Poster MPN-237

Selinexor alone and in combination with JAK inhibitors suppresses pro-inflammatory cytokine secretion from primary myelofibrosis cells ex vivo

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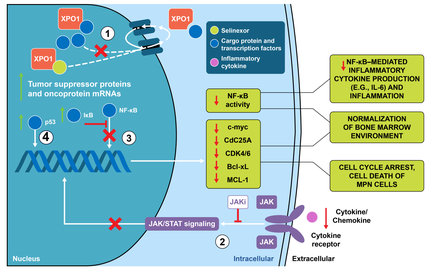
Introduction

- Selinexor is an oral selective inhibitor of the nuclear export protein exportin 1 (XPO1)[1]
- In combination with ruxolitinib, selinexor has shown rapid and sustained spleen and symptom responses, including potential of disease modification through reduction in driver gene variant allele frequency, and proinflammatory cytokine levels[2]
- MF is characterized by elevated levels of proinflammatory cytokines, which correlate with disease severity[3,4]
  - Many of these cytokines, including IL-6 and TNFα, are transcriptionally regulated by NF-κB[5] and activate the JAK/STAT signaling pathway
- Selinexor inhibits NF-κB activity by preventing nuclear export of its inhibitor IκBα[6]



1. Selinexor inhibits XPO1-mediated nuclear export of cargo proteins, leading to indirect downstream effects:
   2. JAK-STAT pathway inhibition
   3. NF-κB pathway inhibition
   4. p53-driven cell cycle arrest and cell death

BM, bone marrow; JAKi, JAK inhibitor; MPN, myeloproliferative neoplasm.

OBJECTIVE: To assess cytokine release from primary MF PBMCs treated ex vivo with selinexor alone or combined with JAK2 inhibitors: ruxolitinib (additional target JAK1), momelotinib (ACVR1, IKBKE, TBK1), and pacritinib (FLT3, IRAK1, CDF1R)

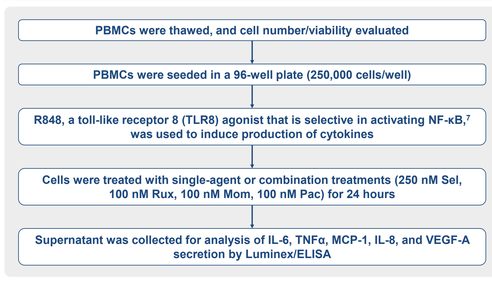
Methods

NF-κB Transcriptional Activity in MPN Cell Lines

- UKE-1 cells (essential thrombocytopenia transformed into acute leukemia; *JAK2*$^{MUT/MUT}$, *TP53*$^{WT/WT}$) were pre-treated with 250 nM of selinexor and/or 100 nM of each JAK inhibitor for 2 hours and then exposed to 20 ng/mL TNFα (PeproTech) for 4 hours in serum-free media
- NF-κB transcriptional activity of the nuclear fraction was measured by chemiluminescent transcription factor assay kit (Thermo Scientific Catalog# 89859)

Experimental Setup for Primary Patient Samples

- Ex vivo analyses were conducted using viably frozen peripheral blood mononuclear cells (PBMCs) from pretreatment samples of patients with JAKi-naïve MF participating in the Phase 3 SENTRY trial (NCT04562389)
- Patients provided informed written consent, and the clinical study was approved by Institutional Review Boards and conducted in accordance with the principles of the Declaration of Helsinki



ELISA, enzyme-linked immunosorbent assay; Mom, momelotinib; Pac, pacritinib; Rux, ruxolitinib; Sel, selinexor.

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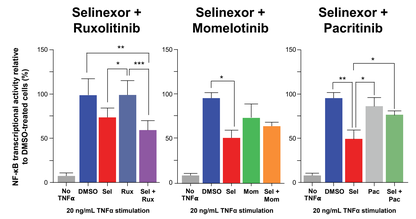
Results

Selinexor Suppressed NF-κB Transcriptional Activity in MPN Cell Lines



Bar graphs represent the average of 4 experiments for Sel + Rux and of 2 experiments for Sel + Mom or Pac.
DMSO, dimethyl sulfoxide; Mom, momelotinib; Pac, pacritinib; Rux, ruxolitinib; Sel, selinexor; TNF, tumor necrosis factor.
*<0.05; **<0.01; ***<0.001

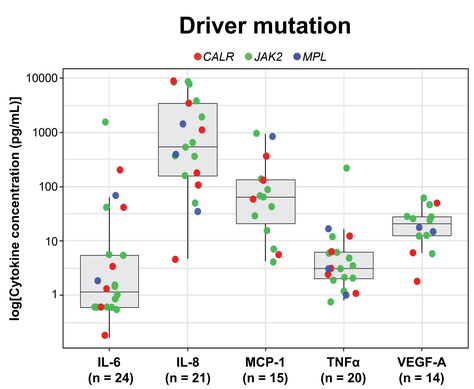
- Selinexor single-agent treatment showed greater inhibition of NF-κB transcriptional activity compared with JAK2 inhibitors
- Selinexor + ruxolitinib–induced reduction in NF-κB transcriptional activity was significantly different from single-agent ruxolitinib
- The effects of selinexor on NF-κB transcriptional activity in combination with momelotinib or pacritinib warrant further dose titration experiments to confirm the findings

Baseline Characteristics of Patient Samples

Characteristic, n (%)	Overall (N = 25)
Driver mutation	
JAK2	14 (56)
CALR	7 (28)
MPL	3 (12)
JAK2 and *MPL*	1 (4)
High-molecular risk*	
Yes	13 (52)
No	12 (48)
***TP53* mutation†**	
Yes	7 (28)
No	18 (72)
MF type	
Primary MF	9 (36)
Post-ET MF	10 (40)
Post-PV MF	5 (20)
Unknown	1 (4)
Screening DIPSS	
Intermediate 1	9 (36)
Intermediate 2 or high risk	16 (64)
Transfusion status	
Transfusion independent	23 (92)
Transfusion dependent	1 (4)
Unknown	1 (4)

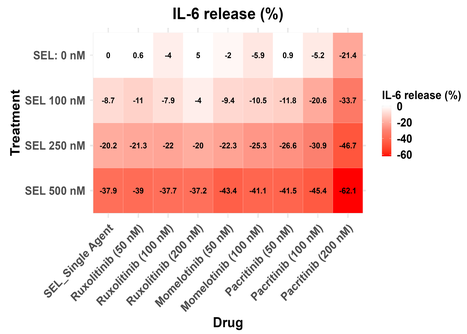
DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocytopenia; HMR, high molecular risk; MF, myelofibrosis; PV, polycythemia vera; *TP53*, tumor protein 53.
*High-molecular risk genes include: *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2*, and *U2AF1*.
†A higher proportion of *TP53* mutant patients were intentionally included to evaluate how the *TP53* status would impact regulation of cytokine release.

PBMCs From Patients With MF Release Detectable Amount of Multiple Cytokines



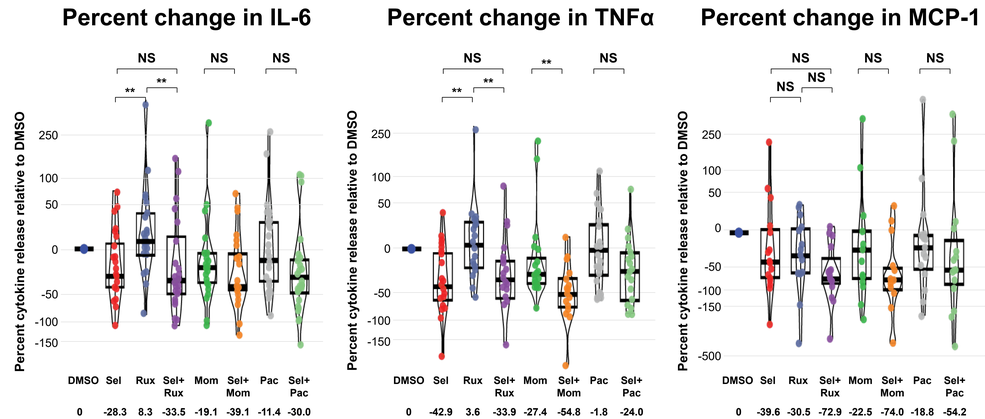
- Baseline concentrations of different cytokines were not affected by different driver mutations
- *TP53* mutation status, bone marrow fibrosis (BMF) grading, and MF type (not shown) did not affect cytokine baseline concentrations

Selinexor Attenuates IL-6 Release by PBMCs From Patients With MF



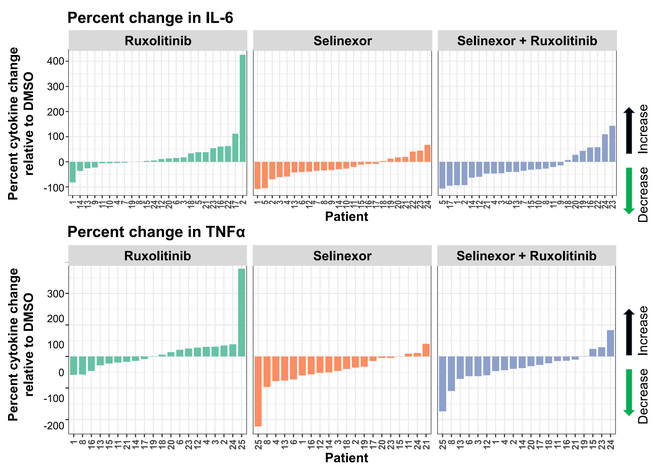
- In MF PBMCs, selinexor reduced release of IL-6 in a dose-dependent manner
- The selinexor-induced reduction of IL-6 release was enhanced in combination with JAK inhibitors
  - Increasing concentrations of ruxolitinib or momelotinib had minimal to no impact
  - Pacritinib, which inhibits IRAK1 impacting the NF-kB pathway, reduced IL-6 release in a dose-dependent manner

Enhanced Reduction of IL-6, TNFα, and MCP-1 Release in PBMCs From Patients With MF With Selinexor + JAKi vs JAKi Alone



- Selinexor as a single agent had a greater median reduction of IL-6, TNFα, and MCP-1 release than ruxolitinib, momelotinib, or pacritinib
- The cytokine suppression was further sustained or enhanced with the combination of JAK inhibitors
- IL-8 and VEGF-a were not affected by either selinexor or ruxolitinib as a single agent at the tested concentrations
- Subgroup analyses of tested samples showed cytokine suppressions were not influenced by BMF grade, driver mutation, or TP53 mutation status (data not shown)

Selinexor Drives Inhibition of IL-6 and TNFα Release Independently of Ruxolitinib



- IL-6 release was inhibited in **~71%** of PBMCs from patients with MF treated with selinexor (alone or with ruxolitinib) versus **~38%** with ruxolitinib alone
- TNFα release was inhibited in **~80%** of PBMCs from patients with MF treated with selinexor (alone or with ruxolitinib) versus **45%** with ruxolitinib alone
- For patient samples that showed large increases in IL-6 or TNFα levels with ruxolitinib alone (#2 and #25, respectively), selinexor alone or in combination with ruxolitinib led to substantial decreases

Conclusions

- **XPO1 inhibition may address key inflammatory and pathophysiologic features of MF**
- **Selinexor effectively suppressed ex vivo NF-κB–regulated proinflammatory cytokine production in PBMCs derived from patients with MF, both as a single agent and in combination with JAKi**
- **The combination of selinexor + ruxolitinib enhanced the inhibition of NF-κB transcriptional activity and multiple proinflammatory cytokines**
- **Selinexor-mediated cytokine inhibition may mitigate key MF hallmarks, including constitutional symptoms and clonal expansion, while providing additive benefit to ruxolitinib**
- **The combinatorial activity of XPO1 inhibition and JAK inhibition supports clinical investigation of selinexor + ruxolitinib in JAKi-naïve MF being evaluated in the ongoing Phase 3 SENTRY trial (NCT04562389)**

References: 1. Xpovio [package insert]. Newton, MA: Karyopharm Therapeutics, Inc; 2022. **2.** Tantravahi SK, et al. *Blood.* 2023;142(Suppl 1):622. **3.** Pemmaraju N, et al. *Cancer.* 2022;128(13):2420-2432. **4.** Zahr AA, et al. *Haematologica.* 2016;101(6):660-671. **5.** Mascarenhas J, et al. *Leukemia.* 2023;37(2):255-264. **6.** Kashyap T, et al. *Oncotarget.* 2016;7(48):78883-78895. **7.** Zhou Y, et al. *Front Immunol.* 2021;11:617522.
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