

Topic: Biomedical Research

**Development of BET bromodomain inhibitor ZEN-3694 for the treatment of solid tumor and hematological malignancies and synergy with Standard of Care (SOC) therapies**

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Targeting the interaction between bromodomain and extra-terminal domain (BET) proteins and acetyl-lysine on chromatin and transcription factors is a new therapeutic approach in clinical trials for cancer treatment. The BET proteins are involved in several transcriptional programs that drive cancer proliferation and metastasis. By using a combination of molecular modeling, structure activity relationship studies, biophysical and biomolecular assays, we developed a robust platform to assay different chemical scaffolds for inhibitory potency against BET bromodomains. Potent compounds were screened in cellular assays and in vivo models to further support preclinical development. Our clinical candidate ZEN-3694 binds selectively, suppresses oncogene expression, and inhibits proliferation in several models of hematological malignancies and solid tumors.

In vitro, ZEN-3694 has strong inhibitory activity with submicromolar IC50 values in several cell lines including castration-resistant prostate cancer (CRPC) and triple negative breast cancer (TNBC). ZEN-3694 also demonstrated synergy in vitro with Standard of Care (SOC) therapies in a wide variety of malignancies including Breast, Prostate, Lung, Melanoma, AML, and DLBCL. In vivo, xenograft studies in AML, CRPC and TNBC cancer models have shown ZEN-3694 to be well-tolerated and efficacious in a dose-dependent manner by inhibiting tumor growth.

Additionally, ZEN-3694 targets mechanisms of enzalutamide resistance in CRPC including constitutively active androgen receptor splice variant AR-V7 and induction of glucocorticoid receptor expression. ZEN-3694 is scheduled to enter phase I clinical studies in metastatic CRPC in Q1 2016.