Addition of Early Docetaxel to Enzalutamide for Metastatic Hormone-Sensitive Prostate Cancer: A Trial Emulation Approach based on the ENZAMET (ANZUP 1304) trial

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1. Background

Randomised controlled trials (RCTs) have demonstrated that adding docetaxel or novel androgen receptor pathway inhibitors (ARPIs) to androgen deprivation therapy (ADT) improved overall survival (OS) in metastatic hormone-sensitive prostate cancer (mHSPC).[1-10]

However, no trial has directly tested the addition of early docetaxel in mHSPC treated with a novel ARPI and ADT.

2. Study question

To evaluate the effect of combining docetaxel with enzalutamide versus enzalutamide alone on OS in mHSPC and assess whether this effect varied by disease volume.

3. Methods

1. Specification of Target Trial

Hypothetical 2 X 2 Factorial Trial

Population: mHSPC
(Eligibility criteria as per ENZAMET[5-6])

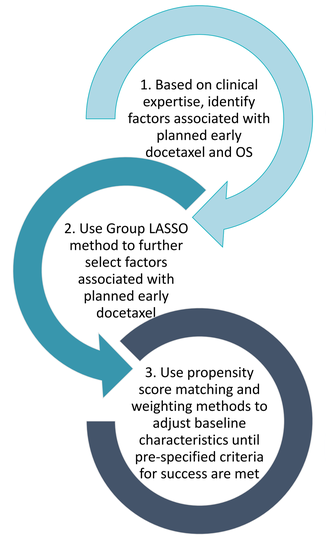
Enzalutamide	Docetaxel	
	Yes	No
Yes	✓ Docetaxel ✓ Enzalutamide	✗ Docetaxel ✓ Enzalutamide
No (NSAA)	✓ Docetaxel ✗ Enzalutamide	✗ Docetaxel ✗ Enzalutamide

All treatment strategies include ADT i.e. testosterone suppression alone for those receiving enzalutamide and testosterone suppression plus nonsteroidal antiandrogen (NSAA) for those not receiving enzalutamide

Primary outcome: Overall survival
(Time from randomisation to death from any cause).

2. Emulation of Target Trial

Calibration Process



Criteria for Emulation success

1. Absolute standardised mean differences for baseline characteristics between the two groups ≤ 0.1
2. Replicate key findings of CHAARTED trial for those not assigned Enzalutamide
3. Replicate key findings of ENZAMET trial (based on planned final OS analysis)

4. Results

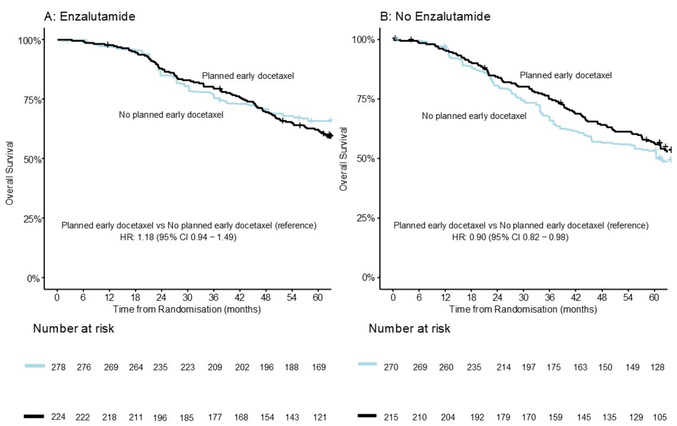
Included 987 participants with complete baseline characteristics data

Table 1: Baseline Characteristics of the unmatched and matched population

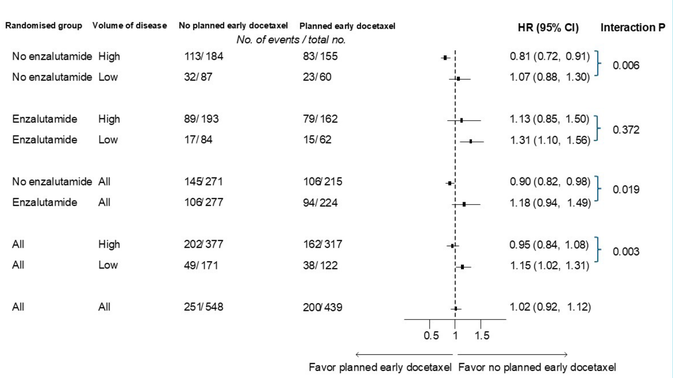
Characteristic[a]	Unmatched population		Matched population	
	No planned early docetaxel (N = 548)	Planned early docetaxel* (N = 439)	No planned early docetaxel (N = 548)	Planned early docetaxel* (N = 439)
Age, years	71 (8)	67 (8)	67 (8)	67 (8)
Volume of disease†				
High	218 (40)	317 (72)	377 (69)	317 (72)
Low	330 (60)	122 (28)	171 (31)	122 (28)
Number of bone metastases				
1 – 3	202 (37)	82 (19)	115 (21)	82 (19)
4 or more	212 (39)	310 (71)	371 (68)	310 (71)
None	134 (25)	47 (11)	62 (11)	47 (11)
BMI (kg/m²)	28 (5)	28 (5)	28 (6)	28 (5)
Previous LHRHA	345 (63)	373 (85)	461 (84)	373 (85)
Clinician estimated the prognosis, years	4 (2)	4 (2)	4 (2)	4 (2)
Baseline PSA (ng/mL)	78 (796)	76 (305)	75 (461)	76 (305)
Baseline hemoglobin (g/L)	119 (50)	121 (44)	124 (44)	121 (44)
Baseline ALP (U/L)	158 (326)	221 (350)	206 (332)	221 (350)
Time since distant metastases were first diagnosed (months)	3 (7)	2 (3)	2 (4)	2 (3)
Time since primary cancer was first diagnosed (months)	33 (46)	17 (37)	19 (35)	17 (37)

Descriptive summaries presented are mean (standard deviation), or n (%). ALP = Alkaline Phosphatase. BMI = Body Mass Index. LHRHA = Luteinizing Hormone-Releasing Hormone Agonist. M=Metastasis. PSA = Prostate-Specific Antigen.
[a] Group LASSO selected baseline characteristics predictive of planned early docetaxel for propensity score analysis.
* Early use is defined as docetaxel at or close to the time of starting testosterone suppression. Among the 419 participants who received docetaxel, the median number of cycles administered was 6
† Defined as visceral metastases or four or more bone metastases with at least one beyond the vertebrae and pelvis, or both, as per CHAARTED criteria.

Weighted Kaplan-Meier Curves for OS



Subgroup analysis for OS



Adding early docetaxel to enzalutamide did not appear to extend OS in unselected mHSPC, regardless of disease volume.

Conversely, among those not assigned enzalutamide, early docetaxel was associated with longer survival, particularly in cases of high-volume disease.

These findings do not support the routine use of early docetaxel with enzalutamide.

@ANZUPTrials @yysoon01

Abstract #2422P

Reference: 1. Sweeney CJ et al. NEJM 2015. 2. Kyriakopoulos CE et al. JCO 2018. 3. James ND et al. Lancet 2016. 4. Clarke NW et al. Ann Oncol 2019. 5. Davis ID et al. NEJM 2019. 6. Sweeney CJ et al. Lancet Oncol 2023. 7. Armstrong AJ et al. JCO 2022. 8. James ND et al. NEJM 2017. 9. Fizazi K et al. NEJM 2017. 10. Chi KN et al. NEJM 2019

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