Dear Reader,

Sponsors of clinical studies create study reports. A study report describes how a study was done and what the results of the study were. This is a summary of such a report. It is meant for the general reader. Complex medical explanations have been avoided as much as possible.

You may be interested in this summary because you want to learn about treatment options for lung cancer. This summary describes the results of a single study. The results cannot be assumed to apply for everybody.

This study started in March 2012 and is still ongoing. Its lay title is "LUX-Lung 8: A Phase III Trial of Afatinib (BIBW 2992) Versus Erlotinib for the Treatment of Squamous Cell Lung Cancer After at Least One Prior Platinum Based Chemotherapy". This summary includes information collected up to March 2015. The sponsor is Boehringer Ingelheim.

What was the study about?

This study compared two anti-cancer medicines ("afatinib" and "erlotinib") with each other. Both of these medicines are already used to treat patients with Non-Small Cell Lung Cancer (NSCLC). The patients in this study had a special type of incurable NSCLC (stage IIIB/IV squamous cell NSCLC). Only patients who already had 4 cycles of chemotherapy (platinum-based doublet chemotherapy) were allowed into this study.

Why was the research needed?

Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer. It takes the lives of about 880 000 patients each year in the world. Unfortunately, lung cancer is often diagnosed late. This means that surgery is no longer possible and that the cancer has already spread into other organs (metastasized). Only 15 out of every 100 people diagnosed with incurable NSCLC (15%) will survive for 5 years or more after diagnosis. Therefore, new medicines are needed to treat this type of lung cancer. Two medicines which work in a similar way were tested in this study.

All patients in this study had a special type of incurable NSCLC (stage IIIB/IV squamous cell NSCLC). For most patients, the cancer had already spread to other organs. This study tested whether afatinib is more effective than erlotinib in stopping the cancer from growing.

Which medicines were studied?

Researchers studied the medicines "afatinib" and "erlotinib" as the second treatment given after diagnosis of NSCLC (second-line therapy). Both medicines stop the tumour from growing and spreading by blocking growth signals.

- **Afatinib** binds very tightly and irreversibly to several growth signals (epidermal growth factor receptor and human epidermal growth factor receptors 2, 3, and 4) so that they can no longer function
- **Erlotinib** binds temporarily to a growth signal (epidermal growth factor receptor) so it cannot function for some time

What did the researchers want to know?

Researchers wanted to know which medicine is more effective at stopping cancer growth. To find this out, they measured:

- the time from starting the medicines until the cancer grew again or the patient died (progression-free survival), and
- the time from starting the medicines until the patients died from cancer or for any other reason (overall survival).

In addition, researchers collected information on the side effects of both medicines.

Who participated in the study?

Patients with a special type of incurable NSCLC (stage IIIB or IV squamous cell NSCLC) took part in the study. Only patients who had already had anti-cancer therapy (4 cycles of platinum-based doublet chemotherapy) were allowed in the study.

The analysis of progression-free survival was done on 7 October 2013. At this time, 669 patients had been included in the study.

The analysis of overall survival was done after 632 patients had died. At this time, a total of 795 patients had been included in the study; 666 were men and 129 were women. On average patients were 64 years old. The youngest patient was 35 years and the oldest patient was 88 years. Patients were from all over the world (Argentina, Austria, Canada, Chile, China, Denmark, France, Germany, Greece, Hungary, India, Ireland, Italy, Korea, Mexico, Netherlands, Portugal, Singapore, Spain, Taiwan, Turkey, United Kingdom, United States).

How was this study performed?

Patients were divided into 2 groups of similar size. It was decided by chance who got into which group (randomised). One group took afatinib; the other group took erlotinib. Patients knew which medicine they took. Doctors and researchers also knew which medicine the patients took. This is called “open-label design”.

The medicines were taken as follows:

- **Afatinib group**: Patients took 1 tablet with 40 mg of afatinib every day. The doctor could increase the dose to 50 mg every day or reduce the dose to 30 mg or 20 mg every day. This depended on whether the side effects were tolerable to the patient.

- **Erlotinib group**: Patients took 1 tablet with 150 mg of erlotinib every day. The doctor could reduce the dose to 100 mg or 50 mg every day. This depended on whether the side effects were tolerable to the patient.

Except for taking different treatments, all patients followed the same procedures:

- They visited the study doctor about once per month.
- At these visits, the patients answered questions about their health.
- At some specific visits, the size of their tumour was measured and their blood was tested.

The doctors looked after each patient and they checked their results. The doctors did more medical tests when needed. Together with the patients they decided whether the dose of the medicines should be changed. The patients took the medicines as long as they did not have side effects that they could not tolerate. If the side effects became too strong, the doctors and the patients decided whether the medicines should be stopped.

In this study, all patients stopped the study medicines when their cancer grew again. These patients started taking other medicines.

What were the results of this study?

This study compared 2 different medicines for the treatment of lung cancer. Researchers used 2 different methods to see which one was more effective. The results of both methods are available in this lay summary.

First, researchers measured the time it took from starting the medicines until the cancer started growing again or the patient died (progression-free survival). This was calculated on 7 October 2013. Patients could still join the study after this date.

Second, researchers measured the time it took from starting the medicines until the patients died from cancer or for any other reason (overall survival).

To be sure that the results they got were reliable, researchers tested whether the results could have come about by chance. This was done by using statistical tests. Some of these statistical tests involved the calculation of so-called p-values. A small p-value (smaller than 0.05) shows that the differences between the treatments are unlikely due to chance. Larger p-values show that differences between the treatments are possibly due to chance.

How long did patients take each medicine?

When progression-free survival was analysed, 329 patients had taken afatinib and 332 patients had taken erlotinib. At this time, patients had taken afatinib (median of 59 days) slightly longer than they had taken erlotinib (median of 57 days).

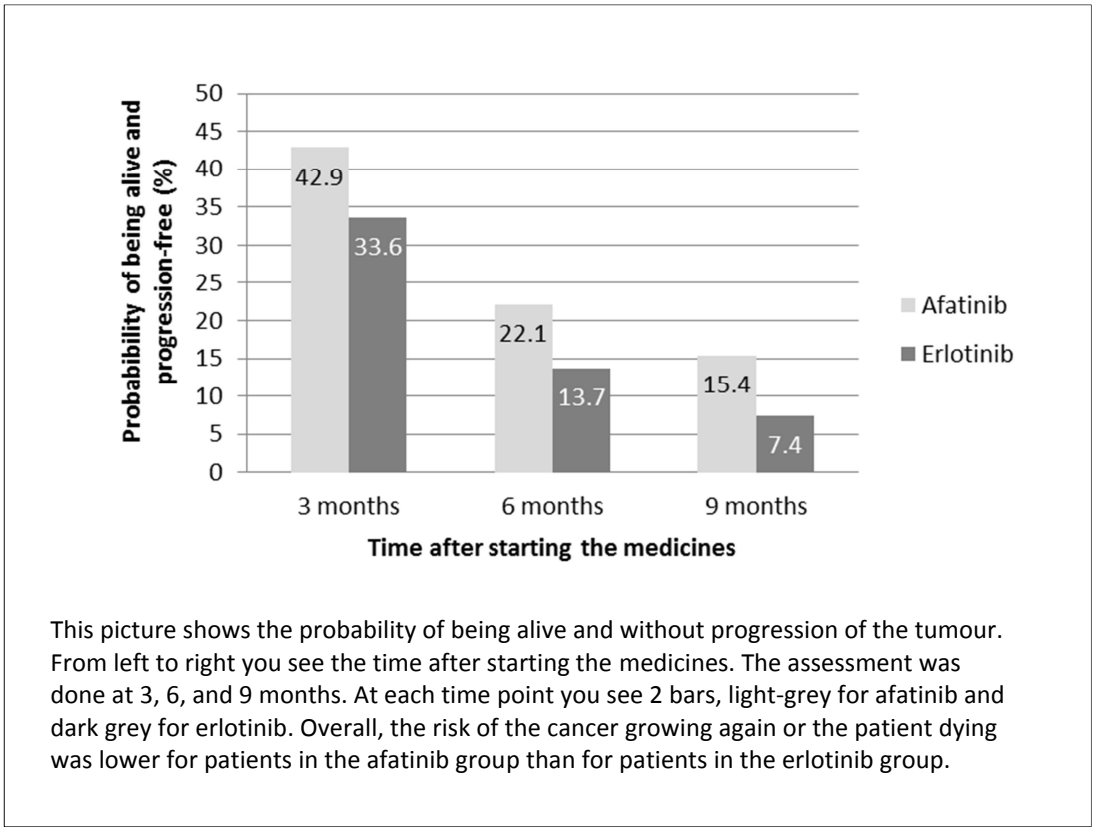
When overall survival was analysed, 392 patients had taken afatinib and 395 patients had taken erlotinib. At this time, patients had taken afatinib (median of 65 days) longer than they had taken erlotinib (median of 58 days).

Was there a difference between the 2 medicines for ‘progression-free survival’?

Yes. In this study a difference between the 2 medicines was seen for progression-free survival. There was an advantage for the patients who took afatinib. The proportion of patients who were alive and for whom the cancer had not grown was higher in the afatinib group than in the erlotinib group.

The risk of the cancer growing again or the patient dying was 17.8% lower for patients in the afatinib group than for patients in the erlotinib group. This result was unlikely to have come about by chance (p=0.0427). The average (median) time it took from starting the medicines until the cancer started growing again or the patient died was 2.43 months for patients who took afatinib and 1.94 months for patients who took erlotinib.

The graph below shows the probability of being alive and progression-free at 3, 6, and 9 months after patients started taking the medicines.



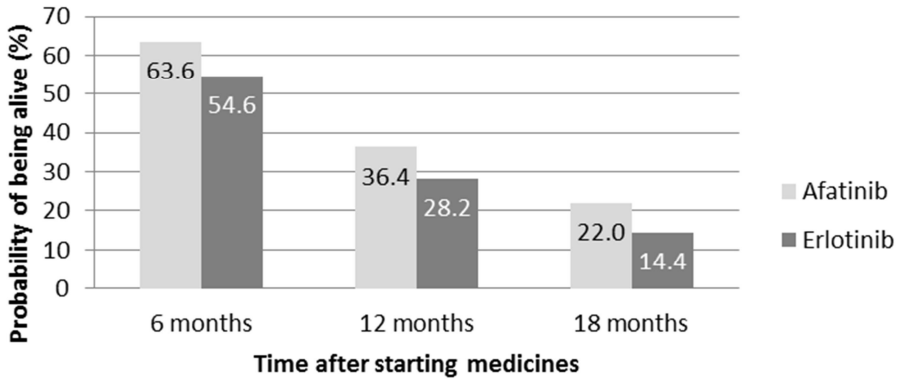
This picture shows the probability of being alive and without progression of the tumour. From left to right you see the time after starting the medicines. The assessment was done at 3, 6, and 9 months. At each time point you see 2 bars, light-grey for afatinib and dark grey for erlotinib. Overall, the risk of the cancer growing again or the patient dying was lower for patients in the afatinib group than for patients in the erlotinib group.

Was there a difference in between the 2 medicines for 'overall survival'?

Yes. In this study a difference between the 2 medicines was seen for overall survival. There was an advantage for the patients who took afatinib. The proportion of patients who were alive was higher in the afatinib group than in the erlotinib group.

The risk of dying was 19.2% lower for patients in the afatinib group than for patients in the erlotinib group. This result was unlikely to have come about by chance (p=0.0077). The average (median) time it took from starting the medicines until the patient died was 7.92 months for patients who took afatinib and 6.77 months for patients who took erlotinib.

The graph on the next page shows the probability of being alive at 6, 12, and 18 months.



This picture shows the probability of being alive. From left to right you see the time after starting the medicines. The assessment was done at 6, 12, and 18 months. At each time point you see 2 bars, light-grey for afatinib and dark grey for erlotinib. Overall, the risk of dying was lower for patients in the afatinib group than for patients in the erlotinib group.

Which side effects did patients have?

A side effect is any medical problem seen during a study. Some side effects are caused by the study medicines, and some side effects are caused by other tablets and pills taken by the patient. Others are caused by the disease, and some have yet a different cause. Some side effects might only happen 1 time, for 1 patient, and last for a very short period of time. Other side effects might happen many times, for many patients, and last for a long period of time. Researchers keep track of all medical problems patients have during a study.

In this study almost all patients (93.4% in the afatinib group and 81.3% in the erlotinib group) had side effects that doctors believed were caused by the study medicines. This is very common in studies with patients who have incurable lung cancer. Patients mostly had problems with their stomach, intestines, and skin.

In the afatinib group 25.3% of patients and in the erlotinib group 16.2% of patients had severe side effects (CTCAE grade 3) likely caused by the study medicines. The table on the next page shows severe (CTCAE grade 3) side effects likely caused by afatinib or erlotinib. Only severe (CTCAE grade 3) side effects that were seen in more than 3 patients in either group are shown.

	Afatinib (392 patients)	**Erlotinib (395 patients)**
Patients who had severe (CTCAE grade 3) side effects related to the study medicines	99 patients (25.3%)	64 patients (16.2%)
Frequent, loose bowel movements (Diarrhoea)	39 patients (9.9%)	9 patients (2.3%)
Upset stomach (Nausea)	4 patients (1.0%)	3 patients (0.8%)
Inflamed and sore mouth (Stomatitis)	9 patients (2.3%)	s0 patients (0.0%)
Abnormal change in color, appearance or texture of skin (Rash)	14 patients (3.6%)	24 patients (6.1%)
Outbreak of skin with pimples (Dermatitis acneiform)	3 patients (0.8%)	8 patients (2.0%)
Swelling or irritation of mucus membranes (Mucosal inflammation)	6 patients (1.5%)	0 patients (0.0%)
Feeling tired (Fatigue)	2 patients (0.5%)	5 patients (1.3%)

Most side effects were manageable, and most patients could stay on treatment for as long as they had a benefit. Some patients left the study because of side effects. The percentage of patients who left the study because of side effects was similar in both groups, with 20.2% in the afatinib group and 17.0% in the erlotinib group.

The same percentage of patients in the afatinib (44.1%) and erlotinib (44.1%) groups had serious side effects. This means that they had side effects that made them go to the hospital or stay in the hospital. Or these side effects needed urgent attention by a doctor, were life-threatening, or led to death. Several serious side effects were likely caused by the study medicines. More patients in the afatinib group (12.0%) than in the erlotinib group (5.6%) had such serious side effects. In the afatinib group 6 patients (1.5%) and in the erlotinib group 5 patients (1.3%) died from serious side effects likely caused by study medicines.

What else is important to know?

Comments on the study

This summary only shows results from this study. Other studies may have different results. This summary was written in May 2016.

Important notice

This study does not represent all the knowledge about the medications studied. Patients should not change their current therapy based on their understanding of the results from any single study. Patients should talk with their physician before making any changes in their therapy.

Are there follow-up studies?

No follow-up studies are planned.

Where can I find more information?

The protocol number of the study is 1200.125. The full title of the study is:

"LUX-Lung 8: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy"

Please visit the following website to find a scientific summary of the study results:

http://trials.boehringer-ingelheim.com/trial_results.html.

You can find more details at www.clinicaltrialsregister.eu by searching for the EudraCT number 2011-002380-24) or at www.clinicaltrials.gov by searching for the NCT number (NCT01523587).