Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor:	Pfizer Inc.
Medicine Studied:	Xtandi® (enzalutamide)
Protocol Number:	MDV3100-13 (C3431004)
Dates of Study:	17 December 2014 to 31 January 2023
Title of this Study:	A Study of Enzalutamide in Men With Nonmetastatic Prostate Cancer That Came Back After Treatment [A Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High-Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy]
Date of this Report:	20 December 2023

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is prostate cancer?

Prostate cancer is a common type of cancer in men, and it is often a slow-growing cancer with few symptoms. Prostate cancer starts in the prostate, which is a small, walnut-sized gland that lies at the base of the bladder in men and is part of the male reproductive system.

Early-stage prostate cancer is “nonmetastatic”, which means cancer has not yet spread to other parts of the body. This is treated by surgically removing the prostate or by treating the prostate with radiation, or both. But, prostate cancer can come back for some patients after treatment with surgery or radiation. There is also a risk of “metastasis” for these patients, which means the spread of prostate cancer to other parts of the body.

What is enzalutamide?

Enzalutamide is a capsule that is swallowed and is approved to treat men with advanced prostate cancer.

Enzalutamide is an “androgen receptor inhibitor”. Androgens are a group of hormones that include testosterone. Androgen receptor inhibitors lessen how often androgens like testosterone connect with “androgen receptors”, which are proteins in the body that attach to androgens. This action may help to slow the growth of prostate cancer.

What was the purpose of this study?

The purpose of this study was to find out if taking enzalutamide with leuprolide, or taking enzalutamide only, is better than taking leuprolide only in helping participants go longer without their prostate cancer spreading to other parts of the body or dying from any cause.

Leuprolide is an approved medication in the United States that helps with symptoms of prostate cancer. In this study, leuprolide was injected under the skin or into a muscle.

This study included men with nonmetastatic prostate cancer that came back after treatment with surgery or radiation, or both, and who were at high risk of metastasis or further worsening of prostate cancer.

They were placed into 1 of 3 groups at random:

- Group 1: Enzalutamide plus leuprolide.
- Group 2: Placebo plus leuprolide.
  A placebo does not have any medicine in it, but it looks just like enzalutamide. This means that those assigned to placebo plus leuprolide got only leuprolide as the active medicine.
- Group 3: Enzalutamide only.

Researchers wanted to know:

- **Did the participants taking enzalutamide with leuprolide or enzalutamide only go longer without their prostate cancer spreading to other parts of the body, or dying from any cause, than those who received leuprolide only?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Study doctors checked whether participants met the study requirements. Then, participants were placed into 1 of 3 treatment groups at random:

Enzalutamide plus leuprolide	Placebo plus leuprolide	Enzalutamide
Participants in this group took enzalutamide once daily and received leuprolide once every 12 weeks.	Participants in this group took placebo once daily and received leuprolide once every 12 weeks.	Participants in this group took enzalutamide once daily.
Participants, study doctors, and staff knew that these groups were receiving leuprolide. This is called “open-label” treatment. But, they did not know during the study whether these participants were taking enzalutamide or placebo. This is called “blinded” treatment.		Participants, study doctors, and staff knew that this group was taking enzalutamide only.

Study doctors checked the participants’ blood “prostate-specific antigen”, also called PSA, levels throughout the study.

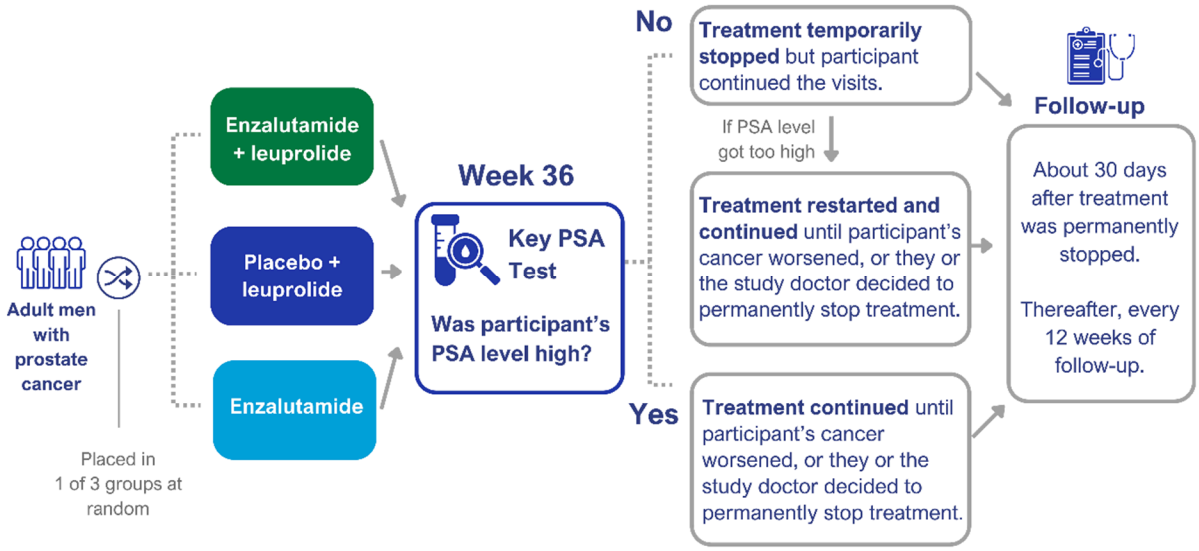
PSA is a protein made by the prostate that helps doctors monitor prostate cancer. High levels of PSA in the blood may mean that the participants’ prostate cancer was coming back or worsening.

Participants were to take their assigned study medication until their prostate cancer worsens, or they or the study doctor decides to permanently stop treatment. Depending on the participants' PSA levels after 36 weeks of treatment, the study doctors decided if a participant was to have a temporary break from treatment.

Study doctors continued to check participants after permanently stopping treatment. This is called "follow-up" period.

Figure 1 below shows how the study was done.

Figure 1. How was this study done?



Throughout the study, participants had regular study visits. During these visits, participants:

- had blood samples taken, so study doctors could monitor their PSA levels.
- underwent imaging tests, so study doctors could check whether participants' prostate cancer was worsening or spreading.
- had different health checks for their overall health.

Researchers then compared the results of study participants across treatment groups. This was done to see how well enzalutamide with or without leuprolide worked compared to leuprolide only in helping participants go longer without their prostate cancer spreading to other parts of the body or dying from any cause.

Where did this study take place?

The Sponsor ran this study at 174 locations in 17 countries in North America, Europe, and the rest of the world.

When did this study take place?

It began on 17 December 2014 and is ongoing.

Who participated in this study?

The study included adult men with nonmetastatic prostate cancer that came back after treatment with surgery or radiation, or both, and who were at high risk of metastasis or further worsening of prostate cancer.

- A total of 1068 men participated.
- All participants were from 49 to 93 years of age.

Of the 1068 participants who started the study, 7 participants did not receive a study medication.

At the time the Sponsor reviewed the information collected:

- 557 participants (52.2%) were still receiving treatment.
- 504 participants (47.2%) stopped treatment. The most common reasons for stopping treatment were medical problems that participants had during the study and worsening of prostate cancer.

A total of 278 participants who stopped treatment were no longer in the study. The most common reasons for not completing the follow-up period were because the participants died, or they left before the study was over by their choice.

How long did the study last?

The study is ongoing. On 31 January 2023, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

Did the participants taking enzalutamide with leuprolide or enzalutamide only go longer without their prostate cancer spreading to other parts of the body, or dying from any cause, than those who received leuprolide only?

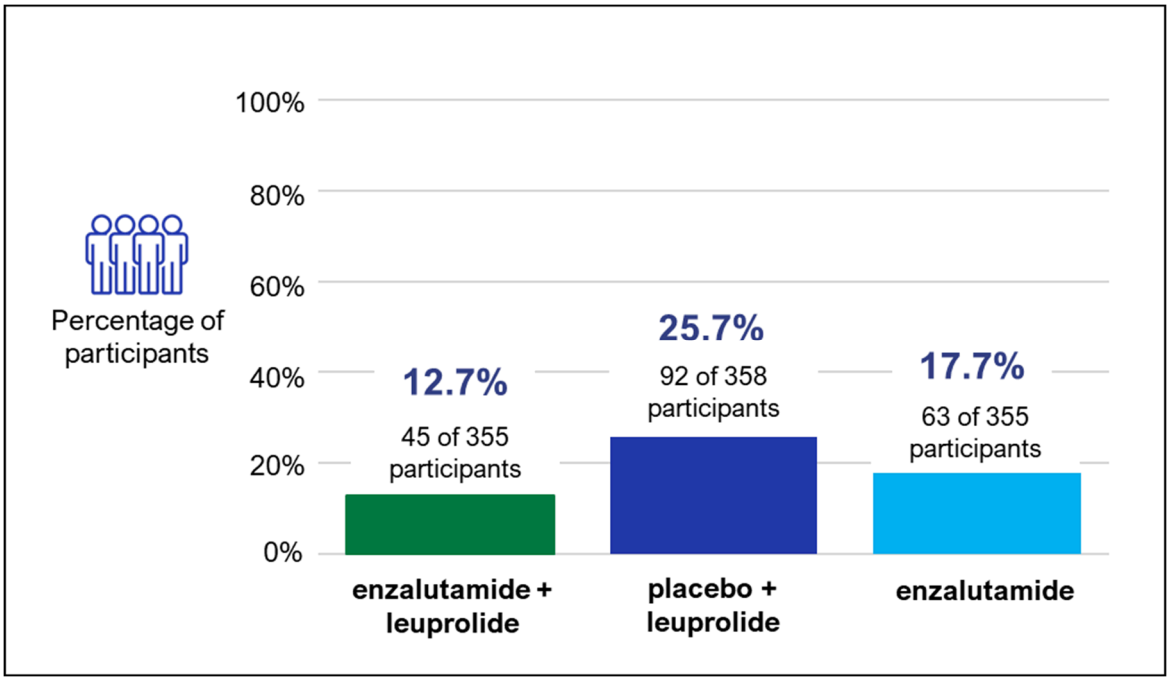
Researchers wanted to make sure they had collected enough information before they began their review.

On 31 January 2023, researchers determined they had enough information on participants' "metastasis-free survival" to answer the study's main question.

> **Metastasis-free survival**, or **MFS**, is the length of time that participants lived without their cancer getting worse, or dying, after starting study treatment.
>
> Researchers checked for **MFS events** during the study to answer the main question. MFS events are occurrences of participants' prostate cancer spreading to other parts of the body, or participant death from any cause.

Figure 2 below shows fewer participants who took enzalutamide plus leuprolide (12.7%) and enzalutamide only (17.7%) had MFS events compared to those who received leuprolide only (25.7%).

Figure 2. How many participants had an MFS event?



These results show that participants who took enzalutamide, with or without leuprolide, went longer without their prostate cancer spreading to other parts of the body, or dying, than those who received leuprolide only.

This means that, compared to those who received leuprolide only:

- participants who took enzalutamide with leuprolide were **57.6%** less likely to have metastases or die.
- participants who took enzalutamide only were **36.9%** less likely to have metastases or die.

The researchers have decided that the results **are not** likely the result of chance.

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

Researchers looked at the records of the 1061 participants who got at least 1 dose of any of the study medications in this study.

The table below shows how many participants had at least 1 medical problem:

Enzalutamide plus leuprolide	Placebo plus leuprolide	Enzalutamide
343 out of 353 participants (97.2%)	345 out of 354 participants (97.5%)	347 out of 354 participants (98.0%)

The table below shows how many participants stopped taking their assigned study medication due to a medical problem they had during the study:

Enzalutamide plus leuprolide	Placebo plus leuprolide	Enzalutamide
73 out of 353 participants (20.7%)	36 out of 354 participants (10.2%)	63 out of 354 participants (17.8%)

The most common medical problems – those reported by at least 15% of participants in any of the 3 groups – are described in Table 1 below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by at least 15% of participants in any group are listed.
- The **2nd** column tells how many of the 353 participants taking enzalutamide with leuprolide reported each medical problem. Next to this number is the percentage of the 353 participants taking enzalutamide with leuprolide who reported the medical problem.
- The **3rd** column tells how many of the 354 participants taking placebo with leuprolide reported each medical problem. Next to this number is the percentage of the 354 participants taking placebo with leuprolide who reported the medical problem.

- The **4th** column tells how many of the 354 participants taking enzalutamide only reported each medical problem. Next to this number is the percentage of the 354 participants taking enzalutamide only who reported the medical problem.
- For example, using these instructions, you can see how many participants were reported with hot flashes:
  - 243 out of 353 participants (68.8%) in the **enzalutamide plus leuprolide** group.
  - 203 out of 354 participants (57.3%) in the **placebo plus leuprolide** group.
  - 77 out of 354 participants (21.8%) in the **enzalutamide only** group.

Table 1. Commonly reported medical problems by study participants

Medical Problem	Enzalutamide Plus Leuprolide (353 Participants)	Placebo Plus Leuprolide (354 Participants)	Enzalutamide (354 Participants)
Hot flashes	243 out of 353 participants (68.8%)	203 out of 354 participants (57.3%)	77 out of 354 participants (21.8%)
Feeling tired	151 out of 353 participants (42.8%)	116 out of 354 participants (32.8%)	165 out of 354 participants (46.6%)

Table 1. Commonly reported medical problems by study participants

Medical Problem	Enzalutamide Plus Leuprolide (353 Participants)	Placebo Plus Leuprolide (354 Participants)	Enzalutamide (354 Participants)
Joint pain	97 out of 353 participants (27.5%)	75 out of 354 participants (21.2%)	81 out of 354 participants (22.9%)
High blood pressure	82 out of 353 participants (23.2%)	69 out of 354 participants (19.5%)	67 out of 354 participants (18.9%)
Fall	74 out of 353 participants (21.0%)	51 out of 354 participants (14.4%)	56 out of 354 participants (15.8%)
Back pain	60 out of 353 participants (17.0%)	54 out of 354 participants (15.3%)	62 out of 354 participants (17.5%)
Nausea	42 out of 353 participants (11.9%)	29 out of 354 participants (8.2%)	54 out of 354 participants (15.3%)
Enlargement of breasts in men	29 out of 353 participants (8.2%)	32 out of 354 participants (9.0%)	159 out of 354 participants (44.9%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Enzalutamide Plus Leuprolide (353 Participants)**	**Placebo Plus Leuprolide (354 Participants)**	**Enzalutamide (354 Participants)**
Nipple pain	11 out of 353 participants (3.1%)	4 out of 354 participants (1.1%)	54 out of 354 participants (15.3%)

Did study participants have any serious medical problems?

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.

The following number of participants had serious medical problems.

- 123 out of 353 participants (34.8%) in the **enzalutamide plus leuprolide** group.
- 112 out of 354 participants (31.6%) in the **placebo plus leuprolide** group.
- 131 out of 354 participants (37.0%) in the **enzalutamide only** group.

Table 2 below lists the most common serious medical problems – those experienced by at least 2% of participants in any group – in the study.

Instructions on how to read Table 2 are the same as those for Table 1.

Table 2. Commonly reported serious medical problems by study participants

Serious Medical Problem	Enzalutamide Plus Leuprolide (353 Participants)	Placebo Plus Leuprolide (354 Participants)	Enzalutamide (354 Participants)
Fainting	9 out of 353 participants (2.5%)	4 out of 354 participants (1.1%)	2 out of 354 participants (0.6%)
Blood in urine	8 out of 353 participants (2.3%)	4 out of 354 participants (1.1%)	8 out of 354 participants (2.3%)
Joint problem resulting in joint tissues breaking down over time	8 out of 353 participants (2.3%)	3 out of 354 participants (0.8%)	2 out of 354 participants (0.6%)
Lung infection	8 out of 353 participants (2.3%)	4 out of 354 participants (1.1%)	5 out of 354 participants (1.4%)
Narrowing or blockage of blood vessels in the heart	2 out of 353 participants (0.6%)	1 out of 354 participants (0.3%)	8 out of 354 participants (2.3%)

The following number of participants had serious medical problems that researchers thought may be related to at least 1 of the study medications.

Enzalutamide plus leuprolide	Placebo plus leuprolide	Enzalutamide
26 out of 353 participants (7.4%)	8 out of 354 participants (2.3%)	17 out of 354 participants (4.8%)

- The most common of the related serious medical problems was fainting, which happened to 3 participants in the enzalutamide with leuprolide group and 2 participants in the placebo with leuprolide group. None of the participants in the enzalutamide only group had this serious medical problem.
- The rest of the related serious medical problems happened in no more than 2 participants in each treatment group.

A total of 130 out of 1068 participants (12.2%) died during the study. The most common cause of death across the 3 groups was worsening of prostate cancer. Researchers do not believe that any of the deaths were related to any of the study medications.

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **MDV3100-13 or C3431004**

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT02319837**
www.clinicaltrialsregister.eu	Use the study identifier **2014-001634-28**

Pfizer and Astellas Pharma developed enzalutamide.

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!