**CUDC-907, a dual PI3K and HDAC inhibitor, with broad activity against castration-resistant prostate cancer**

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**Background:** Castration-resistant prostate cancer (CRPC) is a heterogeneous disease comprised of multiple molecular and histologic subtypes. Multiple resistance mechanisms are associated with the development of CRPC including aberrant activation of AR signaling, PI3K/AKT/mTOR pathway, and amplification or overexpression of Myc. Loss of dependence on AR signaling also occurs in double-negative prostate cancer and neuroendocrine prostate cancer (NEPC). New treatments are needed to reduce mortality related to metastatic CRPC.

**Methods:** Cell-based fluorescent reporter assays of full-length AR (AR-FL) and AR splice variant 7 (AR-V7) abundance were established in HEK 293T cells. High-content, high-throughput screens were performed with the HEK 293T AR-FL and AR-V7 reporter cell lines to identify small molecule inhibitors that reduce AR abundance. Screen hits were evaluated in multiple human prostate cancer cell lines to examine effects on AR-FL, AR-Vs, and Myc protein and RNA levels; on growth inhibition; and cell cycle. Dose response curves were also generated using a larger panel of benign prostate epithelial and prostate cancer cell lines.

CWR22Rv1, LuCaP 35CR, and LuCaP 145.1 xenografts were established in NSG mice and treated with either vehicle alone or CUDC-907 75 mg/kg po daily (five days on and two days off) for up to three weeks.

**Results:** CUDC-907 (Fimepinostat), a first-in-class dual PI3K and HDAC inhibitor, was identified as the top hit in kinase inhibitor screens in the HEK 293T AR-FL and AR-V7 reporter cell lines. On-target effects on PI3K and HDAC as well as the inhibition of AR-FL, AR-Vs, and Myc expression were identified in multiple human prostate cancer cell lines at sub-micromolar treatment doses of CUDC-907. A broad range of phenotypically diverse prostate cancer cell lines including NEPC exhibited enhanced sensitivity to CUDC-907 relative to benign prostate epithelial cell lines. CUDC-907 appears to impact transcription of AR and Myc but not mRNA or protein stability. Enforced ectopic expression of AR-FL, myristoylated AKT1, or Myc alone was incapable of rescuing the effects of CUDC-907 in the CWR22Rv1 cell line. Preclinical trials of CUDC-907 in prostate cancer cell line and patient-derived xenograft models indicate significant inhibition of tumor growth.

**Conclusions:** CUDC-907 is a clinical therapeutic agent (currently in trials for B cell lymphomas) for which we provide evidence of activity across diverse human prostate cancer cell lines and xenograft models. CUDC-907 is likely working through multiple modes of action including inhibition of AR and Myc expression. Further characterization of the global effects of CUDC-907 on the transcriptome and chromatin landscape of prostate cancer is ongoing.

**Conflict of Interest:** None.

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