Efficacy, safety, tolerability and pharmacokinetics of EPI-506 (ralaniten acetate), a novel androgen receptor (AR) N-terminal domain (NTD) inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC) progressing after enzalutamide and/or abiraterone.

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INTRODUCTION

- Despite new hormonal therapies, the treatment of CRPC continues to be a challenge due to continued AR signaling.[1]
- EPI-506 is a first-in-class, highly-specific small molecule that binds to a novel target on the AR, the N-terminal domain (NTD) and directly inhibits AR transcriptional activity by blocking the interaction of the AR with transcriptional proteins.[2-4]
- EPI-506 has the potential to affect a broader AR population (e.g., AR splice variants) and circumvent AR-driven resistance mechanisms implicated in treatment-resistant CRPC tumors **(Figure 1).**

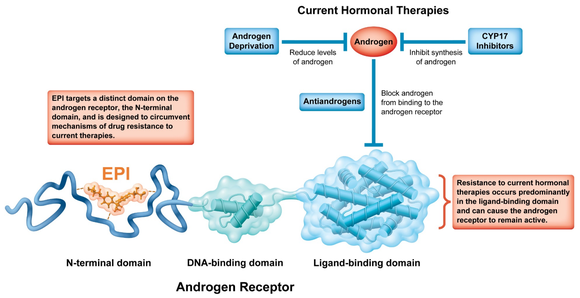
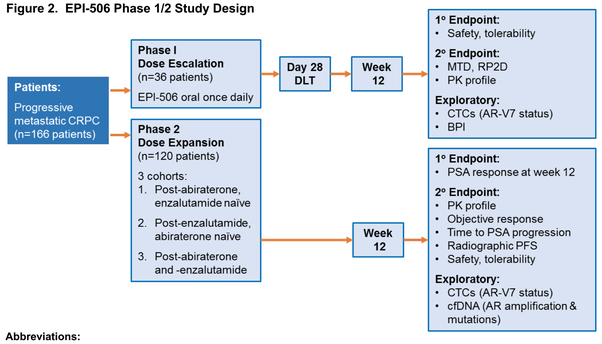


Figure 1. Targeting the AR N-terminal domain (NTD) vs. Ligand-binding domain (LBD).
EPI targets the AR NTD, a region critical for AR transactivation. By contrast, current hormonal therapies work by either depleting levels of androgen, inhibiting the synthesis of androgen, or by preventing androgen binding to the AR, all of which require an intact AR LBD, an area often mutated or truncated in known AR-driven resistance mechanisms. By targeting the AR NTD, EPI-506 may circumvent mechanisms of drug resistance to current therapies.

STUDY DESIGN

This is an ongoing, open-label, single-arm, Phase 1/2 study evaluating the safety, PK, maximum tolerated dose (MTD), and anti-tumor activity of EPI-506 in men with mCRPC who have progressed after prior enzalutamide and/or abiraterone treatment. (NCT02606123)

Figure 2. EPI-506 Phase 1/2 Study Design



Abbreviations:
DLT – Dose Limiting Toxicity; MTD – Maximum Tolerated Dose; PK – Pharmacokinetic; RP2D – Recommended Phase 2 Dose; PFS – Progression-free survival

Table 1: Main Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Male subjects > 18 years with adenocarcinoma of the prostate without neuroendocrine or small cell features • Presence of metastatic disease with one or more bone lesions on bone scan or by the presence of soft-tissue disease as assessed by CT/MRI • Progression despite prior abiraterone and/or enzalutamide, as assessed by prostate-specific antigen (PSA) • Asymptomatic or minimally symptomatic patients • ECOG performance status of 0 or 1 • Castration levels of testosterone	• Have received more than 1 line of chemotherapy for the treatment of mCRPC • Prior use of biologic therapy, cytotoxic chemotherapy, or hormonal agents within 4 weeks prior to start of study drug • Use of prior radionuclide (e.g., strontium-89 or samarium) • Use of radium-223 dichloride within 28 days prior to the start of study drug • Known intracerebral disease or brain metastasis • Known cardiovascular disease; hematologic, hepatic, or renal insufficiency

RESULTS (At time of data cut-off: May 29, 2017)

Table 2: Patient Disposition

Enrolled (# of patients)	21
Dose level (# of patients)	
80 mg	3
160 mg	3
320 mg	3
640 mg	6
1280 mg	3
2400 mg	3
Discontinued (# of patients)	17
Due to adverse events	2
Due to progressive disease	13
Due to withdrawal of consent	2
Ongoing (# of patients)	4
Intra-patient Dose Escalation	
# patients	5
# escalations	8
Exposure (in days) Median (range)	87 (21-444)

Table 3: Patient Characteristics

Age (yrs) Median (range)	72 (58 – 87)
PSA at screening (ng/mL) Median (range)	91.0 (2.9 – 1934.5)
ECOG PS, n (%)	
0	12 (57%)
1	9 (43%)
Gleason score at initial diagnosis, n (%)	
≤ 7	8 (38%)
8-10	12 (57%)
Not available	1 (5%)
Time since initial diagnosis (months) Median (range)	68 (21 – 238)
Prior systemic CRPC therapy, n	
Enzalutamide only	9
Abiraterone only	3
Enzalutamide and Abiraterone	9
Chemotherapy	8
Radium 223	5
Sipuleucel-T	4
Denosumab/zoledronic acid	12
No. of all prior PCa therapies, n (%)	
≤ 4	2 (10%)
> 4	19 (90%)
Metastases at screening, n	
Only soft tissue	2
Only bone lesions	10
Both soft tissue and bone	9
Visceral	
Liver	1
Lung	5

Table 4: Most Commonly Reported Adverse Events (any cause)

	All Grades, N (%)
Diarrhea	8 (38%)
Nausea	7 (33%)
Pain in extremities	6 (29%)
Decreased appetite	4 (19%)
Fatigue	4 (19%)
Anemia	3 (14%)
Arthralgia	2 (10%)
Dizziness	2 (10%)
Fall	2 (10%)

Table 5: Adverse Events ≥ Grade 3

	N (%)	Relationship to study drug
Anemia	3 (14%)	Not related
Neutropenia	2 (10%)	Not related
Arthralgia	1 (5%)	Not related
AST elevated	1 (5%), DLT	Possibly related
Amylase elevated	1 (5%)	Probably related
Gastrointestinal hemorrhage	1 (5%)	Not related
Urinary Retention	1 (5%)	Not related
Syncope	1 (5%)	Not related
Thrombocytopenia	1 (5%)	Not related

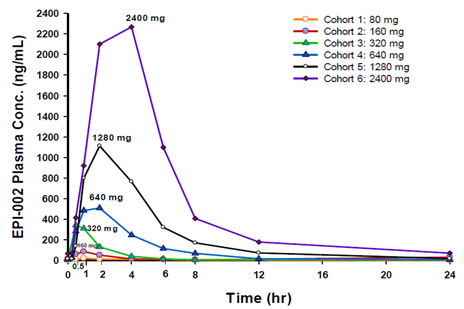


Figure 3. Mean EPI-002 plasma concentration-time profiles across EPI-506 dose cohorts. EPI-002 (active moiety of EPI-506 prodrug) plasma profiles indicate dose-proportionality for C_{max} and AUC following once-daily administration of 80 mg through 2400 mg EPI-506. The EPI-506 prodrug was not detected in plasma at any measured time point across dose groups.

Table 6: EPI-002 Steady-State Pharmacokinetics Following 8 Days of Once-Daily EPI-506 Administration (Mean ± S.D.)

PK Parameter	Cohort 1 80 mg (n=3)	Cohort 2 160 mg (n=3+1 IPDE)	Cohort 3 320 mg (n=3)	Cohort 4 640 mg (n=6)	Cohort 5 1,280 mg (n=3 + 3 IPDE)	Cohort 6 2,400 mg (n=3)
C_{max} (ng/mL)	26 ± 9.3	131 ± 90	393 ± 515	763 ± 426	1,547 ± 880	2,372 ± 813
** t_{max} (hr)	1.00 (1.00 - 4.00)	0.75 (0.50 - 1.00)	1.00 (0.50 - 2.00)	1.50 (0.50 - 4.00)	1.50 (1.00 - 4.00)	4.00 (2.00 - 4.00)
C_{last} (ng/mL)	8.4 ± 9.6	19 ± 19.9	5.8 ± 2.0	8.4 ± 5.8	21 ± 6.5	70 ± 25
*$AUC_{0\text{-}24h}$ (ng*h/mL)	100 ± 18	415 ± 226	815 ± 765	2,541 ± 819	5,722 ± 1703	13,829 ± 6758

IPDE; Intra-patient dose escalation, * AUC_{last} presented for 80 mg and 160 mg, EPI-002 concentrations at the 24 hour timepoint were not detected (BLQ), ** t_{max}; presented as Median (Min-Max)

Simulated human intestinal fluid *in vitro* EPI-506 stability studies demonstrated rapid and complete biotransformation of EPI-506 to EPI-002 within 5-minutes of incubation correlating with lack of detection of EPI-506 (prodrug) and the presence of EPI-002 (active compound) in patient plasma. EPI-506 administered with a low-fat meal indicated a negative food-effect (≤60% decrease in AUC) up to 640 mg and positive food-effect at 1280 mg and 2400 mg dose levels corresponding to 40% and 20% increase in AUC, respectively.

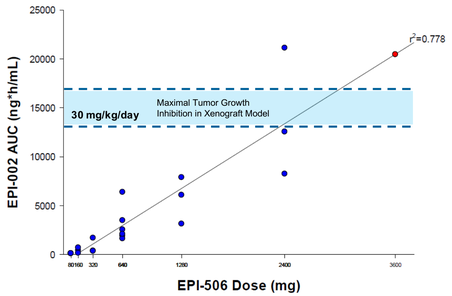


Figure 4. Individual mCRPC patient day 8 steady-state EPI-002 plasma AUC_{24h} and LNCaP xenograft NOD-SCID mouse model target AUC range indicating maximal tumor growth inhibition. Observed patient AUC exposures (blue data points) up to 2400 mg/day (Cohort 6). Simulated mean AUC in patients at 3600 mg/day QD (red data point) via linear regression.

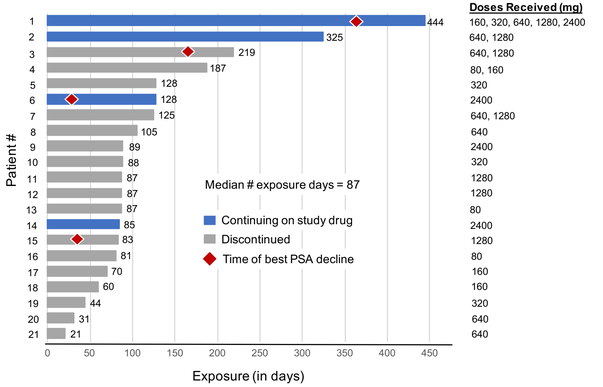


Figure 5. Duration of treatment. Median exposure at time of data cut-off was 87 days (range 21-444). Three patients have had prolonged treatment (median of 325 days; range 219 – not reached), after intra-patient dose escalation.

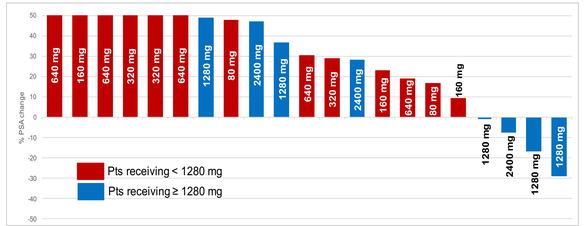


Figure 6. Maximal PSA change at any time from baseline. PSA declines (ranging from 4-29%) and stable disease (unchanged PSA) have been observed at higher dose cohorts (>1,280 mg).

SUMMARY

- This trial is the first to evaluate targeting the AR NTD, a region critical for transcriptional function of all known AR species.
- EPI-506 is well-tolerated with an acceptable safety profile.
- PK data indicates dose-proportionality.
- PSA declines and stable disease have been observed at higher dose cohorts in this ongoing study.
- Human exposures at higher dose levels correlate to the exposure ranges that demonstrated tumor regression in a preclinical LNCaP xenograft mouse model.
- The study is currently enrolling patients in two additional cohorts dosed at 3600 mg once-daily or 1800 mg twice-daily (3600 mg total daily dose).

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