The androgen receptor (AR) pathway continues to drive most castration-resistant prostate cancer (CRPC) even in late stages of the disease through resistance mechanisms including gain-of-function mutations in the C-terminal ligand-binding domain (LBD) and constitutive expression of 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-driv- en anti-androgen resistance.

A Phase I clinical trial of the f_irst-generation AR NTD inhibitor, EPI-506, (a triacetate prodrug of EPI-002 - Ralaniten) demonstrated improved potency, metabolic stability and pharmaceutical properties, are discussed in this poster. EPI-506 was well tolerated and showed improved response in combination with enzalutamide in castration-resistant prostate cancer (CRPC) even in late stages.

BACKGROUND

Structure of the androgen receptor (AR) and mechanism of inhibitions. The AR is organized in 3 distinct domains: the LBD, involved in binding with androgens, the DBD, which orchestrates the transactivation of the receptor. Inhibiting the NTD can inhibit 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-driv- en anti-androgen resistance.

Next generation Anitens are metabolically stable and have high per- meability, resulting in improved PK properties across species.

CONCLUSION

• Promising next-generation Aniten compounds have been identified and display:
  a. Similar potency in vitro to the ‘lutamides
  b. Activity in several in vitro cell lines, including enzalutamide resistant models
  c. On-target NTD inhibition with minimal activity against other nuclear hormone receptors
  d. No PKR agonist activity and no inhibition of the GABA-Acholine channel which is responsible for inducing seizures in enzalutamide or apalutamide treated patients
  e. Favorable metabolic profile in vivo (Caro-2 and hepatocytes)
  f. Favorable in vivo metabolic profile with high exposure and long half life
  g. Comparable activity to enzalutamide in AR dependent LNCaP and VCaP xenografts
  h. Qualitatively improved response in combination with enzalutamide

Based upon the above criteria, EPI-7386 selected as the IND candidate with phase 1 study anticipated 1Q 2020

Next generation Anitens are active and well tolerated in castrated mice bearing AR dependent xenografts

Next generation Anitens demonstrate up to 20-fold improvement on the inhibition of androgen-induced AR transcriptional activity

Next generation Anitens are metabolically stable and have high permeability, resulting in improved PK properties across species

Figure 2: Effect against androgen-induced PSA-fucosetase activity in LNCaP cells

(A) A dose-dependent decrease in AR-transcriptional activity was demonstrated in LNCaP cells trans- fected with the PSA reporter gene and incubated with increasing concentrations of androgens (EPI-7386). (B) Summary of ESI calculated across multiple independent experiments.

Figure 3: Anitens activity and selectivity in AR WT and V7 models

(A) The selectivity of Anitens for AR WT versus other nuclear receptor LBDs was assessed using the GeneAlex assay (Thermo Fisher). Estrogen receptors-a (ERa) and ERb, progesterone receptor (PR), glucocorticoid receptor (GR), vitamin D receptor (VDR), androgen receptor (AR) LBD activity was measured using the Discr- eet functional assay while GABA-A (GABA-A) channel antagonism was tested with CEREP binding assay. (C) The transcriptional activity was measured in LNCaP cells using a full-length LUC reporter gene (luciferase activity was measured in transfected LNCaP cells using the PSA reporter gene) in LNCaP 6W (Wt AR splice variants lacking the LBD) or LNCaP 6H (H AR splice variants lacking the LBD) were used for LNCaP cell line. Data is summarized in table 1 and represented in graphs 1-4.