SY-1365, a potent and selective CDK7 inhibitor, exhibits anti-tumor activity in preclinical models of hematologic malignancies and demonstrates interactions with the BCLXL/BCL2 mitochondrial apoptosis signaling pathway in leukemia

**Introduction**

- CDK7 is an important regulator of transcription through regulation of RNA Pol II and CDK9, and cell cycle progression through regulation of cell cycle kinases CDK1, CDK2, CDK4 and CDK6.
- CDK7 has been implicated in the pathogenesis of multiple malignancies, including hematologic malignancies.
- SY-1365, a selective inhibitor of CDK7, has been developed to exploit tumor dependencies driven by CDK7 and is in clinical development with advanced solid tumors.
- SY-1365 in vitro sensitivity is associated with regulation of mitochondrial apoptosis antagonists, and is synergistic with the BCL2 inhibitor venetoclax.
- In AML xenografts, intermittent dosing of SY-1365 has potent anti-leukemic activity as a single agent, and enhances response to venetoclax in combination.

**SY-1365 Potently Inhibits Proliferation of Hematologic Malignancy Models in vitro**

- SY-1365 induces MCL1 downregulation in AML cell lines.

**SY-1365 Enhances Activity of the BCL2 Inhibitor Venetoclax in AML Models**

- SY-1365 synergizes with venetoclax in AML cell lines in vitro.

**Conclusions**

- SY-1365 has potent anti-tumor activity as a single agent, and enhances response to venetoclax in combination.
- SY-1365 synergizes with the BCL2 inhibitor venetoclax in AML cell lines in vitro, and enhances responses to venetoclax in KG-1 AML xenografts in vivo.
- SY-1365 is currently being assessed in a phase 1 trial in adult patients with advanced solid tumors.

**References**

- *Syros Pharmaceuticals, 620 Memorial Drive, Cambridge, MA 02139; *Knights Cancer Institute, Oregon Health Sciences University, Portland OR 97239.