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:	Crizotinib (PF-02341066)
Protocol Number:	A8081013
Dates of Study:	22 March 2011 to 07 September 2023
Title of this Study:	Study to Learn About the Safety and Effectiveness of Crizotinib in Participants With Tumors, Except Non-Small Cell Lung Cancer, That Are Positive for Anaplastic Lymphoma Kinase (ALK). [Phase 1b Open-Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors With Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus]
Date(s) of this Report:	01 March 2024

– Thank You –

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

This summary will describe the study results. If you or your child 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 tumor with defect in anaplastic lymphoma kinase (ALK) gene?

The ALK gene provides instructions for making a protein called ALK receptor tyrosine kinase, which is part of a family of proteins called receptor tyrosine kinases (RTKs). When there are alterations to the ALK gene, it can lead to cancer growth and this type of cancer is called ALK-positive cancer. As they grow, the cancer cells can form into a tumor and spread to other parts of the body. When the cancer spread to other parts of the body it is called an advanced cancer.

What is Crizotinib?

Xalkori® (crizotinib [kriz-oh-tee-nib]) is an anti-cancer medication used to treat ALK-positive lung cancers. It is approved in the United States (US), Europe, and countries in East Asia including South Korea, Taiwan, Japan, and China, for the treatment of locally advanced (cancer has not spread to distant regions of the body but has spread to nearby organs) or metastatic (cancer has spread outside lungs) non-small cell lung cancer (NSCLC) that are ALK-positive. Crizotinib may be able to block receptor tyrosine kinases, potentially reducing tumor size and stopping ALK-positive lung cancers from being able to grow and spread. Therefore, crizotinib is known as an "ALK-inhibitor" medication. Crizotinib was given in capsule form and was taken by mouth.

Participants with advanced anaplastic large cell lymphoma (ALCL) and other advanced tumors (excluding NSCLC) for which no standard therapy is available were eligible to participate in this study if they were positive for tumor with a specific type of genetic makeup (ALK genetic event) by local ALK testing.

What was the purpose of this study?

The purpose of this study was to assess the safety of crizotinib in participants with advanced ALK-positive ALCL or other advanced tumors other than NSCLC known to have an ALK genetic event. The researchers monitored the participants for any medical problems that happened while they were taking crizotinib and after they stopped taking crizotinib.

The researchers also wanted to know if any of the participants' cancer shrank in size during the study. To do this, they measured "Objective Response Rate". This is the percentage of participants whose cancer disappeared or got smaller during treatment.

Researchers wanted to know:

- **How safe was the treatment with crizotinib in participants with tumors involving ALK genetic event (excluding NSCLC) and what medical problems did participants have during the study?**
- **How well did crizotinib treatment work to keep tumors involving ALK genetic event (excluding NSCLC) from growing or to make them shrink in size?**

What happened during the study?

How was the study done?

This was an "open-label" study. This means researchers and participants knew what study medication each participant was receiving.

Researchers tested crizotinib on groups of study participants to find out about medical problems. Only participants who were at least 15 years of

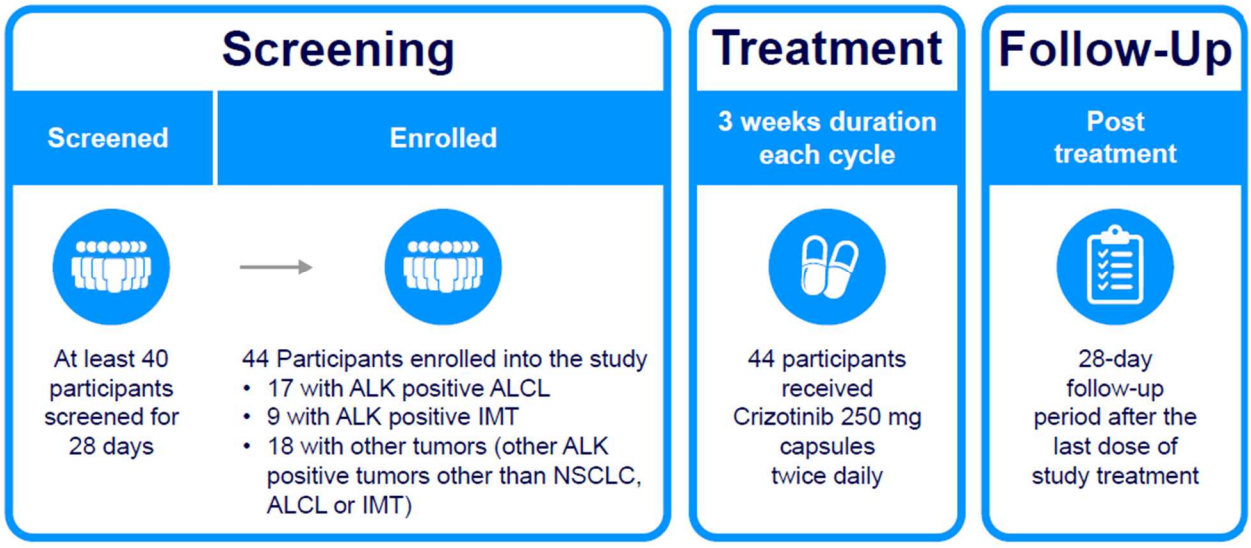
age and with ALK genetic event confirmed by genetic testing at the study site, could enter the study.

Overall, the study consisted of an initial consultation (Screening Visit), treatment period and follow-up period. The figure below shows what happened during this study (Figure 1).

All participants were “screened” to see if they qualified to be in the study. Participants who qualified for treatment after screening entered the treatment period. Treatment administration was broken up into cycles with each cycle consisting of 21 days.

Participants were to take crizotinib 250 mg twice daily every 12 hours for 21 days in each cycle. Crizotinib was given as capsules and was taken by mouth twice daily at around the same time every morning and every evening. Crizotinib dose was reduced to 200 mg twice daily or 250 mg once daily if the participants had any medical problems. Participants were to be treated until their cancer stopped responding or got worse or they were unable to follow the study-required visits or procedures at study site or until they developed unacceptable medical problems or got pregnant (for women). Participants that were doing well on crizotinib when study ended were given the option to continue with crizotinib treatment in another study. This is often described as a rollover study.

Figure 1: Study Design



ALCL = Anaplastic Large Cell Lymphoma; ALK = Anaplastic Lymphoma Kinase; IMT = Inflammatory Myofibroblastic Tumor; NSCLC = Non-Small Cell Lung Cancer

Researchers took samples of blood and urine from participants during the study to find out about the disease status. Researchers also checked the participants' health during the study and asked them how they were feeling.

Where did this study take place?

The Sponsor ran this study at 16 locations in 7 countries in Asia, European Union (EU), and US.

When did this study take place?

It began on 22 March 2011 and ended on 07 September 2023.

Who participated in this study?

The study included 44 participants who were at least 15 years of age and were diagnosed with ALK-positive tumor other than NSCLC:

- 17 with ALCL,
- 9 with inflammatory myofibroblastic tumor (IMT), and
- 18 with other tumors (other than NSCLC, ALCL or IMT; eg, tumor of nerve tissue in children (neuroblastoma).

Among the 44 participants, 5 were adolescents (at least 15 to less than 18 years of age).

- A total of 22 men and 3 boys participated.
- A total of 17 women and 2 girls participated.
- All participants were between 15 and 73 years of age.

End of treatment: Of the 44 participants who started treatment in this study, 22 (50.0%) participants discontinued treatment because their cancer worsened, 13 (29.5%) participants stopped treatment in this study due to other issues, 2 (4.5%) participants experienced unacceptable medical problems, 2 (4.5%) participants passed away, 2 (4.5%) participants refused to continue treatment, 1 (2.3%) participant discontinued treatment due to poor health condition, and 2 (4.5%) participants discontinued treatment because a doctor decided it was best for the participant to stop treatment. One (1) of the 5 adolescent participants left the study due to poor health conditions. For the 13 participants who discontinued treatment in this study due to other issues, 11 continued to receive crizotinib treatment in the rollover study (including 4 adolescent participants), and 1 participant switched to commercial crizotinib.

How long did the study last?

Study participants were in the study for varied amount of time and could remain in the study for as long as they were benefiting from the treatment as decided by the investigator. The entire study took approximately 12 years and 6 months to complete.

Researchers reported the initial results of this study in September 2019 when the primary objective was met. This was called the 'interim analysis'. The researchers then reported the final results of this study in September 2023. This is a summary of those reports.

What were the results of the study?

How many participants with tumors involving ALK genetic event (excluding NSCLC) had medical problems that were serious or severe during treatment with crizotinib?

Researchers looked at the medical problems that participants had during the study treatment. Researchers also looked at results of laboratory tests to see if there were any abnormal results of concern. This helped researchers decide if each dose was safe and well tolerated.

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

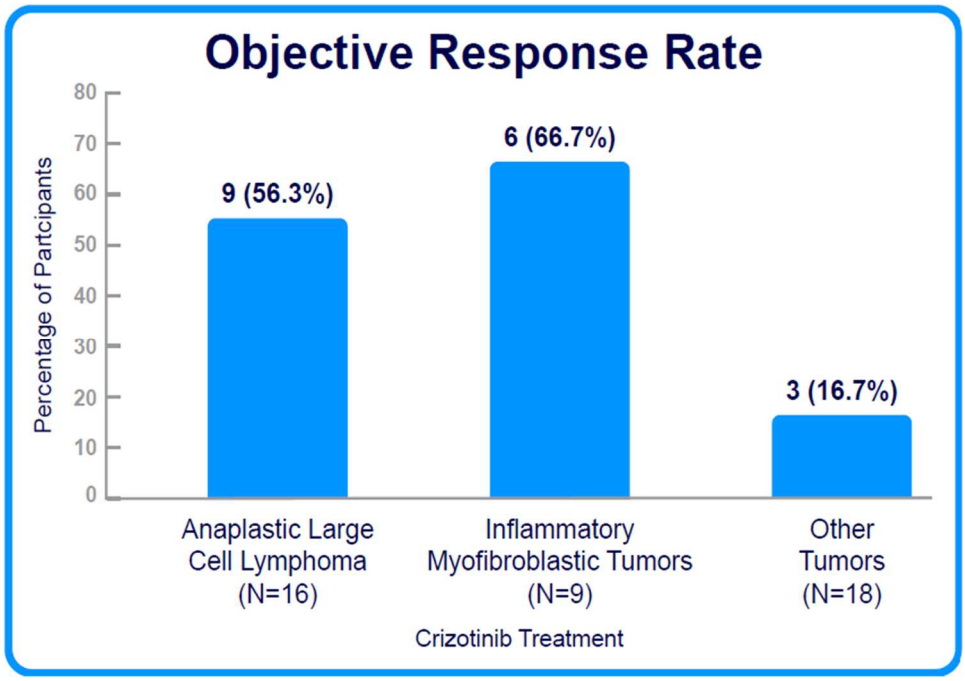
What percentage of participants in the study had their tumors involving ALK genetic event (excluding NSCLC) get better when taking crizotinib?

- 8 out of 16 participants (50.0%) in the ALCL group had a 'Complete Response' (CR), which means that their tumor completely disappeared. 1 out of 16 participants (6.3%) in the ALCL group

achieved a ‘Partial Response’ (PR), which means that their tumor got smaller, but did not disappear. 1 out of 3 adolescent participants had a CR and 1 out of 3 adolescent participants had a PR.

- 1 out of 9 participants (11.1%) in the IMT group had a CR. 5 out of 9 participants (55.6%) in the IMT group achieved a PR. 1 out of 2 adolescent participants had a PR.
- 3 out of 18 participants (16.7%) in the other tumors group had a PR.
- Therefore, 9 out of 16 participants (56.3%) with ALCL, 6 out of 9 participants (66.7%) with IMT, and 3 out of 18 participants (16.7%) with other tumors met the criteria of objective response (CR + PR) which is the percentage of participants whose cancer got better (their tumor shrank or disappeared) during treatment with crizotinib (Figure 2).

Figure 2: Objective Response Rate



Based on these results, the researchers have decided that crizotinib treatment may offer a new standard of care for study participants who had tumors involving ALK genetic event (excluding NSCLC).

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.

Overall, 43 out of 44 (97.7%) participants in this study had at least 1 medical problem. A total of 24 (54.5%) participants stopped the drug temporarily because of medical problems. All the 5 (100.0%) adolescent participants included in this study had at least 1 medical problem. 4 out 5 (80.0%) adolescent participants stopped the drug temporarily because of medical problems. The most common medical problems – those reported by more than 20% of participants – 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 20% of participants are listed.
- The **2nd** column tells how many of the 44 participants taking the study medication reported each medical problem. Next to this number is the percentage of the 44 participants taking the study medication who reported the medical problem.
- Using these instructions, you can see that 22 out of the 44 (50.0%) participants taking the study medication reported eyesight problem (vision disorder).

Table 1. Commonly reported medical problems by study participants	
Medical Problem	**Number of Participants (44 Participants)**
Vision disorder	22 out of 44 participants (50.0%)
Sign of liver damage (elevated transaminases)	21 out of 44 participants (47.7%)
Loose stools (diarrhea)	20 out of 44 participants (45.5%)
Nausea	19 out of 44 participants (43.2%)
Vomiting	19 out of 44 participants (43.2%)
Abdominal pain	15 out of 44 participants (34.1%)
Swelling in body parts due to fluid	15 out of 44 participants (34.1%)

accumulation (oedema)	
Low levels of white blood cells (neutropenia)	14 out of 44 participants (31.8%)
Fever (pyrexia)	13 out of 44 participants (29.5%)
Cough	12 out of 44 participants (27.3%)
Nose and throat infection (upper respiratory infection)	12 out of 44 participants (27.3%)
Low levels of red blood cells in blood (anaemia)	11 out of 44 participants (25.0%)
Decreased appetite or not feeling hungry	10 out of 44 participants (22.7%)
Feeling tired (fatigue)	10 out of 44 participants (22.7%)
Low levels of white blood cells in blood (leukopenia)	10 out of 44 participants (22.7%)

Physical weakness (asthenia)	9 out of 44 participants (20.5%)
Constipation	9 out of 44 participants (20.5%)
Shortness of breath (dyspnoea)	9 out of 44 participants (20.5%)
Headache	9 out of 44 participants (20.5%)

All 5 (100.0%) adolescent participants experienced nausea.
Four (4 [80.0%]) adolescent participants experienced diarrhea, low levels of white blood cells in blood (leukopenia), nose and throat infection (upper respiratory infection), and vomiting.

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.

Overall, 19 out of 44 participants (43.2%) had serious medical problems. Of these, researchers believed 10 (22.7%) participants had serious medical problems that were related to the study treatment.

- The most common serious medical problems were muscle protein increased in the blood (blood creatine phosphokinase increased) in 4 (9.1%) participants, disease worsening in 3 (6.8%) participants, and respiratory failure in 2 (4.5%) participants.
- The serious medical problems related to the study medication were muscle protein increased in the blood in 4 (9.1%) participants, heart

failure (cardiac failure), stroke (cerebral infarction), blood clots in the veins (deep vein thrombosis), diarrhea, damaged lung tissue (interstitial lung disease), reduced blood flow to the heart (myocardial ischemia), nausea, and vomiting in 1 (2.3%) participant each.

Three (3 [60.0%]) adolescent participants had serious medical problems. Common serious medical problem of muscle protein increased in the blood, diarrhea, nausea, and vomiting were reported in 1 (20.0%) participant each; all of which were considered to be related to study medication.

A total of 6 participants (2 in the ALCL group and 4 in the other tumors group) died within 28 days after taking the last dose of crizotinib, and 15 participants died more than 28 days after taking the last dose of crizotinib. Most of the participants passed away due to disease under study. None of the adolescent participants died during the study.

Where can I learn more about this study?

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

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number A8081013

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

www.clinicaltrials.gov	Use the study identifier **NCT01121588**
www.clinicaltrialsregister.eu	Use the study identifier **2010-022978-14**

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 or your child 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!