Abstract/Poster MPN-527

Selinexor plus ruxolitinib impact on symptom burden in patients with myelofibrosis and potential mechanism of action via inhibition of NF-κB and activation of p53 pathways

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Introduction

- Selinexor, an investigational, first-in-class oral selective exportin 1 (XPO1) inhibitor, in combination with ruxolitinib in JAK inhibitor–naïve patients with MF, in a phase 1 trial has shown rapid, deep, and sustained spleen and symptom responses with an associated reduction in markers of disease burden, including a reduction in variant allele frequency (VAF)[1]
- Ruxolitinib and other Janus kinase (JAK) inhibitors, the standard of care in intermediate- and high-risk myelofibrosis (MF), primarily target the JAK/STAT pathway commonly overactivated in MF, but their ability to modify the disease and impact overall survival remains unclear[2]
- Understanding overlap of spleen and symptom responses with molecular pathway(s) responsible for potential synergy between selinexor and ruxolitinib may provide a better determination of the most appropriate use of these agents
- Here, we elucidate the molecular pathways impacted by XPO1 inhibition and relevant to MF that may lead to clinically meaningful improvements in spleen volume reduction and symptom burden

Methods

SENTRY (XPORT-MF-034) Study Design (NCT04562389)

Phase 1a
Dose escalation

Phase 1b
Dose expansion

Selinexor PO
40 mg QW
+
ruxolitinib*
N = 3

Selinexor PO
60 mg QW
+
ruxolitinib*
N = 3

Selinexor PO
40 mg or 60 mg QW
+
ruxolitinib*
N = 18

Primary endpoints:
- Maximum tolerated dose/ recommended Phase 3 dose
- Safety (AEs)

Select secondary endpoints:
- SVR35
- TSS50
- Anemia response

*Ruxolitinib dosing per label

Nonclinical methods

- Selinexor and ruxolitinib were assessed as single agents or in combination in human myeloproliferative neoplasm (MPN) cell lines (UKE-1, ELF-153) with varied *JAK2*^{V617F} and *TP53* mutations (*TP53*mut). Impact on cytokine production was measured in drug-treated polarized THP-1 cells

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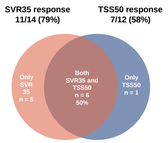
For comments or questions, please contact Srinivas K Tantravahi at Srinivas.Tantravahi@hci.utah.edu

Results

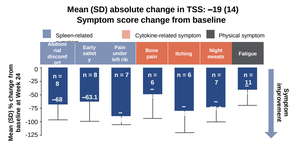
- As of February 1, 2024, 14 patients with JAKi-naïve MF received at least one dose of selinexor 60 mg plus ruxolitinib in Phase 1 of SENTRY
  - Mean treatment duration: 55.6 weeks (range 9-117)
- Most common AEs (any grade) were nausea (79%), anemia (64%), thrombocytopenia (64%), fatigue (57%), and constipation (57%); nausea was transient in nature with a median duration of approximately two cycles
- After the maximum follow-up time of 86 weeks for spleen volume reduction (SVR) and 85 weeks for total symptom reduction (TSS), the probabilities of maintaining SVR and TSS response in the 60 mg cohort were both 100%

Majority of patients in SENTRY Phase 1 achieved both SVR35 and TSS50; symptom score reductions were observed across all subdomains

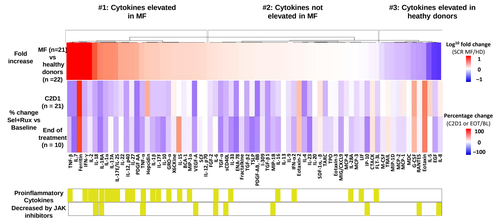
Overlap of SVR35 and TSS50 response at Week 24



Symptom improvement at Week 24

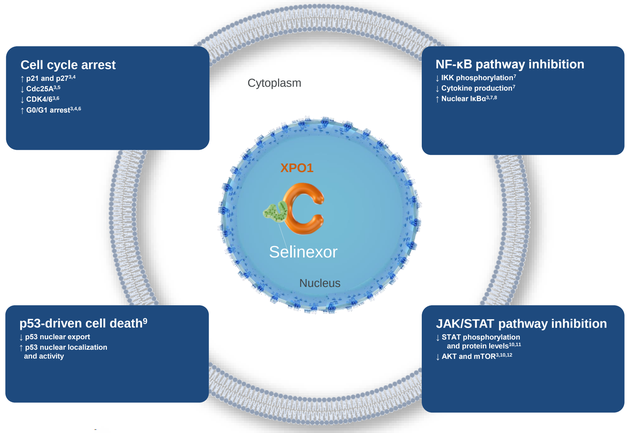


Selinexor (40 mg or 60 mg QW) plus ruxolitinib decreased NF-κB– and inflammation-related cytokines in patients with MF



- Decrease of NFκB-related proinflammatory cytokines elevated in MF patients was rapid (C2D1) and durable (end of treatment)
- Reduction in proinflammatory cytokines may help alleviate symptom burden and impact disease modification

Selinexor's pluripotent mechanism of action has the potential to synergize with ruxolitinib in heterogeneous diseases like MF by targeting both JAK and non-JAK pathways



Cell cycle arrest
↑ p21 and p27[3,4]
↓ Cdc25A[3,5]
↓ CDK4/6[3,6]
↑ G0/G1 arrest[3,4,6]

NF-κB pathway inhibition
↓ IKK phosphorylation[7]
↓ Cytokine production[7]
↑ Nuclear IκBα[3,7,8]

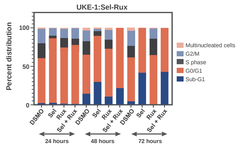
p53-driven cell death[9]
↓ p53 nuclear export
↑ p53 nuclear localization and activity

JAK/STAT pathway inhibition
↓ STAT phosphorylation and protein levels[10,11]
↓ AKT and mTOR[1,10,12]

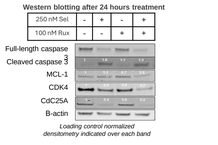
In nonclinical studies, selinexor:
- Increased malignant cell death in human MF cells[9]
- Reduced activity of the proinflammatory NF-κB pathway[7]
- Increased apoptosis of *JAK2*mut MF CD34+ cells but not of healthy donor cells[13]
- Showed synergism with ruxolitinib and other therapeutic agents in cell lines with or without *JAK2*^{V617F} and *TP53* mutations[14]

Cell cycle arrest induced by selinexor with or without ruxolitinib leads to apoptosis in MPN cells

Cell cycle analysis



Caspase activation and cell cycle proteins

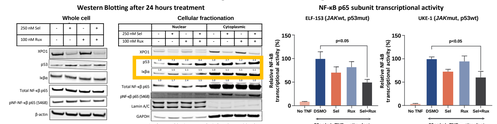


Antiproliferative activity

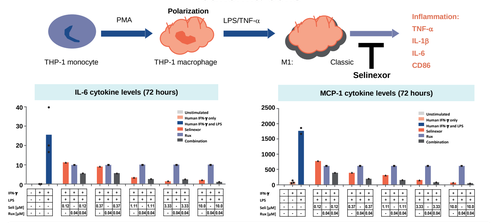
Line	Selinexor IC_{50} (nM) (72 hours)	Ruxolitinib IC_{50} (nM) (72 hours)	Combination analysis (Bliss model) *Synergy ≥10, additivity 0-10*	
			Selinexor range	Ruxolitinib range
ELF-153 (*JAK2*wt; *TP53*mut)	689.8	28,389.7	0-4 μM	0-20 μM
			3.01 (additive)	
UKE-1 (*JAK2*^{V617F}; *TP53*wt)	703.9	168.9	0-0.1 μM	0-20 μM
			11.89 (synergistic)	

p53-mediated cell cycle regulation leading to apoptosis may explain the reduction in VAF seen in patients in SENTRY Phase 1

Selinexor-induced nuclear sequestration of p53 and IκBα and reduced transcriptional activity of NF-κB



Potent suppression of proinflammatory cytokines IL-6 and MCP-1 by selinexor + ruxolitinib following LPS stimulation in THP-1 leukemia cells



Reductions in plasma cytokines levels seen in patients with SENTRY Phase 1 may be attributed to the inhibition of NF-κB–driven proinflammatory cytokine production

Conclusions

- Selinexor plus ruxolitinib was well-tolerated, with promising signals of durable reductions in symptom burden and spleen volume
- The non-clinical results point to a pleiotropic mechanism of action in which XPO1 inhibition targets multiple oncogenic pathways beyond JAK/STAT, including inhibition of NF-κB-driven proinflammatory cytokines and p53-mediated cell cycle regulation leading to apoptosis, that may explain the efficacy of selinexor in combination with ruxolitinib in MF
- A Phase 3 trial of selinexor 60 mg in combination with ruxolitinib (SENTRY Phase 3; NCT04562389) and a Phase 2 of selinexor monotherapy (SENTRY-2 [XPORT-MF-044]; NCT05980806) are currently evaluating selinexor as the backbone therapy in JAK inhibitor–naïve patients with MF

References **1.** Tantravahi SK, et al. *Blood*. **2.** Levavi H, et al. *Clin Adv Hematol Oncol*. 2022. **3.** Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018. **4.** Gravina GL, et al. *BMC Cancer*. 2015. **5.** Garg M, et al. *Oncotarget*. 2017 **6.** Tan M, et al. *Am J Physiol Renal Physiol*. 2014. **7.** Kashyap T, et al. *Oncotarget*. 2016.
8. Turner JG, et al. *Oncotarget*. 2016. **9.** Yan D, et al. *Clin Cancer Res*. 2019. **10.** Walker CJ, et al. *Blood*. 2013. **11.** Cheng Y, et al. *Mol Cancer Ther*. 2014. **12.** Argueta C, et al. *Oncotarget*. 2018. **13.** Lu M, et al. Poster presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023. **14.** Maloof M, et al. Poster presented at: 15th International Congress for Myeloproliferative Neoplasms; November 2-3, 2023.
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Abbreviations: AE, adverse event; C2D1, cycle 2 day 1; BL, baseline; DMSO, dimethyl sulfoxide; LPS, lipopolysaccharide; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PMA, phorbol 12-myristate 13 acetate; PO, orally; QW, once weekly; Rux, ruxolitinib; SD, standard deviation; Sel, Selinexor; SVR, spleen volume reduction; TSS, total symptom reduction; VAF, variant allele frequency; XPO1, exportin 1.