Clinical Trial Results – Layperson Summary

A study to compare alectinib with crizotinib as the first treatments given to people with a type of lung cancer called '*ALK*-positive non-small cell lung cancer'

See the end of the summary for the full title of the study.

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

- Members of the public.
- People who took part in the study.

This summary is based on information known up until November 29th 2019. The study is closed to recruitment and is still ongoing, so more information may become available at a later date.

The study started in August 2014 and is expected to end in late 2022/early 2023. At the time of writing this summary, the study is still happening – this means that study doctors are still collecting information.

No single study can tell us all we need to know about the risks and benefits of a medicine. The results from this study may be different from other studies with the same medicine.

- This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

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Thank you to the people who took part in this study

The people who took part in this study have helped researchers to answer important questions about anaplastic lymphoma kinase (*ALK)*-positive non-small cell lung cancer (NSCLC), written as '*ALK*-positive lung cancer' in this summary, and the medicines being looked at (alectinib and crizotinib).

Key information about this study

- This study looks at two different medicines used to treat people with 'late stage' *ALK*-positive lung cancer.
- This study is being done to compare alectinib with crizotinib in people who have not received any anti-cancer therapy before. All participants have 'late stage' *ALK*-positive lung cancer.
- People are being given either alectinib or crizotinib, which was the standard treatment at the time when the study began. It was decided by chance which study medicine each person would be given.
- This study included 303 people in 34 countries.
- People received alectinib for about 35 months on average before their *ALK*-positive lung cancer got worse (i.e., until their cancer grew bigger or spread to other parts of the body). This was more than three times longer than for people who received crizotinib (around 11 months).
- After 5 years, a higher percentage of people were alive after having alectinib as their first treatment (62.5%) than people who were given crizotinib as their first treatment (45.5%).
- People took alectinib for about 28 months, and 39% of people (59 out of 152) had serious side effects. People took crizotinib for a shorter period of around 11 months, and 32% of people (48 out of 151) had serious side effects.

1. General information about this study

Why was this study done?

ALK-positive NSCLC is specific type of lung cancer. It is caused by an overactive 'enzyme' in the body called ALK (anaplastic lymphoma kinase), which is genetically altered and causes lung cells to grow abnormally. Crizotinib was the first treatment designed to reduce the effects of overactive ALK and was the standard treatment for people with 'late-stage' *ALK*-positive lung cancer at the start of this study.

However, people with *ALK*-positive lung cancer have a high risk of their cancer spreading to the brain. Crizotinib can't reach the brain very well and doesn't work for very long if the cancer has spread there (called a 'metastasis'), so new medicines are needed to improve outcomes for people who have or are at risk of their cancer spreading to the brain.

Therefore, this study was done for two reasons. Firstly, to see if alectinib may give people longer until their *ALK*-positive lung cancer got worse (grew or spread), compared with crizotinib. Secondly, to see if alectinib also works in patients whose cancer had or had not spread to the brain.

What are the study medicines?

Crizotinib (Xalkori™) is an existing medicine given to people with 'late-stage' *ALK*-positive lung cancer.

- Crizotinib works by slowing down how quickly cancer cells can multiply and can help to stop tumours from growing, but may not work as well when the cancer has spread to the brain.

Alectinib (ALECENSA™) is the medicine that is being studied here.

- Alectinib works in a similar way to crizotinib, but may be more effective at delaying the time until people's *ALK*-positive lung cancer gets worse, whether or not the cancer has spread to the brain.

What did researchers want to find out?

- Researchers did this study to compare alectinib with the existing standard of care at the time (crizotinib), to see how well alectinib worked in treating 'late-stage' *ALK*-positive lung cancer (see section 4 "What are the latest results from this study?").
- They also wanted to find out how safe the medicine was by checking how many people had side effects when taking alectinib (see section 5 "What were the side effects?"). Side effects (also known as 'adverse reactions') are unwanted medical problems (such as a headache) that happen during the study.

The main question that researchers wanted to answer was:

1. How long did people receive alectinib for before their *ALK*-positive lung cancer got worse (grew or spread), compared with people who received crizotinib?

Other questions that researchers wanted to answer included:

2. How long did people have before their *ALK*-positive lung cancer got worse (grew or spread), based on whether the cancer had, or had not, spread to the brain before the study started?
3. What proportion of people had tumours that got smaller or shrunk completely, after receiving alectinib or crizotinib?
4. Did people live longer when given alectinib as their first treatment compared with crizotinib, when followed up for a period of up to five years?

What kind of study was this?

This was a 'Phase 3' study and involved a larger number of people that followed earlier studies in animals, healthy individuals ('Phase 1') and a smaller number of people with *ALK*-positive lung cancer ('Phase 2').

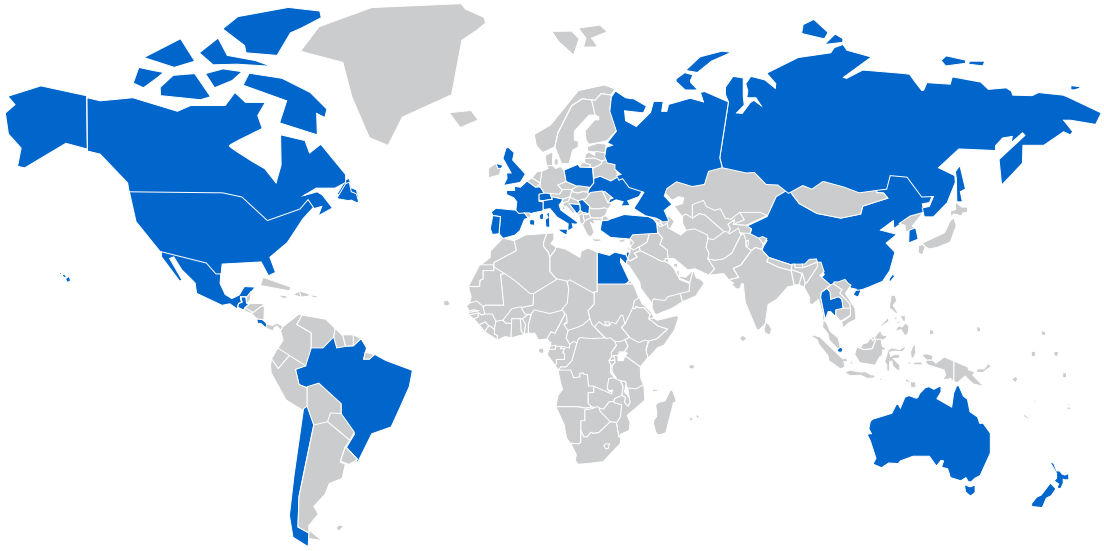
In this study, a larger number of people with *ALK*-positive lung cancer took either alectinib or crizotinib. This was to find out if alectinib gave people more time before their *ALK*-positive lung cancer got worse (grew or spread) and to find out more about the possible side effects of alectinib.

This was an 'open label' study, meaning that patients, doctors and study staff knew which medicines people were taking.

Where did the study take place?

A total of 161 study centres, across 31 countries around the world were involved in forming the study and were on standby to begin recruiting people with *ALK*-positive lung cancer to take part.

At 98 study centres, across 29 countries, 303 people with confirmed *ALK*-positive lung cancer were then selected to receive one of the study medicines (see section 3 "What happened during the study?"). The following map shows the countries where patients were involved in this study:



- Australia
- Bosnia and Herzegovina
- Brazil
- Canada
- Chile
- China
- Costa Rica
- Egypt
- France
- Guatemala
- Hong Kong
- Israel
- Italy
- Mexico
- New Zealand
- Poland
- Portugal
- Russia
- Serbia
- Singapore
- South Korea
- Spain
- Switzerland
- Taiwan
- Thailand
- Turkey
- Ukraine
- United Kingdom
- USA

2. Who took part in this study?

In this study, 303 adults with untreated, confirmed *ALK*-positive lung cancer took part.

People who took part in the study were between 18 and 91 years of age.
132 of the 303 people (44%) were male and 171 of the 303 people (56%) were female.

Before receiving alectinib or crizotinib, 122 out of 303 people (40%) had *ALK*-positive lung cancer, which had already spread to the brain.

People could take part in the study if they had:

- *ALK*-positive lung cancer that had spread to other parts of the lung or body (called 'late-stage', 'advanced' or 'metastatic' disease).
- Healthy enough lives such that they could carry out their usual activities and were out of bed for more than 50% of waking hours.
- Not received any other medicines for their *ALK*-positive lung cancer.

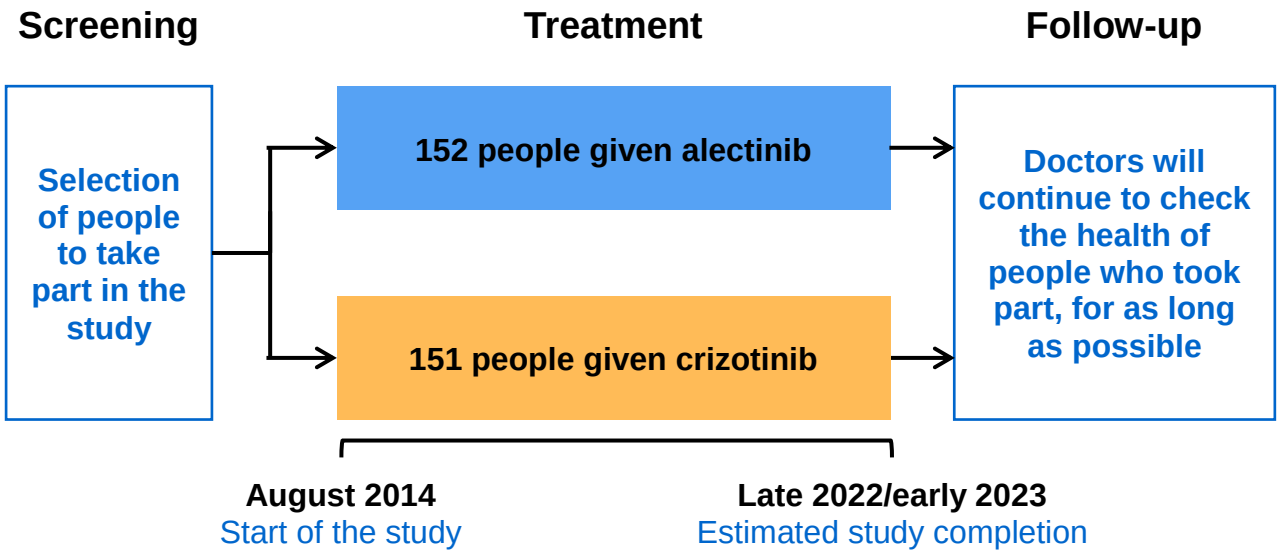
People could not take part in the study if they had:

- Any other cancers in the last three years.
- Any stomach, gut or liver problems that could affect how well the body takes up (or 'absorbs') medicines.
- A slow heart rate, also known as 'symptomatic bradycardia'.

3. What happened during the study?

During the study, people were selected by chance, to get one of the two study medicines below. The study medicines were selected at random by a computer:

- **Alectinib** – given in capsule form (600mg dose) and taken by mouth twice daily.
- **Crizotinib** – given in capsule form (250mg dose) and taken by mouth twice daily.



During the study, people were only allowed to take the study medicine they were selected to receive. Once people's lung cancer got worse (grew or spread), they could either continue to receive their study medicine, or be treated with another treatment after they left the study. This was decided by the study doctor.

This study is ongoing, so some people are still being treated with alectinib or crizotinib. This summary presents the most relevant data to date, up until 29th November 2019.

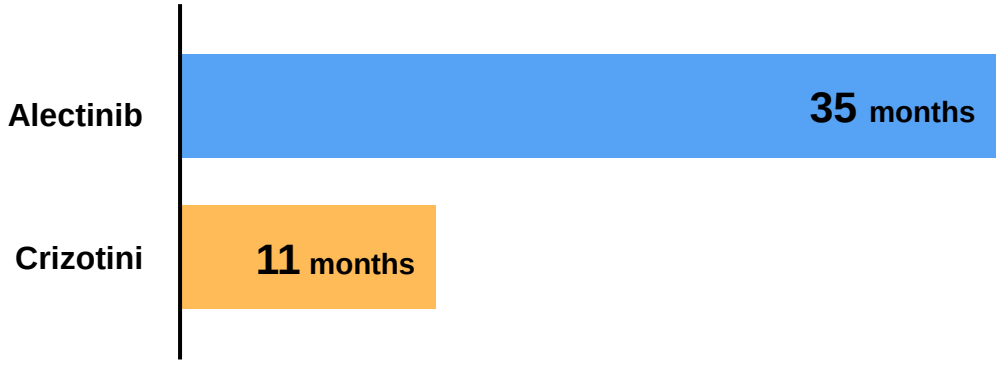
4. What are the latest results from this study?

Question 1: How long did people receive alectinib for before their *ALK*-positive lung cancer got worse (grew or spread), compared with people who received crizotinib?

Researchers looked at the length of time between the date when each person entered the study and when their *ALK*-positive lung cancer got worse. Below are the results from the start of the study until the date at which this effect of alectinib versus crizotinib was most recently analysed, which was on 30th November 2018.

People who were given alectinib had around **35 months** on average before their *ALK*-positive lung cancer got worse. This compares with around **11 months**, on average, for people who were given crizotinib.

How long, on average, people in each group lived without worsening of their *ALK*-positive lung cancer:



After 4 years on treatment, 44% of people on alectinib did not have any worsening of their *ALK*-positive lung cancer. This number was not-estimable for people on crizotinib because the majority of patients had experienced a worsening of their cancer before the 4-year time point, meaning that the number of patients was too small to calculate a percentage.

Question 2: How long did people have before their *ALK*-positive lung cancer got worse (grew or spread), based on whether the cancer had, or had not, spread to the brain before the study started?

Another piece of information that researchers collected was whether the time until people's *ALK*-positive lung cancer got worse was different between people whose cancer had, or had not, spread to their brain before the start of the study. This information was collected from the start of the study and was most recently analysed on 30th November 2018.

Of people treated with alectinib, 64 out of 152 (42%) **had brain tumours at the start of the study** compared with 58 out of 151 (38%) people treated with crizotinib. In these patient groups, the average amount of time until their *ALK*-positive lung cancer got worse with each study medicine was:

- **Alectinib: 25 months.**
- **Crizotinib: 7 months.**

In people **without brain tumours at the start of the study**, the average amount of time until people's *ALK*-positive lung cancer got worse with each study medicine was:

- **Alectinib: 39 months.**
- **Crizotinib: 15 months.**

Question 3: What proportion of people had tumours that got smaller or shrunk completely, after receiving alectinib or crizotinib?

Another piece of information that researchers collected was how many people responded to their study medicine, in other words, whether their *ALK*-positive lung cancer got smaller or shrunk completely. Below are the results from the start of the study until 1st December 2017, when these data were last analysed:

A total of 126 out of 152 (**83%**) people responded to treatment with alectinib:

- 7 out of 152 people (5%) who were receiving alectinib had their *ALK*-positive lung cancer shrink completely (called a 'complete response').
- 119 out of 152 people (78%) who were receiving alectinib had their *ALK*-positive lung cancer shrink partly (called a 'partial response').

A total of 114 out of 151 (**76%**) people responded to treatment with crizotinib:

- 3 out of 151 people (2%) who were receiving crizotinib had their *ALK*-positive lung cancer shrink completely (called a 'complete response').
- 111 out of 151 people (74%) who were receiving crizotinib had their *ALK*-positive lung cancer shrink partly (called a 'partial response').

Question 4: Did people live longer when given alectinib as their first treatment compared with crizotinib, when followed up for a period of up to five years?

Researchers also looked at the survival rates (percentage of people alive) for people who were given alectinib or crizotinib as their first treatment. These results were last analysed on 29th November 2019.

It is estimated that **62.5%** of people who were given **alectinib** as their first treatment are still alive up to 5 years after entering the study. For those who received **crizotinib** as their first treatment, it is estimated that **45.5%** of people are still alive up to 5 years after entering the study.

Not all of the people in this study are still being followed up by study doctors, and it is important to remember that these survival rates are estimates, calculated based on the number of people who are still in the study.

This section only shows the key results from the study at this point. You can find information about all other results on the websites listed the end of this summary (see section 8).

5. What were the side effects?

Side effects or ‘adverse events’ are unwanted medical problems that happen during the study. Not all of the people in this study had all of the side effects.

A lot of research is needed to know whether a medicine causes these side effects. When new medicines are being investigated, study doctors keep track of all of the side effects that people have, as they may or may not be caused by the medicine.

This section tells you about the serious and common side effects that happened with alectinib or crizotinib in this study.

Serious side effects

A side effect is considered ‘serious’ if it is life-threatening, needs hospital care, causes lasting problems or death.

People took alectinib for a period of about 28 months and 39% of people (59 out of 152) had at least one serious side effect in this time. In comparison, people took crizotinib for a shorter period of around 11 months and 32% of people (48 out of 151) had at least one serious side effect in this time.

The three most common serious side effects are shown in the following table in either treatment group up until 29th November 2019, which is the date of the most recent analysis.

Serious side effects reported in this study	People taking alectinib	People taking crizotinib
A type of infection which affects the lungs, called ‘pneumonia’	5% (8 out of 152 [number of people in this treatment group])	3% (4 out of 151 [number of people in this treatment group])
A non-infectious form of pneumonia, called ‘pneumonitis’	1% (2 out of 152)	3% (4 out of 151)
A blood clot in the lung, known as a ‘pulmonary embolism’	1% (2 out of 152)	2% (3 out of 151)
Higher levels of something called ‘ALT’ in the blood, which could be a sign of liver damage	Less than 1% (1 out of 152)	3% (4 out of 151)

Some people in the study died due to side effects that may, or may not, have been related to one of the study medicines. The numbers of people who died in each treatment group due to a side effect were:

- 7 out of 152 people (5%) in the alectinib group.
- 7 out of 151 people (5%) in the crizotinib group.

Causes of death related to side effects for the 7 people taking alectinib or crizotinib were:

- Alectinib group: 2 deaths of unknown cause; 1 loss of heart function (‘cardiac arrest’); 1 sudden damage to the kidneys (‘acute kidney injury’); 1 higher levels of something called ‘creatinine’ in the blood, 1 lung infection and 1 ruptured ovarian cyst.
- Crizotinib group: 1 sudden death; 1 loss of heart function (‘cardiac arrest’), 1 bleeding within the brain (‘cerebral haemorrhage’), 1 type of bacterial infection affecting the tissue beneath the skin, muscles and organs (‘necrotising fasciitis’); 1 shortage of breath (‘dyspnoea’); 1 non-infectious form of pneumonia, called ‘pneumonitis’ and 1 respiratory failure.

A small number of patients experienced side effects that indicated that they may need to stop taking the study medicine. After speaking to the study doctors, a total of 22 people in the alectinib group (15%) and 22 people in the crizotinib group (15%) stopped taking their study medicine because of a side effect (serious or non-serious).

Most common side effects

The most common side effects are shown in the following table – these are the ten most common side effects that occurred in either of the treatment groups.

Most common side effects reported in this study	People taking alectinib	People taking crizotinib
Constipation	37% (56 out of 152)	34% (51 out of 151)
Low level of red blood cells (anaemia)	26% (40 out of 152)	8% (12 out of 151)
Feeling tired (fatigue)	22% (34 out of 152)	19% (28 out of 151)
Higher levels of something called 'bilirubin' which could be a sign of liver damage	22% (33 out of 152)	1% (2 out of 151)
Fluid retention in the limbs (peripheral oedema)	19% (29 out of 152)	33% (50 out of 151)
Higher levels of something called 'ALT' in the blood, which could be a sign of liver damage	18% (27 out of 152)	34% (51 out of 151)
Higher levels of something called 'AST' in the blood, which could be a sign of heart or kidney damage	17% (26 out of 152)	29% (44 out of 151)
Feeling sick (nausea)	16% (25 out of 152)	50% (75 out of 151)
Diarrhoea	16% (24 out of 152)	46% (70 out of 151)
Throwing up (vomiting)	10% (15 out of 152)	41% (62 out of 151)

Other side effects

You can find information about side effects other than the 10 most common ones, shown above, on the websites listed at the end of this summary – see section 8.

6. How has this study helped research?

The information presented here is from a single study of 303 people with *ALK*-positive lung cancer. At this point in time, the study is ongoing. These results, so far, are helping researchers learn more about *ALK*-positive lung cancer and alectinib, including how effective alectinib is and what the common side effects are.

The results from this study show that alectinib is more effective than crizotinib in treating 'late-stage' *ALK*-positive lung cancer in people who have not had any other treatment for their cancer. On average, people taking alectinib had a period of three-times longer without worsening of their *ALK*-positive lung cancer compared with people taking crizotinib (**35 months with alectinib** and **11 months with crizotinib**).

No single study can tell us everything about the risks and benefits of a medicine. The results from this study may be different from other studies with the same medicine.

- This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

7. Are there plans for other studies?

Other studies looking at the safety and effectiveness of alectinib are taking place. These studies are looking at the use of alectinib in different situations, for example:

- In Japanese and Asian people with 'late-stage' *ALK*-positive lung cancer.
- In people with 'early stage' *ALK*-positive lung cancer, rather than 'late stage' *ALK*-positive lung cancer that is described in this summary.

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/results/NCT02075840
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004133-33/results
- https://forpatients.roche.com/en/trials/cancer/lung-cancer/a-study-comparing-alectinib-with-crizotinib-in-treatmen-47622.html

If you would like to find out more about the results of this study, the full title of the latest scientific paper is, "Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced *ALK*-positive non-small-cell lung cancer in the ALEX study". The authors of the scientific paper are: T. Mok, D.R. Camidge, S.M. Gadgeel, R. Rosell, R. Dziadziuszko, D.-W. Kim, M. Pérol, S.-H.I. Ou, J.S. Ahn, A.T. Shaw, W. Bordogna, V. Smoljanović, M. Hilton, T. Ruf, J. Noé & S. Peters.

The paper is published online in the journal 'Annals of Oncology', volume number 31, on pages 1056–1064.

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Contact a representative at your local Roche office.
- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/.

If you took part in this study and have any questions about the results:

- Speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is, “Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Crizotinib in Treatment-Naïve Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer”.

The study is known by the acronym ‘ALEX’.

- The ClinicalTrials.gov identifier for this study is: NCT02075840.
- The EudraCT number for this study is: 2013-004133-33.
- The protocol number for this study is: BO28984.