Lessons learned from the metastatic castration-resistant prostate cancer phase 1 trial of EPI-506, a first-generation androgen receptor N-terminal domain inhibitor

Ronan Le Moigne, Han-Jie Zhou, Jon K. Obst, C. Adriana Banelo, Kunzhong Jian, David Williams, Peter Virtsik, Raymond J. Andersen, Marianne D. Sadar, Frank Perabo, Kim N. Chi

ESSA Pharmaceuticals Inc., Houston, TX and South San Francisco, CA, USA, 4Department of Genome Sciences Centre, BC Cancer Agency, 675 West 10th Avenue, Vancouver, BC V5Z 1L3, Canada, 5Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada,

INTRODUCTION

Androgen compounds bind to the N-terminal domain (NTD) of the androgen receptor (AR) to inhibit its transcriptional activity. EPI-506, a first-trace prodrug of EPI-002 (a alaninate), was the first AR NTD inhibitor tested in a First-in-Human phase 1 study in patients with metastatic castration-resistant prostate cancer (mCRPC) failing enzalutamide and/or abiraterone (NCT02606123). The drug was well-tolerated but required high doses to achieve meaningful exposures. At doses >1280 mg, EPI-506 treatment resulted in PSA declines. However, these did not achieve 50% and were of short duration, reflecting doses >1280 mg, EPI-506 treatment resulted in PSA declines. Howev-

EPI-506/002 is a first in class NTD inhibitor of the androgen receptor. (A) Structure of the androgen receptor (AR) and mechanisms of inhibition. The AR is organized in 3 distinct domains: the LBD, involved in binding with androgens, the NTD, and the NBD, which orchestrates the transcriptional activity of the receptor. Inhibiting the NTD with Anitens allows the inactivation of the AR downstream of the LBD, and an effective strategy to downregulate the AR without impacting AR downstream activity. (B) EPI-002, a rapidly dosed trace prodrug of EPI-002, was the first NTD small molecule from the Aniten family of compounds.

EPI-506/002 showed minor PSA declines in patients with mCRPC, due to insufficient exposure

EPI-506/002 is highly metabolized via oxidation and glucuronidation in patient samples, suggesting a first pass effect

CONCLUSION

- EPI-506 was tested in a phase 1 trial and showed PSA declines, but all declines were less than 50%
- The drug was well-tolerated, but exposure was insufficient due to significant metabolism
- EPI-002 and EPI-506 exhibited extensive metabolism in both human hepatocytes and clinical samples, but demonstrated different metabolic pathways in vitro vs. in patients
- Oxidation was the major metabolic pathway seen in the phase 1 clinical samples while O-glucuronidation was the major metabolic pathway seen in in vitro hepatocytes
- Patient plasma samples identified 19 metabolites, including the highly abundant oxidation metabolite M19, which was inactive in an AR-driven reporter assay
- More potent and stable molecules have been synthesized to address EPI-506/002’s metabolic and potency limitations. These next-generation Anitens are currently being prepared for IND filing (see Abstract 220, poster board 221)

Figure 1: EPI-506/002 is a first in class NTD inhibitor of the androgen receptor

Figure 2: EPI-002 clinical activity and day 8 PK

Figure 3: EPI-002 metabolite identification

Figure 4: EPI-002 metabolites are inactive in LNCaP PSA-Luciferase cell line

A portion of the data presented in the poster was funded by US National Cancer Insti-

stitute (R01 CA105304) awarded to Marianne Sadar.