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 December 2011 and is still ongoing. Its lay title is "LUX-Lung 7: A Phase IIb Trial of Afatinib (BIBW2992) Versus Gefitinib for the Treatment of 1st Line EGFR Mutation Positive Adenocarcinoma of the Lung". This summary includes information collected up to August 2015. The sponsor is Boehringer Ingelheim.

What was the study about?

This study compared two anti-cancer medicines ("afatinib" and "gefitinib") 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 incurable adenocarcinoma. They had not yet received chemotherapy for the treatment of incurable disease. Only patients who had adenocarcinoma with a special marker (activating EGFR mutations) were allowed in this study. This was done because the chances of success were higher in tumours with the marker. Activating EGFR mutations are known to drive tumour growth and survival.

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 that work in a similar way were tested in this study.

All patients in this study had recently learned that they have incurable NSCLC. For most patients, the cancer had already spread to other organs. This study tested whether afatinib is more effective than gefitinib in stopping the cancer from growing.

Which medicines were studied?

Researchers studied the medicines "afatinib" and "gefitinib" as the first treatment given after diagnosis of advanced/metastatic NSCLC (first-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
- **Gefitinib** 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),
- the time from starting the medicines until the patients stopped taking the medicines for any reason (time to treatment failure), and
- the time from starting the medicines until the patients died from cancer or for any other reason (overall survival). As the study is still ongoing, the overall survival analysis will be done later.

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

Who participated in the study?

Only patients with incurable adenocarcinoma of the lung (stage IIIB or IV) took part in this study. Their tumour needed to have a special marker (activating EGFR mutations Del 19 and/or L858R). The patients did not have any chemotherapy for the treatment of incurable disease before.

Altogether 319 patients took part; 122 were men and 197 were women. Patients were on average 62 years old. The youngest patient was 30 years and the oldest patient was 89 years. Most patients were from Asia (159; from China, Hong Kong, Korea, Singapore, Taiwan) and from Europe (110; from France, Germany, Ireland, Norway, Spain, Sweden, and United Kingdom). Some patients were from Canada (31) and Australia (19).

How was this study performed?

The 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 gefitinib. 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.

- **Gefitinib group**: Patients took 1 tablet with 250 mg of gefitinib every day. A reduction of the dose is not an option provided in the prescribing information. If the side effects became intolerable, the patients could stop taking the medicine for 14 days. If the patients felt better after the pause, they started the medicine again.

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 doctor and the patients decided whether the medicines should be stopped.

In this study, most patients stopped the medicines when their cancer grew again. These patients then started taking other medicines. Some patients continued even when their cancer grew again. For these patients the doctors thought that the medicines would still help.

What were the results of this study?

This study compared 2 different medicines for the treatment of lung cancer. Researchers used 3 different methods to see which one was more effective. The results of 2 out of 3 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 calculation was done when 250 patients had either of these events.

Second, researchers measured the time it took from starting the medicines until the patients stopped taking the medicines for any reason (time to treatment failure).

Third, researchers plan to measure the time from starting the medicines until the patients die from cancer or for any other reason (overall survival). As the study is still ongoing, this analysis of overall survival will be done later.

To be sure that the results they got for progression-free survival and time to treatment failure 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?

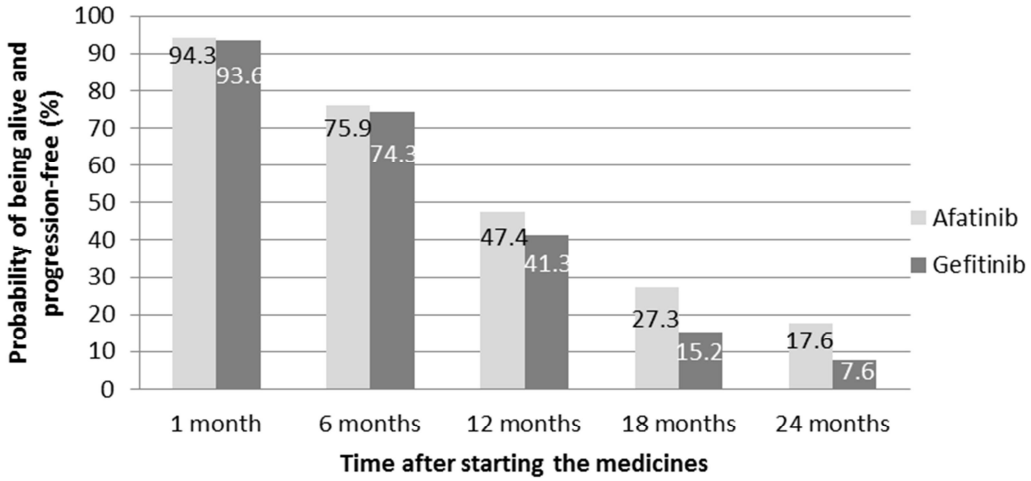
A total of 160 patients took afatinib and 159 patients took gefitinib. Patients generally took afatinib (median of 415.5 days) longer than they took gefitinib (median of 351.0 days).

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 gefitinib group.

The risk of the cancer growing again or the patient dying was 26.8% lower for patients in the afatinib group than for patients in the gefitinib group. This result was unlikely to have come about by chance (p=0.0165). The average (median) time it took from starting the medicines until the cancer started growing again or the patient died was 11.04 months for patients who took afatinib and 10.94 months for patients who took gefitinib.

The graph below shows the probability of being alive and progression-free at 1, 6, 12, 18, and 24 months after patients started taking the medicines.



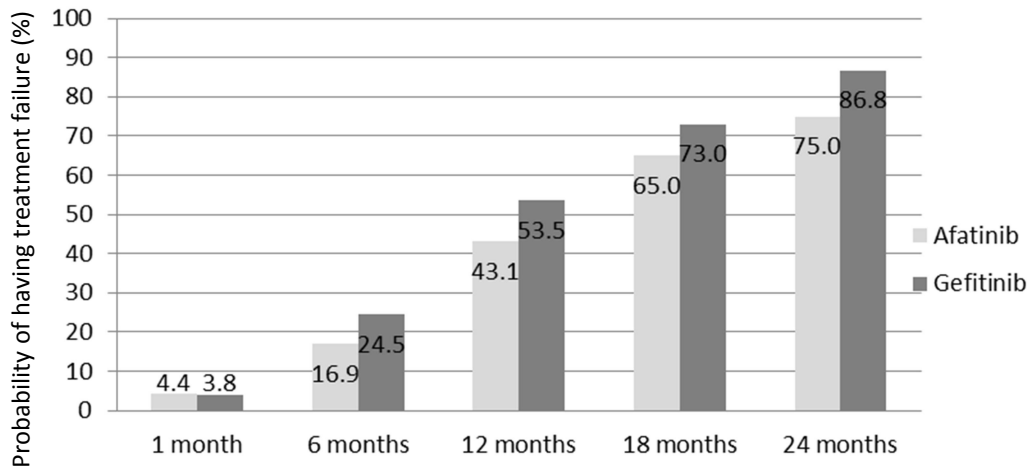
This picture shows the probability of being alive and without progression of the tumour. From left to right you see the time after starting the medicines. The assessment was done at 1, 6, 12, 18, and 24 months. At each time point you see 2 bars, light-grey for afatinib and dark grey for gefitinib. Overall, risk of the cancer growing again or the patient dying was lower for patients in the afatinib group than for patients in the gefitinib group.

Was there a difference in between the 2 medicines for 'time to treatment failure'?

Yes. In this study a difference between the 2 medicines was seen for time to treatment failure. There was an advantage for patients who took afatinib. Patients in the afatinib group were less likely to have treatment failure than patients in the gefitinib group.

The risk of having treatment failure was 27.2% lower for patients in the afatinib group than for patients in the gefitinib group. This result was unlikely to have come about by chance (p=0.0073). The average (median) time it took from starting the medicines until the patients stopped taking the medicines for any reason was 13.67 months for patients who took afatinib and 11.53 months for patients who took gefitinib.

The graph on the next page shows the probability of having treatment failure after 1,6,12, 18, and 24 months.



This picture shows the probability of having treatment failure. From left to right you see the time after starting the medicines. The assessment was done at 1, 6, 12, 18, and 24 months. At each time point you see 2 bars, light-grey for afatinib and dark grey for gefitinib. Overall, the risk of having treatment failure was lower for patients in the afatinib group than for patients in the gefitinib 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 the 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 (97.5% in the afatinib group and 96.2% in the gefitinib 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 29.4% of patients and in the gefitinib group 16.4% 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 gefitinib. Only severe (CTCAE grade 3) side effects that were seen in more than 3 patients in either group are shown.

	Afatinib (160 patients)	**Gefitinib (159 patients)**
Patients who had severe (CTCAE grade 3) side effects related to the study medicines	47 patients (29.4%)	26 patients (16.4%)
Frequent, loose bowel movements (Diarrhoea)	19 patients (11.9%)	2 patients (1.3%)
Inflamed and sore mouth (Stomatitis)	6 patients (3.8%)	0 patients (0.0%)
Abnormal change in colour, appearance, or texture of skin (Rash)	8 patients (5.0%)	4 patients (2.5%)
Feeling tired (Fatigue)	4 patients (2.5%)	0 patients (0.0%)
Feeling weak (Asthenia)	5 patients (3.1%)	0 patients (0.0%)
Increase in enzyme indicating liver injury (Alanine aminotransferase increased)	0 patients (0.0%)	12 patients (7.5%)
Increase in enzyme indicating liver injury (Aspartate aminotransferase increased)	0 patients (0.0%)	4 patients (2.5%)

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 14.4% in the afatinib group and 13.8% in the gefitinib group.

A similar percentage of patients in the afatinib (44.4%) and gefitinib (37.1%) 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 (10.6%) than in the gefitinib group (4.4%) had such serious side effects. In the afatinib group no patient (0.0%) and in the gefitinib group 1 patient (0.6%) 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 1200.123. The full title of the study is:

LUX-Lung 7: A randomised, open-label Phase IIb trial of afatinib versus gefitinib as first-line treatment of patients with EGFR mutation positive advanced adenocarcinoma of the lung

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 (2011-001814-33) or at www.clinicaltrials.gov by searching for the NCT number (NCT01466660).