THE COMBINATION OF SELINEXOR (KPT-330), A SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE), & THE FLT3 INHIBITOR QUIZARTINIB SHOWS ANTI-TUMOR ACTIVITY IN ACUTE MYELOID LEUKEMIA (AML) IN-VITRO AND IN-VIVO

Robert O. Carlson, William Senapedis, Trinayan Kashyap, Ori Kalid, Yosef Landesman and Sharon Shacham

Karyopharm Therapeutics, Inc., Natick, MA, USA

Abstract

AML cells overexpress the nuclear exporter Exportin 1 (XPO1; CRM1) and higher XPO1 levels correlate with poor outcomes in AML and other cancers. Selinexor (KPT-330), a novel SINE, antagonizes XPO1 and shows potent cytotoxicity for AML cells in vitro and in vivo, independent of genotype, while largely sparing normal hematopoietic cells. Mechanistic studies show that selinexor induces nuclear localization and activation of multiple tumor suppressor proteins (TSPs) and reduces levels of oncoproteins such as c-Myc and FLT3 and KIT, leading to rapid apoptosis of AML cells. We have recently reported preliminary Phase 1 results in which treatment with oral selinexor has led to durable disease stabilization and responses in patients with relapsed refractory AML across multiple genotypes. Quizartinib is a selective inhibitor of FLT3, a receptor tyrosine kinase for which the FLT3-ITD mutant is frequently a driver for AML. Quizartinib has shown significant activity in AML and the drug is scheduled to enter Phase 3 in FLT3-ITD AML patients this year. We report here the results of in-vitro and in-vivo studies of Selinexor and quizartinib alone or in combination on proliferation and survival of MV-4-11 AML cells.

To characterize the in-vitro and in-vivo effects of combining selinexor with quizartinib on AML cell survival relative to treatment with either drug alone, we treated MV-4-11 AML cells with used cell culture and xenograft studies. CellTiter-Glo® was used to measure in vitro cell proliferation. For xenograft studies, MV-4-11 cells were grown as subcutaneous tumors in NOD-SCID mice.

Selinexor and quizartinib showed high synergistic inhibition of MV-4-11 proliferation in vitro, and the combination showed synergistic potency. In the MV-4-11 AML xenograft model in NOD-SCID mice, a combination of selinexor with quizartinib also had an apparent synergistic effect on tumor growth relative to the drugs administered as monotherapies. Suboptimal doses of selinexor (5 or 10 µg/kg PO QD)XO3 had no effect or induced a 60% median tumor growth inhibition (TGI), respectively, at the end of the study. Quizartinib 0.5 or 10 mg/kg QD induced 26% TGI or 91% regression, respectively, over the same timeframe. The combination of the suboptimal doses of selinexor (5 µg/kg) and quizartinib (0.5 µg/kg) induced 67% tumor regression. While 10 µg/kg quizartinib induced modest weight loss, selinexor (0.5 µg/kg quizartinib), and the combination were well-tolerated with expected weight gain and full survival. Quizartinib is a potent inhibitor of in-vitro and in-vivo AML cell survival and functions by nuclear localization/activation of TSPs and reduction in FLT3 and other oncoproteins. Direct FLT inhibition with quizartinib also results in killing of FLT3 abnormal AML cells. The combination of selinexor and quizartinib shows additive cytotoxicity on AML cells in vitro. Moreover, the combination of suboptimal doses of selinexor with quizartinib was well tolerated and was dramatically more effective than either drug alone, leading to robust xenograft regression. This synergistic effect provides rationale for the investigation of a selinexor/quizartinib combination in the clinic with the potential for enhanced efficacy in AML relative to treatment with these drugs as monotherapies.

Export 1 (XPO1)

- Export 1 (XPO1; Crm1) is the major nuclear exporter with emerging efforts beneficial for a variety of disease states, including cancer, viral infection, brain damage and a variety of autoimmune inflammatory conditions.
- Selinexor, the most advanced SINE, has been tested in ~300 patients to date in three ongoing Phase 1 trials, with promising signs of efficacy, tolerability and safety.

Summary/Conclusions

The combination of selinexor with Flt3 inhibitor quizartinib showed synergistic potency against in-vitro survival of the AML cell line MV-4-11. In MV-4-11 xenografts, an ineffective dose of selinexor combined synergistically with a partially effective dose of quizartinib to induce tumor regression. The combination of selinexor and quizartinib combination in the clinic with the potential for enhanced efficacy in AML relative to treatment with these drugs as monotherapies.

Poster and Presentations

• Promising signs of efficacy, tolerability and safety.

Results Summary and Conclusions

- The effect of combining selinexor with quizartinib on in vitro survival of the MV-4-11 cell line was evaluated. The graph depicts the dose response of quizartinib in the presence of a range of selinexor concentrations. IC50 values for selinexor or quizartinib alone were 81 nM and 450 nM, respectively. In the selected study, IC50 values determined in SB were a function of selinexor concentration, demonstrating that increasing dose of selinexor synergistically increases the potency of quizartinib.
- The combination of selinexor and quizartinib showed synergistic potency against in-vitro survival of the AML cell line MV-4-11. Selinexor induces decreased levels of proteins derived from capped mRNA associated with eIF4E mRNA (including F3 and KIT), leading to rapid apoptosis of AML cells. Nuclear retention of capped mRNA proteins was observed for c-Myc and F3, both of which are important AML oncogenes (Flt3 was not detectable in MV-4-11).

Contact: Robert Carlson, email: robert@karyopharm.com

Website: http://www.karyopharm.com