Phase 1/2 Study of EPI-7386 in Combination with Enzalutamide (Enz) Compared with Enz Alone in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC): Preliminary Results from the Phase 1 (P1) Dose-optimization Component of the Study

Andrew Laccetti, MD, MS[1]; Gurkamal Chatta, MD[2]; Nicholas Iannotti, MD[3]; Christos E. Kyriakopoulos, MD[4]

[1]Memorial Sloan Kettering Cancer Center; [2]Roswell Park Comprehensive Cancer Center; [3]Hematology Oncology Associates of the Treasure Coast; [4]Carbone Cancer Center, University of Wisconsin-Madison

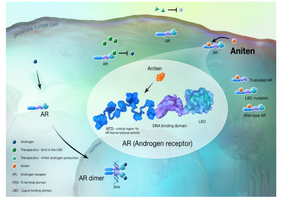
ABSTRACT

Background: EPI-7386 is a next generation aniten designed to inhibit androgen receptor (AR) activity by binding to the N-terminal domain (NTD) of the AR while effectively blocking transcription despite AR resistance mechanisms driven by the ligand-binding domain (LBD), including point mutations and splice variants. This mechanism postulates that EPI-7386 may benefit patients (pts) whose metastatic castration-resistant prostate cancer (mCRPC) is progressing after treatment with latest generation antiandrogens where LBD driven resistance is common. Additionally, preclinical models demonstrate the combination of EPI-7386 with enzalutamide (Enz) results in a deeper blockade of the AR pathway (per RNAseq and ChIPseq data) and greater antitumor activity, prompting initiation of this study.

Methods: This Phase 1/2 multicenter, open-label clinical trial (NCT05075577) is enrolling mCRPC pts on androgen deprivation therapy and naïve to second-generation antiandrogens (one line of prior chemotherapy allowed). Phase 1 (P1) of the study examines escalating doses of EPI-7386 in combination with a fixed dose of Enz. The main objective of P1 is to evaluate the pharmacokinetics (PK) and safety of EPI-7386 and Enz when administered in combination to establish the recommended Phase 2 combination doses (RP2CDs) and address any possible drug-drug interactions. Once the RP2CDs are established, Phase 2 of the study will commence as a two-arm, 2:1 randomized trial evaluating the antitumor activity of EPI-7386 in combination with Enz versus Enz alone.

Results: Seven pts have enrolled in the first 2 cohorts: 3 in cohort 1 (600 mg QD EPI-7386 + 120 mg QD Enz) and 4 in cohort 2 (800 mg QD EPI-7386 + 120 mg QD Enz). No DLTs were observed, and the safety profile was consistent with second-generation antiandrogens (e.g., Grade 1 or 2 AEs of fatigue and hot flashes). PK results demonstrated Enz exposure was minimally impacted by EPI-7386, while, as expected, EPI-7386 exposure was reduced 60-80% by Enz (well-established CYP3A4 inducer). The observed EPI-7386 exposures remained in the clinically relevant range suggested by preclinical xenograft studies. Antitumor activity data are currently available for the first 5 enrolled pts. Two of 3 pts in cohort 1 achieved a rapid decline in PSA levels by week 4, with at least PSA90 by 3 months from starting combination treatment. The third patient in cohort 1, for which a suboptimal PSA response was observed, exhibited reduced exposures to both Enz and EPI-7386 likely due to receiving concomitant primidone (strong CYP3A4 inducer). In cohort 2, 1 pt achieved PSA80 by week 4 and 1 pt by week 12.

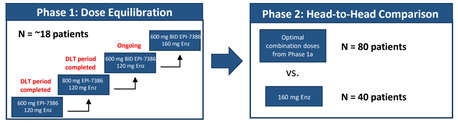
EPI-7386 Mechanism of Action



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.

Study Design

- Phase 1/2 multi-center open-label study enrolling mCRPC patients naïve to second-generation antiandrogens
- Two-part study: Phase 1 dose-equilibration followed by Phase 2 open-label randomized study



PHASE 1 RATIONALE

- This Phase 1 study focuses on the PK and safety of EPI-7386 and Enz when administered in combination to establish the RPD2 for both drugs
- In vitro EPI-7386 is a strong inhibitor of CYP2C8, which is the main enzyme involved in the metabolism of Enz
  - *EPI-7386 when administered in combination with Enz **might increase** the plasma level of the latter*
- Enz is a potent inducer of CYP3A4, which is involved in the metabolism of EPI-7386.
  - *EPI-7386 plasma levels **may be lowered** when administered in combination with Enz (thus requiring dose adjustments)*

Patient Baseline Characteristics

Parameter	EPI-600mg QD + Enz 120mg QD n=3	EPI-800mg QD + Enz 120mg QD n=4
Median age (range), yrs	71.5 (68-73) yrs	73.0 (61-86) yrs
ECOG performance status, n (%)		
0	0 (0%)	2 (50.0%)
1	3 (100.0%)	2 (50.0%)
Bone Only Disease	2 (66.6%)	2 (50.0%)
Prior Chemotherapy, n (%)	**2 (66.6%)**	**3 (75.0%)**

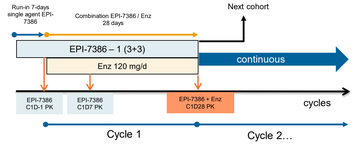
No DLTs Observed in the First 2 Cohorts - Safety Profile Consistent with Second Generation Anti-androgens

	Related to EPI-7386			Related to Enz			Related to both			Total n (%)
TRAE* Term (n=7)	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	
Arthralgia	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)
Blood cholesterol increased	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)
Dysuria	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	1 (14.3)
Fatigue	1 (14.3)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (28.6)
Hot flush	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	2 (28.6)	1 (14.3)	0 (0)	4 (57.1)
Hypertension	1 (14.3)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (28.6)
Hypertriglyceridemia	0 (0)	2 (28.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (28.6)
Oedema peripheral	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)
Paraesthesia	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)
Rash maculo-papular	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)

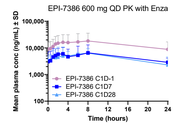
* AE Relatedness as reported by investigators; AEs in above table are tabulated by subject occurrences >2.5%

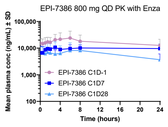
Enz Caused a Significant Decrease in EPI-7386 Exposure, While EPI-7386 Did Not Significantly Impact Enz PK Parameters

- To assess possible drug-drug interactions and establish PK parameters at steady state, a 7-day run-in phase with EPI-7386 alone was initiated at the beginning of Cycle 1 for each dose level. Enz was then introduced at C1D1, and EPI-7386 PK parameters were again measured at cycle 1 day 7 and cycle 1 day 28.
- Enz PK parameters were captured at the end of Cycle 1 and compared with published data



Analyte	Dose	Enz dose	Day	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (hr-ng/mL)	Cmin (ng/mL)
EPI-7386	600 mg EPI-7386	120 mg QD	-1	6.7	18,300	340,000	8,460
			7	5.7	7,390	117,000	2,710
			28	6	6,550	111,000	2,190
EPI-7386	800 mg EPI-7386	120 mg QD	-1	4.5	25,700	406,000	11,800
			7	4.1	11,300	218,000	6,420
			28	4.8	9,430	151,000	3,670



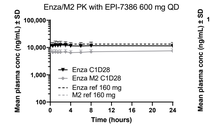


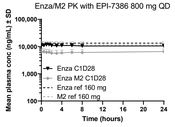
Impact of Enz on EPI-7386

- Significant decrease (~ 60%) in the AUC of EPI-7386 caused by Enz, likely by Enz CYP3A4 induction
- Yet the exposure of EPI-7386 is still within the efficacy exposure range observed in mouse xenograft studies (~ 10uM total fraction drug)

Analyte	Dose	EPI-7386 dose	Day	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (hr-ng/mL)	Cmin (ng/mL)
Enzalutamide	120 mg	600 mg QD	28	2	13,100	280,000	10,900
Enzalutamide	120 mg	800 mg QD	28	2.5	12,200	257,000	9,900
Enzalutamide projection[1]	120 mg	NA	steady state	1.1	11,000	230,000	ND
Enzalutamide reference[2]	160 mg	NA	steady state	2.5	16,590	321,500	12,000
N-desmethyl enzalutamide	120 mg	600 mg QD	28	18.7	7,640	171,000	6,470
N-desmethyl enzalutamide	120 mg	800 mg QD	28	12.3	6,690	150,000	5,410
N-desmethyl enzalutamide projection[1]	120 mg	NA	steady state	ND	9,510	208,725	7,928
N-desmethyl enzalutamide reference[2]	160 mg	NA	steady state	ND	12,680	278,300	10,570

[1] Gibbons et al, Clin Pharmacokinet, 2015 ; [2] Enzalutamide NDA, Clin Pharm section

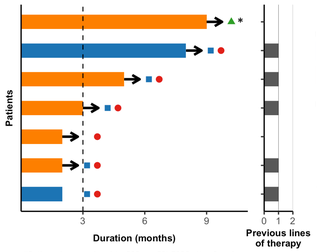




Impact of EPI-7386 on Enz

- EPI-7386 does not significantly impact Enz PK parameters (~25% decrease in M2 metabolite)
- Importantly, there is no increase in Enz exposure through potential CYP2C8 inhibition, which leaves "room" for increasing the dose of Enz in future cohorts to 160 mg QD

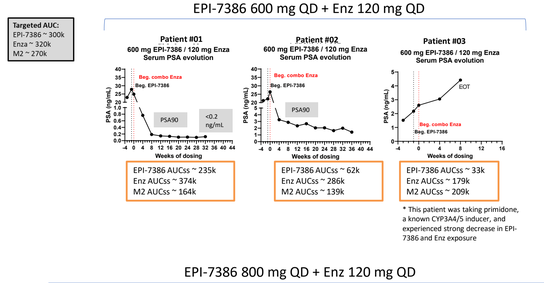
Treatment Duration



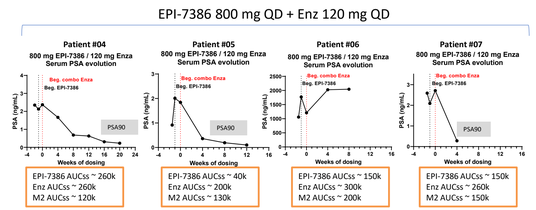
*Patient dose escalated to 800 mg EPI-7386 after 9 cycles of 600 mg EPI-7386.

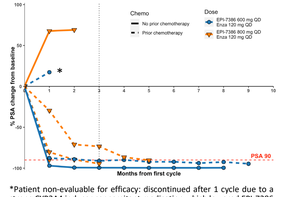
- **7 patients enrolled in the first 2 cohorts and 6 are currently ongoing:**
  - One patient discontinued after 1 cycle due to a drug-drug interaction with a concomitant medication (primidone, CYP3A4 inducer) resulting in negligible exposure to EPI-7386
- **5/7 patients received prior chemotherapy**

PSA Change: 5/6 Evaluable Patients Showed PSA Decrease > 90% to Date, Regardless of the Previous Chemotherapy Status



* This patient was taking primidone, a known CYP3A4/5 inducer, and experienced strong decrease in EPI-7386 and Enz exposure





*Patient non-evaluable for efficacy: discontinued after 1 cycle due to a strong CYP3A4 inducer concomitant medication which lowered EPI-7386 and Enz exposure

PSA Responses Compares Favorably to Historical Controls

Patient Population	Agent	PSA90 (90 Days)	Study Type	Patient Number	PSA90 (Overall)	Reference
mCRPC pre-chemo (PREVAIL)	ENZ	37%	Pivotal	819	47%	Beer et al., NEJM 2014; Armstrong et al., Eu Assoc of Uro 2020
mCRPC pre-chemo (PREMISE	ENZ		Observational	1171	45%	Payne et al., Int J of Cancer 2021
mCRPC pre-chemo (COU-AA-302)	ABI		Pivotal	539	31%	Ryan et al., NEJM 2013; Xu et al., Clin Cancer Res 2015
mCRPC pre-chemo (ACIS)	ABI		Pivotal	490	47%	Saad et al., Lancet Oncol 2021
mCRPC pre-chemo (ACIS)	ABI+APA		Pivotal	492	53%	Saad et al., Lancet Oncol 2021
mCRPC post-chemo (AFFIRM)	ENZ	13%	Pivotal	800	25%	Scher et al., NEJM 2021; Armstrong et al., Cancer 2017
mCRPC post-chemo (PREMISE)	ENZ		Observational	418	31%	Payne et al., Int J of Cancer 2021
mCRPC post-chemo (COU-AA-301)	ABI	13%	Pivotal	790	14%	Xu et al., Clin Cancer Res 2015

CONCLUSIONS

- **Combination of EPI-7386 and Enzalutamide at the doses tested is safe and well tolerated**
- **No significant effect of EPI-7386 on Enzalutamide exposure**
- **Enzalutamide significantly reduces EPI-7386 exposure (likely through induction of CYP3A4)**
- **Deep and durable PSA reductions observed in 5/6 evaluable patients (despite prior chemotherapy and lower than full dose of Enzalutamide)**
- **EPI-7386 600 mg BID + Enz 120 mg QD cohort currently enrolling**
  - **Based on safety and PK data from this cohort, another cohort testing 600 mg BID + Enz 160 mg QD could be enrolled**

This study is managed by the Prostate Cancer Clinical Trials Consortium (PCCTC). ESSA Pharma Inc. is sponsoring the study. Astellas Pharma and Pfizer are providing enzalutamide for this study.