Plain Language Clinical Study
Summary

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 medicine 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(s) Studied: Palbociclib (PD-0332991)

Protocol Number: A5481027

Dates of Study: 23 March 2015 to 24 February 2025

Title of this Study: A Study of Palbociclib (PD-0332991) Plus Letrozole Versus Placebo Plus Letrozole For 1st Line Treatment of Postmenopausal Asian Women With ER (+), HER2 (-) Advanced Breast Cancer (PALOMA-4)

[A Multicenter, Randomized, Double-Blind Phase 3 Study of Palbociclib (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Previously Untreated Asian Postmenopausal Women With ER (+), HER2 (-) Advanced Breast Cancer]

Pfizer

Date(s) of this Report: 15 December 2025

– 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. Do you have any questions about the study or the results? If so, please contact the doctor or staff at your study site.

Why was this study done?

What is advanced breast cancer?

Breast cancer is a disease in which abnormal breast cells grow out of control and form tumors. Sometimes, breast cancer can spread from the breast to other parts of the body, most often to the bones, lungs, liver, or brain. This is called advanced breast cancer. Advanced breast cancer cannot be cured with surgery or radiation therapy, but treatments may help slow down its development and help the patient live longer.

Some types of breast cancer need sex hormones (which are chemical messengers in the body, such as estrogen or progesterone) or a protein called HER2 (human epidermal growth factor receptor 2), or both, to grow. These sex hormones and/or proteins are recognized by receptors on the breast cancer cells. Breast cancer cells with hormone receptors are called hormone receptor positive.

Participants in this study had advanced breast cancer with estrogen receptors (a type of hormone receptor) but few or no HER2 receptors. This type of breast cancer is called estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER [+], HER2 [-] for short) breast cancer.

This type of advanced breast cancer (ER [+], HER2 [-]) might be sensitive to hormone treatment. Hormone treatment slows or stops the growth of hormone receptor-positive tumors by preventing the cancer cells from getting the hormones they need to grow.

What is palbociclib?

Palbociclib (pal-boh-sye-klib), also known as IBRANCE®, is an approved medicine that is used to treat hormone receptor positive, HER2 (-) breast cancer. Palbociclib targets the functioning of specific proteins or enzymes called cyclin-dependent kinases (CDK4 and CDK6). These enzymes are important for

normal cell division and they may cause cancer cells to grow and spread. Certain cancers are more likely to have disturbances in CDK4 and CDK6. Palbociclib prevents the CDK4 and CDK6 enzymes from functioning, which stops cancer cells from dividing and stops the growth of cancer cells. In this study, palbociclib was taken as a capsule, by mouth.

What is Letrozole?

Letrozole is a medicine that is approved for the treatment of advanced breast cancer that is sensitive to hormone treatment. Letrozole lowers estrogen levels in women who have already stopped menstruating (postmenopausal), which may slow the growth of certain types of breast tumors that need estrogen to grow in the body. In this study, letrozole was taken as a tablet, by mouth.

What was the purpose of this study?

The purpose of this research study was to compare the effect of palbociclib plus letrozole, with placebo plus letrozole in Asian women with ER (+), HER2 (-) advanced breast cancer who had not received any previous systemic treatment for their advanced disease and have already experienced menopause (postmenopausal). A placebo does not have any medicine in it, but it looks just like the study medicine.

Researchers wanted to compare the length of time from starting the study to when the cancer started to get worse for participants in the 2 treatment groups (palbociclib plus letrozole and placebo plus letrozole).

They did this by looking at the progression-free survival (PFS) of participants taking palbociclib plus letrozole. The PFS is the length of time during and after receiving a treatment for cancer that a participant lives without the cancer getting worse. They then compared this with the PFS of participants taking placebo plus letrozole to see which treatment was more effective in slowing down the progression of the disease.

Researchers wanted to know:

Did the participants taking palbociclib plus letrozole have a better PFS than participants taking placebo plus letrozole?

What happened during the study?

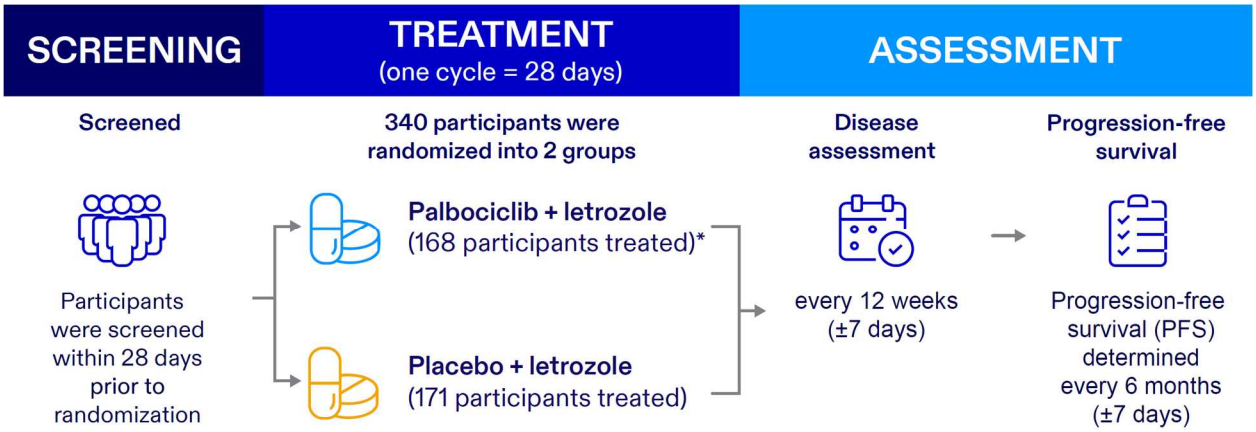
How was the study done?

The study doctors checked each participant to make sure they were able to take part in the study. This is known as screening.

Participants were then assigned to either palbociclib plus letrozole or placebo plus letrozole, by chance alone. This is known as a "randomized" study. This was done to make the groups similar to ensure a fair comparison of the results between these groups. A participant had an equal chance (a 1 in 2 chance) of receiving palbociclib plus letrozole or placebo plus letrozole. The study participants, study doctors, and researchers did not know who took palbociclib plus letrozole and who took placebo plus letrozole. This is known as a "blinded" study.

Figure 1 shows what happened during the study.

Figure 1. Study plan



*169 participants were randomized to the palbociclib plus letrozole group, but 1 participant did not take any study treatment.

Each treatment cycle lasted 4 weeks (28 days).

- Participants in the palbociclib plus letrozole group took palbociclib by mouth every day for 21 days once a day, followed by 7 days of not taking it. They also received letrozole by mouth every day once a day without interruption.
- Participants in the placebo plus letrozole group took placebo by mouth every day for 21 days once a day, followed by 7 days of not taking it. They also received letrozole by mouth every day once a day without interruption.

Participants could continue receiving the study medicine for as long as they continued to benefit from it and the study was ongoing.

Researchers monitored the participant's cancer during the study. Researchers also checked the participant's health during the study and asked them how they were feeling.

The checks on the participant's cancer and health continued after the participants stopped taking the study medicine. These checks were done for as long as the study was ongoing.

Where did this study take place?

The Sponsor ran this study at 52 locations in 5 countries across Asia.

When did this study take place?

It began 23 March 2015 and ended 24 February 2025.

Who participated in this study?

The study included Asian women who had experienced menopause with ER (+), HER2 (-) advanced breast cancer.

- A total of 340 women participated.
- All participants were between the ages of 29 years and 70 years.

Participants were to be treated until:

- Their cancer got worse.
- They left the study by their own choice.
- They were unable or unwilling to follow the instructions of the study team.
- The doctor decided it was best for a participant to stop being in the study.
- They had unacceptable medical problems.
- The participant died.

Of the 340 participants randomized to the study, 339 participants were treated. All study participants discontinued from all study activities at the end of the study. A total of 14 participants in the palbociclib plus letrozole group and 7 participants in the placebo plus letrozole group transitioned into a rollover study to continue their follow-up.

How long did the study last?

The amount of time that participants were in the study varied, depending on how they responded to treatment. The entire study took around 10 years to complete.

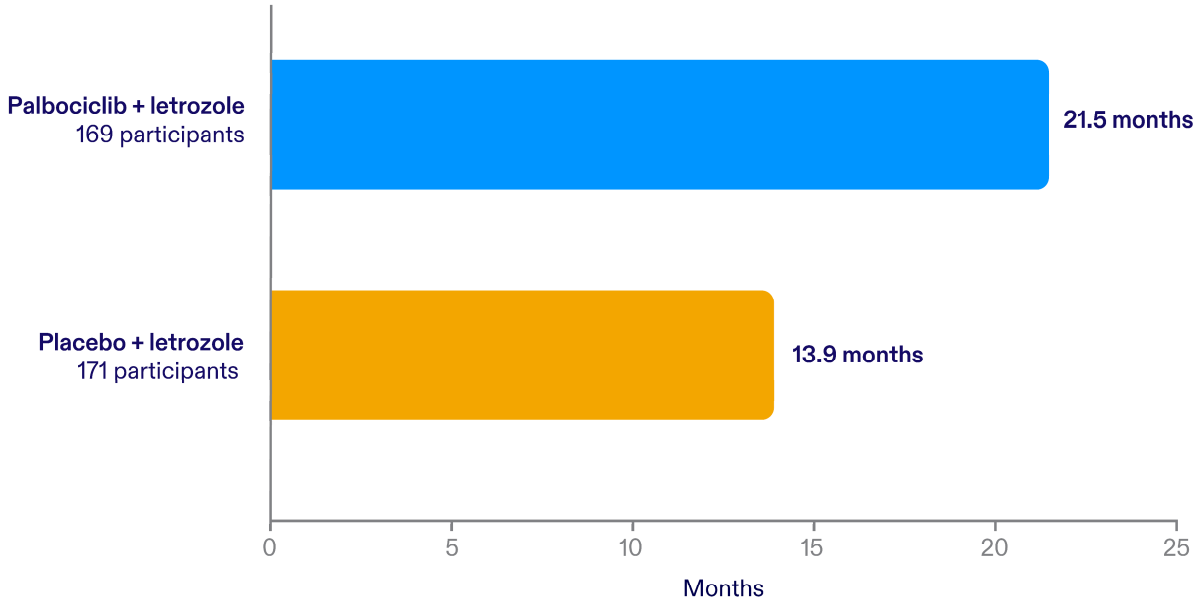
When the study ended in February 2025, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. Before this, the Sponsor had also created a report of the study results from the information collected up to August 2020. This is a summary of both reports.

What were the results of the study?

Did the participants taking palbociclib plus letrozole have a better PFS than participants taking placebo plus letrozole?

Researchers determined the median PFS (in months) for participants in the palbociclib plus letrozole group and for participants in the placebo plus letrozole group as shown in Figure 2 below. The median is the middle number in a set of values when these values are arranged from smallest to largest.

Figure 2. Median progression-free survival



Researchers found that participants in the palbociclib plus letrozole group had a longer median PFS (21.5 months) compared to the participants in the placebo plus letrozole group (13.9 months).

Based on these results, the researchers have decided that the results are not likely the result of chance. Adding palbociclib to letrozole may help participants with advanced breast cancer.

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 medicine might have on a participant.

A total of 323 out of the 339 treated participants (95.3%) had at least 1 medical problem. This included all 168 participants (100%) in the palbociclib plus letrozole group and 155 out of 171 participants (90.6%) in the placebo plus letrozole group. A total of 20 participants (5.9%) left the study because of medical problems. The most common medical problems – those reported by 20% or more of participants in either treatment group – are described 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 20% or more of participants in either treatment group are listed.

  Some medical problems were grouped together because they were the same type of problem but reported differently. For example, all the problems that meant low or decreased levels of neutrophils

were grouped together under the term “low count of white blood cells called neutrophils”. Groups like this are known as clustered medical problems or cluster terms. They are marked with a star (*) in this report. Table 1 does not contain the individual medical problems that make up these cluster terms.

- The **2nd** column of Table 1 tells how many of the 168 participants who took palbociclib plus letrozole reported each medical problem. Next to this number is the percentage of the 168 participants who took palbociclib plus letrozole and reported the medical problem.
- The **3rd** column of Table 1 tells how many of the 171 participants who took placebo plus letrozole reported each medical problem. Next to this number is the percentage of the 171 participants who took placebo plus letrozole and reported the medical problem.
- Using these instructions, you can see that 165 out of the 168 participants (98.2%) who took palbociclib plus letrozole reported a low count of white blood cells called “neutrophils”*. Twenty-nine (29) out of the 171 participants (17.0%) who took placebo plus letrozole reported a low count of white blood cells called “neutrophils”*.

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Palbociclib Plus Letrozole (168 Participants)**	**Placebo Plus Letrozole (171 Participants)**
Low count of white blood cells called "neutrophils"*	165 out of 168 participants (98.2%)	29 out of 171 participants (17.0%)
Low white blood cell count*	144 out of 168 participants (85.7%)	24 out of 171 participants (14.0%)
Low level of "platelets" that help blood to clot*	86 out of 168 participants (51.2%)	7 out of 171 participants (4.1%)
Low red blood cell count*	80 out of 168 participants (47.6%)	18 out of 171 participants (10.5%)
Increased level of a liver protein (enzyme) called "AST" in the blood	61 out of 168 participants (36.3%)	49 out of 171 participants (28.7%)
Increased level of a liver protein (enzyme) called "ALT" in the blood	60 out of 168 participants (35.7%)	58 out of 171 participants (33.9%)
Infections*	56 out of 168 participants (33.3%)	54 out of 171 participants (31.6%)

*cluster term

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.

A total of 53 out of 339 participants (15.6%) had serious medical problems.

- Thirty-four (34) out of 168 participants (20.2%) who took palbociclib plus letrozole had at least 1 serious medical problem. Of these, 12 participants (7.1%) had at least 1 serious medical problem considered related to the study medicine.
- Nineteen (19) out of 171 participants (11.1%) who took placebo plus letrozole had at least 1 serious medical problem. Of these, 5 participants (2.9%) had at least 1 serious medical problem considered related to the study medicine.

The most frequently reported serious medical problem was infections*. This was reported in 11 participants (5 participants who took palbociclib plus letrozole and 6 participants who took placebo plus letrozole).

A total of 10 out of 339 participants (2.9%) died during the study treatment period (from the start of treatment, up to and including 28 days after the last dose).

- Five (5) out of 168 participants (3.0%) who took palbociclib plus letrozole died during the study treatment period and an additional 97 out of 168 participants (57.7%) died during the follow-up period.
- Five (5) out of 171 participants (2.9%) who took placebo plus letrozole died during the study treatment period and an additional 121 out of 171 participants (70.8%) died during the follow-up period.

Most of the deaths were due to the cancer getting worse. One (1) participant, who took palbociclib plus letrozole, was recorded to have died due to side effects of the study treatment. The exact cause of this participant's death was unknown but medical problems from the treatment could not be ruled out.

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 **A5481027**

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

www.clinicaltrials.gov	Use the study identifier **NCT02297438**

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

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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!

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