**EPI-7386**

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

**EPI-7386 inhibits AR-associated transcriptional activity similar to lutamides but with some differences, while the combinations with LBD inhibitors exhibit a broader and deeper inhibition**

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

**EPI-7386 was well tolerated in rat and dog toxic studies and is predicted to achieve clinically relevant exposures in humans**

The majority of metastatic castration-resistant prostate cancers (mCRPC) progress on anti-androgen therapy with many 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 truncated constitutively active splice variants of AR that lack the LBD (e.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 can inhibit its transcriptional activity even in the presence of LBD-driven anti-androgen resistance.

EPI-7386 represents a new generation of NTD inhibitors (Androz). EPI-7386 has demonstrated potent activity in vitro expressing full-length AR, with an IC50 ~ 400 nM on the inhibition of AR-driven genes. Importantly, EPI-7386 is capable of inhibiting both the full-length AR and AR splice variants which are resistant to currently approved antiandrogens such as lutamides (enzalutamide, apalutamide, darolutamide). These observations translated into anti-proliferative activity in both full-length and AR-V7-driven cell lines.

A Phase 1 clinical trial of EPI-7386 in mCRPC patients failing enzalutamide (Enza) showed promising efficacy, safety, and tolerability with a starting dose of 200 mg QD. Repeat dose showed no accumulation between D1 and D23.

**Results**

**Figure 1. Anitens are first-in-class NTD inhibitors of the androgen receptor.**

**Figure 2. Cellular Transwell assay (CTWA) of AR target-engaged by EPI-7386: (A) NTD target-engaged and EPI-7386 blocks AR-driven transcriptional activity (Transfection Reagents: BeadMax Transfection Reagents, Invitrogen). (B) EPI-7386 blocking AR-driven activity in luciferase reporter assays in C4-2B, CHO, 293T, and HeLa cell lines. (C) EPI-7386 blocks AR-driven activity in SH-SY5Y and A549 cells treated with EPI-7386 (Enzyme MTC test) with cells treated with vehicle showing complete rescue of luciferase activity as a result of compound engagement to its target.”

**Figure 3. Transcriptional analysis of gene expression in LNCaP cells.**

**Figure 4. Transcriptional analysis of gene expression in CaP4T2s.**

**Figure 5. In vivo activity in CTCP xenograft models.**

**Figure 6. Preclinical profile of EPI-7386, a second-generation N-terminal domain androgen receptor inhibitor for the treatment of prostate cancer.**

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

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**Abstract 3556**

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

**Background**

The majority of metastatic castration-resistant prostate cancers (mCRPC) 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 truncated constitutively active splice variants of AR that lack the LBD (e.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 can inhibit its transcriptional activity even in the presence of LBD-driven anti-androgen resistance.

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**Summary**

Clinical compound EPI-7386 displays preclinically:

- Engagement with AR
- On-target activity against the transcriptional activity of the AR, overall similar to lutamides but with a few notable qualitative and quantitative differences
- Superior activity to enzalutamide in AR-V7-driven cellular models by inhibiting both AR-FR and AR-V7 regulated genes
- Complementarily with the second generation of lutamides in inhibiting the AR-associated transcriptional activity, with broader and deeper inhibition of the AR pathway demonstrated in suboptimal doses
- Activity in several in vivo and in vitro CTCP cell lines including enzalutamide-resistant cell lines
- Dose response activity with a minimal active exposure ~ 80,000 ng/ml”h, and target active exposure ~ 300,000 ng/ml”h, in mouse VCaP xenograft models
- Tolerability in 28-days toxic studies in rats and dogs at AUC ~ 200,000 ng/ml”h, with activity seen on androgen-sensitive target organs.
- Favorable human PK parameters supporting QD dosing.

The Phase 1 dose escalation clinical trial of EPI-7386 is ongoing in men with mCRPC progressing on standard of care (including the latest antiandrogens).

Study design

- 3+3 design
- n ~ 18 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: comparison
- AR-V7: response

Timeline

- First in man dosing began Q3 2020