

Dear Reader,

Pharmaceutical companies (sponsors) plan and conduct clinical studies to test medicines. Afterwards, they write 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. The sponsor for this study was Boehringer Ingelheim.

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 may not apply to everybody.

This study started in December 2011. Only a few patients are still in the ongoing study. 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 April 2016.

What was the study about?

This study compared 2 cancer medicines (afatinib and gefitinib) to each other. Both medicines are already used to treat patients with Non-Small Cell Lung Cancer (NSCLC). The patients in this study had incurable adenocarcinoma, which is a specific type of NSCLC. Only patients who had adenocarcinoma with a special marker (activating EGFR mutations) were allowed in this study. An activating EGFR mutation is known to drive tumour growth. The chance of treatment success is higher in patients who have tumours with the EGFR marker.

All patients in this study recently learned that they had incurable adenocarcinoma. They had not yet received chemotherapy for the treatment of their incurable adenocarcinoma. For most patients, the cancer had already spread to other organs (metastatic cancer). This study tested whether afatinib is more effective than gefitinib as the first medicine to treat their cancer.

Why was the research needed?

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 at a late stage. This means that surgery is no longer possible and that the cancer has already spread into other organs (metastasised). Only 15 out of every 100 people (15%) diagnosed with incurable NSCLC will survive for 5 years or more after diagnosis. New medicines are needed to treat this type of lung cancer. Two medicines that work in a similar way to treat NSCLC were compared in this study.

Which medicines were studied?

The researchers studied 2 medicines, afatinib and gefitinib, as the first treatment given after diagnosis of advanced/metastatic adenocarcinoma (first-line therapy). Both medicines stop tumours from growing and spreading by blocking tumour growth signals.

- Afatinib permanently blocks several growth signals (EGFR and other similar growth signals) so that they can no longer function.
- Gefitinib temporarily blocks growth signals (EGFR) so that they cannot function for some time.

What did the researchers want to know?

Researchers wanted to know which medicine is more effective at stopping the cancer from growing and benefiting patients' survival. 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).
- The time from starting the medicines until the patients died from cancer or from any other cause (overall survival).

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

Who participated in the study?

Only adult 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 mutation Del 19 and/or L858R). The patients had not yet received any chemotherapy for the treatment of their incurable adenocarcinoma.

A total of 319 patients took part; 122 were men and 197 were women. Patients were on average 63 years old. The youngest patient was 30 years and the oldest patient was 89 years. Most patients were from Asia (159 patients from China, Hong Kong, Korea, Singapore, and Taiwan) and from Europe (110 patients from France, Germany, Ireland, Norway, Spain, Sweden, and United Kingdom). Some patients were from Canada (31 patients) and Australia (19 patients).

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 and the other group took gefitinib. Patients knew which medicine they took. Doctors also knew which medicine the patients took. This is called an 'open-label design'.

The medicines were taken as follows:

- **Afatinib group:** Patients took 1 tablet of 40 mg 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 patients experienced any side effects and if the side effects were tolerable to the patient.
- **Gefitinib group:** Patients took 1 tablet of 250 mg gefitinib every day. A reduction of the dose was not allowed. If the side effects became intolerable, the patients could stop taking the medicine for up to 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.
- Doctors collected information on side effects.
- At some specific visits, the size of their tumour was measured and their blood was tested to check their health.

The doctors looked after each patient and checked their results. The doctors did more medical tests when needed. Together with the patients they decided whether the dose of the medicine 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 on the study medicines 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 incurable adenocarcinoma. The researchers used 3 different methods to see which medicine was more effective.

First, the 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, the 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, the researchers measured the time from starting the medicines until the patients died from cancer or from any other cause (overall survival). At the time of this analysis, 226 patients had died. Patients still alive had been followed up for an average (median) time of 42.6 months.

To be sure that the results are reliable, researchers test whether the results could have come about by chance alone. This is done by using statistical tests. Some of these statistical tests involve the calculation of probabilities or so-called 'p-values'. A small p-value (smaller than 0.05) shows that the differences between the medicines are unlikely due to chance. Larger p-values show that differences between the medicines are possibly due to chance. The number of patients in this study was not high enough to use such tests to confirm differences between medicines. In such a case, researchers use the p-value as an initial test result (exploratory study).

How long did patients take each medicine?

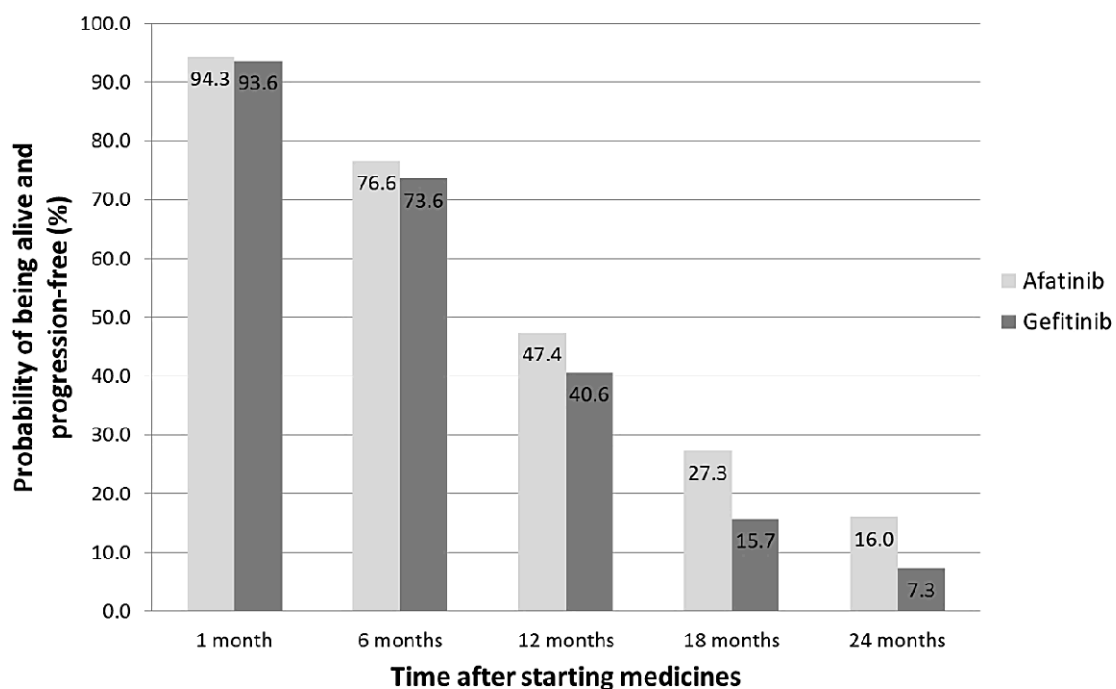
A total of 160 patients took afatinib and 159 patients took gefitinib. Patients generally took afatinib longer (median of 415.5 days) than they took gefitinib (median of 351.0 days).

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 26.3% lower for patients in the afatinib group than for patients in the gefitinib group. This result was unlikely to have come about by chance ($p=0.0178$). 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 10.91 months for patients who took gefitinib. These results are based on information collected during the study up to April 2016. These findings are similar to the previous results that were based on information collected up to August 2015.

The graph on the next page shows the probability of being alive and progression-free after patients started taking the medicines.



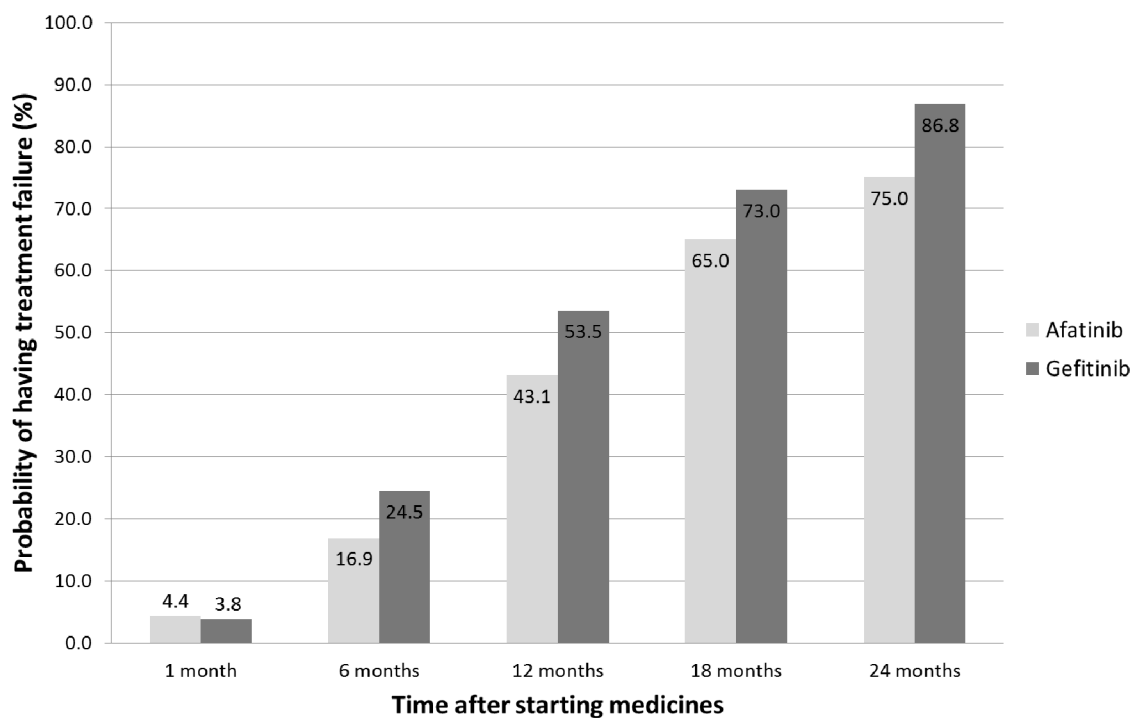
This picture shows the probability of being alive and without the cancer growing again (progression-free). From left to right you see the time after starting the medicines. This picture shows the assessments done at 1, 6, 12, 18, and 24 months. At each time point, you see 2 bars, light grey for afatinib and dark grey for gefitinib. Overall, the probability of being alive and without the cancer growing again was higher for patients in the afatinib group than for patients in the gefitinib group. A larger difference between the afatinib group and the gefitinib group was seen over time.

Was there a difference 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 the 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 treatment failure was 25.0% lower for patients in the afatinib group than for patients in the gefitinib group. This result was unlikely to have come about by chance ($p=0.0136$). 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. These results are based on information collected during the study up to April 2016. These findings are similar to the previous results that were based on information collected up to August 2015.

The graph on the next page shows the probability of having treatment failure after patients started taking the medicines.



This picture shows the probability of having treatment failure. From left to right you see the time after starting the medicines. This picture shows the assessments 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.

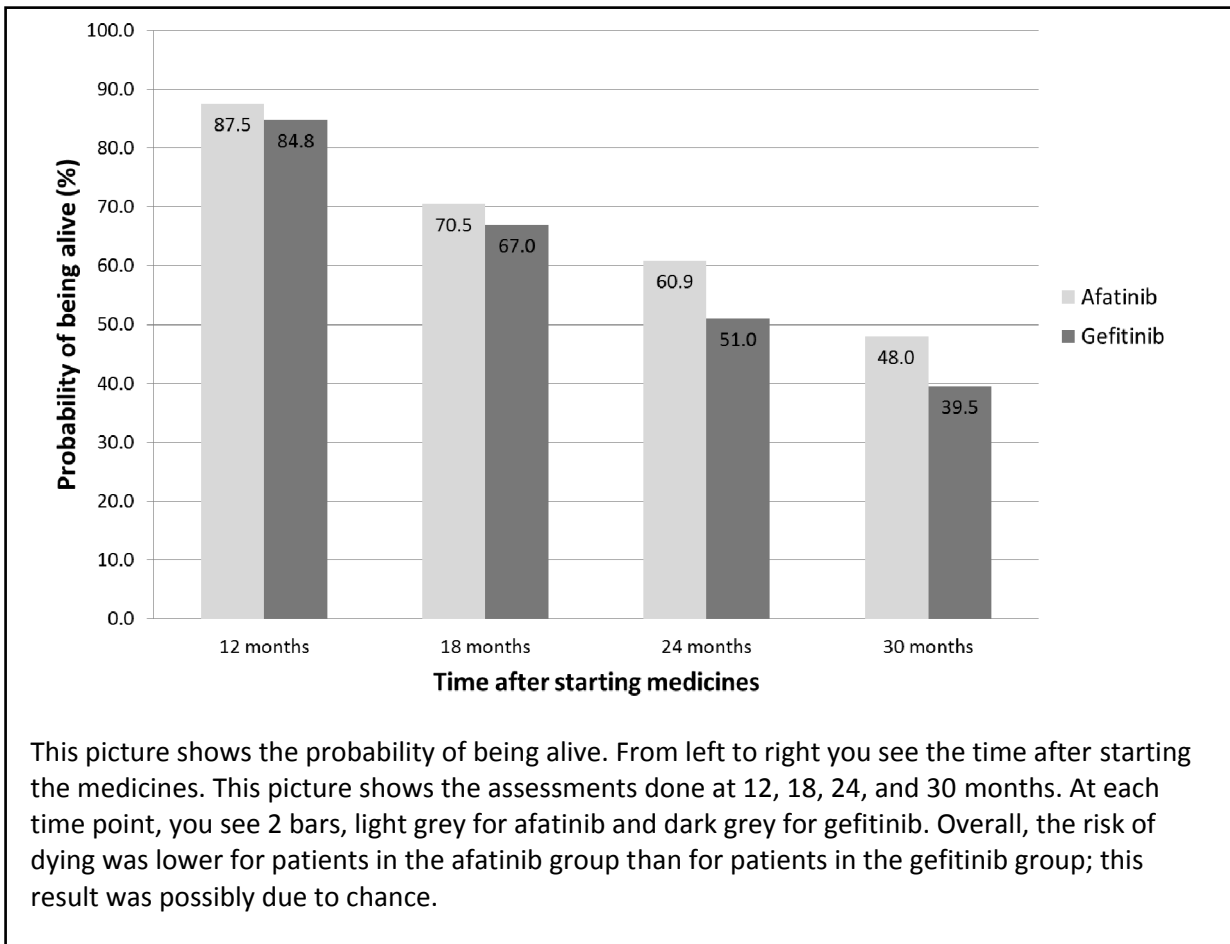
Was there a difference between the 2 medicines for 'overall survival'?

At the time of the analysis of overall survival, 109 patients (68.1%) in the afatinib group and 117 patients (73.6%) in the gefitinib group had died. Most patients had already stopped taking afatinib or gefitinib and had started other cancer treatments at the time they died. Patients still alive had been followed-up for an average (median) time of 42.6 months.

The risk of dying was 14.0% lower for patients in the afatinib group than for patients in the gefitinib group. This result was possibly due to chance ($p=0.2580$). The number of patients in this study was not high enough to use statistical tests to confirm a difference in overall survival between groups. Most patients took other cancer treatments after stopping afatinib and gefitinib. These other cancer treatments may have affected the results for overall survival.

The average (median) time it took from starting the medicines until the patient died was 27.86 months for patients who took afatinib and 24.54 months for patients who took gefitinib.

The graph below shows the probability of being alive after patients started taking the medicines.



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

In this study, almost all patients (97.5% of patients in the afatinib group and 96.2% of patients 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.

A total of 29.4% of patients in the afatinib group and 17.6% of patients in the gefitinib group had severe side effects likely caused by the study medicines. A 'severe' side effect means it made the patient go to the hospital, stay longer in the hospital, or prevented the patient from carrying out their normal activities, but the side effect was not life-threatening. Few patients (1.9% of patients in the afatinib group and 1.3% of patients in the gefitinib group) had very severe side effects likely caused by the study medicines. A 'very severe' side effect means it was life-threatening and needed urgent attention by a doctor.

The table below shows severe side effects likely caused by afatinib or gefitinib. Only severe 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 side effects related to the study medicine	47 patients (29.4%)	28 patients (17.6%)
Frequent, loose bowel movements (Diarrhoea)	20 patients (12.5%)	2 patients (1.3%)
Abnormal change in colour, appearance, or texture of skin (Rash)	8 patients (5.0%)	4 patients (2.5%)
Inflamed and sore mouth (Stomatitis)	6 patients (3.8%)	0 patients (0%)
Feeling weak (Asthenia)	5 patients (3.1%)	0 patients (0%)
Feeling tired (Fatigue)	4 patients (2.5%)	0 patients (0%)
Increase in enzyme indicating liver injury (Alanine aminotransferase increased)	0 patients (0%)	12 patients (7.5%)
Increase in enzyme indicating liver injury (Aspartate aminotransferase increased)	0 patients (0%)	4 patients (2.5%)

Most side effects were manageable with the allowed dose adjustments for afatinib, 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 15.6% in the afatinib group and 13.2% in the gefitinib group. Only 6.3% of patients in each group left the study early due to side effects related to the study medicines.

A similar percentage of patients in the afatinib (46.3%) and gefitinib (40.3%) 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 the death of the patient. Several serious side effects were likely caused by the study medicines. More patients in the afatinib group (10.6%) than in the gefitinib group (5.7%) had serious side effects related to the study medicines. No patient in the afatinib group and 1 patient (0.6%) in the gefitinib group died from serious side effects likely caused by study medicines. No patient in the afatinib

group and 4 patients (2.5%) in the gefitinib group had a serious side effect of interstitial lung disease (a disease that affects the space around the air sacs of the lungs) that was likely caused by study medicines.

What else is important to know?

Comments on the study

This summary shows results only from this study. Other studies may have different results.

Important notice

This study does not represent all of 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).