**Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung: final analysis of the randomised phase 3 Lux-Lung 8 trial**

**Supplementary appendix**

## Table of Contents



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## Supplementary Tables

| Adverse event | Afatinib (n=392) | | | | Erlotinib (n=395) | | | |
|---|---|---|---|---|---|---|---|---|
| | All grades | Grade 3 | Grade 4 | Grade 5 | All grades | Grade 3 | Grade 4 | Grade 5 |
| Total | 174 (44.4%) | 58 (14.8%) | 19 (4.8%) | 77 (19.6%) | 175 (44.3%) | 66 (16.7%) | 15 (3.8%) | 71 (18.0%) |
| Pneumonia | 26 (6.6%) | 7 (1.8%) | 2 (<1%) | 9 (2.3%) | 16 (4.1%) | 8 (2.0%) | 3 (<1%) | 3 (<1%) |
| Malignant neoplasm progression | 23 (5.9%) | | 3 (<1%) | 20 (5.1%) | 16 (4.1%) | | | 16 (4.1%) |
| Diarrhoea | 18 (4.6%) | 12 (3.1%) | 3 (<1%) | | 7 (1.8%) | 4 (1.0%) | | |
| Dehydration | 12 (3.1%) | 6 (1.5%) | 4 (1.0%) | | 4 (1.0%) | 3 (<1%) | | |
| Dyspnoea | 12 (3.1%) | 4 (1.0%) | 3 (<1%) | 3 (<1%) | 30 (7.6%) | 11 (2.8%) | 3 (<1%) | 10 (2.5%) |
| General physical health deterioration | 11 (2.8%) | 4 (1.0%) | 1 (<1%) | 5 (1.3%) | 6 (1.5%) | 4 (1.0%) | | |
| Pulmonary embolism | 10 (2.6%) | 4 (1.0%) | | 4 (1.0%) | 5 (1.3%) | 1 (<1%) | 2 (<1%) | |
| Sepsis | 9 (2.3%) | 1 (<1%) | 3 (0.8%) | 4 (1.0%) | 2 (<1%) | | 1 (<1%) | 1 (<1%) |
| Acute renal failure | 9 (2.3%) | 4 (1.0%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | | |
| Asthenia | 6 (1.5%) | 4 (1.0%) | | 1 (<1%) | 3 (<1%) | 2 (<1%) | 1 (<1%) | |
| Anaemia | 5 (1.3%) | 3 (<1%) | 1 (<1%) | | 2 (<1%) | 1 (<1%) | | |
| COPD | 5 (1.3%) | 3 (<1%) | | | 4 (1.0%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| Haemoptysis | 5 (1.3%) | 2 (<1%) | | 2 (<1%) | 10 (2.5%) | 2 (<1%) | 1 (<1%) | |
| Abdominal pain | 5 (1.3%) | 3 (<1%) | 1 (<1%) | | 5 (1.3%) | 3 (<1%) | 1 (<1%) | |
| Convulsion | 4 (1.0%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) | | | |
| Atrial fibrillation | 4 (1.0%) | 3 (<1%) | | | 2 (<1%) | | | |
| Interstitial lung disease | 4 (1.0%) | 1 (<1%) | 1 (<1%) | 2 (<1%) | 1 (<1%) | | | 1 (<1%) |
| Vomiting | 4 (1.0%) | 2 (<1%) | | | 5 (1.3%) | 3 (<1%) | 1 (<1%) | |
| Death | 4 (1.0%) | | | 4 (1.0%) | 2 (<1%) | | | |
| Pyrexia | 3 (<1%) | 2 (<1%) | | | 4 (1.0%) | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pleural effusion | 3 (<1%) | | 1 (<1%) | | 6 (1.5%) | 4 (1.0%) | | |
| Dizziness | 2 (<1%) | 2 (<1%) | | | 4 (1.0%) | 1 (<1%) | | |
| Pneumothorax | 2 (<1%) | | | | 4 (1.0%) | | | |
| Bronchitis | 2 (<1%) | | | | 6 (1.5%) | 6 (1.5%) | | |
| Lung infection | 2 (<1%) | 1 (<1%) | | 1 (<1%) | 5 (1.3%) | 2 (<1%) | 1 (<1%) | 1 (<1%) |
| Metastases to CNS | 2 (<1%) | | 1 (<1%) | 1 (<1%) | 6 (1.5%) | 2 (<1%) | 1 (<1%) | |
| Respiratory failure | 2 (<1%) | 1 (<1%) | | 1 (<1%) | 12 (3.0%) | 1 (<1%) | 3 (<1%) | 8 (2.0%) |
| Hypercalcaemia | 1 (<1%) | | 1 (<1%) | | 6 (1.5%) | 2 (<1%) | 2 (<1%) | |
| Chest pain | | | | | 6 (1.5%) | 4 (1.0%) | | |
| Myocardial infarction | | | | | 4 (1.0%) | 1 (<1%) | | 3 (<1%) |

Data shown n (%) are serious adverse events in ≥1% of patients with serious adverse events (all grades), or ≥1% of patients with grade 3–5 serious adverse events in any treatment group.

***Table S1:*** **Serious adverse events**

| Adverse event | Afatinib (n=392) | | | | Erlotinib (n=395) | | | |
|---|---|---|---|---|---|---|---|---|
| | All grades | Grade 3 | Grade 4 | Grade 5 | All grades | Grade 3 | Grade 4 | Grade 5 |
| Total | 390 (100%) | 124 (32%) | 23 (6%) | 77 (20%) | 385 (98%) | 138 (35%) | 18 (5%) | 71 (18%) |
| Diarrhoea | 293 (75%) | 39 (10%) | 3 (<1%) | | 164 (42%) | 12 (3%) | 1 (<1%) | |
| Rash or acne* | 272 (69%) | 26 (7%) | | | 277 (70%) | 42 (11%) | | |
| Fatigue* | 132 (34%) | 18 (5%) | 1 (<1%) | 1 (<1%) | 120 (30%) | 23 (6%) | 3 (<1%) | |
| Stomatitis* | 115 (29%) | 16 (4%) | | | 39 (10%) | 2 (<1%) | | |
| Decreased appetite | 97 (25%) | 12 (3%) | | | 103 (26%) | 8 (2%) | | |
| Nausea | 81 (21%) | 6 (2%) | | | 65 (17%) | 4 (1%) | 1 (<1%) | |
| Dyspnoea | 79 (20%) | 12 (3%) | 3 (<1%) | 3 (<1%) | 94 (24%) | 18 (5%) | 4 (1%) | 10 (3%) |
| Cough | 67 (17%) | 2 (<1%) | | | 69 (18%) | 2 (<1%) | | |
| Vomiting | 51 (13%) | 3 (<1%) | | | 41 (10%) | 4 (1%) | 1 (<1%) | |
| Haemoptysis | 49 (13%) | 2 (<1%) | | 2 (<1%) | 49 (12%) | 2 (<1%) | 1 (<1%) | |
| Constipation | 43 (11%) | | | | 43 (11%) | 1 (<1%) | | |
| Paronychia* | 43 (11%) | 2 (<1%) | | | 20 (5%) | 1 (<1%) | | |
| Pruritus | 38 (10%) | 1 (<1%) | | | 52 (13%) | | | |
| Weight decreased | 38 (10%) | 2 (<1%) | | | 52 (13%) | 2 (<1%) | | |
| Dry skin | 36 (9%) | 2 (<1%) | | | 47 (12%) | | | |
| Anaemia | 34 (9%) | 8 (2%) | 2 (<1%) | | 43 (11%) | 7 (2%) | | |

Data shown n (%) are adverse events in >10% of patients with adverse events (all grades). *Grouped terms.

***Table S2:*** **All-cause adverse events**

| | Afatinib (n=392) | | | | Erlotinib (n=395) | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event** | All grades | Grade 3 | Grade 4 | Grade 5 | All grades | Grade 3 | Grade 4 | Grade 5 |
| Total | 104 (26.5%) | 60 (15.3%) | 2 (0.5%) | | 56 (14.2%) | 37 (9.4%) | | |
| Diarrhoea | 58 (14.8%) | 22 (5.6%) | 2 (0.5%) | | 14 (3.5%) | 5 (1.3%) | | |
| Rash or acne* | 23 (5.9%) | 15 (3.8%) | | | 37 (9.4%) | 28 (7.1%) | | |
| Stomatitis* | 12 (3.1%) | 11 (2.8%) | | | | | | |
| Fatigue* | 5 (1.3%) | 4 (1.0%) | | | 3 (<1.0%) | 2 (<1.0%) | | |

Data shown n (%) are adverse events in >1% of patients (all grades). *Grouped terms.

***Table S3:*** **Adverse events leading to dose reduction**

| | Afatinib (n=392) | | | | Erlotinib (n=395) | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event** | All grades | Grade 3 | Grade 4 | Grade 5 | All grades | Grade 3 | Grade 4 | Grade 5 |
| Total | 80 (20.4%) | 33 (8.4%) | 16 (4.1%) | 2 (<1%) | 66 (16.7%) | 35 (8.9%) | 8 (2.0%) | 7 (1.8%) |
| Diarrhoea | 16 (4.1%) | 9 (2.3%) | | | 6 (1.5%) | 4 (1.0%) | | |
| Malignant neoplasm progression | 7 (1.8%) | 2 (<1%) | 3 (<1%) | 1 (<1%) | 2 (<1%) | | 1 (<1%) | 1 (<1%) |
| Rash | 6 (1.5%) | 4 (1.0%) | | | 4 (1.0%) | 3 (<1%) | | |
| Pneumonia | 6 (1.5%) | 2 (<1%) | 3 (<1%) | | 1 (<1%) | | | |
| Dyspnoea | 5 (1.3%) | 3 (<1%) | | | 6 (1.5%) | 4 (1.0%) | | 1 (<1%) |

Data shown n (%) are adverse events in ≥1% of patients (all grades) resulting in treatment discontinuation, or ≥1% of patients with grade 3–5 adverse events resulting in treatment discontinuation in any treatment group.

***Table S4:*** **Adverse events leading to treatment discontinuation**

## Supplementary Figures

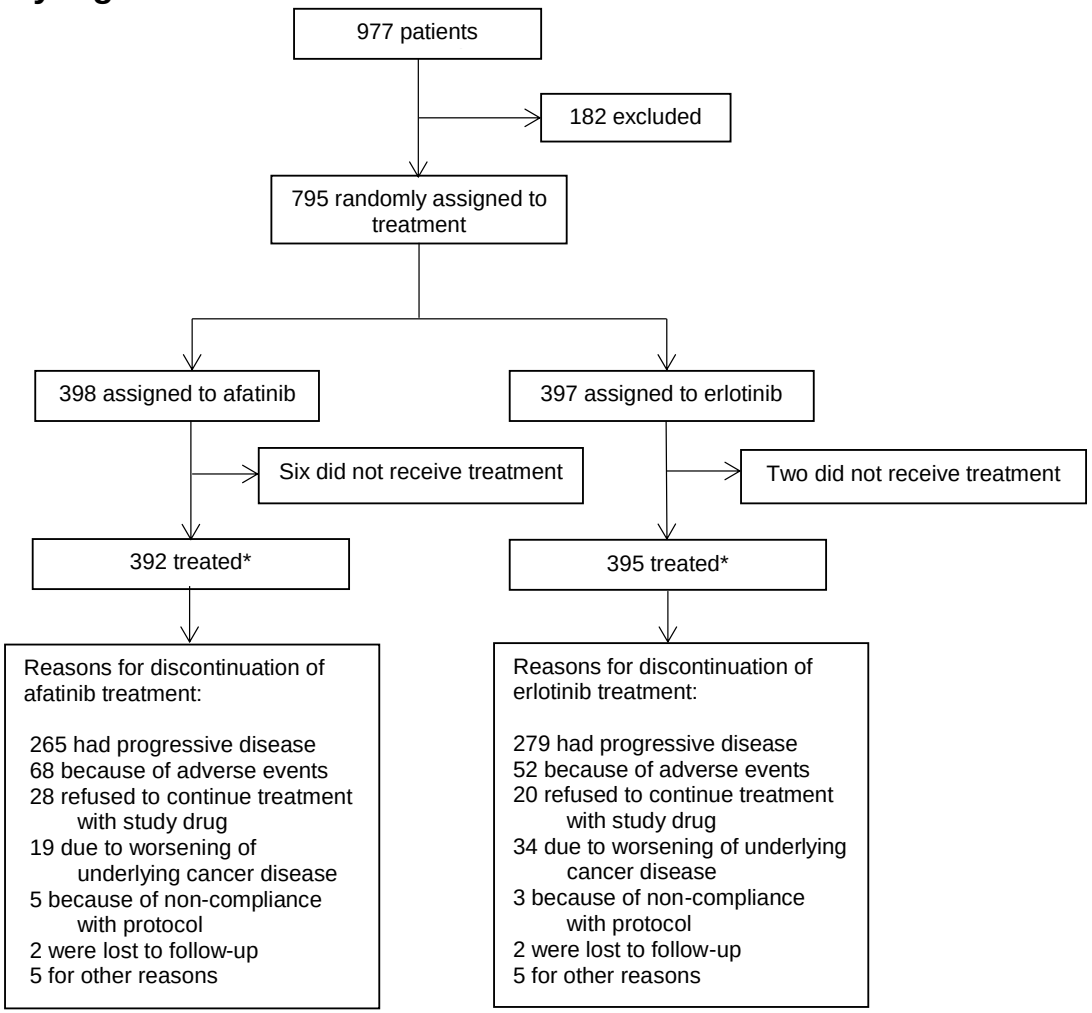


***Figure S1:* Trial profile**

*Received at least one dose of study drug.

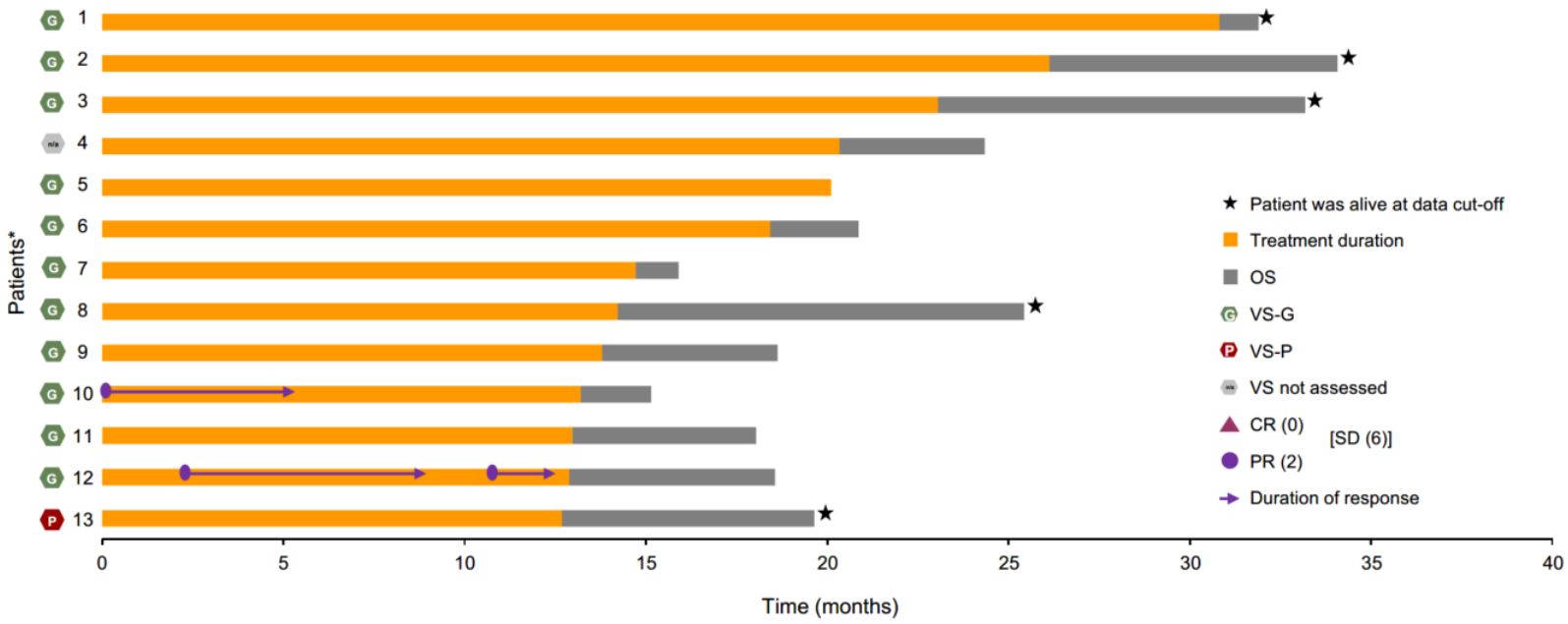


***Figure S2S1*: Efficacy outcomes and biomarkers in patients who received long-term benefit on erlotinib**

*Patients were ordered and numbered by treatment duration (at data cut-off). Next-generation sequencing was undertaken in 3/13 patients with long-term benefit. Mutation data was available for only 1 patient (not annotated in figure).

CR=complete response; PR=partial response; OS=overall survival; SD=stable disease; VS-G=VeriStrat-Good; VS-P=VeriStrat poor; WT=wild-type.