Effects of enzalutamide on overall survival ± early docetaxel, in participants aged less than 70 yrs versus greater than or equal to 70 yrs in ENZAMET (ANZUP 1304)

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1. Background

- Androgen receptor pathway inhibitors (ARPIs) such as enzalutamide (ENZA) plus testosterone suppression (TS) are now standard of care for people with metastatic hormone-sensitive prostate cancer (mHSPC).
- Triplet therapy incorporating docetaxel chemotherapy with an ARPI and TS is now used for chemo-fit people with predominantly synchronous high volume mHSPC.
- Older patients may have more co-morbidities and higher rates of frailty.

2. Methods

- The ENZAMET clinical trial randomised participants (pts) with mHSPC to receive TS plus either non-steroidal anti-androgen (NSAA) or ENZA.
- Pre-specified stratification factors included: age (<70yrs vs ≥70yrs); volume of disease (high vs low), planned use of concurrent docetaxel (DTX); and Adult Comorbidity Evaluation (ACE-27 score of 0-1 (none or 1 mild comorbidity) versus 2-3 (moderate, severe, and/or multiple comorbidities).
- In this post-hoc analysis, we assess the efficacy and tolerability of ENZA in patients with mHSPC by age quartiles.
- Statistical methods: Survival analyses (overall survival and deterioration free survival) and adverse event rates were considered by age quartiles.

3. Study Design

Design:
Open label multi-national randomised phase 3 clinical trial

Target Population:
1125 participants with mHSPC

Treatments:
Testosterone suppression + Enzalutamide (160mg)/NSAA ± docetaxel

Endpoints:
Primary: OS
Secondary: PSA-PFS

4. Results

- 514/1125 (46%) pts aged ≥70yrs.
- The rate of DTX usage was lower in pts aged ≥ 70 yrs (35% vs 52%).
- When analysed by age quartiles: DTX usage declines the older age group with the largest drop is in the highest age quartile (74-96 yrs) (table 1).

Characteristic	[41,63) N = 281[1]	[63,69) N = 281[1]	[69,74) N = 281[1]	[74,96] N = 282[1]
Age (Years)				
N	281	281	281	282
Mean (SD)	58 (4)	66 (2)	72 (2)	79 (4)
Median (IQR)	59 (55, 62)	67 (65, 68)	72 (70, 73)	78 (76, 81)
Range	41, 63	63, 69	69, 74	74, 96
N missing	0	0	0	0
M0 recorded at initial diagnosis (Mx/UK→M0)	96 (34%)	105 (37%)	128 (46%)	113 (40%)
Volume of disease strata				
High	153 (54%)	145 (52%)	147 (52%)	157 (56%)
Low	128 (46%)	136 (48%)	134 (48%)	125 (44%)
Docetaxel chemotherapy strata (missing set to no)	162(58%)	136 (48%)	130 (46%)	75 (27%)
Treatment Arm				
Conventional NSAA	135 (48%)	149 (53%)	136 (48%)	142 (50%)
Enzalutamide	146 (52%)	132 (47%)	145 (52%)	140 (50%)
ACE-27 strata				
0-1	224 (80%)	216 (77%)	206 (73%)	188 (67%)
2-3	57 (20%)	65 (23%)	75 (27%)	94 (33%)
ACE-27 co-morbidity score				
0	125 (44%)	89 (32%)	75 (27%)	49 (17%)
1	99 (35%)	127 (45%)	131 (47%)	139 (49%)
2	33 (12%)	39 (14%)	51 (18%)	58 (21%)
3	24 (8.5%)	26 (9.3%)	24 (8.5%)	36 (13%)

[1]n (%)

Table 1: Baseline characteristics by Age Quartiles

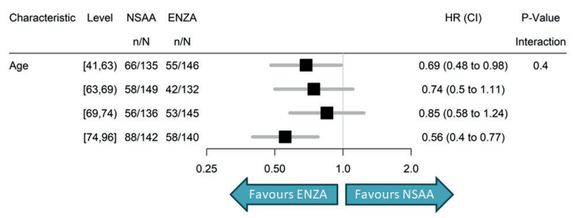

Figure 1: Subgroup Analyses for Overall survival (OS) according to age quartiles

5. Analysis of Efficacy

- The beneficial effects of ENZA on OS are maintained in pts aged ≥70yrs regardless of the planned use of early DTX (Table 2).
- Analysis by age quartiles demonstrates improved outcomes even in those aged ≥74yrs (Figure 1).

Characteristic	N	Deaths	HR	95% CI
Full cohort	1125	476	0.70	0.58-0.84
Age alone				
<70yrs All	611	239	0.75	0.58-0.97
≥70yrs All	514	237	0.64	0.50-0.83
Age and DTX				
<70yrs and DTX	322	147	0.87	0.63-1.20
≥70yrs and DTX	181	84	0.73	0.47-1.12
<70yrs and No DTX	289	92	0.62	0.41-0.94
≥70 and No DTX	333	153	0.60	0.44-0.83

Table 2: Hazard ratios (HR) and confidence intervals (CI) for effects of ENZA vs NSAA on OS in subgroups according to age and planned DTX

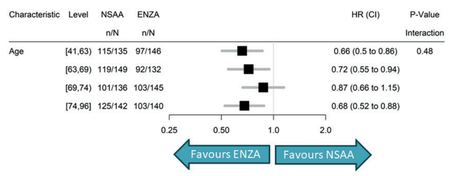

Figure 2: Subgroup analyses for deterioration-free survival* according to age quartiles

		Conventional NSAA, N = 562					Enzalutamide, N = 563			
Characteristic	**N**	**[41,63), N = 135[1]**	**[63,69), N = 149[1]**	**[69,74), N = 136[1]**	**[74,96], N = 142[1]**	**N**	**[41,63), N = 146[1]**	**[63,69), N = 132[1]**	**[69,74), N = 145[1]**	**[74,96], N = 140[1]**
Reason										
Adverse event		6 (4.4%)	5 (3.4%)	8 (5.9%)	6 (4.2%)		12 (8.2%)	8 (6.1%)	20 (14%)	23 (16%)
Clinical progression		70 (52%)	69 (46%)	69 (51%)	80 (56%)		49 (34%)	47 (36%)	40 (28%)	44 (31%)
Clinician preference		18 (13%)	28 (19%)	16 (12%)	29 (20%)		7 (4.8%)	7 (5.3%)	5 (3.4%)	5 (3.6%)
Death		1 (0.7%)	2 (1.3%)	2 (1.5%)	4 (2.8%)		1 (0.7%)	4 (3.0%)	2 (1.4%)	8 (5.7%)
Other		2 (1.5%)	3 (2.0%)	0 (0%)	1 (0.7%)		3 (2.1%)	3 (2.3%)	2 (1.4%)	2 (1.4%)
Patient preference		13 (9.6%)	9 (6.0%)	9 (6.6%)	6 (4.2%)		7 (4.8%)	2 (1.5%)	5 (3.4%)	6 (4.3%)
Treatment Ongoing (not ceased)		25 (19%)	33 (22%)	32 (24%)	16 (11%)		67 (46%)	61 (46%)	71 (49%)	52 (37%)

[1]n (%)
Pts with ongoing treatment appear in last row.

Table 3: Reasons for Discontinuation by Age Quartiles

6. Tolerability of ENZA in older pt

- It is important to balance efficacy and longevity against toxicity and potential effects on quality of life when treating older pts.
- Pts in the oldest quartile have similar rates of G3-5 AEs with ENZA compared to younger pts: Age 74-96 HR 0.77 (95% CI 0.63-0.93) vs Age 41-63 HR 0.66 (95% CI 0.56-0.78), p=0.002.
- Pts aged 69-74 had higher rates of toxicity, probably reflecting higher rates of DTX use compared to the oldest quartile.
- Similarly, rates of adverse events of interest (fatigue, cognitive disturbance, memory impairment, fall, generalised muscle weakness, seizure and hypertension) were highest in ages 69-74 years (Figure 3).
- Total AEs (not normalised for time on therapy) were greater with ENZA, as previously reported. AE rates increased with age in the ENZA group.
- AEs leading to ENZA treatment discontinuation were almost twice as likely in ages 69-74 and 74-96 years compared to younger quartiles (Table 3).

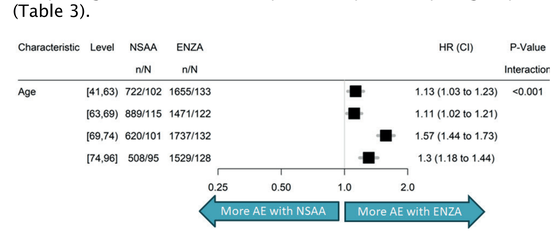

Figure 3: Subgroup Analyses for Rate of AEs of Interest according to age quartiles

7. Conclusion

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

- Older pts treated with TS+ENZA ± DTX have improved survival consistent with the findings in younger pts
- Older pts have a higher incidence of AEs more likely to be related to ENZA treatment
- Further research is needed to optimise dosing for all pts.
- People aged >70 years with mHSPC should be considered for ENZA treatment
- Geriatric assessment and plans to address vulnerabilities should be a part of the treatment paradigm in order to maintain quality of life and independence.

*As defined in Stockler MR et al J Clin Oncol 2022

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