Preclinical Efficacy Of The Novel, Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) On Castration Resistant Prostate Cancer

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Abstract

Exportin 1/ Chromosomal Maintenance Protein 1 (XPO1/CRM1) is a key nuclear export protein whose inhibition leads to the nuclear accumulation of tumor suppressor proteins such as p53, FOXO, PTEN, pRB and I-κB. Selinexor is an orally bioavailable XPO1 inhibitor that represents a novel class of small molecule compounds with potent activity against a wide variety of cancers. Here we report the activity of Selinexor against Castration resistant prostate cancer (CRPC).
CRPC progression is mediated by activation of various adaptive Androgen Receptor (AR) signaling pathways. These pathways are currently being targeted by novel anti-androgen therapies such as abiraterone acetate and enzalutamide with favorable outcomes. However, resistance to anti-androgen therapy can be developed through deregulation of tumor suppressor pathways. XPO-1 is highly expressed in prostate cancer cells and therefore we tested the effects of Selinexor on CRPC cells and tumors models. Treatment of the C4-2B prostate cancer cell line with Selinexor *in vitro* significantly inhibited cell proliferation and resulted in nuclear accumulation of p53 and p21. In addition, Selinexor inhibited expression of the tumor-promoting gene Ubiquitin-Conjugating Enzyme E2C (UBE2C), which is activated by AR in these cells. Selinexor was also tested in tumor graft models of two patient tumors in castrated male mice. The MDA-PCa-133 tumor is an adenocarcinoma derived from a clinical CRPC bone metastasis. Subcutaneous MDA-PCa-133 tumors in castrated male mice express full-length AR and Prostate-Specific Antigen (PSA) but lack expression of p53. The MDA-PCa-144-13 tumor is a small cell carcinoma derived from a lethal variant of prostate cancer with anaplastic clinical phenotype and does not express AR or PSA but expresses a gain-of-function p53 mutant. Vehicle or Selinexor treatment (10 mg/kg p.o. QoDX3 M/W/F) of MDA-PCa-133 tumors for 34 days resulted in almost complete inhibition of tumor growth with a 30-fold reduction of PSA ($p<0.001$). Treatment of MDA-PCa-144-13 tumors for 22 days also resulted in significant reduction of tumor volume (>8 fold compared to vehicle only; $p<0.0047$). Immunohistochemical analysis of MDA-PCa-133 tumors showed that Selinexor induced nuclear accumulation of XPO1 cargos FOXO3a and p27 with concomitant reduction in the proliferation marker KI67.
In conclusion, Selinexor demonstrated robust inhibition of CRPC tumor growth and activated multiple tumor suppressors in prostate cancer cells. Selinexor is now being evaluated in Phase 1 clinical studies in patients with advanced hematological and solid tumor cancers, and preliminary results show adequate tolerability with evidence of anti cancer activity. Future clinical studies in patients with CRPC are planned and will provide more information on the use of Selinexor as monotherapy and in combination with anti-androgen therapy of CRPC.

Objective

The objective of this study was to test the effect of Selinexor, a selective inhibitor of nuclear export, in prostate cancer cells in culture and in patient-derived CRPC xenograft tumor growth in mice. This is a co-clinical study that complements ongoing clinical study of Selinexor with CRPC patients.

Background

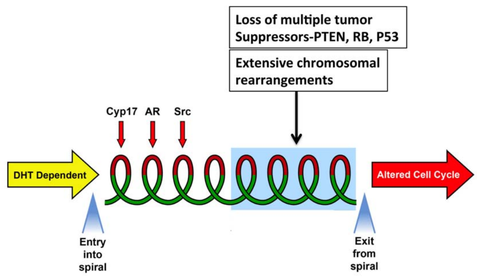

Fig. 1. Loss of tumor suppressors signaling facilitates in androgen/AR-independent spiral progression of CRPC

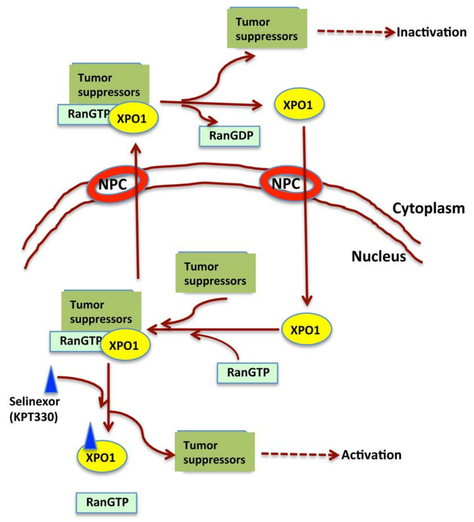

Fig. 2. Selinexor inhibits nuclear export of tumor suppressors resulting stabilization and activation of tumor suppressors signaling

Results

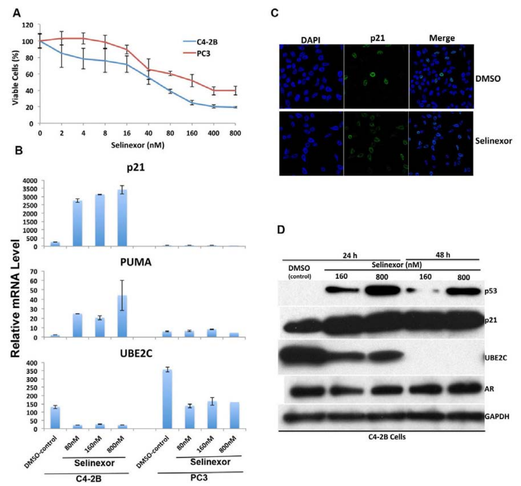

Fig.3. A. Impact of Selinexor on cell proliferation in C4-2B (with wild type p53) and PC3 (with deleted p53) prostate cancer cells B. Selinexor activates expression of p53 tumor suppressor target genes, p21 and PUMA but inhibits expression of UBE2C genes. C. Increased p21 expression in C4-2B nuclei. D. Selinexor activates p53 and p21 but inhibits UBE2C proteins in C4-2B cells.

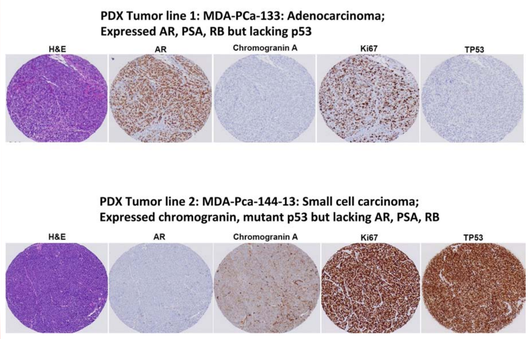

Fig.4. Properties of two different patient derived xenografts (PDX), MDA-PCa-133 and MDA-PCa-144-13, derived from CRPC patients with bone metastasis and anaplastic prostate cancer, respectively.

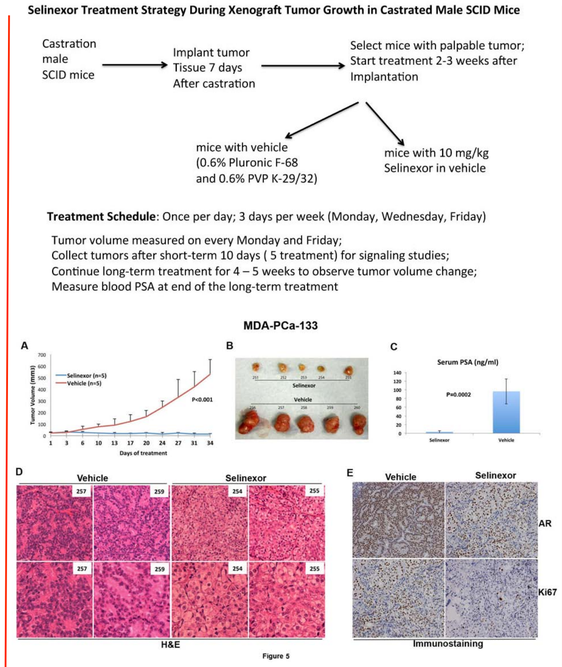

Fig.5. Impact of Selinexor treatment on a prostate adenocarcinoma PDX- MDA-PCa-133. A. Tumor volume change. B. Tumors upon completion of treatment. C. Serum PSA level. D. H&E staining of tumors displays cellular changes. E. Immunostaining to measure AR and ki67 (proliferation).

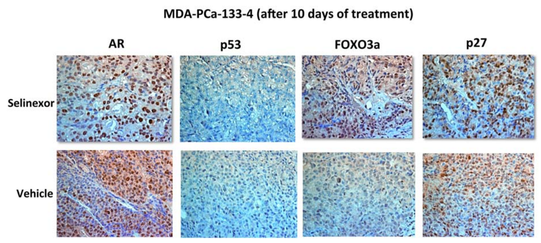

Fig.6. Immunohistochemistry to measure expression of various markers in MDA-PCa-133 tumors after short-term Selinexor treatment.

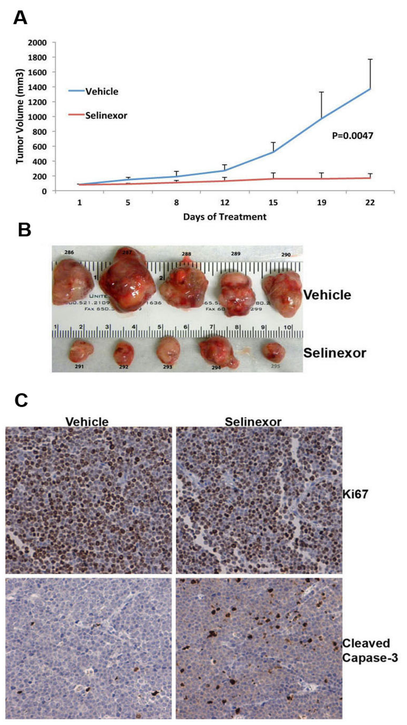

Fig.7. Impact of Selinexor treatment on a prostate small cell carcinoma PDX- MDA-PCa-144-13. A. Tumor volume change. B. Tumors upon completion of treatment. C. Immunostaining to measure proliferation (ki67), and cell death (cleaved caspase-3).

Conclusions

- **The inhibition of XPO1-mediated nuclear export by Selinexor resulted in nuclear accumulation of tumor suppressors; p53, p21, FOXO3a, and p27 proteins in prostate cancer cells. Selinexor treatment also resulted in nuclear retention of AR in androgen depleted prostate cancer cells.**
- **Strong inhibition of tumors growth, of castration resistant PDX by Selinexor indicates that inhibition of XPO1 mediated nuclear export can be a targeted therapy in metastatic CRPC and in anaplastic prostate cancer with small cell carcinoma phenotype**

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