Phase 1/2 Trial of Oral EPI-7386 (masofaniten) in Combination with Enzalutamide Compared with Enzalutamide Alone in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC): Phase 1 Results and Phase 2 Design.

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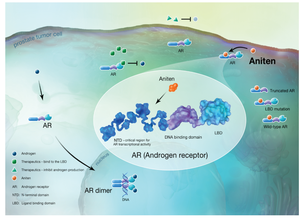
Background

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 act directly or indirectly through the LBD of the AR either by competing with androgen binding to the LBD (lutamides) or by inhibiting the androgen production (centrally or through CYP17 inhibition).

Masofaniten (EPI-7386), as a next generation aniten, inhibits androgen receptor (AR) activity by binding the N-terminal domain and blocking transcription, irrespective of ligand-binding domain resistance mechanisms. Preclinically, combining masofaniten + enzalutamide results in a deeper blockade of the AR pathway and greater antitumor activity than either agent alone.

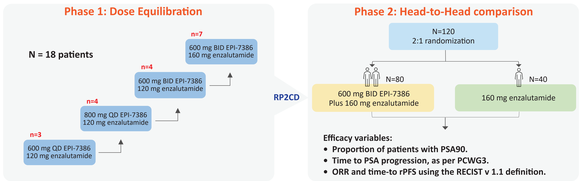


This Phase 1/2 multicenter, open-label clinical trial (NCT05075577; EU CT 2023-509336-25-00) is conducted in mCRPC patients on androgen deprivation therapy naïve to second-generation antiandrogens (one prior line of chemotherapy in the metastatic hormone sensitive setting allowed). The Phase 1 (P1) component of the study, which has completed enrollment (n=18), evaluated escalating doses of masofaniten + enzalutamide for safety, potential drug-drug interactions and pharmacokinetics (PK) to identify the recommended Phase 2 (P2) combination dose (RP2CD).

The P2 component of the study is a two arm, 2:1 randomized trial evaluating antitumor activity of masofaniten + enzalutamide versus enzalutamide single agent in the same patient population. Approximately 120 patients will be randomized in study: 80 patients in the masofaniten 600 mg BID + enzalutamide 160 mg QD arm, and 40 patients in the single agent enzalutamide at 160 mg QD arm.

Study Design

- Phase 1/2 multi-center open-label study enrolling mCRPC patients naïve to second-generation antiandrogens (prior docetaxel in mHSPC allowed).
- ~50 sites planned between US, Canada, Australia and Europe.
- Two-part study: Phase 1 dose-equilibration followed by Phase 2 open-label randomized study.



Enrollment in Phase 1 has completed, recommended Phase 2 combination dose (RP2CD) was established **at 600 mg BID EPI-7386 + 160 mg QD enzalutamide.**

Phase 2 enrollment is open in US, Canada, Australia, and Europe (France, Spain, and Belgium).

Spain - Reference Member State (Site Name/PI Last Name)	France (Site Name/PI Last Name)	Belgium (Site Name/PI Last Name)
Hospital Universitario 12 de Octubre/ Gonzalez Billalabeitia	Centre Leon Berard/ Rechon (Coordinating Site)	CHU HELORA: Hopital de Mons - site Kennedy/ Caisert
NEXT Oncology Madrid, Hospital Universitario Quironsalud Madrid/ Boni	Institut de Cancerologie de l'Ouest - Site Angers/ Abadie-Lacourtoisie	Grand Hopital de Charleroi/ Gizzi
Vall d'Hebron Institut d'Oncologia/ Carles	Institut de Cancerologie de l'Ouest - Site Saint Herblain/ Bompas	UCL Saint-Luc, Brussels/ Sironi
Hospital Universitario Marques de Valdecilla/ Duran Martinez	CHU de Poitiers/ Bmambux	
Hospital Universitario La Paz/ Pinto Marin	Institut Claudius Regaud/ Oncopole/ CHU Toulouse/ Mourey	
Hospital Clinica/ Mellado	Gustave Roussy/ Naoun	
Hospital Germans Trias I Pujol - ICO Badalona/ Ochoa de Olza Amat	Centre Hospitalier Universitaire de Brest - Hopital La Cavale Blanche/ Bphumraan	
Hospital Duran I Reynals - ICO Bellvitge/ Prulats Rodriguez	Institut Bergonie/ Teyssonneau	
Institut Catala d'Oncologia Girona (ICO Girona) - Hospital Universitari de Girona Dr Josep Trueta/ Sala	Institut regional du Cancer de Montpellier - ICM Val d'Aurelle/ Tosi	
Hospital Universitario Virgen de la Victoria/ Santos		

List of sites and principal investigators participating in the EU.

Patients enrolled in Phase 1 trial displayed characteristics associated with early treatment failure on enzalutamide single agent

Baseline Patient Characteristics

Demographics	n (%) or Median (range)
Ethnicity	
Not Hispanic or Latino	18 (100%)
Race	
Asian	0 (0%)
Black or African American	0 (0%)
White	18 (100%)
Age	76 (61, 90)
BMI	29.6 (25.1, 36.2)

Clinical labs	Median (range)
Testosterone (nmol/L)	0.36 (0.10, 1.21)
Albumin (g/dL)	4.20 (3.40, 4.90)
LDH (U/L)	175 (130, 585)
ALP (U/L)	90 (63, 263)
Hemoglobin (g/dL)	13.80 (10.90, 15.50)
Neutrophil:lymphocyte ratio	3.04 (1.34, 8.50)

Disease natural History	n (%) or Median (range)
ECOG Score	
1	9 (50%)
0	9 (50%)
Years since diagnosis	6.8 (2.8, 20.0)
Gleason at biopsy	
< 8	7 (44%)
≥ 8	9 (56%)
Gleason score at prostatectomy	
7	2 (67%)
9	1 (33%)
Prior prostatectomy	3 (17%)
Time to CRPC (months)	34 (18, 156)
PSA Doubling time (months)	2.70 (0.71, 9.26)
PSA at Screening	3 (1, 988)
High-risk disease	15 (83%)

Radiographic metrics	n (%)
Number of bone lesions at BL	
0	2 (11%)
1 - 4	9 (50%)
5 - 20	4 (22%)
> 20	3 (17%)
Number of nodal mets at BL	
0	10 (56%)
≥ 1	8 (44%)
Number of visceral mets at BL	
0	16 (89%)
≥ 1	2 (11%)
High volume disease	9 (50%)
Metastases at PCa diagnosis	6 (43%)

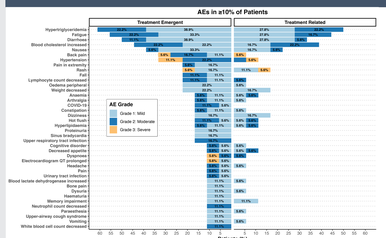
Prior/concomitant treatments	n (%)
Prior lines of therapy	
0 - 2	7 (39%)
3 - 4	10 (56%)
> 4	1 (5.6%)
Prior chemo	8 (44%)
Prior ADT	18 (100%)
Prior 1st gen. anti-androgens	8 (44%)
Prior immunotherapy	1 (5.6%)
Opioids >14 days	2 (11%)
Opioids ever	6 (33%)
Prior radiation therapy	4 (22%)

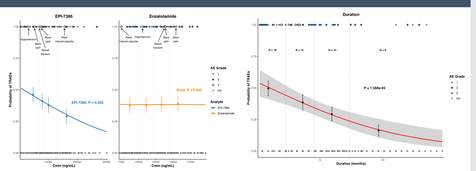
ALP: Alkaline phosphatase; BL: Baseline; CRPC: castrate resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; HSPC: hormone sensitive prostate cancer; LDH: Lactate dehydrogenase; Mets: metastasis; PCa: Prostate cancer; PSA: prostate specific antigen, PSAdt: PSA doubling time. High risk disease based on Emmett et al, 2024 and Armstrong et al, 2018; high volume disease based on CHAARTED study, Kyriakopoulos et al, 2018.

14/18 patients enrolled in the Phase 1 present ≥2 risk factors (blue font) of early treatment failure on enzalutamide:

- LDH ≥ ULN, ALP ≥ ULN, Albumin < 35g/L, de novo metastatic disease at Dx, < 3 Years since initial Dx, > 5 bone mets, presence of visceral mets, PSAdt < 2.8 months, opioid use > 14 days (Armstrong et al, Ann Onc, 2018 ; Emmett et al, BJU Int 2021; Emmett et al, 2024).

Combination Regimens are Well Tolerated

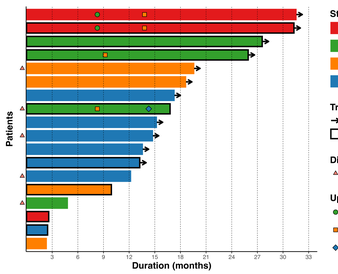




* AE Relatedness as reported by investigators; AE percentages are calculated by subject occurrences at the highest grade reported.

- No greater probability of treatment-related adverse events (AEs) was observed at higher EPI-7386 or enzalutamide PK exposures.
- AEs are not increasing in frequency over time and no patients experienced treatment discontinuation due to an AE.
- Dose modification occurred in 2/18 patients: Grade 2 fatigue (enzalutamide 120 mg to 80 mg) and Grade 3 rash (masofaniten 600 mg BID to QD + enzalutamide 160 mg to 120 mg).
- Most frequent adverse events are related either to AR inhibition or gastrointestinal tract irritation, Grade 1 and 2 in severity, and consistent with enzalutamide safety data (label information).
- In Cohort 4, one Grade 3 rash, maculo-papular event deemed as probably related to the combination treatment, was observed after administration of EPI-7386 and enzalutamide in combination which was managed with dose modification. No related SAEs observed.

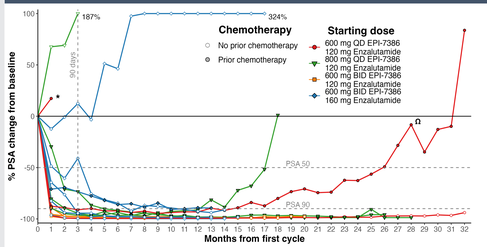
> 60% of Patients are still on study with median follow up of 15.2 months



18 patients enrolled:

- 11 ongoing.
- 7 discontinued.
  - 5 for disease progression.
  - 2 for non-related events while having reached PSA90.
    - 1 brain abscess.
    - 1 non-cancer related death.
- 8 patients received prior chemo in mHSPC.
- 5 patients have measurable radiographic disease.
- 2 patients are non-evaluable for efficacy per protocol due to limited drug exposure.
  - 1 patient who experienced Gr 3 rash (at day 1 of combination).
  - 1 patient taking a concomitant CYP3A4 inducer resulting in negligible concentrations of masofaniten.

Combination treatment PSA and radiographic responses compare favorably with historical single agent enzalutamide data



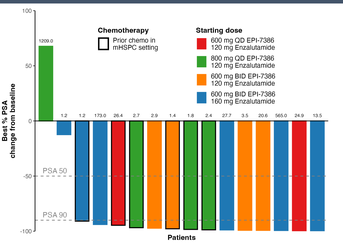
*Two patients are not evaluable for efficacy: one patient that experienced a DDI with a concomitant drug, and another DLT patient (not plotted past baseline).

[D] Patient had palliative radiotherapy during Cycle 29.

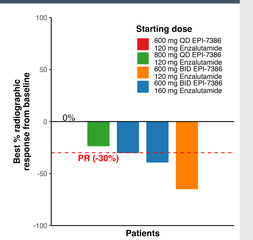
PSA response rates in evaluable patients are:

- PSA50 88% (14/16 pts).
- PSA90 88% (14/16 pts).
- PSA <0.2 ng/ml 63% (10/16 pts).

Rapid, deep and durable PSA responses observed independently from starting levels of PSA and combination dose/regimen.



- n=16, with two non-evaluable patients removed from plot.
- Best current PSA response observed during the study.
- The number listed on the x-axis corresponds to the PSA level (ng/mL) at baseline before treatment start.



- Best current radiographic response observed in the 5 patients with measurable disease.
- No patients with measurable disease had prior chemotherapy.
- Assessment was made according to RECIST1.1 / PWGC3 criteria.

No association observed between PSA response and previous chemotherapy or combination dose regimens:

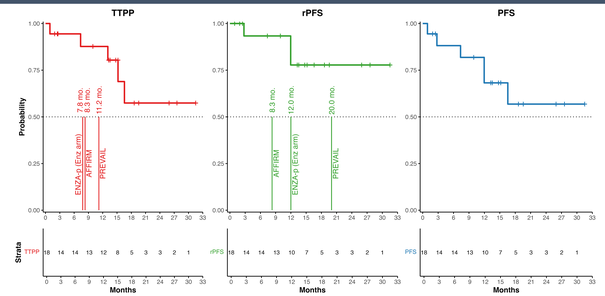
- 6/16 evaluable patients received prior docetaxel in mHSPC setting.

3/5 patients with measurable disease experienced a PR (60% ORR).

After 15.2 months of follow up, median progression is not yet reached

The Phase 1 masofaniten + enzalutamide is immature for time-to-event parameters

- 11 of the 18 patients are still on treatment.
- Data compares favorably to other 1st line mCRPC trials testing enzalutamide single agent[1,2,3] with the limitation of cross-trial comparisons.
- Data supports initiation of the Phase 2 randomized trial.



Time to PSA progression (TTPP) and rPFS references:
[1]Enza-P - Emmett et al, 2024
[2]AFFIRM - Scher et al, 2012, Armstrong et al, 2017
[3]PREVAIL - Beer et al, 2014; Beer et al; 2017

Conclusions

The combination of masofaniten and enzalutamide at all dose/schedule regimens tested in the Phase 1 component of the study continues to be well tolerated and efficacy parameters are proving to be durable in this patient population.

- Of note, the vast majority (14/18) of mCRPC patients enrolled in the Phase 1 part presented 2 or more risks of early failure to enzalutamide single agent treatment.
- 88% of the patients dosed with masofaniten + enzalutamide (independently of dose level received and starting levels of PSA) achieved a PSA decline > 90%. PSA90 was also achieved in < 90 days in 69% of patients and PSA < 0.2 ng/mL in 63% of the patients.
- With a current median follow up of 15.2 months, time-to-event parameters continue to compare favorably with historical data of single agent enzalutamide in a similar patient population.
- The Phase 2 component of the study is currently open to enrollment at ~33 sites in US, Canada and Australian clinical sites. Expansion to include 22 European sites in France, Spain, and Belgium is in progress.

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