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), AR amplification and expression of constitutively active truncated AR splice variants lacking the LBD, such as AR-V7. A new method of inhibiting the androgen 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 androgen resistance.

EPI-7386 represents a new generation of NTD inhibitors (antitumors) and is designed to inhibit transcriptional activity of the AR by interacting with the NTD. In doing so, EPI-7386 is active against both full-length AR and splice variant AR.

EPI-7386 inhibition is on target, LBD independent and is predicted to achieve high exposures in humans.

EPI-7386 is active in a variety of castrate-sensitive and resistant prostate cancer xenograft models and is predicted to achieve high exposures in humans.

EPI-7386 was well tolerated in rat and dog toxicology studies and is predicted to achieve high exposures in humans.

**Conclusion**

EPI-7386 inhibits androgen-induced transcriptional activity.

**Figure 2:** Effect against androgen-induced PSA-luciferase activity in LNCaP cells.

**Figure 3:** PSA-luciferase activity in LNCaP cells treated with 5uM EPI-7386 versus vehicle.

**Figure 4:** Transcriptional analysis from Nanosetting androgen receptor panel (ISB castor AR-dependent genes) in LNCaP cells.

**Figure 5:** Tumor growth and AR signaling inhibition in xenograft models.

**Figure 6:** Toxicology summary, human-presumed exposures and solid form of EPI-7386.

**Table 1:** Clinical drug candidates.