CLINICAL TRIAL 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 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: Lorlatinib (PF-06463922)

Protocol Number: B7461001

Dates of Trial: 08 January 2014 to present

Title of this Trial: Phase 1/2 Study of PF-06463922 (an ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations

Date of this Report: 9 November 2018

– Thank You –

Pfizer, the Sponsor, would like to thank you for your participation in this clinical trial and provide you a summary of results representing everyone who participated.
If you have any questions about the study or results please contact the doctor or staff at your study site.

WHY WAS THIS STUDY DONE?

Lung cancer is the name for cancer that starts in the lungs. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Some patients have NSCLC that is referred to as "ALK-positive" or "ROS1-positive". These patients have changes in their genes that can cause cancer cells to grow.

The Sponsor is developing an investigational medicine called lorlatinib to treat ALK-positive and ROS1-positive lung cancers. There are certain proteins called "kinases" that help cancer cells to grow. As they grow, the cancer cells can form into a tumor and spread to other parts of the body, such as the brain. Lorlatinib may be able to block kinases, potentially reducing tumor size and stopping ALK-positive and ROS1-positive lung cancers from being able to grow and spread. Lorlatinib is known as an "ALK-inhibitor" medication.

This was the first study to test lorlatinib in humans. At the time this study began, lorlatinib was not approved for use outside of research studies. Since that time, lorlatinib has been approved in the United States for certain patients.

The researchers wanted to learn more about the effects of lorlatinib, and to find the correct dose for treating ALK-positive and ROS1-positive lung cancer patients. This study was divided into 2 parts: phase 1 and phase 2.

The purpose of the study was to answer the following questions:

- **For phase 1, what "dose-limiting toxicities" did patients have at each dose during their first treatment cycle?**
  "Dose-limiting toxicities" (DLTs) are certain medical problems caused by taking lorlatinib which require the patient to lower the dose or stop taking the medicine (permanently or temporarily). DLTs can be many things, and may include, for example, fever with a low count of white blood cells or swelling in the pancreas.

- **For phase 2, how many patients would have a reduction in tumor size after taking lorlatinib?**

WHAT HAPPENED DURING THE STUDY?

A total of 54 patients with ALK-positive or ROS1-positive NSCLC joined phase 1 of the study. 32 patients (59%) were women and 22 patients (41%) were men.

For phase 1, researchers wanted to find the right dose for treating NSCLC. Patients entered the study in small groups of 3 to 17 patients. Each group was given a different dose of lorlatinib, and the patients were watched closely for any medical problems. The doses for each group ranged from 10 mg to 200 mg lorlatinib given either once a day or twice a day. Patients took lorlatinib in "cycles" that lasted 21 days.

There was no specific amount of time that patients were required to stay in phase 1 of the study. Of the 54 patients who started the study, 19 patients were still in the study as of March 2017. 35 patients left the study by their own choice, because of a medical problem, or because a doctor decided it was best for a patient to stop the study.

After researchers decided on the correct dose of lorlatinib (100 mg once a day), they started phase 2 of the study. A total of 275 patients joined phase 2. 157 patients (57%) were women and 118 patients (43%) were men. All patients were between the ages of 19 and 85 years old.

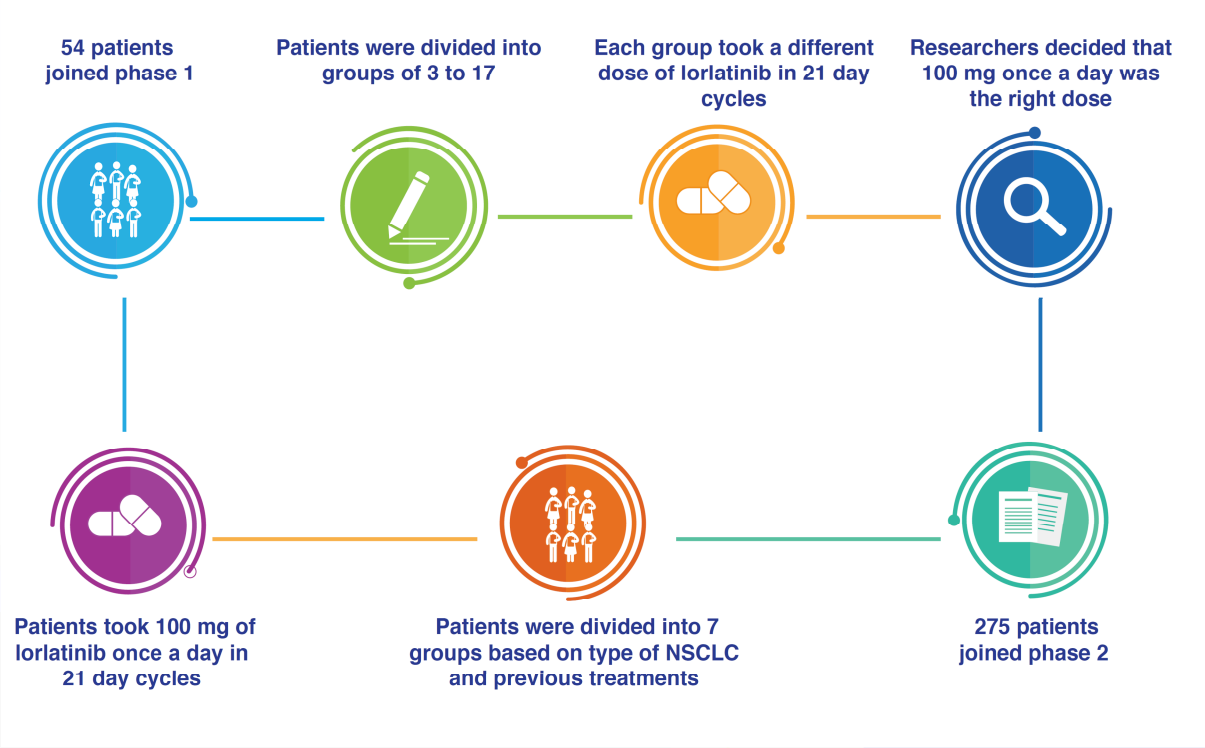
For phase 2, patients were placed in groups based on what type of NSCLC they had and what treatments they'd already tried. Some of the patients in this study had already taken chemotherapy, an ALK-inhibitor medicine called crizotinib, or other ALK-inhibitor medicines. Patients were assigned to the following treatment groups:

- Group 1: Patients with ALK-positive cancer and no previous treatments.
- Group 2: Patients with ALK-positive cancer who got worse despite taking crizotinib.
- Group 3: Patients with ALK-positive cancer who got worse despite taking crizotinib and chemotherapy.
- Group 4: Patients with ALK-positive cancer who got worse despite taking 1 prior ALK-inhibitor medication different from crizotinib. These patients may also have had chemotherapy.

- Group 5: Patients with ALK-positive cancer who got worse despite taking 2 prior ALK-inhibitor medications. These patients may also have had chemotherapy.
- Group 6: Patients with ALK-positive cancer who got worse despite taking 3 prior ALK-inhibitor medications. These patients may also have had chemotherapy.
- Group 7: Patients with ROS1-positive cancer. These patients may or may not have had previous treatments.

During phase 2, all patients took 100 mg of lorlatinib once each day. They took lorlatinib in treatment cycles of 21 days. Patients were watched closely for any medical problems and to see how lorlatinib was working.

There was no specific amount of time that patients were required to stay in phase 2 of the study. Of the 275 patients who started this phase of the study, 157 patients were still in the study as of March 2017. 118 patients left the study by their own choice, because of a medical problem, or because a doctor decided it was best for a patient to stop the study.



Patients joined the study at 1 of 47 centers in Asia, Australia, Europe, and North America. The study began in January 2014, and was still ongoing as of November 2018. This report is a summary of the study results up to March 2017.

WHAT WERE THE RESULTS OF THE STUDY?

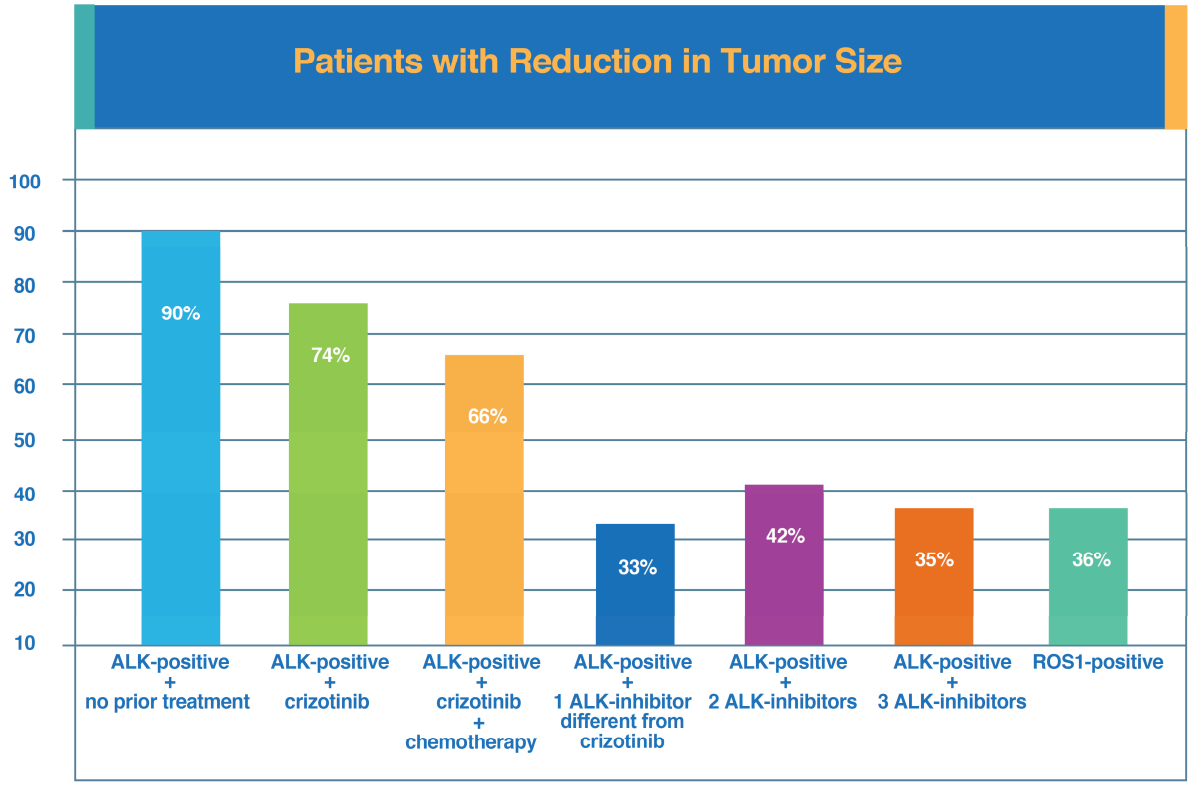
For phase 1, what "dose-limiting toxicities" did patients have at each dose during their first treatment cycle?

During phase 1, researchers wanted to find the correct dose of lorlatinib for treating patients with NSCLC. To find the correct dose, the researchers needed to know how many patients in each dose group had a DLT during their first 21-day treatment cycle, and what the DLTs were.

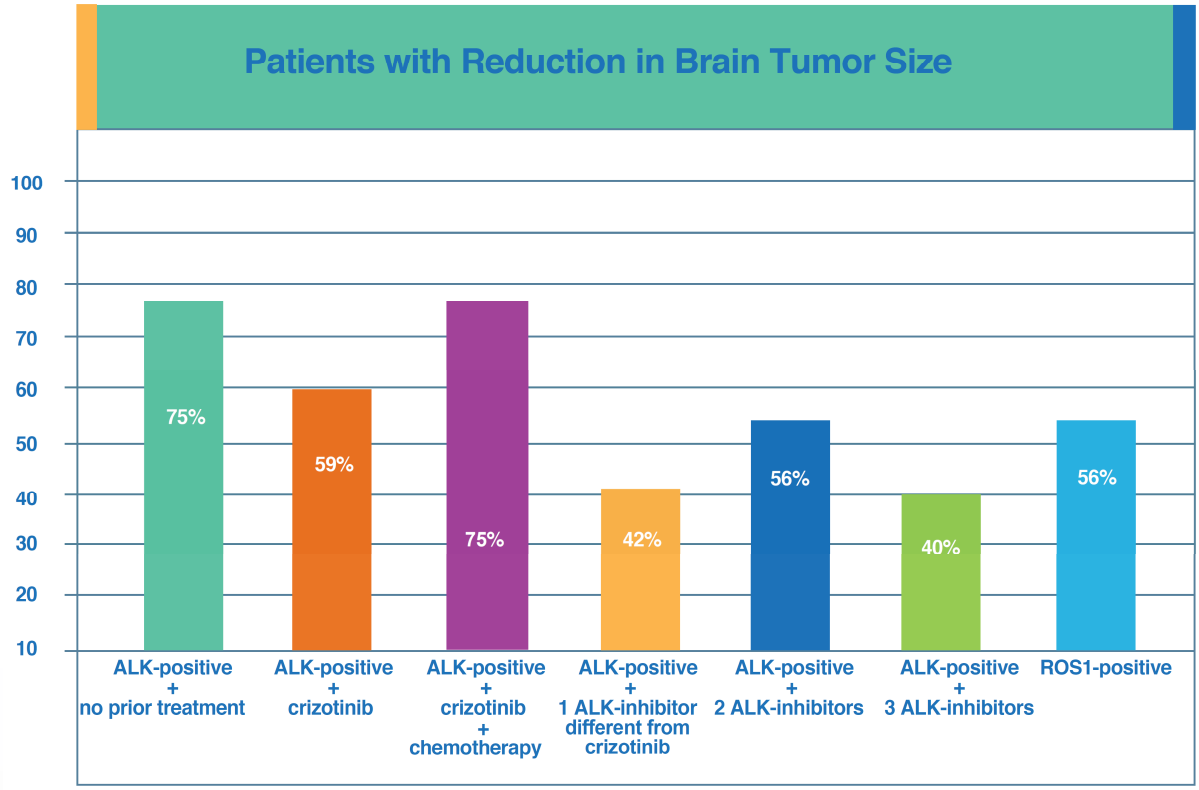
There was 1 patient who had a DLT. This patient took 200 mg of lorlatinib once a day. However, most of the patients who took either 150 mg or 200 mg of lorlatinib once a day had other medical problems that caused them to temporarily stop or lower their dose of lorlatinib. Using this information, the researchers decided that 100 mg once a day was the correct lorlatinib dose for treating patients with NSCLC.

For phase 2, how many patients had a reduction in tumor size after taking lorlatinib?

For phase 2, there were patients in each treatment group who showed a reduction in tumor size after taking lorlatinib. The average results were different for each treatment group, with 33% to 90% of patients in the treatment groups showing a reduction in tumor size. The chart on the following page shows the results for each treatment group.



The researchers also wanted to know if lorlatinib would help patients with NSCLC that had spread to the brain. There were patients in each treatment group who showed a reduction in brain tumor size after taking lorlatinib. The average results were different for each treatment group, with 40% to 75% of patients in the treatment groups showing a reduction in brain tumor size. The chart on the following page shows the results for each treatment group.



This does not mean that everyone in this study had these results. Other studies may produce different results, as well. These are just some of the main findings of the study, and more information may be available at the websites listed at the end of this summary.

WHAT MEDICAL PROBLEMS DID PATIENTS 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 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 the side effects of an experimental drug might be.

During phase 1 of the study, all 54 patients (100%) had at least 1 non-serious medical problem (that means a medical problem that is not life-threatening, does not cause

lasting problems, or does not need hospital care). A total of 5 patients (9%) in phase 1 left the study due to medical problems. The most common non-serious medical problems reported during phase 1 are listed below.

Most Common Non-Serious Medical Problems During Phase 1 (Reported by More Than 5% of Patients)

Medical Problem	Lorlatinib (54 Patients treated)
Swelling/fluid retention	40 (74%)
High cholesterol	31 (57%)
Nerve damage	24 (44%)
Low number of red blood cells	17 (31%)
Feeling tired	17 (31%)
High level of a type of fat in the blood	17 (31%)
Respiratory tract infection	16 (30%)
Back pain	14 (26%)
Diarrhea	13 (24%)
Constipation	11 (20%)
Trouble breathing	11 (20%)
Headache	11 (20%)
Pain in joint	11 (20%)
Nausea	10 (19%)
Feeling weak	10 (19%)
Ringing in ears	9 (17%)
Vomiting	9 (17%)
Cough	9 (17%)
Cognitive disorder	8 (15%)

Upper abdominal pain	6 (11%)
Trouble walking	6 (11%)
Swelling of the airways (bronchitis)	6 (11%)
Low potassium in blood	6 (11%)
Low magnesium in blood	6 (11%)
Rash	6 (11%)
Slowed speech	6 (11%)
Numbness	6 (11%)
Dizziness	6 (11%)
Urinary tract infection	6 (11%)
Low number of platelets in blood	5 (9%)
Stomach pain	5 (9%)
Fever	5 (9%)
Low phosphate in blood	5 (9%)
High blood pressure	5 (9%)
Changes in facial expression	5 (9%)
Trouble with speech	5 (9%)
Memory problems	5 (9%)
Blurry vision	4 (7%)
Trouble seeing	4 (7%)
Feeling confused	4 (7%)
Feeling anxious	4 (7%)
Trouble with speech caused by muscle problems	4 (7%)
Pain in arms or legs	4 (7%)
Pain in muscles or bones	4 (7%)
Not seeing well	3 (6%)

Acid reflux	**3 (6%)**
Dry skin	**3 (6%)**
Hair loss	**3 (6%)**
Nose bleed	**3 (6%)**
Unable to control bladder	**3 (6%)**
Feeling irritable	**3 (6%)**
Changes to sense of taste	**3 (6%)**
Trouble paying attention	**3 (6%)**
Neck pain	**3 (6%)**
Pain in muscles	**3 (6%)**
Muscle weakness	**3 (6%)**

During phase 2 of the study, 273 out of 275 patients (99%) had at least 1 non-serious medical problem. A total of 20 patients (7%) in phase 2 left the study due to medical problems. The most common non-serious medical problems reported during phase 2 are listed below.

Most Common Non-Serious Medical Problems During Phase 2 (Reported by More Than 5% of Patients)	
Medical Problem	**Lorlatinib 100 mg (275 Patients treated)**
Swelling/fluid retention	**159 (58%)**
High level of a type of fat in the blood	**155 (56%)**
High cholesterol	**145 (53%)**
Nerve damage	**90 (11%)**
Trouble breathing	**60 (22%)**
Joint pain	**54 (20%)**
Diarrhea	**49 (18%)**

Cough	47 (17%)
Dizziness	42 (15%)
Headache	42 (15%)
Constipation	39 (14%)
Nausea	39 (14%)
Feeling tired	37 (13%)
Arm or leg pain	32 (12%)
Low number of red blood cells	31 (11%)
Back pain	27 (10%)
Muscle pain	27 (10%)
Weakness	26 (9%)
Vomiting	24 (9%)
Being forgetful	24 (9%)
Rash	23 (8%)
Trouble sleeping	22 (8%)
Fever	21 (8%)
High blood sugar	20 (7%)
High blood pressure	20 (7%)
Respiratory tract infection	19 (7%)
Ringing in ears	19 (7%)
Trouble with thinking, remembering, or solving problems	18 (7%)
Chest pain	16 (6%)
Low level of a type of protein in the blood	16 (6%)
Muscle and joint pain	16 (6%)
Memory loss	16 (6%)
Feeling irritable	16 (6%)

Bloating	**15 (5%)**
Low level of potassium in the blood	**15 (5%)**
Muscle weakness	**15 (5%)**
Feeling anxious	**15 (5%)**
Trouble breathing during exercise	**15 (5%)**
Low appetite	**14 (5%)**

WERE THERE ANY SERIOUS MEDICAL PROBLEMS?

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

During phase 1, 28 out of 54 patients (52%) had at least 1 serious medical problem. During phase 2, 89 out of 275 patients (32%) had at least 1 serious medical problem.

As of March 2017, for phase 1, a total of 27 out of 54 patients (50%) died during the study or the follow-up period. For phase 2, a total of 64 out of 275 patients (23%) died during the study or the follow-up period. The study doctors determined that none of these deaths (0%) were related to taking lorlatinib.

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 this study protocol, please visit:

www.clinicaltrials.gov Use the study identifier **NCT01970865**

www.clinicaltrialsregister.eu Use the study identifier **2013-002620-17**

Please remember that researchers look at the results of many studies to find out which medicines work best and are safest for patients. This study is still ongoing as of November 2018.

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