Selinexor (KPT-330), a Novel Selective Inhibitor of Nuclear Export (SINE), Shows Single Agent Efficacy Against Alveolar Soft Part Sarcoma (ASPS) in Vivo

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ABSTRACT

Chromosomal Region Maintenance Protein 1/Exportin 1 (CRM1/XPO1) is a key nuclear export protein whose disruption leads to the widespread accumulation of toxic Exportin 1 (XPO1) dependent proteins (TSPs) and systemic cancer with a high incidence of chemoresistance. For this reason, there is considerable interest in developing agents that selectively disrupt CRM1/XPO1 for the treatment of cancer. A novel class of agents, the Selective Inhibitors of Nuclear Export (SINEs), are small molecules that selectively disrupt CRM1/XPO1. One such agent, selinexor, has shown promising activity in hematological and solid cancer patients (Clinicaltrials.gov NCT01607892 and NCT01607905). We tested the compounds with activity against a wide variety of cancers. Selinexor is currently in Phase 1 clinical studies in hematological and solid cancer patients (Clinicaltrials.gov NCT01607892 and NCT01607905). We tested the compounds with activity against a wide variety of cancers. Selinexor is currently in Phase 1 clinical studies in hematological and solid cancer patients (Clinicaltrials.gov NCT01607892 and NCT01607905). We tested the compounds with activity against a wide variety of cancers. Selinexor is currently in Phase 1 clinical studies in hematological and solid cancer patients (Clinicaltrials.gov NCT01607892 and NCT01607905).

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INTRODUCTION

The mechanism of human neoplasms requires loss of regulation of multiple tumor suppressor pathways and/or their associated pathways. APC, p53, p16, p14ARF, and p21 are crucial tumor suppressor pathways. These tumor suppressor pathways act at distinct stages of the cell cycle through induction of apoptosis and cell cycle arrest and are mutated in almost all cancers. For this reason, disruption of pathways involved in the cell cycle, cell death, angiogenesis, and apoptosis in cancer cells is an attractive target for cancer treatment.

Selinexor inhibits nuclear retention of TSPs in ASPS cells

Selinexor inhibits DNA synthesis and induces growth arrest and cell death in ASPS cells

Selinexor reduces pro-proliferative and survival protein expression and induces cell death via apoptosis in vitro

Selinexor reduces pro-proliferative and survival protein expression and induces cell death via apoptosis in vitro

Selinexor causes nuclear accumulation of several TSPs, reduction in proliferation, and induction of apoptosis and fibrosis in ASPS-KY xenografts

Summary and Conclusions

• Selinexor is currently in Phase 1 clinical trials with >240 hematological and solid tumor patients treated and is showing evidence of broad spectrum anti-cancer activity and good tolerability.

• In ASPS cells in vitro and in vivo, selinexor acts through XPO1 inhibition to foster nuclear accumulation of TSPs and other critical regulatory proteins, leading to reduction in proliferative and pro-proliferative proteins and subsequent cell cycle arrest and death by apoptosis of ASPS cells

Furman et al. from two mice treated with vehicle (T1, T2) and four mice treated with 20 mg/kg selinexor (T3-T6) were harvested and evaluated by histological analysis for apoptosis and fibrosis by staining with TUNEL and Masson’s trichrome. Selinexor caused nuclear accumulation of several TSPs, reduction in proliferation, and induction of apoptosis and fibrosis in ASPS-KY xenografts.