Poster #MPN-999

A Study to Evaluate Single-Agent Selinexor Versus Physician's Choice in Participants With Previously Treated Myelofibrosis

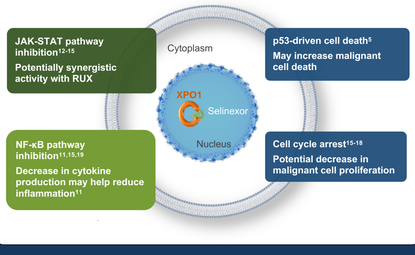
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Introduction

- Myelofibrosis (MF) is a fatal, heterogeneous myeloproliferative neoplasm (MPN) characterized by clinical hallmarks of cytopenias, bone marrow fibrosis, splenomegaly, and constitutional symptoms[1-3]
- While JAK-STAT pathway dysregulation is recognized as a key driver of MF, the clinical benefit of JAK inhibitors (JAKi), the only approved treatment for over a decade, is limited by resistance, insufficient tolerability, and lack of disease-modifying activity[2-4]
- Thus, there is an unmet need for novel therapies targeting disease-relevant pathways beyond JAK-STAT[2]
- Selinexor (SEL), an oral XPO1 inhibitor that has shown promise in preclinical and clinical studies alone and in combination with JAKi, may regulate multiple MF-relevant pathways, including those involved in mediating a proinflammatory tumor micro-environment, which is characterized by elevated levels of cytokines/signaling factors (eg, IL-6, IL-8, TNFα and hepcidin) and anemia that contribute to disease progression and systemic symptom development[5-9]
- This study presents SEL monotherapy vs physician's choice in previously JAKi-exposed patients with MF, a challenging patient population[9,10]

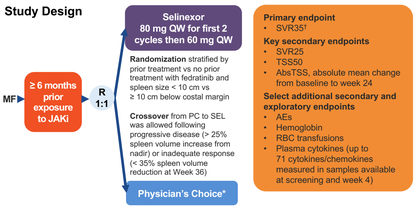
XPO1 Inhibition Is Potentially a Fundamental Mechanism in the Treatment of Myelofibrosis That Targets Both JAK-STAT and Non–JAK-STAT Pathways[5,11-19]



Methods

- This phase 2, global, multicenter, randomized, open-label study evaluated the safety and efficacy of single-agent SEL versus treatment of physician's choice (PC) in patients with previously treated MF (NCT04562870)
  - 16 sites located in China, France, Greece, Hungary, Italy, Poland, Spain, and the United States

Study Design



Primary endpoint
- SVR35†

Key secondary endpoints
- SVR25
- TSS50
- AbsTSS; absolute mean change from baseline to week 24

Select additional secondary and exploratory endpoints
- AEs
- Hemoglobin
- RBC transfusions
- Plasma cytokines (up to 71 cytokines/chemokines measured in samples available at screening and week 4)

Intent-to-treat (ITT) population: all patients randomized to study treatment

Efficacy evaluable (EE) population: SEL-treated patients (inclusive of crossover patients) or PC patients who had a spleen volume assessment at anytime or > 0 TSS at baseline and any non-missing TSS evaluations post-baseline, respectively

All selinexor treated population: EE population including crossover patients

*Physician's choice included RUX treatment, fedratinib, chemotherapy (e.g., hydroxyurea), anagrelide, corticosteroid, hematopoietic growth factor, androgen, interferon, and may include supportive care only with no MF treatment; no investigational therapies allowed.

†Spleen response rate (defined as SVR35) will be analyzed and compared between the two treatment arms using the ITT population per IRC assessment evaluated after all patients received at least 24 weeks of treatment or discontinued treatment. Analyses of endpoints was nominal only.

- Enrollment was limited to 24 patients (SEL, n=12; PC, n=12) in mid-2023 to focus on the phase 3 trial of SEL + RUX in patients with JAKi-naïve MF (SENTRY)

Conclusions

- XPO1 inhibition by selinexor targets multiple fundamental mechanisms underlying the four key hallmarks of MF with the potential for disease modification[5,11-19]
- These data demonstrate that selinexor monotherapy has the potential for:
  - Spleen volume reduction and symptom improvements in previously JAKi-exposed patients with myelofibrosis, including those refractory to JAKi
  - Stabilization and, in some cases, improvement of hemoglobin levels, resulting in reduced transfusion burden, in contrast to PC
  - Reduction of pro-inflammatory cytokines associated with myelofibrosis constitutional symptoms and anemia
- Selinexor monotherapy was generally well tolerated, with no TEAEs leading to treatment discontinuation
- The effects of XPO1 inhibition on pathways beyond those impacted by JAKi suggests potential monotherapy activity as well as additive if not synergistic effects in combination with JAKi, supporting the ongoing Phase 2 SENTRY-2 trial of single-agent selinexor (NCT05980806) and the Phase 3 SENTRY trial of selinexor plus RUX combination (NCT04562389) in JAKi-naïve MF

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Abbreviations: AbsTSS, absolute mean change from baseline to week 24 with last observation carried forward imputation for missing data at week 24; AE, adverse event; AUC, area under the curve; BID, twice a day; C1D1, cycle 1 day 1; C_{max}, maximum concentration; DIPSS, Dynamic International Prognostic Scoring System; EE, efficacy evaluable; EOT, end of treatment; ePRO, electronic **patient-reported** outcome; ET, essential thrombocytopenia; IRC, Independent Radiology Committee; ITT, intent-to-treat; JAK, janus kinase; JAKi, janus kinase inhibitor; MF, myelofibrosis; MFSAF v4.0, Myelofibrosis Symptom Assessment Form version 4.0; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PC, physician's choice; PV, polycythemia vera; QW, once weekly; R, randomization; RBC, red blood cell; RUX, ruxolitinib; SD, standard deviation; SEL, selinexor; SVR, spleen volume reduction; SVR25, spleen volume reduction ≥ 25%; SVR35, spleen volume reduction ≥ 35%; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TSS, Total Symptom Score; TSS50, Total Symptom Score reduction of ≥ 50%.

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Results

- Data cut off: October 31, 2024
- Demographics and baseline characteristics for the two arms were similar
- Patient population was heavily pretreated with 2 mean prior lines of therapy in both arms

Demographics and Baseline Disease Characteristics

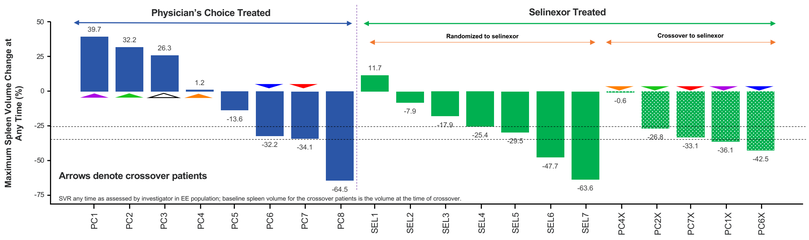
	PC (n=12)	SEL (n=12)	Total (N=24)
Age, years, median (min, max)	71 (60, 79)	70 (43, 78)	70 (43, 79)
Age category			
18–50	0	1 (8)	1 (4)
51–64	3 (25)	4 (33)	7 (29)
65–74	6 (50)	5 (42)	11 (46)
≥ 75	3 (25)	2 (17)	5 (21)
Sex, n (%)			
Male	5 (42)	9 (75)	14 (58)
Female	7 (58)	3 (25)	10 (42)
MF type, n (%)			
Post-PV MF	4 (33)	3 (25)	7 (29)
Post-ET MF	3 (25)	3 (25)	6 (25)
Primary MF	5 (42)	6 (50)	11 (46)
Region			
United States	0 (0)	3 (25)	3 (12)
European Union	9 (75)	6 (50)	15 (63)
China	3 (25)	3 (25)	6 (25)
Baseline spleen volume (cm³), mean (SD)	2373 (1410)	1870 (910)	2132 (1198)

- Mean (SD) time on treatment 9.3 (10.5) months for SEL and 6.7 (7.2) months for PC (9/12 PC patients received RUX or a RUX combo as their PC option)
- 6 patients crossed over from PC to SEL due to progressive disease or lack of response
- 2 patients (SEL2 and SEL6) are still on SEL treatment after ~2 years, and 1 patient (PC8) is still on RUX after ≥ 2 yrs

	PC (n=12)	SEL (n=12)	Total (N=24)
Screening DIPSS, n (%)			
Intermediate 1	2 (17)	6 (50)	8 (33)
Intermediate 2	8 (67)	3 (25)	11 (46)
High risk	2 (17)	3 (25)	5 (21)
Time from last prior treatment to randomization, weeks, median (min, max)	6 (3, 49)	5 (3, 52)	6 (3, 52)
Number of prior lines of treatment, mean (min, max)*	2 (1, 3)	2 (1, 4)	2 (1, 4)
Driver mutation, n (%)			
JAK2	8 (67)	9 (75)	17 (71)
CALR	2 (17)	1 (8)	3 (13)
Triple negative	2 (17)	2 (17)	4 (17)
TSS†, mean (SD)	17.1 (15.3)	18.6 (14.4)	NA
Hemoglobin‡ (g/dL), mean (SD)	9.4 (1.9)	10.3 (2.2)	NA

*11/12 SEL patients and 11/12 PC patients received RUX or other JAKi as most recent prior therapy, prior to randomization. †Based on the Myelofibrosis Symptom Assessment Form version 4.0 (excluding fatigue) in patients with nonzero baseline score (SEL: n=8; PC: n=11). ‡Baseline hemoglobin calculated based on the rolling mean.

Spleen Volume Reduction and Symptom Improvement With Selinexor Monotherapy Compared With PC (Efficacy Evaluable)

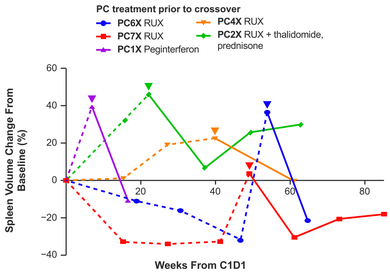


- In the efficacy evaluable population, greater SVR rates were observed with SEL monotherapy compared with PC
  - 11/12 patients in SEL had SVR vs 4/8 in PC

Spleen volume reduction	PC	SEL
Intention to treat		
SVR25 at Week 24, n/N (%)	2/12 (17%)	3/12 (25%)
SVR35 at Week 24, n/N (%)	1/12 (8%)	1/12 (8%)
Efficacy evaluable		
SVR25 at any time, n/N (%)	3/8 (38%)	8/12 (67%)
SVR35 at any time, n/N (%)	1/8 (13%)	4/12 (33%)

Efficacy evaluable patients (inclusive of crossover patients).
SVR any time assessed by investigator. For crossover patients, SVR was calculated based on new spleen volume baseline at time of crossover.

Patients Refractory or Intolerant to PC Achieved Spleen Volume Reduction After Crossover to Selinexor Monotherapy



Arrow denotes crossover baseline timepoint. Dotted line represents PC treatment before crossover; solid line represents SEL treatment after crossover. For crossover patients, all spleen volume changes were calculated based on baseline at screening timepoint. 5/6 patients received 80 mg and 1/6 received 60 mg (prior peginterferon) as initial SEL dose. One patient withdrew consent shortly after crossover to SEL arm and is not included in analysis.

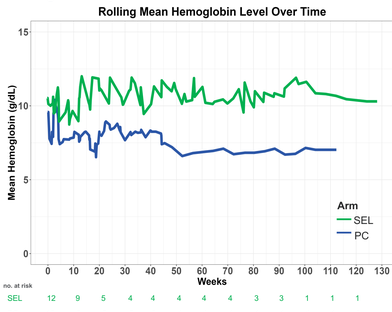
- Median time from last PC treatment to crossover was 3 weeks
- All crossover patients who were evaluable had observable decrease in spleen volume
  - 4/5 patients who crossed over to SEL achieved SVR25
  - 4/5 efficacy-evaluable patients who crossed over to SEL received RUX as PC

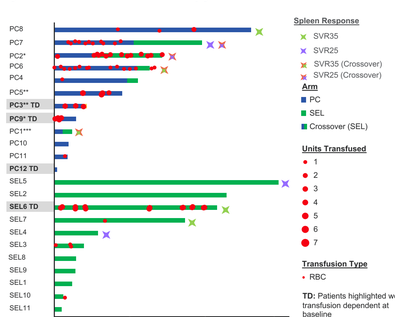
Total Symptom Score response	PC	SEL	All SEL treated
TSS50 at Week 24, n/N (%)	0/9	2/7 (29%)	2/11 (18%)
Baseline TSS, mean (SD)	17.3 (17.1)	18.8 (15.6)	17.6 (15.5)
AbsTSS at Week 24, mean (SD)	-0.0 (5.4)	-5.9 (14.0)	-3.7 (15.6)

TSS evaluable population: >0 TSS at baseline and any non-missing TSS evaluations post-baseline; patients with missing data at week 24 were considered non-responders. All SEL treated includes patients who crossed over from PC to SEL.
Note: Fatigue is excluded from TSS analysis. When multiple scores entered on the same date, the average of the scores used.

- Symptom improvements (TSS50 and AbsTSS) were observed in patients who received SEL monotherapy but not PC
- Changes in TSS at Week 24 in two evaluable patients after crossover were -3.8 and +20.0

Hemoglobin Improvements and Reduced Transfusion Frequency With Selinexor Monotherapy





TD: Patients highlighted were transfusion dependent at baseline
*RUX combo
**Danazol/prednisone/folic acid
***Peginterferon

At data cutoff, mean hemoglobin value was higher in the SEL arm compared to PC
- Change from rolling mean baseline in SEL was +1.7% compared with PC -26.7%

- Hemoglobin improvements* were achieved by 3/12 (25%) patients in SEL vs 1/12 (8%) patients in PC

*Hemoglobin improvements defined as Hgb change from baseline ≥ 1.5 g/dL without transfusions in the preceding 12 weeks.

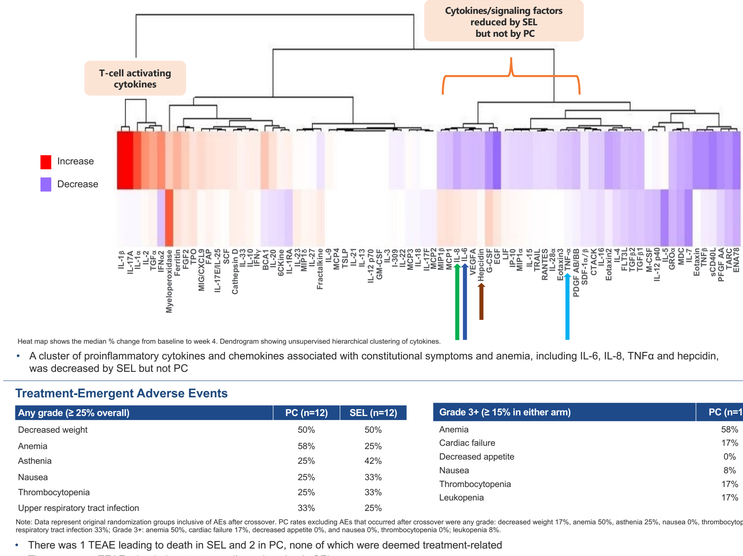
	Units transfused	Total months	Avg transfused units per month
PC (n=12)	91	80	1.14
SEL*,† (n=11)	59.5	111	0.54

*One patient in SEL only received 1 dose but was later transfused with 9 units. This patient is excluded.
†Does not include SEL after crossover.

Cytokines and Chemokines Relevant to Myelofibrosis Decreased With Selinexor Monotherapy

Cytokines associated with MF pathogenesis and constitutional symptoms → **IL-6 median change: SEL -29%; PC+19%**; **IL-8 median change: SEL -37%; PC+25%**; **TNFα median change: SEL -25%; PC-4%**

Signaling factor associated with anemia → **Hepcidin median : SEL -30%; PC+6%**



Heat map shows the median % change from baseline to week 4. Dendrogram showing unsupervised hierarchical clustering of cytokines.

- A cluster of proinflammatory cytokines and chemokines associated with constitutional symptoms and anemia, including IL-6, IL-8, TNFα and hepcidin, was decreased by SEL but not PC

Treatment-Emergent Adverse Events

Any grade (≥ 25% overall)	PC (n=12)	SEL (n=12)
Decreased weight	50%	50%
Anemia	58%	25%
Asthenia	25%	42%
Nausea	25%	33%
Thrombocytopenia	25%	33%
Upper respiratory tract infection	33%	25%

Grade 3+ (≥ 15% in either arm)	PC (n=12)	SEL (n=12)
Anemia	58%	17%
Cardiac failure	17%	0%
Decreased appetite	0%	17%
Nausea	8%	17%
Thrombocytopenia	17%	0%
Leukopenia	17%	8%

Note: Data represent original randomization groups inclusive of AEs after crossover. PC rates excluding AEs that occurred after crossover were any grade: decreased weight 17%, anemia 50%, asthenia 25%, nausea 0%, thrombocytopenia 8%, and upper respiratory tract infection 33%; Grade 3+: anemia 50%, cardiac failure 17%, decreased appetite 0%, and nausea 0%, thrombocytopenia 0%; leukopenia 8%.

- There was 1 TEAE leading to death in SEL and 2 in PC, none of which were deemed treatment-related
- There were no TEAEs that led to treatment discontinuation in SEL