Abstract/Poster #107

Selinexor-Driven Regulation of Proinflammatory Cytokines May Lead to Stabilization of Hematologic Parameters and Bone Marrow Function in Patients With Myelofibrosis: Case Studies From the Phase 1 SENTRY Trial

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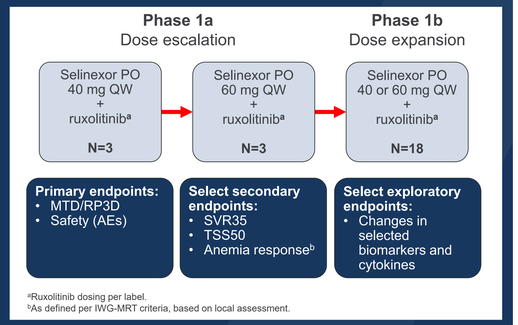
Introduction

- Ineffective bone marrow (BM) erythropoiesis and associated anemia can lead to extramedullary hematopoiesis, which, along with splenomegaly and constitutional symptoms, are key hallmarks of MF[1]
  - These disease characteristics are regulated by multiple proinflammatory cytokines that are elevated with MF[1]
- Selinexor, an investigational, first-in-class oral selective inhibitor of XPO1, in combination with ruxolitinib in JAKi-naive patients with MF, has shown rapid, deep, and sustained spleen and symptom responses with associated reductions in proinflammatory cytokines and VAFs of driver genes (*JAK2*, *CALR*, and *MPL*)[2-4]
- We previously demonstrated that selinexor has a pluripotent mechanism of action in which XPO1 inhibition targets multiple JAK/STAT and non-JAK/STAT oncogenic pathways, including inhibition of NF-κB–driven proinflammatory cytokines and p53-mediated cell cycle regulation leading to apoptosis, which may explain the efficacy and synergy of selinexor in combination with ruxolitinib[3,5]
- Here, we present case studies of 2 patients from the Phase 1 portion of SENTRY (NCT04562389); these patients received long-term treatment and showed evidence of general improvement in BM parameters, with supporting in vitro characterization of selinexor dose-dependent effects on TGF-β/SMAD and TNF-α/IL-6/MCP1 synthesis

Methods

- Patient profiles from the Phase 1 portion of the SENTRY (NCT04562389) study of selinexor (40/60 mg QW) plus ruxolitinib in patients with treatment-naive MF include safety/tolerability, spleen volume changes (SVR35), and symptom improvements (TSS50 based on modified Myelofibrosis Symptom Assessment Form v4.0, [fatigue excluded]), anemia improvement/hemoglobin increase, driver gene VAF changes, and cytokine plasma levels

Phase 1 Study Design



[a]Ruxolitinib dosing per label.
[b]As defined per IWG-MRT criteria, based on local assessment.

- BM biopsies were obtained at screening and at Week 24; slide pairs were stained centrally for reticulin, CD61, and CD71, and independent digital images of stained BM slides were evaluated to calculate the density and spatial analysis of megakaryocytes (MKs), the percentage of CD71-positive erythroid (ERY) cells, and the area of reticulin fibers
- Nonclinical methods
  - TGF-β/SMAD pathway activity was assessed using HEK-Blue™ TGF-β reporter cells
  - Production of MF-related cytokines was assessed using polarized THP-1 cells
- Peripheral blood cytokines from 22 patients were clustered into 3 groups based on their levels at the screening visit compared with those of 20 healthy donors
  - For the 2 cases presented here, each cytokine plasma level after 4 weeks of selinexor plus ruxolitinib treatment was compared with the cytokine plasma level at the screening visit

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Results

Case studies from SENTRY Phase 1

Patient characteristics used to determine high-risk status (MIPSS70)

Patient 1

Risk Criteria	Result	Risk Criteria	Result
Severe anemia (hemoglobin <8 g/dL)	10.3	CALR type 1/like mutation	Absent
Moderate anemia (hemoglobin 8–10 g/dL)	10.3	HMR category	No
Leukocytosis (leukocyte count >25×10⁹/L)	178	Unfavorable karyotype	Normal karyotype
Thrombocytopenia (platelet count <100×10⁹/L)	192	MIPSS70	High
Peripheral blood blast count ≥2%	1%	MIPSS-plus v2.0	Intermediate
BM fibrosis grade ≥2	MF-2	Driver mutation	*JAK2*^{V617F}; 51% VAF
Constitutional symptoms (TSSv4)	42		

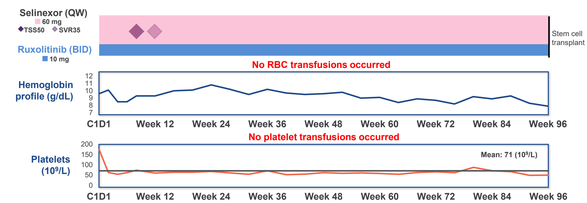
Patient 2

Risk Criteria	Result	Risk Criteria	Result
Severe anemia (hemoglobin <8 g/dL)	9.7	CALR type 1/like mutation	Absent
Moderate anemia (hemoglobin 8–10 g/dL)	9.7	HMR category	No
Leukocytosis (leukocyte count >25×10⁹/L)	61	Unfavorable karyotype	No[a]
Thrombocytopenia (platelet count <100×10⁹/L)	305	MIPSS70	High
Peripheral blood blast count ≥2%	NA	MIPSS-plus v2.0	High
BM fibrosis grade ≥2	MF-1	Driver mutation	JAK2^{V617F}; 86% VAF
Constitutional symptoms (TSSv4)	45		

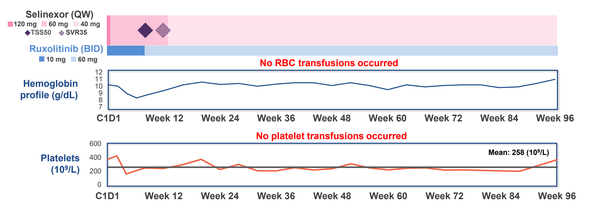
[a]46,XX,DEL(20)(q11.2q13.1)[20].

Selinexor exposure and efficacy

Clinical profiles

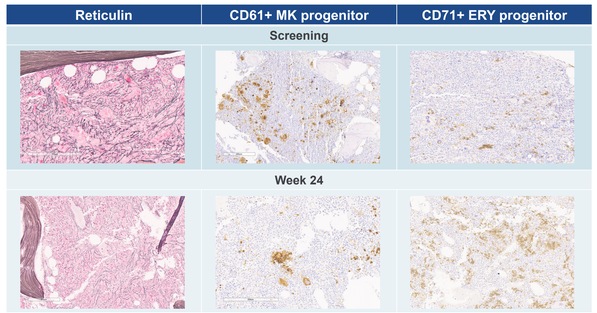


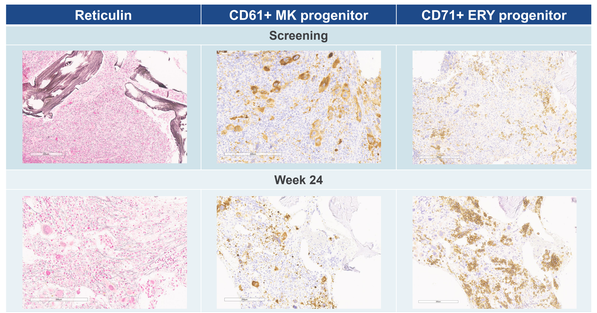
- TSS50 was first achieved at cycle 3 and was 57% at Week 24
- SVR35 was first achieved at cycle 4 and was 55% at Week 24



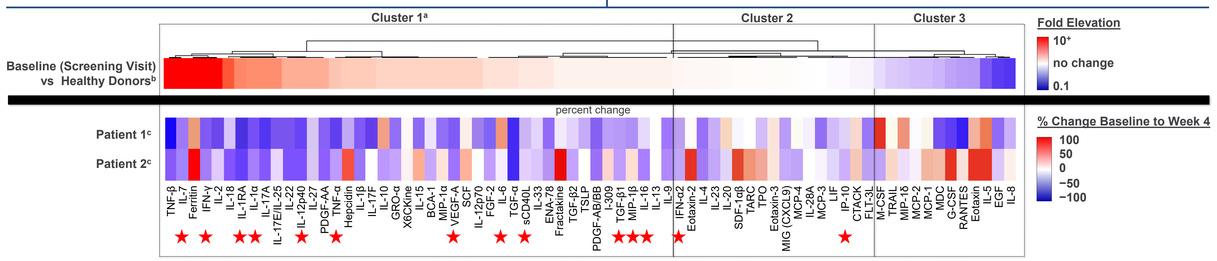
- TSS50 was first achieved at cycle 3 and was 71% at Week 24
- SVR35 was first achieved at cycle 4 and was 63% at Week 24

Improvements of reticulin density and ERY and MK cells in BM biopsies





Reduction in NF-κB and proinflammatory cytokine expression after selinexor + ruxolitinib combination



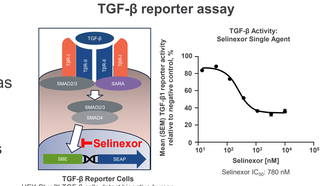
★ Indicates inflammatory NF-κB–driven cytokines.
[a]Cluster 1 shows 43 cytokines increased in patients with MF compared with healthy donors (45-fold to 1.5-fold increase).
[b]Top track indicates the fold change in baseline levels of peripheral blood cytokines from 22 patients enrolled in SENTRY compared with 20 healthy donors.
[c]Bottom two tracks show peripheral blood cytokine changes during treatment with selinexor and ruxolitinib for each patient at Week 4 and compared with those at their baseline screening visit.

- **Median decreases of 60% (Patient 1) and 40% (Patient 2) in cytokines elevated with MF and previously shown to be NF-κB targets and inflammation related[6] were observed**

Nonclinical TGF-β/SMAD pathway and plasma cytokine regulation

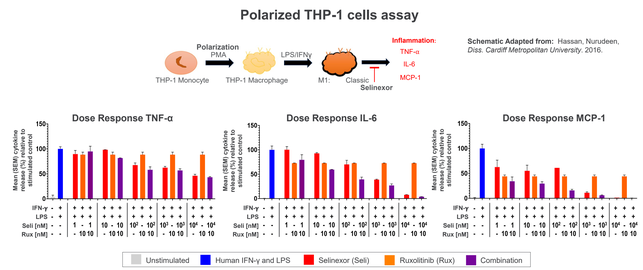
Selinexor inhibited TGF-β activity and TGF-β/SMAD signaling in a dose-dependent manner

- Dysregulation of the TGF-β/SMAD pathway contributes to ineffective hematopoiesis and clinical cytopenias
- Selinexor's inhibitory effect on this pathway may lead to improved erythroid cell number in BM biopsies from patients with MF



TGF-β Reporter Cells
HEK-Blue™ TGF-β cells detect bioactive human and murine TGF-β by monitoring the activation of the TGF-β/SMAD pathway.

Selinexor and ruxolitinib showed synergistic effects in decreasing the proinflammatory cytokines TNF-α, IL-6, and MCP-1



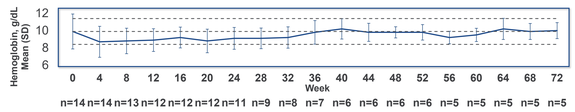
Schematic Adapted from: Hassan, Nurudeen, *Dis. Cardiff Metropolitan University*, 2016.

- Selinexor reduced cytokine secretion in an inflammatory model of THP-1 cells polarized with IFN-γ (0.5 ng/mL) and LPS (0.1 ng/mL), even with a shorter exposure duration (24 hours) and higher stimulation than previously reported[3]

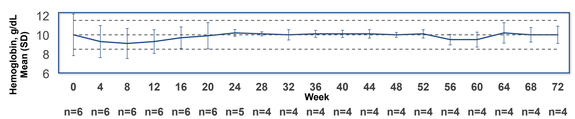
Hemoglobin changes in the selinexor 60-mg cohort from SENTRY Phase 1

- As of February 1, 2024, 14 patients with JAKi-naive MF received at least 1 dose of selinexor 60 mg plus ruxolitinib

Mean hemoglobin was generally stable up to 72 weeks in the overall population (N=14)



Hemoglobin recovered and stabilized in patients without RBC transfusions (N=6)



Dashed lines represent mean baseline hemoglobin and ±1.5 g/dL.

Conclusions

- These results provide evidence of how XPO1 inhibition by selinexor decreases NF-κB–driven cytokine production and TGF-β/SMAD activation and supports the potential impact of selinexor-induced regulation of MF-related cytokines on BM function and hematopoiesis
- Improved BM parameters associated with hemoglobin and platelet stabilization were observed in these patients who remained on long-term treatment
- Both patients achieved SVR35 and TSS50 responses even though 1 patient received suboptimal ruxolitinib doses
- The effects of selinexor observed in the 2 patients were also seen in the larger cohort with stabilization of hemoglobin
- These preliminary, exploratory findings will be confirmed in the larger Phase 3 (NCT04562389) portion of SENTRY, which is ongoing

Abbreviations: AE, adverse event; BM, bone marrow; BID, twice daily; C1D1, Cycle1/Day 1; CALR, calreticulin; ERY, erythroid; HMR, high molecular risk; IC_{50}, half-maximal inhibitory concentration; IFN, interferon; IL, interleukin; IWG-MRT, International Working Group for Myeloproliferative Neoplasms Research and Treatment; JAK2, Janus kinase 2; JAKi, Janus kinase inhibitor; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MF, myelofibrosis; MIPSS70, Mutation-Enhanced International Prognostic Scoring System 70; MK, megakaryocyte; MPL, myeloproliferative leukemia virus oncogene; MTD, maximum tolerated dose; NA, not applicable; NF-κB, nuclear factor-κB; PMA, phorbol myristate acetate; PO, by mouth; QW, once weekly; RBC, red blood cell; RP3D, recommended Phase 3 dose; SBE, Smad-binding element; SD, standard deviation; SEM, standard error of the mean; SMAD, Suppressor of Mothers Against Decapentaplegic; SVR, spleen volume reduction; SVR35, SVR ≥35%; TGF, transforming growth factor; TNF, tumor necrosis factor; TSS, Total Symptom Score; TSS50, TSS reduction ≥50%; XPO1, exportin 1; VAF, variant allele frequency.

References: 1. Tefferi A. *Am J Hematol*. 2023;98(5):801-821. **2.** Ali H, et al. *Blood*. 2022;140(Suppl 1):3986-3987. **3.** Tantravahi SK, et al. 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. Presented at the European Hematology Association Congress, June 13–16, 2024, Madrid, Spain. 4. Tantravahi SK., et al. 622 Selinexor plus ruxolitinib in JAK inhibitor (JAKi)-naïve patients with myelofibrosis: Long term follow up from XPORT-MF-034 suggestive of disease modification. Presented at the American Society of Hematology Annual Meeting & Expo, December 9-12, 2023, San Diego, CA, USA. 5. Maloof ME., et al. 123 Activity of selinexor as a single agent and synergistic activity with approved/investigational myelofibrosis therapies in vitro. Presented at the 15th International Congress for Myeloproliferative Neoplasms, November 2–3, 2023, Brooklyn, NY, USA. **6.** Liu T, et al. *Signal Transduct Target Ther*. 2017;2:17023.

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