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: Avelumab, crizotinib, and lorlatinib

Protocol Number: B9991005 (Javelin Lung 101)

Dates of Study: 18 December 2015 to 13 July 2022

Title of this Study: Study on Use of Avelumab in Combination with Crizotinib or Lorlatinib in Patients with NSCLC

[A Phase 1b/2, Open-Label, Dose Finding Study to Evaluate Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination With Either Crizotinib or PF-06463922 in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer]

Date(s) of this Report: 12 July 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 non-small cell lung cancer?

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 people have NSCLC that is referred to as “ALK-positive”. These people have changes in a gene that makes a protein called anaplastic lymphoma kinase (ALK). If this happens, an abnormal form of ALK is produced that may cause the cancer cells to grow and spread.

Some patients have NSCLC that is referred to as “ALK-negative”. These patients do not have changes to the genes that makes the ALK protein. These patients could potentially have different causes for the cancer cells to grow and spread.

What is avelumab?

Avelumab (avelum-ab) was a new investigational cancer drug that was not approved for lung cancer treatment at the time of this study. Avelumab works by allowing the immune system to fight against cancer cells. It does this by stopping or preventing the action of a protein known as programmed death receptor ligand-1 (PD-L1). This helps the body’s immune system

fight the tumor cell. Avelumab is given as an infusion injection (drip) into a vein that lasts around an hour. Avelumab has been approved for the treatment of a different cancer type.

What is lorlatinib?

Lorlatinib (lor-la'-ti-nib) is a medicine that works by blocking the activity of ALK. Lorlatinib is known as an "ALK-inhibitor" medication. As cancer cells grow, they can form into a tumor and spread to other parts of the body, including the brain. By blocking ALK, lorlatinib may help to slow down the growth or spread of ALK-positive tumors.

Lorlatinib is already approved for use in many countries to treat adults with advanced or recurrent NSCLC that is ALK-positive. Advanced means the cancer cells have spread outside the lung where the tumor started. Recurrent cancer is cancer that has come back after treatment. Lorlatinib is approved in the United States under the trade name Lorbrena®, in the European Union under Lorviqua®, and in India under Lorbriqua®. Lorlatinib is given as a tablet and is taken by mouth once daily.

What is crizotinib?

Crizotinib (Cris-tin-ib) is another medicine that works by blocking the activity of ALK. Crizotinib is known as an "ALK-inhibitor" medication. In this study, crizotinib was being studied to see what effect it had on tumors without the ALK (ALK-negative NSCLC), when it was combined with avelumab.

Crizotinib is also called Xalkori®. This treatment is approved in the United States (US), Europe, and countries in East Asia including South Korea, Taiwan, Japan, and China, for 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) NSCLC that are

ALK-positive. Crizotinib is given as a capsule and is taken by mouth twice daily at around the same time every morning and every evening.

What was the purpose of this study?

The purpose of this study was to investigate combinations of treatments for NSCLC. Some patients have NSCLC that does not get better with one sort of treatment. Some other patients initially get better with one treatment and then the treatment stops working. Combining treatments may mean that a patient still gets the benefit of another treatment if one treatment in the combination stops working for them.

In this study, researchers wanted to learn more about the safety and tolerability of combining avelumab and crizotinib for participants with ALK-negative NSCLC and avelumab and lorlatinib for participants with ALK-positive NSCLC.

The researchers also wanted to know if any of the patients' NSCLC tumors got smaller or disappeared during the study. To do this, they measured many things, including the "Objective Response Rate". This is the percentage of participants whose cancer disappeared ("Complete Response") or got smaller ("Partial Response") during treatment.

Researchers wanted to know:

- **What was the response of ALK-negative NSCLC to treatment with avelumab and crizotinib?**
- **What was the response of ALK-positive NSCLC to treatment with avelumab and lorlatinib?**
- **What was the safety and tolerability of the combination of avelumab and crizotinib, and the combination of avelumab and lorlatinib?**
- **What medical problems, if any, did the 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 divided into 2 groups. The groups were called 'Group A' and 'Group B'.

- Participants in Group A had ALK-negative NSCLC and took avelumab (given by infusion on the first day of each 14-day treatment cycle) and crizotinib (given as a capsule and taken by mouth twice a day).

- Participants in Group B had ALK-positive NSCLC and took avelumab (given by infusion on the first day of each 14-day treatment cycle) and lorlatinib (given as a tablet and taken by mouth, once a day).

In this study, avelumab was given by infusion on the first day of each treatment cycle. Participants who took crizotinib or lorlatinib were given a capsule or tablet that was taken as advised by the researchers at the study center. This was an open label study. This means the participants and researchers knew who took each type of study medication and the dose that they were given.

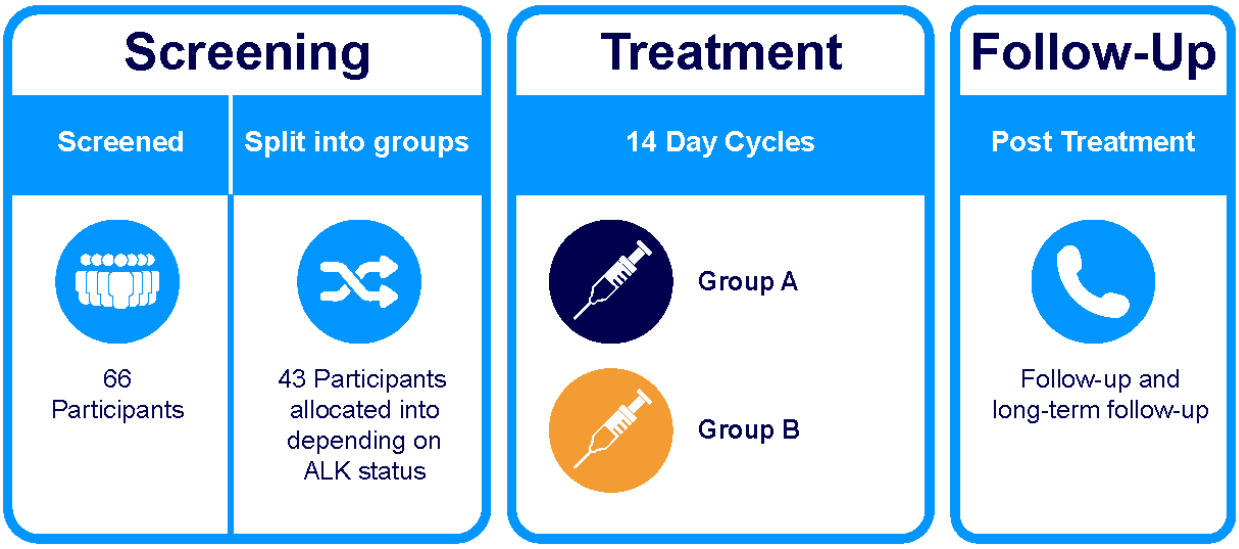
Participants visited the study center on Day 1 of every 14-day treatment cycle. They also attended an end of the study visit. Follow-up visits were also done around 30, 60, and 90 days after stopping the study medication. Participants were also followed for long-term safety. This was for 24 months after the last participant joined the study.

At the start of the study, there were 12 participants in Group A and 12 participants in Group B. For more participants to join these groups, the group needed to show that their NSCLC tumors had disappeared or shrunk. When the researchers looked at the effect of the treatment and its safety for Group A, they decided that no more participants were able to join this group. Group A was kept at the 12 original participants.

In Group B, there were enough participants out of the first 12 participants who had their NSCLC tumors disappear or shrink. Therefore, this group was able to allow more participants to join. This meant there were 31 participants treated in Group B.

Figure 1 shows what happened during the study.

Figure 1: Study Design



Group A: 12 participants with ALK-negative NSCLC were treated with avelumab and crizotinib.
Group B: 31 participants with ALK-positive NSCLC were treated with avelumab and lorlatinib.
Follow-up was for 90 days after last treatment and long-term follow-up was for 24 months after the last participant joined the study.

Where did this study take place?

The Sponsor ran this study at 16 locations in 6 countries in North America, Europe, Asia, and Australia.

When did this study take place?

It began 18 December 2015 and ended 13 July 2022.

Who participated in this study?

This study included participants whose NSCLC had worsened and spread to other areas of the body. In Group A, the participants had NSCLC that was ALK-negative and had previously been treated. In Group B, the participants had NSCLC that was ALK-positive and had either been previously treated or had not had any previous treatment.

- A total of 18 men participated

- A total of 25 women participated
- All participants were between the ages of 30 and 77 years.

Participants were treated until one of the following occurred:

- Their cancer got worse
- They left the study by their own choice
- They had unacceptable medical problems, or
- The study ended.

All of the 43 participants stopped taking the study treatment. The most common reason for participants stopping study treatment was because their cancer got worse. There were 30 participants who entered the follow up phase of the study. In the follow up phase, the participants were not treated but followed for safety.

There were 14 participants who did not complete the follow up part of the study. This was because of 3 reasons:

- They passed away (8 participants)
- By their own choice (3 participants), or
- They left the study due to another unspecified reason (3 participants).

There were 18 participants who entered the long-term follow up part of the study. Of these participants, 17 passed away and 1 participant left the study for other reasons.

How long did the study last?

The amount of time that each participant was in the study varied. The entire study took 6 years and almost 7 months to complete.

The study was closed early due to a change in treatment options for NSCLC.

When the study ended in July 2022, 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?

What was the response of ALK-negative NSCLC to treatment with avelumab and crizotinib?

In Group A, none of the participants who were treated with avelumab and crizotinib had a "Complete Response". A Complete Response means the NSCLC has completely disappeared. There were 3 participants (25.0%) who had a "Partial Response". A Partial Response means that the NSCLC got smaller but did not disappear.

The Objective Response Rate, which includes the Complete Response plus the Partial Response was 25.0% (see Figure 2).

There were 5 participants (41.7%) who had their NSCLC worsened.

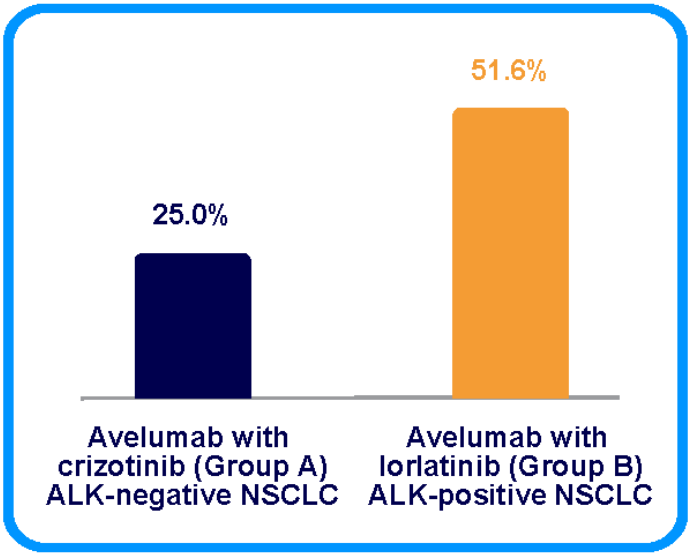
What was the response of ALK-positive NSCLC to avelumab and lorlatinib?

In Group B, 1 participant (3.2%) who was treated with avelumab and lorlatinib had a "Complete Response". There were 15 participants (48.4%) who had a "Partial Response".

The Objective Response Rate of Complete Response plus Partial Response was 51.6% (see Figure 2).

There were 7 participants (22.6%) who had their NSCLC worsen.

Figure 2: Objective Response Rate



What effect did treatment with a combination of avelumab and crizotinib, or avelumab and lorlatinib, have on participant's NSCLC?

The researchers have decided that treatment with avelumab and crizotinib in Group A had very little effect on the cancer in participants with ALK-negative NSCLC tumors.

The researchers have decided that treatment with avelumab and lorlatinib in Group B did see an effect on the cancer in participants with ALK-positive NSCLC tumors. There was not enough data to tell if the effect was any different than other treatments for 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 was the safety and tolerability of the combination of avelumab and crizotinib, and the combination of avelumab and lorlatinib?

To find out if the study treatment was tolerated, the researchers looked to see how the treatment affected participants. They did this by looking at the medical problems and dose limiting toxicities that participants experienced during the study.

A “dose limiting toxicity” means that the participant had a medical problem from taking study treatment that was serious enough to prevent treatment from continuing.

- A total of 5 out of 12 (41.7%) participants in Group A treated with avelumab and crizotinib had dose limiting toxicity.
  The researchers considered avelumab 10 mg/kg every 2 weeks and 250 mg crizotinib twice a day to be higher than the maximum dose that could be tolerated by participants.
- A total of 2 out of 28 (7.1%) participants in Group B treated with avelumab and lorlatinib had a dose limiting toxicity.

  The researchers considered avelumab 10 mg/kg every 2 weeks and 100 mg lorlatinib once a day to be the maximum dose that could be tolerated by participants.

  Note: This information was not available for the other 3 participants in Group B.

Note: medical problems are discussed in the next section of this summary.

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.

All 12 (100%) participants in Group A and all but 1 participant in Group B (30 out of 31 [96.8%] participants) 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 20% of participants in Group A or Group B – 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 in either group are listed.
- The **2nd** column tells how many of the Group A participants taking avelumab and crizotinib reported each medical problem. Next to this number is the percentage of the 12 participants taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the Group B participants taking avelumab and lorlatinib reported each medical problem. Next to this number is the percentage of the 31 participants taking the study medication who reported the medical problem.
- Using these instructions, you can see that 7 out of the 12 (58.3%) participants in Group A reported nausea. There were 5 out of 31 (16.1%) participants in Group B who reported nausea (feeling about to vomit).

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Group A Avelumab and Crizotinib (12 Participants)**	**Group B Avelumab and Lorlatinib (31 Participants)**
Nausea	7 out of 12 participants (58.3%)	5 out of 31 participants (16.1%)
Vomiting	6 out of 12 participants (50.0%)	6 out of 31 participants (19.4%)
Decreased appetite (not feeling hungry)	5 out of 12 participants (41.7%)	2 out of 31 participants (6.5%)
ALT liver test increased	4 out of 12 participants (33.3%)	9 out of 31 participants (29.0%)
Rash	4 out of 12 participants (33.3%)	5 out of 31 participants (16.1%)
Low red blood cell count	3 out of 12 participants (25.0%)	6 out of 31 participants (19.4%)
AST liver test increased	3 out of 12 participants (25.0%)	7 out of 31 participants (22.6%)

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Group A Avelumab and Crizotinib (12 Participants)**	**Group B Avelumab and Lorlatinib (31 Participants)**
Chills	3 out of 12 participants (25.0%)	2 out of 31 participants (6.5%)
Diarrhea (loose stools)	3 out of 12 participants (25.0%)	7 out of 31 participants (22.6%)
Muscle pain	3 out of 12 participants (25.0%)	6 out of 31 participants (19.4%)
High temperature or fever	3 out of 12 participants (25.0%)	6 out of 31 participants (19.4%)
Constipation	2 out of 12 participants (16.7%)	7 out of 31 participants (22.6%)
Cough	1 out of 12 participants (8.3%)	7 out of 31 participants (22.6%)
Limb swelling (e.g., arms and/or legs)	1 out of 12 participants (8.3%)	12 out of 31 participants (38.7%)

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Group A Avelumab and Crizotinib (12 Participants)**	**Group B Avelumab and Lorlatinib (31 Participants)**
Joint pain	0	13 out of 31 participants (41.9%)
High level of cholesterol in blood	0	19 out of 31 participants (61.3%)
High level of triglycerides (a type of fat) in blood	0	18 out of 31 participants (58.1%)
Low levels of thyroid hormone	0	8 out of 31 participants (25.8%)
Nerve damage to extremities such as hands, feet, or arms	0	7 out of 31 participants (22.6%)
Weight increased	0	8 out of 31 participants (25.8%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

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, 5 participants (41.7%) in Group A and 21 participants (67.7%) in Group B had at least 1 serious medical problem.

Serious medical problems experienced by more than 1 participant were:

- Lung inflammation: 1 out of 12 (8.3%) participants in Group A and 2 out of 31 (6.5%) participants in Group B.
- Pneumonia: 3 out of 31 (9.7%) participants in Group B
- Blocked blood vessel in lung: 2 out of 31 (6.5%) participants in Group B.
- Confused state: 2 out of 31 (6.5%) participants in Group B.

Serious medical problems considered related to treatment were reported by 2 participants (16.7%) in Group A and 6 participants (19.4%) in Group B. All of these related serious medical problems were reported by single participants apart from 2 cases of lung inflammation (6.5%) in Group B.

There were 10 out of 12 (83.3%) participants in Group A and 15 out of 31 (48.4%) participants in Group B participants that died during the study. Most of these deaths were due to the participant’s cancer getting worse. Of the deaths, 21 out of 25 (84%) deaths occurred in participants more than 30 days after their last dose of study medication.

There was only 1 out of the 25 (4%) deaths that the researchers believed was related to study medication. This was in a participant in Group B who died due to shortness of breath.

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 B9991005

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

www.clinicaltrials.gov	Use the study identifier **NCT02584634**
www.clinicaltrialsregister.eu	Use the study identifier **2015-001879-43**

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!