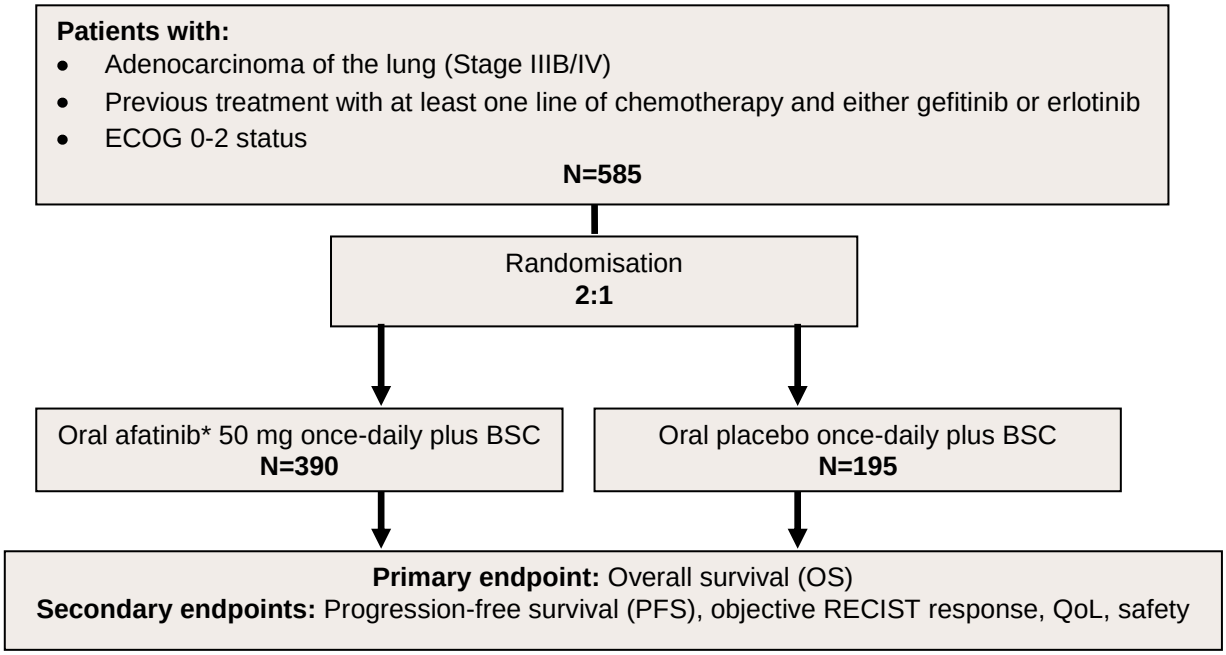
The LUX-Lung 1 clinical trial

FACTSHEET

1. What is the LUX-Lung 1 trial?[1]

LUX-Lung 1 is a clinical Phase IIb/III randomised, double-blind study evaluating afatinib* in combination with best supportive care (BSC) versus placebo plus BSC in patients with advanced non-small-cell lung cancer (NSCLC). Patients' disease has progressed after prior chemotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) gefitinib or erlotinib treatment. Due to the study inclusion criteria a high proportion of patients that may have mutated EGF receptors in their tumours were included.

2. What is the LUX-Lung 1 trial design?



3. How many patients were involved in the LUX-Lung 1 trial?

585 male and female patients took part in the LUX-Lung 1 trial.

4. Where was the LUX-Lung 1 trial conducted?

*Afatinib is an investigational compound. Its safety and efficacy have not yet been fully established.

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The LUX-Lung 1 trial was carried out at 84 centres in 15 countries worldwide: USA, Canada, UK, Germany, the Netherlands, France, Spain, Italy, Belgium, China, Taiwan, South Korea, Singapore, Hong Kong and Thailand.

5. What were the clinical endpoints of the trial?

The primary endpoint was overall survival (OS). The secondary endpoints were progression-free survival (PFS), tumour shrinkage as determined by Response Evaluation Criteria in Solid Tumors (RECIST response), disease related symptom control (quality of life; QoL) and safety.

6. What were the LUX-Lung 1 trial results?

Even though the primary endpoint (OS) has not been met, afatinib* has shown to prolong PFS from 1.1 to 3.3 months, which means a threefold increase in time until disease progression. The PFS in this trial was confirmed by independent review. These results are supported by a significant increase in disease control rate (DCR; the share of patients with stabilised tumours or tumour shrinkage) and objective response rate (ORR; share of patients with tumour shrinkage or absence of tumour) compared to placebo. Furthermore, afatinib* demonstrated meaningful improvements of lung cancer related symptoms such as cough, shortness of breath (dyspnea) and pain.

Overall survival (OS) vs. Progression-free survival (PFS)

OS is the time between inclusion in a trial and the end of the patient's life by any cause (not necessarily disease related). This clinical endpoint may be **confounded by subsequent treatments** that might be given after disease progression. As individuals begin to receive more and more treatments, the ability to show survival improvement by the study medication (afatinib*) alone becomes more and more difficult.

Subsequent treatments are not provided in a controlled setting. In addition, OS can be confounded by causes of mortality unrelated to cancer.

PFS is a measure of the clinical benefit from a specific therapy. It is defined as the time between treatment initiation and objective tumour progression or death from any cause. PFS is regarded as a **more appropriate indicator of the specific/individual activity of the tested drug, as it is not obscured by subsequent treatments.** Furthermore, it describes a time period in which study medication is controlled.

	Independent review	
	Afatinib* arm	Placebo arm
Partial response (PR) regardless of confirmation	13%	0.5%
Partial response (PR) confirmed	7%	0.5%
Stable disease (SD)	51%	18%
Disease control rate (DCR)	58%	19%

There were no unexpected safety findings for afatinib*.

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NOTE: Due to its design, a high percentage of patients that may have mutated EGF receptors have been included in the LUX-Lung 1 study. With this 'EGFR-mutation enriched patient population' it was observed that these patients generally live longer than the general non-mutated patient population.

When it was observed that the cancer progressed during the trial, patients were still in a condition to receive one or more subsequent therapies including chemotherapy, antiangiogenic drugs, TKIs, or radiotherapy. Compared to the afatinib* arm, an increased number of patients in the control arm subsequently received a wider range and more lines of chemotherapy, as well as more subsequent treatment with EGFR TKIs.

A subgroup analysis of the LUX-Lung 1 trial was recently announced, suggesting benefit from afatinib* in lung cancer patients most likely to have an epidermal growth factor receptor (EGFR) mutation.[2] This data was presented at the Chicago Multidisciplinary Symposium in Thoracic Oncology 2010, USA and showed a significant four-fold extension (4.4 months vs. 1.0 month for placebo) in PFS.

The sub-group included in the analysis comprised two-thirds of all patients from the study (391/585) who were most likely to have EGFR mutations. This was determined by clinical criteria based on their response to and duration of prior treatment with EGFR-TKIs.[3]

7. Is afatinib* being investigated in further tumour types?

The LUX-Lung 1 trial is part of the LUX-Lung clinical trial programme investigating afatinib* in a number of different lung cancer patient populations.

Afatinib* is also being investigated for use in a number of other solid tumours, including breast cancer, head and neck cancer, colorectal cancer, and glioblastoma.

References:

1. Miller *et al*. Phase IIb/III double-blind randomized trial of BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2 + best supportive care (BSC) versus placebo + BSC in patients with NSCLC failing 1–2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1). Oral presentation at the 35th European Society of Medical Oncology (ESMO) annual meeting, Milan, October 2010. Abstract ID: LBA1.
2. Miller *et al*. Subgroup analysis of LUX-Lung 1: A randomized Phase III Trial of Afatinib (BIBW 2992) + Best Supportive Care (BSC) versus Placebo + BSC in Patients with NSCLC Failing 1-2 Lines of Chemotherapy and Erlotinib or Gefitinib. Oral presentation at Chicago Multidisciplinary Symposium in Thoracic Oncology, Chicago, USA, 10 December, 2010.
3. Jackman D *et al*. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 2010; 28 (2): 357-60.

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