A new generation of N-terminal domain androgen receptor inhibitors in castration resistant prostate cancer models

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Abstract #MO34-04

EPI-002 specifically binds to the transactivation unit 5 (Tau5) of AR NTD to block essential interactions with AR LBD, and orchestrate the transactivation of the receptor. It was demonstrated that EPI-002 blocks transcriptional activity of AR in vitro and in vivo. A new generation of NTD transcriptional inhibitors (Anitens) are predicted to display a favorable pharmacokinetic profile and can cross the blood brain barrier in human brain tissue to induce anti-androgen resistance.

CONCLUSION
- Promising next-generation Anitens compounds have been identified and display: a. Similar potency in vitro to the ‘lutamides in full length AR models b. Activity in several in vitro cell lines, including enzalutamide resistant models c. On-target NTD inhibition with minimal activity against other steroid receptors d. No PXR agonist activity, predicting no induction of CYP enzymes e. Low brain penetration combined with no inhibition of the GABA-CI channel which is responsible for inducing seizures in enzalutamide & apalutamide-treated patients
- Favorable metabolic profile in preclinical species, predicting high exposure and long half-life in humans g. Superior activity as an enzalutamide, as single agent or in combination, in the enzalutamide resistant model VCaP
- Inhibiting the AR with both an NTD and a LBD agent induces deeper and more consistent antitumor responses

A Phase 1 study of EPI-7386 in mCRPC patients will begin 1Q2020

Next generation Anitens are active in castrated mice bearing enzalutamide sensitive and resistant AR dependent xenografts

Next generation Anitens are metabolically stable across preclinical species and are predicted to display a favorable pharmacokinetic profile in human

AR inhibition is on target through the N-terminal domain and effective in AR-V7 driven models

Figure 1: Anitens are first in class NTD inhibitors of the androgen receptor. In this study, the selectivities of Anitens for AR NTD versus other nuclear receptor LBDs were assessed using the Gadd45α assay (Thermo), an estrogen receptor (ER) assay (Hennegouven Labs), and a progesterone receptor (PR) assay (Virshl et al). (A) Compound selectivity for AR NTD compared to the Gadd45α assay (Thermo), an estrogen receptor (ER) assay (Hennegouven Labs), and a progesterone receptor (PR) assay (Virshl et al). (B) Graph showing the selectivity of EPI-002 specifically for AR NTD versus all other receptor LBDs. (C) Graph showing the selectivity of EPI-002 specifically for AR NTD versus all other receptor LBDs.

Figure 2: Effect against androgen-induced PSA-luciferase activity in LNCaP cells (A) 4-day decrease in PSA-luciferase activity in LNCaP cells treated with EPI-002 transfection with the PSA reporter gene and co-cultured with different Anitens compounds in the presence of androgen (R1881). (B) Summary of IC50s calculated across multiple independent experiments. Independent experiments were done with AR-V7 cells treated with EPI-002 and PSA reporter gene transfection that measured antitumor activity against AR-V7.

Figure 3: Anitens activity and selectivity in AR WT and V7 models (A) The selectivity of Anitens for AR NTD versus other nuclear receptor LBDs was assessed using the Gadd45α assay (Thermo). Estrogen receptor-α (ERα) and ERβ, progesterone receptor (PR), androgen receptor (AR) were used for the Gadd45α assay. (B) Graph showing the selectivity of EPI-002 specifically for AR NTD versus all other receptor LBDs.

Figure 4: Next generation Anitens are metabolically stable across preclinical species and are predicted to display a favorable pharmacokinetic profile in human. (A) Compound stability was assessed in human, mouse, rat, and dog hepatocytes. (B) Human PMR parameter in vitro using in vitro metabolism parameters (PMR) for all metabolic pathways. (C) Summary of A and FID PK parameters after a single dose in male CD-1 mouse (n=3). (D) Summary of metabolic parameters for enzalutamide and EPI-7386. (E) PK parameters after a single dose in male CD-1 mouse (n=3), single female and female CD-1 mouse (n=3), and B6 strain (n=3) (F) Graph of (G) and (H) profile of EPI-7386. (I) Pharmacokinetics (PK) and tissue exposure after a single therapeutic dose of EPI-7386 in VCaP, highlighting lower tumor penetration with EPI-7386.

Figure 5: In vivo activity in CIRC xenograft models (A) Tumor growth in male NCG mice bearing LNCaP tumors. Castration was performed when tumors reached ~100 mm3 and at 100 mm3 on day 41. (B) Tumor growth in male SCID Beige mice bearing VCaP tumors. Castration was performed when tumors reached ~100 mm3 and at 100 mm3 on day 41. (C) Individual tumor volume change measured on day 41. (D) Summary of clinical responses in the VCaP study shows more homogenous tumor responses measured on day 41. (E) PK parameters of EPI-7386 and enzalutamide showed 1 dose AUC". (F) Summary of clinical responses in the VCaP study shows more homogenous tumor responses measured on day 41.

Figure 6: Clinical responses in the VCaP study show more homogenous tumor responses measured on day 41. (A) Tumor growth in male NCG mice bearing LNCaP tumors. Castration was performed when tumors reached ~100 mm3 and at 100 mm3 on day 41. (B) Tumor growth in male SCID Beige mice bearing VCaP tumors. Castration was performed when tumors reached ~100 mm3 and at 100 mm3 on day 41. (C) Individual tumor volume change measured on day 41. (D) Summary of clinical responses in the VCaP study shows more homogenous tumor responses measured on day 41. (E) PK parameters of EPI-7386 and enzalutamide showed 1 dose AUC...