Plain Language Summary of Publication

Future ONCOLOGY

A plain language summary of the EORTC 1333/PEACE-3 study of enzalutamide alone vs enzalutamide plus radium-223 in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases

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

You can read the original article (in English) 'Enzalutamide plus Radium-223 in Metastatic Castration-Resistant Prostate Cancer: results of the EORTC 1333/PEACE-3 trial' in *Annals of Oncology* for free at: https://www.annalsofoncology.org/article/S0923-7534(25)00203-0/fulltext.

Summary

What is this summary about?

Enzalutamide and **radium-223** are two different types of medicines normally used separately to treat prostate cancer that has spread to other parts of the body (**metastatic castration-resistant prostate cancer**; **mCRPC**). Both medicines are usually given with **androgen deprivation therapy** (**ADT**). Radium-223 is only used in people with mCRPC whose cancer has spread to their bones (called bone metastases). When the study began, enzalutamide was only used to treat patients with castration-resistant disease; nowadays, it is also used to treat earlier stages of prostate cancer that are hormone-sensitive.

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

- **Metastatic:** Meh-tuh-STA-tik
- **Enzalutamide:** EN-zuh-LOO-tuh-mide
- **Radiological:** ray-dee-uh-LOJ-uh-kuhl
- **Progression-free:** pruh-GRESH-uhn-free

This summary describes the early results of a study called EORTC 1333, or 'PEACE-3'. The researchers compared enzalutamide plus ADT treatment alone against enzalutamide plus ADT combined with radium-223 in people with mCRPC with bone metastases who had not been treated for mCRPC. Patients, however, may have been treated for earlier stages of prostate cancer. They wanted to see if there was any difference in how long patients lived before their cancer got worse based on medical scans (**radiological progression-free survival**). They also looked for any difference in how long patients lived and the side effects of combining the two therapies.

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What were the results of the study?
In people with mCRPC, combined treatment with enzalutamide plus ADT and radium-223 showed a trend towards an increased time that patients lived without their cancer getting worse compared with enzalutamide plus ADT alone. The combined treatment was also found to improve how long they lived. More people had broken bones (**fractures**) in the combination group, but the use of medication to keep bones strong partway through the study helped reduce the risk of fractures in both treatment groups. Most side effects were moderate and manageable.

What do the results mean?
In people not treated for mCRPC before, combining enzalutamide plus ADT with radium-223 treatment can slow down their cancer compared with taking enzalutamide plus ADT alone. The results suggest that people live longer if they have this combined treatment. Therefore, combining enzalutamide and radium-223 could be a new option for doctors to treat people with mCRPC with bone metastases. However, it should be given with medication to keep bones strong.

It is worth noting that, when this study began, enzalutamide was mainly used to treat patients who had castration-resistant prostate cancer. Today, enzalutamide is used to treat earlier stages of prostate cancer. This means that treatments received for earlier stages of prostate cancer may differ between patients enrolled in PEACE-3 and those who are being treated in routine clinical practice today.

Enzalutamide: An oral medicine that stops prostate cancer cells from using male sex hormones, like testosterone, to grow.
Radium-223: A radioactive type of medicine that acts like calcium and, when injected into a person, is taken up by newly formed bone, such as within cancer metastases. The radiation is extremely short acting meaning that it only affects cells near to where it is taken up. This includes dividing cells such as the prostate cancer cells that have spread to the bone, which it kills.
Metastatic castration-resistant prostate cancer (mCRPC): Prostate cancer that has spread to other parts of the body and no longer responds to the effects of castration.
Prostate: A male reproductive gland that helps the body make semen and is found below the bladder.
Androgen deprivation therapy (ADT): Hormone therapy used to treat prostate cancer. The treatment works by blocking production of male sex hormones called androgens (for example, testosterone) that the cancer needs to grow. It is the first treatment offered for advanced prostate cancer, and is often continued alongside other treatments as the cancer progresses.
Radiological progression-free survival: How long a patient lives or until their cancer gets worse as seen with a medical scan.
Fracture: A break in the bone, ranging from small cracks to a complete break.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you understand the findings from recent research. This is a summary of the PEACE-3 study. The results of this study may be different from the results of other studies. Doctors and patients should make treatment decisions based on all available information, not on the results of a single study.

Who should read this article?

This summary may be helpful for people with prostate cancer and their families and caregivers, patient advocates, and healthcare professionals who are interested in knowing more about this topic.

Who sponsored this study?

This was an academic study led by The European Organisation for Research and Treatment of Cancer (EORTC), a pan-European non-profit cancer research organization. The study was conducted in collaboration with Clinical Trial Ireland (CTI), the Canadian Urological Oncology Group (CUOG), the Latin American Cooperative Oncology Group (LACOG), and the French group GETUG/UNICANCER. The work was supported by educational grants (funding provided to the academic institutions to cover the costs of the study) from Bayer HealthCare Pharmaceuticals and Astellas Pharma Europe Ltd. This manuscript was **sponsored** by Bayer HealthCare Pharmaceuticals.

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.

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What is metastatic castration-resistant prostate cancer?

Metastatic castration-resistant prostate cancer, or mCRPC, is a type of advanced prostate cancer.

Metastatic means that the cancer has spread to other parts of the body.

Most prostate cancers need male sex hormones called androgens, such as testosterone, to grow. Castration is a way of stopping the testicles from producing these androgens. This can either be through treatments used to block these hormones (ADT), which is known as medical castration, or surgery to remove the testicles, known as surgical castration. Castration can stop or slow the growth of prostate cancer cells for most patients with prostate cancer. However, sometimes prostate cancer cells can overcome the effects of castration and grow even with low levels of androgens. This is known as castration-resistant prostate cancer.

Why are researchers studying the combination of enzalutamide plus radium-223 treatments?

Enzalutamide and radium-223 affect prostate cancer cells in different ways. The researchers wanted to see if combining enzalutamide with radium-223 would be beneficial to people with mCRPC with bone metastases. As well as these medicines, everyone who took part in the study received ADT as part of their routine prostate cancer treatment. Patients were randomly divided into two groups. Half the patients received enzalutamide plus ADT alone. The other half received enzalutamide plus ADT and radium-223.

How do enzalutamide and radium-223 work?

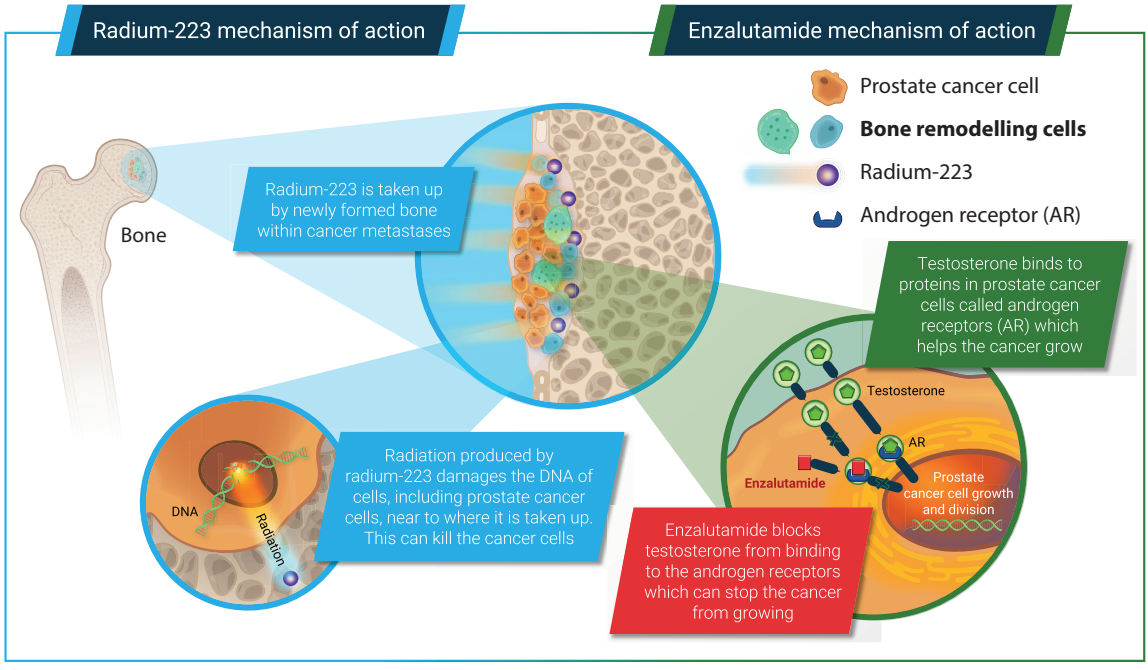

Illustration adapted from Shore N, *et al.* (2024) Treatment intensification with radium-223 plus enzalutamide in patients with metastatic castration-resistant prostate cancer. *Front. Med.* 11:1460212. doi: 10.3389/fmed.2024.1460212

Bone remodelling cells: Cells with special properties that are found in bones and can either break down or form new bone.

Radium-223

- A radioactive treatment that damages the DNA of cells. This can kill the cancer cells
- Radium-223 is taken up into bones, including at sites of bone metastases
- The radioactive properties of radium-223 are short-acting, meaning most of the effects will occur in cells near where it is taken up
- In some people who have mCRPC and bone metastases, radium-223 alone can increase how long they live

Enzalutamide

- A medicine that prevents prostate cancer cells from being able to use male sex hormones (like testosterone) to grow
- In most people with mCRPC, enzalutamide alone can increase how long they live
- Enzalutamide is often the first medicine used to treat people when they are diagnosed with mCRPC

Why was this study done?

There is a need to find new and better ways to treat people with mCRPC. One option may be through combining medicines that kill the cancer cells in different ways.

- The main aim of the study was to see if combining enzalutamide plus ADT and radium-223 improved how long people with mCRPC lived before their disease got worse compared with enzalutamide plus ADT alone.
- The researchers also wanted to see if adding radium-223 treatment to enzalutamide plus ADT helped people with mCRPC live longer.
- They also wanted to know if enzalutamide plus ADT and radium-223 increased the length of time until patients started a new cancer treatment compared with enzalutamide plus ADT alone.
- People with mCRPC whose cancer has spread to the bones often suffer from bone pain and are at risk of fractures or other problems with their bones. The researchers wanted to see if there was any difference between the two treatment groups in how long it took for bone pain to get worse (**pain progression**). They also wanted to see if there was any difference in when fractures or other bone complications caused by the cancer occurred or required treatment.
- The researchers also wanted to know what the **side effects** were when radium-223 treatment was added to enzalutamide plus ADT and if they were different than with just enzalutamide plus ADT alone.

Pain progression: When the level of pain a patient experiences gets worse. This is measured by answers to a questionnaire on pain as well as the use of certain painkillers called opioids.
Side effect: A reaction (expected or unexpected) to a medicine or treatment. This is usually a negative and unintended effect.

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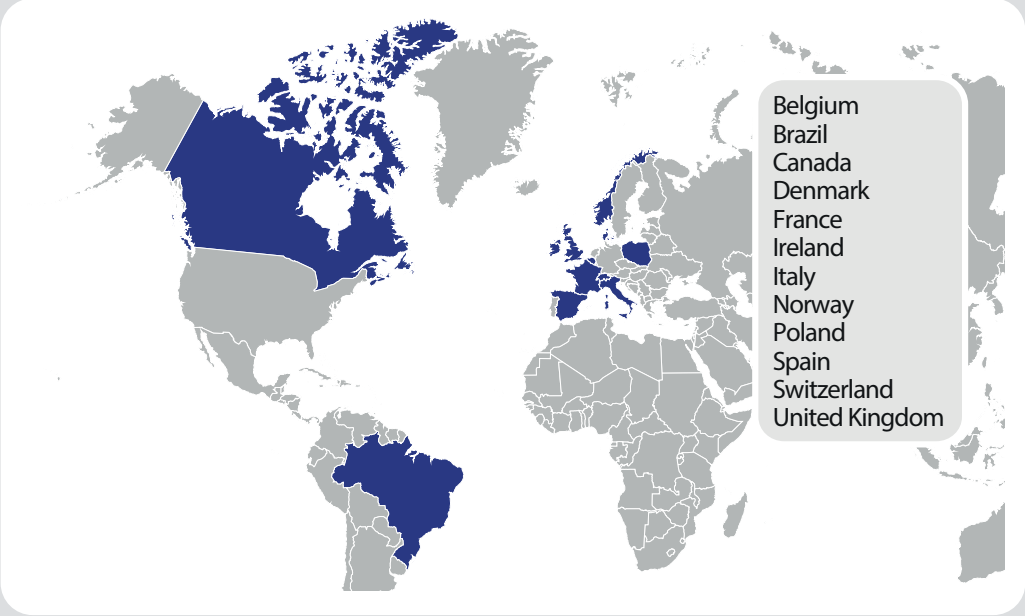
How was this study carried out?

When and where did this study happen?

Patients were enrolled in the PEACE-3 study from November 2015 to March 2023 across 12 countries.



The data that were published and are presented here show the main results of the PEACE-3 study. Data for the study are still being collected to better understand differences in how long patients live after receiving the study treatments.

At the time of this analysis, patients had been involved in the study for a **median** of 3.5 years.

Median: The median is the middle number when a list of numbers is arranged in order.
Lymph nodes: Found throughout your body, lymph nodes contain millions of specialised blood cells called lymphocytes that help fight infection and destroy harmful cells.

Who was allowed to take part in the PEACE-3 study?

To take part in PEACE-3, patients:

- Were aged 18 years or over with mCRPC
- Had at least two bone metastases (this was increased to four or more bone metastases in Europe in July 2018)
- Had no bone pain or only mild bone pain
- Did not have metastases in parts of the body other than bones and **lymph nodes**
- Had not been treated previously for their mCRPC

  Treatment for earlier stages of prostate cancer was allowed, and these treatments could include:
  - Chemotherapy (medicines that damage and kill cancer cells that are dividing)
  - Abiraterone (a medicine that stops testosterone from being produced, and is often a first-choice treatment for mCRPC)

What were the patients treated with?

In total, 446 patients were enrolled into the study. They were randomly divided into two treatment groups on top of existing ADT that they may have been receiving:

222 patients were treated with **enzalutamide plus ADT and radium-223**

- Radium-223 was injected into the blood once a month for six months
- Enzalutamide was taken as a pill once a day

224 patients were treated with **enzalutamide plus ADT alone**

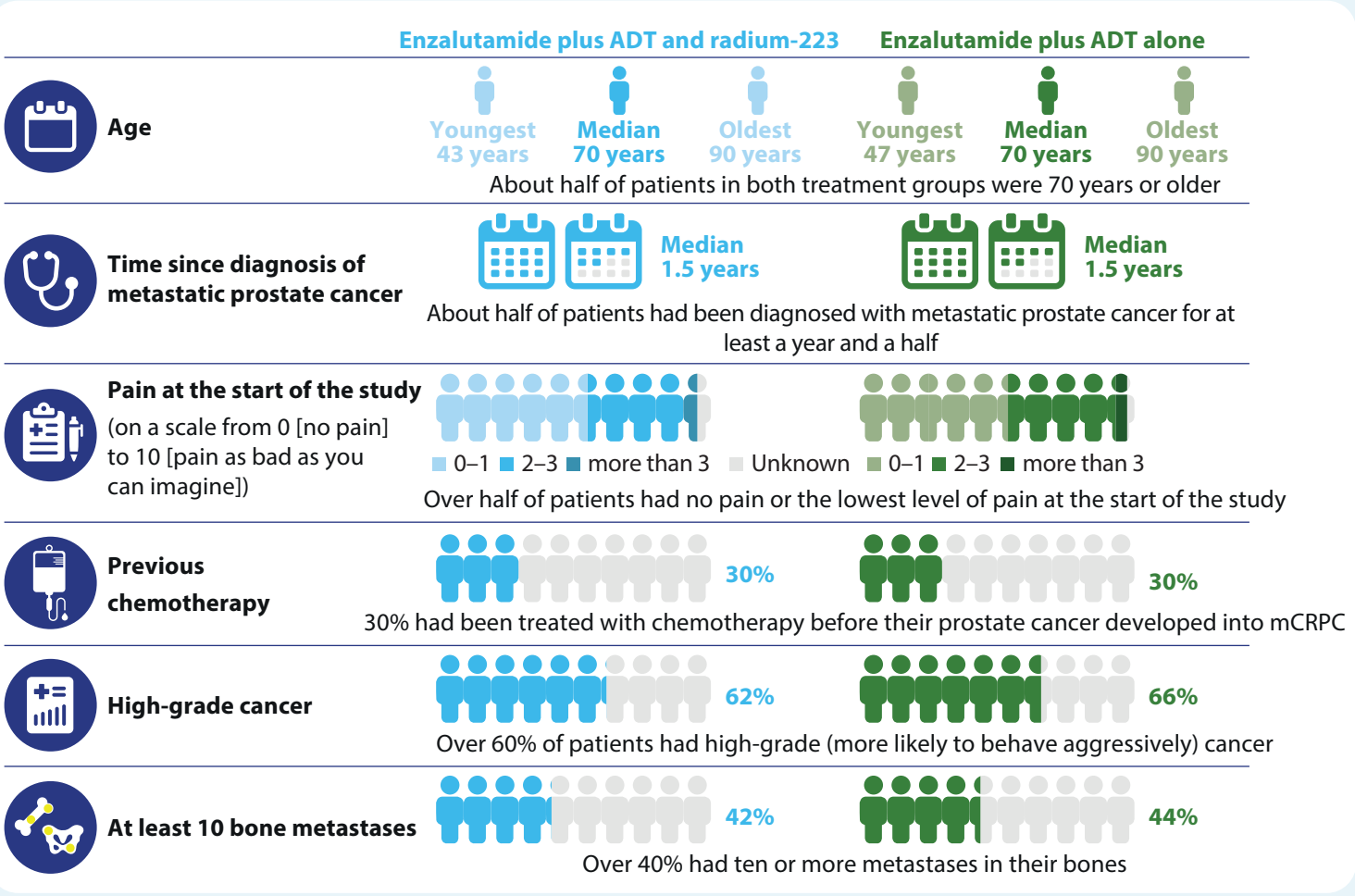
- Enzalutamide was taken as a pill once a day

Before **March 2018:** taking medication to protect bones was optional, meaning the treating doctor chose whether it was given to patients

After **March 2018:** taking medication to protect bones was mandatory, meaning all patients were given it

Who took part in the study?

The patients in the two treatment groups had similar features when they started the study.



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The median time for receiving the study treatments was 17 months for those in the enzalutamide plus ADT and radium-223 treatment group, and 14 months for those in the enzalutamide plus ADT alone treatment group.

How many patients treated in the enzalutamide plus ADT and radium-223 group received the full course of radium-223?

A full course of radium-223 treatment is six doses (one dose per month, for 6 months).

Treated with a full course (6 doses) of radium-223

88%

What were the results of the study?

Did it take longer for the cancer to get worse in either treatment group?

For patients who were treated with enzalutamide plus ADT and radium-223, it took longer until medical scans showed that their cancer had got worse or until they died (radiological progression-free survival). The median time that patients lived before scans showed their cancer had got worse was about 3 months longer for patients treated with enzalutamide plus ADT and radium-223.

Median radiological progression-free survival

Treated with enzalutamide plus ADT and radium-223

19 months

Treated with enzalutamide plus ADT alone

16 months

The benefit of the enzalutamide plus ADT and radium-223 treatment was seen in different types of patients. The results were not influenced by the level of pain patients had at the start of the study, if they had been treated with chemotherapy at an earlier stage of prostate cancer, or if they had not been given medication to keep their bones strong at any point during the study.

Was there a difference in how long patients in the different treatment groups lived?

The median overall survival (the length of time when half of patients were still alive) was 7 months longer for patients who were treated with enzalutamide plus ADT and radium-223. The trial has not finished and data about the patients are still being collected. This means that the median overall survival could change.

Median overall survival

Treated with enzalutamide plus ADT and radium-223

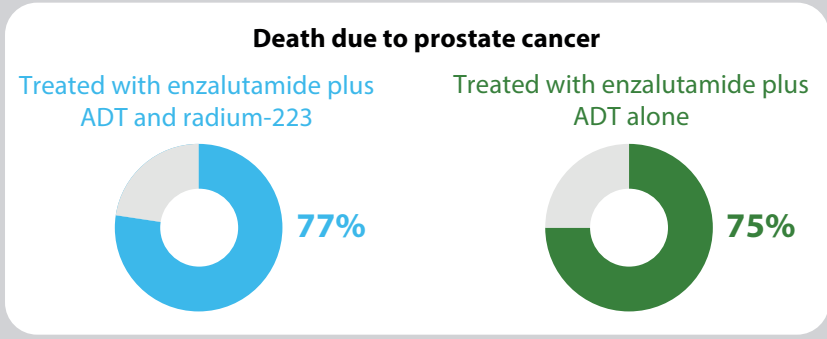
42 months

Treated with enzalutamide plus ADT alone

35 months

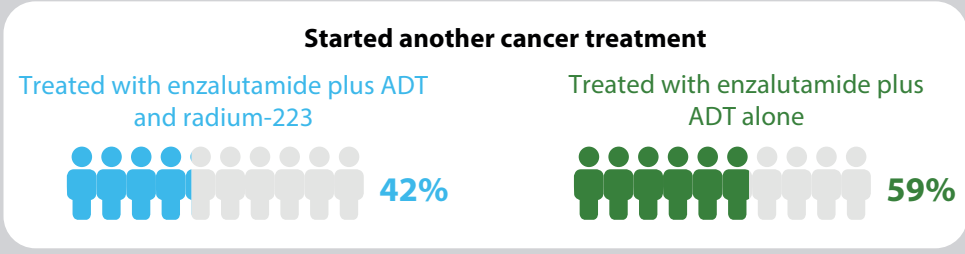
What was the main cause of death among patients?

In both treatment groups the main cause of death was prostate cancer. This was expected for the group of patients who took part in the study. Other causes of death included conditions affecting the heart or blood vessels (cardiovascular disease).



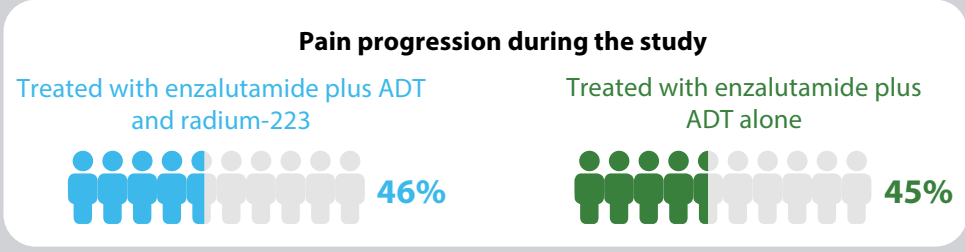
Was there any difference between the treatment groups for how many patients needed to start another new cancer treatment?

At the time of the study analysis, fewer patients treated with enzalutamide plus ADT and radium-223 had started a new treatment for mCRPC.



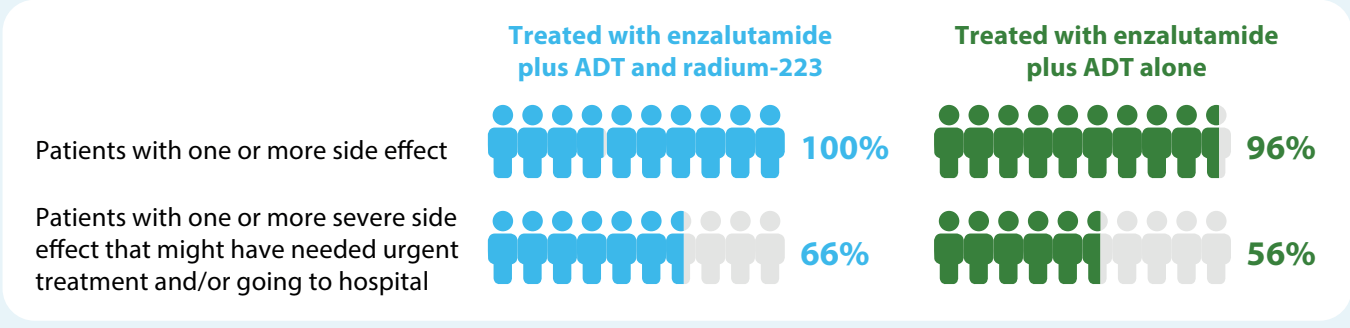
Which treatment group had the longest time until pain symptoms got worse?

There was no difference between the two treatment groups in the time it took for patients' pain to worsen (pain progression).



What were the side effects of the treatments?

Almost all patients had at least one side effect during their treatment. Many patients in both treatment groups had one or more severe side effects that might have needed urgent treatment and/or required them to go to hospital. These severe side effects were more common in patients treated with enzalutamide plus ADT and radium-223. Based on previous studies with these treatments, this level of side effects was anticipated.



There was no difference in the number of patients in each treatment group who had to stop their treatment because of side effects.

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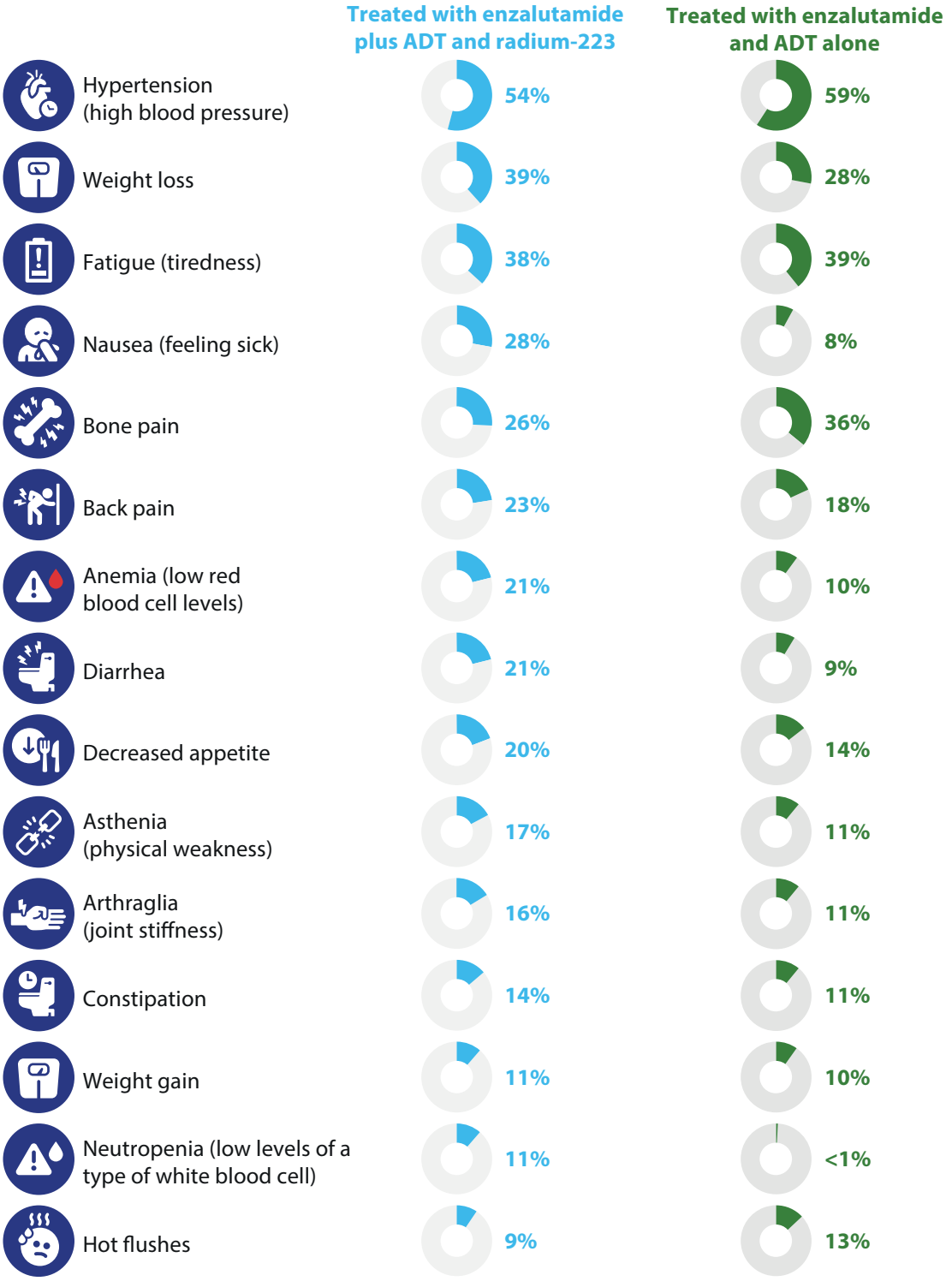
Side effects seen in at least 10% (more than 22) of patients in either treatment group



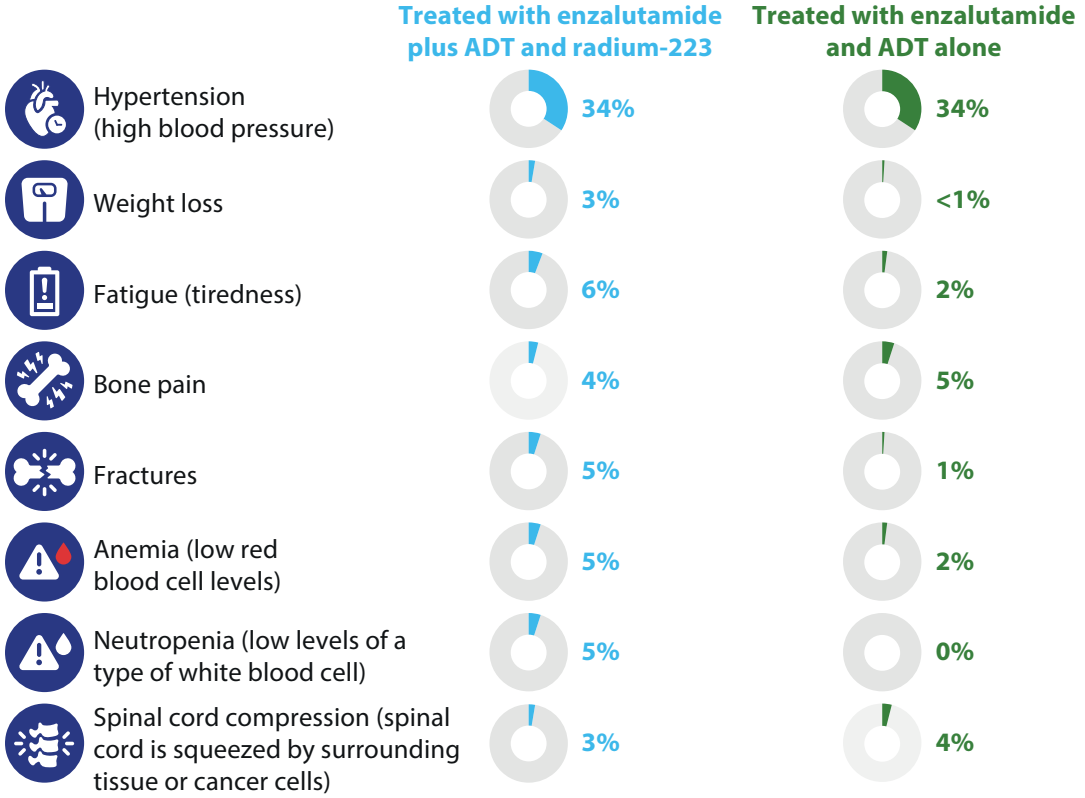
Asthenia: A general feeling of physical weakness and/or a lack of energy and strength
Fatigue: A constant feeling of extreme tiredness and lack of energy

What were the most common severe or life-threatening side effects?

Side effects are not all of the same severity. The severity is classified according to the following criteria:

Mild	Moderate	Severe but not life-threatening	Life-threatening	Death
No symptoms or only mild symptoms that do not need to be treated	Affect some daily activities and may need minor treatment	Significantly affect daily activities and may require hospitalization	Requiring urgent medical attention	Related to side effects

Severe or life-threatening side effects seen in at least 3% (6 or more) of patients in either treatment group



There were no deaths due to side effects related to either study drug.

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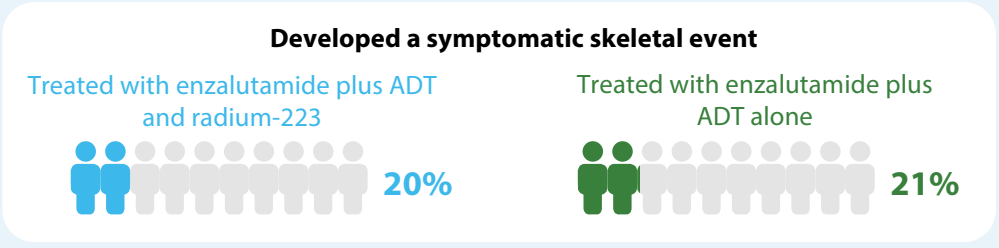
Which treatment group had the longest time until they experienced fractures or other bone problems caused by their cancer or cancer treatment?

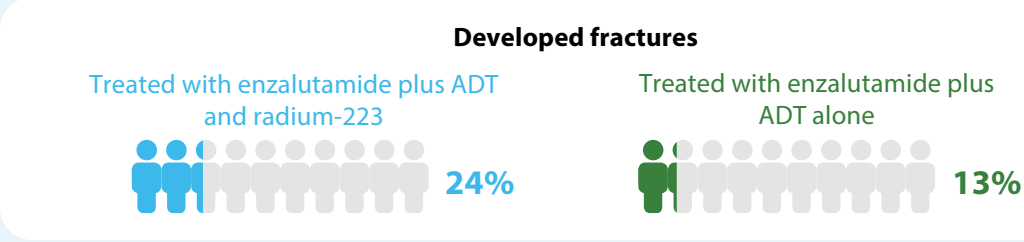
People with mCRPC are at increased risk of developing fractures or other bone problems. This can be due to their cancer or cancer treatment causing areas of the bone or spine to become weak or painful; treatment, including surgery or radiation, may be needed to manage the symptoms. These are called **symptomatic skeletal events**. Over the entire study, there was no difference between the two treatment groups in the average time it took for patients to develop a symptomatic skeletal event.



Symptomatic skeletal event: A broken bone or other bone-related complication due to the cancer or treatment for the cancer. This can include injury to the spinal cord or treatment, including radiation or surgery, to manage the symptoms.

Was there any difference between the treatment groups for how many patients developed fractures?

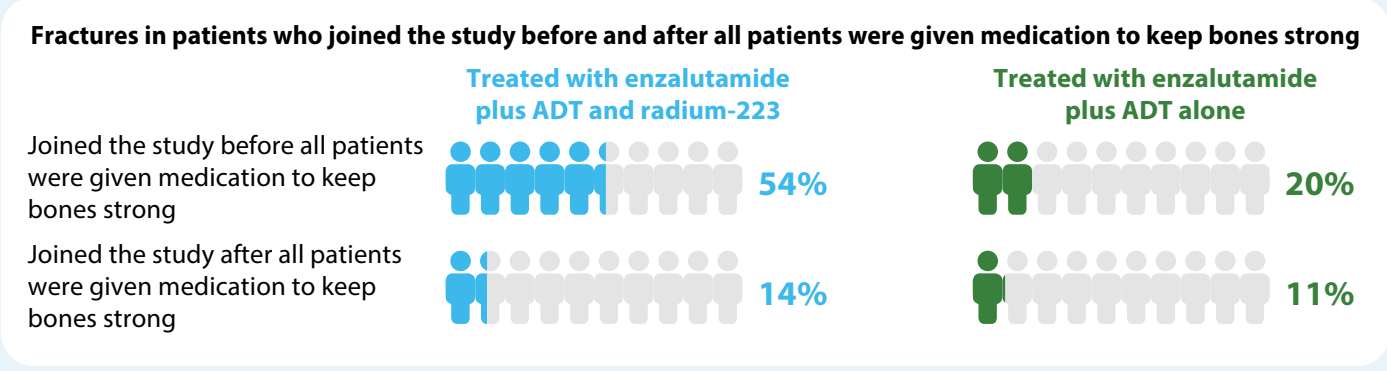
More patients who were treated with enzalutamide plus ADT and radium-223 developed any fracture; these may or may not have been related to treatment and can include symptomatic skeletal events.



Did taking additional medication to keep bones strong reduce the number of fractures seen in patients?

A previous study found that radium-223 combined with another treatment increased the number of fractures in patients. As a result of these findings, in March 2018 (over 2 years into the study), it was decided that all patients should be given medication to keep their bones strong. Before that time, the decision was left to the doctor treating the patient.

Fewer fractures were seen in both treatment groups after the decision to give medication to keep bones strong to all patients.



Was there any difference between the treatment groups for osteonecrosis of the jaw?

In total, 13 patients from both treatment groups developed osteonecrosis of the jaw. It was more common in patients who were treated with enzalutamide plus ADT and radium-223 (5%) compared with patients who were treated with enzalutamide alone (1%).

Osteonecrosis of the jaw: Death of the tissue in the jawbone caused by a lack of blood supply. This can be caused by certain cancer treatments and medication to keep bones strong.

What were the limitations of the PEACE-3 study?

Patients were enrolled in the PEACE-3 study from November 2015 to March 2023. This is a long time for enrolment onto a clinical trial. In that time, how prostate cancer is treated has changed. For example, when the study began, enzalutamide was only used to treat patients with castration-resistant disease; nowadays, it is also used to treat patients with earlier stages of prostate cancer that are hormone-sensitive. As such, before progression to mCRPC, it is now common for patients to have already received enzalutamide or a similar acting medicine, such as abiraterone, to treat an earlier stage of their cancer. However, in PEACE-3 only 1 in 40 (less than 3%) patients had previously been treated with abiraterone and patients were not allowed to enrol in the trial if they had been treated with enzalutamide before. This means that treatments received for earlier stages of prostate cancer may differ between patients enrolled in PEACE-3 and those who are being treated in routine clinical practice today.

What do the results of the PEACE-3 study mean?

- Compared with patients who were treated with enzalutamide on its own, patients who were treated with enzalutamide plus ADT and radium-223 had an improved chance of:
  - » Living longer before their cancer got worse.
  - » Living longer.
  - » Having a longer time until they needed a different type of cancer medicine.
- There was no difference between the two groups in:
  - » The time it took for their pain to get worse.
  - » The time it took for them to develop or need treatment for a fracture or other bone problem caused by their cancer.
- Almost all patients had side effects no matter which treatment they received.
  - » Severe or life-threatening side effects were more common in patients treated with enzalutamide plus ADT and radium-223, highlighting the importance of close monitoring.
  - » There was no difference in the number of patients in each treatment group that had to stop treatment because of side effects.
- The number of fractures was reduced when patients were given medication to keep their bones strong.
  - » This confirms the importance of giving medication to keep bones strong at the same time as enzalutamide and radium-223.
- This study found that adding radium-223 to enzalutamide plus ADT may be beneficial first-choice treatment for people with mCRPC that has spread to their bones.
  - » Combining enzalutamide and ADT with radium-223 may be considered for people with mCRPC with bone metastases.

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Where can readers find more information?

Original article
The original article 'Enzalutamide plus Radium-223 in Metastatic Castration-Resistant Prostate Cancer: results of the EORTC 1333/PEACE-3 trial' can be read for free in *Annals of Oncology* at: https://www.annalsofoncology.org/article/S0923-7534(25)00203-0/fulltext

Educational resources
More information about prostate cancer can be found on the website of Europa Uomo, a European advocacy movement at:
https://www.europa-uomo.org

Further information is also available on the American Cancer Society website at:
https://www.cancer.org/cancer/types/prostate-cancer.html

The European Society of Medical Oncology (ESMO) provides patient-focussed information on prostate cancer at:
https://www.esmo.org/for-patients/patient-guides/prostate-cancer

Further patient-focussed information on prostate cancer is provided by the National Institutes of Health (NIH) at:
https://www.cancer.gov/types/prostate

Trial registration site
You can read more about the PEACE-3 study at the following trial registration website:
https://clinicaltrials.gov/study/NCT02194842

The PEACE-3 study started in November 2015 and is ongoing. The estimated end date is December 2028. For more information on clinical studies in general, please visit the following websites:
https://www.clinicaltrials.gov/study-basics/learn-about-studies
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are

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Disclosure statement
The following authors have reported consulting fees or payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events. Bertrand Tombal: Accord, Amgen, Astellas, Bayer, Myovant, MSD, Ferring, Pfizer. Fred Saad: Janssen, Merck, Pfizer, BMS, Novartis, Sanofi, AstraZeneca. Enrique Gallardo: Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, BMS, Ipsen, Johnson & Johnson, Merck, MSD, Pfizer, Recordati, Roche. Andrey Soares: Novartis, AstraZeneca, Janssen, MSD, Pfizer, Bayer. Yohann Loriot: Amgen, Sanofi, Astellas, Pfizer, Merck KGaA, Janssen, Exelexis, BMS, Roche, MSD, Tahio, Orion, Incyte, Gilead, Tyra, Lilly, AstraZeneca. Ray McDermott: Astellas, Bristol Myers Squibb, MSD, Ipsen, Novartis, Pfizer, Bayer. Silke Gillessen: Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Innomedica, Ipsen, Macrogenics, MSD, Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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This manuscript was funded by Bayer HealthCare Pharmaceuticals. Bayer HealthCare Pharmaceuticals were provided the opportunity to review the manuscript during development, but all decisions on content were made by the authors.

Ethical disclosure

A local institutional review board or independent ethics committee approved the trial. The trial was conducted according to the requirements of each country's regulatory authorities and by the Declaration of Helsinki and the good clinical practice guidelines of the International Council for Harmonisation. All patients provided written informed consent.

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