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First results from ZZ-First: a randomized phase II trial of enzalutamide with or without talazoparib in metastatic hormone-naïve prostate cancer

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BACKGROUND

- Metastatic hormone-naïve prostate cancer (mHNPC) is a lethal form of prostate cancer[1]. Presence of high-volume of disease associates with poor prognosis .
- DNA damage repair (DDR) gene aberrations are present in 20-25% of metastatic prostate cancers, primarily affecting homologous recombination repair (HRR)-mediated repair pathways [2-4].
- Co-targeting the androgen receptor (AR) and DDR pathways has shown synergy in phase III trials for mCRPC[5], but the optimal target population for this therapeutic approach remains unclear.

METHOD

- Multicenter, open-label, randomized, investigator-initiated phase II clinical trial (Figure 1).
- Randomization was stratified based on HRR mutation status, using an in-house custom NGS panel.

PRIMARY ENDPOINT

- PSA-complete response (PSA-CR) (PSA<0.2 ng/mL) after 12 months of therapy in pts with mHNPC in the ADT+ENZA+TALA arm.

SECONDARY ENPOINTS

- PSA-CR rate at any time point and at month 7.
- PSA response (< 4 ng/mL) at 7 and 12 months
- PSA progression-free survival (PSA-PFS)
- Radiologic PFS (rPFS) as per RECIST v.1.1/PCWG3
- Time to castration resistance (TTCR)
- Overall survival (OS)
- Safety and tolerability (CTCAE v.5.0).

EXPLORATORY ENDPOINTS

- To study predictive and/or prognostic factors biomarkers based on tumor and liquid biopsies
- To assess changes in whole-body diffusion-weighted imaging (DWI) MRI and correlate with pts outcomes.

STATISTICS

- PSA-CR defined as the percentage of pts in the interventional arm with PSA<0.2 ng/mL after 12 months of treatment.
- H0: 20% of pts with PSA-CR ; H1≥40% of pts with PSA-CR.
- The analysis was conducted with the one-sided exact binomial test set at a nominal alpha level of 0.05.
- Considering a drop-out rate of 10%, 36 pts in the interventional arm were planned to attain 80% power.
- The PSA-CR benchmark to meet the primary endpoint is ≥12 of 36 pts (34.3%) after 12 months of therapy.

Abbreviations: **ADT:** Androgen deprivation therapy; **ASCO/CAP:** American Society of Clinical Oncology/College of American Pathologists; **CT:** Computed tomography; **CTCAE:** Common Terminology Criteria for Adverse Events; **DDR:** DNA damage response; **EoS:** End of study; **HR:** hormone receptor; **MRI:** magnetic resonance imaging; **PD:** Progressive disease; **PSA:** Prostate-specific antigen; **R:** Randomization.

OBJECTIVE

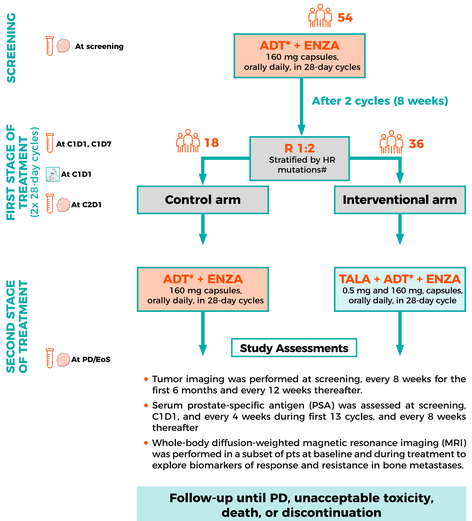
- To assesses the safety and efficacy of combining TALA and ENZA in non-molecularly selected pts with mHNPC.

STUDY DESIGN

Figure 1. ZZ-First Study Design (NCT04332744).

Key Inclusion Criteria.

- Male ≥18 years.
- Histologically confirmed adenocarcinoma of the prostate without predominance of small-cell or neuroendocrine features (ASCO/CAP guidelines).
- High-volume metastatic disease documented on bone scan or CT/MRI scan.
- Life expectancy ≥ 12 months.
- Prior (neo)adjuvant ADT-based regimen is allowed if PD occurred while on non-castrate testosterone levels > 12 months after discontinuation.
- No prior treatment with enzalutamide, apalu-tamide, darolutamide or abiraterone acetate.
- PSA ≥ 4 ng/mL at diagnosis or before starting ADT therapy.
- No prior systemic therapy for metastatic prostate cancer.



- Tumor imaging was performed at screening, every 8 weeks for the first 6 months and every 12 weeks thereafter.
- Serum prostate-specific antigen (PSA) was assessed at screening, C1D1, and every 4 weeks during first 13 cycles, and every 8 weeks thereafter
- Whole-body diffusion-weighted magnetic resonance imaging (MRI) was performed in a subset of pts at baseline and during treatment to explore biomarkers of response and resistance in bone metastases.

Follow-up until PD, unacceptable toxicity, death, or discontinuation

* Pts to continue treatment with ADT throughout the study (except for surgical orchiectomy).

Randomization will be stratified based on HR gene alterations detected in the baseline biopsy (presence versus absence/unknown).

RESULTS

1. Recruitment and Patient Disposition

- Between October 2020 and May 2022, 54 pts were enrolled across eight hospitals in Spain: 37 in the ENZA+TALA arm and 17 in the ENZA arm.
- At data cutoff date (February 21, 2024), 19 (51.4%) pts in the ENZA+TALA arm and 9 (52.9%) pts in the ENZA arm remained on therapy.
- The median follow-up was 30.6 months (range, 4.2-40.1 months).

Table 1. Patient Demographic Characteristics at Baseline.

Baseline characteristics n (%)	Control (n = 17)	Interventional (n = 37)	Overall (n = 54)
Age, median (range), years	69.0 (55.0; 82.0)	68.0 (47.0; 86.0)	68.0 (47.0; 86.0)
ECOG PS, %			
0	11 (64.7%)	23 (62.2%)	34 (63.0%)
1	6 (35.3%)	14 (37.8%)	20 (37.0%)
Gleason score			
<8	2 (12.5%)	4 (10.8%)	6 (11.3%)
≥8	14 (87.5%)	32 (86.5%)	46 (86.8%)
NA	0 (0.0%)	1 (2.7%)	1 (1.9%)
Missing	1	0	1
Clinical subtype of disease			
Bone only (+/- nodal)	14 (82.4%)	23 (62.2%)	37 (68.5%)
Visceral (+/- bone and nodal)	3 (17.6%)	14 (37.8%)	17 (31.5%)
Nodal disease only	0 (0.0%)	0 (0.0%)	0 (0.0%)
HR gene alterations			
Absence/Unknown	15 (88.2%)	32 (86.5%)	47 (87.0%)
Absence	13 (76.5%)	30 (81.1%)	43 (79.6%)
Unknown	2 (11.8%)	2 (5.4%)	4 (7.4%)
Presence	2 (11.8%)	5 (13.5%)	7 (13.0%)
Metastases			
Syncronic	17 (100%)	36 (97.3%)	53 (98.1%)
Methacronic	0 (0.0%)	1 (2.7%)	1 (1.9%)
PSA at first diagnosis (ng/mL)			
Median (Min; Max)	71.5 (11.1; 7,700.0)	170.0 (6.6; 2,390.0)	164.6 (6.6; 7,700.0)

Abbreviations: **ECOG PS:** Eastern Cooperative Oncology Group performance status; **HR:** hormone receptor, **PSA:** Prostate-specific antigen. n (%), number of pts (percentage based on N); N, Number of pts in the ITT population.

2. Efficacy Endpoints

- C13D1 PSA-CR in ENZA+TALA arm was 73% meeting the primary endpoint (95% CI, 55.9%-86.2%, p<0.001), and 64.7% in the control arm.
- Median rPFS was not reached for ENZA+TALA arm vs. 31.1 months for ENZA (hazard ratio 0.5, 95% CI 0.2–1.4) (Figure 2).
- Median PSA-PFS was not reached in any of the treatment arms (Figure 3).
- The 2-year rPFS and OS rates were 78.5% and 88.8% for ENZA+TALA vs. 58.8% and 82.4% for ENZA, respectively.

Figure 2. Radiologic PFS according to RECIST v.1.1.

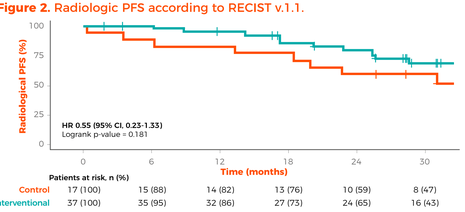
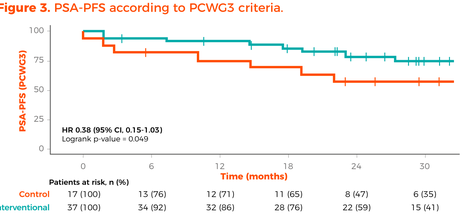


Figure 3. PSA-PFS according to PCWG3 criteria.



3. Safety Endpoints

- In the TALA+ENZA arm, the most common treatment emergent adverse events (TEAEs) of any grade (G) were fatigue (83.8%; 13.5% G≥3), hot flush (40.5%; 0% G≥3), anemia (67.6%; 37.8% G≥3), and neutropenia (29.7%; 10.8% G≥3) (Table 2).
- Treatment-related deaths occurred in two pts in the ENZA+TALA arm who developed acute leukemia after 26.0 and 32.8 months on treatment.
- The dose of TALA was reduced in 14 of the 37 (37.8%) pts in interventional arm. Treatment with ENZA was reduced in 1 pt (5.9%) in the control arm and in 3 pts (8.1%) in the TALA+ENZA arm.

Table 2. TEAEs by maximum severity of 20% incidence.

	Control (n = 17)		Interventional (n = 37)		Overall (n = 54)	
TEAEs	**Any Grade**	**G3-G5**	**Any Grade**	**G3-G5**	**Any Grade**	**G3-G5**
Any TEAE	**16 (94.1)**	**4 (23.5)**	**37 (100.0)**	**22 (59.5)**	**53 (98.1)**	**26 (48.1)**
Haematologic	**0 (0.0)**	**0 (0.0)**	**28 (75.7)**	**16 (43.2)**	**28 (51.9)**	**16 (29.6)**
Anaemia	0 (0.0)	0 (0.0)	25 (67.6)	14 (37.8)	25 (46.3)	14 (25.9)
Neutropenia	0 (0.0)	0 (0.0)	11 (29.7)	3 (8.1)	11 (20.4)	3 (5.6)
Non-Haematologic	**16 (94.1)**	**4 (23.5)**	**37 (100.0)**	**12 (32.4)**	**53 (98.1)**	**16 (29.6)**
Fatigue	9 (52.9)	0 (0.0)	31 (83.8)	5 (13.5)	40 (74.1)	5 (9.3)
Hot flush	9 (52.9)	0 (0.0)	15 (40.5)	0 (0.0)	24 (44.4)	0 (0.0)
Arthralgia	4 (23.5)	0 (0.0)	11 (29.7)	0 (0.0)	15 (27.8)	0 (0.0)
Back pain	2 (11.8)	0 (0.0)	10 (27.0)	0 (0.0)	12 (22.2)	0 (0.0)
Constipation	4 (23.5)	0 (0.0)	7 (18.9)	0 (0.0)	11 (20.4)	0 (0.0)
Diarrhoea	4 (23.5)	0 (0.0)	7 (18.9)	1 (2.7)	11 (20.4)	1 (1.9)
SARS-CoV-2 infection	5 (29.4)	0 (0.0)	6 (16.2)	0 (0.0)	11 (20.4)	0 (0.0)
Decreased appetite	1 (5.9)	0 (0.0)	8 (21.6)	0 (0.0)	9 (16.7)	0 (0.0)

CONCLUSIONS

- **TALA+ENZA showed promising antitumor activity in high volume mHNPC, the tolerability profile is in line with prior studies of PARP inhibitors.**
- **Treatment and follow up is ongoing for key secondary endpoints; correlative biomarker studies are ongoing.**

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