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Long-term Response to Selinexor in Patients with Myelofibrosis and Refractory or Intolerant to JAK Inhibitors: Follow-up Results of a Single Center, Phase II, Investigator-initiated Trial (IIT).

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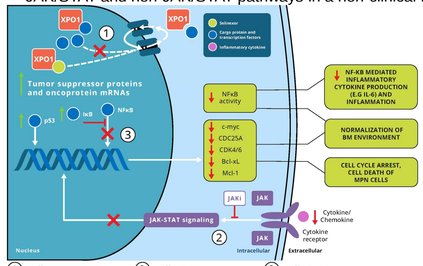
INTRODUCTION

- Selinexor is a targeted inhibitor of the nuclear export protein XPO1.
- It has selective activity against primary myelofibrosis cells and decreased myeloproliferation in a *JAK2*^{V617F}-driven mouse model, presenting a compelling justification for clinical investigation in myelofibrosis.
- Selinexor-mediated XPO1 inhibition can mechanistically modulated JAK/STAT and non-JAK/STAT pathways in a non-clinical model.



① **Selinexor** inhibition of XPO1-mediated nuclear cargo protein export

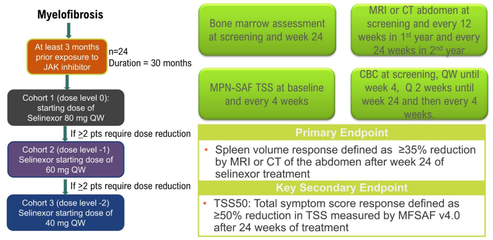
② **Selinexor** mediated JAK-STAT pathway inhibition

③ **Selinexor** mediated NF-κB pathway inhibition P53-driven cell death Cell cycle arrest

AIM & METHODS

Aim: To determine the single agent efficacy of selinexor for treatment of patients with MF who are refractory or intolerant to JAK inhibitors.

ESSENTIAL Trial Design



- MF patients refractory or intolerant to ruxolitinib (RUX) were treated with selinexor, given orally at a starting dose of 80, 60 mg or 40 mg once a week (NCT03627403). Antiemetics were administered as needed.
- The primary endpoint is the rate of ≥ 35% spleen volume reduction (SVR) at week 24 as assessed by MRI or CT abdomen.
- The circulating levels of 53 cytokines were assessed using the human 48-plex cytokine panel A, TGFB, Ferritin and Hepcidin panels. A total of 48 different plasma samples from 17 patients taken at baseline (BL), week 12, week 24, and end of treatment (EOT) were assessed.

RESULTS

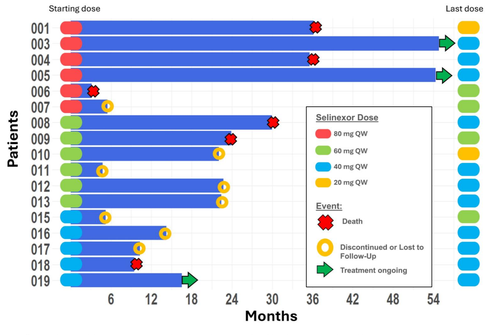
- 17 patients were treated on this study, with starting doses of selinexor from 40mg QW to 80mg QW. Three patients remain on treatment as of August 2024.

Table 1. Patient Characteristics

	Treated Patients (N=17)
Age (years), median (range)	66 (43-80)
Duration of prior JAKi therapy (months), median (range)	13 (0.5-96)
Female, n (%)	8 (47)
DIPSS risk, n(%)	
low	1
intermediate-1	7
intermediate-2	9
Driver Mutation, n (%)	
JAK2	11
CALR	5
MPL	1
HMR, n (%)	10 (59)

DIPSS, Dynamic International Prognostic Scoring System; HMR, High Molecular Risk

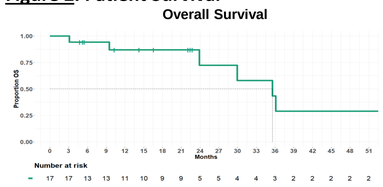
Figure 1. Treatment Duration and Disposition



For patients with treatment ongoing, last dose received is shown as colored bar

- Median overall survival was 35 months (range 2.8 to 54.8 months).
- Median progression-free survival was not reached (not shown)

Figure 2. Patient Survival



- Many Patients Experience Symptom Score Reductions
- Some Patients were Enrolled with low TSS at Baseline

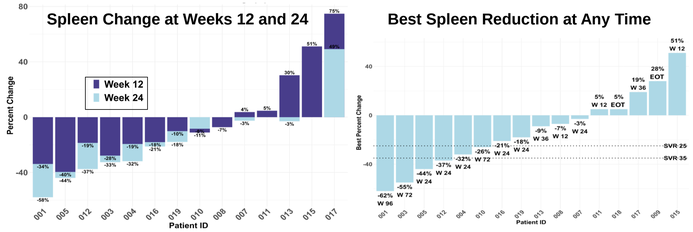
Table 2. Total Symptom Score Changes

Patient Number	TSS at Baseline	Lowest TSS (% from Baseline)	TSS at Week 24 (% from Baseline)	Time of Lowest TSS
005	30	3(-90%)	17 (-43%)	C43D1
001	66	7(-89%)	7(-89%)	C7D1
017	58	14 (-76%)	23 (-60%)	C5D1
008	20	8 (-60%)	NE	C4D1
011	22	10 (-54%)	NE	C1D8
012	70	36 (-49%)	40 (-43%)	C5D1
015	15	9 (-40%)	NE	EOT (C6D8)
013	23	16 (-30%)	45 (95%)	C6D1
009	14	11 (-21%)	NE	C3D1
007	28	23 (-18%)	32 (14%)	C6D1
018	77	63 (-18%)	NE	C2D1
019	43	36 (-16%)	43 (0%)	C3D1/C4D1
006	35	37 (6%)	NE	C2D1
004	4	16 (300%)	37 (+825%)	C6D1
010	0	3 (infinte)	3 (infinite)	C7D1/EOT
003	NE	NE	NE	NE
016	NE	19 (NA)	NE	C6D22/EOT

NA, not applicable, NE, not evaluated

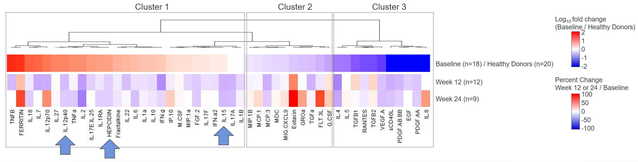
- At week 24, 3 of 11 patients had ≥ 35% SVR and 5 of 11 pts had ≥ 25% SVR.
- Long-term, durable, spleen volume reductions were observed.

Figure 3. Spleen Volume Changes



- Clustering of cytokine changes defined three broad clusters, with cluster 1 showing increases in baseline levels compared to healthy donors
- Decreases in pro-inflammatory cytokines were observed with a median reduction in cytokine levels, most prominently in cluster 1.
- Important MF-related cytokines were reduced, including a median 20% reduction was seen in hepcidin from BL to week 12, 34% in IL-15, and 29% in IL-12p40.

Figure 4. Median Changes in Circulating Cytokines



- Two patients have received selinexor for more than 4 years and remain on study
- One patient (003) who was initially transfusion dependent became transfusion independent while on study and maintained independence for more than 1 year
- Several patients experienced stabilization. One patient (013) requiring concomitant hydroxyurea treatment.

Figure 5. Hemoglobin levels

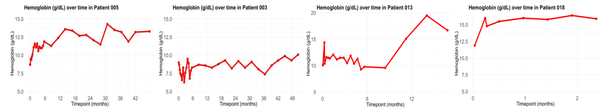


Table 3. Treatment-Emergent Adverse Events

Adverse Event	Number of patients, %
Grade 3 or Higher (>10%)	
Anemia	4 (24%)
Fatigue	4 (24%)
Flu-Like Symptoms	2 (12%)
Thrombocytopenia	2 (12%)
Weight Loss	2 (12%)
Anorexia	2 (12%)
Dizziness	2 (12%)
Dyspnea	2 (12%)
Hypoxia	2 (12%)
Hypertension	2 (12%)
Grade 1-2 (>20%)	
Nausea	15 (88%)
Fatigue	11 (65%)
Anorexia	11 (65%)
Diarrhea	10 (59%)
Dysgeusia	8 (47%)
Abdominal Pain	7 (41%)
Dizziness	7 (41%)
Weight Loss	7 (41%)
Vomiting	7 (41%)

CONCLUSION

- Long-term administration of selinexor was feasible, dose reduction was possible without loss of spleen response, in MF patients. Long-term stabilization of hemoglobin was observed in several patients.
- Selinexor treatment led to a reduction in hepcidin and pro-inflammatory cytokines in MF, especially cytokines regulated by NF-κB activity (IL-15, IL-12p40 and others), consistent with selinexor's proposed mechanism of action.
- A Phase 2 trial of selinexor monotherapy (NCT05980806) is currently ongoing in JAK inhibitor–naïve MF patients.

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