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PRECLINICAL ACTIVITY OF SELINEXOR, AN INHIBITOR OF XPO1, IN SARCOMA

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Introduction

i. XPO1 inhibits nuclear cargo proteins, including tumor suppressors (e.g., p53), cell cycle regulators (e.g., p21), and many more.
ii. Selective Inhibitors of Nuclear Export (SINE) that block XPO1 from binding to cargo proteins are in clinical trials as anticancer therapeutics.
iii. We evaluated the effects of selinexor, an orally bioavailable SINE, in preclinical models of sarcoma.

Conclusions

1. Selinexor has potent in vitro and in vivo activity against a wide variety of sarcoma models.
2. Selinexor induced G2 arrest independent of known molecular mechanisms in GIST and LPS.
3. These studies further justify the exploration of selinexor in clinical trials targeting various sarcoma subtypes.

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Fig. 1 Anti-proliferative activity of selinexor in a variety of sarcoma cell lines in vitro.

Fig. 2 Anti-proliferative activity of selinexor in a variety of sarcoma models in vivo.

Fig. 3 Histological changes and reduced cell proliferation following selinexor treatment.

Fig. 4 Selinexor induced cell cycle arrest in GIST independent of KIT signaling pathway.

Fig. 5 Selinexor induced cell cycle arrest and apoptosis in LPS differently from Nutlin-3a.

Fig. 6 Selinexor acts independently of p53 in LPS.