**Preclinical development of the second-generation N-terminal domain androgen receptor inhibitor, EPI-7386, for the treatment of prostate cancer**

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**Pre-clinical development of the second-generation N-terminal domain androgen receptor inhibitor, EPI-7386, for the treatment of mCRPC**

The majority of metastatic castration-resistant prostate cancers (mCRPCs) progress on anti-androgen therapy with rising prostate-specific antigen (PSA), revealing a persistent dependence on the androgen receptor (AR) pathway. Despite standard-of-care treatments targeting the AR axis, anti-androgen resistance inevitably arises through numerous mechanisms including AR gene amplification, mutations in the ligand-binding domain (LBD), and the expression of hormone constitutively active splice variants of AR (a.g., AR-V7).

New methods of inhibiting the androgen pathway are needed to overcome these AR-based mechanisms of resistance against full-length, mutated, and splice variant AR. One approach is through selective inhibition of the N-terminal domain (NTD) of the AR, which inhibits its transcriptional activity even in the presence of LBD-driven anti-androgen resistance. EPI-7386 represents a new generation of NTD inhibitors (Antara). It is designed to inhibit transcriptional activity of the AR by interacting with the NTD, thereby being active against both full-length and splice variant AR.

A Phase 1 clinical trial of EPI-7386 is underway and its preclinical efficacy, selectivity, and safety profile are presented.

**BACKGROUND**

1. Andromes are first-in-class NTD inhibitors of the androgen receptor (AR) and mechanism of action. The AR comprises three main functional domains: the LBD, involved in binding with androgens, the NTD, and the LBD, which contains the transcriptional activity domain. Inhibition of the NTD can therefore inhibit androgen-driven transcription via AR.

2. EPI-7386 interacts with AR independently of its activation state.

**RESULTS**

3. EPI-7386 inhibits AR-mediated transcriptional activity of both AR-FL and AR-V7 and AR-dependent cell proliferation.

4. EPI-7386 interacts with the AR independently of its activation state.

5. EPI-7386 inhibits AR-associated transcriptional activity similar to enzalutamide but with some differences while the combination with enzalutamide exhibits a broader and deeper inhibitory effect.

6. EPI-7386 is active in a variety of castrate-sensitive and -resistant prostate cancer xenograft models.

7. EPI-7386 was well tolerated in rat and dog tox studies and is predicted to achieve clinically relevant exposures in humans.

**SUMMARY**

Clinical candidate EPI-7386 displays preclinically:

- Full-length AR target engagement measured in cells.

- Similar potency to the ‘latencies’ in full-length AR driven models in vitro.

- On-target activity against the transcriptional activity of the AR, overall similar to enzalutamide but with a few notable qualitative and quantitative differences.

- Combination treatment with enzalutamide displays broader and deeper inhibition of AR-associated transcriptional activity than higher dose of each single agent.

- Superior activity to enzalutamide in AR-V7-driven cellular models by inhibiting both AR-FL and AR-V7-regulated genes.

- Activity in several in vitro and in vivo CRPC cell lines including enzalutamide resistant models.

- Dose response activity with a minimal active exposure > 800 ng/mL in mouse VCaP xenograft models.

- Toleration in 28-days tox studies in rats and dogs at AUC 2,000,000 ng*hr/mL with activity seen on androgen-sensitive and -resistant viable target organs.

- Favorable human PK parameters supporting QD dosing.

EPI-7386 IND was cleared by the FDA and the Phase 1 study starts in Q2 2020 with initial starting dose of 20mg.

**FIRST IN HUMAN CLINICAL STUDY**

- **Patient population**: mCRPC patients progressing on standard of care (including the latest antitrogens)

- **Study design**: 3+3 design

- **Study endpoints**: Recombined Phase 2 dose (RP2D) Safety and PK

- **Correlative studies**

  - CTCAE AR-V7

  - Immunohistochemistry

  - TMA

  - Study starts Q2 2020

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**Declaration of Competing Interest**

Declarations of relevant interests (if any) are submitted with each manuscript (see the Instructions for Authors).**