Selinexor plus ruxolitinib in JAK inhibitor–naïve myelofibrosis: Phase 3 SENTRY trial

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BACKGROUND

XPO1 + JAK inhibition: Targeting key drivers of disease biology in myelofibrosis[1-9]

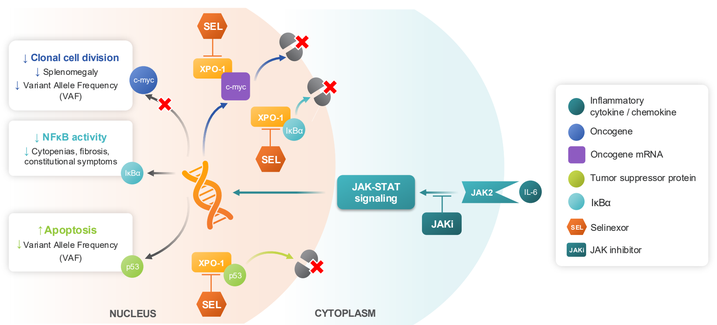
Myelofibrosis pathophysiology
- JAK–STAT activation drives malignant clone proliferation, splenomegaly, and disease-related symptoms
- XPO1 activity is essential for MPN cell survival
- Associated with limited overall survival and progressive clonal evolution

Current standard (ruxolitinib)
- Standard frontline therapy
- Improves splenomegaly and symptoms
- Limited depth and durability of spleen response
- Limited direct impact on clonal burden

Selinexor (XPO1 inhibition)
- Oral selective XPO1 inhibitor
- Restores tumor suppressor function
- Promotes apoptosis and reduction in malignant clonal burden

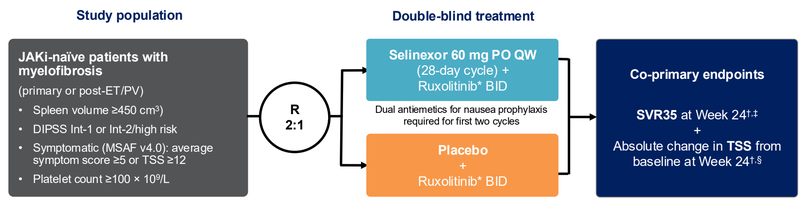
OBJECTIVE: To evaluate the efficacy and safety of selinexor + ruxolitinib in patients with JAK inhibitor–naïve myelofibrosis

Dual targeting of JAK–STAT signaling and XPO1-mediated nuclear export enhances depth of response and may improve disease control



METHODS

Study design of SENTRY
A global, double-blind, randomized, placebo-controlled Phase 3 study



Stratification:
- DIPSS risk: Int-1 vs Int-2 or high risk
- Spleen volume: <1800 cm³ vs ≥1800 cm³ by MRI/CT scan
- Baseline platelet counts: 100–200 × 10⁹/L vs >200 × 10⁹/L

Select secondary endpoints
- **Overall survival**
- **Safety**

Select exploratory endpoint
- **VAF reduction**

Statistical analysis plan
- Sequential testing of co-primary endpoints (one-sided α = 0.025)
  - Stratified CMH for SVR35
  - MMRM for TSS

Data cutoff: February 20, 2026

*Ruxolitinib dose based on platelet count per prescribing information. †Both endpoints are powered at >80%. ‡SVR35 was analyzed using a stratified CMH test according to randomization stratification factors. Odds ratios with 95% confidence intervals and one-sided *P*-values are reported. §TSS measured by the MFSAF v4.0 (excluding fatigue) analyzed using a mixed-effects model for repeated measures that included treatment group, visit, baseline score, and stratification factors. Longitudinal least-squares adjusted means with 95% confidence intervals and one-sided *P*-values are reported.
SENTRY: XPORT-MF-034 (NCT04562389)

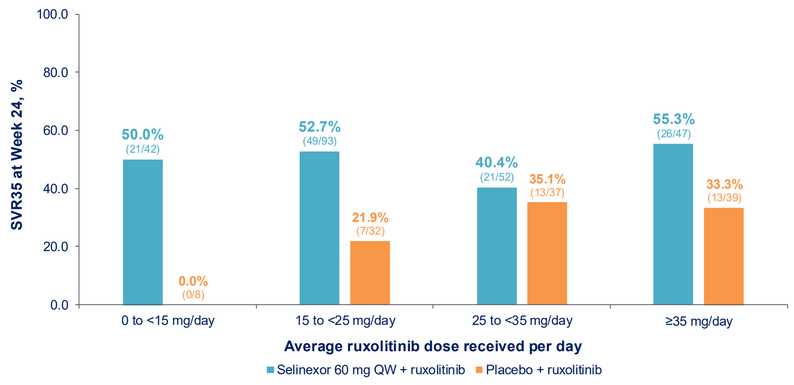
RESULTS

Patient disposition and treatment exposure were similar between arms

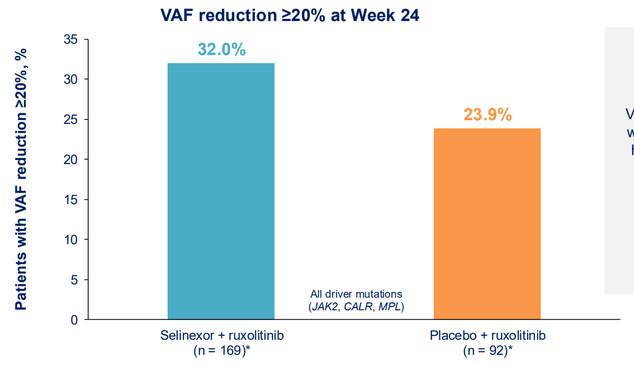
		Selinexor + ruxolitinib	Placebo + ruxolitinib
Patient disposition	Randomized	235	118
	Treated	234 (99.6%)	116 (98.3%)
	Discontinued double-blind treatment*	86 (36.8%)	41 (35.3%)
	Adverse event	21 (9.0%)	10 (8.6%)
	Physician decision†	18 (7.7%)	12 (10.3%)
	Pregnancy	0	1 (0.9%)
	Splenic progression	14 (6.0%)	12 (10.3%)
	Withdrawal by patient	26 (11.1%)	3 (2.6%)
	Transformation to AML	4 (1.7%)	2 (1.7%)
	Other	3 (1.3%)	1 (0.9%)
Treatment exposure	Median weekly selinexor/placebo dose (mg/week)	51.7	60.0
	Median daily ruxolitinib dose (mg/day)	23.0	29.9
	Median follow-up at data cutoff (February 20, 2026)	11.2 months	11.1 months

The study opened for enrollment in June 2023; the first patient was randomized on December 29, 2023, and the last patient was enrolled on September 9, 2025. Percentages reported are based on the number of patients treated. *End of treatment defined as discontinuation of both study treatments. ‡Physician decision included proceed to transplant.

Selinexor maintained spleen responses despite reduced ruxolitinib dosing



Higher rates of driver gene VAF reduction ≥20% with selinexor + ruxolitinib vs ruxolitinib alone as early as Week 24



Association with SVR35
VAF reduction ≥20% was associated with higher likelihood of achieving SVR35

OR 3.22
95% CI: 1.81, 5.72;
nominal one-sided *P* < 0.001

*Cochran-Mantel-Haenszel test stratified by randomization factors. Placebo arm scaled 2:1 to compensate for randomization ratio.

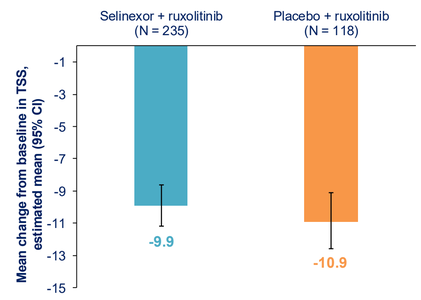
Baseline characteristics were well balanced between treatment arms

Characteristic	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Age, years		
Median (range)	66 (20–86)	67 (33–87)
Sex, n (%)		
Male	142 (60.4)	61 (51.7)
Myelofibrosis subtype, n (%)		
Primary myelofibrosis	119 (50.6)	60 (50.8)
Post-polycythemia vera myelofibrosis	56 (23.8)	26 (22.0)
Post essential thrombocythemia myelofibrosis	59 (25.1)	32 (27.1)
DIPSS, n (%)†		
Intermediate 1	134 (57.0)	64 (54.2)
Intermediate 2	83 (35.3)	41 (34.7)
High risk	18 (7.7)	13 (11.0)
Time since myelofibrosis diagnosis, months		
Median (range)	3.1 (0.3–316.9)	4.4 (0.3–270.2)
Hemoglobin level, g/dL		
Median (range)	11.4 (6.4–18.3)	11.4 (6.7–17.2)
Platelet count, 10^9/L		
Median (range)	325 (67–1313)	324 (101–2001)
Peripheral blasts, %		
Median (range)	0.0 (0.0–9.0)	0.0 (0.0–15.0)
Red blood cell transfusion, n (%)		
Dependent at baseline	14 (6.0)	8 (6.8)

Characteristic	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Molecular profile, n (%)		
JAK2	155 (66.0)	81 (68.6)
CALR	57 (24.3)	21 (17.8)
MPL	13 (5.5)	8 (6.8)
High-molecular risk mutations‡	75 (31.9)	45 (38.1)
Other§	10 (4.3)	8 (6.8)
Bone marrow fibrosis Grade, n (%)*		
Grade 0	5 (2.1)	3 (2.5)
Grade 1	31 (13.2)	11 (9.3)
Grade 2	111 (47.2)	54 (45.8)
Grade 3	76 (32.3)	43 (36.4)
Missing	12 (5.1)	7 (5.9)
ECOG performance status score, n (%)¶		
0	101 (43.0)	52 (44.1)
1	124 (52.8)	61 (51.7)
2	10 (4.3)	5 (4.2)
Spleen volume, cm^3		
Median (range)	1385 (450–9210)	1448 (464–7929)
Mean±SD	1636±1020	1651±1038
TSS (excluding fatigue)		
Median (range)	21.7 (2.1–53.9)	19.6 (3.0–58.3)
Mean±SD	22.7±11.9	22.2±13.0

*Bone marrow was centrally evaluated. †DIPSS comprises four risk categories: low, intermediate-1, intermediate-2, and high risk. ‡High molecular risk genes include *ASXL1, EZH2, IDH1, IDH2, SRSF2, U2AF1*. §Other included multiple driver mutations, triple-negative, and missing. ¶ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability.

No difference in AbsTSS between treatment arms at Week 24
Both arms demonstrated similar improvement in symptoms

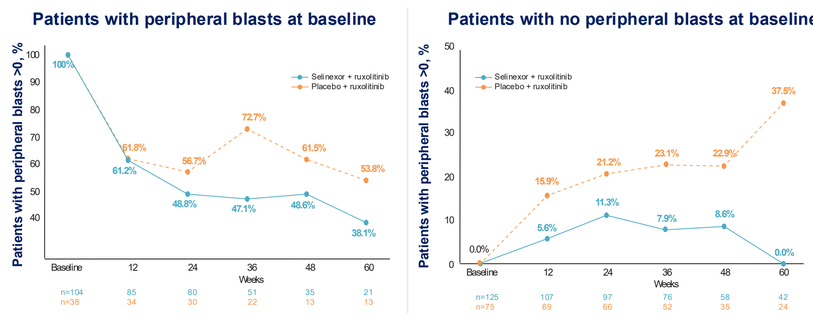


TSS	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Change in absolute TSS at Week 24 Estimated mean (95% CI)	-9.9 (-11.2, -8.6)	-10.9 (-12.6, -9.1)
Adjusted mean difference (95% CI)	0.97 (-1.07, 3.02); one-sided *P* = 0.825	

- **Reductions in TSS were consistent across symptom domains**

Adjusted absolute mean change from baseline, adjusted mean difference, 95% CI, and one-sided *P*-value are based on mixed-effects model for repeated measures adjusted for randomization stratification factors and baseline TSS.

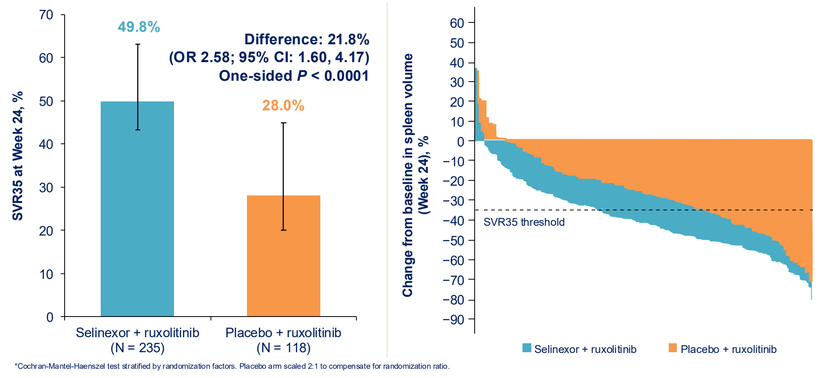
Selinexor + ruxolitinib reduced circulating peripheral blasts vs ruxolitinib alone



- **Reduced circulating peripheral blasts in patients with detectable peripheral blasts at baseline**
- **More patients with 0% peripheral blasts at baseline maintained 0% through the course of treatment**

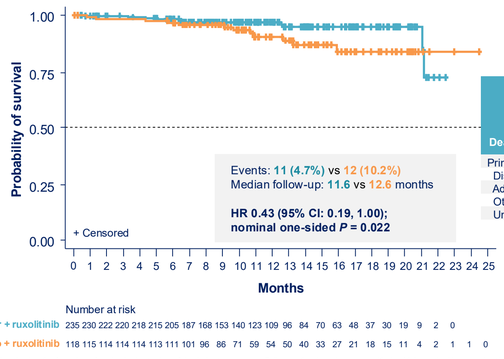
Based on post hoc data analysis.

Significantly higher SVR35 at Week 24 with selinexor + ruxolitinib vs ruxolitinib alone



*Cochran-Mantel-Haenszel test stratified by randomization factors. Placebo arm scaled 2:1 to compensate for randomization ratio.

Meaningful overall survival with selinexor + ruxolitinib vs ruxolitinib alone



Events: 11 (4.7%) vs 12 (10.2%)
Median follow-up: 11.6 vs 12.6 months

HR 0.43 (95% CI: 0.19, 1.00);
nominal one-sided *P* = 0.022

Deaths	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Primary cause of death, n (%)		
Disease progression	3 (1.3)	3 (2.5)
Adverse event	3 (1.3)	5 (4.2)
Other	5 (2.1)	1 (0.8)
Unknown	0	3 (2.5)

OS is defined as the duration from date of randomization to date of death due to any cause. Follow-up time based on reverse Kaplan-Meier method by swapping the censoring status. OS analysis stratified by the randomization stratification factors. Hazard ratio based on Cox Proportional Hazard model with Efron's method of handling ties.

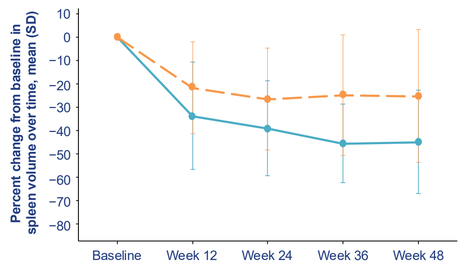
Safety profile was manageable and consistent with known profiles of both agents, and serious AEs were similar between arms

	Selinexor + ruxolitinib (N = 234*)	Placebo + ruxolitinib (N = 116*)
TEAEs, n (%)		
Any Grade	232 (99.1)	113 (97.4)
Grade ≥3	164 (70.1)	58 (50.0)
Serious TEAEs	63 (26.9)	28 (24.1)
Leading to treatment discontinuation†	34 (14.5)	10 (8.6)
Death due to TEAEs‡	2 (0.9)	3 (2.6)

*Three patients total did not receive treatment (n = 1, selinexor; n = 2, placebo) and were excluded from this analysis. †Treatment discontinuation defined as discontinuation of any study treatment, either selinexor/placebo or ruxolitinib. ‡Reasons for death: acute kidney injury, cardiopulmonary failure, drowning, pleural effusion, respiratory failure, and sudden death. TEAEs may reflect contributions from either agent.

Rapid, deep, and sustained spleen volume reduction with selinexor + ruxolitinib vs ruxolitinib alone

Percent change from baseline in spleen volume over time



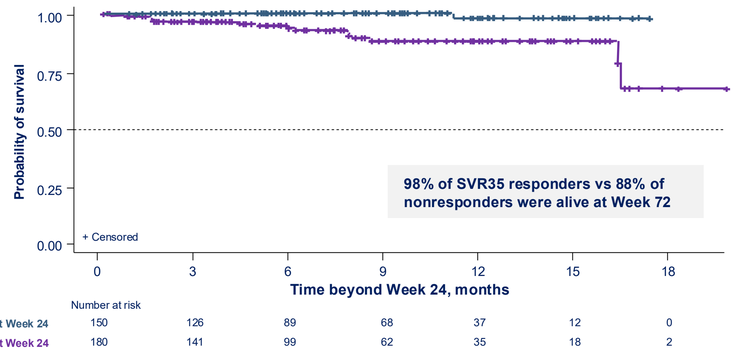
SVR35 rates over time

SVR35*	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Week 12, n (%)	116 (49.4)	24 (20.3)
Week 24, n (%)	117 (49.8)	33 (28.0)
Week 36, n/n1† (%)	97/207 (46.9)	23/100 (23.0)
At any time, n (%)	159 (67.7)	53 (44.9)

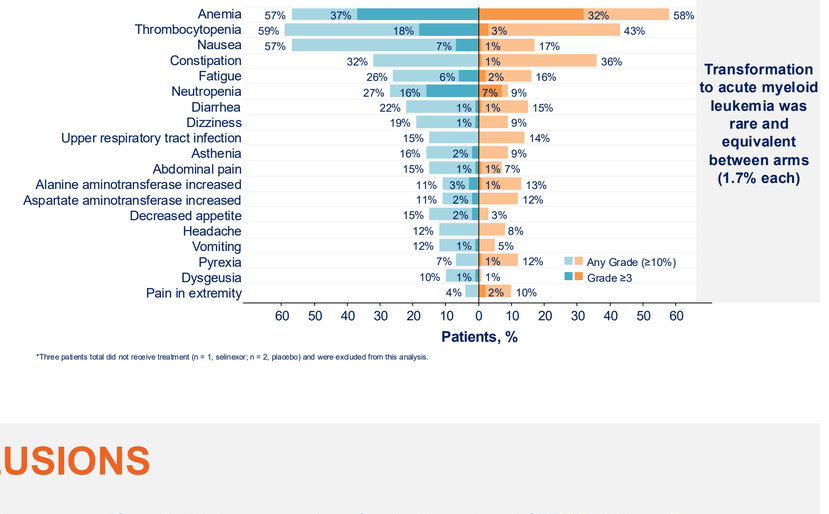
OR 2.59 (95% CI: 1.64, 4.10)
Nominal *P* < 0.0001

*SVR35 at any time defined as proportion of patients with SVR35 to any post-baseline assessment regardless of visit window before any new anti-MF therapy or disease progression. †n1 = number of patients who completed spleen assessment or discontinued the study prior to the specific timepoint.

SVR35 at Week 24 predicted overall survival irrespective of treatment
Landmark analysis at Week 24



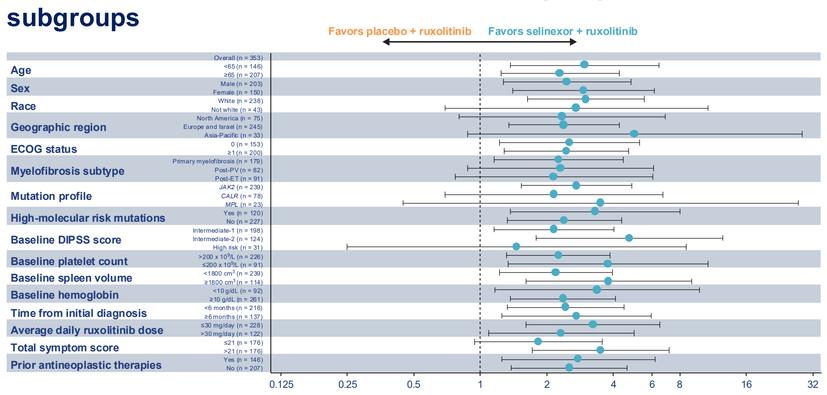
Treatment-emergent adverse events



Transformation to acute myeloid leukemia was rare and equivalent between arms (1.7% each)

*Three patients total did not receive treatment (n = 1, selinexor; n = 2, placebo) and were excluded from this analysis.

Consistent SVR35 benefit observed across prespecified subgroups



CONCLUSIONS

- **Selinexor + ruxolitinib achieved rapid, deep, and sustained spleen volume reductions;** a **significantly higher** proportion of patients achieved **SVR35** at Week 24 vs ruxolitinib alone
  - **Consistent SVR35** across ruxolitinib dosing
- Mean change in **absolute TSS** was **similar** between groups, with meaningful reductions from baseline
- **Meaningful overall survival** was observed
  - **SVR35** at Week 24 predicted **overall survival**
- **Higher** rates of **VAF reduction** were observed with selinexor + ruxolitinib as early as Week 24, supporting a relationship between molecular response and clinical outcomes
- **Safety profile** was **manageable** and consistent with known profile of both agents

Selinexor + ruxolitinib represents a novel treatment strategy in JAK inhibitor–naïve myelofibrosis

ABBREVIATIONS

AbsTSS, absolute total symptom score; AML, acute myeloid leukemia; BID, twice daily; CALR, calreticulin; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; ET, essential thrombocythemia; HR, hazard ratio; Int, intermediate; JAK, Janus kinase; *JAK2*, Janus kinase 2; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MSAF, Myelofibrosis Symptom Assessment Form; MMRM, mixed-effects model for repeated measures; MPL, myeloproliferative leukemia protein; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; OR, odds ratio; OS, overall survival; PO, orally; PV, polycythemia; QW, once weekly; R, randomization; SD, standard deviation; STAT, signal transducer and activator of transcription; SVR35, spleen volume reduction of at least 35% from baseline; TEAE, treatment-emergent adverse event; TSS, total symptom score; VAF, variant allele frequency; XPO1, exportin-1.

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