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(s) Studied: Ibrance® (palbociclib)

Protocol Number: A5481023 (PALOMA-3)

Dates of Study: 26 September 2013 to 28 September 2022

Title of this Study: Palbociclib Combined With Fulvestrant in HR-Positive, HER2-Negative Metastatic Breast Cancer After Endocrine Failure

[Multicenter, Randomized, Double-Blind, Placebo Controlled, Phase 3 Trial of Fulvestrant (Faslodex®) With or Without Palbociclib ± Goserelin in Women With HR-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy]

Date(s) of this Report: 16 August 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 advanced breast cancer?

Sometimes breast cancer can spread from the breast to other parts of the body, most often to the bones, lungs, liver, or brain. When the cancer spreads, it is called metastatic breast cancer.

The participants in this study had hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 negative (HER2-negative), metastatic breast cancer.

- A hormone receptor is a receptor molecule that binds to a specific hormone. A breast cancer is classified as HR-positive if its cells have receptors for the hormones estrogen and progesterone. Estrogen and progesterone attach to the receptors and give the breast cancer the signal to grow.
- HER2-negative means that the participants have no or a very low level of HER2 proteins in the breast cells (too much of this protein would mean that there is another type of cancer present).

What is palbociclib and what is fulvestrant?

- Ibrance® (EYE-brans), also known as palbociclib, is an approved medicine that is used to treat HR-positive, HER-negative breast cancer. Palbociclib is a type of cancer growth blocker that targets proteins called cyclin dependent kinase 4 and 6 (CDK4 and CDK6) on cancer cells. These proteins stimulate cancer cells to grow and divide. Palbociclib is taken by mouth.
- Fulvestrant (Faslodex®) is a drug that is approved for the treatment of HR-positive metastatic breast cancer and may be used alone or

together with other medicines such as palbociclib. Fulvestrant is given by injection into the muscle of each buttock.

- Participants who had not gone through the menopause were also treated with goserelin (Zoladex®) during the study. Having gone through the menopause means no longer having monthly periods. Goserelin (Zoladex® or generic) is a drug that is approved to treat breast cancer in women who have not gone through the menopause.

What was the purpose of this study?

The purpose of this research study was to compare the effect of palbociclib plus fulvestrant with placebo plus fulvestrant in women with HR-positive, HER-negative metastatic breast cancer that had continued to grow after hormone treatment. A placebo does not have any medicine in it, but it looks just like the study medication.

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

They did this by looking at the "progression-free survival" (PFS) of participants taking palbociclib plus fulvestrant. The PFS is the length of time during and after receiving a treatment for cancer that a patient lives without the cancer getting worse. They then compared this with the PFS of participants taking placebo plus fulvestrant.

Researchers wanted to know:

- **How long was the PFS for participants taking palbociclib plus fulvestrant, compared to participants taking placebo plus fulvestrant?**

- **What medical problems did participants have during the study?**

What happened during the study?

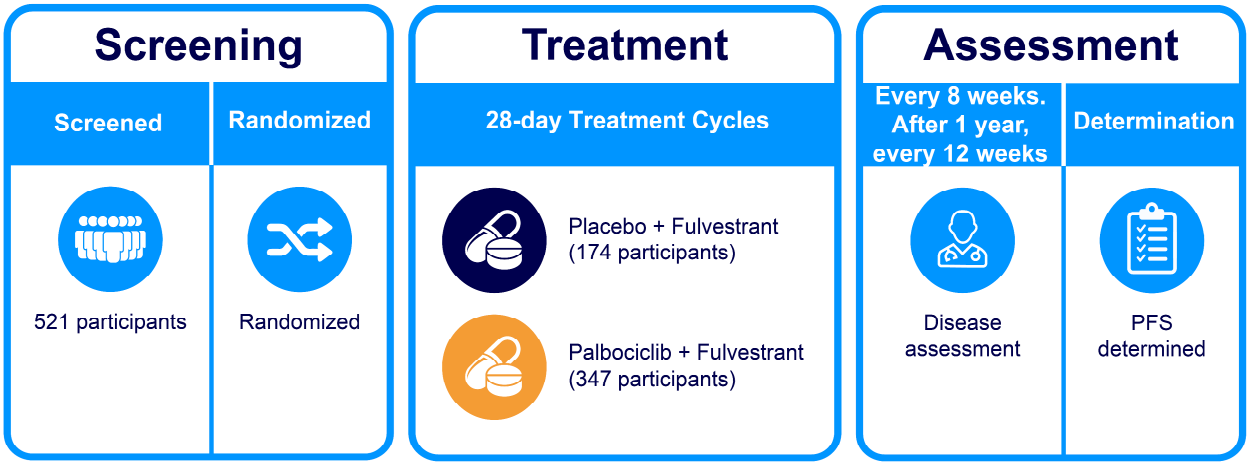
How was the study done?

First, a study doctor checked each participant to make sure they were able to join the study. This is known as a screening period.

Participants were then randomized (assigned by chance alone) into treatment groups. A participant had a 2 in 3 chance of receiving palbociclib and fulvestrant, and a 1 in 3 chance of receiving fulvestrant and placebo. The study participants, study doctors and researchers did not know who took which treatment. This is known as a "blinded" study.

Figure 1 shows what happened during the study.

Figure 1: Study Design



Of the 521 participants who were randomized in this study, 4 participants were not treated (2 in each treatment group).

Each treatment cycle lasted 4 weeks (28 days).

- Participants in the palbociclib plus fulvestrant group took palbociclib by mouth every day for 21 days, followed by 7 days of not taking it. They also received an injection of fulvestrant on the 1st and 15th day of the first cycle. After this, fulvestrant was given on the 1st day of each of the following cycles.
- Participant in the placebo plus fulvestrant group took placebo by mouth every day for 21 days, followed by 7 days of not taking it. They also received an injection of fulvestrant on the 1st and 15th day of the first cycle. After this, fulvestrant was given on the 1st day of each of the following cycles.
- Participants from both groups also received goserelin if they had not gone through the menopause. Goserelin was given as an under-the-skin injection every 28 days.

Participants could continue receiving study treatment 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.

Where did this study take place?

The Sponsor ran this study at 144 locations in 17 countries in Asia, Australia, Europe, North America, and Russia.

When did this study take place?

It began 26 September 2013 and ended 28 September 2022.

Who participated in this study?

The study included participants with metastatic breast cancer that was HR-positive and HER2-negative. Some participants had gone through the menopause, and some had not.

- A total of 521 women were randomized in the study.
- All participants were between the ages of 29 and 88.

Of the 521 participants who were randomized in this study, 4 participants were not treated. Of the 517 participants who started treatment, 504 participants discontinued the study treatment because:

- The participant's cancer got worse (this was the most common reason)
- The participant died
- The participant experienced medical problems
- The participants left before the study was over by their choice or a doctor decided it was best for a participant to stop being in the study.

There were 13 participants who were still receiving study treatment at the end of the study. These participants were transitioned to commercial treatment or enrolled in a continuation study.

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 about 9 years to complete.

When the study ended in September 2022, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. Before this, the Sponsor had also created reports of the study results from

the information collected up to December 2014, March 2015, October 2015, and April 2018. This is a summary of all the reports.

What were the results of the study?

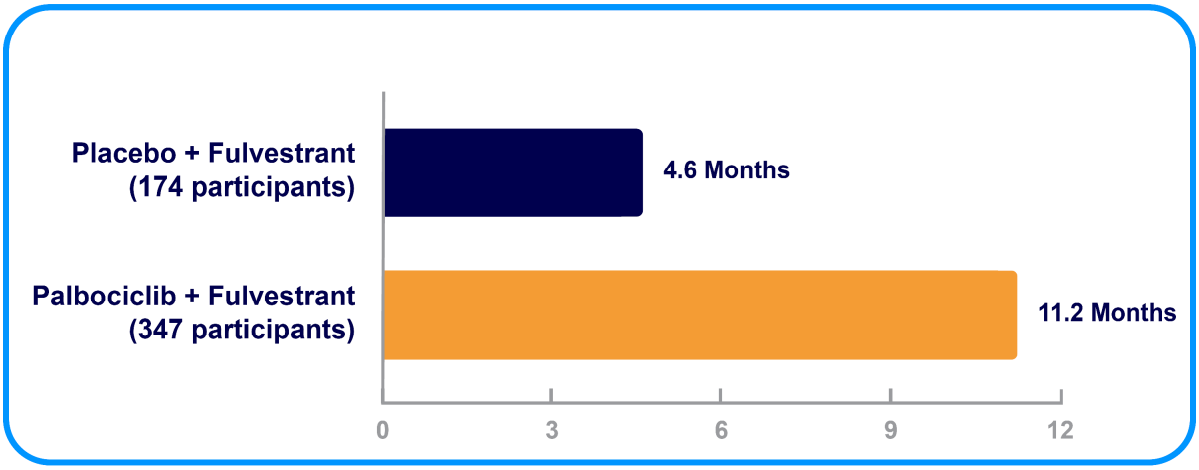
Researchers determined the PFS of participants based on the information they collected for 521 participants up to October 2015.

Medical problems were summarized based on the information collected up to September 2022 for the 517 participants who received at least 1 dose of study medicine, and are shown in the next section.

How long was the PFS for participants taking palbociclib plus fulvestrant, compared to participants taking placebo plus fulvestrant?

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

Figure 2: Median Progression-Free Survival



Researchers found that participants who took palbociclib plus fulvestrant had a longer median PFS compared to participants who took placebo plus fulvestrant.

Based on these results, the researchers have decided that the results are not likely the result of chance. Adding palbociclib to fulvestrant may help participants with metastatic breast cancer that has progressed after hormonal therapy.

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.

A total of 502 out of 517 (97.1%) participants in this study had at least 1 medical problem. Most participants stopped treatment with the study medication because their cancer worsened, they had medical problems, or their doctor thought they should stop. The most common medical problems – those reported by more than 25% of participants in each group – are described below.

Below are instructions on how to read Table 1 and Table 2.

Instructions for Understanding Table 1 and Table 2.

- The **1st** column lists medical problems that were commonly reported during the study. All medical problems reported by more than 25% of participants in either treatment group are listed in Table 1. All serious medical problems reported by more than 2 participants are listed in Table 2.
- The **2nd** column tells how many of the 345 participants who took palbociclib plus fulvestrant reported each medical

problem. Next to this number is the percentage of the 345 participants who took palbociclib plus fulvestrant who reported the medical problem.

- The **3rd** column tells how many of the 172 participants who took placebo plus fulvestrant reported each medical problem. Next to this number is the percentage of the 172 participants who took placebo plus fulvestrant who reported the medical problem.
- Using these instructions, you can see that in Table 1, a total of 291 out of the 345 participants (84.3%) who took palbociclib plus fulvestrant reported low neutrophil count (a neutrophil is a type of white blood cell). A total of 6 out of the 172 participants (3.5%) who took placebo plus fulvestrant reported low neutrophil count.

Table 1. Commonly reported medical problems by study participants

Medical Problem	Palbociclib plus fulvestrant (345 Participants)	Placebo plus fulvestrant (172 Participants)
Low neutrophil count (a type of white blood cell)	291 out of 345 participants (84.3%)	6 out of 172 participants (3.5%)

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Palbociclib plus fulvestrant (345 Participants)**	**Placebo plus fulvestrant (172 Participants)**
Low leukocyte count (a type of white blood cell)	208 out of 345 participants (60.3%)	9 out of 172 participants (5.2%)
Infections	190 out of 345 participants (55.1%)	62 out of 172 participants (36.0%)
Feeling tired	151 out of 345 participants (43.8%)	56 out of 172 participants (32.6%)
Nausea	126 out of 345 participants (36.5%)	52 out of 172 participants (30.2%)
Low red blood cell count	111 out of 345 participants (32.2%)	23 out of 172 participants (13.4%)
Mouth pain and sores	107 out of 345 participants (31.0%)	25 out of 172 participants (14.5%)

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Palbociclib plus fulvestrant (345 Participants)**	**Placebo plus fulvestrant (172 Participants)**
Headache	102 out of 345 participants (29.6%)	38 out of 172 participants (22.1%)
Diarrhea (loose stools)	95 out of 345 participants (27.5%)	35 out of 172 participants (20.3%)
Joint pain	90 out of 345 participants (26.1%)	42 out of 172 participants (24.4%)
Low blood platelets	89 out of 345 participants (25.8%)	0

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.

- In total, 78 participants out of 345 (22.6%) who took palbociclib plus fulvestrant had serious medical problems. Of these, 27 (7.8%) were considered related to the study medication.

- In total, 33 participants out of 172 (19.2%) who took placebo plus fulvestrant had serious medical problems. Of these, 3 (1.7%) were considered related to the study medication.

Table 2. Commonly reported serious medical problems by study participants

Medical Problem	Palbociclib plus fulvestrant (345 Participants)	Placebo plus fulvestrant (172 Participants)
Infections	20 out of 345 participants (5.8%)	8 out of 172 participants (4.7%)
Fever	5 out of 345 participants (1.4%)	1 out of 172 participants (0.6%)
Worsening cancer	4 out of 345 participants (1.2%)	0
Low neutrophil count (a type of white blood cell)	4 out of 345 participants (1.2%)	0
Blocked blood vessel in lung	4 out of 345 participants (1.2%)	0
Blood clots	3 out of 345 participants (0.9%)	0

Table 2. Commonly reported serious medical problems by study participants		
Medical Problem	**Palbociclib plus fulvestrant (345 Participants)**	**Placebo plus fulvestrant (172 Participants)**
Low neutrophil count (a type of white blood cell) with fever	3 out of 345 participants (0.9%)	0
Fluid around lungs	2 out of 345 participants (0.6%)	3 out of 172 participants (1.7%)

A total of 11 participants died within 28 days of their last dose of study medication. Of these, 9 deaths were due to the cancer worsening, and for 2 participants the cause of death was not known.

During the 9 years of the study, a total of 390 participants died more than 28 days after their last dose of study medication. This included participants who had stopped study treatment but were still followed in the study. Most of the deaths were due to the cancer worsening.

There were no deaths that were considered to be due to study treatment toxicity (where the cause of death was known).

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 A5481023

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

www.clinicaltrials.gov	Use the study identifier **NCT01942135**
www.clinicaltrialsregister.eu	Use the study identifier 2013-002580-26

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!