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Selinexor, a selective inhibitor of nuclear export (SINE), shows enhanced activity in combination with PD-1/PD-L1 blockade in syngeneic murine models of colon cancer and melanoma

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Exportin-1 (XPO1) is a nuclear export protein with >220 cargo proteins, including tumor suppressors and cell cycle modulators. Selinexor is a SINE (Selective Inhibitor of Nuclear Export) compound that has been administered to >900 cancer patients in Phase I and II trials to date, with evidence of efficacy and tolerability. Selinexor blocks nuclear export of NFAT1c, STAT1 and STAT3, which are implicated in regulating the inhibitory T cell receptor PD-1 and its ligand, PD-L1. We hypothesized that selinexor would upregulate T cell checkpoint molecule expression, and that combination treatment with anti-PD-1 or anti-PD-L1 would thereby enhance the ability of selinexor to elicit antitumor activity.

Selinexor increased PD-1 gene expression by ~2-fold in normal lymphocytes and induced PD-L1 gene expression in tumor cell lines. Mice bearing syngeneic colon tumors (colon26) treated with selinexor and anti-PD-1 for 2 weeks demonstrated a significant reduction in tumor growth rate ($P < 0.05$), while monotherapy with either agent had no significant effect on tumor growth. Similar results were obtained in mice bearing syngeneic B16F10 melanoma tumors, whereby combined treatment with selinexor + anti-PD-1 was superior to either single agent alone ($p < 0.034$). Combined therapy of mice bearing B16F10 tumors with selinexor and anti-PD-L1 was similarly effective, with significantly smaller tumors at the study endpoint ($p < 0.001$). No weight loss or signs of toxicity were evident in any *in vivo* study.

Immunophenotypic analysis by flow cytometry revealed that selinexor alone or in combination with anti-PD-1/anti-PD-L1 significantly increased the percentage of splenic NK cells ($p \leq 0.050$), while selinexor ± anti-PD-L1 significantly increased the percentage of splenic Th1 T cells ($p \leq 0.011$), all compared to vehicle treated mice. Interestingly, combining selinexor with anti-PD-L1 significantly decreased the percentage of splenocytes that expressed PD-L1 ($p < 0.001$). These data indicate that the efficacy of selinexor may be enhanced by disrupting the pre-existing PD-1/PD-L1 signaling in effector cells (T and NK cells).

Altogether, these data suggest that the efficacy of selinexor in combination with anti-PD-1 or anti PD L1 in mouse syngeneic tumor models may be due to both disrupting immunosuppressive PD-1/PD-L1 signaling and increasing the frequency of potentially tumor reactive NK cells and Th1 T cells. This provides a rational basis for this treatment combination as a novel therapeutic approach for advanced cancer.

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