Oral EPI-7386 in Patients with Metastatic Castration-Resistant Prostate Cancer: Results From the First-in-Human Dose Escalation Phase 1a Study

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Abstract

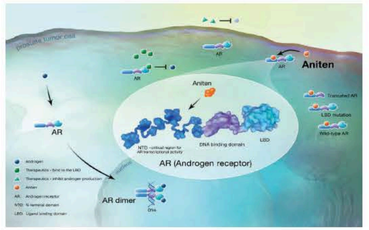
Background: EPI-7386 is a next generation aniten, a new class of compounds designed to inhibit androgen receptor (AR) activity by binding to the N-terminal domain (NTD) of the AR, thus blocking AR transcription even in the presence of AR resistance mechanisms driven by alterations to the AR ligand-binding domain (LBD), including mutations and splice variants. Here we report Phase 1a results of the first-in-human (FIH) study (NCT04421222).

Methods: Study EPI-7386-CS-001 is a Phase 1, open-label, multicenter, dose escalation (Phase 1a) and expansion (Phase 1b) study designed to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity (assessed by PSA declines, objective response and changes in ctDNA fraction) of EPI-7386 in mCRPC patients progressing on standard of care treatment, including next generation antiandrogen(s) and chemotherapy. The study was originally designed to assess up to 5 doses of EPI-7386 (200, 400, 600, 800, and 1000 mg QD); due to 600 mg QD showing exposure saturation while demonstrating a favorable safety profile, two additional cohorts were added examining BID schedules (400 and 600 mg BID).

Results: 31 patients were enrolled in the QD cohorts and 8 in the BID cohorts. Patients had a median of 4 lines of prior therapy for mCRPC: 83% received abiraterone and at least one lutamide, and 58.1% had at least one line of prior chemotherapy. Median PSA doubling time was 2.5 months, median ctDNA fraction 29% with 83% of samples showing non-AR molecular alterations, 29% of patients had visceral disease with serum markers of neuro-endocrine differentiation (e.g. neuro-specific-enolase). No DLTs were observed, EPI-7386 was safe and well tolerated at all doses/schedules evaluated. Related adverse events (AEs) were Grade 1 and 2 and consistent with AEs associated with second-generation antiandrogens.
EPI-7386 showed a long half-life (>24 hours) and accumulated after continuous daily dosing with steady state achieved after Day 8. For doses above 400 mg QD, exposures were at or above those associated with anti-tumor activity in animal models. Signals of anti-tumor activity were observed in patients with fewer than 3 lines of treatment for mCRPC, no visceral metastases and no prior chemotherapy (~30%) showing significant and lasting PSA responses and/or decreases in ctDNA, and/or radiographically documented tumor shrinkage.

Conclusions: Phase 1a treatment with EPI-7386 monotherapy was safe and well tolerated up to a daily dose of 1200 mg (600 mg BID), achieved target clinical exposures and showed preliminary signals of antitumor activity. Phase 1b of the study is open with enrollment focused on pre-chemotherapy, post-second generation anti-androgens treated mCRPC patients in one cohort, and non-mCRPC patients whose tumors are more likely to be predominantly AR-driven in a second, proof of concept cohort. Two doses will be evaluated (600 mg BID and QD) based on FDA Project Optimus recommendations.

Mechanism of Action of EPI-7386



The AR is activated by androgen binding to the LBD which induces the dimerization and nuclear translocation of the AR. Activated AR then regulates the expression of genes involved in prostate cancer progression. Current AR-targeted therapies work directly or indirectly through the LBD of the AR either by competing with androgen binding to the LBD (lutamide) or by inhibiting the androgen production (centrally or through CYP17 inhibition). EPI-7386 targets the NTD of the AR and can inhibit AR transcriptional activity. Anitens are active against wild type and altered AR forms, and therefore, can bypass many resistance mechanisms to current AR-targeted therapies

EPI-7386 Phase 1a/1b Monotherapy Study (First-in-Human) is Designed to Answer 4 Main Questions

- *Are safety and tolerability of EPI-7386 acceptable for use in post-2nd generation anti-androgen mCRPC patient population?*
- *Do drug exposures exceed the predicted efficacious thresholds observed in a preclinical enzalutamide-resistant model?*
- *Can we define patient populations where EPI-7386 may be more/less active?*
- *Can we define the role of intra-patient tumor heterogeneity on drug efficacy?*
- *Is there clinical evidence of androgen-pathway inhibition?*
- *Is there evidence of clinically important efficacy signals (as measured by different parameters)?*

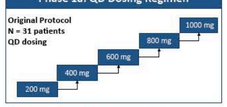
Recommended Expansion Phase Dose(s)

Phase 1 Design and Patient Baseline Characteristics

- **First-in-human phase 1 multi-center open-label study enrolling mCRPC patients failing standard-of-care therapy**
- **Two-part study: Phase 1a dose-escalation followed by Phase 1b dose expansion**

Phase 1a: QD Dosing Regimen

Original Protocol
N = 31 patients
QD dosing



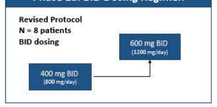
- No limitations on the # prior lines of therapy
- Visceral metastases permitted
- Prior chemotherapy permitted

Parameter	QD n = 31
Median age (range), yrs	72 (50-85) yrs
ECOG performance status, n (%)	
0	7 (22.6)
1	24 (77.4)
Median no. lines of prior therapy (range)	7 (4-13)
Median no. lines of prior therapy for mCRPC (range)	4 (2-10)
Type of prior therapy, n (%)	
Abiraterone ("ABI")	27 (87.1)
Enzalutamide ("ENZ")	25 (80.6)
Both (ABI + ENZ)	22 (71.0)
Darolutamide/Apalutamide	4 (12.9)
Chemotherapy	18 (58.1)

- **Patients enrolled in the Phase 1a under the QD dosing regimen were heavily pretreated:**
  - **Existing AR-directed therapies expected to be ineffective**

Phase 1a: BID Dosing Regimen

Revised Protocol
N = 8 patients
BID dosing



- Limited to ≤ 3 prior lines of therapy
- Exclusion of visceral metastases
- One line of prior chemotherapy permitted

Parameter	BID n = 8
Median age (range), yrs	70 (53-78)
ECOG performance status, n (%)	
0	5 (62.5)
1	3 (37.5)
Median no. lines of prior therapy for mCRPC (range)	2 (1-4)
Type of prior therapy, n (%)	
ABI	6 (75.0)
ENZ	2 (25.0)
Both (ABI + ENZ)	2 (25.0)
Darolutamide/Apalutamide	2 (25.0)
Chemotherapy	**4 (50.0)**

- **Patients enrolled under the BID dosing**
- **Regimen are by design less heavily pretreated:**
  - **Yet 50% received prior chemotherapy**

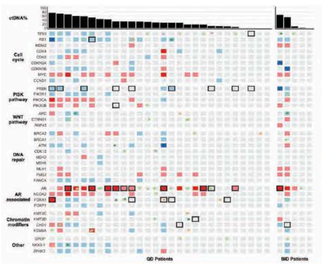
Patients Enrolled in the Phase 1a had Rapidly Progressive Disease

Parameter	QD n = 31
Median baseline PSA, (range), ng/ml	82.9 (9.70 - 2842)
Median baseline PSA doubling time (range), months	**2.5 (<0.0 – 35.8)**
Median baseline ctDNA** % (range)	29 (4-73)
Visceral Disease, n (%)	9 (29)
NSE* > 10 ng/ml, n (%)	8 (25.8)

Parameter	BID n = 8
Median Baseline PSA levels, (range), ng/ml	10.7 (4.91- 570)
Median baseline PSA doubling time (range), months	**2.8 (0.9-6.4)**
Median baseline ctDNA % (range)	7.5 (0-65)
NSE* > 10 ng/ml, n (%)	1 (12.5)

*Neuron-specific enolase (NSE) is an enzyme that is found in the cytoplasm of neurons and neuroendocrine cells. Increased serum levels of NSE may occur in patients with of neuroendocrine tumors

Molecularly, Patients Enrolled in the Phase 1a had a High % of non-AR Molecular Alterations at Baseline



Molecular characterization	QD n = 28
AR-associated alterations	**86%**
• AR amplification	50%
• AR mutations	29%
• AR structural alterations	36%
Non-AR-associated alterations	**93%**
• PI3K pathway	57%
• DNA repair	61%
• WNT pathway	21%
• TP53	46%
• Rb1	39%

Molecular characterization	BID n = 5
AR-associated alterations	**80%**
• AR amplification	60%
• AR mutations	20%
• AR structural alterations	20%
Non-AR-associated alterations	**60%**
• PI3K pathway	40%
• DNA repair	40%
• WNT pathway	40%
• TP53	40%
• Rb1	40%

High % of non-AR molecular alterations is characteristic of advanced mCRPC patients unlikely to respond to AR-targeted therapies

EPI-7386 is Well Tolerated at all Dose Levels and Schedules (QD and BID Regimens) Administered in the Phase 1a (n=39)

TRAE* Term (n=39)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
Anemia	4 (10.2)	2 (5.1)	1 (2.5)	7 (17.9)
Aspartate aminotransferase increased	2 (5.1)	0 (0)	0 (0)	2 (5.1)
Diarrhea	3 (7.7)	2 (5.1)	0 (0)	5 (12.8)
Fatigue	1 (2.5)	5 (12.8)	0 (0)	6 (15.4)
Hot flush	0 (0)	4 (10.2)	0 (0)	4 (10.2)
Nausea	6 (15.4)	1 (2.5)	0 (0)	7 (17.9)

* AE Relatedness as reported by investigators; AEs in above table are tabulated by subject occurrences ≥2.5%

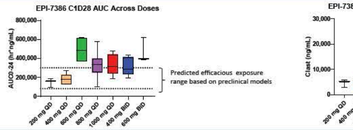
- All TRAEs (exception of one occurrence later considered non-related Grade 3 Anemia) are Grade 1 and 2
- No apparent dose-dependency was observed
- All Grade 2 TRAEs of diarrhea occurred at doses ≥ 600 mg QD dose reduction rate (8.1%) due to related AEs (5 cases of Grade 2 diarrhea in 2 subjects)

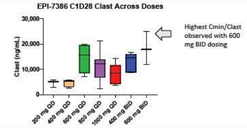
SAEs were Uncommon and all Attributed to Disease Progression

SAE Term (n=39)	Subject n (%)
Acute kidney injury	2 (5.1)
Anemia	1 (2.5)
Anxiety	1 (2.5)
Back pain	1 (2.5)
Chest pain (non-cardiac)	1 (2.5)
Deep vein thrombosis (leg)	1 (2.5)
Disease progression	1 (2.5)
Diverticulitis	1 (2.5)
General physical health deterioration	1 (2.5)

SAE Term (n=39)	Subject n (%)
Malignant pleural effusion	1 (2.5)
Pathological fracture	1 (2.5)
Pulmonary embolism	2 (5.1)
Pulmonary oedema	1 (2.5)
Pyrexia	1 (2.5)
Spinal cord compression	1 (2.5)

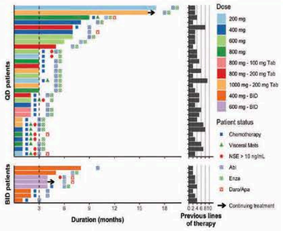
EPI-7386 Human Exposures Reached the Predicted Efficacious Thresholds Observed in Preclinical Models





- EPI-7386 has a long half-life (>24hrs) which supports QD administration
- The steady state AUC EPI-7386 exposure increased with higher doses and all doses tested reached exposures above the minimum target drug threshold
- Doses > 400 mg per day of EPI-7386 exhibit AUC concentrations generally above the highest target drug threshold
- At 600 mg BID, improvement in PK parameters were noted with stable exposure >> 300K AUC throughout the first cycle, and ~ 18K ng/mL (> 30 uM) EPI-7386 as C_{min}/C_{max}
  - Outperformed the saturated PK at 1000 mg QD and improved exposure in comparison to 400 mg BID
  - **Did at least as well as the 600 mg QD cohort**

Longer Duration of Treatment is Associated with Less Prior Therapy for mCRPC



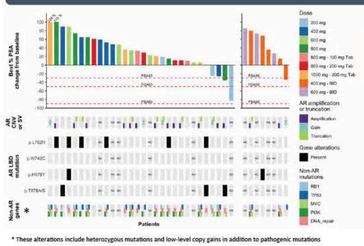
QD Dosing Regimen Patients
- ~30% of patients across all dose levels remained on therapy longer than 3 months
- Patients who progressed before or at 12 weeks had: >10 ng/mL NSE, visceral metastases and received prior chemotherapy and >3 lines of therapy for mCRPC
- One patient was treated for 18 months and one patient is currently on study at 1000 mg dose QD in cycle 17
- **No obvious dose response observed**

BID Dosing Regimen Patients
- ~60% of patients across the two dose levels remained on therapy longer than 3 months
  - Only one of these patients received prior chemotherapy
- 1 patient still on study

Conclusions

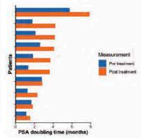
- EPI-7386 monotherapy was safe and well tolerated up to a daily dose of 1200 mg (600 mg BID), achieved target clinical exposures and showed preliminary signals of antitumor activity in a clinically-defined patient subset
- Phase 1b Dose Expansion is ongoing and testing 2 doses/schedules of single agent EPI-7386 in a less heavily pretreated mCRPC patient population (i.e., chemotherapy naive, post-second-generation antiandrogens)

PSA Decreases/Stabilizations were Observed in a Clinically-Defined Subset of Patients



* These alterations include heterozygous mutations and low-level copy gains in addition to pathogenic mutations

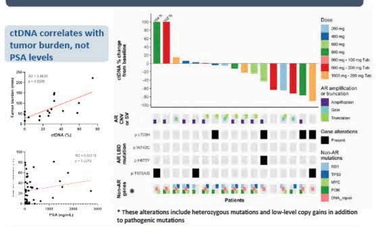
Deeper and more durable PSA decrease/stabilization together with **increases in PSA doubling time** were observed in less pre-treated patients with no visceral disease and less DNA genomic aberrations in non-AR oncogenic pathways



- Changes in PSA doubling time before and after treatment
- Values obtained from three historical measurements and the first three months on treatment
- Calculations derived from the MSK Doubling Time Nomogram

% ctDNA Decreases were Observed even in Patients whose PSA Levels were Increasing

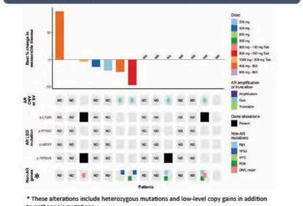
ctDNA correlates with tumor burden, not PSA levels



* These alterations include heterozygous mutations and low-level copy gains in addition to pathogenic mutations

- **ctDNA declines were observed in patients harboring AR point mutations**
  - Also observed in patient with WT AR with other non –AR mutations
- **No clear dose response observed for the %ctDNA decrease at week 12**

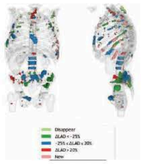
Changes in Measurable Target Lesions were Observed in Patients on Therapy for more than 12 Weeks

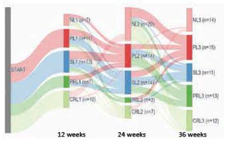


* These alterations include heterozygous mutations and low-level copy gains in addition to pathogenic mutations

- **Fourteen patients remained in the study for > 12 weeks**
- **Seven of these patients had measurable disease at baseline:**
  - **Decreases in measurable disease were observed in 5/7 of these patients even in the absence of PSA decreases**
- **Six of these patients had bone disease only**

Heterogeneity in Tumor Response was Characteristically Observed Using AIQ's Platform (example of patient scan changes)





- **Using AIQ technology, which quantifies the spatiotemporal heterogeneity of treatment response across all lesions, significant heterogeneity in tumor response to EPI-7386 was observed**

Next Steps

Phase 1b doses/schedules recommendation

- Based upon the totality of the Phase 1a dose-escalation and in line with FDA Project Optimus, two dose-schedules will be evaluated in two sequential cohorts in the Phase 1b Dose Expansion part of the study: 600 mg BID and 600 mg QD
- In the Window of Opportunity Phase 1b, the 600 mg BID dose schedule will be evaluated

Phase 1b: Dose Expansion
- **mCRPC @** 600 mg QD & 600 mg BID
  - ≤ 3 prior lines of therapy, no visceral disease, no prior chemotherapy
- 2 Cohorts: 600 mg QD & BID dosing
- Deep biological patient characterization

Phase 1b: Window of Opportunity
- **Non-metastatic CRPC patients @** 600 mg BID
- 1 Cohort: 600 mg BID dosing
- 12 weeks of EPI-7386 monotherapy treatment before starting standard of care therapy