EPI-7386 is a novel N-terminal domain androgen receptor inhibitor for the treatment of prostate cancer

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BACKGROUND

The androgen receptor (AR) pathway continues to drive most castration-resistant prostate cancer (CRPC) growth in late stages of the disease through resistance mechanisms, including gain-of-function mutations in the C-terminal ligand binding domain (LBD) and expression of constitutively active truncated AR splice variants lacking the LBD, such as AR-V7. Selective inhibition of the N-terminal domain (NTD) of the AR can inhibit its transcriptional activity even in the presence of LBD driven anti-androgen resistance. A Phase I clinical trial of the first-generation AR NTD inhibitor, EPI-506, (a bisacetril prodrug of EPI-022 - ralnetitram) demonstrated PSA declines in enzalutamide and/or abiraterone resistant metastatic CRPC patients. However, PSA declines were less than 50% and of short duration. The drug was well-tolerated but required high doses to achieve meaningful exposures, and steady-state concentration was well below those required for in vitro efficacy, re-vealing the need for more potent and metabolically stable NTD inhibitors.

EPI-7386 represents a new generation of NTD inhibitors (Anitens) and its characteristics are presented.

EPI-7386 demonstrates up to 20-fold improvement on inhibition of androgen-induced transcriptional activity

CONCLUSIONS

EPI-7386 is predicted to display a favorable pharmacokinetic profile in humans and can be dosed as a suspension to support toxicity studies.

EPI-7386 is active in castrated mice bearing enzalutamide emerging-resistant and refractory AR dependent xenografts

The next-generation Anitens compound EPI-7386 has been selected as clinical candidate and displays:

a. Similar potency in vitro to the ‘futamides in full length AR models
b. Activity in several in vitro cell lines, including enzalutamide resistant models
c. On-target NTD inhibition demonstrated by activity on AR-V7 driven gene expression
d. Superior activity to enzalutamide, as single agent, or in combination in the VCaP aphic fiber xeno-grafts, an enzalutamide emerging-resistant model e. Confirmed activity in the enzalutamide refractory xenograft tumors 22Rv1 and LnCAP-PS3
f. No on-target activity noticed in a non-functional AR PC-3 xenograft tumor
g. Wide therapeutic index as demonstrated by the dose response in VCaP xenografts
h. High exposure reachable in toxicology species with drug formulated as a suspension formulation

EPI-7386 IND filing scheduled for 1Q 2020, and Phase 1 study starting soon thereafter