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Plain Language Summary of Publication

Enzalutamide with standard first-line therapy for metastatic hormone-sensitive prostate cancer: a plain language summary of the ENZAMET trial (ANZUP 1304)

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Author affiliations can be found at the end of this article

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Where can I find the original article on which this summary is based?

This is a summary of the ENZAMET clinical trial. The findings were originally published in *The New England Journal of Medicine* in July 2019, with associated quality of life published in the *Journal of Clinical Oncology* in March 2022. Longer-term survival outcomes were published in *Lancet Oncology* in March 2023. These articles can be read at the following links.

'Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer' available to read for free at: https://www.nejm.org/doi/full/10.1056/nejmoa1903835

'Health-Related Quality of Life in Metastatic, Hormone-Sensitive Prostate Cancer: ENZAMET (ANZUP 1304), an International, Randomized Phase III Trial Led by ANZUP' available available to read for free at: https://ascopubs.org/doi/full/10.1200/JCO.21.00941

'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' available for a fee at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00063-3/abstract

Summary

How to say (download PDF and double click sound icon to play sound)...

- **Enzalutamide:** en-za-LOO-ta-mide
- **Xtandi:** ex-TAN-dee
- **Androgen:** AN-druh-jen
- **Testosterone:** tes-TOSS-teh-rone
- **Docetaxel:** doh-seh-TAX-el

What is this summary about?

ENZAMET is a large international clinical trial involving people with **metastatic hormone sensitive** prostate cancer (mHSPC). Prior to the trial, standard treatment included **testosterone** suppression and sometimes, **chemotherapy**. However, the researchers thought enzalutamide, an anti-**androgen** (hormone) medicine, which helps to block the effects of testosterone, might be helpful if added to testosterone suppression.

What are the key takeaways?

ENZAMET showed that the addition of enzalutamide to standard testosterone suppression treatment for mHSPC improved **survival**, resulting in an increase in the percent of participants alive at 5 years from 57% to 67%. Enzalutamide extended the time until the cancer grew. Side effects were in keeping with what was already known about enzalutamide and these risks were outweighed by improved cancer control in the long-term.

What are the main conclusions reported by the researchers?

The combination of testosterone suppression plus enzalutamide is a very **effective first-line treatment** for mHSPC.

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Metastatic: Cancer that has spread to other parts of the body (beyond the prostate and nearby **lymph glands** in the case of prostate cancer).
Lymph gland: A small bean-shaped structure that is part of the body's immune system and often represents the first site of metastatic spread of cancer.
Hormone: A signalling protein which leads to specific changes in other organs or tissue's usual function.
Hormone sensitive: A period when the cancer can be treated effectively by blocking hormones from supporting the cancer's growth.
Testosterone: A hormone produced mainly in the testes, but also in the ovaries (in females) and adrenal glands.
Chemotherapy: A treatment for cancer (and some other conditions) using chemical substances or other drugs intended to kill cancer cells.
Androgen: A male sex hormone, such as testosterone.
Survival: The period of time an individual is alive after cancer diagnosis, or after treatment is started.
Effective: Proven to be successful in achieving a positive or desired effect.
First-line treatment: The first treatment(s) given for a disease.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research.

Enzalutamide is used to treat the condition under study that is discussed in this summary. Approval varies by country; please check with your local provider for more details.

Who is this article for?

This summary of the ENZAMET trial may be helpful for patients, their families, patient advocates, and healthcare professionals, including people wishing to understand treatment options for patients with metastatic hormone-sensitive prostate cancer (mHSPC).

Who sponsored this study?

ENZAMET was a clinical trial led by the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group and was sponsored by the University of Sydney and coordinated by the NHMRC Clinical Trials Centre.

Sponsor: A company or organisation that oversees and pays for a clinical research study. The sponsor also collects and analyses the information from the study.

Why was the study carried out?

- Prostate cancer is one of the most frequently diagnosed cancers. When it is detected early and localised to the prostate, it can be cured using a combination of surgery or **radiotherapy**, sometimes alongside medicines that lower **testosterone**. Unfortunately, sometimes if it comes back after surgery or radiotherapy or when prostate cancer has already spread from the prostate (**metastatic**), it is no longer curable, though treatment(s) can allow patients to live for a number of years.
- In the past, testosterone suppression with either an injection, or surgery to remove the testicle, was the first and only treatment given to people with metastatic prostate cancer. This is because prostate cancers rely on testosterone to survive, and suppressing or lowering testosterone causes prostate cancer cells to go to sleep, and in some cases, die. Prostate cancers that are effectively controlled through testosterone suppression are termed, hormone-sensitive.
- Lowering the testosterone level using testosterone suppression in patients with metastatic hormone sensitive prostate cancer (mHSPC) allows cancer control for some time, however more effective treatments are needed to make it work for longer.

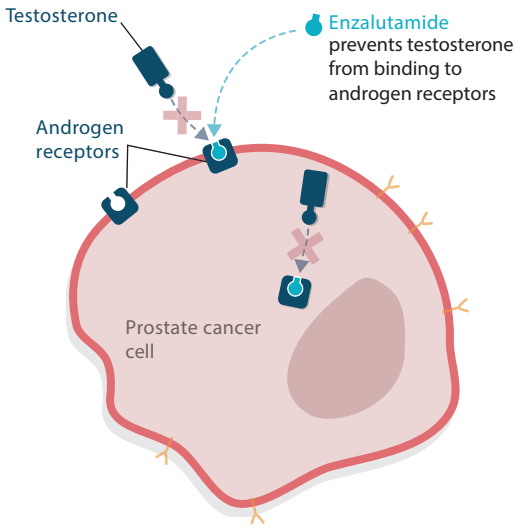
- Inevitably, prostate cancer may worsen despite lowering of testosterone. When this occurs, the prostate cancer is then referred to as metastatic castrate-resistant prostate cancer (mCRPC).

- Enzalutamide (also known by the trade name Xtandi®) is a drug that attaches to the **androgen receptor**, a protein on the surface of cells. Attachment of enzalutamide prevents testosterone (and other androgens) from accessing the cancer cell, which in turn reduces cancer growth.

- Enzalutamide has been shown to improve survival in people with mCRPC as it blocks androgens other than testosterone that also support the growth of prostate cancer cells, after the androgen receptor has stopped responding to testosterone suppression alone.

- Enzalutamide belongs to a class of drugs called 'non-steroidal anti-androgens' or **NSAAs**, which act by blocking the androgen receptor on cells, so that testosterone cannot access the prostate cancer cell. Other drugs in this class include first generation NSAAs, bicalutamide and flutamide, and newer generation agents including apalutamide and darolutamide. First generation NSAAs, attach less strongly to the androgen receptor than the newer agents.

How enzalutamide works



- The ENZAMET trial asked whether using enzalutamide alongside testosterone suppression shortly after diagnosis of mHSPC would increase the length of life of people with prostate cancer. Enzalutamide with testosterone suppression was compared with testosterone suppression plus an alternative, albeit older NSAA such as bicalutamide or flutamide, which was considered standard treatment in some countries (although this varied). The trial also tested whether enzalutamide would increase the time it took for the cancer to regrow with a low testosterone, and what effects enzalutamide had on **quality of life**.

Radiotherapy: A cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumours.
Androgen receptor: A protein present on the surface of cells that allows binding of androgens, such as testosterone, to initiate a chemical reaction or pathway.
Non-steroidal anti-androgen (NSAA): A group of medications, which bind to the androgen receptor on the surface of cells.
Quality of life: Measures of the well-being and overall health of a person or group of people, often evaluating the effects of cancer and/or the treatments used in cancer.

- In addition, because chemotherapy (docetaxel) is sometimes given when starting testosterone suppression to prolong life, some people in the ENZAMET trial also received docetaxel as part of their usual care after a discussion with their doctor.

- All study participants received testosterone suppression (standard of care), and half the people in the trial received enzalutamide while the other half received an older type of NSAA (such as bicalutamide or flutamide), which was previously considered an alternative standard-of-care.

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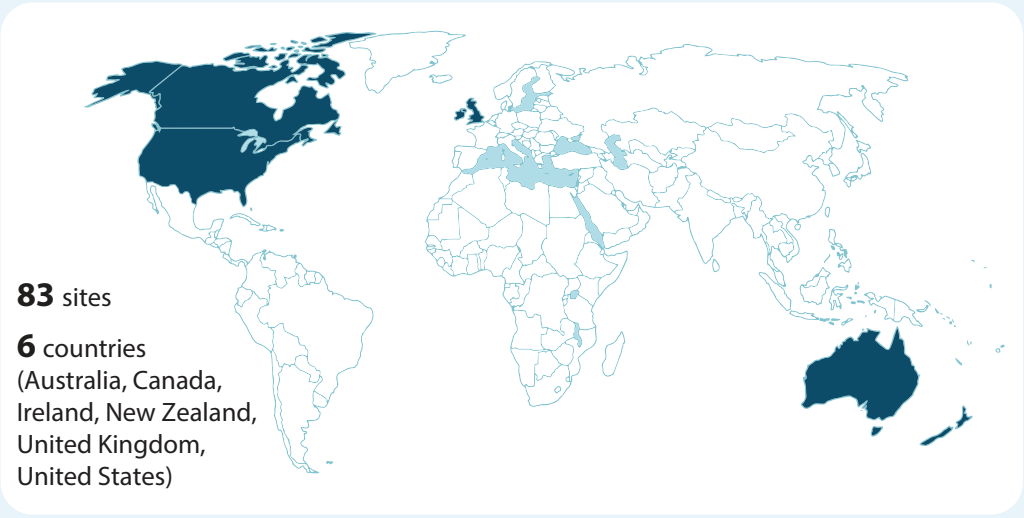
Who took part in the study?

ENZAMET included 1,125 people from 83 sites in six countries diagnosed with mHSPC. Participants ranged in age from 41 to 96, with the midpoint of the age range being 69.



- The 'volume' of prostate cancer describes the pattern of spread of prostate cancer and number of spots (cancer deposits) on a scan. About half of the participants had 'low volume' metastatic disease and about half had 'high volume', according to standardised definitions.
- About 4 out of 10 had 'metachronous metastatic prostate cancer'. This is prostate cancer that previously appeared to be localised to the prostate gland and has previously been treated with the intention of eliminating it, but then comes back later in other parts of the body.
- About 6 out of 10 participants had 'synchronous metastatic prostate cancer'. This is metastatic prostate cancer found at the same time the cancer is originally diagnosed. Synchronous metastatic prostate cancer is likely to be more aggressive (regrow more quickly on testosterone suppression), and participants may be more likely to benefit from more intensive treatment, when compared with metachronous prostate cancer.
- Docetaxel chemotherapy was planned to be given to approximately 45% of participants in both treatment groups.

All participants had:

- Confirmed metastatic prostate cancer on computerised tomography (also known as CT) and/or bone scan.
- Normal or near-normal kidney, liver, and bone marrow function (bone marrow is an essential part of the body, as it contains stem cells that produce blood cells and the cells that make up the immune system).
- A good level of overall function ('performance status).

None of the participants had:

- Prior treatment with other therapies known to be active in this setting (however a short period of prior testosterone suppression with or without docetaxel was allowed).
- A history of seizure (or 'fit'), fainting, mini-stroke, or serious heart disease.
- Diagnosis of another cancer within the previous five years.

Testosterone suppression was permitted as part of the original treatment for prostate cancer before it became metastatic, if treatment had finished at least a year before entry into the study.

- ENZAMET was a randomly assigned, open-label phase 3 clinical trial. Though the safety and effectiveness of enzalutamide had already been investigated in phase 1 and 2 clinical trials, this phase 3 clinical trial investigated whether enzalutamide was a better treatment for metastatic hormone sensitive prostate cancer than standard of care.

- Unlike 'blinded' studies where the participants and/or researchers may not know which treatment participants are receiving, in an open-label study, participants and researchers know which treatment has been assigned, however because it is randomly assigned, participants nor doctors and researchers cannot choose which group to assign the individual to. In ENZAMET, all participants knew if they were receiving enzalutamide or a NSAA.

In this research study, participants had an equal (50%) chance of being assigned to either:

- **Group 1 'Standard of Care'** where participants received testosterone suppression continuously throughout the trial and an older NSAA such as bicalutamide, nilutamide or flutamide; or,
- **Group 2 'Enzalutamide'** where participants received testosterone suppression and enzalutamide 160mg (four capsules) taken daily.

Some participants (503 of 1125 participants or 45%) in both groups also received docetaxel chemotherapy, based on decisions they made with their treating doctors.

Participants received the assigned treatment until the cancer worsened, they experienced serious or intolerable **side effects**, or they or their doctor recommended a change in treatment.

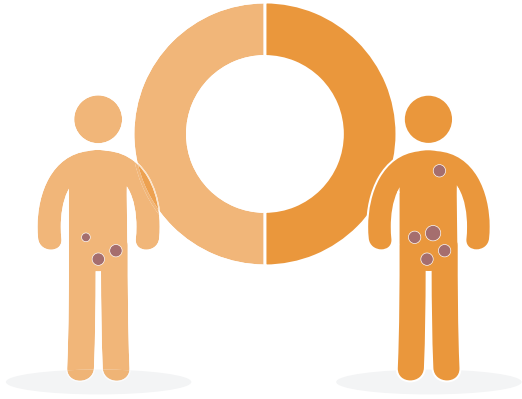
Side effect: An effect of a medicine that is beyond its desired effect. Side effects can be harmful.

Trial demographics

1125 participants with mHSPC

Approximately **50%** had **low volume** metastatic disease

(less than 4 areas of bone spread and no involvement of the liver)

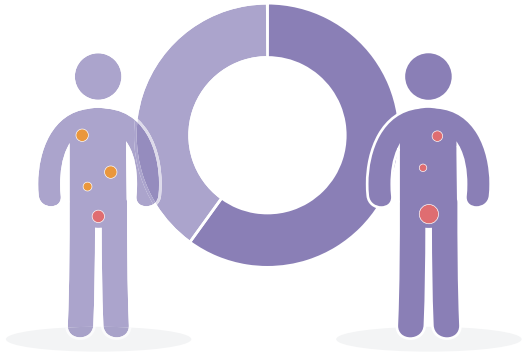


Approximately **50%** had **high volume** metastatic disease

(4 or more areas of bone spread and /or involvement of the liver)

Approximately **40%** had **metachronous** metastatic disease

(prostate cancer that initially appeared to be localised and been treated, but has come back in other parts of the body)



Approximately **60%** had **synchronous** metastatic disease

(metastatic prostate cancer found at the same time the cancer is originally diagnosed)

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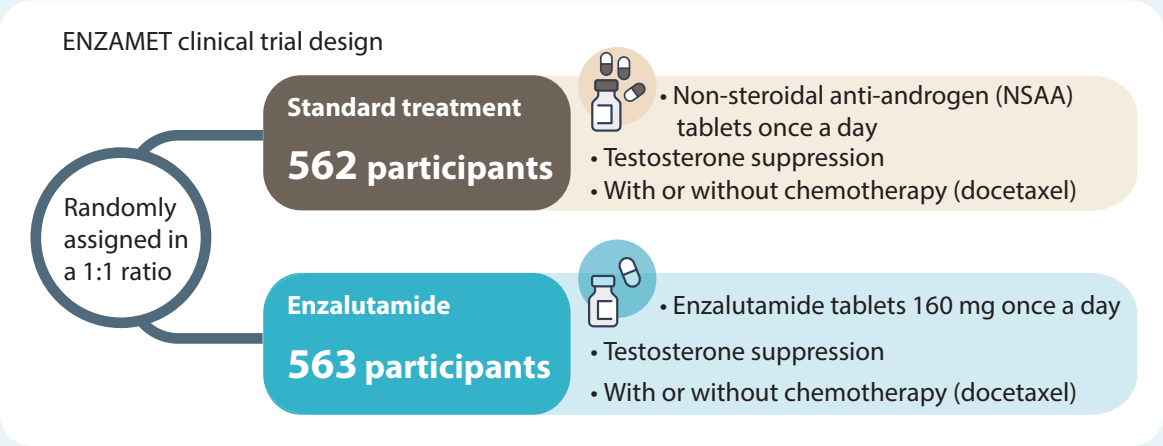
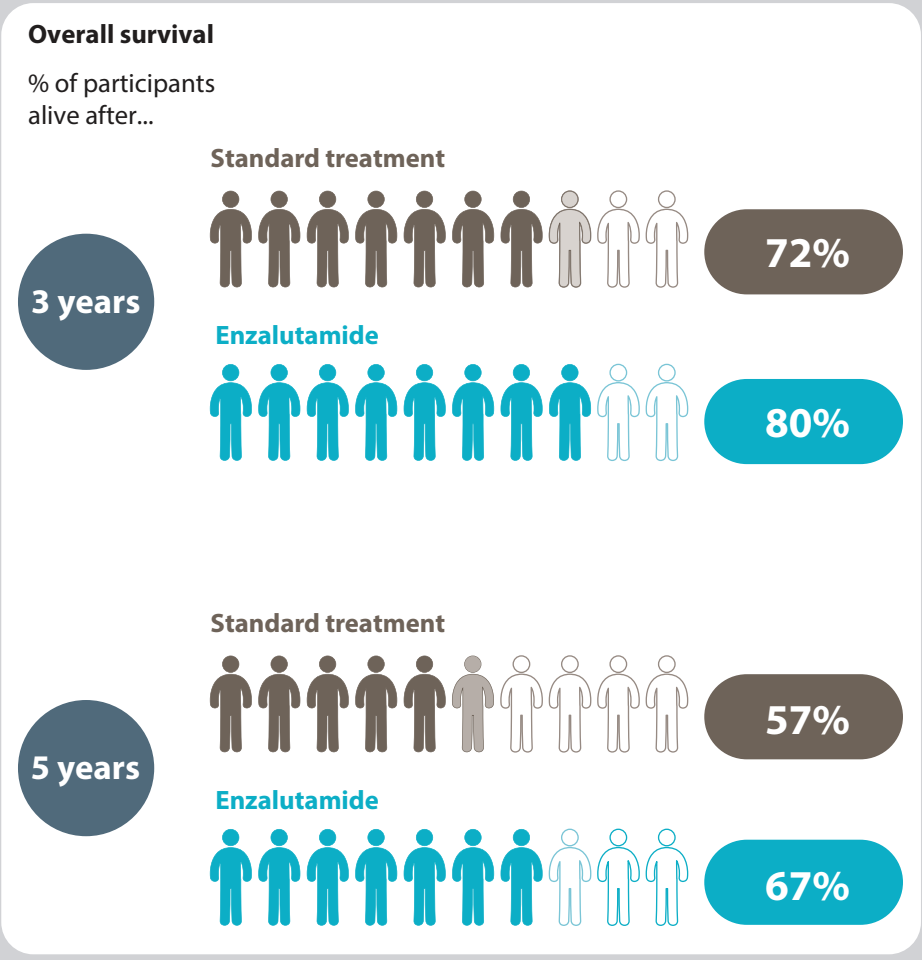


What were the overall results of the study?

The trials **primary endpoint** was overall survival, defined as the time from study enrolment to the time of death from any cause. The key **secondary endpoints** included 'progression-free survival' which is the time from study **enrolment** until signs of cancer progression (worsening) or growth were detected, indicated by either (a) a significant increase in blood PSA or prostate specific antigen level (an elevated level of which is commonly observed in people with prostate cancer), symptoms, scans or (b) a change in treatment. Other endpoints included side-effects of treatment and the effects on quality of life.

The results of the trial showed that the addition of enzalutamide to the standard of care increased the chance of being alive at 5 years by 10%. The survival rate at 5 years in the enzalutamide group was 67%, versus 57% in the standard of care group. The results also showed that prostate cancer took longer to start regrowing in the enzalutamide group than in the standard of care group.



Primary endpoint: The main result that is measured at the end of a study to see if a given treatment worked.
Secondary endpoint: Those that may provide supportive information about a therapy's effect on the primary endpoint or demonstrate additional effects on the disease or condition.
Enrolment: Officially register as a participant in the clinical trial.

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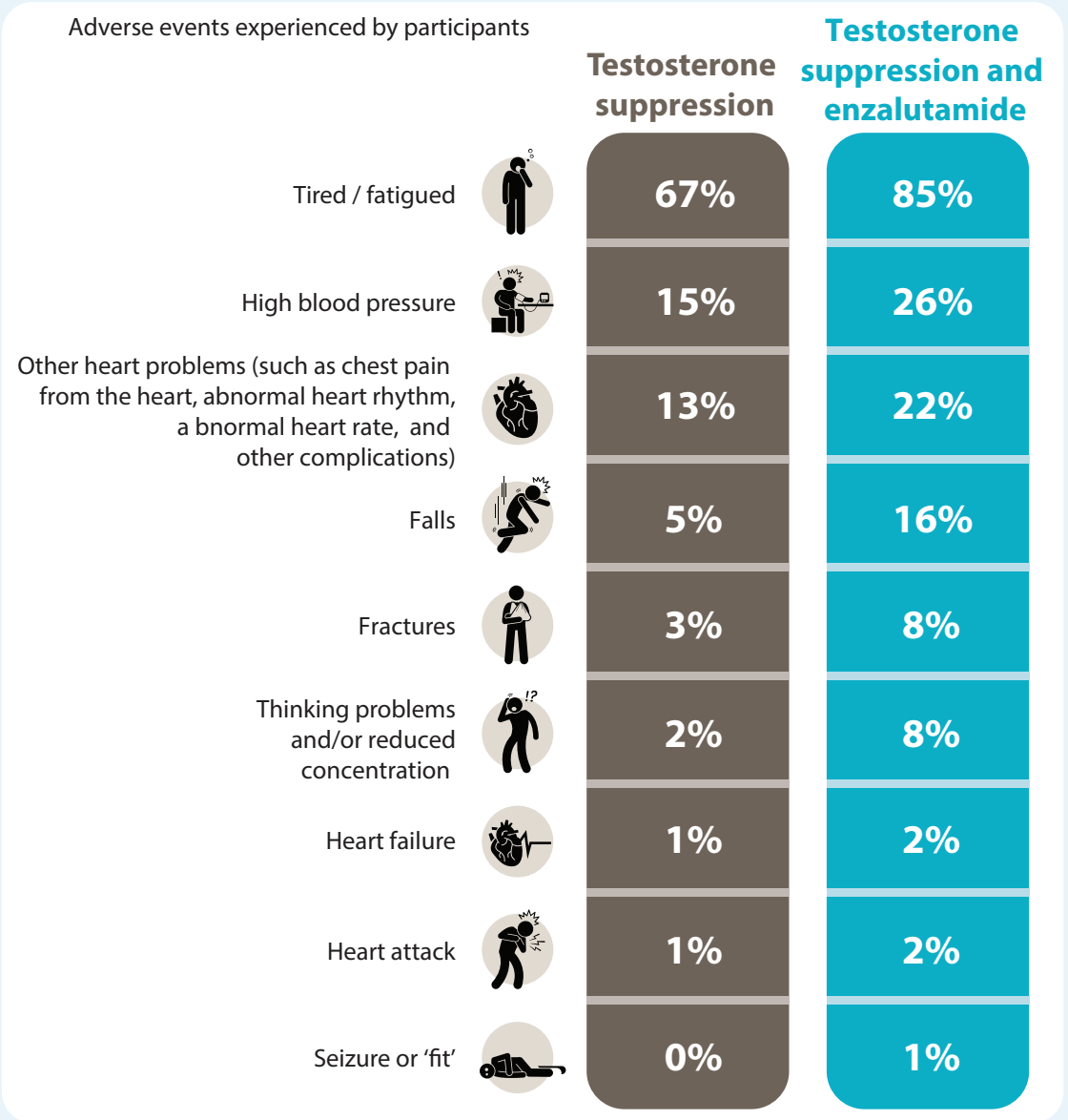
The benefits of adding enzalutamide were evident regardless of whether:

- The participant also received docetaxel,
- They had low- or high-volume disease, or,
- The cancer had spread at the time of initial prostate cancer diagnosis or was found later

Some people who received enzalutamide initially reported experiencing more fatigue, reduced ability to think clearly, and overall felt slightly worse physically, but these effects were not large and were outweighed by the benefits of the treatment (acknowledging that experiences and personal values differ between individuals with cancer). Enzalutamide often became better tolerated by adjusting the dose and these side effects were balanced by improved cancer control, which in turn led to delayed or fewer symptoms from their prostate cancer. Participants receiving testosterone suppression and enzalutamide experienced longer time on treatment.

What were the most common side effects?

The main side effects considered important by the researchers included fatigue, high blood pressure and increased risk of heart problems, falls, thinking problems and/or reduced concentration, and seizures, which were more common in participants taking enzalutamide. However, serious side effects resulting in hospital admission were uncommon in either group.



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What do the results of this study mean?

- Combining enzalutamide with testosterone suppression increased the chance of living longer with prostate cancer for most participants in the ENZAMET trial. Enzalutamide appeared to be helpful for most participants in the study. Regardless of whether the participant had low- or high-volume prostate cancer, and whether their cancer was initially localised or not, enzalutamide was associated with a lengthening in survival when compared with the standard of care.
- It might not be necessary to add docetaxel to testosterone suppression plus enzalutamide for all: if it is used, it should perhaps be reserved for people with the most aggressive prostate cancer types, provided the person is well enough to have chemotherapy. This is a conversation patients should have with their treating doctor.
- The side effects of enzalutamide were most prominent early in treatment but were managed in many cases with dose reduction. Less than 1 in 5 participants required a dose reduction to manage a side effect occurring due to enzalutamide. The potential benefits of enzalutamide included improved cancer control, improvement in the symptoms of the cancer, and delay or prevention of future complications of the cancer.
- Enzalutamide is now funded and available for first-line treatment in combination with testosterone suppression for mHSPC in Australia, and some other jurisdictions.

Where can readers find more information on this study?

This is a summary of the ENZAMET clinical trial, which was originally published in *The New England Journal of Medicine* in July 2019, with associated quality of life published in the *Journal of Clinical Oncology* in March 2022, and longer-term survival outcomes published in *Lancet Oncology* in March 2023, which are summarised in this Plain Language Summary. Participants in the ENZAMET clinical trial were enrolled between March 2014 and March 2017.

The ENZAMET original papers are available on request to the authors or via ResearchGate.

Enzalutamide with standard first-line therapy in metastatic prostate cancer links:

- Davis ID, Martin AJ, Stockler MR, Begbie S et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med.* 2019;381(2). doi:10.1056/NEJMoa1903835.
- Stockler MR, Martin, AJ, Dhillon, HM, Begbie, SD et al. Health-Related Quality of Life in Metastatic, Hormone-Sensitive Prostate Cancer: ENZAMET (ANZUP 1304), an International, Randomized Phase III Trial Led by ANZUP. *J Clin Oncol.* 2021;40(8). doi: 10.1200/JCO.21.00941.
- Sweeney CJ, Martin AJ, Stockler MR, Begbie S et al. 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. *Lancet Oncol.* 2023;24(4). doi: 10.1016/S1470-2045(23)00063-3.

Additionally, some information about the ENZAMET clinical trial is available via:

- The Australia and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) website using the search function at: https://anzup.org.au/.
- Clinicaltrials.gov using the ENZAMET clinical trial identifier, NCT02446405 at: https://clinicaltrials.gov/study/NCT02446405.

During the ENZAMET clinical trial, samples of blood and tumour samples were collected from participants. These samples are now being analysed by scientists to help further understand the benefits of enzalutamide in the treatment of mHSPC. Results from this research may result in the development of future clinical trials.

Acknowledgements

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Disclosure statement

The authors of this PLSP include; consumers and consumer-members from the ANZUP consumer advisory panel, as well as several original authors from the ENZAMET publication(s). Ciara Conduit – reports honoraria from Astra Zeneca, Bristol-Myers Squibb and Janssen; travel/conference support from Merck and Bayer. Andrisha-Jade Inderjeeth - Speaker fee honoraria from; BMS, Pfizer and Astellas. Eibhlin Mulroe - works for Cancer Trials Ireland. Robert R. Zielinski – Honoraria from Astra Zeneca and Pfizer, and Speaker fees from Pierre Fabre and Janssen. 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