# Clinical prognostic factors within the high volume (HV) subgroup of metastatic hormone sensitive prostate cancer (mHSPC) in ENZAMET (ANZUP 1304)


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## 1. Background

- Androgen deprivation therapy (ADT) + androgen receptor pathway inhibitor (ARPI) +/- docetaxel (D) is standard of care for mHSPC.
- Synchronous, high volume mHSPC (Synch HV) leads to poorer clinical outcomes compared with pts with metachronous (Metach) and low volume (LV) disease, despite improved overall survival (OS) with enzalutamide across subgroups in ENZAMET (Fig 1 schema).
- Clinical and biological factors in the HV subgroup may further refine disease risk.

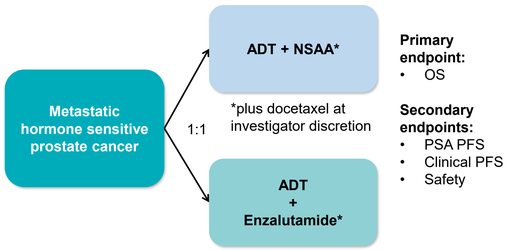


***Fig 1.*** *ENZAMET (ANZUP 1304) trial*

## 2. Aim

- To determine if intrinsic tumour features and the burden of metastatic bone disease associate with clinical outcomes and refine risk within the HV subgroup of mHSPC in ENZAMET.

## 3. Method

- Participants in ENZAMET received testosterone suppression (TS) plus non-steroidal anti-androgen or TS plus ENZA.
- Post-hoc analyses of T-stage, Gleason score (GS), visceral metastases, and bone burden (BB) were performed in the following subgroups:
  - Synch HV
  - Metach HV
  - Synch LV
- High BB was defined by the upper quartile of alkaline phosphatase (ALP) at trial enrolment.
- BB analyses excluded pts with visceral mets.
- Endpoints: OS, prostate cancer specific survival (PCSS), and PSA progression-free survival (PSA PFS).
- Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by univariable Cox models.

## 4. Results

### PROGNOSTIC FACTORS WITHIN HV SUBGROUPS

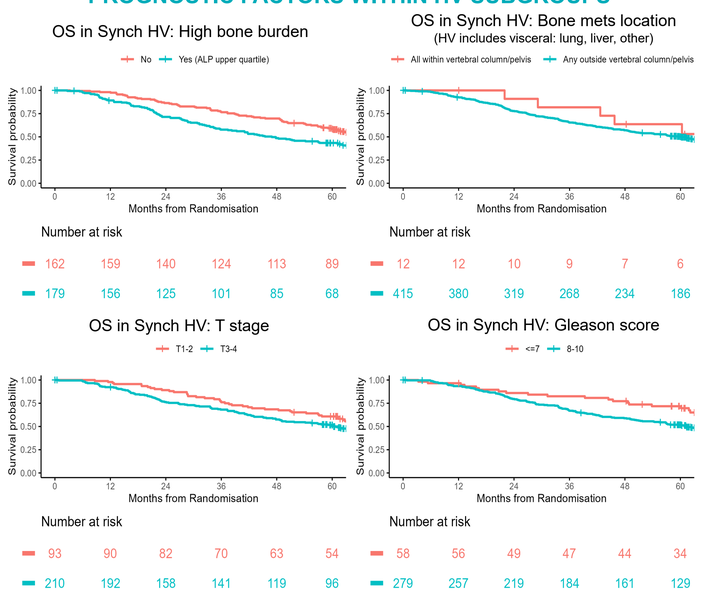


***Fig 2.*** *OS in Synch HV subgroup by clinical factors (all treatments combined)*

| Synch HV, N=439 | N | OS HR (95% CI) | p-val | 5-year OS (%) |
|---|---|---|---|---|
| Bone burden (high / low) | 179 / 162 | 1.64 (1.23-2.2) | <0.001 | 43 v 59 |
| Bone location (extensive / limited to vert/pelvis) | 415 / 12 | 1.41 (0.58-3.42) | 0.448 | 50 vs 64 |
| Gleason (8-10 / <8) | 279 / 58 | 1.80 (1.14-2.83) | 0.012 | 52 v 72 |
| Visceral met (y / n) | 95 / 344 | 1.0 (0.74-1.36) | 1.0 | 54 v 50 |
| T-stage (T3-4 / T1-2) | 210 / 93 | 1.2 (0.86-1.69) | 0.29 | 52 v 61 |
| **Metach HV, N=163** | **N** | **OS HR (95% CI)** | **p-val** | **5-year OS (%)** |
| Bone burden (high / low) | 41 / 77 | 2.17 (1.32-3.55) | 0.002 | 37 v 58 |
| Gleason (8-10 / <8) | 79 / 68 | 1.61 (0.99-2.62) | 0.056 | 49 v 66 |
| T-stage (T3-4 / T1-2) | 69 / 55 | 1.40 (0.81-2.40) | 0.227 | 55 v 62 |

***Table 1.*** *OS in Synch and Metach HV subgroups by clinical factors*

### OUTCOMES BY VARIABLES OF INTEREST

- Synch HV: 52% had high BB (ALP>150 IU/L), 93% had ≥4 bone mets and 97% had ≥1 bone met outside pelvis/vertebrae (*Table 2*).
  - High BB (HR 1.64, p<0.001) and high GS (HR 1.80, p=0.01) were associated with shorter OS, but not T-stage (*Figure 2* and *Table 1*).
  - Bone mets limited to vertebral column and pelvis (despite HV status by presence of visceral mets) were associated with greater 5-year OS compared with extensive bone mets (OS HR 1.41, p=0.449, 5-year OS: 64% vs 50%)
  - Similar associations observed for PCSS and PSA PFS (not GS for latter).
  - Patients receiving TS+ENZA did not have significantly different OS by treatment with docetaxel (not randomised), within bone burden subgroups (low/high) (*Figure 3*). Similar findings were observed in all HV patients receiving TS+ENZA.
- Metach HV:
  - High BB was associated with poorer OS (HR 2.17, p=0.002) and PCSS (HR 2.25, p=0.002. Similarly, GS was associated with OS (1.61, p=0.056) and PCSS (HR 1.75, p=0.043) (*Table 1*).
- Synch LV:
  - No factors were associated with OS in Synch LV including bone met location, GS and T-stage.
- LV by number of bone mets:
  - In the LV subgroup, presence of ≥4 bone mets (by definition, limited to vertebrae/pelvis) was associated with greater 5-year OS compared to non-visceral HV disease (*Figure 4*).

### SYNCH HV (ADT+ENZA) BY BONE BURDEN AND DOCETAXEL

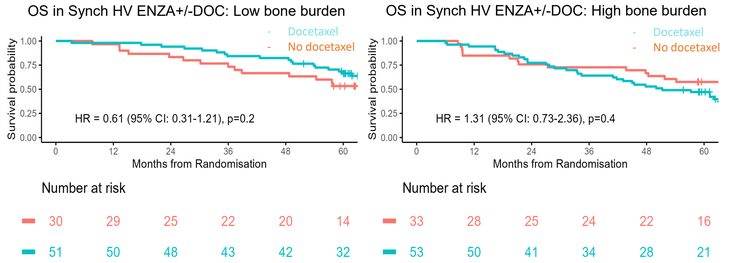


***Fig 3.*** *OS in Synch HV (TS+ENZA arm) by docetaxel x bone burden (docetaxel not randomised)*

### OUTCOMES OF LV SUBGROUP WITH ≥4 BONE METASTASES WITHIN VERTEBRAL BODIES AND PELVIS

| Subgroup (treatments arms combined) | 5-year OS (95% CI), % |
|---|---|
| HV (≥4 bone mets with ≥1 beyond vertebrae/pelvis + no visceral + BB high) | 42 (34-49) |
| HV (≥4 bone mets with ≥1 beyond vertebrae/pelvis + no visceral + BB low) | 58 (52-65) |
| LV (≥4 bone mets within vertebrae/pelvis)^ | 69 (57-84) |

^within this group: 62% Synch, 38% Metach

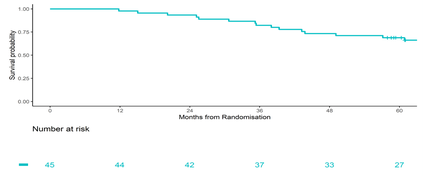


***Fig 4.*** *OS in LV with ≥4 bone mets (vertebrae/pelvis)*

| Characteristic | Conventional NSAA, N = 225[1] | Enzalutamide, N = 214[1] | Overall, N = 439[1] |
|---|---|---|---|
| T Stage (TX/T0 set to missing) | | | |
| T1-2 | 50 (22%) | 43 (20%) | 93 (21%) |
| T3-4 | 97 (43%) | 113 (53%) | 210 (48%) |
| Missing | 78 (35%) | 58 (27%) | 136 (31%) |
| Gleason score | | | |
| <=7 | 33 (15%) | 25 (12%) | 58 (13%) |
| 8-10 | 142 (63%) | 137 (64%) | 279 (64%) |
| Missing | 50 (22%) | 52 (24%) | 102 (23%) |
| Distant metastases (missing set to no) | 225 (100%) | 214 (100%) | 439 (100%) |
| Bone | 218 (97%) | 209 (98%) | 427 (97%) |
| Lung | 32 (14%) | 37 (17%) | 69 (16%) |
| Pleura | 3 (1.3%) | 2 (0.9%) | 5 (1.1%) |
| Liver | 9 (4.0%) | 12 (5.6%) | 21 (4.8%) |
| Adrenal | 6 (2.7%) | 1 (0.5%) | 7 (1.6%) |
| Other | 6 (2.7%) | 7 (3.3%) | 13 (3.0%) |
| Visceral metastases | 49 (22%) | 46 (21%) | 95 (22%) |
| Visceral metastases: pulmonary or other | | | |
| Non-pulmonary | 17 (35%) | 9 (20%) | 26 (27%) |
| Pulmonary | 32 (65%) | 37 (80%) | 69 (73%) |
| Number of bone metastases | | | |
| 1 - 3 | 11 (4.9%) | 7 (3.3%) | 18 (4.1%) |
| 4 or more | 207 (92%) | 202 (94%) | 409 (93%) |
| None | 7 (3.1%) | 5 (2.3%) | 12 (2.7%) |
| Location of bone metastases | | | |
| All within the vertebral column and pelvis | 6 (2.8%) | 6 (2.9%) | 12 (2.8%) |
| Any outside the vertebral column and pelvis | 212 (97%) | 203 (97%) | 415 (97%) |
| High bone burden (Baseline ALP in upper quartile)** | 93 (53%) | 86 (51%) | 179 (52%) |
| ALP U/L | | | |
| Median (IQR) | 149 (92, 355) | 149 (95, 288) | 149 (94, 316) |
| [Range] | [44 - 5,388] | [38 - 3,344] | [38 - 5,388] |
| Baseline* ALP > ULN | 128 (57%) | 134 (63%) | 262 (60%) |
| Docetaxel chemotherapy strata (missing set to no) | 137 (61%) | 133 (62%) | 270 (62%) |

***Table 2.*** *Clinical characteristics of Synch HV subgroup in ENZAMET*

## 5. Conclusions

- High ALP, as an indicator of bone burden in patients without visceral metastases, was prognostic in HV mHSPC for OS, PCSS, and PSA PFS.
- High GS, but not T-stage, was significantly associated with poorer outcomes in HV mHSPC.
- Patients with Synch HV mHSPC receiving TS+ENZA and high BB did not have a clear benefit if treated with early docetaxel.
- LV disease with ≥4 bone mets is associated with better OS compared with non-visceral HV disease.
- These data may help with identification of pts with poorest prognosis mHSPC for future studies of further therapy intensification.

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*Scan to learn more about the ENZAMET study*


*This study was conducted by the Australian and New Zealand Urogenital and Prostate Trials Group Ltd (ANZUP) in collaboration with the NHMRC Clinical Trials Centre, University of Sydney. This ANZUP investigator-initiated study was financially supported by Astellas Pharma Inc. ANZUP was supported by the Australian Government through Cancer Australia Support for Cancer Clinical Trials. The NHMRC CTC was supported by an NHMRC Program Grant.*

**Clinical trial identifiers:** NCT02446405

**Acknowledgments:** We thank the trial participants, principal investigators, co-investigators, and study coordinators at all participating centres for their commitment to this trial.


**Abstract #4794**