE Met the Primary Efficacy Endpoint in the Prespecified Full Analysis and Randomized Analysis Populations (Part 2)



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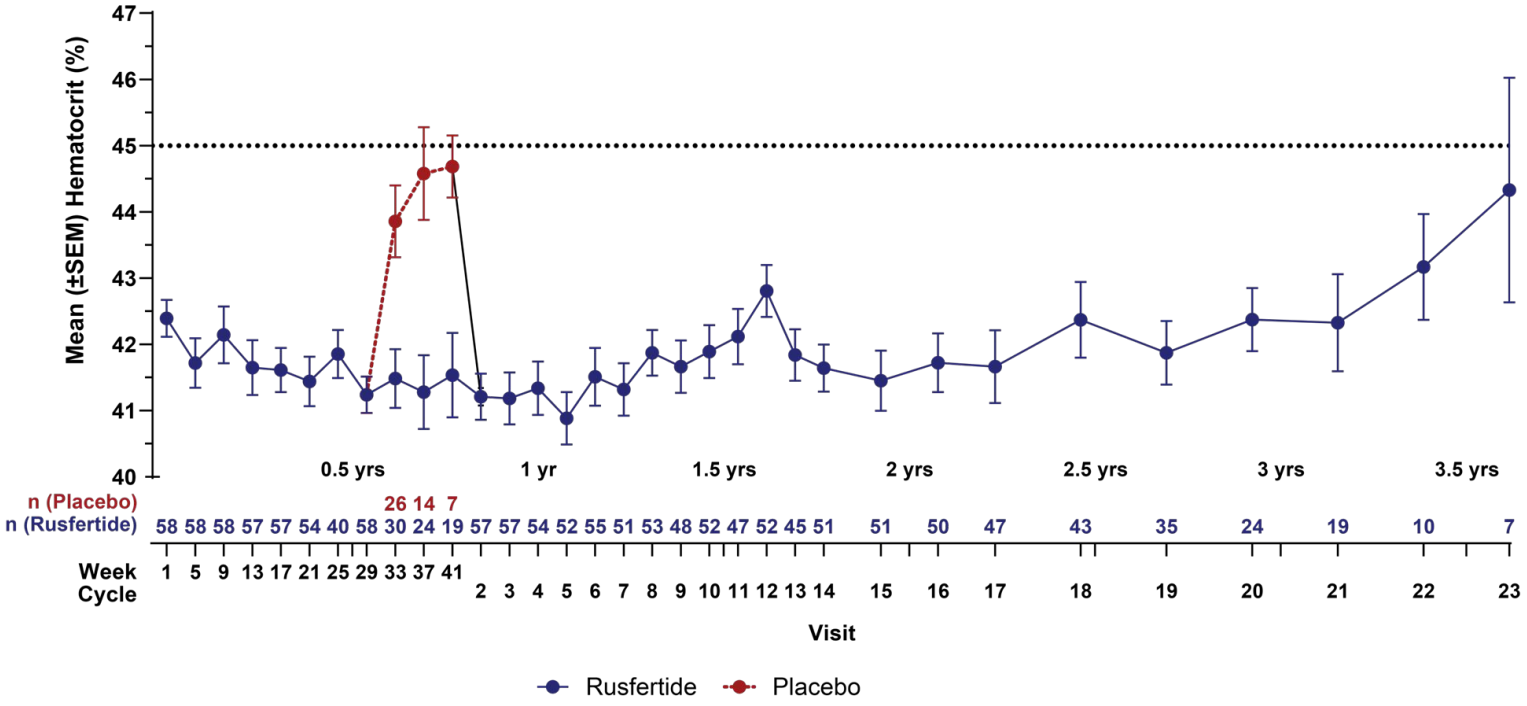
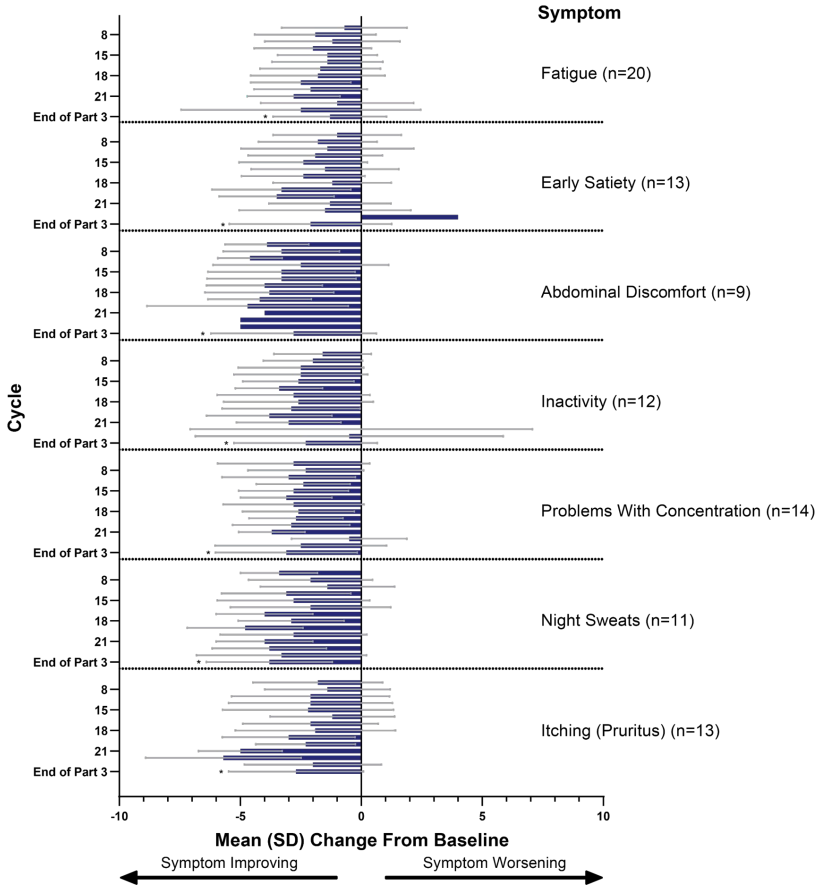
Rusfertide Consistently Maintained Hct <45% in Patients for ≥3 Years



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

Rusfertide improved symptoms

Rusfertide Improved Several Symptoms (Assessed Using the MPN-SAF) Throughout the Duration of the Study



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

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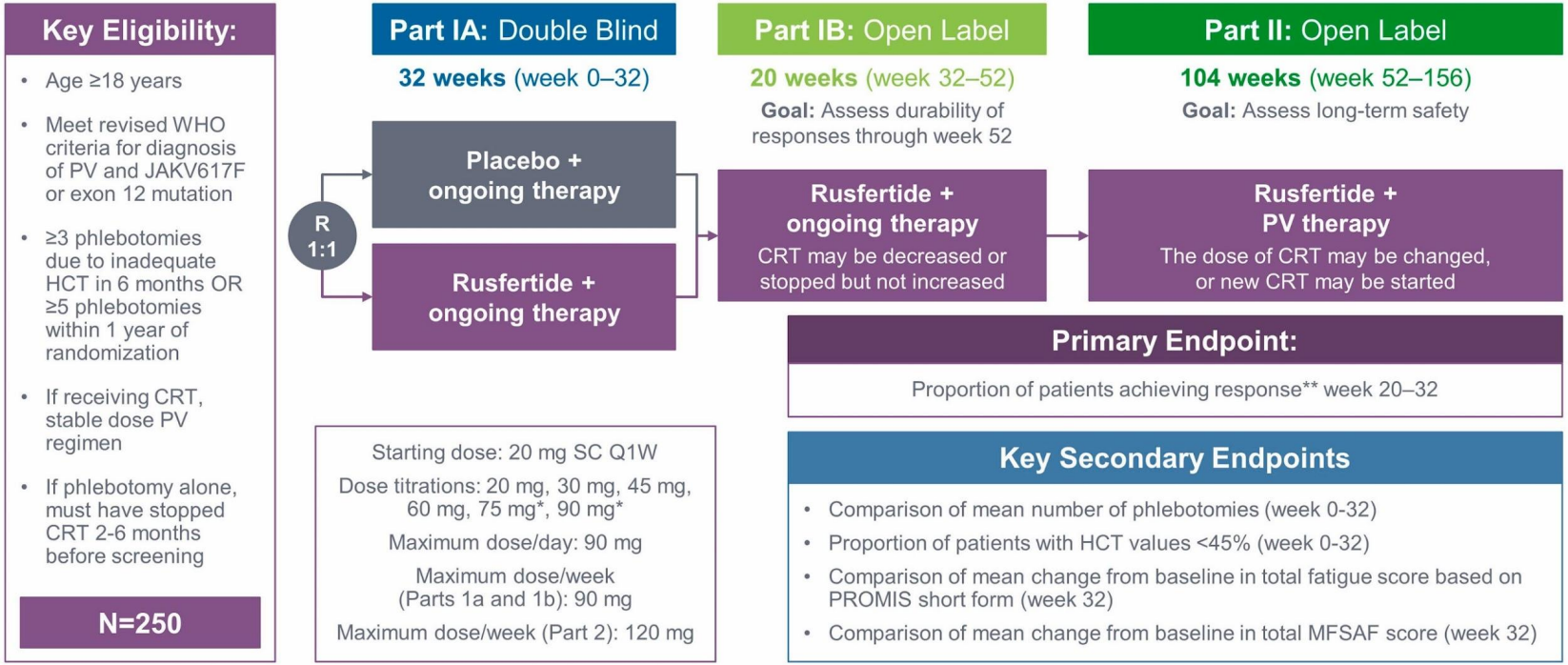
Phase 3 VERIFY trial

250 PV patients to be randomized across 100 global sites — Screening initiated in Q1, 2022



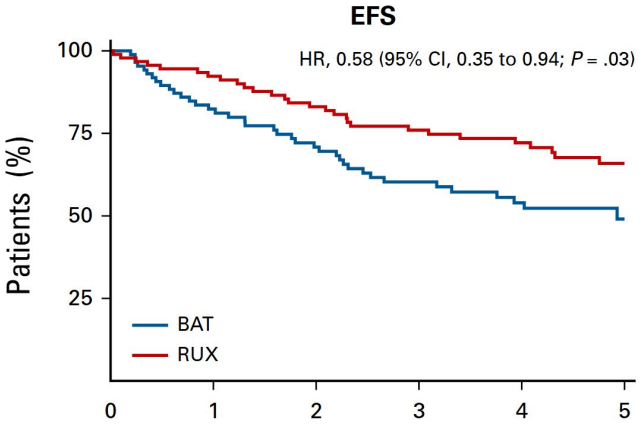
*Doses >60 mg require 2 injections. **Response defined as absence of phlebotomy eligibility. Phlebotomy eligibility is defined as a confirmed HCT ≥45% and that is at least 3% higher than the baseline OR HCT ≥48%. CRT, cytoreductive therapy.
ClinicalTrials.gov Identifier: NCT05210790

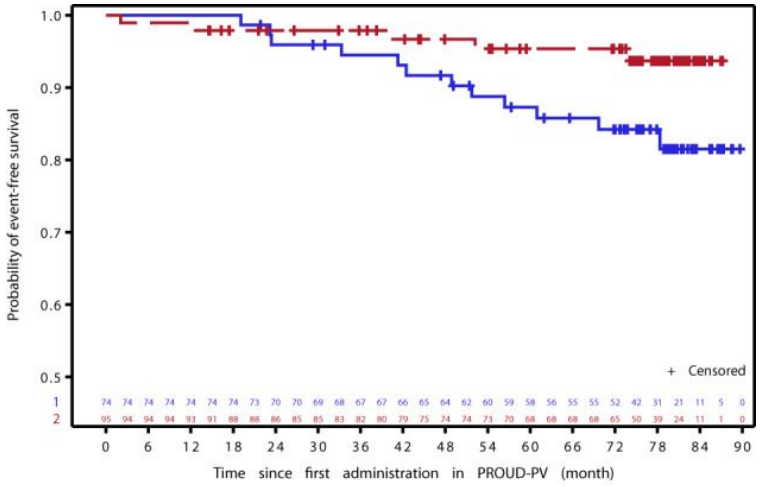
Verstovek et al. Blood (2022) 140 (Supplement 1):3929-3931

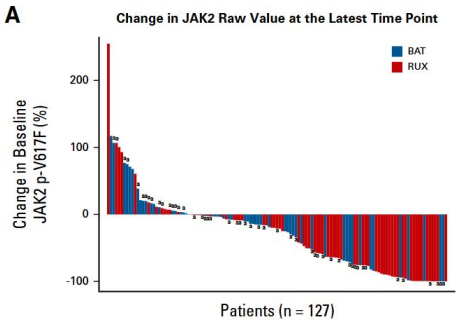
Phase 3 VERIFY Trial: Positive Topline Results

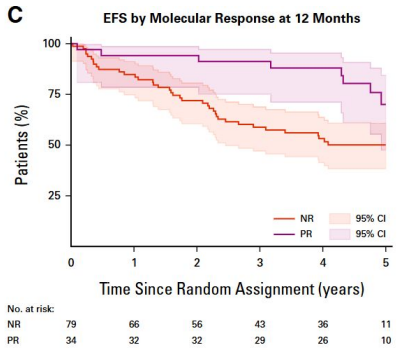
- Primary endpoint: absence of phlebotomy eligibility
  - 77% vs 33% for rusfertide vs placebo treated patients during weeks 20-32; *P*<0.0001
- First key secondary endpoint:
  - Mean 0.5 vs 1.8 phlebotomies/patient in the rusfertide vs placebo arm during wks 0-32; *P*<0.0001
- Other three pre-specified key secondary endpoints were also achieved with statistical significance
  - Hematocrit control (proportion of patients with Hct < 45%)
  - PROs: PROMIS Fatigue SF-8a3 and MFSAF TSS-7 v.4.0
- No new safety findings. All SAEs deemed unrelated. Majority of AEs were G1-2 injection site reactions; no evidence of an increased risk of cancer with rusfertide.

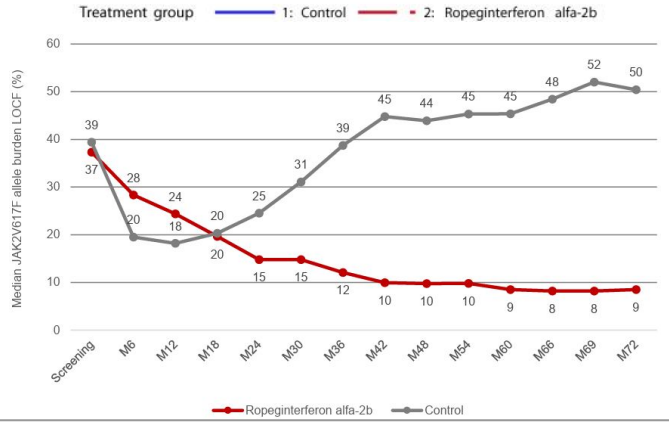
Better EFS and *JAK2* VAF Reductions With Ruxolitnib and Ropeginterferon in PV





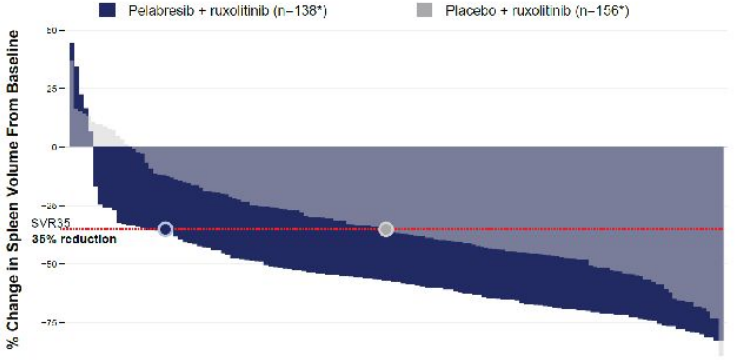






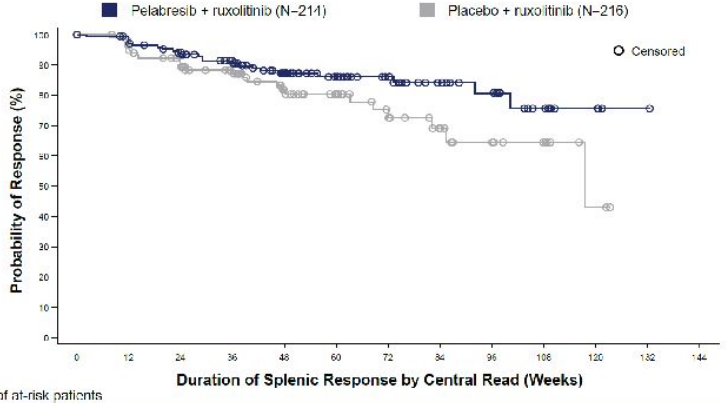
48-Week Update of MANIFEST-2 Trial

1a. Percent Change in Spleen Volume From Baseline at Week 48



Data cutoff date: March 29, 2024. Spleen volume assessed by central read.
*Waterfall plots represent patients who have baseline and Week 48 data

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	5	2	0	0

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)

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

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)	

Data cutoff date: March 29, 2024.

Leukemic Transformation

- As of August 30, 2024, accelerated and blast phase progression, adjudicated independently by external experts, was reported in 6.1% (13/212) of patients in the pelabresib + ruxolitinib arm and 4.2% (9/214) of patients in the placebo + ruxolitinib arm (**Table 2**)

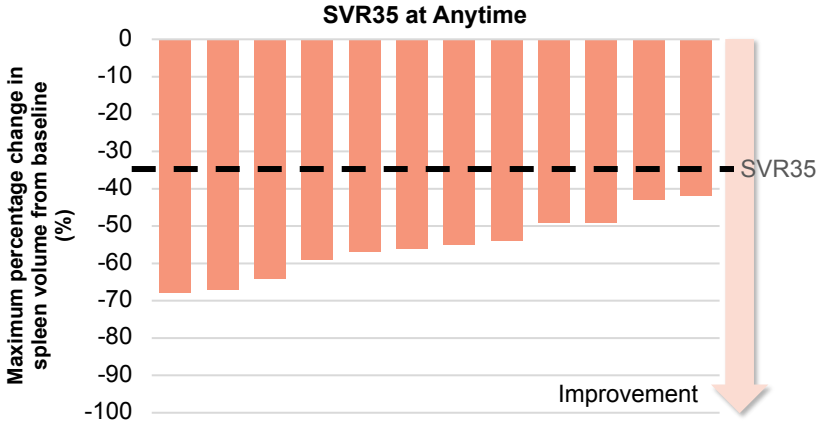
Table 2. Accelerated- and Blast-Phase Progression*,†

	Pelabresib + ruxolitinib (N=212)			Placebo + ruxolitinib (N=214)		
	Accelerated and blast phase	Accelerated phase	Blast phase	Accelerated and blast phase	Accelerated phase	Blast phase
As of March 29, 2024 data cutoff, n (%)‡	13 (6.1)	2 (0.9)	11 (5.2)	5 (2.3)	3 (1.4)	2 (0.9)
As of August 30, 2024 data cutoff, n (%)§	13 (6.1)	2 (0.9)	11 (5.2)	9 (4.2)	3 (1.4)	6 (2.8)

*Assessment based on local laboratory results, AEs, and documented disease progression. Leukemic transformation confirmed by a bone marrow blast count of ≥20% or a peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10^9/L that lasts for at least 2 weeks. †Most recent leukemic transformation data. ‡Minimum of 48 weeks of leukemia-free survival follow-up; median follow-up 17.1 months. §Minimum of 72 weeks of leukemia-free survival follow-up. The last adjudication November 4, 2024 with the cutoff as of August 30, 2024 showed a ratio of 11:6.

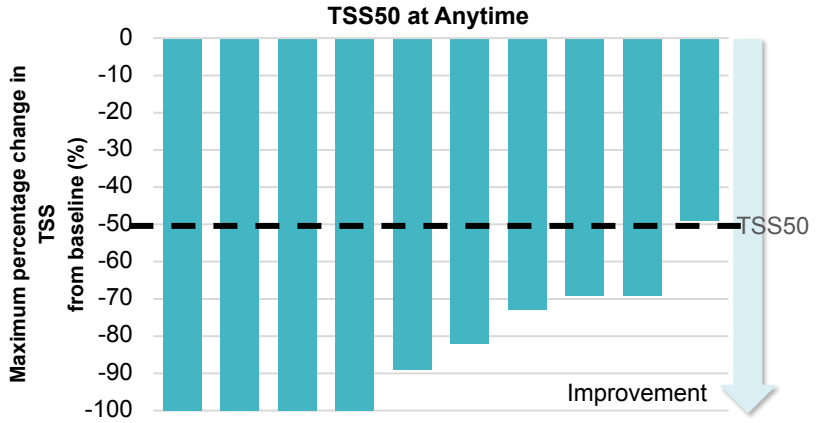
Selinexor in MF; Results From Ph1 Portion

Population	Timepoint	SVR35 Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	10/12† (83)
	Week 24	**11/12 (92)**
Intent-to-treat	Week 12	10/14 (71)
	Week 24	**11/14 (79)**



All patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved an SVR35 at anytime

Population	Timepoint	TSS50 Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	8/10‡ (80)
	Week 24	**7/9§ (78)**
Intent-to-treat	Week 12	8/12 (67)
	Week 24	**7/12 (58)**

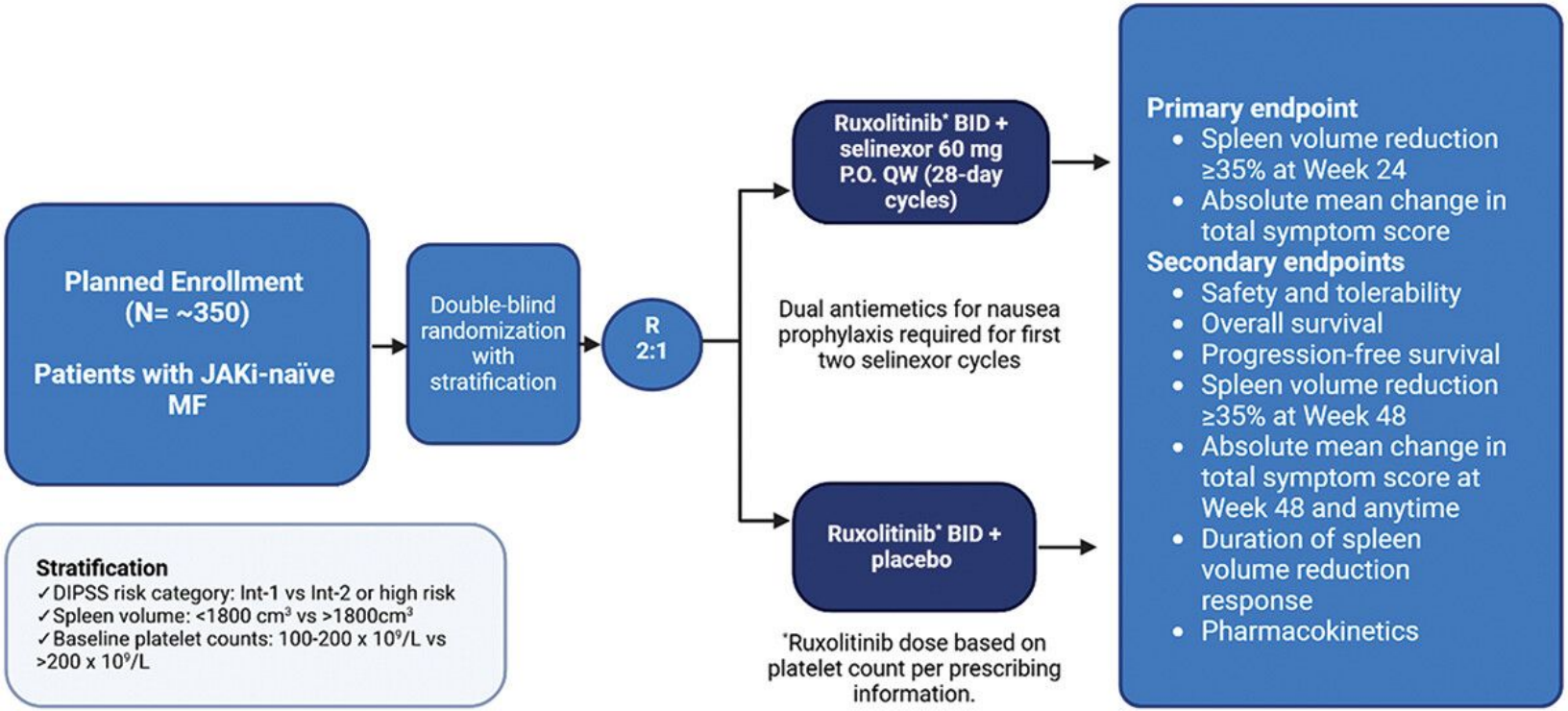


90% of patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved an TSS50 at anytime

SVR, spleen volume reduction; TSS, total symptom score.

*Data cutoff date: August 01, 2023; †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; §Two patients discontinued prior to Week 24, and one had missing data.

SENTRY: A Phase 3 Trial in JAKi-Naive Int/High-Risk MF



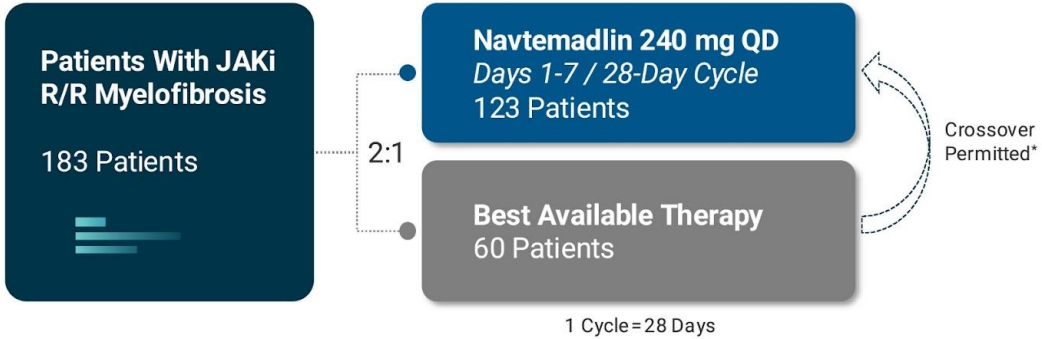
Phase 3 Study Design

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.

Results From Ph3 BOREAS Trial

- Clinical: Navtemadlin vs BAT
  - SVR35 at w24: 15% with navtemadlin vs 5% with BAT
  - TSS50 at w24: 24% with navtemadlin vs 12% with BAT
  - Mean absolute change in TSS: -4.6 with navtemadlin vs +0.9 with BAT

- ≥ 50% driver gene VAF reduction at w24: 21% with navtemadlin vs 12% with BAT
- Improved BM by 1 or 2 grades at w24: 47% with navtemadlin vs 24% with BAT
- Median change in CD34+ cells at w24: -70% with navtemadlin vs -38% with BAT
- Reduction of CD34+ cells, driver gene VAF, and inflammatory cytokines correlated with SVR

Study KRT-232-109, Phase 1b/2 Design

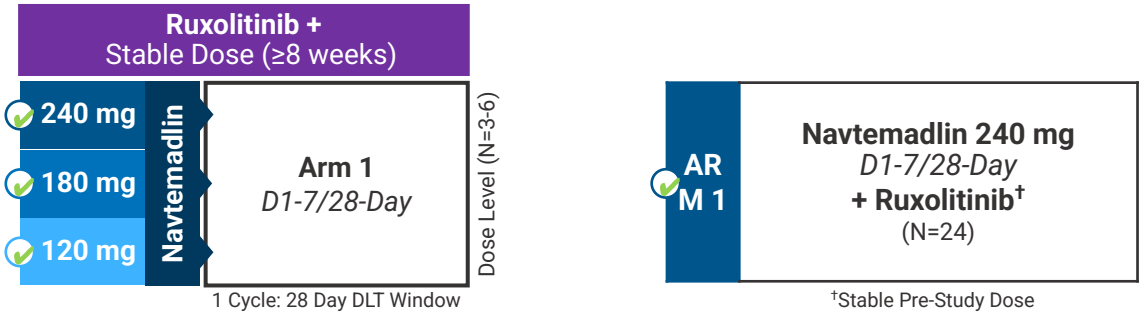
A Global, Open-Label, Multicenter Phase 1/2 Study of the Safety and Efficacy of Navtemadlin Combined With Ruxolitinib in Patients With Primary Myelofibrosis, Post–Polycythemia Vera MF or Post–Essential Thrombocythemia MF Who Have Suboptimal Response to Ruxolitinib

ENROLLMENT → **PHASE 1 (DOSE ESCALATION)** → **PHASE 2 (DOSE EXPANSION)**

Patients with suboptimal response to ruxolitinib after ≥18 weeks of treatment

No evidence of response or progression on ruxolitinib*

≥100×10^9/L platelets

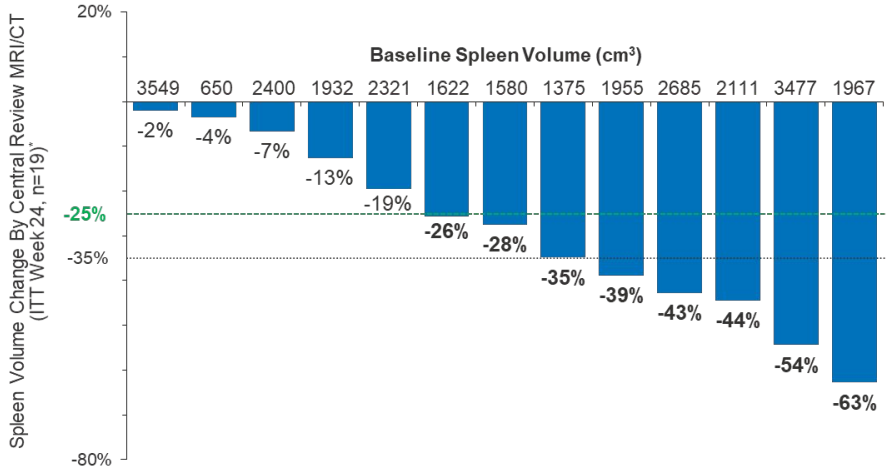


PRIMARY ENDPOINT	KEY SECONDARY ENDPOINTS
• Phase 1: **Navtemadlin RP2D in combination with ruxolitinib** • Phase 2: **Spleen response rate at Week 24** SVR by Central Review MRI/CT	• **Improvement of MFSAF v4.0 TSS ≥50% at Week 24** • Spleen response duration • RBC transfusion independence • Spleen response rate at any time point from baseline

*Patients have neither achieved a spleen response by IWG-MRT criteria, nor have had evidence of progression in spleen or symptoms while on ruxolitinib.
Abbreviations: CT, computed tomography; D, day; DLT, dose limiting toxicity; MF, myelofibrosis; MFSAF v4.0, myelofibrosis symptom assessment form version 4.0; MRI, magnetic resonance imaging; RBC, red blood cell; RP2D, recommended phase 2 dose; SVR, spleen volume reduction; TSS, total symptom score.

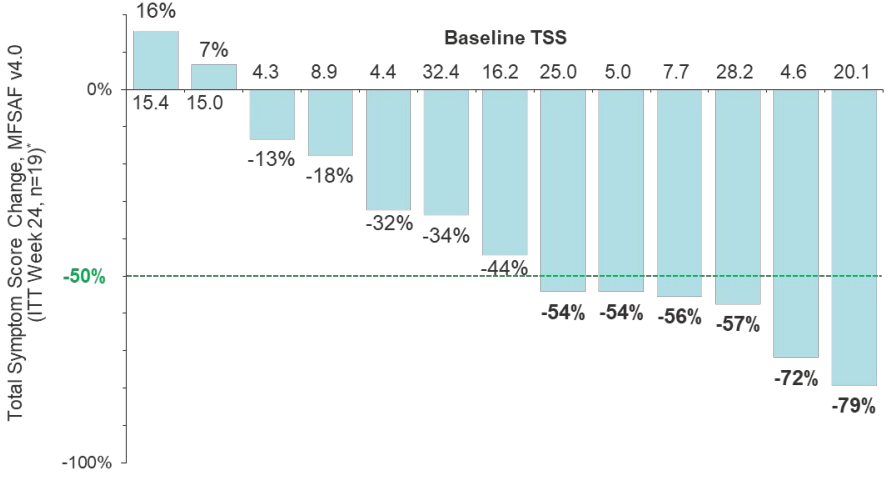
Results from KRT-232-109 trial

SVR-25, w24: 42% (n=8/19)
SVR-35, w24: 32% (n=6/19)



Baseline Rux Dose (mg BID)	25	20	25	5	20	15	15	5	5	5	20	25	10
Week 24 Rux Dose (mg BID)	25	20	25	5	20	15	10	5	5	5	10	15	10
Prior Rux Duration (Yrs)	9.1	2.5	2.6	1.1	2.1	8.1	1.2	1.9	1.4	1.7	5.8	0.7	1.3

TSS-50, w24, by MFSAF v4.0 TSS: 32% (n=6/19)

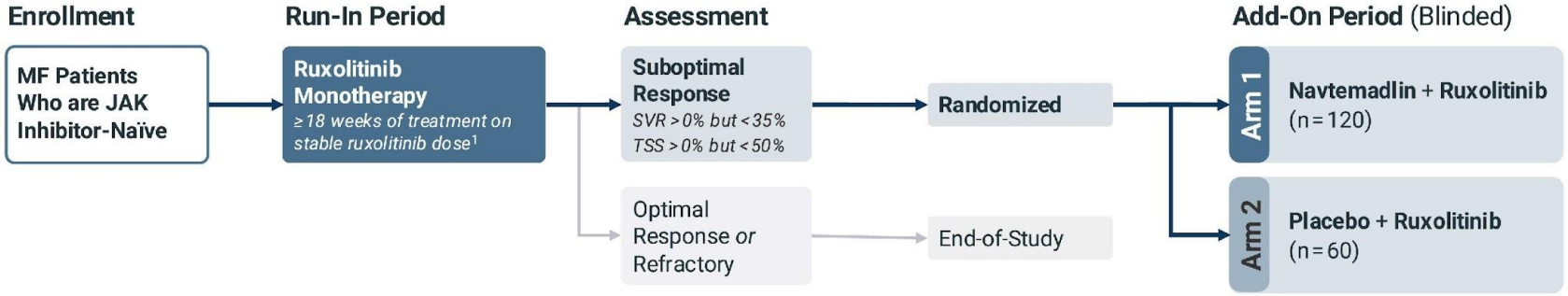


Baseline Rux Dose (mg BID)	25	20	15	5	25	15	20	5	10	20	5	25	5
Week 24 Rux Dose (mg BID)	15	20	10	5	25	15	20	5	10	10	5	25	5
Prior Rux Duration (Yrs)	0.7	2.1	1.2	1.9	2.6	8.1	2.5	1.1	1.3	5.8	1.7	9.1	1.4

Data cut-off: 02 May 2023.
*Six patients discontinued prior to Week 24 assessment.
Abbreviations: BID, twice-a-day; ITT, intent-to-treat; MFSAF v4.0, myelofibrosis symptom assessment form version 4.0; Rux, ruxolitinib.

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.

Efficacy and Safety of Fedratinib From FREEDOM-2

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

Screening period (≤ 35 days) | Randomized treatment phase | Endpoints and assessments

Key eligibility criteria

- Age ≥ 18 years
- Primary, post-PV, or post-ET MF
- MPN-associated MF DIPSS ≥ int-2
- Spleen volume ≥ 450 cm^3 or palpable spleen ≥ 5 cm below LCM
- Platelets ≥ 50 $\times 10^9$/L
- ANC ≥ 1 $\times 10^9$/L
- Prior ruxolitinib treatment[a]
- PB blasts < 5%
- Normal baseline thiamine[b]

R 2:1 (N = 192)

- Fedratinib 400 mg once daily
- Crossover permitted
- BAT (78% received ruxolitinib as BAT)[c]

Treatment until lack of efficacy or intolerance

Primary endpoints

- SVR35 at EOC6

Key secondary endpoints

- TSS50[d] at EOC6
- SVR25 at EOC6
- Safety

Platelets analysis

- Hematology assessments at screening, C1-3 D1 and D15, D1 of each subsequent cycle, 30-day follow-up
- Primary and key secondary endpoints by **low (50-<100 x 10^9/L)** and **high (≥ 100 x 10^9/L)** baseline platelet count

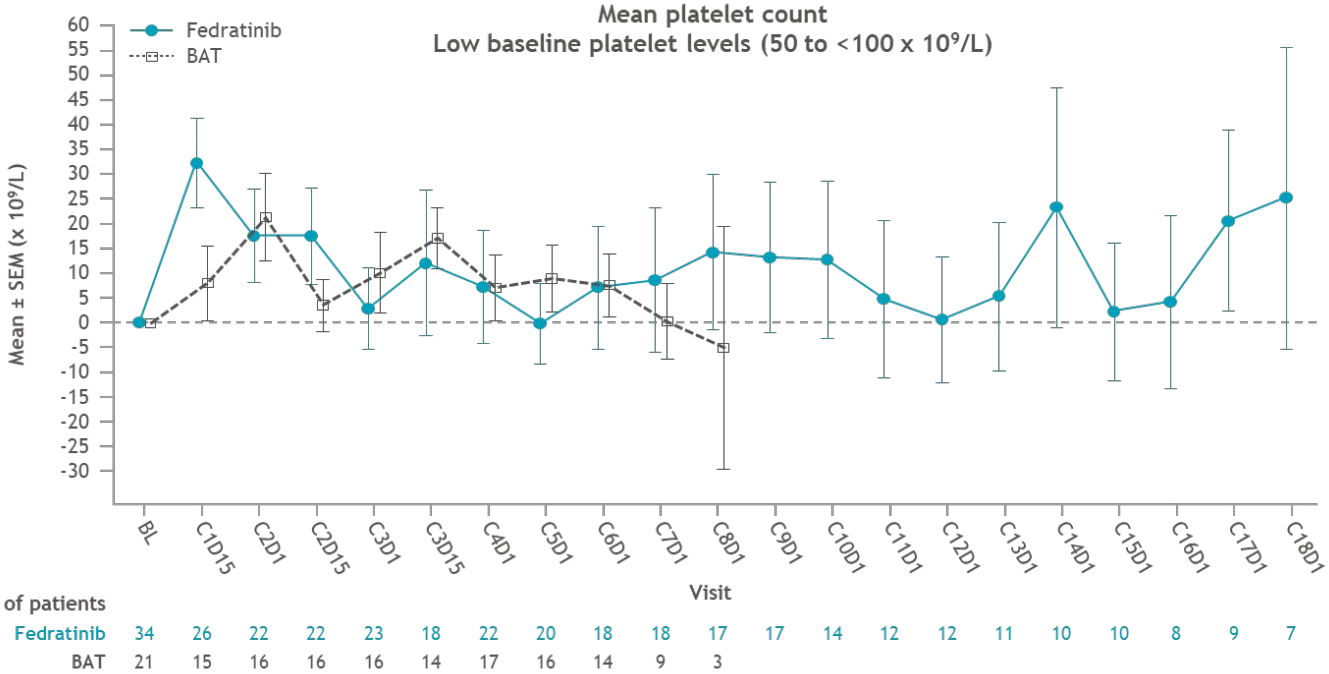
Follow-up

- Survival
- Subsequent therapies
- New malignancy
- Progression of MF to AML

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.

Efficacy and Safety of Fedratinib From FREEDOM-2



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	34	26	22	22	23	18	22	20	18	18	17	17	14	12	12	11	10	10	8	9	7
BAT	21	15	16	16	16	14	17	16	14	9	3										

Patients with low baseline platelet levels showed an early increase in platelet count, with a greater initial increase in the fedratinib arm (+45%) versus the BAT arm (+12.6%) at C1D15

Platelet levels above baseline were maintained for ≥ 2 months

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

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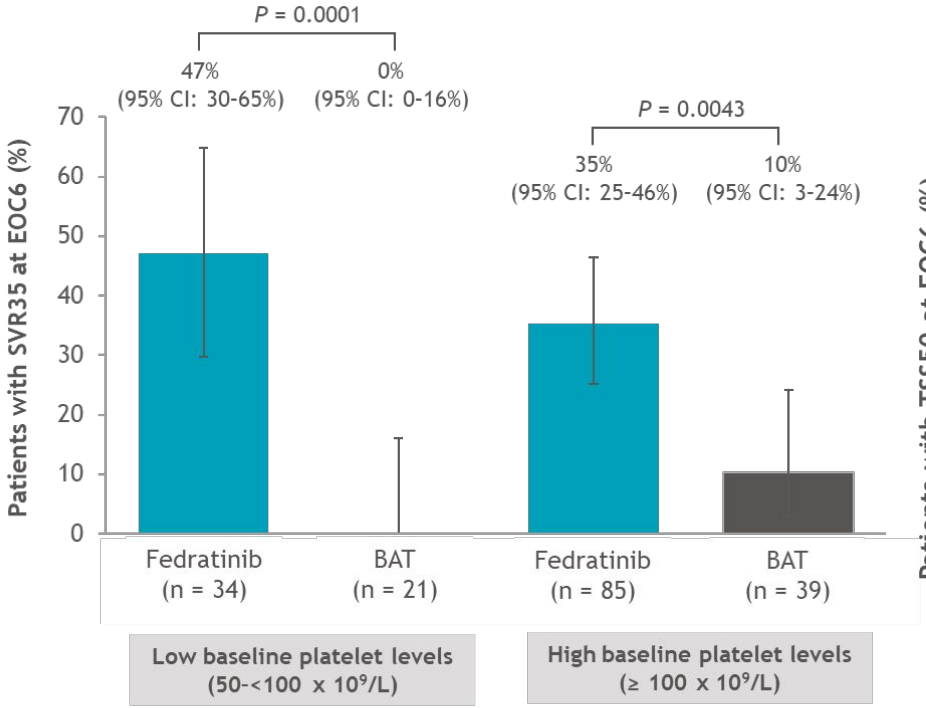

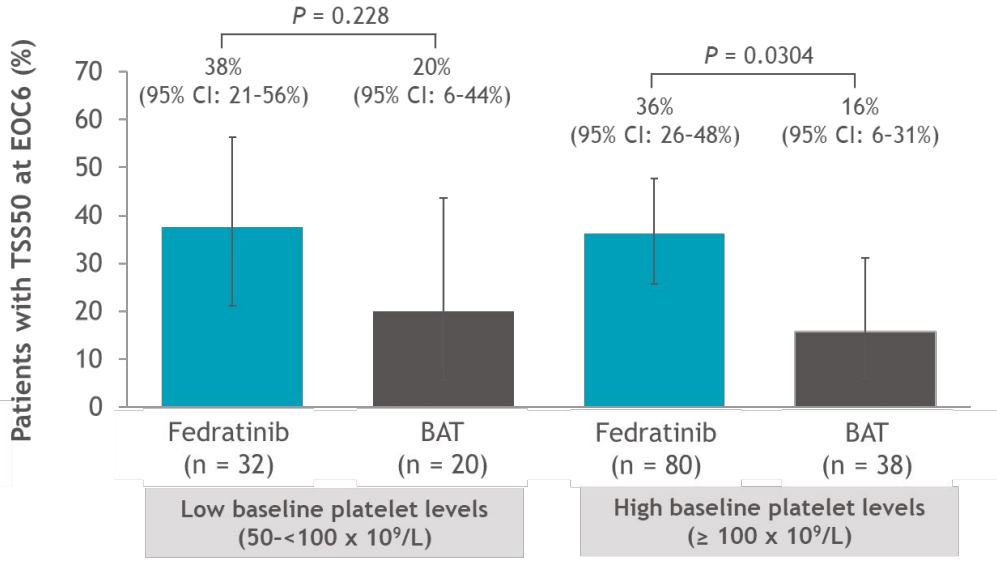

Among evaluable patients, both those with low and high baseline platelet levels had higher rates of spleen and symptom responses at EOC6 with fedratinib treatment vs BAT

THANK YOU