ABSTRACT:

EPI-002 and Enzalutamide Combination Therapy as a Potential Therapeutic Benefit for Castration-Resistant Prostate Cancer Patients

Development of castration-resistant prostate cancer (CRPC) is thought to be dependent on androgen receptor (AR) transcriptional activity. Resistance to current therapies is linked to constitutively active AR splice variants that lack the ligand-binding domain (LBD). Metastatic tumours heterogeneously express varying levels of AR splice variants to full-length AR (fl-AR). AR splice variant V7 is frequently expressed and correlated with poor prognosis in patients. Since current therapies such as enzalutamide target the fl-AR LBD, which is absent in AR variants, an amino-terminal domain (NTD) inhibitor that blocks transcriptional activities of all AR species may significantly improve survival of CRPC patients. EPI-002 binds to the AR NTD and inhibits transcriptional activity of AR. Hypotheses tested in this thesis include: (1) EPI-002 inhibits transcriptional activity of endogenous and exogenous V7 in human prostate cancer cell lines, and (2) combination therapy of EPI-002 and antiandrogen enzalutamide demonstrates greater inhibition of transcriptional activities of mixed AR populations than each treatment alone.

V7 transactivation was measured with EPI-002 treatment in AR-negative PC3 cells. Combined transcriptional activities with probasin-, PSA- and ARR3-luciferase AR-driven reporters were measured in androgen-sensitive LNCaP cells ectopically expressing V7, and androgen-independent LNCaP95 cells endogenously expressing V7. EPI-002 and enzalutamide monotherapies and in combination were evaluated with mixed AR populations in LNCaP and LNCaP95. Cell growth of LNCaP95 was measured with combination treatment.

EPI-002 inhibited constitutive transcriptional activity of V7 alone. EPI-002 monotherapy and in combination with enzalutamide demonstrated greater inhibition of transcriptional activities of V7 expressed approximately 1:1 with fl-AR in LNCaP than enzalutamide monotherapy. With low V7 levels compared to fl-AR, enzalutamide monotherapy and in combination with EPI-002 generally showed greater inhibition of AR transcriptional activities in LNCaP95 than EPI-002 monotherapy. It was observed that V7 activity demonstrated differential gene regulation of AR-driven reporters employed. Proliferation of LNCaP95 cells was inhibited by EPI-002 monotherapy and in combination with enzalutamide, with enzalutamide monotherapy having no effect.

Data shown here begins to reveal: 1) proof-of-principle that AR NTD inhibitor EPI-002 blocks all AR species in a heterogeneous tumour population; and 2) a potential therapeutic benefit for CRPC patients with EPI-002 in combination with enzalutamide.