



Prospettive future per la terapia del paziente con mielofibrosi

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Combination Therapies: Different Settings, Different Modalities

Inh. Class		Setting		Modalities		
Drug ^a		JAKi naive	JAKi R/R/I	Monotherapy	Add-on	Combo RUX
Pelabresib	BET	✓	✓	✓	✓	✓
Navitoclax	Bcl-xL	✓	✓		✓	✓
INCB057643	BET		✓	✓	✓	
BMS-986158	BET	✓	✓	✓		✓ & FED
Parsaclisib	PI3Kδ		✓		✓	✓
Luspatercept	TGF-β trap		✓		✓	
Selinexor	XPO1	✓		✓		✓
Navtemadlin	MDM2		✓	✓	✓	

BET= Bromodomain and Extraterminal Domain Proteins. **Bcl-xL**= B-cell lymphoma-extra large (*BCL2-like 1*).
PI3Kδ= Phosphatidylinositol 3-kinase delta. **Luspatercept**= ligand trap for various members of the TGF-β superfamily.
Navtemadlin= Inhibitor of murine double minute 2 (MDM2). **XPO1**: nuclear exportin-1

List not exhaustive

The MANIFEST-2 study is a global, randomized, double-blind, Phase III trial

investigating the efficacy and safety of the combination therapy of PELA+RUX versus PBO+RUX in JAKi-naïve patients with MF^{1,2}

Study population

JAKi-naïve patients with MF (N=430)

(primary or post-ET/PV)

- DIPSS Int-1 risk or higher
- Spleen volume ($\geq 450 \text{ cm}^3$)
- Platelet count $\geq 100 \times 10^9/\text{L}$
- TSS ≥ 10 (≥ 3 for two symptoms, MFSAF v4.0)
- Peripheral blast count $< 5\%$
- ECOG PS ≤ 2

Double-blind
randomization
(1:1)

Treatment arms

PELA
125 mg* PO QD
Day 1-14

+

RUX
Per label with a 5 mg
BID lower starting dose†
Day 1-21

21-day cycles

PBO
PO QD
Day 1-14

+

RUX
Per label with a 5 mg
BID lower starting dose†
Day 1-21

Primary endpoint

- SVR35 response at Week 24

Key secondary endpoints

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

Safety

- AEs of all grades and serious AEs

- The MANIFEST-2 study met its primary endpoint, showing a statistically significant improvement in SVR35 response at Week 24 with PELA+RUX compared with PBO+RUX in JAKi-naïve patients with MF¹
- Here, we present follow-up efficacy and safety outcomes at Week 72; in addition, longer-term analyses were conducted for PFS,[‡] OS, and LFS, although the study was not powered for survival outcomes

*The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD. †RUX was started at 10 mg BID (baseline platelet count 100-200 $\times 10^9/\text{L}$) or 15 mg BID (baseline platelet count $> 200 \times 10^9/\text{L}$) with a mandatory dose increase by 5 mg BID after 1 cycle and a maximum dose of 25 mg BID as per the label. ‡Defined as the time from randomization to documented progression, or death from any cause. AE, adverse event; BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; Int, intermediate; JAKi, Janus kinase inhibitor; LFS, leukemia-free survival; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; OS, overall survival; PBO, placebo; PELA, pelabresib; PFS, progression-free survival; PO, orally; PV, polycythemia vera; QD, once daily; RUX, ruxolitinib; SVR35, $\geq 35\%$ reduction in spleen volume from baseline; TSS, total symptom score; TSS50, $\geq 50\%$ reduction in total symptom score from baseline.

1. Rampal R, et al. *Nat Med*. 2025;31(5):1531-1538; 2. Rampal R, et al. Presented at EHA 2024 [Oral S22 1].

Patient characteristics across treatment arms

Characteristic ¹		PELA+RUX (N=214)	PBO+RUX (N=216)
Age — years	Median (min, max)	66 (19, 84)	66 (26, 88)
Sex — n (%)	Female / male	85 (39.7) / 129 (60.3)	94 (43.5) / 122 (56.5)
	White / Asian / Black	160 (74.8) / 35 (16.4) / 2 (0.9)	163 (75.5) / 42 (19.4) / 0
Race — n (%)	American Indian or Alaska Native	1 (0.5)	0
	Not reported / Unknown	15 (7.0) / 1 (0.5)	11 (5.1) / 0
	Primary myelofibrosis	107 (50.0)	110 (50.9)
Myelofibrosis subtype — n (%)	Post-polycythemia vera myelofibrosis	45 (21.0)	53 (24.5)
	Post-essential thrombocytopenia myelofibrosis	62 (29.0)	53 (24.5)
Dynamic International Prognostic Scoring System — n (%)	Intermediate-1	128 (59.8)	127 (58.8)
	Intermediate-2	75 (35.0)	74 (34.3)
	High-risk	11 (5.1)	15 (6.9)
Mutations — n (%)	JAK2 V617F	124 (57.9)	122 (56.5)
	CALR	45 (21.0)	50 (23.2)
	MPL	11 (5.1)	13 (6.0)
	Triple negative*	8 (3.7)	8 (3.7)
	High molecular risk mutations†	91 (42.1)	79 (36.9)
Hemoglobin — g/dL	Median (range)	10.9 (5.8-18.0)	11.0 (6.7-17.9)
	≤10 — n (%)	70 (32.7)	76 (35.2)
Platelets — × 10 ⁹ /L	Median (min, max)	285 (99, 1303)	287 (66, 1084)
	>200 × 10 ⁹ /L — n (%)	154 (72)	157 (72.7)
Peripheral blasts	Mean (SD)	0.8 (1.18)‡	0.8 (1.25)§
RBC transfusions [‡] — patient n (%)	Requiring RBC transfusion at baseline	22 (10.3)	21 (9.7)
Transfusion dependent at enrollment ^{§,¶} — patient n (%)		8 (3.7)	2 (0.9)
	0	107 (50.0)	109 (50.5)
ECOG performance status — n (%)	1	97 (45.3)	95 (44.0)
	≥2	10 (4.7)	10 (4.6)
	Missing	0	2 (0.9)
Spleen volume (central read) [#]	Median spleen volume (range) — cc	1308.89 (200.24-7117.03)	1382.97 (277.87-5540.45)
Total symptom score ^{**}	Median total symptom score (range)	26.6 (7.3-66.4)	24.7 (9.0-68.4)
	0	6 (2.8)	3 (1.4)
	1	32 (15.0)	35 (16.2)
Bone marrow fibrosis grade — n (%)	2	58 (27.1)	67 (31.0)
	3	81 (37.9)	82 (38.0)
	Missing	37 (17.3)	29 (13.4)

*Triple-negative status was missing for 55 patients (28 in the PELA+RUX arm and 27 in the PBO+RUX arm); †High molecular risk mutations include ASXL1, EZH2, IDH1, IDH2, SRSF2, and U2AF1 mutations. ‡n=208. §n=207.

‡RBC transfusions refer to number of patients who received any RBC transfusion during the 12-week baseline period prior to dosing. §Transfusion dependent at enrollment is defined as having received ≥6 units of RBC transfusions

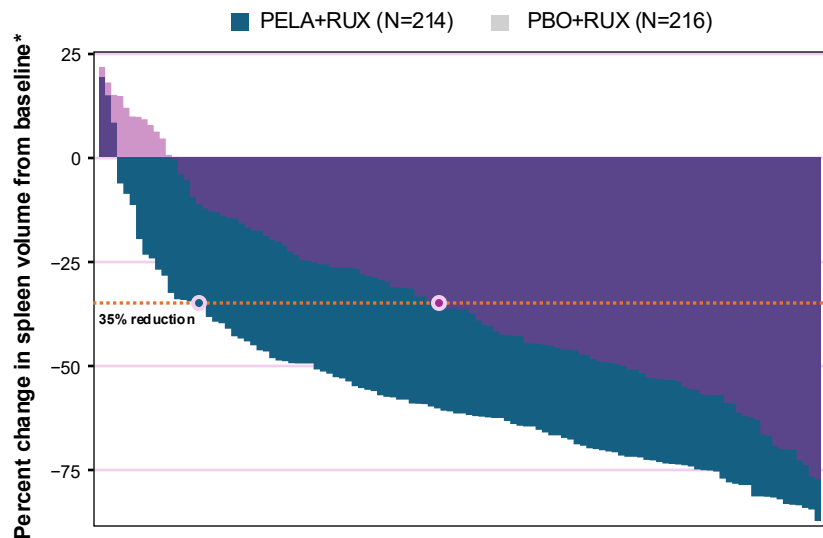
during the 12-week baseline period prior to dosing. ¶Randomization of patients was based on local read. **Patients with baseline TSS values of <10 have ≥2 individual symptoms score ≥3 at baseline.

ASXL1, ASXL transcriptional regulator 1; CALR, calreticulin; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; IDH1/2, isocitrate dehydrogenase 1/2; JAK2, Janus kinase 2; max, maximum; min, minimum;

MPL, MPL proto-oncogene, thrombopoietin receptor; PBO, placebo; PELA, pelabresb; RBC, red blood cell; RUX, ruxitinib; SD, standard deviation; SRSF2, serine and arginine rich splicing factor; TSS, total symptom score; U2AF1, U2 small nuclear RNA auxiliary factor 1.

1. Rampal R, et al. Presented at EHA 2024 [Oral S221].

Sustained and durable improvements in spleen volume with PELA+RUX versus PBO+RUX at Week 72



ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at Week 72	46.3	29.2
Difference[†] (95% CI)	16.7 (7.9-25.4)	

Mean % change in spleen volume at Week 72[‡]	-57.2 (n=114)	-34.9 (n=119)
95% CI	-61.0, -53.3	-39.0, -30.7

	PELA+RUX (N=214)	PBO+RUX (N=216)
Loss of SVR35 response and >25% increase in spleen volume from nadir, % (n/N)*	22.7 (40/176)	25.8 (34/132)

80% of responders in the PELA+RUX arm maintained their response for 72 weeks compared with 73% in the PBO+RUX arm

Data cutoff date: August 30, 2024.

Spleen volume assessed by central read.

*Waterfall plots represent patients who have baseline and Week 72 data. [†]Calculated by stratified Cochran-Mantel-Haenszel test. [‡]Patients without Week 72 assessment are considered non-responders.

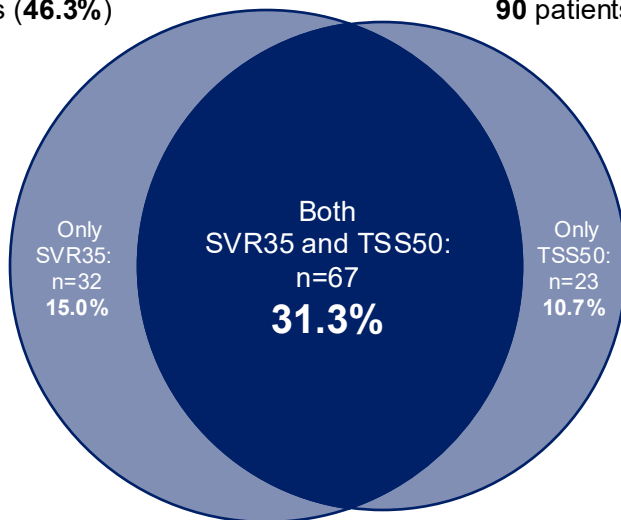
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, $\geq 35\%$ reduction in spleen volume from baseline.

Nearly twice as many patients achieved both SVR35 and TSS50 responses with PELA+RUX versus PBO+RUX at Week 72

PELA+RUX (N=214)

SVR35 response:
99 patients (**46.3%**)

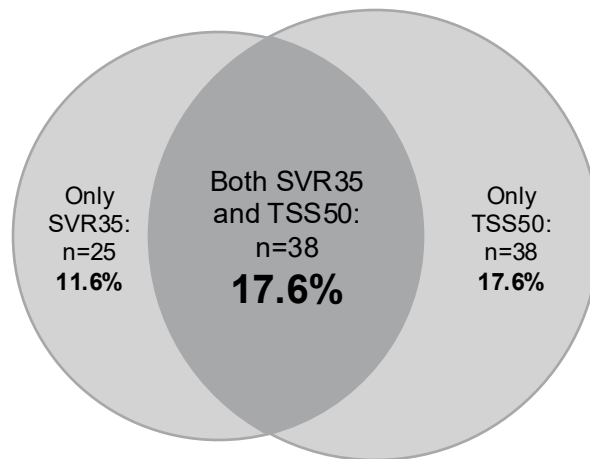
TSS50 response:
90 patients (**42.1%**)



PBO+RUX (N=216)

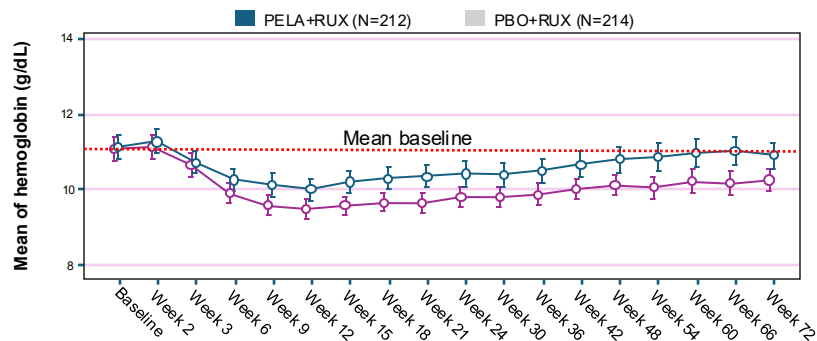
SVR35 response:
63 patients (**29.2%**)

TSS50 response:
76 patients (**35.2%**)



Dual SVR35 / TSS50 responders at Week 72

Hemoglobin response, and RBC transfusions, with PELA+RUX versus PBO+RUX



Number of at-risk patients

PELA+RUX	212	204	209	199	193	189	186	185	184	181	171	168	162	156	148	144	139	136
PBO+RUX	214	206	211	209	207	205	204	199	196	195	185	179	175	170	161	152	145	139

ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Hemoglobin response, ^{†‡} % (n/N) (95% CI)	16.4 (35/214) (11.4-21.31)	9.3 (20/216) (5.39-13.12)
Hemoglobin response, ^{†‡} in patients with anemia (baseline <10 g/dL), % (n/n) (95% CI)	20.9 (14/67) (11.16-30.63)	16.9 (12/71) (8.18-25.62)

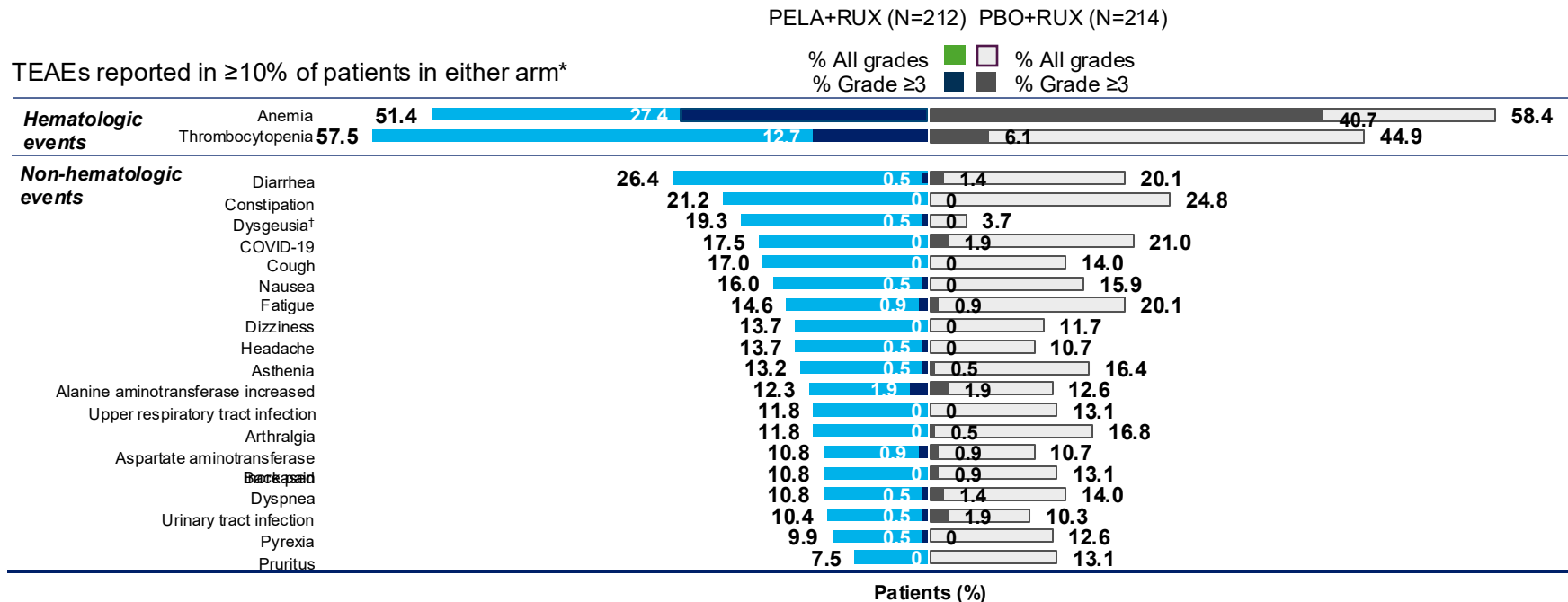
Fewer patients in the PELA+RUX arm versus the PBO+RUX arm required RBC transfusions[§] over 72 weeks:

- Weeks 0 to 24: 24.1% (35/145) versus 36.4% (59/162)
- Weeks 25 to 48: 19.3% (28/145) versus 30.9% (50/162)
- Weeks 49 to 72: 19.3% (28/145) versus 25.3% (41/162)

Data cutoff date: August 30, 2024. *Safety population received ≥ 1 dose of study drug. [†]Hemoglobin response is defined as a ≥ 1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the prior 12 weeks in the ITT population. [‡]Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. [§]RBC transfusions refer to number of patients who received any RBC transfusion during the first 24 weeks after Cycle 1 Day 1, during the 25-48 weeks after Cycle 1 Day 1 or during the 49-72 weeks after Cycle 1 Day 1. CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RBC, red blood cell; RUX, ruxolitinib.

Treatment-emergent adverse events at Week 72 data cutoff

The most frequent TEAEs in both treatment arms were low grade (Grade <3)



Data cutoff date: August 30, 2024.

*Safety population: received ≥1 dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blind treatment period is defined as an adverse event that has a start date on or after the first dose of PELA/PBO and before 30 days after the last dose of PELA/PBO 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.

COVID-19, coronavirus disease 2019; MF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; TEAE, treatment-emergent adverse event.

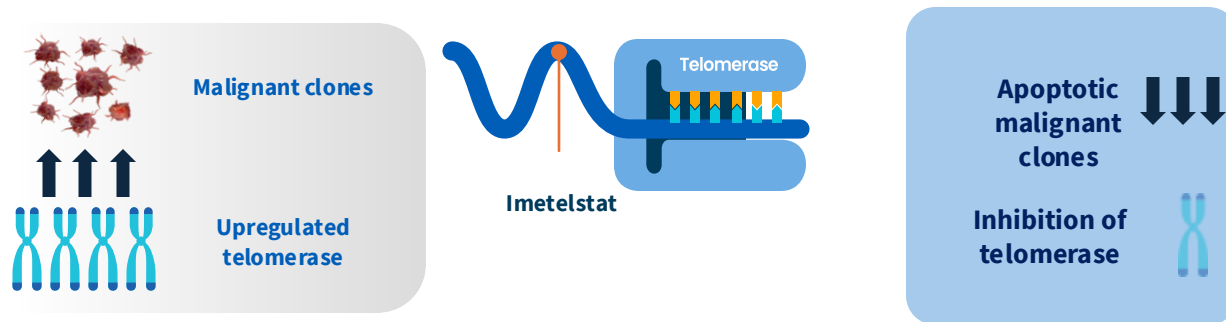
Accelerated- and blast-phase progression

	PELA+RUX			PBO+RUX		
	Accelerated and blast phase*	Accelerated phase	Blast phase	Accelerated and blast phase*	Accelerated phase	Blast phase
As of March 29, 2024, (Week 48) data cutoff, % (n/N)^{†,‡}	6.1 (13/213)	0.9 (2/213)	5.2 (11/213)	2.3 (5/214)	1.4 (3/214)	0.9 (2/214)
As of August 30, 2024, (Week 72) data cutoff, % (n/N)^{§,¶}	6.1 (13/214)	0.9 (2/214)	5.1 (11/214)	4.2 (9/214)	1.4 (3/214)	2.8 (6/214)

- As of August 30, 2024, accelerated- and blast-phase progression, adjudicated independently by external experts, was reported in 6.1% (13/214) of patients on PELA+RUX and in 4.2% (9/214) of patients on PBO+RUX
- An early imbalance in cases of leukemic transformation was observed with PELA+RUX compared with PBO+RUX. Over time, the imbalance in proportion of patients with transformation to blast phase decreased. Overall, the observed frequency was in line with what is typically seen in MF

*Assessment based on local laboratory results, adverse events, and documented disease progression. Leukemic transformation confirmed by a bone marrow blast count of $\geq 20\%$ or a peripheral blood blast content of $\geq 20\%$ associated with an absolute blast count of $\geq 1 \times 10^9/L$ that lasts for at least 2 weeks. [†]Minimum of 48 weeks of leukemia-free survival follow-up; median follow-up: 17.1 months. [‡]The denominator of 213 includes 1 patient who crossed over from placebo + ruxolitinib. [§]Minimum of 72 weeks of leukemia-free survival follow-up. The last adjudication in March 2025, with the cutoff as of August 30, 2024, showed a ratio of 11:6. [¶]The denominator of 214 for PELA+RUX includes 2 patients who crossed over from PBO+RUX.

Telomerases in Cancer Cells and Telomerase Inhibition to Treat Hematological Malignancies



• Telomeres:

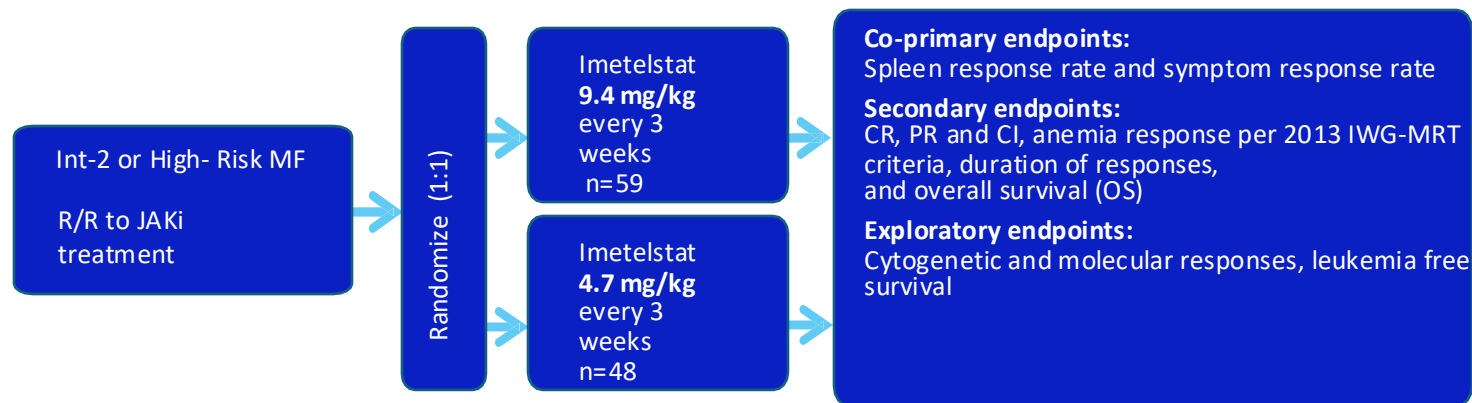
- TTAGGG repeats, cap chromosome ends
- Shorten without telomerase
- Accelerated loss under stress

• Telomerase:

- Synthesizes telomeric DNA
- Not/poorly active in normal somatic cells; transiently upregulated in normal hematopoietic progenitor cells
- Highly upregulated in malignant stem/progenitor cells, enabling continued and uncontrolled proliferation

Imetelstat is approved by the FDA and the European Commission for:

- the treatment of adult patients with LR-MDS with RBC-TD who are ineligible for ESAs or have relapsed or refractory/unsatisfactory response to ESAs
- It also received FDA and EU Orphan Drug designation, and FDA-Fast Track, for patients with Intermediate-2 and high risk myelofibrosis.



Patient Population:

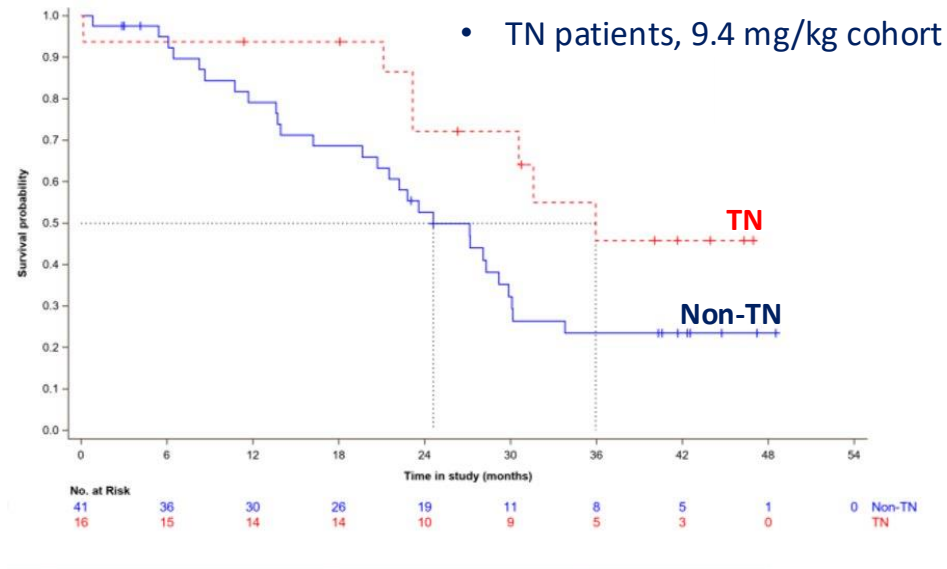
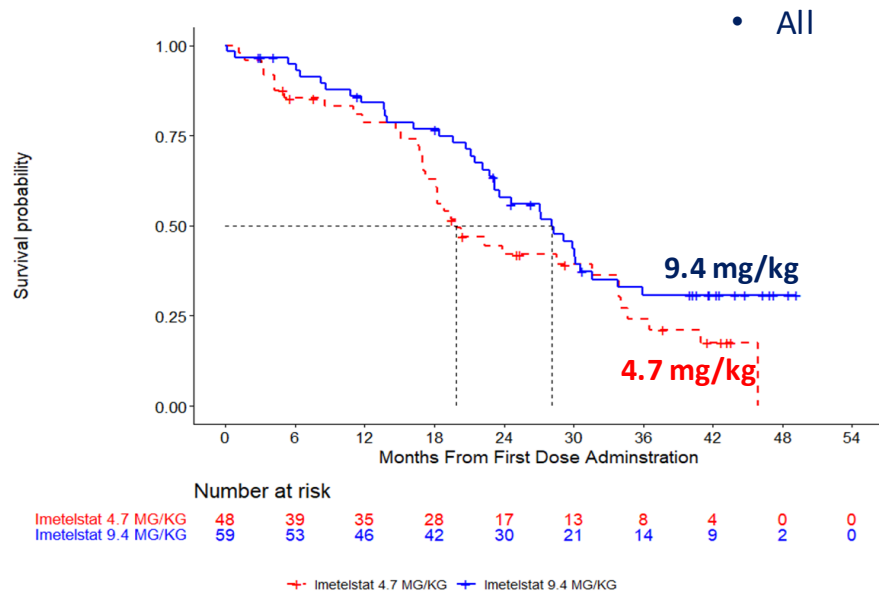
- Patients with Intermediate-2 or High-risk MF (Int-2/High-risk) patients who have relapsed after or are refractory to prior treatment with a janus kinase (JAK) inhibitor
- Relapsed or refractory o JAKi defined as documented progressive disease during or after JAKi:
 - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and EITHER:
 - No reduction in spleen volume or size after 12 weeks of JAKi therapy, OR
 - Worsening splenomegaly at any time after the start of JAKi therapy documented by:
 - Increase in spleen volume from nadir by 25% measured by MRI or CT, or
 - Increase in spleen size by palpation

IMbark Phase 2 Key Efficacy Data Showed Spleen and Symptom Response and Disease Biomarkers Improvements

	4.7 mg/kg (n=48)	9.4 mg/kg (n=59)
Symptoms Response at week 24 (TSS reduction $\geq$ 50 %) n(%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR $\geq$ 35% by IRC), n(%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Transfusion independence of 12 weeks n/N (%)	2/14 (14.3%)	3/12 (25.0%)
Reduction in bone marrow fibrosis, n/N (%)	4/20 (20.0%)	16/37 (43.3%)
$\geq$ 25% Reduction in VAF of JAK2, CALR, or MPL, n/N (%)	1/18 (5.6%)	8/19 (42.1%)

NE= not estimable

IMbark Phase 2 Key Efficacy Data Showed Impact on OS, Particularly in TN Patients



- OS correlated with improvement of BM fibrosis (HR 0.30; 95%CI, 0.10-0.92; p= 0.036)
- OS also showed a trend of correlation with $\geq 20\%$ VAF reduction (HR 0.49; 95%CI, 0.20-1.23)

IMbark Phase 2 Key Safety Data

	4.7 mg/kg (n=48)		9.4 mg/kg (n=59)	
n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Thrombocytopenia	11 (23)	11 (23)	29 (49)	24 (41)
Anemia	15 (31)	15 (31)	26 (44)	23 (39)
Neutropenia	5 (10)	5 (10)	21 (36)	19 (32)

Thrombocytopenia and neutropenia:

- Median time to thrombocytopenia and neutropenia is 9 weeks (~ 3 cycles)
- Reversible: median duration ~2 weeks
- Manageable with dose hold and modification: median time to first dose reduction 21 weeks (~7 cycles)
- Grade 3 hemorrhages and Infections were 5% and 10%, respectively

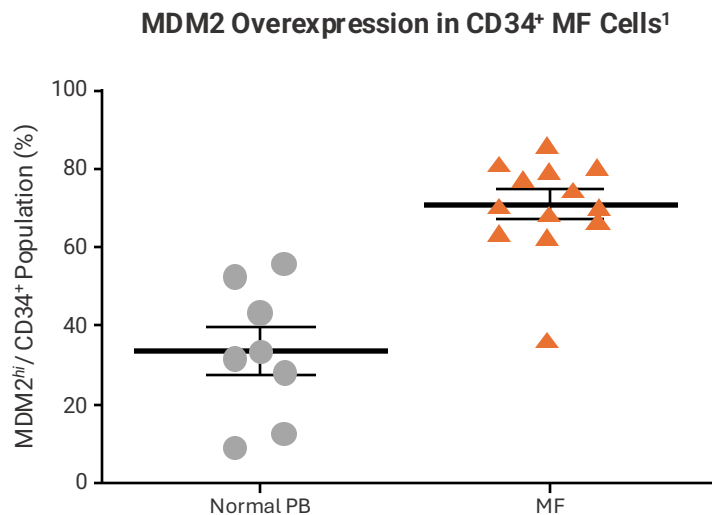
Gastrointestinal AEs:

- >G3 nausea, vomiting and diarrhea were <3% with 9.4 mg/kg

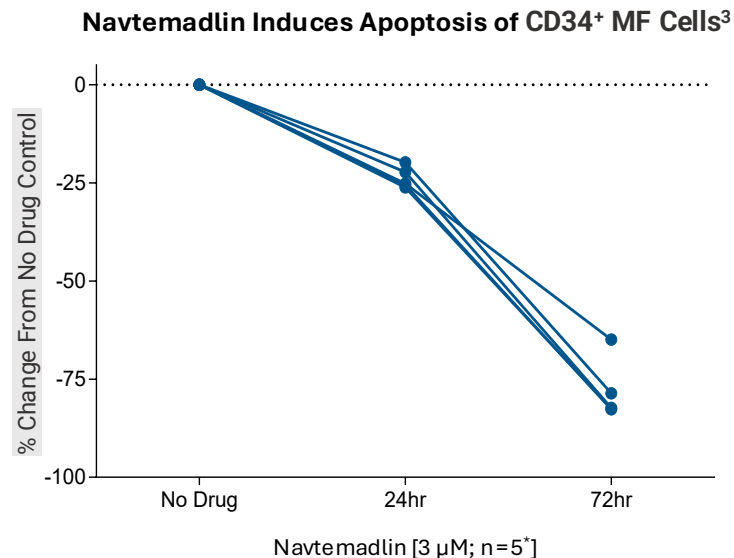
Liver function tests:

- Majority of worsening ALT, AST and Alk Phosp and bilirubin were G1, >G3 in less than 3% at 9.4 mg/Kg and recovered to normal or baseline levels.

Navtemadlin is a potent, selective, orally available best-in-class inhibitor of MDM2 that restores p53 function



MDM2 overexpression in circulating CD34⁺ MF progenitors²



Navtemadlin induces apoptosis of *TP53*^{WT} CD34⁺ MF progenitors by overcoming MDM2 dysregulation³

Note: 95% of MF patients are *TP53*^{WT}.

¹Figure adapted from Lu M, et al. *Blood* 2017. ²Nakatake M, et al. *Oncogene* 2012. ³Clevenger T, et al. EHA 2023; 386820. Abstract P991.

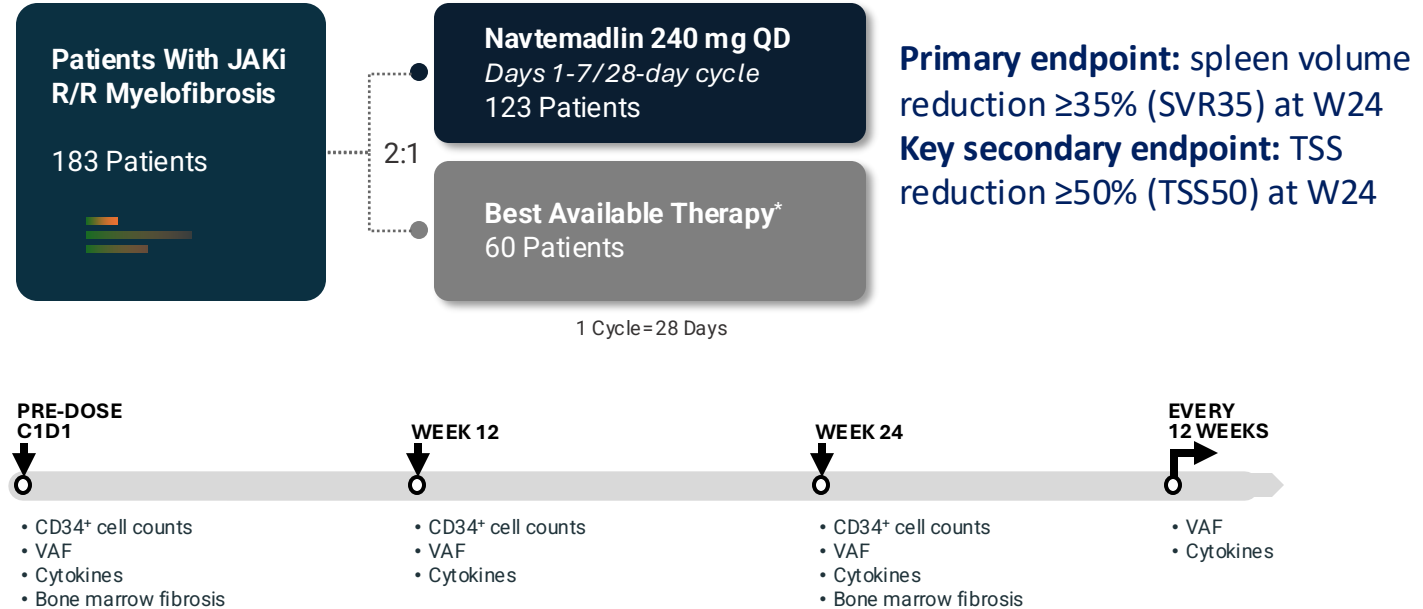
A Randomized Open-Label Phase 3 Study of Navtemadlin in $TP53^{WT}$ Subjects With Myelofibrosis, Relapsed or Refractory to JAKi (*BOREAS* trial)

Stratification Factors:

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

Physician's Choice (BAT):

- Hydroxyurea
- Chemotherapy
- Peg Interferon
- IMiDs

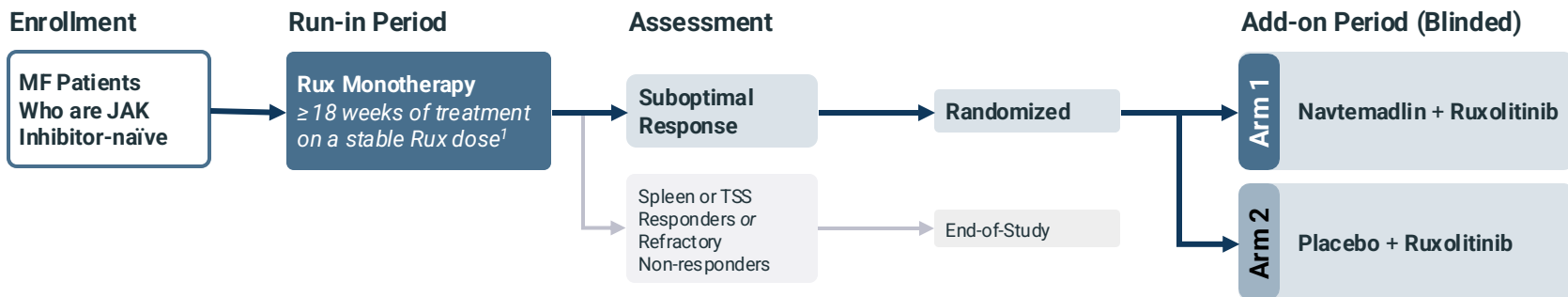


Note: BOREAS enrollment was closed at 183 patients.

*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.

Phase 3, Add-on vs PBO, Study of Navtemadlin in Suboptimal Responders to Ruxolitinib (*Poiesis trial*)



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 $\geq 450 \text{ cm}^3$
- Platelet count $\geq 100 \times 10^9/\text{L}$

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

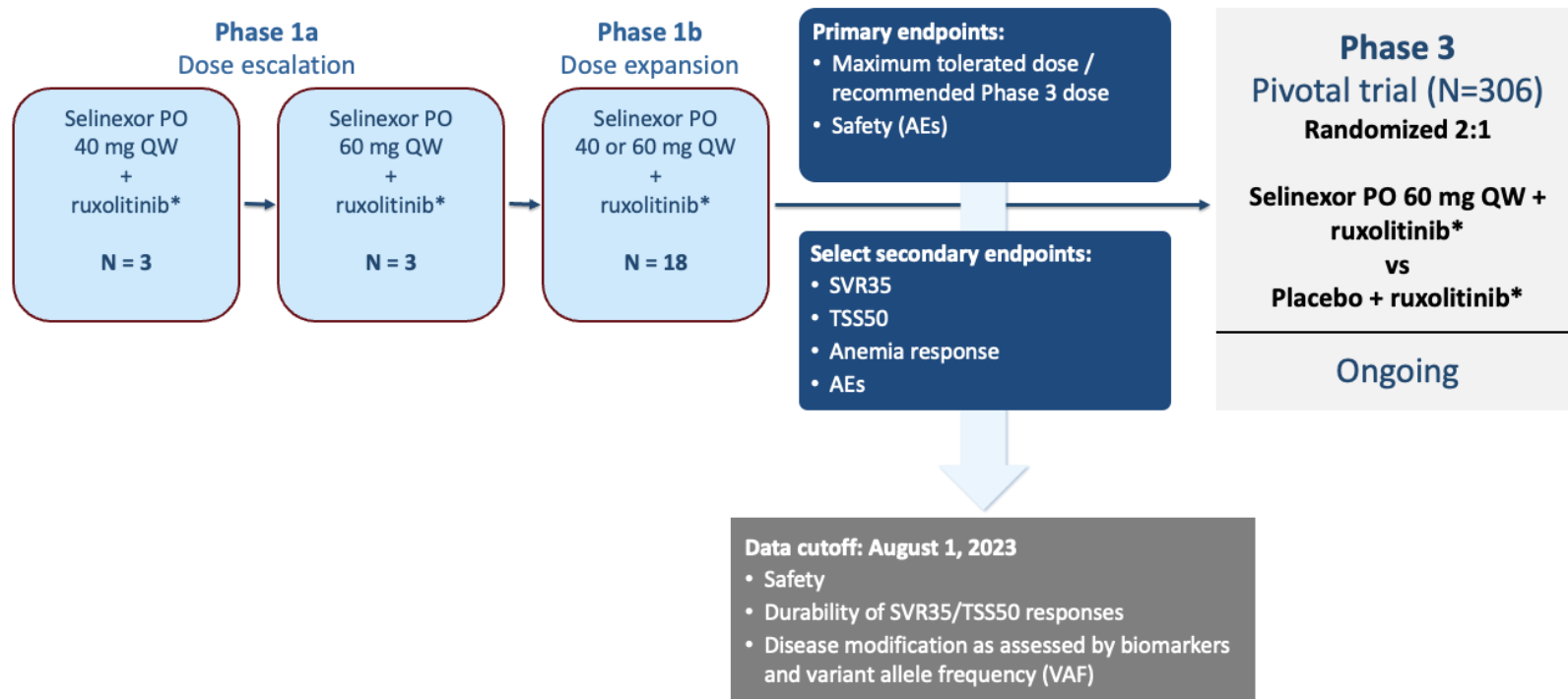
- Targeted SVR and TSS reduction 24 weeks after randomization

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

¹Stable ruxolitinib is $\geq 5 \text{ mg BID}$ that does not require treatment hold or dose adjustment during the eight weeks prior to add-on navtemadlin or placebo.

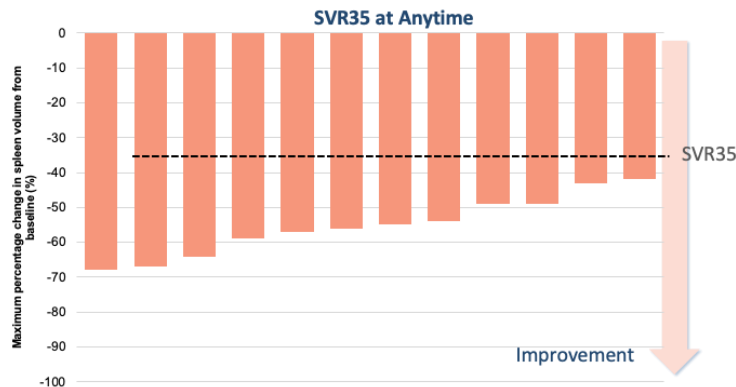
Abbreviations: BID, twice daily; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; Rux, ruxolitinib; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

A Phase 1/3 Study of Selinexor plus Ruxolitininb for JAKi Naïve Patients with MF (*XPORT-MF-304-SENTRY trial*)



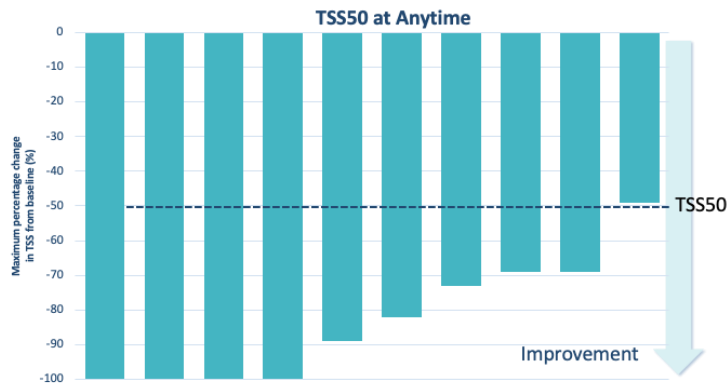
Spleen Volume Reduction (SVR) and TSS With Selinexor (60 mg QW) Plus Ruxolitinib

SVR35		
Population	Timepoint	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

TSS50		
Population	Timepoint	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

TEAEs of Selinexor (60 mg QD)

TEAEs ^a	Selinexor 60 mg + ruxolitinib (N = 14)
Any grade (≥25% 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)
Decreased appetite	4 (28.6)
Dysgeusia	4 (28.6)
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)

3.3 kg Median weight gain at Week 24

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

48% Transfusion-independent patients had stable Hb levels^b

Median Hb levels (g/dL)

10.1

Baseline

9.3

Week 12

10.2

Week 24

Median platelet levels
($\times 10^9/L$)

258

Baseline

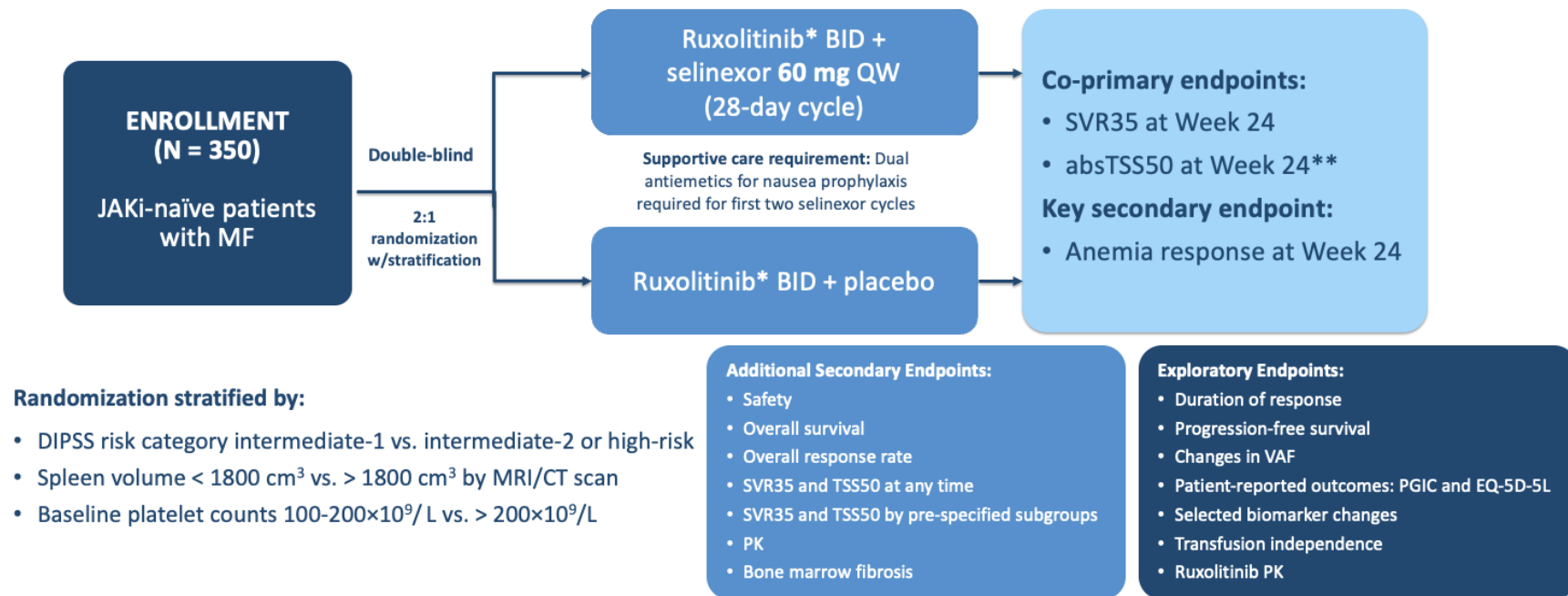
164

Week 12

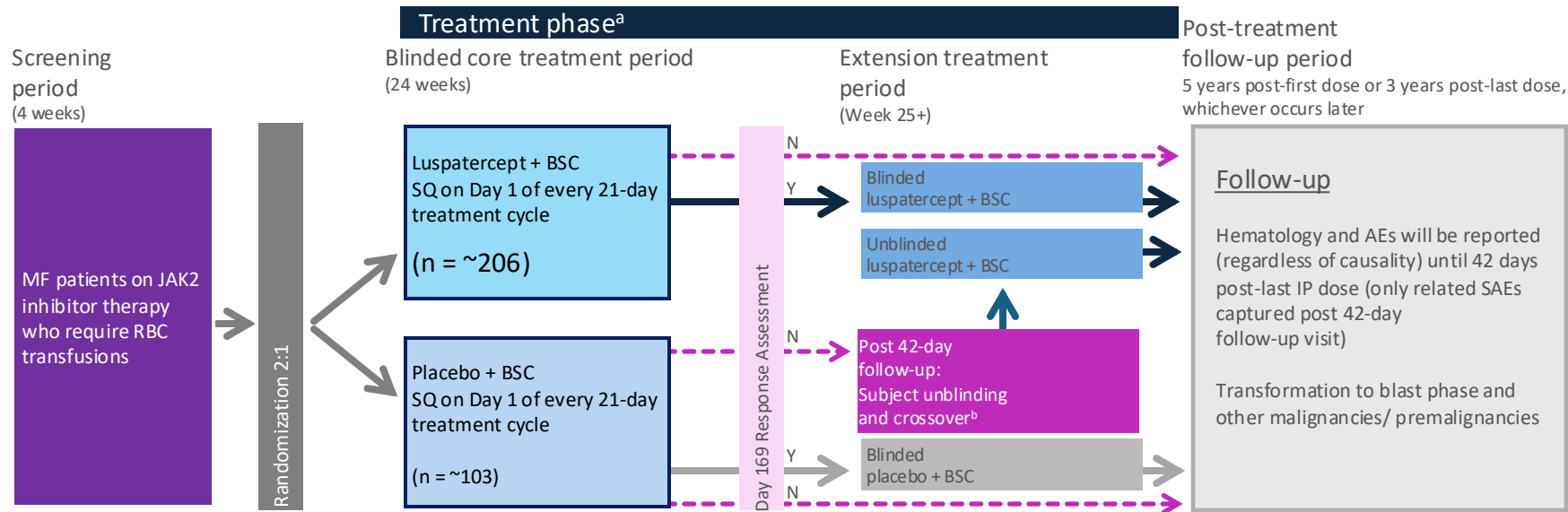
193

Week 24

Phase 3 Trial Design of Selinexor plus Ruxolitininb for JAKi Naïve Patients with MF (*XPORT-MF-304- SENTRY trial*)

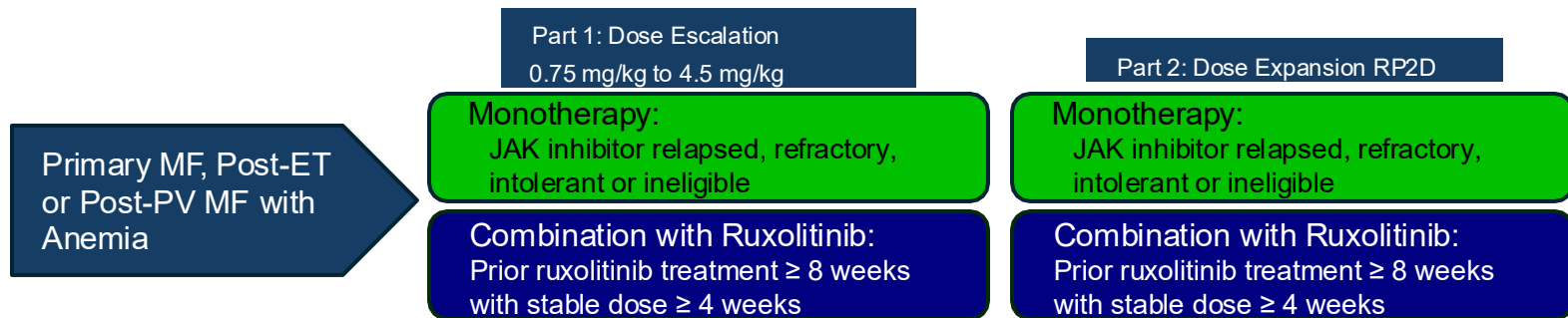


Luspatercept: *INDEPENDENCE* Phase 3, Double-blind, Randomized Study



^a Study unblinding will occur after analysis of the primary endpoint and with DMC consultation; ^b Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessments as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation. AE, adverse event; BSC, best supportive care; DMC, Data Monitoring Committee; EOT, end of treatment; IP, investigational product; JAK, Janus kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasms; N, patient did not meet Day 169 Response Assessment criteria; RBC, red blood cells; SAE, serious adverse event; SQ, subcutaneous; Y, patient met Day 169 Response Assessment criteria. INDEPENDENCE study protocol amendment 1 (Data on file).

Elritercept (KER-050), a TGF-beta inhibitor: Phase 2 RESTORE Study



<u>Key Eligibility</u>	<u>Objectives and Endpoints</u>	<u>Study Status</u>
- Transfusion dependent (TD): average of ≥6 RBC units/12 weeks with ≥ 1 transfusion within 28 days prior to treatment - Non-transfusion dependent (Non-TD): baseline hemoglobin < 10 g/dL, with or without transfusions - Baseline platelet count ≥ 25 x 10⁹/L	- Primary: To evaluate safety and tolerability of elritercept as monotherapy or in combination with ruxolitinib in participants with MF - Secondary/Exploratory: To evaluate effects of elritercept on anemia, spleen volume, symptom score, exploratory biomarkers	- Part 1 Dose Escalation complete - RP2D* identified as 3.75 mg/kg Q4W with option to up-titrate to 5 mg/kg Q4W - Part 2 Dose Expansion open and enrolling - Total of 54 participants enrolled as of data cutoff date

*RP2D = recommended part 2 dose.

MF = myelofibrosis; ET = essential thrombocytosis; PV = polycythemia vera; JAK = Janus kinase; Q4W = every 4 weeks, transfusion dependent.

INCA33989: A Mutant-Specific Antibody for Patients with *CALR* Mutation

- INCA33989 has a unique mechanism of action compared with other available therapies
 - INCA33989 is a high-affinity, fully human IgG1 monoclonal antibody that selectively targets mutCALR in complex with TPO-R (MPL) to inhibit cell signaling and proliferation¹

