Targeting the bromodomain of p300/CBP for the treatment of castration resistant prostate cancer

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Background: Therapeutic strategies for castrate resistant prostate cancer (CRPC) include targeting degradation of androgen receptor (AR) and AR variants (ARV). E1A binding protein (p300) and CREB binding protein (CBP) are two closely related histone acetyl transferase proteins that are critical transcriptional co-activators of AR. We have developed CCS1477 which is a potent, selective and orally active small molecule inhibitor of the bromodomain of p300/CBP and investigated its role in regulating androgen receptor expression and function.

Methods: Binding affinity of CCS1477 to p300, CBP and BRD4, was measured in a surface plasmon resonance (SPR) assay. Potency and functional activity (proliferation and biomarker knockdown) was demonstrated in a prostate cells lines in vitro (22Rv1, VCaP). In vivo efficacy, linked to inhibition of biomarkers, was determined in 22Rv1 and LNCaP xenograft models.

Results: CCS1477 binds to p300 and CBP with high affinity (Kd=1.3/1.7nM) and selectivity (Kd=222nM; BRD4). It is a potent inhibitor of cell proliferation in prostate cell lines (IC50=96nM,22Rv1; 49nM,VCaP) with minimal effect in AR-ve lines. In 22Rv1 cells, p300/CBP inhibition down-regulates AR-FL, AR-V7 and c-Myc protein by Western and this is accompanied by profound inhibition of c-Myc, KLK3 and TMPRSS2 genes measured by qPCR. The in vivo PK properties of CCS1477 are consistent with qd or qod oral dosing in mouse. CCS1477 dosed at 10mg, 20mg/kg qd or 30mg/kg qod, caused complete tumour growth inhibition over 28 days in a 22RV1 xenograft model, included extended duration in the absence of the drug for a further 24 days. This was accompanied by complete inhibition of plasma PSA and significant knockdown of tumour AR-FL, AR-V7, and C-Myc protein as well as C-Myc and TMPRSS2 mRNA expression. At 100mg/kg, a single dose of CCS1477 induces expression of cleaved PARP and when dosed orally every three days, causes tumour regression in the 22Rv1 model. Furthermore, CCS1477 results in almost complete tumour growth inhibition in a bicalutamide resistant LNCaP xenograft model, when given alone or in combination with enzalutamide.

Conclusions: Taken together these data support the clinical testing of CCS1477 in castrate resistant prostate cancer by down-regulating of AR, AR-SV and c-Myc expression and function.

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