**Abstract**

Metastatic Castration Resistant Prostate Cancer (mCRPC) is a major unmet medical need due to its high morbidity and mortality. Current standards of care for mCRPC include androgen-deprivation therapy (ADT), and upon failure, patients are administered secondary ADT with anti-androgen receptor (AR) antagonists such as enzalutamide and abiraterone. While most patients display an initial response to these agents, eventually all become resistant via various mechanisms. One mechanism often results in constitutive AR signaling including mutations of the AR, and the generation of AR splice variants that bypass the ligand binding domain. Other mechanisms of resistance to AR antagonists include up-regulation of the glucocorticoid receptor (GR) and partial to complete loss of AR signaling through neuroendocrine differentiation. Recent evidence suggests that BET bromodomain inhibitors (BETi) could be efficacious in AR-resistant prostate cancer (PC), and modulation of BET family proteins and genes may be a potential target. While preclinical studies with BETi have shown promising results, the overall clinical benefit of BETi in mCRPC patients is still to be determined. Here we report on the anti-tumor activity and mechanism of action of ZEN-3694, a novel BETi that is well tolerated in advanced prostate cancer patients. The results of this study indicate that ZEN-3694 holds promise as a novel therapeutic approach for mCRPC.

**Introduction**

BET bromodomain-containing proteins are involved in transcriptional regulation, histone acetylation and acetylated lysine function in histones and promote gene transcription. The BET family includes BRD2, BRD3, BRD4 and BRD7, which are involved in the regulation of gene expression, cell proliferation, cell differentiation, and survival. BETi, including ZEN-3694, can inhibit AR signaling through the modulation of BET family proteins and genes, leading to the down-regulation of AR, GR, and many other genes involved in the proliferation of AR-positive prostate cancer cells. A recent study showed that ZEN-3694 can inhibit AR signaling and cell proliferation in a BET-dependent manner. In addition, ZEN-3694 can inhibit AR signaling and cell proliferation in a BET-independent manner.

**Results**

ZEN-3694 can inhibit AR signaling and cell proliferation in a BET-dependent manner. In addition, ZEN-3694 can inhibit AR signaling and cell proliferation in a BET-independent manner. The results of this study indicate that ZEN-3694 holds promise as a novel therapeutic approach for mCRPC.

**Conclusion**

ZEN-3694 is a novel BETi that is well tolerated in advanced prostate cancer patients. The results of this study indicate that ZEN-3694 holds promise as a novel therapeutic approach for mCRPC.