Anti-tumor activity of novel nuclear export inhibitors (NEIs) in multiple xenograft models

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INTRODUCTION

CRM1 is essential for the nuclear export of a variety of proteins involved in oncogenesis. Many CRM1 cargo proteins are tumor suppressor transcription factors which can be nuclearized via CRM1-dependent nuclear export sequences (NESs). Nuclear sequestration of these proteins can lead to growth and/or apoptosis in cancer cells. CRM1 is targeted by a natural product leptomycin B (LMB) which covalently binds to CRM1 and thereby inhibits its ability to shuttle cargo proteins to the cytoplasm.

KOS-1815 is more efficacious than LMB in an HCT-116 tumor model. A single injection of KOS-1815, dosed at 15 mg/kg, resulted in >15× reduction in tumor volume as compared to vehicle-treated controls. Similarly, weekly administration of LMB at its MTD leads to a significant decrease in tumor growth (KOS-1688) in an HCT-116 tumor model. KOS-1815 is more efficacious than LMB (KOS-1688) in an HCT-116 tumor model. An equally efficacious dose of KOS-2385 is better tolerated than KOS-1815 in a SiHa model.

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KOS-1815 DEMONSTRATES ANTI-TUMOR EFFICACY IN MULTIPLE MOUSE TUMOR MODELS

KOS-1815 has improved tolerability and drug exposure compared to LMB

KOS-1815 has improved tolerability and drug exposure compared to KOS-1688. KOS-1815 was compared to LMB and KOS-1688 in a mouse hollow fiber model, as well as in several in vivo xenograft models. Weekly administration of KOS-1815 to mice bearing SiHa cervical cancer xenografts weekly administration of LMB at its MTD. Similarly, weekly administration of KOS-1815 to mice bearing HCT-116 colon cancer xenografts leads to a significantly greater tumor growth inhibition as compared to vehicle-treated controls. KOS-1815 is more efficacious than LMB (KOS-1688) in an HCT-116 tumor model. An equally efficacious dose of KOS-2385 is better tolerated than KOS-1815 in a SiHa model.

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