Selinexor, a Selective Inhibitor of Nuclear Export (SINE) Compound, Shows Synergistic Anti-tumor Activity when Combined with PD-1 Blockade in a Mouse Model of Colon Cancer

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ABSTRACT

Introduction: Selinexor is an oral, first-in-class SINE compound that specifically binds to the primary nuclear exporter XPO1/CHMP1A. XPO1 exports over 200 cargos, including major tumor suppressor proteins (TSPs), leading to their functional inactivation. Inhibition of XPO1 results in nuclear retention of TSPs and restores their normal functions. Interestingly, XPO1 also mediates the export of NFATC1, STAT3 and STAT5, which have been implicated in regulation of the inflammatory T-cell PD-1 (PD1TAT); STAT3 (and its ligand, PD-L1). Therefore, we hypothesized that selinexor treatment will result in up-regulation of PD-1 and PD-L1, making tumor cells more amenable to immunotherapy.

Figure 1. Mechanisms of action of selinexor (a) and PD-1 (b)

Selinexor is a SINE compound that increases the nuclear retention of TSPs, leading to tumor suppression by inhibiting the nuclear export receptor XPO1. Selinexor has been tested in >450 patients to date in Phase 1 and 2 clinical trials with promising signs of toxicity and safety.

RESULTS

Selinexor Induces PD-1 and PD-L1 Gene Expression in vitro and ex vivo

Ex vivo, leukocytes from mouse or normal human donors were incubated in culture with varying concentrations of selinexor for 4-6 hours. To do leukocytes from mice or human donors treated with selinexor were harvested at 6-8 hours post dose and measured by flow cytometry. Selinexor was extracted and quantitated by LC-MS/MS and relative to pre-treatment was quantitated by PCR.

Inhibition of Proliferation, Induction of Apoptosis and Reduction in PD-L1 and PD-L2 Protein Levels in Selinexor-Anti-PD1 Combination Treated Colon26-derived Xenografts

Vehicle Selinexor 1mg/kg(Wt) Anti-PD1 100mg/kg Anti-PD1 + Anti-PD1 1mg/kg(Wt) Vehicle Selinexor 1mg/kg(Wt) Anti-PD1 100mg/kg Anti-PD1 + Anti-PD1 1mg/kg(Wt)

IC50 analysis of Colon26 mouse xenografts treated with selinexor, anti-PD1 and anti-PD1 plus combination. Note decreased expression of PD-L1 and PD-L2 induction of apoptosis. Selinexor decreased cell proliferation (Ki67) in selinexor alone and in combination. Treatment xenografts.

Hypothesis and Suggested Model

1. Nuclear factor of activated T cells (NFAT) transcriptional activity is increased expression of cytokines (RANTES and nuclear NFAT-p) and increased expression of cytokines (RANTES and nuclear NFAT-p)

2. Calcium influx through L-type calcium channels leads to increased expression of multiple phosphatase kinases

3. Nuclear retention of NFAT-p by selinexor therapy results in increased expression of multiple phosphatase kinases

Enhanced Nuclear NFAT2 in Lymphocytes from a Selinexor-treated Thymoma Patient

Inmunohistochemical analysis was performed on a thymoma patient's tumor biopsies obtained at pre and post-Sellexron treatment to show increased nuclear staining intensity of NFAT2 and a lesser extent of NFAT1 post-treatment.

SUMMARY

7. Selinexor synergizes with anti-PD1 to inhibit tumor proliferation and to induce apoptosis in vivo

8. Selinexor treatment down regulates PD-L1 and PD-L2 proteins on tumor cells, which is hypothesized to cooperate with anti-PD1 treatment in blocking tumor cell-induced T cell-suppression

9. Selinexor may also enhance TCR signaling via nuclear retention of NFAT-p and Ap-1

10. These data provide rational support for further investigation of selinexor-anti-PD1 combination in pre-clinical and clinical studies.