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[1], Han-Jie Zhou[1], Jon K. Obst[2], C. Adriana Banuelos[2], Kunzhong Jian[3], David Williams[3], Peter Virsik[1], Raymond J. Andersen[3], Marianne D. Sadar[2], Frank Perabo[1], Kim N. Chi[4]

[1]ESSA Pharmaceuticals Inc., Houston, TX and South San Francisco, CA, USA, [2]Department 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, [4]Department of Medical Oncology, BC Cancer Agency, 600 West 10th Avenue, Vancouver, V5Z 1L3, Canada

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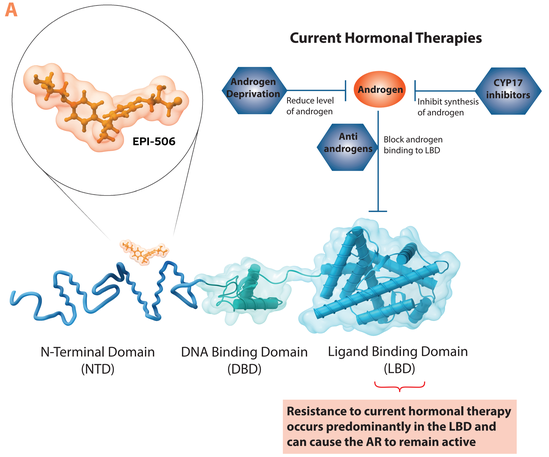
Contact info:
rlemoigne@essapharma.com

INTRODUCTION

Aniten compounds bind to the N-terminal domain (NTD) of the androgen receptor (AR) to inhibit its transcriptional activity. EPI-506, a triacetate prodrug of EPI-002 (ralaniten), 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 the low potency and short half-life of EPI-002. To understand EPI-506's metabolic vulnerabilities, patient plasma samples were analyzed to identify metabolites.



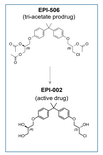
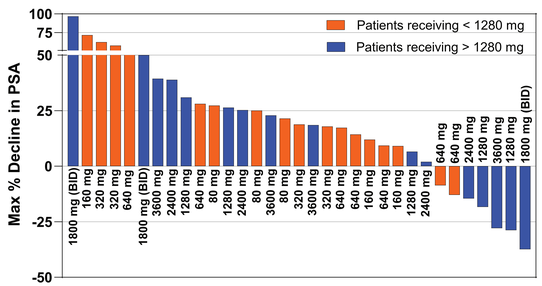
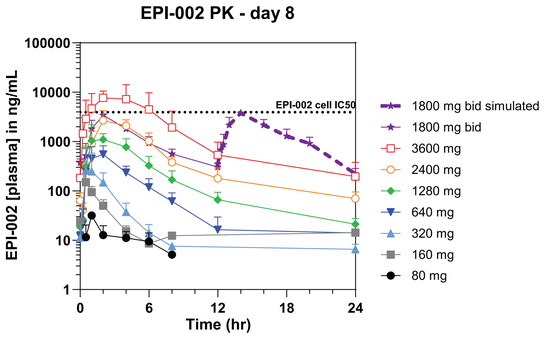


Figure 1: EPI-506/002 is a first in class NTD inhibitor of the androgen receptor
(A) Structure of the androgen receptor (AR) and mechanisms of inhibitions. The AR is organized in 3 distinct domains: the LBD, involved in binding with androgens, the DBD, and the NTD, which orchestrate the transactivation of the receptor. Inhibiting the NTD with Anitens allows the inactivation of the AR downstream of the LBD, and is an effective strategy to counteract the resistance mechanism involving the LBD (mutations, splice variants). (B) EPI-506, a rapidly cleaved triacetate prodrug of EPI-002, was a first-in-class oral small molecule from the Aniten family of compounds.

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





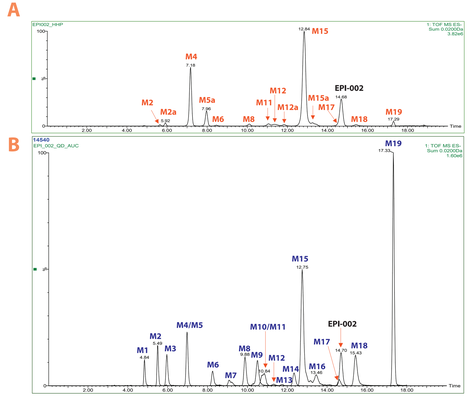
C

PK parameter	Cohort 1 EPI-506 80 mg qd	Cohort 2 EPI-506 160 mg qd	Cohort 3 EPI-506 320 mg qd	Cohort 4 EPI-506 640 mg qd	Cohort 5 EPI-506 1280 mg qd	Cohort 6 EPI-506 2400 mg qd	Cohort 7 EPI-506 1800 mg bid	Cohort 8 EPI-506 3600 mg qd
n	3	4	4[a]	7[b]	7[c]	4	3	2
C_{max} (ng/mL)	26.3 (9.31)	134 (95.2)	345 (437)	768 (391)	1,528 (806)	2,888 (1,257)	3,430 (118)	8,397 (1,396)
t_{max} (h)	1.00 (0.98-4.00)	0.72 (0.52-1.00)	0.99 (0.50-1.97)	1.93 (0.50-4.00)	1.92 (1.00-4.05)	1.98 (1.90-4.08)	2.00 (1.95-2.00)	2.5 (1.00-4.00)
AUC_{tau} (ng.h/mL)	94.3 (8.65)	257 (83.7)	680 (692)	2,439 (678)	5,858 (1,602)	13,545 (5,331)	14,443 (2,429)	42,988 (24,841)
$t_{1/2}$ (h)	-	-	1.6 (0.4)	3.2 (1.8)	5.4 (1.2)	-	-	-

Below Quantification Limit (<5.00 ng/mL)
[a] n=3 for t1/2
[b] n=6 for t1/2
[c] n=4 for t1/2 and Vz/F

Figure 2: EPI-506/002 clinical activity and day 8 PK
(A) Maximal PSA change at any time from start of multi-dose period. PSA declines (ranging from 8-37%) have been observed, especially in higher dose cohorts (≥ 1,280 mg). (B) Mean steady-state EPI-002 plasma concentration-vs-time profiles across EPI-506 dose cohorts. EPI-002 plasma profiles from day 8 multiple-dose samples indicate that EPI-002 plasma drug levels above cellular IC50 were not reached for long-periods. The EPI-506 prodrug was not detected in plasma at any measured time point across dose groups. (C) EPI-002 steady-state plasma pharmacokinetics following 8 days of EPI-506 administration (mean ± SD).

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



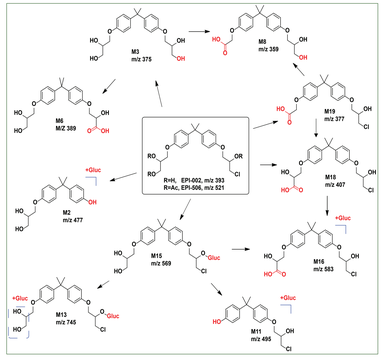


Figure 3: EPI-002 metabolite identification
Extracted ion chromatograms from metabolite profiling of EPI-002 incubated in human hepatocytes incubation (A) and human plasma samples (B). Samples were analyzed using UPLC/MS method. (A) Samples of EPI-002 were incubated in human hepatocytes for 4 hours. (B) Three plasma samples from patients (one 80 and two 3,600 mg doses), were pooled across timepoints and metabolites were analyzed. (C) Proposed major metabolic scheme of main metabolites of EPI-002.

Results:
The major metabolic pathway in human hepatocytes is via direct O-glucuronidation. Direct oxidation is also observed with the loss of chlorine followed by cysteine conjugation (exemplified by M4), but is much less common.
The major metabolic pathway in human plasma samples is via oxidation (exemplified by M19, M18, etc). Direct O-glucuronidation is also observed (exemplified by M15, M12, etc.) but is less common.

EPI-002 metabolites are inactive on the AR pathway

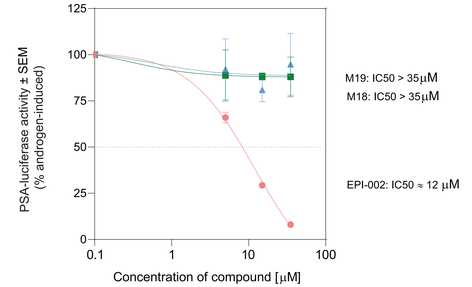


Figure 4: EPI-002 metabolites are inactive in LNCaP PSA-Luciferase cell line
(A) A dose-dependent decrease in AR pathway activity is demonstrated by incubating LNCaP cells transiently-expressing a PSA-driven luciferase construct with different Aniten compounds, in the presence of androgens (R1881).

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-dependent 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 J21)

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