Selinexor (KPT-330) Radio-Sensitizes Non-Small Cell Lung Cancer Cells In-Vitro and In-Vivo

Tami Rashal, Sivan Elloul, Marsha Crochiere, Trinayan Kashyap, William Senapedis, Ryan George, Sharon Friedlander, Maya Ilouze, Yosef Landesman, Robert O. Carlson, Nir Peled, Michael Kauffman, Sharon Schacham, Yaacov Lawrence

(1) Karyopharm Therapeutics Inc, Newton, MA; (2) SBH Sciences, Natick, MA; (3) Tel HaShomer Hospital, Ramat–Gan, Israel

ABSTRACT

The primary nuclear export protein, Exportin 1 (XPO1/CRM1), is overexpressed in many cancers and the overexpression correlates with poor prognosis. Selective inhibitors of Nuclear Export (SINE) compounds are a family of small-molecule bioavailable drugs that bind covalently to the primary nuclear export protein, XPO1, and with high specificity and selectivity block nuclear export of specific subsets of RNAs central to carcinogenesis, viral infection and induction of apoptosis. These results provide a rationale basis for combining selinexor with RT.

Together, our results suggest that selinexor treatment sensitizes cells to RT by preventing single-strand DNA break repair via downregulation of DDR protein expression. In contrast, selinexor reduces cell cycle arrest at G1 in p53 deficient H1299 cells, allowing DNA damage accumulation and induction of apoptosis. These results provide a rationale basis for combining selinexor with RT in clinical trials studies.

INTRODUCTION

Exportin-1 (XPO1/CRM1) is the major nuclear export protein with >1,000 cargos, including proteins and nucleic acids, central to carcinogenesis, signaling induction, and replication, and information.

• XPO1 is overexpressed in several cancer indications and its levels correlate with poor prognosis.
• SINEs induce nuclear retention of proteins and RNAs to exert effects beneficial for a variety of disease states, including cancer cell cycle, cell death, and damage and a variety of autocrine/paracrine conditions.
• Selinexor, the most advanced SINE, has been tested in >500 patients to date in Phase I trials with promising signs of efficacy, tolerability and safety.

XP01 is Expressed in All NSCLC Cells Tested

NSCLC cells express XP01.

Immunofluorescence of XP01 expression in NSCLC cell lines (H1299, A549, NCIH1299, NCIH226, NCIH2122, A549 and 2 normal lung fibroblast cells).

NSCLC cell lines were treated with 5, 10, 20 mg/kg PO, local radiation therapy (1.5 or 3 Gy) or combination selinexor and local radiation therapy for 24 hours.

CONCLUSIONS

Our work suggests the SINE compound, selinexor, is a promising NSCLC therapeutic as a stand-alone agent and in combination with RT. We demonstrated that selinexor dose-dependently lowers the expression of several DDR proteins in NSCLC cell lines, including RAD51 (HR protein), CHK1, MSH2 and MSH6 (both belong to mismatch repair response); including RAD51 (HR protein), CHK1, MSH2 and MSH6 (both belong to mismatch repair response). This reduction presumably limits the capacity of the cell to repair DNA damage induced by DNA-damaging chemotherapy and RT, and potentially leading to apoptosis. Selinexor is currently in Phase II clinical trials for the treatment of hemorrhagic malignancies and solid tumors. Phase II clinical trials are using selinexor as a single therapy and combination studies with other anticancer drugs have yet to begin. Combination study with selinexor and radiation has recently started and enrolled the first patients. Our work describes here and the tolerability of selinexor observed in Phase I clinical trials, suggests that selinexor may be a promising therapeutic for the treatment of NSCLC.

Website: www.karyopharm.com, email: Sivan.Elloul@karyopharm.com