The androgen receptor (AR) pathway continues to drive most castration-resistant prostate cancers (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 expression of constitutively active truncated AR splice variants lacking the LBD, such as AR-V7. A new method of inhibiting the AR pathway is needed to overcome these AR-based mechanisms of resistance. One possibility is through selective inhibition of the N-terminal domain (NTD) of the AR which can inhibit its transcriptional activity even in the presence of LBD-driven anti-androgen resistance.

EPI-7386 inhibits androgen-induced transcriptional activity

Figure 2: AR activity is selectively in full-length AR and AR-V7 models

(A) Androgen-induced proliferation of LNCaP and castration-resistant variants of LNCaP with or without EPI-7386 treatment and vehicle control. (B) Expression levels of AR-V7 mRNA measured by qPCR in LNCaP cells treated with vehicle control and EPI-7386. (C) Androgen-induced proliferation of LNCaP cells treated with vehicle control and EPI-7386. (D) Expression levels of AR-V7 mRNA measured by qPCR in a VCaP cell line treated with vehicle control and EPI-7386.

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

Figure 3: EPI-7386 activity and selectivity in full-length AR and AR-V7 models

(A) Androgen-induced proliferation of LNCaP and castration-resistant variants of LNCaP with or without EPI-7386 treatment and vehicle control. (B) Expression levels of AR-V7 mRNA measured by qPCR in LNCaP cells treated with vehicle control and EPI-7386. (C) Androgen-induced proliferation of LNCaP cells treated with vehicle control and EPI-7386. (D) Expression levels of AR-V7 mRNA measured by qPCR in a VCaP cell line treated with vehicle control and EPI-7386.

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

Figure 4: EPI-7386 activity in castrated mice bearing enzalutamide emerging-resistant and refractory AR xenografts

(A) Example of AR-activity in castrated mice bearing enzalutamide resistant xenografts. EPI-7386 inhibits AR activity and demonstrates in vivo anti-tumor activity. (B) Summary of PK parameters of EPI-7386 in cynomolgus monkeys. (C) Summary of pharmacodynamics and efficacy in vivo. (D) Summary of safety and tolerability findings in vivo. (E) Summary of in vitro human parameters based on in silico model simulation. (F) PK parameters of EPI-7386 after a single PO dose of 5 mg/kg in male Beagle dogs. (G) Summary of efficacy findings in vivo. (H) Summary of in vitro human parameters based on in silico model simulation. (I) PK parameters of EPI-7386 after a single PO dose of 5 mg/kg in male Beagle dogs.

EPI-7386 is tolerated at high dose in tox species and is predicted to achieve high exposure in humans

Figure 5: Toxicology overview, human projected exposure and zonal form of EPI-7386

(A) Single dose toxicity testing for EPI-7386 in 3 different species including beagle, dog and rats. (B) Summary of toxicology findings in beagle dogs. (C) Summary of safety and tolerability findings in beagle dogs. (D) Summary of efficacy findings in beagle dogs. (E) Summary of in vitro human parameters based on in silico model simulation. (F) PK parameters of EPI-7386 after a single PO dose of 5 mg/kg in male Beagle dogs. (G) Summary of efficacy findings in beagle dogs. (H) Summary of in vitro human parameters based on in silico model simulation. (I) PK parameters of EPI-7386 after a single PO dose of 5 mg/kg in male Beagle dogs.

CONCLUSION

- The next-generation Antien compound EPI-7386 has been selected as the clinical candidate and displays:
  a. Similar potency in vitro to the ‘lutamides in full-length AR models
  b. On target NTD inhibition demonstrated by activity on AR-V7 driven gene expression
  c. Activity in several in vitro and in vivo CRPC cell lines, including enzalutamide resistant models.
  d. Superior activity to enzalutamide in a PDX model displaying resistance to ADT and LBD inhibitors
  e. Dose response activity with a minimal active exposure of 90,000 ng/mL in mouse xenograft models
  f. Tolerability in a 14 days DRF in rats and dogs at AUC ≤ 100,000 ng.h/mL, with activity seen on androgen-sensitive target organs.
  g. Favorable human PK parameters supporting QD dosing
  h. Bioequivalence between the suspension formulation and the tablet that will be used in the clinical trial

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

First in human clinical study

Patient population

- mCRPC patients progressing on standard of care (including the latest antidepressants)

Study design

- 3+3 design
- n = 30 patients for dose escalation
- n = 10 patients for dose expansion

Study endpoints

- Recommended Phase 2 dose (RP2D)
  - Safety and PK
  - PSA response

Correlative studies

- CTC AR-V7
- cDNA

Timeline

- FPI beginning of 2Q 2020