A Phase 1 Trial of Oral EPI-7386 in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC): Update From the First-in-Human Study

Russell Pachynski, MD[1]; Nicholas Iannotti, MD[2]; Andrew Laccetti, MD, MS[3]; Bradley Carthon, MD, PhD[4]; Kim N. Chi, MD, FRCP(C)[5]; Matthew Smith, MD, PhD[6]; Nicholas Vogelzang, MD, FACP, FASCO[7]; Wilson Tu[8]; Edmond M. Kwan, MBBS, PhD[8]; Alex Wyatt, PhD[8,9]; Karen Villaluna[10]; Brett Younginger, PhD[10]; Alessandra Cesano, MD, PhD[10]

[1]Washington University School of Medicine in St. Louis; [2]Hematology Oncology Associates of the Treasure Coast; [3]Memorial Sloan Kettering Cancer Center; [4]Winship Cancer Institute of Emory University; [5]British Columbia Cancer Center Vancouver; [6]Massachusetts General Hospital; [7]Comprehensive Cancer Centers of Nevada, [8]Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia; [9]Michael Smith Genome Sciences Centre, BC Cancer; [10]ESSA Pharma Inc.

Abstract

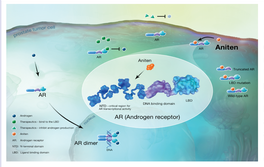
Background:
EPI-7386 is a next generation aniten, a novel class of compounds designed to inhibit androgen receptor (AR) activity by binding to the N-terminal domain (NTD). Preclinical data supports disruption of AR regulated gene transcription even in the presence of resistance mechanisms including ligand-binding (LBD) domain point mutations and truncated splice variants. Here we report preliminary results from the ongoing Phase 1 first-in-human trial of EPI-7386 in mCRPC (NCT04421222).

Methods:
This Phase 1, open-label, multicenter, dose escalation (Part 1a) and expansion (Part 1b) trial was designed to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of EPI-7386 in mCRPC patients (pts) progressing on standard of care treatment, including next generation antiandrogen(s) and chemotherapy. Although originally designed to assess up to 5 doses of EPI-7386 (200, 400, 600, 800, and 1000 mg QD), two additional cohorts were added in the Phase 1a to evaluate 400 and 600 mg BID due to 600 mg QD showing exposure saturation while demonstrating a favorable safety profile. The Phase 1b is ongoing and currently evaluating the 600 mg BID dose regimen.

Results:
31 pts were enrolled in the QD cohorts and 14 in the BID cohorts (8 in Phase 1a and 6 in Phase 1b). Pts enrolled in the QD schedule had a median of 4 lines of prior therapy for mCRPC, 77% received abiraterone and at least one other next generation AR inhibitor (NGAI) and 58% had at least one line of prior chemotherapy. Pts enrolled in the BID cohorts had a median of 2 prior lines of therapy for mCRPC, 75% received prior abiraterone and one NGAI, and 50% had one line of prior chemotherapy. The median number of prior treatments (including at least one NGAI) for mCRPC pts enrolled to date in the Phase 1b is 2 (no prior chemotherapy allowed for this cohort). No DLTs were observed in the dose escalation part of the study; EPI-7386 was safe and well tolerated at all doses/schedules evaluated. All related adverse events (AEs) were Grade 1 and 2 and consistent with AEs associated with NGAI. For doses above 400 mg QD, exposures were at or above those associated with antitumor activity in animal models. Evidence of antitumor activity (including duration of treatment > 12 weeks, decrease in PSA levels or increases in PSA doubling time and/or decreases in ctDNA, and/or radiographically documented tumor shrinkage) were observed in pts with fewer than 3 lines of treatment for mCRPC, no visceral metastases and no prior chemotherapy.

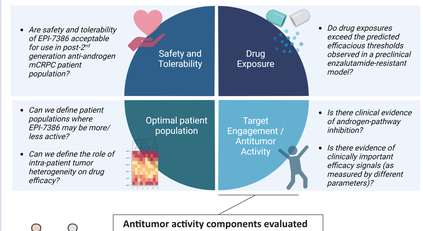
Conclusions:
EPI-7386 single agent was safe, well tolerated up to a daily dose of 1200 mg (600 mg BID), achieved target clinical exposures and showed preliminary signals of antitumor activity in heavily-pretreated mCRPC pts. Part 1b is open with enrollment focused on pre-chemotherapy, post-NGAI treated mCRPC pts. Two doses will be evaluated (600 mg BID and 600 mg 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. 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 androgen production.
EPI-7386 targets the NTD and is 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?*
- *Is there clinical evidence of androgen-pathway inhibition?*
- *Can we define the role of intra-patient tumor heterogeneity on drug efficacy?*
- *Is there evidence of clinically important efficacy signals (as measured by different parameters)?*

Antitumor activity components evaluated

To assess the antitumor activity of EPI-7386, 4 components were measured and integrated in a composite response model. These components are:
- Duration of treatment (< or > 12 weeks)
- Changes in PSA or PSA doubling time (PSAdt)
- Changes in circulating tumor DNA (ctDNA)
- Changes in radiographic measurements of tumor burden

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 (completed)
Original Protocol
N = 31 patients
QD dosing
200 mg, 400 mg, 600 mg, 800 mg, 1000 mg

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

Phase 1a: BID Dosing Regimen (completed)
Revised Protocol
N = 8 patients
BID dosing
400 mg BID (800 mg/day)
600 mg BID (1200 mg/day)

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

Phase 1b - Cohort A: BID Dosing Regimen (currently ongoing)
Revised Protocol
N = 6 (expecting a total of 12)
BID dosing
600 mg BID (1200 mg/day)

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

Parameter	QD n = 31
Median age (range), yrs	72 (50-85)
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**

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 mCPRC (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**

Parameter	BID n = 6
Median age (range), yrs	74 (62-81)
ECOG performance status, n (%)	
0	4 (66.7%)
1	2 (33.3%)
Median no. lines of prior therapy for mCPRC (range)	2 (2)
Type of prior therapy, n (%)	
ABI	2 (33.3%)
ENZ	1 (16.6%)
Both (ABI + ENZ)	3 (50.0%)
Darolutamide/Apalutamide	1 (16.6%)

- **Patients enrolled under the BID dosing regimen are by design less heavily pretreated**

Patients Enrolled in the Phase 1 had Rapidly Progressive Disease

Phase 1a: QD Dosing Regimen	
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%)

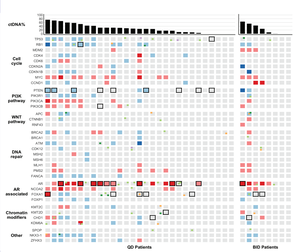
Phase 1a: BID Dosing Regimen	
Parameter	BID n = 8
Median Baseline PSA levels, (range), ng/ml	10.7 (4.91- 570)
Median baseline PSA doubling time (range), months	**2.8 (0.9-6.4)**
Median baseline ctDNA % (range)	7.5 (0-65)
NSE* > 10 ng/ml, n (%)	1 (12.5%)

Phase 1b: BID Dosing Regimen	
Parameter	BID n = 7
Median Baseline PSA levels, (range), ng/ml	7.3 (1.03-34.28)
Median baseline PSA doubling time* (range), months**	**1.6 (0.95 -7.5)**
NSE* > 10 ng/ml, n (%)	3 (60.0%)**

*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
**Percentage is based on n=5 as 2 subjects did not have NSE data available
*** Doubling-time formula derived from the MSK Doubling Time Nomogram (https://www.mskcc.org/nomograms/prostate/psa_doubling_time).

All patients have rapid progressive disease as documented by rapid PSA doubling time

Patients Enrolled In Phase 1a are Enriched in Molecular Alterations Associated with Multi-drug Resistant Disease and Poor Prognosis



Molecular characterization	QD n = 29
AR-associated alterations	**83%**
• AR amplification	48%
• AR mutations	31%
• AR structural alterations	34%
Non-AR-associated alterations	**90%**
• PI3K pathway	55%
• DNA repair	59%
• WNT pathway	21%
• TP53	45%
• RB1	38%

Molecular characterization	BID n = 8
AR-associated alterations	**75%**
• AR amplification	63%
• AR mutations	25%
• AR structural alterations	13%
Non-AR-associated alterations	**63%**
• PI3K pathway	25%
• DNA repair	38%
• WNT pathway	25%
• TP53	25%
• RB1	25%

High % of alterations outside of the AR-axis are 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 and 1b Cohort A (n = 45)

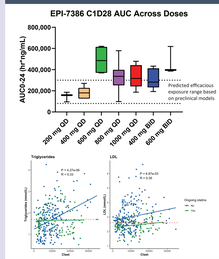
TRAE* Term (n=45)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
Anemia	4 (8.8%)	1 (2.2%)	1 (2.2%)	6 (13.3%)
Aspartate aminotransferase increased	2 (4.4%)	0 (0%)	0 (0%)	2 (4.4%)
Diarrhea	4 (8.8%)	2 (4.4%)	0 (0%)	6 (13.3%)
Fatigue	4 (8.8%)	5 (11.1%)	0 (0%)	9 (20.0%)
Hot flush	0 (0%)	4 (8.8%)	0 (0%)	4 (8.8%)
Nausea	7 (15.5%)	2 (4.4%)	0 (0%)	9 (20.0%)

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

- All TRAEs are Grade 1 and 2 except one case of Grade 3 hypertension (in a patient with pre-existing Grade 2 hypertension and poor compliance to anti-hypertensive therapy) and one Grade 3 anemia (in a patient with pre-existing Grade 2 anemia and rapid bone disease progression with marrow involvement). Both of these events were later considered unlikely related to EPI-7386 administration.
- No apparent dose-dependency was observed
- All Grade 2 TRAEs of diarrhea occurred at doses ≥ 600 mg QD
- Dose reduction rate (6.7%) due to related AEs (2 cases of Grade 1 diarrhea, 1 case of Grade 2 diarrhea in 3 subjects)

18 SAEs Have Been Reported and All Attributed to Disease Progression or Underlying Co-morbidities

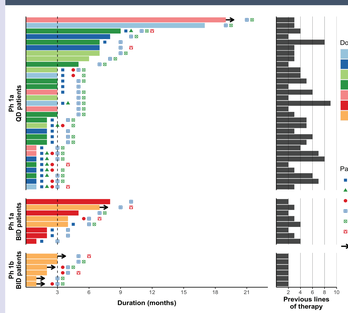
EPI-7386 Human Exposures Reached the Predicted Efficacious Thresholds Observed in Preclinical Models



- EPI-7386 has a long half-life (>24hrs) and its steady state exposure increases with higher doses
- 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 Cmin
- 600 mg BID was chosen as one of the doses/regimens to be further assessed in the Phase 1b
- Serum Triglyceride and LDL levels increase with higher trough level of EPI-7386.
- This effect is not observed in patients treated with statins
- Such metabolic effects have been observed with androgen deprivation therapy[1] and suggest inhibition of AR pathway and target engagement of EPI-7386

[1]Choi et al. Metabolic effects of androgen deprivation therapy. Korean J Urol. 2015

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



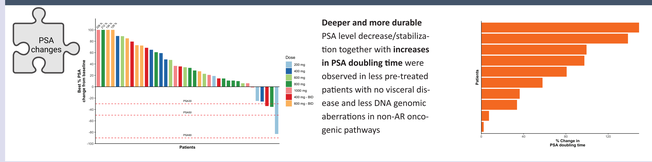
Duration of treatment

Phase 1a QD 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**

Phase 1a BID Patients
- ~60% of patients across the two dose levels remained on therapy longer than 3 months
  - Four of these patients received prior chemotherapy
- 1 patient still on study (did not receive prior chemotherapy)

Phase 1b BID Patients
- Six patients enrolled to date and 4 currently on study
- No patients received prior chemotherapy or had visceral disease

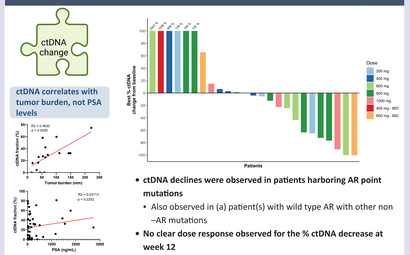
PSA Decreases/Stabilizations were Observed in a Clinically-Defined Subset of Patients



Deeper and more durable PSA level 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

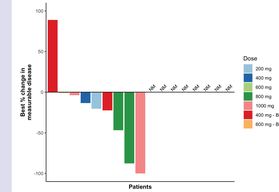
Of 25 patients that completed three cycles of treatment but did not have a PSA decrease, 10 nevertheless showed increases in PSA doubling time[1](40%). Percent change calculated from three historical measurements and the first three months on treatment.
[1]Doubling-time formula derived from the MSK Doubling Time Nomogram (https://www.mskcc.org/nomograms/-prostate/psa_doubling_time).

% ctDNA Decreases were Observed Even in Patients Whose PSA Levels were Increasing



- **ctDNA declines were observed in patients harboring AR point mutations**
  - Also observed in (a) patient(s) with wild type 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



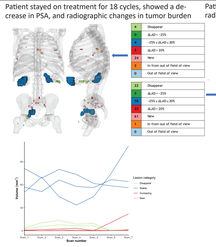
Seventeen patients remained in the study for > 12 weeks

Nine of these patients had measurable disease (nodal) at baseline:
- Decreases in measurable disease were observed in 7/9 of these patients even in the absence of PSA decrease

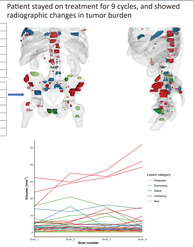
NM = not measurable (i.e., bone only)

Heterogeneity in Tumor Response was Characteristically Observed Using AIQ's Platform

Patient stayed on treatment for 18 cycles, showed a decrease in PSA, and radiographic changes in tumor burden



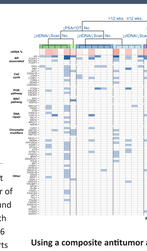
Patient stayed on treatment for 9 cycles, and showed radiographic changes in tumor burden



Using AIQ's technology (aiq-solutions.com), which quantifies the spatiotemporal heterogeneity of treatment response across all lesions, significant heterogeneity in tumor response to EPI-7386 was observed. Lesion categories were determined by the % change in tumor volume from the latest scan to the baseline scan.

Patients with a High Mutational Burden Across Multiple Oncogenic Pathways Show Less Response to AR Inhibition by EPI-7386

In this advanced patient population, the number of genomic alterations found by ctDNA correlates with the duration of EPI-7386 treatment. This supports EPI-7386 benefiting patients that are less advanced, molecularly.



Using a composite antitumor activity model including the elements described above, a dendrogram analysis shows that patients deriving clinical benefit from EPI-7386 administration tend to have a disease prevalently driven by AR-axis alterations, lacking other alterations associated with multi-drug resistant disease.

Conclusions and Next Steps

- 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 which is primarily driven by AR molecular alterations
- The Phase 1b Dose Expansion is ongoing and testing 2 doses/schedules (600 mg BID and 600 mg QD) of single agent EPI-7386 in a less heavily pretreated mCRPC patient population (i.e., chemotherapy naive, post-second-generation antiandrogens)