Phase 1/2 Trial of Oral EPI-7386 (masofaniten) in Combination with Enzalutamide (Enz) Compared with Enz Alone in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC): Current Phase 1 (P1) results

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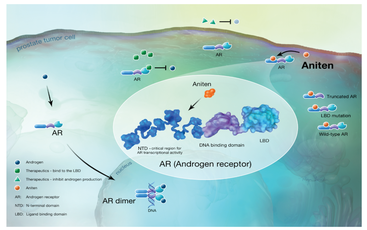
Background

The androgen receptor (AR) is activated by androgen binding to the ligand binding domain (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 the androgen production (centrally or through CYP17 inhibition).



EPI-7386 (adopted name masofaniten) is a next generation aniten designed to inhibit AR activity by binding the N-terminal domain (NTD) and blocking transcription despite resistance driven by point mutations and splice variants in the LBD. In preclinical models, the combination of masofaniten with enzalutamide (Enz) results in a deeper blockade of the AR pathway and greater antitumor activity, prompting this trial.

This Phase 1/2 multi-center, open-label clinical trial (NCT05075577) is enrolling mCRPC pts on androgen deprivation therapy and naïve to second-generation antiandrogens (1 line of prior chemotherapy in the metastatic hormone sensitive (mHSPC) setting allowed). P1 examines escalating doses of masofaniten with Enz. Primary and secondary endpoints of P1 evaluate the safety and pharmacokinetics (PK) of masofaniten and Enz when co-administered to establish recommended Phase 2 combination doses (RP2CDs) and address possible drug-drug interactions (DDIs). Once RP2CDs are established, Phase 2 (P2) will commence as a two arm, 2:1 randomized trial evaluating antitumor activity of masofaniten in combination with Enz versus Enz alone.

P1 completed enrollment with 18 pts in 4 cohorts and 16 pts evaluable for efficacy as per protocol. The combination regimen was well tolerated with a safety profile consistent with Enz monotherapy. One grade 3 rash was observed in cohort 4 evaluating masofaniten 600 mg BID + Enz 160 mg QD. PK results demonstrated Enz exposure was not impacted by concomitant administration of masofaniten, allowing testing of the full dose of Enz (160 mg QD). By contrast, masofaniten exposure was consistently reduced by concomitant administration of Enz (CYP3A4 inducer that metabolizes masofaniten) but remained within the clinically relevant range with the highest exposures and Cmin observed using masofaniten BID dosing. Although efficacy data are still maturing, to date, response rates are PSA50 88% (14/16 pts), PSA90 81% (13/16 pts) and PSA <0.2 ng/mL 56% (9/16 pts) in evaluable pts, regardless of their previous chemotherapy status (6/16 evaluable pts received prior docetaxel in mHSPC setting).

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Conflicts of Interest Disclosure Statement: KV, BY, RLM and AC are ESSA employees and shareholders. All other co-authors have no relevant conflicts to disclose.

Study Design

- Phase 1/2 multi-center open-label study enrolling mCRPC patients naïve to second-generation antiandrogens (prior docetaxel in mHSPC allowed)
- Two-part study: Phase 1 dose-equilibration followed by Phase 2 open-label randomized study

PHASE 1 RATIONALE

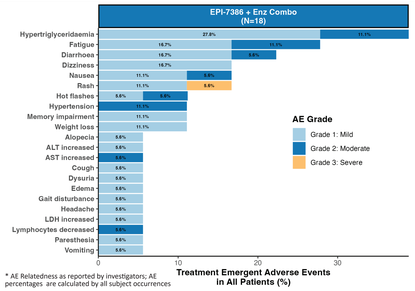
- The Phase 1 study focused on the PK and safety of masofaniten and Enz when administered in combination to establish the RP2CDs for both drugs
- In vitro, masofaniten is a strong inhibitor of CYP2C8, the main enzyme involved in the metabolism of Enz
  - *Masofaniten when administered in combination with Enz **might increase** the plasma level of the latter*
- Enz is a potent inducer of CYP3A4, which is involved in the metabolism of masofaniten
  - *Masofaniten plasma levels **may be lowered** when administered in combination with Enz (thus requiring dose adjustments)*

Patient Baseline Characteristics

Parameter N=18	Cohort 1 Masofaniten 600mg QD + Enz 120mg QD n=3[1]	Cohort 2 Masofaniten 800mg QD + Enz 120mg QD n=4[1]	Cohort 3 Masofaniten 600mg BID + Enz 120mg QD n=4	Cohort 4 Masofaniten 600mg BID + Enz 160mg QD n=7
Median age (range), yrs.	70.0 (68-73)	73.5 (61-86)	72.0 (60-75)	75.0 (65-89)
ECOG performance status, n (%)				
0	0 (0%)	2 (50.0%)	2 (50.0%)	5 (71.4%)
1	3 (100.0%)	2 (50.0%)	2 (50.0%)	2 (28.6%)
Bone Only Disease	1 (33.3%)	4 (100.0%)	3 (75.0%)	1 (14.3%)
Prior Chemotherapy, n (%)	2 (66.6%)	3 (75.0%)	1 (25.0%)	2 (28.6%)
Median Baseline PSA (range), ng/mL	24.9 (2.6-26.4)	2.54 (1.84-1209)	2.13 (1.35- 20.6)[2]	13.5 (1.18-565)[3]

[1]2 of the 3 subjects from the masofaniten 600mg QD cohort dose escalated to the masofaniten 800mg QD cohort after 9 cycles. 2 of the 3 subjects from the masofaniten 800mg QD cohort dose escalated to the masofaniten 600mg BID cohort after 8-10 cycles
[2] Masofaniten 600mg BID + Enza 120mg QD, 1/4 baseline PSA result was obtained with local lab
[3] Masofaniten 600mg BID + Enza 160mg QD , 1/7 baseline PSA result was obtained with local lab

Combination Safety Profile is Consistent with Enz Single Agent



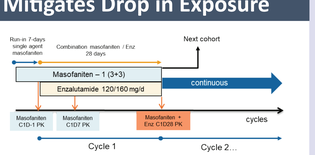
* AE Relatedness as reported by investigators; AE percentages are calculated by all subject occurrences

The combination is safe and well tolerated

- Most frequent adverse events are related either to AR inhibition or the gastrointestinal tract irritation, Grade 1 and 2 in severity, and consistent with Enz safety data (label information)
- In Cohort 4, one Grade 3 rash, maculo-papular event deemed as probably related, was observed after administration of EPI-7386 and Enz in combination during the DLT period resulting in the expansion of the cohort. The patient has since discontinued study on C2D18 due to disease progression (liver metastasis)

DDI with Full Dose Enz is Similar to 120 mg - Masofaniten 600 mg BID Dosing Mitigates Drop in Exposure

- To assess possible DDIs and establish PK parameters at steady state, a 7-day run-in phase with masofaniten alone was initiated at the beginning of Cycle 1 for each dose level. Enz was then introduced at C1D1. Masofaniten, enzalutamide and its N-desmethyl metabolite (M2) were measured.



PK questions assessed during dose finding

Agent	DDI issue	Hypothesis tested
Masofaniten	CYP2C8 inhibitor	Increased enzalutamide exposure Can we use full dose Enz (160 mg)?
Enzalutamide	CYP inducer	Decreased masofaniten exposure Can we dose masofaniten BID?

Masofaniten is a "victim" of Enz

Analyte	Dose / Regimen	Enza dose	Number of patients	Day	T_{max} (hr)	C_{max} (ng/mL)	AUC_{24} (hr-ng/mL)	Clast (ng/mL)
Masofaniten	600 mg QD	120 mg QD	3	-1	6.7	18,300	340,000	8,860
				7	5.7	7,390	117,000	2,880
				28	6	6,550	111,000	2,300
Masofaniten	800 mg QD	120 mg QD	4	-1	4.5	25,700	406,000	12,700
				7	4.1	11,300	218,000	7,840
				28	4.8	9,430	151,000	3,670
Masofaniten	600 mg BID	120 mg QD	4	-1	3.3	28,900	508,250	20,250
				7	2.0	17,150	292,250	13,550
				28	4.3	11,913	233,000	9,685
Masofaniten	600 mg BID	160 mg QD	5-6	-1	8.0	22,833	435,833	16,817
				7	6.2	13,483	273,833	11,948
				28	2.8	11,018	189,600	8,248

Masofaniten is not a "perpetrator" of Enz

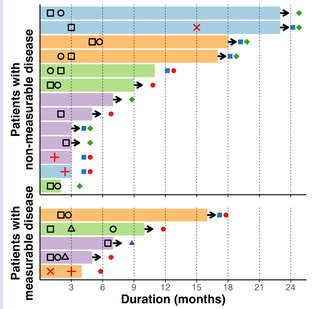
Analyte	Dose	EPI-7386 dose	Number of patients	Day	T_{max} (hr)	C_{max} (ng/mL)	AUC_{24} (hr-ng/mL)	Clast (ng/mL)
Enzalutamide	120 mg	600 mg QD	3	28	2	13,100	280,000	11,500
Enzalutamide	120 mg	800 mg QD	4	28	2.5	12,200	257,000	10,600
Enzalutamide	120 mg	600 mg BID	4	28	2.25	15,050	304,750	12,523
Enzalutamide	160 mg	600 mg BID	5	28	2.1	13,958	300,600	12,186
Enzalutamide projection[2]	120 mg	NA	NA	steady state	1.1	11,000	230,000	ND
Enzalutamide reference[2]	160 mg	NA	NA	steady state	2.5	16,590	321,500	12,000
N-desmethyl enzalutamide	120 mg	600 mg QD	3	28	18.7	7,640	171,000	7,580
N-desmethyl enzalutamide	120 mg	800 mg QD	4	28	12.3	6,690	150,000	6,580
N-desmethyl enzalutamide	120 mg	600 mg BID	4	28	2	7,318	161,750	7,228
N-desmethyl enzalutamide	160 mg	600 mg BID	5	28	2.6	8,424	191,800	8,110
N-desmethyl enzalutamide projection[2]	120 mg	NA	NA	steady state	ND	9,510	208,725	7,928
N-desmethyl enzalutamide reference[2]	160 mg	NA	NA	steady state	ND	12,680	278,300	10,570

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

Summary

Agent	DDI issue	Hypothesis tested	Result	Implication
Masofaniten	CYP2C8 inhibitor	Increased enzalutamide exposure	**NO** Enz PK is not altered by masofaniten	• **Enz dose can be used in combination at the full approved dose of 160 mg QD**
Enzalutamide	CYP3A inducer	Decreased masofaniten exposure	**YES** Masofaniten exposure is decreased by Enz	• Despite a reduced AUC, masofaniten levels are still in an active range • Enz-dependent CYP induction doesn't worsen over time • **Masofaniten 600 mg BID dosing can partially compensate the drop in exposure caused by Enz** • **Enz's effects on masofaniten were similar at 160 mg QD as 120 mg QD; therefore 160 mg QD can be used as RP2CD for Enz**

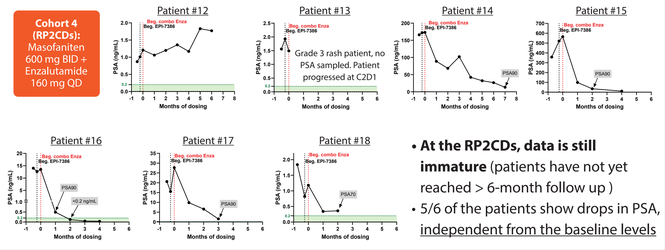
Phase 1 – Current Patient Disposition



- **Out of 18 patients: 13 ongoing, 5 discontinued**
  - Disease progression = 3
  - Brain abscess = 1 (non-related event)
  - Non-cancer-related death = 1 (patient with PSA90 and <0.2 ng/mL)
- **13 have non-measurable disease:** bone only or bone + non-target lesions: 11/13 SD ; 2/13 PD
  - 2 non-evaluable for efficacy (per protocol, due to insufficient drug exposure)
- **5 have measurable disease (RECIST v1.1)**
  - 2/5 PR ; 2/5 SD ; 1/5 PD

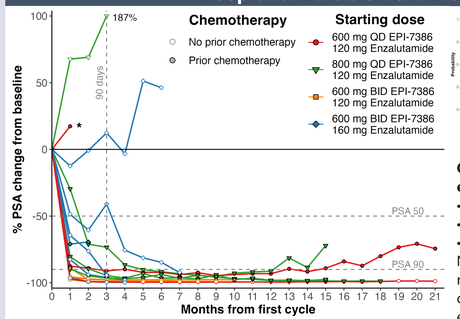
At RP2CDs, PSA Results Show Consistent Drops

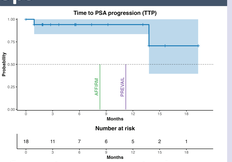
Cohort 4 (RP2CDs): Masofaniten 600 mg BID + Enzalutamide 160 mg QD



- **At the RP2CDs, data is still immature** (patients have not yet reached > 6-month follow up)
- 5/6 of the patients show drops in PSA, independent from the baseline levels

Across All Cohorts, Patients Showed Rapid, Deep and Durable PSA Drops





*Two patients are not evaluable for efficacy: one patient that experienced a DDI with a concomitant drug, and another DLT patient (not plotted past baseline)

Current response rates in evaluable patients are:

- PSA50 88% (14/16 pts)
- PSA90 81% (13/16 pts)
- PSA <0.2 ng/mL 56% (9/16 pts)

No association is seen between response rate and previous chemotherapy status (6/16 evaluable patients received prior docetaxel in mHSPC setting)

Conclusions

Based on the totality of the safety and the PK data from the Phase 1 part of the study , the recommended Phase 2 combination doses are 600 mg BID masofaniten + 160 mg QD Enz

- **Combination of masofaniten and Enz at all doses tested is safe and well tolerated**
- **Masofaniten has no effect on Enz exposure thus allowing the use of full dose per label of Enz in combination**
- **Enz significantly reduces masofaniten exposure (likely through induction of CYP3A4), but BID dosing of masofaniten can mitigate the drop and maintain clinically relevant Cmin**
- **Rapid, deep and durable PSA reductions were observed in patients, regardless of previous chemotherapy status (6/16 evaluable pts received prior docetaxel in mHSPC setting) and lower than full dose of Enz (i.e., 120 mg/day)**
- **To date, 81% of the patients dosed with masofaniten + Enz (independently of dose level received) achieved a PSA decline > 90%. PSA90 was also achieved in < 90 days in 69% of patients**
- **Phase 2 of the study is currently enrolling**