Radiographic progression without PSA progression in metastatic hormone-sensitive prostate cancer (mHSPC): a retrospective analysis from the ENZAMET trial (ANZUP 1304)

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1. Background

- ENZAMET randomized 1125 participants with mHSPC to compare enzalutamide (ENZA) versus a standard non-steroidal anti-androgen (NSAA) and demonstrated superior progression-free survival and overall survival (PFS and OS) with ENZA.
- Radiographic progression in the absence of prior/concurrent PSA progression (rProg1st) is an emerging biomarker of poor clinical outcomes.
- We sought to determine the frequency of rProg1st, and correlate the impact of enzalutamide on transitions between disease states for the ENZAMET cohort.

2. Methods

- The ENZAMET dataset was analyzed using a multi-state Cox proportional hazards regression model, partitioning the clinical experience of participants into 4 states:

(1) Evt-Free (event-free)

(2) rProg1st (radiologic progression recorded without prior/concurrent evidence of confirmed PSA progression per protocol)

(3) OtherProg (All Other type of clinical progression events (PSA and treatment switch, excluding death)

(4) Death

3. ENZAMET Study Design

Design:
Open label multi-national randomized phase 3 clinical trial.

Target Population:
1125 participants with mHSPC

Treatments:
Testosterone suppression (TS) + Enzalutamide (160mg) or NSAA

Endpoints;
Primary: OS
Secondary: PSA-PFS

4. Results

- Radiographic progression was recorded in 388/1125 (34%) participants.
- Radiographic progression without confirmed prior/concurrent PSA progression per protocol (rProg1st) was recorded in 114/1125 (10%) entire cohort.
- rProg1st occurred in 114/388 (29%) who had a documented radiographic progression event.
- rProg1st occurred in similar proportions for those assigned ENZA 55/114 (48%) vs NSAA 59/114(52%).
- Baseline characteristics of the 114 participants with rProg1st were similar to other participants in ENZAMET and were similar in the ENZA and NSAA groups (Table 1).

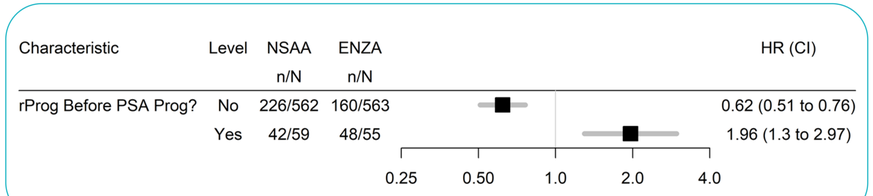
5. Progression events and outcomes

- After rProg1st the risk of death was significantly increased: HR 1.78 (95% CI 1.17-2.71); p=0.0047.
- 5-year OS rates were 24% (95%CI:18-34) in the rProg1st group versus 42% (95%CI: 38-47) in those with other progression (OtherProg) events (Table 2).
- Of those who had not progressed (495/1125) with a median follow-up of 68 months, 8% had died of causes other than prostate cancer.
- As previously reported ENZA prolonged overall survival in the whole trial cohort (N = 1125, HR 0·70, 95%CI 0·58 to 0·84, p < 0·0001).

6. Effect of ENZA on Progression

- **Compared with NSAA, ENZA delayed rProg1st (HR 0.66, 95%CI: 0.46 to 0.96, p = 0.03)**
- **Compared with NSAA, ENZA delayed OtherProg (HR 0.37, 95%CI: 0.31 to 0.44, p < 0.001)**

Figure 1: Subgroup analyses for Overall Survival (OS)



7. Conclusion

This post-hoc analysis of the ENZAMET clinical trial demonstrated that:

- Participants who had radiographic progression without prior/concurrent PSA progression had worse overall survival and the frequency was approximately 10% on either NSAA or enzalutamide. rProg1st likely reflects worse disease biology and fewer effective treatment options for mCRPC.
- Enzalutamide reduced the hazards for, and delayed the times to, rProg1st and OtherProg.
- There are currently no baseline characteristics to help identify rProg1st participants upfront; we plan molecular biological analyses to help prospectively identify this unique group earlier.

Table 1: Baseline characteristics of ENZAMET rProg1st* Cohort (n=114)

Baseline characteristic	NSAA N = 59	ENZA N = 55	ALL N = 114
Age median years (range)	69 (42-86)	69 (51-87)	69 (42-87)
Synchronous metastases**	36 (61%)	36 (65%)	72 (63%)
Volume of disease			
High	32 (54%)	35 64%)	67 59%)
Low	27 (45%)	37 (67%)	47 (41%)
Planned concurrent docetaxel (%)	26 (44%)	37 (67%)	63 (55%)

* rProg1st = radiographic progression without prior/concurrent PSA progression
**Synchronous: M1 at initial diagnosis

Figure 2: OS by Future Progression Status

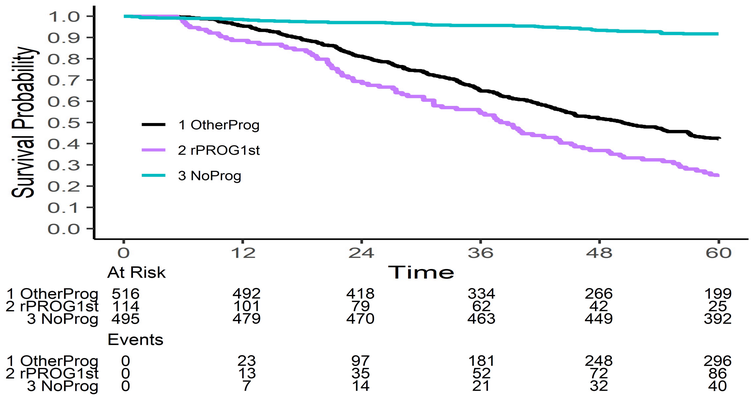


Table 2: OS by Future Progression Status

Characteristic	Time 12	Time 24	Time 36	Time 48	Time 60
Future.Prog.Type					
1 OtherProg	96% (94%, 97%)	81% (78%, 85%)	65% (61%, 69%)	52% (48%, 56%)	42% (38%, 47%)
2 rPROG1st	89% (83%, 95%)	69% (61%, 78%)	54% (46%, 64%)	37% (29%, 47%)	24% (18%, 34%)
3 NoProg	99% (98%, 100%)	97% (96%, 99%)	96% (94%, 98%)	93% (91%, 96%)	92% (89%, 94%)

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