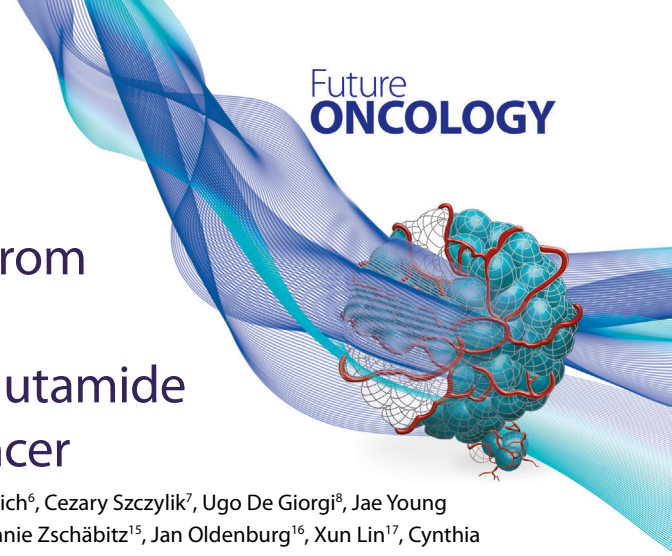
Plain Language Summary of Publication

Future ONCOLOGY



Plain language summary of the results from the TALAPRO-2 study: Talazoparib plus enzalutamide versus placebo plus enzalutamide for patients with advanced prostate cancer

Neeraj Agarwal[1], Arun A Azad[2], Joan Carles[3], Andre P Fay[4], Nobuaki Matsubara[5], Daniel Heinrich[6], Cezary Szczylik[7], Ugo De Giorgi[8], Jae Young Joung[9], Peter C C Fong[10], Eric Voog[11], Robert J Jones[12], Neal D Shore[13], Curtis Dunshee[14], Stefanie Zschäbitz[15], Jan Oldenburg[16], Xun Lin[17], Cynthia G Healy[18], Nicola Di Santo[19], Fabian Zohren[20] & Karim Fizazi[21]

[1]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]PUCRS School of Medicine, Porto Alegre, Brazil; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Innlandet Hospital Trust, Gjøvik, Norway; [7]Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; [8]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [9]National Cancer Center, Goyang, Republic of Korea; [10]Auckland City Hospital, Auckland, New Zealand, and University of Auckland, Auckland, New Zealand; [11]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [12]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [14]Arizona Urology Specialists, Tucson, AZ, USA; [15]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [16]Akershus University Hospital (Ahus), Lørenskog, Norway; [17]Pfizer Inc., La Jolla, CA, USA; [18]Pfizer Inc., Collegeville, PA, USA; [19]Formerly of Pfizer Inc., Durham, NC, USA; [20]Formerly of Pfizer Inc., New York, NY, USA; [21]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

First draft submitted: 5 March 2024, Accepted for publication: 28 May 2024

Summary

What is this summary about?
This summary describes the results from the TALAPRO-2 research study (also known as a clinical trial). The TALAPRO-2 study tested the combination of two medicines called **talazoparib** plus **enzalutamide**. This combination of medicines was used as the first treatment for adult patients with metastatic castration-resistant **prostate cancer**. The combination of talazoparib plus enzalutamide was compared with a placebo plus enzalutamide.

What is metastatic castration-resistant prostate cancer?
Metastatic castration-resistant prostate cancer is a type of cancer that starts in the prostate and has spread to other parts of the body. Castration-resistant means that the cancer continues to grow even when testosterone levels in the blood are reduced to very low levels. Taking medicines to lower testosterone levels in the blood is a standard treatment for men with advanced prostate cancer.

What are the aims of the TALAPRO-2 trial?
TALAPRO-2 looked at if combining talazoparib plus enzalutamide would increase the length of time patients lived before their cancer got worse or they died compared with a placebo plus enzalutamide. Researchers looked at how treatment affected the size and number of **tumors** and the length of time before patients needed to change to a new cancer medicine. Researchers also looked at any **side effects** patients had during the study.

How to say (double click sound icon to play sound)...

- **Enzalutamide:** EN-zuh-LOO-tuh-mide
- **Metastatic:** meh-tuh-STA-tik
- **Placebo:** pluh-SEE-boh
- **Talazoparib:** tal-a-ZOE-pa-rib

Talazoparib: An oral medicine that targets some types of cancer cells and stops them from growing and spreading.

Enzalutamide: An oral medicine that stops male sex hormones, like testosterone, from speeding up prostate cancer cell growth.

Prostate: A male reproductive gland that sits below the bladder and helps to make semen.

Cancer: Abnormal cells that grow and divide without control and may spread to other parts of the body.

Placebo: Sometimes called a sugar pill, a placebo has no active ingredients and has no medical effect. It looks the same, appearance-wise, as the drug that is being tested.

Taylor & Francis
Taylor & Francis Group

10.1080/14796694.2024.2362108

What are the key takeaways?

A total of 805 patients with metastatic castration-resistant prostate cancer took part in the study. Compared with patients who took a placebo plus enzalutamide, the group of patients who took talazoparib plus enzalutamide had a 37% reduced risk of their cancer getting worse or dying. Some patients had tumors that at the start of the study could be measured with scans. Sixty-two percent of patients who took talazoparib plus enzalutamide had their tumors decrease or shrink to the point that they could no longer be seen on scans versus 44% of patients who took a placebo plus enzalutamide. Patients who took talazoparib plus enzalutamide were more likely to have a longer time before they needed to change to a new cancer medicine. The most common side effects of talazoparib plus enzalutamide were low levels of red blood cells (66% of patients) and **neutrophils** (36% of patients), and excessive tiredness or exhaustion (34% of patients).

Tumor: A swelling or lump. In the context of cancer, a tumor is a growth or lump of cancer cells.

Side effect: A reaction (expected or unexpected) to a medicine or treatment you take.

Neutrophil: A type of white blood cell that helps the body fight infections.

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

The original article is titled 'Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial'

You can read the abstract of the original article for free and the full article for a fee at:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01055-3/fulltext

Who is this article for?

The authors of the original published article wrote this summary to help patients, their caregivers, and healthcare professionals understand the results of the TALAPRO-2 study.

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 summary reports the results of a single ongoing study. The results of this study may differ from those of other studies. Doctors should make treatment decisions based on all available evidence and not on the results of just a single study.

Who sponsored this publication?

The TALAPRO-2 study is sponsored by Pfizer Inc. Astellas Pharma Inc. is providing enzalutamide to the patients in TALAPRO-2.

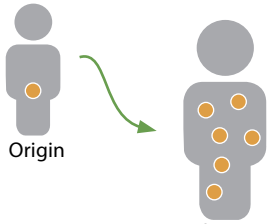
Taylor & Francis
Taylor & Francis Group

What is metastatic castration-resistant prostate cancer?

Metastatic castration-resistant prostate cancer is known as mCRPC. mCRPC is a type of advanced prostate cancer.

m

Metastatic
The cancer has spread to other parts in the body.



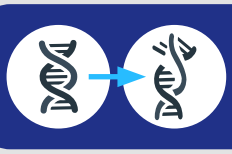
CR

Castration-Resistant
The cancer does not respond to medicines that lower levels of testosterone in the blood.
Testosterone is a male sex hormone.
Hormones work by carrying messages from one part of the body to another.

PC

Prostate Cancer
Cancer that started in the prostate gland.
The prostate is a gland below the bladder and helps make semen.
Testosterone can speed up the growth of some prostate cancers.

What DNA changes can happen in prostate cancer?



Every day, processes inside cells and events outside cells (like radiation from the sun) damage DNA.
DNA is a molecule inside your cells that carries genetic information and passes it on from one generation to the next.

DNA is important, so there are DNA repair genes that tell the cell how to find and repair DNA damage.
A gene is a part of your DNA and has instructions for making proteins. For example, genes are what give you your height, natural hair color, and eye color. Proteins control how a living thing will look and function.

Some patients with prostate cancer have changes in specific DNA repair genes within their tumors, and therefore it is hard for the cells inside the tumor to repair DNA.
BRCA1 and BRCA2 are examples of DNA repair genes.

At the same time, these changes may also make cells responsive to some medicines that treat cancer.

Why are researchers studying the combination of talazoparib plus enzalutamide?

Talazoparib targets and kills cells that do not repair their DNA well.
Some patients with mCRPC have changes in specific DNA repair genes within their tumors. For these patients, treatment with talazoparib can cause their tumors to decrease or shrink to the point that they can no longer be seen on scans.

Enzalutamide stops male sex hormones (like testosterone) from helping prostate cancers to grow.
In some patients who have mCRPC, enzalutamide can increase the length of time they live.
Enzalutamide, combined with medicines to lower testosterone levels in the blood, is approved to treat patients with mCRPC in some countries.

Talazoparib may also help cancer cells become more responsive to enzalutamide.
Enzalutamide may also make the cancer cells more responsive to talazoparib.
Therefore, the combination of talazoparib plus enzalutamide may help the two medicines work together more effectively in patients with or without changes in specific DNA repair genes within their tumors.

Talazoparib in combination with enzalutamide is approved in the United States to treat patients with mCRPC and changes in specific DNA repair genes.
Talazoparib in combination with enzalutamide is approved in the European Union to treat patients with mCRPC with or without changes in specific DNA repair genes who cannot receive chemotherapy.

What are the aims of the TALAPRO-2 study?

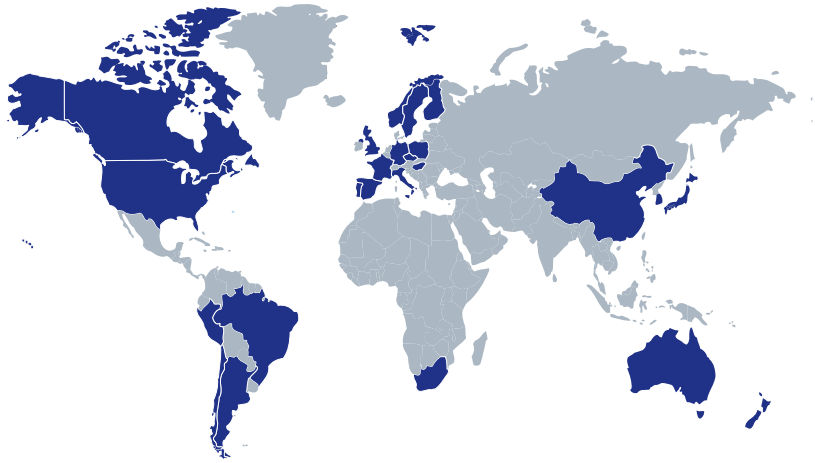
TALAPRO-2 is a Phase 3 study

- A Phase 3 study takes place after the early testing stages. It finds out if a treatment works in a larger number of patients with a certain disease.
- There can be anywhere from several hundred to a few thousand patients included in a Phase 3 study.

The TALAPRO-2 study took place in two parts:

- Part 1 of the TALAPRO-2 study is complete and 19 patients took part.
  - The aim of part 1 was to find out what amount of talazoparib should be used in combination with enzalutamide in part 2 of the study.
  - Researchers found the correct starting amount of talazoparib to be 0.5 milligrams per day when combined with enzalutamide 160 milligrams per day.

Part 2 of the TALAPRO-2 study is ongoing in 26 countries



Countries with investigative centers

Argentina	Portugal
Italy	Czech Republic
Australia	Republic of Korea
Japan	Finland
Belgium	South Africa
New Zealand	France
Brazil	Spain
Norway	Germany
Canada	Sweden
Peru	Hungary
Chile	UK
Poland	Israel
China	USA

Taylor & Francis
Taylor & Francis Group

The main aim of part 2 is to find out if combining talazoparib plus enzalutamide as a patient's first treatment for mCRPC will increase the length of time they live without their cancer getting worse or the patient dying compared with a placebo plus enzalutamide.

Researchers also looked at other outcomes such as how treatment affected the size and number of tumors and any side effects the patients may have.

A side effect is a reaction (expected or unexpected) to a medicine or treatment you take.

Who took part in the study?

Before starting the study, all patients underwent DNA testing to look for changes in specific DNA repair genes within their tumors.

Both patients with and without these changes took part in the study.

805 patients with mCRPC were enrolled. All patients had mild (or no) symptoms and:

Were able to walk and carry out light work.

Were currently taking medicines to lower testosterone levels in the blood or have had their testicles removed to stop the production of testosterone.
- The testicles are a part of the male body that make and store sperm and testosterone.

Had not taken any previous systemic cancer medicines for their mCRPC.
- Systemic means that the medicine could travel through their whole body.

Had not had recent radiation treatment or surgery.
- Radiation treatment uses radiation to kill cancer cells and shrink tumors.

Did not have major problems with their heart, veins or arteries, kidney, liver, blood, or brain; or tumor-related issues with their spinal cord; or other previous cancers.

Had progressive disease, meaning the cancer is growing, spreading, or getting worse.
- Prostate cancer is considered progressive if:
  - The patient's scans show growth or increased spread of the cancer in the bones or other tissues in the body; or
  - **Prostate-specific antigen** (also known as **PSA**) values increase.

PSA: A protein made by the prostate gland and found in the blood.
- In people who have prostate cancer, levels of PSA are often higher than in people who do not have prostate cancer.
- PSA levels can be used to check how prostate cancer changes over time.

What medicines did patients take?

All 805 patients in part 2 of the study took enzalutamide with either talazoparib or placebo.

50% (402 out of 805) were randomly assigned to take talazoparib 0.5 milligrams and enzalutamide 160 milligrams per day

50% (403 out of 805) were randomly assigned to take a placebo and enzalutamide 160 milligrams per day

A placebo has no active ingredients (it is also known as a sugar pill).

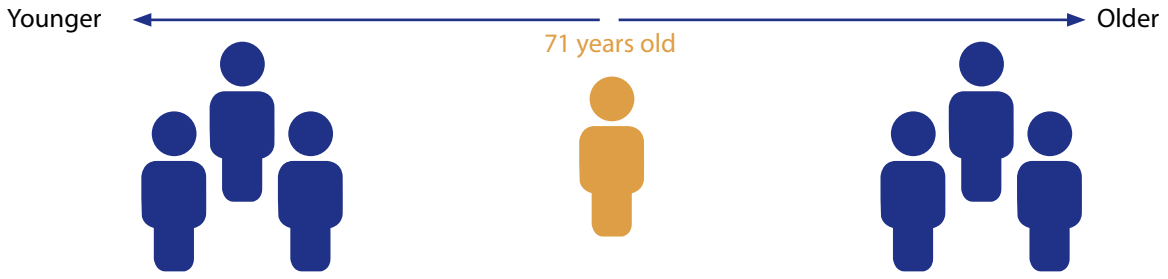
- The placebo and study medicines look alike. Sometimes, patients feel their disease has improved just because they are taking a pill, even if it is only a placebo.
- This study is using a placebo pill to make sure that any changes to a patient's cancer are due to talazoparib in combination with enzalutamide, and not just because they are taking an extra pill.

Neither the patients in the study nor the doctors looking after them know whether the patients are taking talazoparib or placebo.

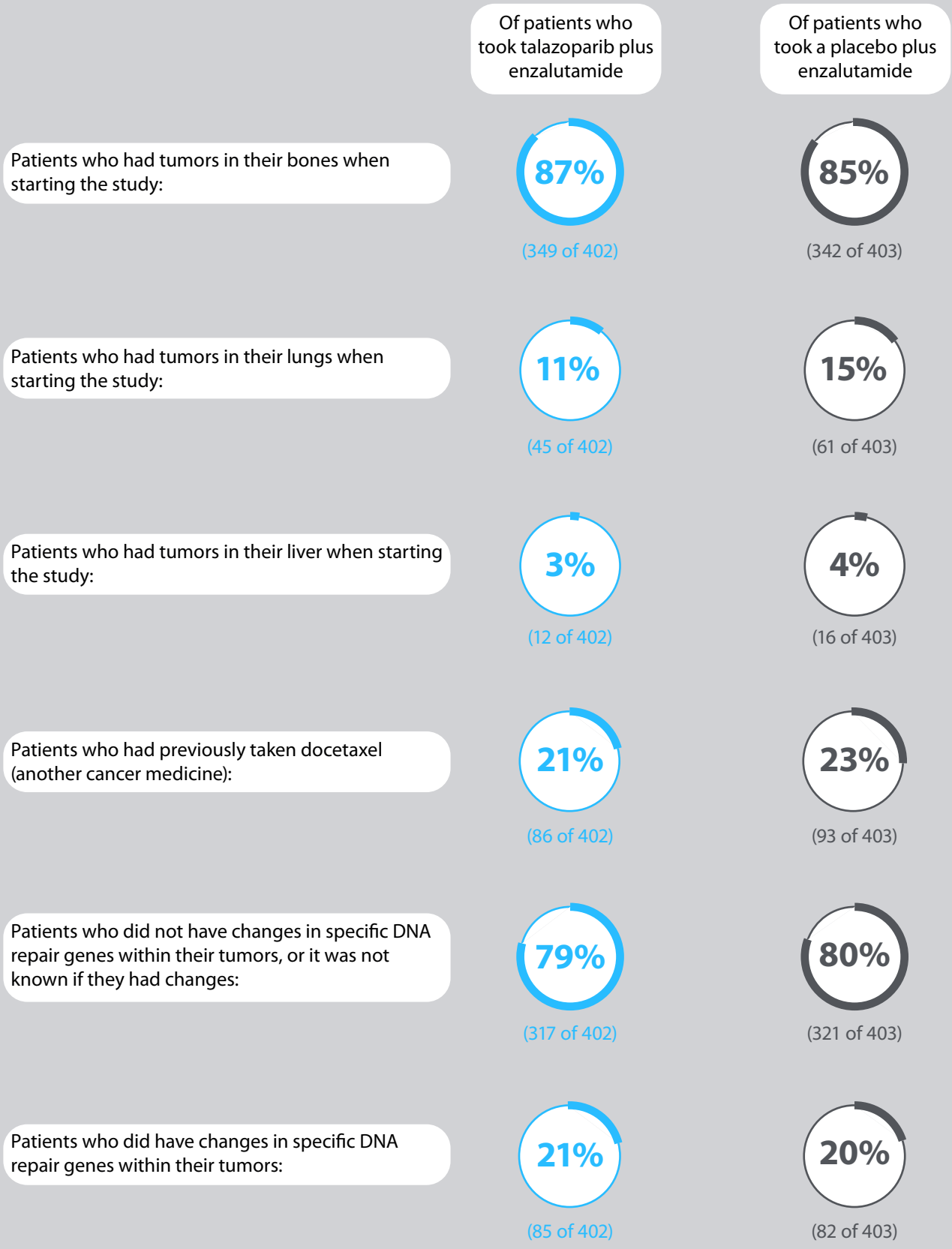
What characteristics did the patients who took part in the study have?

The patients in the talazoparib plus enzalutamide group and the placebo plus enzalutamide group had similar characteristics when they started the study.

About half of all patients in the study were 71 years or older when they started the study



Taylor & Francis
Taylor & Francis Group


Of patients who took talazoparib plus enzalutamide
Of patients who took a placebo plus enzalutamide
Patients who had tumors in their bones when starting the study:
87%
(349 of 402)
85%
(342 of 403)
Patients who had tumors in their lungs when starting the study:
11%
(45 of 402)
15%
(61 of 403)
Patients who had tumors in their liver when starting the study:
3%
(12 of 402)
4%
(16 of 403)
Patients who had previously taken docetaxel (another cancer medicine):
21%
(86 of 402)
23%
(93 of 403)
Patients who did not have changes in specific DNA repair genes within their tumors, or it was not known if they had changes:
79%
(317 of 402)
80%
(321 of 403)
Patients who did have changes in specific DNA repair genes within their tumors:
21%
(85 of 402)
20%
(82 of 403)

How did patients respond to taking talazoparib plus enzalutamide?

Patients who took the combination of talazoparib plus enzalutamide were more likely to live longer before their cancer got worse or they died compared with patients who took a placebo plus enzalutamide.

Researchers looked at:
- How many patients lived overall and how long they lived without their cancer getting worse.
- Whether a patient's cancer getting worse or the patient dying was more or less likely based on which treatment they took.

When comparing the talazoparib plus enzalutamide group with the placebo plus enzalutamide group, patients who took talazoparib plus enzalutamide had a reduced risk of their cancer getting worse or dying. Over the course of the study, the talazoparib plus enzalutamide group had a 37% (37 in 100) reduced risk of their cancer getting worse or dying

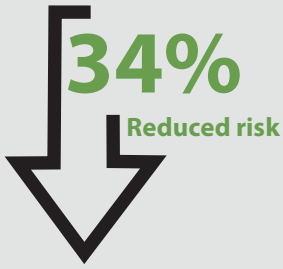
patients who took talazoparib plus enzalutamide
vs
patients who took a placebo plus enzalutamide

Did having changes in specific DNA repair genes affect the chance of a patient's cancer getting worse or the patient dying?

Both patients with and without changes in specific DNA repair genes had a reduced risk of their cancer getting worse or the patient dying if they took talazoparib plus enzalutamide compared with a placebo plus enzalutamide.

Before starting the study, researchers looked for changes in the DNA within the patients' tumors.

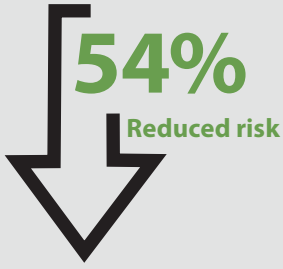
Among patients who had no changes in specific DNA repair genes within their tumors:



When comparing the talazoparib plus enzalutamide group with the placebo plus enzalutamide group:

Over the course of the study, the talazoparib plus enzalutamide group had a 34% (34 in 100) reduced risk of their cancer getting worse or dying.

Among patients who had changes in specific DNA repair genes within their tumors:



When comparing the talazoparib plus enzalutamide group with the placebo plus enzalutamide group:

Over the course of the study, the talazoparib plus enzalutamide group had a 54% (54 in 100) reduced risk of their cancer getting worse or dying.

Taylor & Francis
Taylor & Francis Group

How long did patients taking talazoparib plus enzalutamide live?

Early results suggest that patients who took talazoparib plus enzalutamide had a higher chance of living longer than those who took a placebo plus enzalutamide.

- The full meaning of these results will be clearer as the study continues.

How did treatment affect the size and number of tumors?

Patients who took talazoparib plus enzalutamide were more likely to have their tumors decrease or shrink to the point that they could no longer be seen on scans than those who took a placebo plus enzalutamide.

Some patients had tumors that could be measured by scans when they started the study. When examining these patients over time, researchers found:

	Of patients who took talazoparib plus enzalutamide	Of patients who took a placebo plus enzalutamide
The tumors decreased or shrank to the point that they could no longer be seen on scans:	62% (74 of 120)	44% (58 of 132)
The cancer remained as it was in:	30% (36 of 120)	29% (38 of 132)
The cancer got worse in:	6% (7 of 120)	23% (30 of 132)

Patients who took talazoparib plus enzalutamide were more likely to have a longer time before the PSA levels in their blood started to rise than those who took a placebo plus enzalutamide.

27 months

About half of the patients who took talazoparib plus enzalutamide had 27 months or longer before the PSA levels in their blood started to rise.

18 months

About half of the patients who took a placebo plus enzalutamide had 18 months or longer before the PSA levels in their blood started to rise.

Sometimes a patient's cancer got worse and they needed to start a new cancer treatment. Researchers looked at how long patients had before their cancer got worse and they needed to switch to a new cancer treatment.

Patients who took talazoparib plus enzalutamide were more likely to have a longer time before they needed to switch to a new cancer treatment than those who took a placebo plus enzalutamide.

?

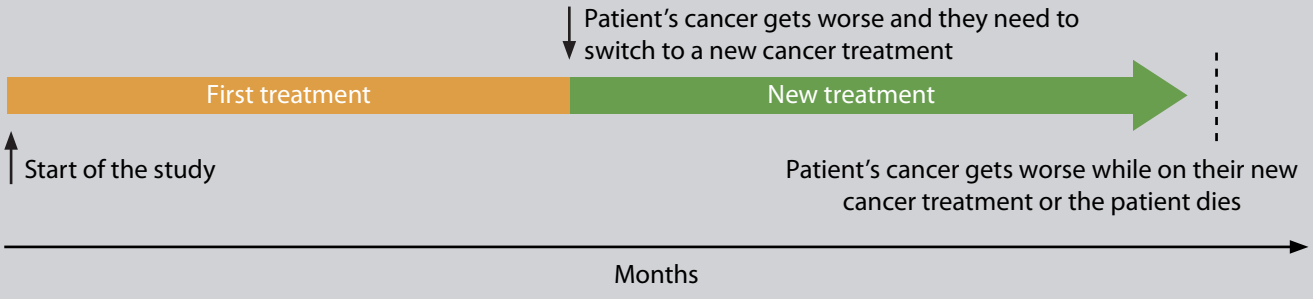
Researchers were not yet able to estimate how long before patients who took talazoparib plus enzalutamide needed to switch to a new cancer treatment.

28 months

About half of the patients who took placebo plus enzalutamide had 28 months or longer before they needed to switch to a new cancer treatment.

Researchers also looked at overall how long patients lived for from the start of study treatment until when their cancer got worse again during the next cancer treatment they received after the study treatment.

Patients who took talazoparib plus enzalutamide were more likely to have a longer time before their cancer got worse again or they died while receiving their new cancer treatment than those who took a placebo plus enzalutamide.



36 months

About half of the patients who took talazoparib plus enzalutamide had 36 months or longer before their cancer got worse again or they died while receiving their new cancer treatment.

18 months

About half of the patients who took placebo plus enzalutamide had 35 months or longer before their cancer got worse again or they died while receiving their new cancer treatment.

Taylor & Francis
Taylor & Francis Group

What side effects did patients experience?

Almost all patients in both groups had side effects. Many had side effects that required urgent treatment from their doctor. The most common side effects included:

A reduction in the number of red blood cells in the patient's blood, also called anemia

Excessive tiredness or exhaustion

A reduction in the number of neutrophils in the patient's blood

- Neutrophils are a type of white blood cell that help fight infections

A reduction in the number of platelets in the patient's blood

- Platelets help the blood clot, for example, when there is a cut

	Of patients who took talazoparib plus enzalutamide	Of patients who took a placebo plus enzalutamide
Patients with 1 or more side effects:	98% (392 of 398)	95% (321 of 401)
Patients who had 1 or more severe side effects that might have required going to the hospital or receiving urgent treatment from their doctor:	75% (299 of 398)	45% (181 of 401)
Patients who had a reduction in the number of red blood cells (anemia):	66% (262 of 398)	17% (70 of 401)
Patients who had previously taken docetaxel (another cancer medicine):	36% (142 of 398)	7% (28 of 401)
Patients who did not have changes in specific DNA repair genes within their tumors, or it was not known if they had changes:	34% (134 of 398)	29% (118 of 401)
Patients who did have changes in specific DNA repair genes within their tumors:	25% (98 of 398)	3% (14 of 401)

No patients in the talazoparib plus enzalutamide group died due to the side effects of the medicine they took. Two patients in the placebo plus enzalutamide group died due to the side effects related to the medicine they took.

How were side effects managed?

Side effects were generally managed by adjusting how much of the medicines a patient took.
- This means they could switch to a lower amount of medicine or stop taking the medicine for a short time.
- Some patients also had other treatments, including a blood transfusion.
  - A blood transfusion is when a patient is given blood or blood cells.

Some patients stopped taking the study medicines because of side effects:

About 20% (2 in every 10) of patients stopped taking talazoparib

About 10% (1 in every 10) of patients stopped taking placebo

About 10% (1 in every 10) of patients in each treatment group stopped taking enzalutamide

The most common reason patients stopped taking talazoparib was because of a decrease in the number of red blood cells (anemia).
- Of the 398 patients in the study, 33 (8%) stopped taking talazoparib because of a decrease in the number of red blood cells (anemia).

Even though side effects caused some patients to pause taking, lower the amount of, or stop taking talazoparib, overall patients still took more than 80% (80 out of 100) of the intended amount of talazoparib.

What is the take-home message?

- Compared with patients who took a placebo plus enzalutamide, patients who took talazoparib plus enzalutamide as a first treatment for mCRPC had an improved chance of:
  - Living longer before their cancer got worse or they died, whether they had changes in specific DNA repair genes or not.
  - Their tumors decreasing or shrinking to the point that they could no longer be seen on scans, if their tumors could be measured at the start of the study.
  - Having a longer time before they need to switch to a new cancer medicine.

- Almost all patients had side effects when taking talazoparib plus enzalutamide.
  - Many had side effects that required urgent treatment from their doctor. No patients died due to side effects from taking these medications.
  - Side effects were generally manageable by briefly stopping treatment or switching to a lower amount of medication.
  - Patients and their doctor should consider whether the benefits outweigh the potential side effects before taking talazoparib plus enzalutamide.

- Talazoparib plus enzalutamide has the potential to become a new therapy option for patients with mCRPC.

Taylor & Francis
Taylor & Francis Group

Where can readers find more information?

Original article

The full title of the original article is 'Talazoparib plus enzalutamide in men with first-line metastatic castrationresistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial,' published in *The Lancet*, 2023, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(23)01055-3
You can read the full article at:
https://www.thelancet.com/journals/lancet/article/ PIIS0140-6736(23)01055-3/fulltext

Educational resources

You can read more about prostate cancer on the American Society of Clinical Oncology Cancer.Net website at:
https://www.cancer.net/cancer-types/prostate-cancer
Patient-focused information on prostate cancer from the National Institutes of Health (NIH) is available at:
https://www.cancer.gov/types/prostate

Trial registration site

You can read more about the Phase 3 TALAPRO-2 study at the following trial registration website:
https://www.clinicaltrials.gov/ct2/show/NCT03395197
The TALAPRO-2 study started in December 2017. The estimated end date is December 2025. For more information on clinical studies in general, please visit:
https://www.clinicaltrials.gov/ct2/about-studies/learn
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are

Acknowledgments

Pfizer and the authors would like to thank all the patients who are participating in this study and their families, as well as the treating physicians, research nurses, study coordinators, and operations staff.

Writing disclosure

Writing support for this summary was provided by Emily Messina, PhD, of CMC Affinity, a division of IPG Health Medical Communications, and was funded by Pfizer.

Financial disclosure

The TALAPRO-2 trial is sponsored by Pfizer Inc. Astellas Pharma Inc. is providing enzalutamide. 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.

Company disclosure

In addition to the peer-review process, with the authors' consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the authors at their discretion and based on scientific or editorial merit only. The authors maintained full control over the manuscript, including content, wording, and conclusions.

Competing interests disclosure

Full author disclosure information can be found in the original article. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the plain language summary apart from those disclosed in the original published article.