

EPI-7386 is a novel N-terminal domain androgen receptor inhibitor for the treatment of prostate cancer

Ronan Le Moigne¹, C. Adriana Banuelos², Nasrin R. Mawji², Teresa Tam², Jun Wang², Kunzhong Jian³, Raymond J. Andersen³, Alessandra Cesano¹, Marianne D. Sadar², Han-Jie Zhou¹, Peter Virsik¹

¹ESSA Pharmaceuticals Inc., Houston, TX, USA

²Department of Genome Sciences Centre, BC Cancer Agency, 675 West 10th Avenue, Vancouver, BC V5Z 1L3, Canada

³ Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada

Background:

The androgen receptor (AR) pathway drives most metastatic castration-resistant prostate cancers (mCRPC) even in late stages of the disease. Anti-androgen resistance mechanisms include AR gene amplification, C-terminal ligand-binding domain (LBD) mutations and expression of constitutively active truncated AR splice variants lacking the LBD (e.g. AR-V7). Selective inhibition of the N-terminal domain (NTD) of the AR can inhibit transcriptional activity even in the presence of LBD-driven resistance. A Phase I clinical trial of the first-generation AR NTD inhibitor, EPI-002, demonstrated minor PSA declines in mCRPC patients, revealing the need for more potent and metabolically stable NTD inhibitors. EPI-7386 represents a second generation of NTD inhibitors (Anitens) that are more active and more metabolically stable than EPI-506.

Methods:

Chemical structure activity relationships were developed to increase molecule potency using a wide variety of CRPC models *in vivo* and *in vitro*. Similarly, the stability and selectivity of the molecule were characterized with screening and functional assays.

Results:

EPI-7386 demonstrated a 20-fold improvement in AR-driven cellular potency compared to EPI-002, while being highly stable in human and animal hepatocytes. *In vitro* proliferation assays demonstrated on-target activity across a panel of prostate cancer cell lines, with activity in AR-V7-driven cellular models. EPI-7386 was able to control tumor growth and induce tumor regressions in several CRPC xenografts, including enzalutamide resistant models. In addition, the combination of enzalutamide with EPI-7386 demonstrated a more robust and more homogeneous antitumor response. Pharmacodynamic markers specific to NTD inhibitors will be presented, in addition to their incorporation in the future clinical plan.

Conclusions:

The next generation Aniten compound EPI-7386 is more active and more metabolically stable than EPI-002. It demonstrated potential as single agent in overcoming anti-androgen clinical resistance as well as in combination therapy in earlier stages of the disease. The clinical strategy supporting the development of this new generation of Aniten will be discussed.

Conflict of Interest:

Ronan Le Moigne – Employee of ESSA Pharma

C. Adriana Banuelos – Shareholder of ESSA Pharma

Nasrin R. Mawji - Shareholder of ESSA Pharma

Teresa Tam - None

Jun Wang - Shareholder of ESSA Pharma

Kunzhong Jian - None

Raymond J. Andersen - Shareholder, Research Funding, Consulting Role of ESSA Pharma

Alessandra Cesano - Employee of ESSA Pharma

Marianne D. Sadar – Shareholder, Research Funding, Consulting Role of ESSA Pharma, Expert Testimony for Pfizer

Han-Jie Zhou - Employee of ESSA Pharma

Peter Virsik - Employee of ESSA Pharma

Funding Acknowledgements:

The work was funded by ESSA Pharmaceuticals.