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: PF-06873600

Protocol Number: C3661001

Dates of Study: 07 March 2018 to 05 April 2023

Title of this Study: A Study of PF-06873600 in People With Breast and Ovarian Cancer

[Phase 1/2a Dose Escalation and Expansion Study Evaluating Safety, Tolerability, Pharmacokinetic, Pharmacodynamics and Anti-Tumor Activity of PF-06873600 as a Single Agent and in Combination With Endocrine Therapy]

Date of this Report: 23 February 2024

– 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 metastatic breast cancer and ovarian cancer?

Breast cancer is a disease where the cells in the breast grow out of control. Sometimes breast cancer can spread from the breast to other parts of the body, most often to the bones, lungs, liver, or brain. Participants in this study had breast cancer that was “advanced or metastatic”. This means that the original cancer has spread from where it started growing and is more difficult to cure.

Cancer that originates in the ovary (female reproductive organ) is called ovarian cancer. Participants with ovarian cancer who no longer respond to standard chemotherapy were enrolled in the study.

The study was conducted in 2 parts: Part 1 and Part 2. Part 1 was divided into Parts 1A, 1B, 1C and Part 2 was divided into Parts 2A and 2C. Majority of the participants in the study had breast cancer and a few others had ovarian cancer. Participants had different types of breast cancer in the study as described below:

- Hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 negative (HER2-negative) breast cancer is a common subtype of metastatic breast cancer (mBC). A hormone receptor is a receptor molecule that binds to a specific hormone. Breast cancer is classified as HR-positive if its cells have receptors for the estrogen and progesterone hormones. Estrogen and progesterone attach to the receptors and give breast cancer the signal to grow. HER 2 is a protein that helps breast cancer cells grow faster. HER2-negative means that the participants have no or a very low level of HER2 proteins in the breast cells.

- Triple negative breast cancer (TNBC) is a type of breast cancer where the cancer cells don't have receptors for estrogen and progesterone and have no or a very low level of HER2 proteins.

What is PF-06873600?

The study drug (PF-06873600) is an investigational cancer medicine. It is taken as a tablet by mouth. This was the first time PF-06873600 was given to people. PF-06873600 is a type of cancer growth blocker that targets specific proteins called Cyclin-Dependent Kinase 2, 4, and 6 (CDK2/4/6). It works by stopping or preventing the action of these proteins which stimulate cancer cells to grow and divide.

In Part 1B and Part 2 of this study, participants received PF-06873600 in combination with fulvestrant and/or letrozole.

Fulvestrant (Faslodex®) is a drug that is approved for the treatment of HR-positive mBC in postmenopausal women whose disease has progressed after hormonal therapy. It is given by injection into the muscle of each buttock.

Letrozole is a drug that is approved for the treatment of advanced breast cancer that is sensitive to hormonal treatment. It interferes with the body's ability to make estrogen. Letrozole is taken as a tablet by mouth.

What was the purpose of this study?

The main purpose of Part 1 was to learn about the safety and tolerability of PF-06873600 when given alone (Parts 1A and 1C) and as a combination treatment with either fulvestrant or letrozole (Part 1B). "Tolerability" refers to how well participants can tolerate taking the study drug.

Researchers wanted to find out what the best and safest ("optimal") dose of the drug was. This will help them decide what dose to give to people in Part 2 and possibly in future studies. Researchers did this by giving participants increasing doses of PF-06873600 in Parts 1A and 1C of the

study. At each dose level, researchers checked if participants had any "dose-limiting toxicities" (DLTs), before deciding if a higher dose could be given. DLTs are medical problems which usually prevent further increases in the dose of the study medication. After evaluating the safety of different doses, dosing schedules and formulations in Parts 1A and 1C researchers wanted to find out the optimal dose of PF-06873600 in combination with fulvestrant or letrozole in Part 1B of the study.

In Part 2 along with the safety, researchers assessed if PF-06873600 in combination with fulvestrant had any positive effects on cancer in participants with HR-positive HER2-negative advanced or mBC at the optimal dose identified in Part 1B.

Researchers wanted to know:

- **How safe and well tolerated was PF-06873600?**
- **Part 1: Did participants have any DLTs?**
- **Part 2: Did participants taking PF-06873600 along with fulvestrant have positive effects on their cancer?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Participants joined either Part 1 or Part 2 of the study. Part 2 was started after the researchers had reviewed some of the results from Part 1 of the study. This study was an "open-label" study, which means that participants and researchers knew which medicines the participants received.

All participants were "screened" to see if they qualify for the study. Participants who qualified for treatment after screening entered the Treatment Phase. Study medication was given to participants continuously. Every 28 days (4 weeks) of treatment was defined as "a cycle". Participants received PF-06873600 continuously in 28-day "treatment cycles" until their cancer got worse, they experienced unacceptable medical problems, a decision was made by the researcher or participant to stop the treatment, or the study was terminated.

About 28 +/- 7 days after their last dose, participants had a Follow-up Visit to check their health. In Part 2, participants had phone calls about every 2 months after the Follow-up Visit until the end of the study or until death of the participant. This was called "Long-term Follow-up".

Part 1A

Participants in Part 1A had HR-positive HER2-negative advanced or mBC. Participants with TNBC and ovarian cancer also participated in Part 1A of the study. Researchers tested increasing doses of PF-06873600 in these participants.

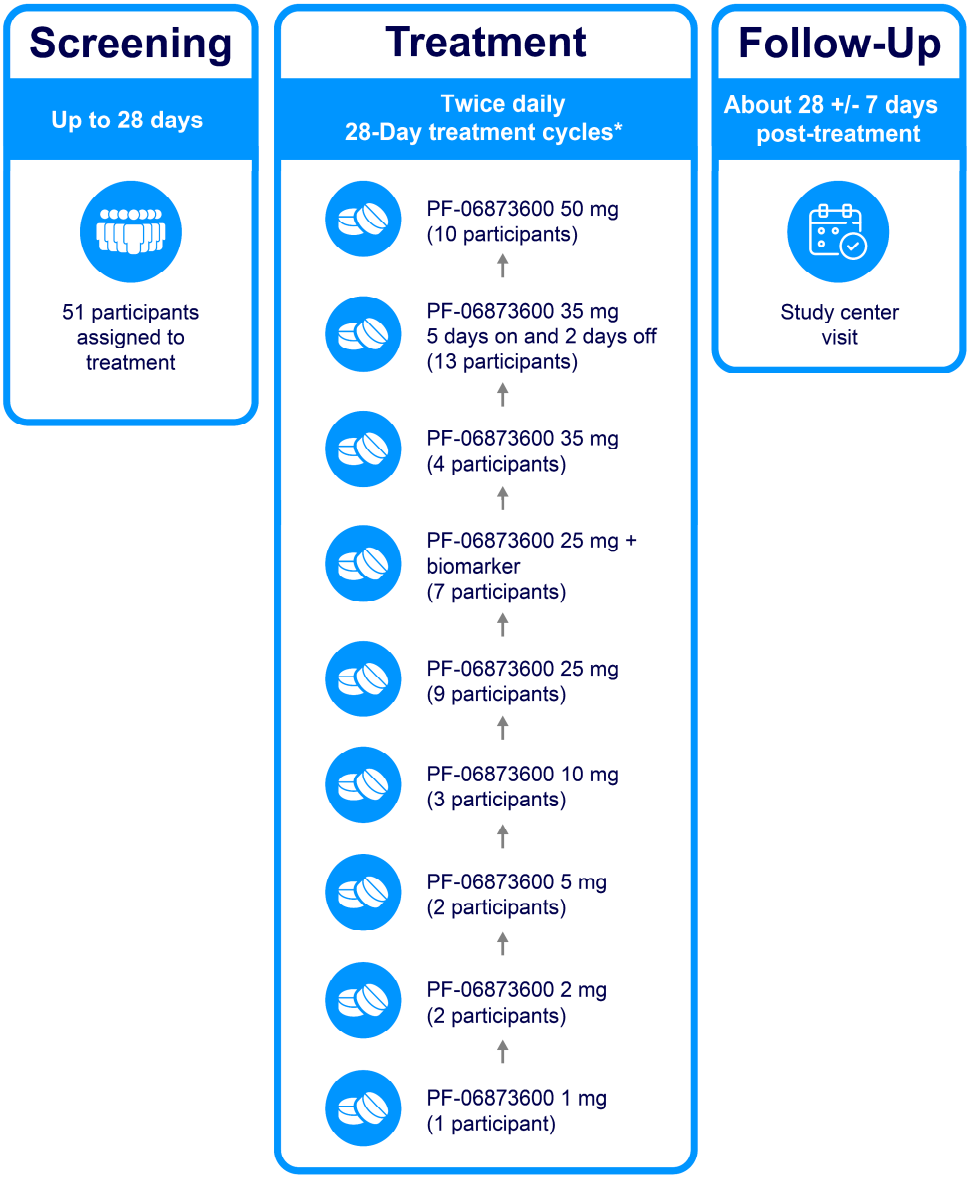
Participants received PF-06873600 twice daily (BID) continuously in each treatment cycle (as shown in Figure 1). The first group of participants were given the lowest dose level; 1 mg of PF-06873600 BID. The safety and tolerability of PF-06873600 was assessed and the dose was increased for

every subsequent group of participants. Each group of participants given a particular dose is called a dosing cohort. The highest dose level tested in Part 1A was 50 mg BID.

A ‘biomarker cohort’ (PF-06873600 25 mg BID) was enrolled to learn how the study medication worked inside the body. A ‘biomarker’ captures what is happening in a cell or an organism at a given moment.

An alternative intermittent dosing schedule was also explored in Part 1A. In each such cycle (as shown in Figure 1), participants took PF-06873600 35 mg BID; 5 days “on” and 2 days “off” for a total of 28 days. This means that participants took the study medication for 5 days (Days 1 to 5) and then took no study medication for the next 2 days (Days 6 to 7).

Figure 1: Study Design for Part 1A



** Treatment continued until participant's cancer got worse, they experienced an unacceptable medical problem, a decision by the researcher or participant to stop the treatment or study termination.*

Part 1C

In Part 1C, researchers studied the safety and effects of 2 modified release (MR) formulations of PF-06873600. MR formulations were designed as short release (6 hour) and long release (12 hour) duration tablet

formulations. They were formulated based on the speed at which the drug releases and acts inside the body. Researchers compared and tested PF-06873600 MR and immediate release (IR) tablet formulations in 2 cohorts:

- Five participants were given 2 single doses of PF-06873600 20 mg MR formulation first for 7 days (lead in period) prior to receiving the IR formulation of PF-06873600 25 mg BID continuously in 28-day treatment cycle. During the initial 7 days participants were first given a single dose PF-06873600 20 mg shorter release tablets followed by a dose of longer release tablets.

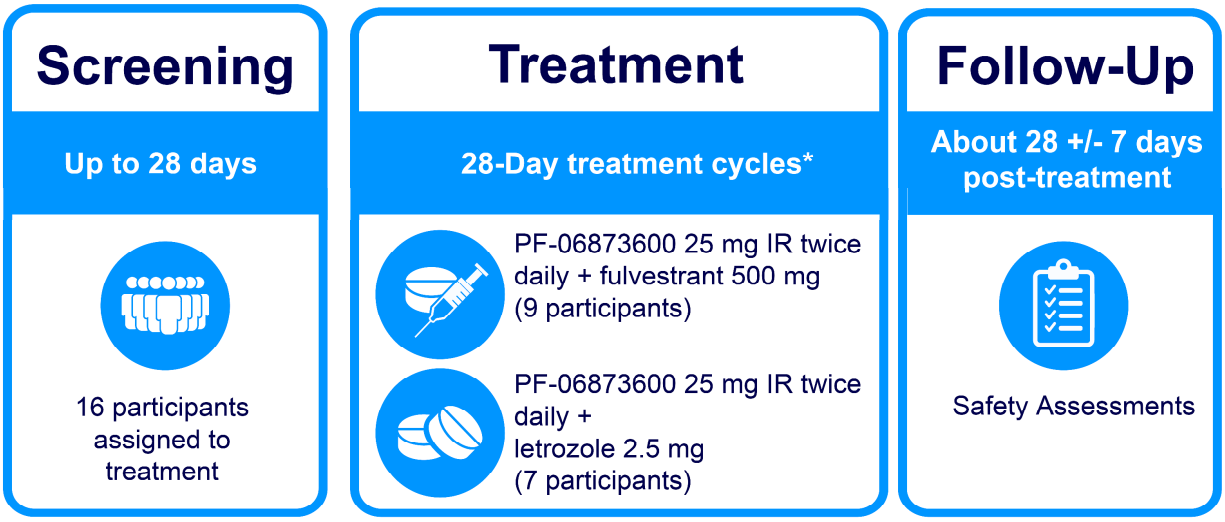
- Six participants were given MR PF-06873600 30 mg long release tablets BID continuously in each treatment cycle.

Part 1B

In Part 1B, researchers assessed the safety of PF-06873600 when given in combination with fulvestrant or letrozole to participants with HR-positive HER2-negative advanced or mBC.

The dose of PF-06873600 in Part 1B was selected based on the results in Parts 1A and 1C. The first group of participants in Part 1B took PF-06873600 25 mg IR tablets BID in combination with fulvestrant 500 mg which was given as 2 injections of 250 mg/5 milliliters each. The second group of participants took PF-06873600 25 mg IR tablets BID in combination with letrozole 2.5 mg once daily. Figure 2 describes the study design for Part 1B.

Figure 2: Study Design for Part 1B



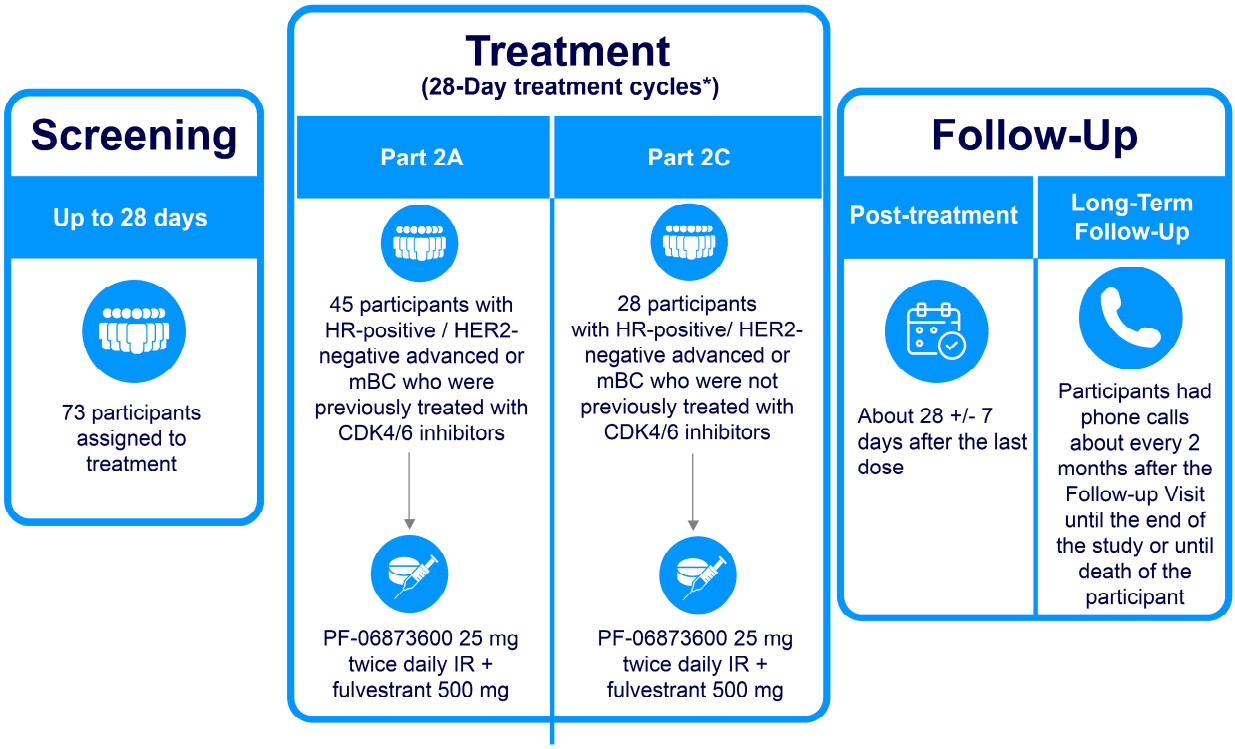
**Treatment continued until participant's cancer got worse, they experienced an unacceptable medical problem, a decision by the researcher or participant to stop the treatment or study termination.*

Part 2

Based on the results of Part 1, researchers tested the effects and safety of PF-06873600 IR tablet formulation in combination with fulvestrant in participants with HR-positive HER2-negative advanced or mBC in Part 2 of the study. As shown in Figure 3, Part 2A included participants previously treated with CDK4/6 inhibitors and Part 2C included participants who were previously not treated with CDK4/6 inhibitors. CDK4/6 inhibitors are agents that act by stopping the action of proteins called Cyclin-Dependent Kinase 4 and 6 (CDK4/6).

Participants received PF-06873600 25 mg IR tablets BID in combination with fulvestrant 500 mg which was given as 2 injections of 250 mg/5 milliliters each.

Figure 3: Study Design for Part 2



**Treatment continued until participant's cancer got worse, they experienced an unacceptable medical problem, a decision by the researcher or participant to stop the treatment or study termination.*

During Part 1 and Part 2, the researchers took samples of blood and urine from the participants. Researchers checked the participants' health and asked them how they were feeling. Researchers also measured the effect of the study treatment on participants' cancer by looking at scans and images of their tumors to evaluate their growth before, during and after treatment.

Where did this study take place?

The Sponsor ran this study at 22 locations in 5 countries in North America, Europe, and Asia.

When did this study take place?

It began on 07 March 2018 and was ongoing at the time when this report was created.

The information collected until 05 April 2023 is reported here.

Who participated in this study?

Participants in Parts 1A and 1C had HR-positive HER2-negative advanced or mBC, TNBC, and ovarian cancer. Parts 1B and 2 included participants who had HR-positive HER2-negative advanced or mBC.

- A total of 153 participants participated in the study, with 151 participants receiving at least one dose of study treatment; 51 participants in Part 1A, 16 participants in Part 1B, 11 participants in Part 1C, 45 participants in Part 2A and 28 participants in Part 2C. All 151 participants treated in the study were female.
- All participants treated in the study were between the ages of 28 and 84 years.

Participants were treated until one of the following occurred:

- Participants' cancer got worse.
- Participants withdrew their consent before the study was over by their own choice.
- A doctor decided it was best for a participant to stop being in the study or the Sponsor terminated the study.
- Participants experienced unacceptable medical problems.
- Participants' overall health deteriorated.

Of the 151 participants who received treatment, most participants (144 participants [95.4%]) stopped the study treatment. Seven participants

(1 participant from Part 2A and 6 participants from Part 2C) were still on treatment at the time when the Sponsor created this report.

The most common reasons for stopping study treatment were because participants' cancer got worse (81 out of 153 [52.9%] participants), they withdrew consent to participate further in the study by their own choice (15 participants [9.8%]), and their overall health deteriorated (12 participants [7.8%]).

Of the 153 total participants enrolled in the study, 80 (52.3%) participants participated in the follow-up phase. Twenty-four out of the 80 (15.7%) participants completed the follow-up phase and 56 participants (36.6%) discontinued the follow-up phase at the time when this report was created. The main reasons for discontinuation were participants withdrew consent to participate further in the study by their own choice (39 participants [25.5%]), lost to follow-up (9 participants [5.9%]), and death (7 participants [4.6%]).

A total of 66 out of 153 (43.1%) participants participated in Long-term Follow-up. Sixty-five participants (42.5%) discontinued, and 1 participant was still in the Long-term Follow-up at the time of this report. The main reasons for discontinuation were study terminated by Sponsor (44 participants [28.8%]), participants withdrew consent to participate further in the study by their own choice (10 participants [6.5%]), death (8 participants [5.2%]), and lost to follow-up (2 participants [1.3%]).

How long did the study last?

The study was initiated (first participant first visit) on 07 March 2018. Participants stayed on the study treatment for a median duration of 112 days (range 1-1093 days). The study was closed (terminated) by the Sponsor in September 2022, and stopped recruiting participants into the study due to a business decision. At the time of this report, some participants were still receiving the study treatment.

In April 2023, when a planned stage of the study was completed, 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?

How safe and well tolerated was PF-06873600?

The researchers assessed the safety and tolerability of PF-06873600 by looking at the medical problems participants had during the study. They also looked at the results of certain tests. Researchers recorded Grade 3, 4 and 5 medical problems reported during the study as defined below:

- Grade 3 medical problems are considered as the events to be severe or medically significant by the study doctors.
- Grade 4 medical problems are those considered as 'life-threatening' (could harm their health) and require urgent intervention by the study doctors.
- Grade 5 medical problems are those that result in death.

Medical problems throughout the whole of the study are discussed in full in the next section of this document.

Part 1: Did participants taking PF-06873600 have any DLTs (alone or together with fulvestrant or letrozole)?

In Part 1, 64 out of 78 participants who received PF-06873600 alone or together with fulvestrant or letrozole were assessed for DLTs during their first treatment cycle (Cycle 1). Of the 64 evaluated participants, 6 (9.4%) participants experienced DLTs in Part 1A of the study.

Two participants in PF-06873600 35 mg BID cohort experienced DLTs:

- One participant had Grade 4 neutrophil count decreased (low white blood cell [WBC] count).
- Another participant had Grade 4 neutrophil count decreased and Grade 4 platelet count decreased (thrombocytopenia).

Four participants in PF-06873600 50 mg BID cohort experienced DLTs:

- One participant each had Grade 4 febrile neutropenia (low WBC count [neutrophil] with fever) and Grade 3 fatigue (tiredness).
- One participant had Grade 4 febrile neutropenia, Grade 4 thrombocytopenia, Grade 5 cardiac arrest, and Grade 4 multiple organ dysfunction syndrome (2 or more organs in the body stop working properly).
- One participant had Grade 3 febrile neutropenia and Grade 3 colitis (inflammation in the large intestine).

No participants in Parts 1B and 1C who received PF-06873600 alone or together with fulvestrant or letrozole, experienced any DLTs during Cycle 1 of treatment.

Did participants in the study have any Grade 3, 4 or 5 medical problems due to the study treatment?

A total of 39 out of 151 (25.8%) participants who received PF-06873600 alone or together with fulvestrant or letrozole had Grade 3 medical problems considered related to the study treatment in the study (Parts 1 and 2). The most common Grade 3 medical problems were anemia (low red blood cell count), neutropenia (low WBC count [neutrophil]) reported

in 20 participants (13.2%) each, and fatigue reported in 12 participants (7.9%).

- A total of 15 out of 151 (9.9%) participants had Grade 4 medical problems considered related to the study treatment. The Grade 4 medical problems reported were:
    - Neutropenia (11 participants [7.3%]), thrombocytopenia (4 participants [2.6%]), leukopenia (low WBC count [leukocyte]), febrile neutropenia and low levels of phosphates in the blood (in 2 participants [1.3%] each), anemia, colitis, stroke (blood supply to a part of the brain is cut off), and multiple organ dysfunction syndrome (in 1 participant [0.7%] each).
- A total of 2 out 151 (1.3%) participants had Grade 5 medical problems considered related to the study treatment. One participant (0.7%) each had cardiac arrest (in Part 1A) and bacterial infection in the digestive tract (in Part 2C).

What were the results of blood pressure and heart rate tests during the study?

- There were 150 participants evaluated for blood pressure and heart rate tests during the study. Of these, 9 participants had decreased top blood pressure reading (systolic blood pressure) and 7 participants had decreased bottom blood pressure reading (diastolic blood pressure).
- One of the 150 participants was reported to have a lower heart rate and 6 participants were reported to have rapid heart rates.

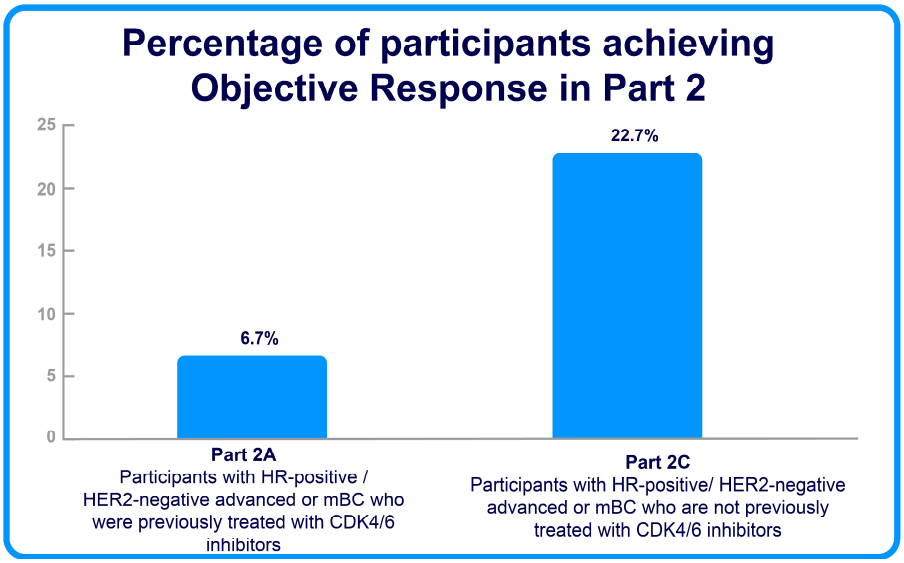
Part 2: Did participants taking PF-06873600 along with fulvestrant have positive effects on their cancer?

To answer this question, the researchers measured the “objective response rate” (ORR), which is the percentage of participants whose cancer got better (their tumor shrank or disappeared on images). Researchers measured the percentage of participants whose tumor decreased/shrank under therapy (called as ‘partial response’ [PR]) and/or disappeared (called as ‘complete response’ [CR]) after treatment.

In Part 2, a total of 67 participants were evaluated for ORR, 45 participants in Part 2A and 22 participants in Part 2C. The ORR was 6.7% (3 out of 45 participants) in Part 2A and 22.7% (5 out of 22 participants) in Part 2C (as shown in Figure 4).

No participants recorded CR; and 6.7% (3 out of 45 participants) in Part 2A and 22.7% (5 out of 22 participants) in Part 2C had their tumor shrink by 30% or more that qualified for PR.

Figure 4: Percentage of Participants Whose Cancer Got Better



This does not mean that everyone taking this drug had similar results. This is a summary 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 147 out of 151 (97.4%) participants who received PF-06873600 alone or together with fulvestrant or letrozole in this study (both in Part 1 and Part 2) had at least 1 medical problem. The most common medical problems – those reported by more than 10% of participants in the whole study – 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 more than 10% of participants of total participants in the study are listed.

- The **2nd** column tells how many of the 151 participants taking the study medication or the combination treatment reported each medical problem. Next to this number is the percentage of the 151 participants taking the study medication or the combination treatment who reported the medical problem.
- Using these instructions, you can see, for example, that 67 out of the 151 (44.4%) participants taking the study medication or the combination treatment reported anemia.

Table 1. Commonly reported medical problems reported by more than 10% of study participants in Part 1 and Part 2

Medical Problem	Parts 1A and 1C - PF-06873600 Part 1B - PF-06873600 + fulvestrant/letrozole Part 2 - PF-06873600 + fulvestrant (151 Participants)
Anemia	67 out of 151 participants (44.4%)
Abdominal pain	21 out of 151 participants (13.9%)
Constipation	38 out of 151 participants (25.2%)
Diarrhea	34 out of 151 participants (22.5%)
Nausea	95 out of 151 participants (62.9%)
Vomiting	54 out of 151 participants (35.8%)

Table 1. Commonly reported medical problems reported by more than 10% of study participants in Part 1 and Part 2	
Medical Problem	**Parts 1A and 1C - PF-06873600 Part 1B - PF-06873600 + fulvestrant/letrozole Part 2 - PF-06873600 + fulvestrant (151 Participants)**
Fatigue	66 out of 151 participants (43.7%)
Liver test levels (aspartate aminotransferase) increased	17 out of 151 participants (11.3%)
Low white blood cell count (leukocyte)	31 out of 151 participants (20.5%)
Low white blood cell count (neutrophil)	47 out of 151 participants (31.1%)
Platelet count decreased	24 out of 151 participants (15.9%)
Decreased appetite	19 out of 151 participants (12.6%)
Pain in a joint	23 out of 151 participants (15.2%)
Dizziness	22 out of 151 participants (14.6%)
Headache	44 out of 151 participants (29.1%)

Table 1. Commonly reported medical problems reported by more than 10% of study participants in Part 1 and Part 2	
Medical Problem	**Parts 1A and 1C - PF-06873600 Part 1B - PF-06873600 + fulvestrant/letrozole Part 2 - PF-06873600 + fulvestrant (151 Participants)**
Cough	16 out of 151 participants (10.6%)
Shortness of breath	16 out of 151 participants (10.6%)
Hair loss	43 out of 151 participants (28.5%)

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 34 out of 151 (22.5%) participants who received PF-06873600 alone or together with fulvestrant or letrozole had serious medical problems in the study (both in Part 1 and Part 2). The most common serious medical problems reported in more than 2 participants include:

- Febrile neutropenia (5 participants [3.3%]),
- Abdominal pain, colitis, and low blood pressure (in 3 participants [2.0%] each).

A total of 13 out of 151 (8.6%) participants in the study had serious medical problems which were considered related to the study treatment. Of these 13 participants, 3 participants were from Part 1A, 2 participants each were from Parts 1B and 2C, 1 participant was from Part 1C, and 5 participants were from Part 2A. The most common serious medical problems related to study treatment reported in more than 1 participant were:

- Febrile neutropenia (5 participants [3.3%]),
- Anemia, neutropenia, colitis, and mouth pain and sores (in 2 participants [1.3%] each).

A total of 19 participants died while being enrolled in the study. Of the 19 participants who died, 5 participants were from Part 1A, 1 participant from Part 1B, 3 participants from Part 1C, 6 participants from Part 2A and 4 participants were from Part 2C. Ten out of 19 participants died because their cancer got worse, and 7 participants cause of death was unknown.

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 C3661001

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

www.clinicaltrials.gov	Use the study identifier **NCT03519178**
www.clinicaltrialsregister.eu	Use the study identifier 2020-001757-40

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!