Anti-Tumor Activity of Selinexor (KPT-330), A First-In-Class Oral Selective Inhibitor of Nuclear Export (SINE) XPO1/CRM1 Antagonist in Patients (pts) with Relapsed / Refractory Multiple Myeloma (MM) or Waldenstrom's Macroglobulinemia (WM)

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ABSTRACT

Background: XPO1 (CRM1) is overexpressed in MM and was identified as an essential protein for WM growth. The XPO1 antagonists KPT-330 and other SINE compounds are active in MM and WM preclinical and clinical models, without significant toxicity. The pivotal phase 1 dose escalation study of KPT-330 in MM and WM includes 2 dose levels of KPT-330: 16.8 mg/m2 and 35 mg/m2 (8 cycles over 21 days) in an oral schedule. In preclinical models KPT-330 shows potent antitumor activity in animal models of MM including osteolytic bone lesions, bone marrow destruction, and increased survival of SCID mice with increased survival of MM xenograft mice and increased survival of SCID mice with increased survival of MM xenograft mice (Schmidt 2013, Martin Gutierrez, MD, Sarah Cannon Research Institute, Nashville, TN) and increased survival of SCID mice with increased survival of MM xenograft mice and increased survival of SCID mice with increased survival of MM xenograft mice (Schmidt 2013, Martin Gutierrez, MD, Sarah Cannon Research Institute, Nashville, TN)

Methods: Patients with advanced hematological malignancies were treated with continuous oral KPT-330 16.8 mg/m2 or 35 mg/m2 (8 cycles over 21 days) for > 8 months (median duration on therapy 89 days, range 8-393 days).

Conclusions: (60%) and Progressive Disease (PD) in 4 have been noted and patients have remained on therapy for > 8 months (median duration on therapy 89 days, range 8-393 days).

SINE treatment also impaired nuclear export of MM cell proteins, including the majority of Tumor Suppressor Proteins (TSP), Cell Cycle Regulators, and NFκB (the inhibitor of nuclear export) (Schmidt 2013, Tami Yau, MSc, CCRP). KPT-330 and other SINE compounds show potent anti-cancer activity in animal models of MM including osteolytic bone lesions, bone marrow destruction, and increased survival of SCID mice with increased survival of MM xenograft mice and increased survival of SCID mice with increased survival of MM xenograft mice (Schmidt 2013, Martin Gutierrez, MD, Sarah Cannon Research Institute, Nashville, TN) and increased survival of SCID mice with increased survival of MM xenograft mice and increased survival of SCID mice with increased survival of MM xenograft mice (Schmidt 2013, Martin Gutierrez, MD, Sarah Cannon Research Institute, Nashville, TN)

KPT-330 shows dose-dependent PK and PD responses in MM and WM patients whose disease is refractory to other therapies. KPT-330 shows dose-dependent PK and PD responses in MM and WM patients whose disease is refractory to other therapies. KPT-330 shows dose-dependent PK and PD responses in MM and WM patients whose disease is refractory to other therapies. KPT-330 shows dose-dependent PK and PD responses in MM and WM patients whose disease is refractory to other therapies.

References: Schmidt 2013, Martin Gutierrez, MD, Sarah Cannon Research Institute, Nashville, TN; Brown 1999, University of Chicago, Chicago, IL; Nashat 2004, Ann Arbor, MI; Rachid 2004, Nashville, TN.