# Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial

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## Summary

**Background** The interim analysis of the ENZAMET trial of testosterone suppression plus either enzalutamide or standard nonsteroidal antiandrogen therapy showed an early overall survival benefit with enzalutamide. Here, we report the planned primary overall survival analysis, with the aim of defining the benefit of enzalutamide treatment in different prognostic subgroups (synchronous and metachronous high-volume or low-volume disease) and in those who received concurrent docetaxel.

**Methods** ENZAMET is an international, open-label, randomised, phase 3 trial conducted at 83 sites (including clinics, hospitals, and university centres) in Australia, Canada, Ireland, New Zealand, the UK, and the USA. Eligible participants were males aged 18 years or older with metastatic, hormone-sensitive prostate adenocarcinoma evident on CT or bone scanning with $^{99m}$Tc and an Eastern Cooperative Oncology Group performance status score of 0–2. Participants were randomly assigned (1:1), using a centralised web-based system and stratified by volume of disease, planned use of concurrent docetaxel and bone antiresorptive therapy, comorbidities, and study site, to receive testosterone suppression plus oral enzalutamide (160 mg once per day) or a weaker standard oral non-steroidal antiandrogen (bicalutamide, nilutamide, or flutamide; control group) until clinical disease progression or prohibitive toxicity. Testosterone suppression was allowed up to 12 weeks before randomisation and for up to 24 months as adjuvant therapy. Concurrent docetaxel (75 mg/m$^2$ intravenously) was allowed for up to six cycles once every 3 weeks, at the discretion of participants and physicians. The primary endpoint was overall survival in the intention-to-treat population. This planned analysis was triggered by reaching 470 deaths. This study is registered with ClinicalTrials.gov, NCT02446405, ANZCTR, ACTRN12614000110684, and EudraCT, 2014-003190-42.

**Findings** Between March 31, 2014, and March 24, 2017, 1125 participants were randomly assigned to receive non-steroidal antiandrogen (n=562; control group) or enzalutamide (n=563). The median age was 69 years (IQR 63–74). This analysis was triggered on Jan 19, 2022, and an updated survival status identified a total of 476 (42%) deaths. After a median follow-up of 68 months (IQR 67–69), the median overall survival was not reached (hazard ratio 0·70 [95% CI 0·58–0·84]; p<0·0001), with 5-year overall survival of 57% (0·53–0·61) in the control group and 67% (0·63–0·70) in the enzalutamide group. Overall survival benefits with enzalutamide were consistent across predefined prognostic subgroups and planned use of concurrent docetaxel. The most common grade 3–4 adverse events were febrile neutropenia associated with docetaxel use (33 [6%] of 558 in the control group *vs* 37 [6%] of 563 in the enzalutamide group), fatigue (four [1%] *vs* 33 [6%]), and hypertension (31 [6%] *vs* 59 [10%]). The incidence of grade 1–3 memory impairment was 25 (4%) versus 75 (13%). No deaths were attributed to study treatment.

**Interpretation** The addition of enzalutamide to standard of care showed sustained improvement in overall survival for patients with metastatic hormone-sensitive prostate cancer and should be considered as a treatment option for eligible patients.

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## Research in context

### Evidence before this study

We searched PubMed and abstracts from the American Society of Clinical Oncology and European Society of Medical Oncology meetings published between database inception and Dec 1, 2013, using the terms "hormone-sensitive", "prostate cancer", AND "metastases". When ENZAMET began recruiting patients in 2013, androgen deprivation therapy with testosterone suppression was the standard of care for patients with metastatic hormone-sensitive prostate cancer. Meta-analyses noted moderate overall survival benefits with the addition of weaker non-steroidal antiandrogens to testosterone suppression. Four prognostic groups receiving testosterone suppression identified by metastatic disease at first diagnosis (de novo or synchronous) or after initial presentation with localised disease (relapsing or metachronous) and either high-volume disease (visceral metastases or four or more bone metastases, or both) or low-volume disease had been defined by previous trials. ENZAMET was amended in 2014 to allow patients and physicians to add docetaxel to testosterone suppression because this drug became the new standard of care for some patients with metastatic hormone-sensitive prostate cancer. During patient recruitment to ENZAMET (from March, 2014, to March, 2017), the addition of docetaxel showed substantial improvement in overall survival of patients with poor prognostic disease and synchronous high-volume disease, a moderate benefit for those with metachronous high-volume and synchronous low-volume disease, and no overall survival benefit for those with metachronous low-volume disease. In 2018, the radiotherapy group of STAMPEDE and HORRAD trials revealed that radiotherapy for primary tumours showed improved overall survival of patients with synchronous low-volume metastatic hormone-sensitive prostate cancer. Also, additional androgen signaling inhibition by testosterone suppression with abiraterone or a more effective androgen receptor signalling inhibitor, such as apalutamide or enzalutamide, increased overall survival for major prognostic subgroups compared with testosterone suppression alone. The PEACE-1 trial in 2021 showed that the addition of abiraterone to testosterone suppression plus docetaxel increased overall survival of patients with synchronous metastatic hormone-sensitive prostate cancer, especially in high-volume disease. The addition of darolutamide to testosterone suppression plus docetaxel also improved overall survival compared with docetaxel plus testosterone suppression.

### Added value of this study

To our knowledge, this study is the first to measure long-term overall survival with a more effective androgen receptor inhibitor added to testosterone suppression versus a weaker androgen receptor inhibitor for patients with good and poor prognosis of metastatic hormone-sensitive prostate cancer. We found that enzalutamide plus testosterone suppression without docetaxel improves overall survival of patients with synchronous and metachronous metastatic hormone-sensitive prostate cancer. Simultaneous treatment of patients with different regimens and prognostic subgroups allowed us to describe the short-term and long-term overall survival and prostate cancer-specific survival (post hoc).

### Implications of all the available evidence

We found that the addition of enzalutamide to testosterone suppression provides a consistent clinical benefit across most prognostic subgroups. Our data also support previous work showing that patients with synchronous metastatic hormone-sensitive prostate cancer benefit from adding effective inhibition of androgen receptor signalling to testosterone suppression plus docetaxel.

## Introduction

The overall survival of patients with metastatic hormone-sensitive prostate cancer is variable, ranging from a 5-year survival of around 30% with testosterone suppression for patients with four or more bone or liver metastases at first diagnosis (ie, synchronous metastatic disease) to 70% for those with metachronous low-volume disease.[1–3] Overall survival is improved by the addition of docetaxel or new androgen receptor inhibitors (eg, enzalutamide and apalutamide or abiraterone, which is an androgen synthesis inhibitor) to testosterone suppression.[4–10] Addition of darolutamide or abiraterone to testosterone suppression plus docetaxel also increased overall survival compared with testosterone suppression plus docetaxel alone.[11,12] Moreover, patients with untreated local disease and a low volume of metastases showed an overall survival benefit when prostate radiation was added to testosterone suppression.[13] Although testosterone suppression plus abiraterone, enzalutamide, or apalutamide improved overall survival of patients with good or poor prognosis metastatic hormone-sensitive prostate cancer, docetaxel had the greatest overall survival effect in those with high-volume disease versus no benefit in those with metachronous low-volume disease, as initially defined by the CHAARTED study[2] and confirmed in 2022 by the STOPCaP M1 Collaboration in an individual patient data meta-analysis.[14]

The ENZAMET trial[6] assessed whether enzalutamide added to standard-of-care testosterone suppression with or without docetaxel (at investigator discretion) would improve overall survival compared with standard of care plus a weak non-steroidal antiandrogen (also known as a first-generation androgen receptor inhibitor) while recognising that docetaxel is not suitable for all patients and shows a variable benefit across metastatic hormone-sensitive prostate cancer subgroups. ENZAMET stratified participants by disease volume and prospectively captured the timing of metastatic presentation (synchronous metastases with initial diagnosis of prostate cancer *vs* metachronous metastases after an initial diagnosis with

localised disease). ENZAMET allowed for the contemporaneous enrolment and inclusion of all prognostic subgroups (synchronous or metachronous presentation with high-volume or low-volume disease) and included participants for whom the treating physician and the patient deemed that docetaxel was suitable or not based on tolerability and likelihood of benefit.[2,14]

The planned first interim analysis (triggered after 235 deaths) was published upon recommendation from the independent data safety monitoring committee, showing a hazard ratio (HR) of 0·67 (95% CI 0·52–0·86; p=0·002) for overall survival after 245 deaths at 34 months of follow up.[6] The interim analysis did not show a clear overall survival benefit of adding enzalutamide to concurrent docetaxel.[6]

Here, we report the planned primary overall survival analysis (triggered after 470 deaths), with the aim of defining the benefit of enzalutamide treatment in different prognostic subgroups (synchronous and metachronous high-volume or low-volume disease) and in patients who received concurrent docetaxel.

## Methods

### Study design and participants

The ENZAMET (Australian and New Zealand Urogenital and Prostate Cancer Trials Group [ANZUP] 1304) open-label, randomised, phase 3 trial was conducted at 83 sites (including clinics, hospitals, or university centres) in Australia, Canada, Ireland, New Zealand, the UK, and the USA.[6] Eligible patients were males aged 18 years or older with metastatic, hormone-sensitive prostate adenocarcinoma evident on CT or bone scanning with $^{99m}$Tc as per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients with a history of seizure or any condition that might predispose them to seizure were excluded because of the known risk of seizures with enzalutamide. Full patient eligibility criteria are in the protocol (appendix p 55).

The protocol was independently reviewed and approved by all participating institution ethics committees. All participants provided written informed consent. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

### Randomisation and masking

Participants were randomly assigned (1:1) to receive either testosterone suppression plus enzalutamide (enzalutamide group) or a weaker non-steroidal antiandrogen (the control group) using a centralised web-based system. The National Health and Medical Research Council (NHMRC) Clinical Trials Centre (University of Sydney, Sydney, NSW, Australia) maintained allocation concealment using minimisation with a random component, stratified according to volume of disease (high [four or more bone lesions, with at least one beyond the vertebrae and pelvis or visceral metastases or both] *vs* low [anyone who did not have high volume]); planned use of concurrent docetaxel (yes *vs* no); planned use of bone antiresorptive therapy (yes *vs* no); comorbidities (Adult Comorbidity Evaluation [ACE-27][15] score 0–1 [none or one mild comorbidity] *vs* 2–3 [moderate, severe, or multiple comorbidities]); and study site. Treatment was open label due to the definitive endpoint being overall survival. Before planned analyses, masking was imposed on draft tabulations of efficacy data by using dummy treatment allocations (appendix p 55).

### Procedures

Testosterone suppression with surgical castration or medically with luteinising hormone-releasing agonist or antagonist therapy was allowed up to 12 weeks before randomisation and previous testosterone suppression was allowed for up to 24 months as adjuvant therapy (eg, with curative radiation treatment) for localised disease and with at least 12 months of treatment completed before study entry. In the enzalutamide group, participants were given oral enzalutamide (160 mg) once per day. In the standard non-steroidal antiandrogen group, patients were given oral bicalutamide, nilutamide, or flutamide, per investigator choice. The dose and schedule were determined as per standard of care detailed in the pamphlet insert of drug prescribing information. Treatment was continued until clinical disease progression or prohibitive toxicity.

Concurrent intravenous docetaxel (75 mg/m$^2$) was allowed for up to six cycles once every 3 weeks without daily prednisone, at the discretion of participants and physicians on the basis of CHAARTED findings,[5] and was incorporated as a stratification factor in the protocol (version 2; amended on Nov 7, 2014) after accrual of 88 participants. Up to two cycles of docetaxel were allowed before randomisation and the choice to prescribe docetaxel was declared before randomisation. Details of docetaxel dosing, supportive care, and dose modifications of enzalutamide and docetaxel are in the protocol (appendix p 55). Participants who had a grade 3 adverse event or higher that was attributed to enzalutamide which could not be ameliorated by medical intervention were able to pause study drug treatment. Subsequently, study drug dosing was restarted at the original dose (160 mg per day) or a reduced dose (120 mg or 80 mg per day). Treatment was discontinued when restarting was delayed by more than 30 days. Standard non-steroidal antiandrogen dose modifications were allowed as per the package insert.

Electrolytes, liver function tests, prostate-specific antigen (PSA), and adverse events were assessed every 3 months and as required. Repeat CT and bone scans were done at PSA progression or clinical progression, or both, and then as clinically indicated by the treating clinician. Scans were also done at and end of treatment

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See **Online** for appendix

for reasons other than progression and assessed by investigators. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02).

### Outcomes

The primary endpoint was overall survival (defined as time from randomisation to death from any cause, or the date of last known follow-up). The secondary endpoints were PSA progression-free survival (defined as time from randomisation to the earliest PSA progression according to the Prostate Cancer Working Group 2 criteria [PCWG2],[16] clinical progression, or death from any cause, whichever occurred first, or the last known date of follow-up without PSA progression), clinical progression-free survival (defined as the earliest sign of radiographic progression using PCWG2 for bone lesions and RECIST [version 1.1][17] for soft tissue lesions, symptoms attributable to cancer progression, or initiation of another anti-cancer treatment for prostate cancer), health-related quality of life (HRQOL), health outcomes relative to costs, and safety. The HRQOL results have been reported elsewhere[18] and health outcomes relative to costs will be published separately.

### Statistical analysis

ENZAMET was designed to follow-up 1100 randomly assigned participants until 470 deaths were recorded to provide more than 80% power to detect a HR of 0·75 with a two-sided type 1 error of 0·05. A 3-year survival of 65% was assumed in controls. The design allowed a formal interim analyses using the Lan–DeMets O'Brien–Fleming error spending function approach at 50%, 67%, and 80% of the total planned information. The null hypothesis of no effect on overall survival was rejected at the first interim analysis.[6] All efficacy analyses of this planned primary analysis after 470 deaths were based on the intention-to-treat population, which includes all randomly assigned participants; full details are in the protocol and statistical analysis plan (appendix p 55). Participants without a reported event were censored when last known to be event free. Study treatment exposure (treatment duration and reasons for cessation) and safety analyses included participants who received at least one dose of any study treatment.

The Kaplan-Meier method was used to summarise time-to-event data. Cox proportional hazards regression was used to estimate HRs and tests of interaction were used to investigate heterogeneity in the effects of enzalutamide versus control in prespecified subgroup analyses.[19] The proportional hazards assumption was investigated using plots of Schoenfeld residuals and the significance threshold for p values was set at less than 0·05. Two-sided 95% CIs were calculated with no adjustment for multiplicity, unless otherwise specified. Because the null hypotheses of no effect with enzalutamide on overall survival, PSA progression-free survival, and clinical-progression-free survival were rejected in the interim analysis, for this analysis we restricted the use of hypothesis testing and calculation of p values to investigate heterogeneity across subgroups and applied the Benjamini-Hochberg method to account for multiple comparisons, setting the α error to 5%. Subgroup analyses (Gleason score [≤7 *vs* 8–10], age (≥70 *vs* <70 years), ECOG performance status (1–2 *vs* 0), visceral metastases (yes *vs* no), metastatic disease present at first diagnosis (yes *vs* no) metachronous metastases (yes *vs* no), volume of disease (low *vs* high), early docetaxel planned (yes *vs* no), anti-resorptive therapy (yes *vs* no), ACE-27 score (2–3 *vs* 1–0)], and geographical region (Ireland and the UK *vs* North America *vs* Australia and New Zealand) were prespecified for overall survival, PSA progression-free survival, and clinical progression-free survival. Additionally, two-way subgroup analyses for docetaxel and volume of disease were prespecified, as were three-way subgroup analyses for M stage at diagnosis, docetaxel, and volume of disease prespecified for overall survival, PSA progression-free survival, and clinical progression-free survival. The effects of enzalutamide according to synchronous high-volume and low-volume disease, metachronous high-volume and low-volume disease, and use of concurrent docetaxel were prespecified to be of particular interest. Specifically, these subgroups have distinct prognoses when managed with testosterone suppression alone such that patients

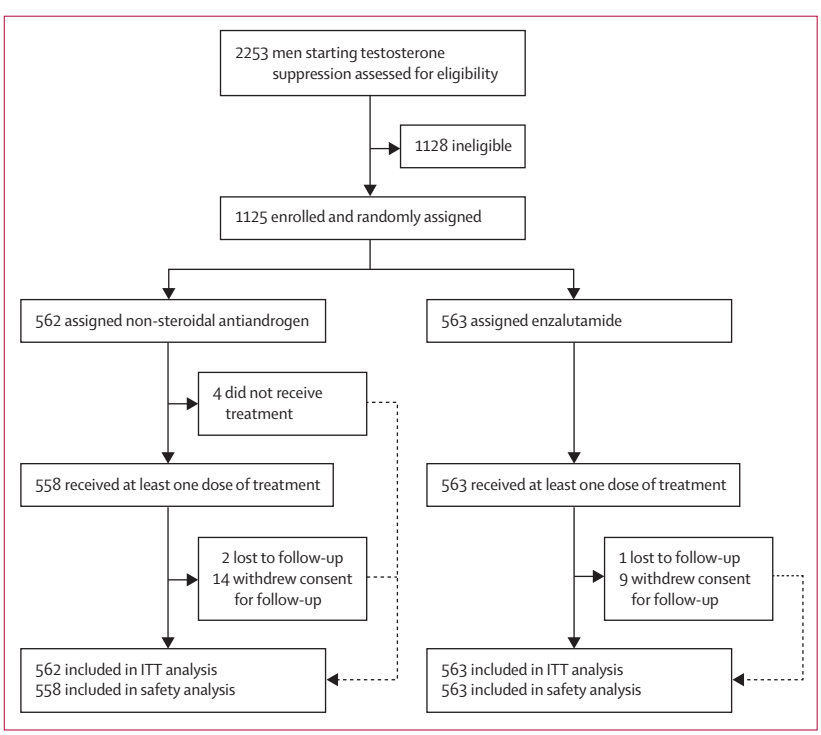


***Figure 1:*** **Trial profile**
ITT=intention-to-treat.

with metachronous low-volume disease have a good prognosis with a median overall survival of around 8 years, those with synchronous low-volume and metachronous high-volume disease have an intermediate prognosis with a median overall survival of around 5 years, and those with synchronous high-volume disease have a poor prognosis with median overall survival of around 3 years.[1–3] Moreover, the prespecified analysis of metachronous versus synchronous disease is specifically presented in light of the findings from related contemporaneous trials.[11,12]

The 5-year timepoint was chosen to describe long-term outcomes because median overall survival was not met for some of the treatment groups and the 5-year timepoint in this study is a reliable estimate with a median follow-up of 68 months (ie, more than 5 years).

Post-hoc exploratory analyses were prostate cancer-specific survival with cause of death adjudicated by the investigator and clinical outcomes of overall survival, prostate cancer-specific survival, and PSA progression-free survival of simultaneously enrolled subgroups (high-volume and low-volume synchronous or metachronous metastatic hormone-sensitive prostate cancer) by treament groups according to the docetaxel strata. Given that many clinical progression-free survival events occurred due to the treatment switch probably because of a PSA rise and that progression-free survival and clinical progression-free survival data were similar, we only report PSA-progression-free survival for this analysis. Prostate cancer-specific survival data for the overall cohort (ITT population) and subgroups are presented to provide insights into the aggressiveness of underlying disease and risk of death from non-cancer causes with extended follow-up. We also report the age and ACE-27 comorbidity score of patients with synchronous high-volume disease chosen for docetaxel (*vs* those not chosen) to gain insights into factors associated with use of docetaxel in the subgroup with greatest consensus of benefit from adding docetaxel to testosterone suppression.

The relevant clinical features for all prespecified and post-hoc exploratory analyses were captured prospectively in case reports and recorded in the trial database. Volume of disease and planned use of concurrent docetaxel were the only clinical features of interest that were stratification factors. In a post-hoc analysis, adverse events were tabulated by term, grade, and severity and the expected number of patients with selected adverse events per 100 000 person-years was calculated to account for different lengths of follow-up between the treatment groups.

All statistical analyses were performed using SAS (version 9.4) and R (version 4.2.1). An independent data safety monitoring committee oversaw the trial. This study is registered with ClinicalTrials.gov (NCT02446405), ANZCTR (ACTRN12614000110684), and the EU Clinical Trials Register (EUCTR2014-003190-42-IE).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Between March 31, 2014, and March 24, 2017, 2253 participants were assessed for eligibility and 1128 were ineligible

| | Control group (n=562) | Enzalutamide group (n=563) |
|---|---|---|
| Age, years | | |
| Median | 69 (64–75) | 69 (63–74) |
| Country | | |
| Australia | 321 (57%) | 324 (58%) |
| Canada | 107 (19%) | 97 (17%) |
| Ireland | 43 (8%) | 39 (7%) |
| New Zealand | 19 (3%) | 20 (4%) |
| UK | 50 (9%) | 63 (11%) |
| USA | 22 (4%) | 20 (4%) |
| ECOG performance status | | |
| 0 | 404 (72%) | 405 (72%) |
| 1 | 152 (27%) | 150 (27%) |
| 2 | 6 (1%) | 8 (1%) |
| Planned use of early docetaxel* | 250 (44%) | 253 (45%) |
| Actual use of early docetaxel* | 240 (43%) | 243 (43%) |
| One cycle before randomisation | 53 (9%) | 55 (10%) |
| Two cycles before randomisation | 25 (4%) | 37 (7%) |
| Volume of disease | | |
| High† | 301 (54%) | 301 (53%) |
| Low | 261 (46%) | 262 (47%) |
| Visceral metastases | 70 (12%) | 69 (12%) |
| Liver metastases | 13 (2%) | 14 (2%) |
| Metastatic status at first diagnosis | | |
| M1 (synchronous)‡ | 348 (62%) | 335 (60%) |
| M0 (metachronous)§ | 158 (28%) | 157 (28%) |
| MX¶ | 27 (5%) | 26 (5%) |
| Unknown¶ | 29 (5%) | 45 (8%) |
| ACE-27 score | | |
| 0–1 | 415 (74%) | 419 (74%) |
| 2–3 | 147 (26%) | 144 (26%) |

Data are mean (SD), median (IQR), or n (%). Ethnicity data are not available. ACE=Adult Comorbidity Evaluation. ECOG=Eastern Cooperative Oncology Group. M=metastasis. *Early use defined as docetaxel at or close to the time of starting testosterone suppression. †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. ‡Defined as the first presentation of prostate cancer with metastatic disease (referred to as synchronous metastases or de novo). §Defined as the first presentation of prostate cancer with non-metastatic disease (referred to as metachronous). ¶127 participants in MX and unknown were recorded and analysed as part of the M0 subgroup because patients with intermediate and low risk localised prostate cancer are usually recorded as NX or MX when no staging scans are required. 30 (24%) of those 127 received previous radiotherapy and 97 (75%) were presumably monitored or received prostatectomy. Case report forms collected details of all prostate procedures, including biopsy and transuretheral resection of the prostate, and did not record prostatectomy as a unique field, so we do not know how many of 85 patients had a previous prostatectomy.

***Table 1:*** **Baseline characteristics**

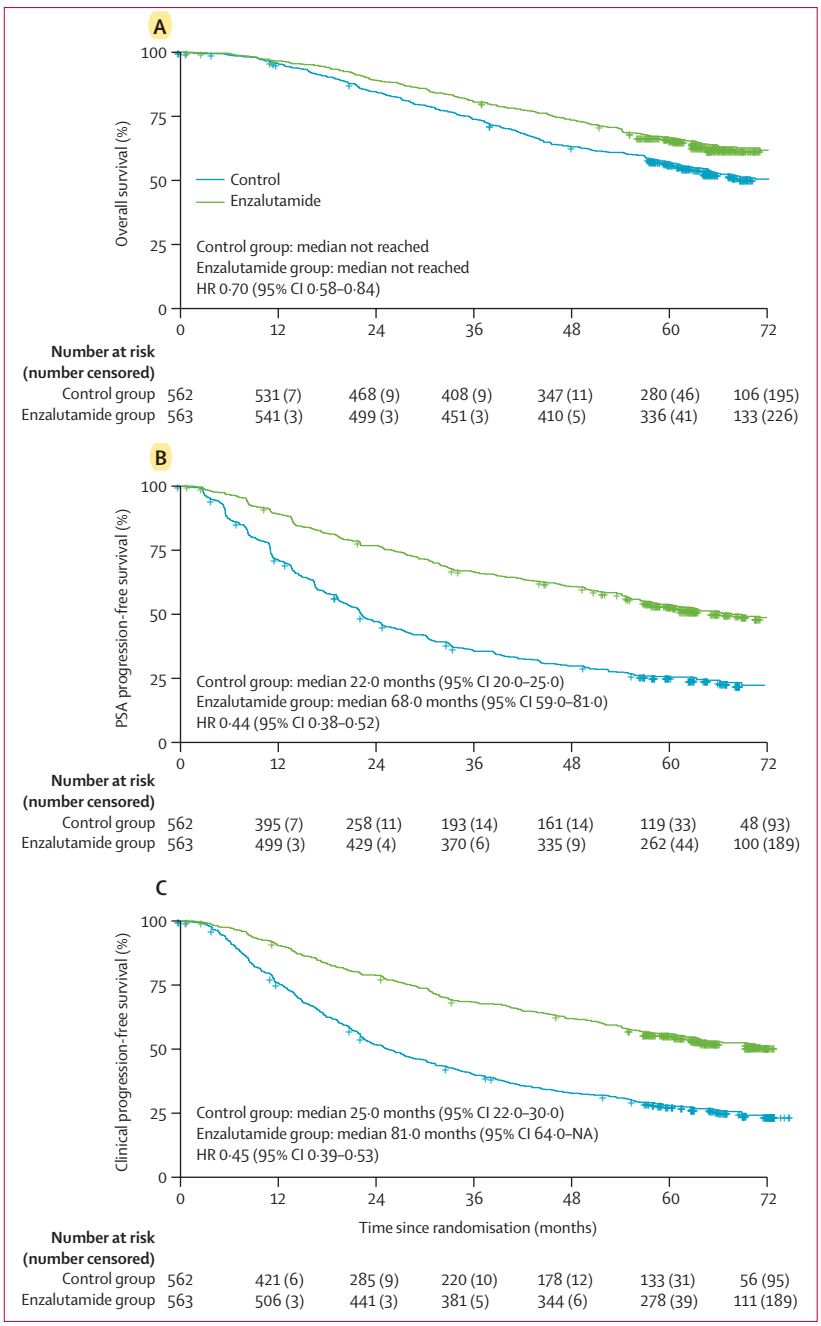


***Figure 2:*** **Kaplan-Meier curves**
(A) Overall survival. (B) PSA progression-free survival. (C) Clinical progression-free survival. The control group received standard non-steroidal antiandrogen therapy. 476 patients had overall survival events (268 events in the non-steroidal antiandrogen group *vs* 208 in the enzalutamide group), 702 had PSA progression-free survival events (423 *vs* 279), and 681 had clinical progression-free survival events (413 *vs* 268). PSA=prostate-specific antigen.

(figure 1). 1125 participants were randomly assigned to the control group (n=562) or the enzalutamide group (n=563; intention-to-treat population), and 558 (99%) participants in the control group and 563 (100%) in the enzalutamide group received at least one dose of study treatment (safety population). The median age was 69 years (IQR 63–74). High-volume disease was present in 602 (54%) of 1125 participants and 683 (61%) had synchronous metastatic disease (table 1). Concurrent docetaxel was planned at randomisation for 503 (45%) participants (250 [44%] of 562 in the control group and 253 [45%] of 563 in the enzalutamide group) but ten participants in each treatment group did not receive planned docetaxel; docetaxel was chosen for 359 (60%) of 602 patients with high-volume disease and 144 (28%) of 523 with low-volume disease. Of 483 (43%) participants who received concurrent docetaxel, 243 (43%) received all doses concurrently with enzalutamide and 240 (43%) received all doses concurrently with standard non-steroidal antiandrogen.

At data cutoff (Jan 19, 2022), 476 deaths had occurred after a median follow-up of 68 months (IQR 67–69). Median time on protocol therapy was 58 months (IQR 49–67) for the enzalutamide group and 23 months (21–25) for the control group. Additionally, 90 (20%) of 450 patients ceased study treatment with standard non-steroidal antiandrogen (control group) due to clinician preference and 33 (7%) due to patient preference, whereas the corresponding numbers were 23 (7%) and 20 (7%) for enzalutamide (appendix p 22).

As of data cutoff, 208 (37%) of 563 participants in the enzalutamide group and 268 (48%) of 562 in the control group had died. Median overall survival was not reached (HR 0·70 [95% CI 0·58–0·84]; p<0·0001), with 5-year overall survival of 57% (0·53–0·61) in the control group and 67% (0·63–0·70) in the enzalutamide group (figure 2A).

The PSA progression-free survival and clinical progression-free survival are shown in figures 2B and 2C. 5-year PSA progression-free survival was 54% (95% 49–58) in the enzalutamide group versus 25% (22–29) in the control group, whereas 5-year clinical progression-free survival was 56% (52–60) versus 28% (24–32; figures 2B, 2C). The post-hoc exploratory analyses of prostate cancer-specific survival is shown in the appendix (pp 6–7; median not reached).

In prespecified analyses of overall survival, PSA progression-free survival, clinical progression-free survival, and post-hoc analysis of prostate cancer-specific survival across prespecified subgroups of interest, tests of interaction with adjustments for multiplicity indicated that there was no statistical evidence that the effect of enzalutamide differed across these subgroups for any of the endpoints (figure 3; appendix pp 4–6). Consistency of the beneficial effect of adding enzalutamide to testosterone plus docetaxel was seen for participants with synchronous but not metachronus disease (figure 4A–C) and outcomes of the other planned predefined prognostic subgroups are shown in the appendix (pp 8–9).

At 5 years, the Kaplan-Meier estimates of the proportion of participants remaining on treatment were 22% in the control group and 48% in the enzalutamide group. Discontinuation due to treatment-related adverse events occurred in 25 (5%) of 558 participants who received

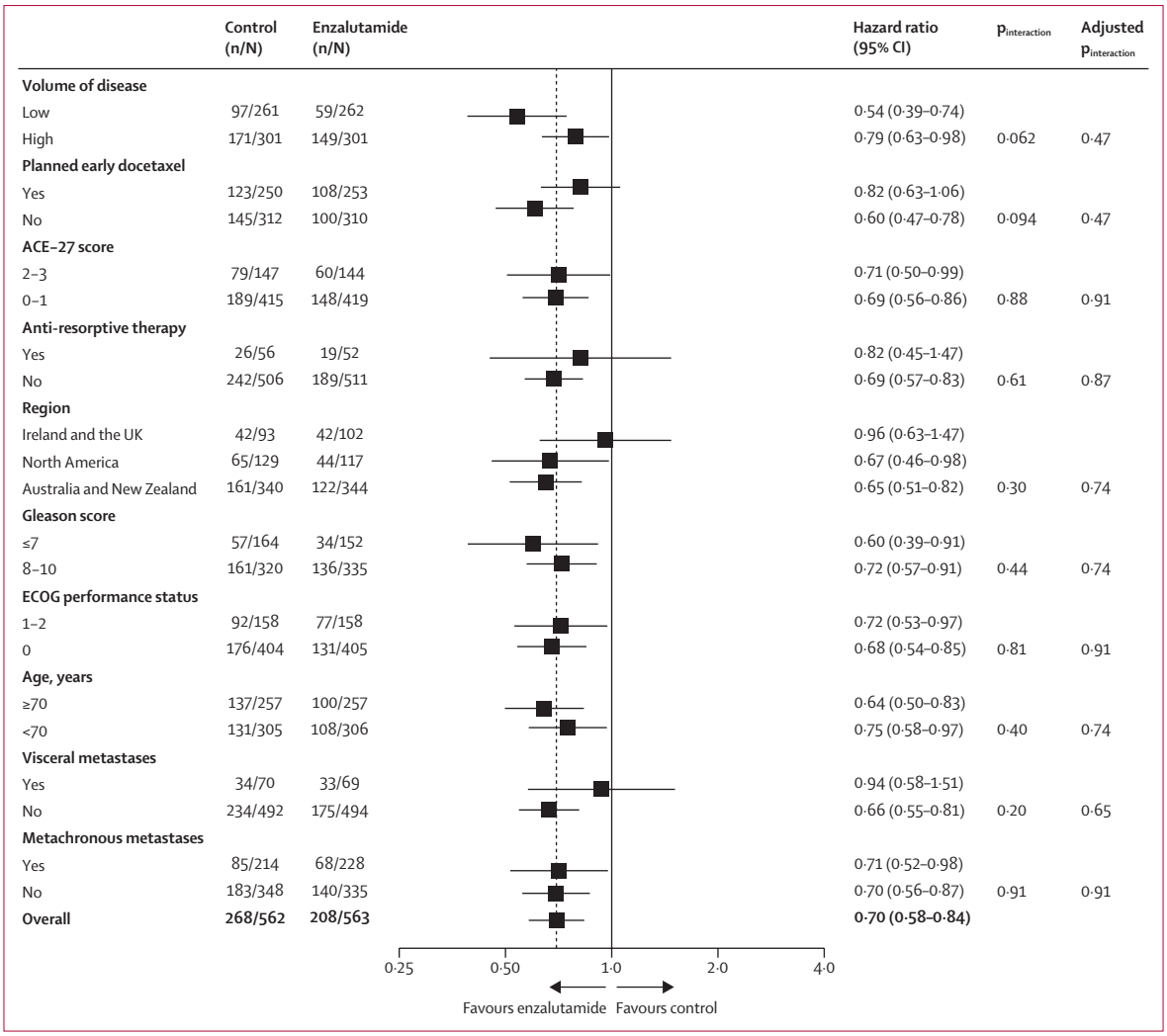


***Figure 3:*** **Pre-specified subgroup analysis of overall survival**

The control group received standard non-steroidal antiandrogen therapy. Size of black shaded boxes is proportional to the number of events. Dashed vertical line indicates the overall hazard ratio in all patients. Synchronous disease is defined as the first presentation of prostate cancer with metastatic disease and metachronous defined as the first presentation of prostate cancer with non-metastatic disease. ACE=Adult Comorbidity Evaluation. ECOG=Eastern Cooperative Oncology Group.

standard non-steroidal antiandrogen and 63 (11%) of 563 participants who received enzalutamide. 490 treatment discontinuations were due to progression of prostate cancer or treatment unrelated deaths (appendix p 22). 353 (85%) of 413 participants who progressed in the control group and 164 (61%) of 268 who progressed in the enzalutamide group received further active therapy at data cutoff (appendix p 23).

The number of patients in the four main prognostic groups were 439 (39%) of 1125 with synchronous high-volume disease, 244 (22%) with synchronous low-volume disease, 163 (14%) with metachronous high-volume disease, and 279 (25%) with metachronous low-volume disease. Use of docetaxel varied across prognostic subgroups. Patients most frequently selected for concurrent docetaxel had poor prognostic disease (270 [62%] of 439 with synchronous high-volume disease, 92 [38%] of 244 with synchronous low-volume disease, 89 [55%] of 163 with metachronous high-volume disease, and 52 [19%] of 279 with metachronous low-volume disease). Notably, patients not chosen for docetaxel in the synchronous high-volume disease subgroup were older and had more comorbidities (appendix p 21).

The updated adverse event data are reported according to worst grade with a focus on predefined adverse events of interest (table 2; >2% grade 3–4 and all grade 5 plus other relevant events). Ten (2%) of 558 participants died due to serious adverse events and 183 (33%) had serious grade 3 or 4 events in the control group whereas 13 (2%) of 563 participants died due to serious adverse events and 264 (47%) had serious grade 3 or 4 events in the enzalutamide group. In terms of participants with any grade 1–5 serious adverse events judged related to

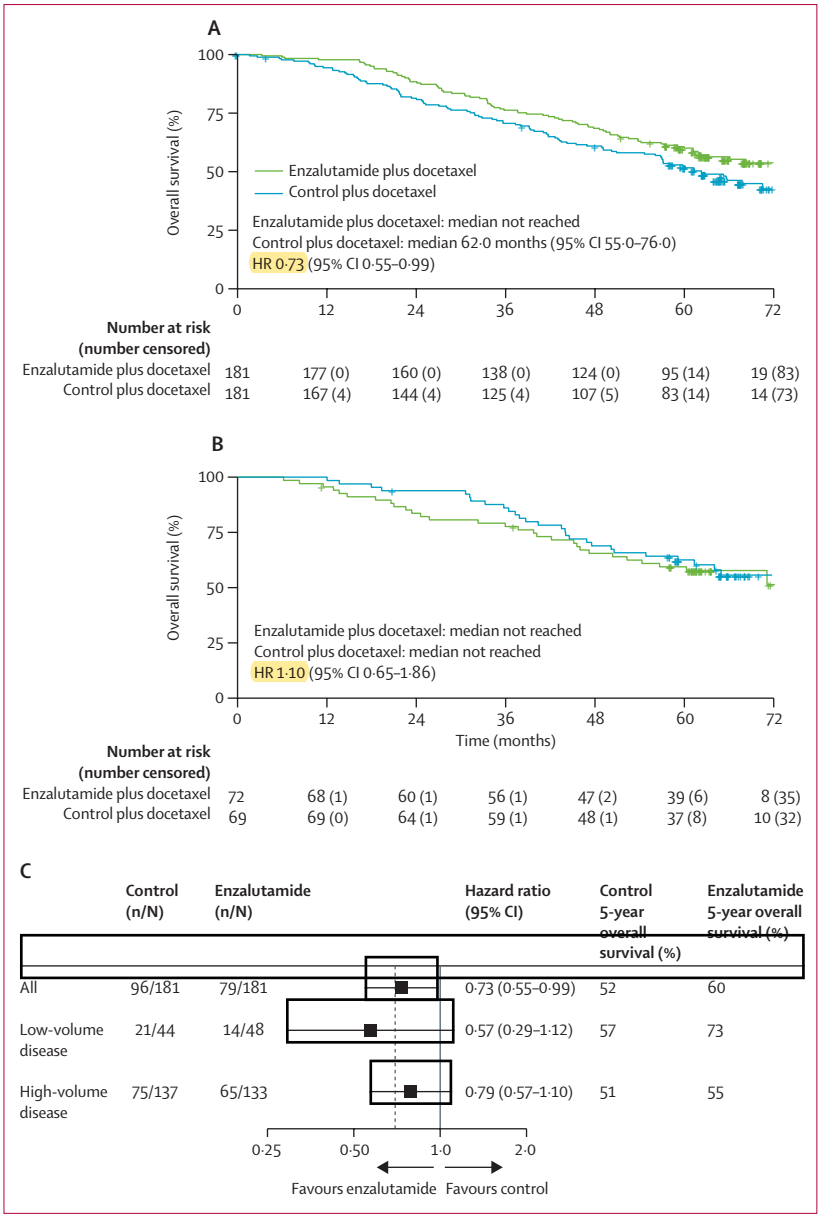


***Figure 4:*** **Prespecified overall survival analyses by prognostic subgroup**
Overall survival in participants with synchronous metastatic disease (A) and metachronous metastatic disease (B) selected to receive docetaxel. (C) Overall survival in prognostic subgroups with synchronous metastatic disease selected to receive docetaxel. Dashed vertical line indicates the hazard ratio (overall survival) point estimate for enzalutamide treatment effect for the whole cohort. M1 synchronous defined as the first presentation of prostate cancer with metastatic disease and M0 metachronous defined as the first presentation of prostate cancer with non-metastatic disease.

treatment, there were six (1%) in the control group versus 20 (4%) in the enzalutamide group, and the most common were two (<1%) patients with pneumonitis versus four (1%) with seizure and four (1%) with hypertension (appendix p 24). No deaths were attributed to enzalutamide. The most common grade 3–4 adverse events were febrile neutropenia associated with concurrent docetaxel use (33 [6%] of 558 in the control group *vs* 37 [6%] of 563 in the enzalutamide group), fatigue (four [1%] *vs* 33 [6%]), and hypertension (31 [6%] *vs* 59 [10%]; table 2). 96 (17%) of 563 participants had a dose reduction of enzalutamide for adverse events. Data for dose reductions of anti-androgen in the control group were not recorded in case report forms. The expected number of events was normalised for time on protocol therapy to adjust for longer exposure in the enzalutamide group (post hoc; appendix p 25). In this analysis even after accounting for treatment exposure, the long-term toxicity data, showed more grade 2 and 3 events (fatigue, cognitive disturbance, impaired concentration, sensory neuropathy, falls, fractures, seizures, hypertension, and heart failure) in participants receiving enzalutamide than in those who received the control. The expected number of patients with selected adverse events per 100 000 person-years, and a list of all adverse events are shown in the appendix (pp 25, 26–54).

Post-hoc exploratory analyses of overall survival, prostate cancer-specific survival, and PSA progression-free survival of all prognostic subgroups in the control and enzalutamide groups with and without docetaxel are shown in the appendix (pp 10–19).

The overall survival and prostate cancer-specific survival Kaplan-Meier curves for the overall cohort (figure 2) and for each subgroup (appendix pp 10, 12) show the effect of the increasing incidence of deaths from other causes with longer follow-up and more so with longer term cancer control with enzalutamide. Forest plots and 5-year PSA progression-free survival, overall survival, and prostate cancer-specific survival are shown for each prognostic subgroup with and without docetaxel in the appendix (pp 16–18).

## Discussion

In this planned analysis of the ENZAMET trial, with a median follow-up of longer than 5 years, we found that the addition of enzalutamide to standard of care (testosterone suppression with or without docetaxel) resulted in a sustained improvement in overall survival, PSA progression-free survival, clinical progression-free survival, and prostate cancer-specific survival (post hoc) compared with standard non-steroidal antiandrogen treatment plus standard of care for patients with metastatic hormone-sensitive prostate cancer. The PSA progression-free and clinical progression-free survival results show that enzalutamide treatment resulted in more durable cancer control than standard non-steroidal antiandrogen treatment across all variables and prognostic subgroups regardless of docetaxel treatment.

However, the magnitude of effect of enzalutamide on overall survival and prostate cancer-specific survival (post hoc) varied across subgroups and with use of concurrent docetaxel. Furthermore, our findings for the patient subgroups put ENZAMET data into context with other relevant phase 3 trials. First, we found an overall survival benefit across most subgroups despite high use (85% of patients) of any subsequent active therapies

| | Control group (n=558) | | | | Enzalutamide group (n=563) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
| Febrile neutropenia | .. | 24 (4%) | 9 (2%) | .. | .. | 30 (5%) | 7 (1%) | .. |
| Fatigue | 375 (67%) | 4 (1%) | .. | .. | 445 (79%) | 33 (6%) | .. | .. |
| Pain | 108 (19%) | 5 (1%) | .. | .. | 139 (25%) | 14 (2%) | .. | .. |
| Lung infection | 13 (2%) | 11 (2%) | 1 (<1%) | 1 (<1%) | 10 (2%) | 13 (2%) | 2 (<1%) | .. |
| Sepsis | .. | .. | 11 (2%) | 1 (<1%) | .. | .. | 6 (1%) | .. |
| Fall* | 24 (4%) | 2 (<1%) | .. | .. | 80 (14%) | 9 (2%) | .. | .. |
| Fracture | 9 (2%) | 7 (1%) | .. | .. | 23 (4%) | 20 (4%) | 1 (<1%) | .. |
| Alanine aminotransferase increased | 42 (8%) | 3 (1%) | .. | .. | 28 (5%) | 4 (1%) | .. | .. |
| Aspartate aminotransferase increased | 38 (7%) | 1 (<1%) | .. | .. | 15 (3%) | 1 (<1%) | .. | .. |
| Neutrophil count decreased | 13 (2%) | 8 (1%) | 10 (2%) | .. | 19 (3%) | 17 (3%) | 14 (2%) | .. |
| Back pain | 152 (27%) | 12 (2%) | .. | .. | 189 (34%) | 17 (3%) | .. | .. |
| Generalised muscle weakness | 18 (3%) | .. | .. | .. | 33 (6%) | 2 (<1%) | .. | .. |
| Musculoskeletal (other) | 239 (43%) | 9 (2%) | .. | .. | 252 (45%) | 16 (3%) | .. | .. |
| Neoplasms (benign or malignant) | 23 (4%) | 18 (3%) | 4 (1%) | .. | 48 (9%) | 21 (4%) | 4 (1%) | .. |
| Cognitive disturbance | 4 (1%) | .. | .. | .. | 15 (3%) | 1 (<1%) | .. | .. |
| Memory impairment | 24 (4%) | 1 (<1%) | .. | .. | 74 (13%) | 1 (<1%) | .. | .. |
| Seizure | .. | .. | .. | .. | 6 (1%) | 1 (<1%) | .. | .. |
| Syncope | 1 (<1%) | 9 (2%) | .. | .. | 1 (<1%) | 24 (4%) | .. | .. |
| Haematuria | 32 (6%) | 6 (1%) | .. | .. | 43 (8%) | 13 (2%) | 2 (<1%) | .. |
| Skin flushing | 355 (64%) | 1 (<1%) | .. | .. | 388 (69%) | 5 (1%) | .. | .. |
| Hypertension | 55 (10%) | 30 (5%) | 1 (<1%) | .. | 90 (16%) | 59 (10%) | .. | .. |
| Hypotension | 14 (3%) | 4 (1%) | .. | .. | 18 (3%) | 6 (1%) | .. | .. |
| Any adverse event | 286 (51%) | 209 (37%) | 46 (8%) | 10 (2%)† | 175 (31%) | 324 (58%) | 51 (9%) | 13 (2%)‡ |

Data are n (%) shown for grade 3–4 adverse events occurring in >2% of participants and all grade 5 adverse events, plus other relevant events associated with enzalutamide. *The falls could be from balance problems, syncope, muscle weakness, or sarcopenia. †Deaths reported as one cardiac arrest, one gastric haemorrhage, one gastrointestional, one general disorder, one sudden death, four infections, and one pneumonitis. ‡Deaths reported as one cardiac disorder, two myocardial infarctions, three not specified, one general disorder, one sudden death, one acidosis, two strokes, one respiratory failure, and one respiratory disorder.

***Table 2:*** **Participants with adverse events**

(including a high rate [76%] of using at least one new hormonal therapy for castration-resistant prostate cancer) in the non-steroidal antiandrogen group. Notably, the PSA progression-free survival and overall survival data for early enzalutamide in those with synchronous high-volume metastatic hormone-sensitive prostate cancer who received concurrent docetaxel were consistent with findings in the overall cohort, despite a median overall survival of longer than 60 months among those who received testosterone suppression plus docetaxel in the non-steroidal antiandrogen group (appendix pp 14–16). For unclear reasons, this finding differs from the median overall survival reported for patients who received testosterone suppression and docetaxel in the contemporary phase 3 PEACE-1 (42 months),[11] CHAARTED (51 months),[2] and ARASENS (42 months)[12] trials and highlights the caution needed for cross-trial comparisons.

Patients with visceral metastases are a unique population among those with high-volume metastatic hormone-sensitive prostate cancer, especially those with liver metastases, who often have poor prognosis. Although in subgroup analyses among patients with visceral metastases, we found enzalutamide treatment to have a greater PSA progression-free survival benefit (HR 0·54 [95% CI 0·36–0·81]) than treatment with non-steroidal antiandrogens, no benefit was found in this subgroup for overall survival. No major overall survival benefit was observed for patients with liver metastases who received abiraterone and testosterone suppression in the LATITUDE trial (HR 0·82, 95% CI 0·41–1·66)[20] or for patients with visceral metastases who received enzalutamide and testosterone suppression in the ARCHES trial (HR 1·16, 0·67–2·00).[21] For those who received apalutamide plus testosterone suppression in TITAN, the overall survival was also not significant (HR 0·76, 0·47–1·23).

Patients chosen for docetaxel and randomly assigned to receive testosterone suppression plus enzalutamide are a subgroup of particular interest. Although ENZAMET was not designed to measure the benefit of adding docetaxel to testosterone suppression plus enzalutamide, our study provides some insights, highlights clinical scenarios in which docetaxel is not suitable, and indicates that those with a worse prognosis who are more likely to benefit when docetaxel is added to testosterone suppression alone[2,14] might also be most likely to benefit from adding docetaxel to testosterone

suppression plus enzalutamide. The high frequency of concurrent docetaxel use in poor prognostic disease observed in our study reflects this bias. Reassuringly, the addition of enzalutamide to docetaxel and testosterone suppression resulted in an overall survival HR of 0·73 (95% CI 0·55–0·90) in patients with synchronous metastases in ENZAMET, which is similar to the overall survival benefit seen in other sentinel phase 3 trials (HR 0·75 [95% CI 0·59–0·95] with addition of abiraterone in PEACE-1[11] and HR 0·71 [0·59–0·85] with addition of darolutamide in ARASENS[12]). However, comparison with the metachronous subgroup, in which no overall survival benefit was seen, is limited by the small sample size and precludes performing a reliable test of interaction. A well powered individual patient data meta-analysis is required to evaluate which patients with metachronous metastatic hormone-sensitive prostate cancer will benefit from adding new hormonal therapies to docetaxel and testosterone suppression.

We also noted that the median age was lower and ACE-comorbidity index scores were generally better for participants with synchronous high-volume disease who received docetaxel than for those who did not receive docetaxel. In this subgroup, we found similar overall survival benefits among those receiving enzalutamide with or without docetaxel, but prostate cancer-specific survival was worse among those who received enzalutamide with docetaxel versus without docetaxel. These findings suggest that patients who were not selected for docetaxel and had synchronous high-volume disease had a better prognosis of disease than did those who were not selected for docetaxel. The older age and greater morbidity of those not selected for docetaxel with more non-prostate cancer deaths explains why the 5-year overall survival is similar despite a better prostate-cancer specific survival. Notably, patients with testosterone suppression plus enzalutamide with docetaxel had better prostate cancer-specific survival and overall survival until 30 months than their counterparts who did not receive docetaxel. This finding could be because the short course of docetaxel (six doses for 18 weeks at commencement of therapy) prevented early deaths caused by aggressive cancer, which is less dependent on androgen receptor signalling. Historically, this subgroup has benefitted the most from adding docetaxel to testosterone suppression compared with testosterone suppression alone.[2,14] In other subgroups, participants who received testosterone suppression plus enzalutamide without docetaxel had similar early prostate cancer-specific survival and overall survival outcomes to those who received testosterone suppression plus enzalutamide with docetaxel. However, patients with synchronous low-volume disease chosen for docetaxel with and without enzalutamide seemed to have worse 5-year prostate cancer-specific survival and overall survival than those with synchronous low-volume disease who were not selected for docetaxel, suggesting that there might be other poor prognostic factors associated with choice of docetaxel in this subgroup which could also identify patients who benefit from adding docetaxel to enzalutamide plus testosterone suppression in the long term.

Participants with metachronous low-volume disease who did not receive docetaxel might have had the most pronounced treatment effect with enzalutamide. This subgroup has the longest overall survival when managed with testosterone suppression alone[1,2,14] and gene expression profiling indicates that patients with low-volume metastatic hormone-sensitive prostate cancer have the most androgen receptor-dependent RNA profile in primary specimens,[22] which might explain the greatest treatment effect of potent androgen receptor inhibition with addition of enzalutamide to testosterone suppression observed in this subgroup.

Metachronous high-volume disease was infrequent in our cohort (163 [14%] of 1125) and these patients can have diverse prognostic features, including those with four bone metastases as the only extent of metastases versus those with liver metastases. These factors and small patient numbers probably account for the non-significant prostate cancer-specific survival and overall survival results with enzalutamide, despite the PSA progression-free survival benefit seen with enzalutamide in this population. ARASENS[12] showed an overall survival of HR 0·61 (95% CI 0·34–1·05) when darolutamide was added to docetaxel in patients with metachronous metastatic hormone-sensitive prostate cancer (13% of the study population). The overall survival at 4 years of 57% for participants treated with testosterone suppression plus docetaxel in this sub-group in ENZAMET was similar to around 60% survival of participants with metachronous high-volume disease in CHAARTED.[2]

Early enzalutamide with and without docetaxel involves an increased treatment burden with more adverse events for patients, so documenting the long-term overall survival benefit and adverse event profile is important. Documentation is particularly relevant in patients with the most favourable prognosis who are more likely to be receiving therapy for many years, such as those with metachronous low-volume metastatic hormone-sensitive prostate cancer. Moreover, our post-hoc analysis of prostate cancer-specific survival in the context of overall survival reveals the increasing relevance of deaths from other causes, particularly in older patients with metastatic hormone-sensitive prostate cancer taking enzalutamide. The short-term adverse event profile associated with enzalutamide (with and without docetaxel use) and the impact on quality of life have been reported previously.[6,18] In these reports, a modest decrease in quality of life with early enzalutamide compounded with the addition of docetaxel was reported. However, after 6 months there was no further incremental decline in quality of life. The long-term adverse event data presented in our study

indicate that enzalutamide had a greater number of cumulative grade 2 and 3 events of fatigue, even after accounting for treatment exposure. The absence of progressive quality of life decline after 6 months, with follow-up of 34 months in the HRQOL result analysis,[18] suggests that most of these events happened early and did not accumulate over time, which could possibly be due to 17% of participants having dose reduction of enzalutamide to a tolerable dose.

The limitations of ENZAMET prevent definitive conclusions of the subgroup analyses given their small sample sizes, open-label design, absence of randomisation to concurrent docetaxel, and post-hoc nature of some exploratory analyses. A randomised phase 3 trial of testosterone suppression plus a more effective androgen receptor inhibitor with or without docetaxel is required and findings from our study can help to design these trials. Also, the extent of metastatic disease was defined by conventional CT of the abdomen and pelvis and a Tc bone scan because prostate-specific membrane antigen (PSMA) PET-CT scans were not widely available during study recruitment. Future studies are also needed to define how advanced imaging techniques, such as PSMA PET-CT imaging, can be used to improve care for patients with metastatic hormone-sensitive prostate cancer. The long-term ENZAMET data confirms known concerns for fatigue, cognition disturbance, falls, and risk of seizures in some patients. However, the open-label design, longer follow-up with greater treatment exposure than companion trials, and inclusion of some patients who were not fit to receive docetaxel limits our ability to compare our study with other trials (some of which mandated docetaxel and required patients to be suitable for docetaxel), which necessitates the design of randomised trials with uniform populations for more definitive assessments of adverse events. For now, the choice of new hormonal therapy will depend on availability and patient comorbidity profile.

Work is ongoing (including ENZAMET and STAMPEDE [NCT00268476]) to identify biomarkers to follow up on published data from the CHAARTED trial, which suggested that a luminal B RNA profile is associated with the benefit of adding docetaxel to testosterone suppression compared with testosterone suppression alone.[22] These studies might identify patients who benefit most from adding docetaxel to testosterone suppression plus a new hormonal therapy. Additionally, studies are needed to identify which patients with intact primary cancer benefit from adding primary prostate radiation to more effective androgen receptor inhibition.

In summary, unless a contraindication exists or there is insufficient access to any of the therapies, patients with metastatic hormone-sensitive prostate cancer of any volume evident on CT or bone scanning with $^{99m}$Tc should be offered optimal hormonal therapy with testosterone suppression plus a more effective androgen receptor inhibitor, such as enzalutamide. Until further data are available, a joint patient and physician decision is needed to individualise treatment with the addition of primary prostate radiation or docetaxel to this regimen.

#### Contributors

All authors reviewed the manuscript and provided feedback. CJS and IDD did the literature search. CJS, IDD, AJM, and MRS contributed to the figures, study design, data collection, data analysis, data interpretation, and writing of the manuscript. SB, LC, KNC, SC, MF, LGH, AMJ, NJL, GM, JM, RM, MM, SAN, FP, WP, DW, MNR, SKS, AlvT, THT, AlaT, FV-B, SGW, DWP, SP, and AYZ contributed to the data collection and interpretation, and writing of the manuscript. CJS, MM, and IDD acquired funding. RRZ contributed to the data interpretation and writing of the original manuscript. CJS, AJM, MRS, and IDD accessed and verified all the data in the study. All authors had full access to all the data in the study and accept responsibility to submit for publication.

#### Declaration of interests

CJS received institutional research grants from Bayer, Sanofi, Astellas Pharma (Pfizer), Dendreon, and Janssen and personal consulting fees from Bayer, Astellas Pharma, Janssen, CellCentric, Point Biopharma, Pfizer, Novartis, Genentech (Roche), Bristol Myers Squibb, Lilly, Hengrui Europe Biosciences, and AstraZeneca. MRS received institutional research grants from Astellas Pharma, Amgen, AstraZeneca, Bionomics, Bristol Myers Squibb, Celgene, Medivation, MSD, Pfizer, Roche, Sanofi, and Tilray. KNC received institutional research grants from AstraZeneca, Bayer, Novartis, Pfizer, Point Biopharma, Roche, and Janssen; personal consulting fees from AstraZeneca, Bayer, Novartis, Pfizer, Point Biopharma, and Roche; institutional consulting fees from Janssen; and honoraria from Janssen and AstraZeneca. SC had stock or ownership interests in Clovis Oncology; received honoraria from Novartis and Clovis Oncology; had a consulting or advisory role for Astellas Pharma, Bayer, Pfizer, Janssen-Cilag, BeiGene, and Novartis; and received payment for speakers' bureaus from Janssen-Cilag and Sanofi (Aventis). MF had a leadership or fiduciary role as a board director for the Royal Australasian College of Surgeons. LGH received institutional research grants, honoraria, and Support for meetings or travel from Astellas Pharma. NJL was on the data safety monitoring board or advisory board for Thoracic Oncology Group of Australia; had a leadership or fiduciary role as a deputy director for Cancer Trials New Zealand; and was a member of the executive committee for New Zealand Society for Oncology. JM had a leadership or fiduciary role as a treasurer for the Irish Society of Medical Oncology; and was a chairman for National Annual Conferences. RM had stock or ownership interests in Bayer; received honoraria from Sanofi, Janssen, Astellas Pharma, Bristol Myers Squibb, MSD, Pfizer, Novartis, and Clovis Oncology; had a consulting or advisory role for MSD Oncology; received research funding from Janssen, Bayer, and Astellas Pharma; provided expert testimony for Pfizer; and received support for meetings or travel from Janssen-Cilag, Roche, and Ipsen. SAN received honoraria from Janssen, Bayer, MSD, AstraZeneca, and Advanced Accelerator Application. FP received honoraria from Bayer and AstraZeneca. DWP received institutional research funding from Medivation, Bristol Myers Squibb, Roche, Exelixis, MSD, Pfizer, Astellas Pharma, Bayer, Symvivo, and Amgen; personal consulting fees from Bristol Myers Squibb, Pfizer, MSD, Cipla, Astellas Pharma, and MSD (Pfizer); institutional consulting fees from Pfizer and MSD; honoraria from Bayer and MSD (Pfizer); and support for meetings or travel from Bristol Myers Squibb, Astellas Pharma, Pfizer, Amgen, MSD (Pfizer), and Janssen. MNR was on the data safety monitoring board or advisory board for Pfizer, Ipsen, EMD, Serono, MSD, and Bayer. SKS received research grants from Novartis/AAA, Genentech, AstraZeneca, Pfizer, and MSD; honoraria from AstraZeneca, Bristol Myer Squibb, MSD, and Janssen; and was on the data safety monitoring board or advisory board as the chair for the data safety monitoring committee at Novartis. AlvT had a leadership or fiduciary role as the head of department for the Te Whatu Ora hospital. THT received honoraria from AstraZeneca. AlvT received honoraria from Novartis and Gilead; support for meetings or travel from MSD, Lilly, Astellas Pharma, and Ipsen; and was on the data safety monitoring board or advisory board for Amgen, Novartis, and MSD. FV-B received institutional research grants from Janssen, MSD, and Seagen and consulting fees from Janssen, MSD, AstraZeneca, and

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### Data sharing

Requests for deidentified individual patient or aggregate data, the corresponding data dictionary with all relevant fields, and informed consent should be directed to the corresponding author and will be reviewed for data sharing by the ENZAMET trial executive committee. Decisions on whether data are to be shared will be adjudicated on the basis of the quality of questions being addressed. The study protocol and statistical analysis plan are available in the appendix.

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