Articles

Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial

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Summary

Background Afatinib, an irreversible ErbB-family blocker, has shown preclinical activity when tested in EGFR mutant models with mutations that confer resistance to EGFR tyrosine-kinase inhibitors. We aimed to assess its efficacy in patients with advanced lung adenocarcinoma with previous treatment failure on EGFR tyrosine-kinase inhibitors.

Methods In this phase 2b/3 trial, we enrolled patients with stage IIIB or IV adenocarcinoma and an Eastern Cooperative Oncology Group performance (ECOG) performance score of 0–2 who had received one or two previous chemotherapy regimens and had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib. We used a computer-generated sequence to randomly allocate patients (2:1) to either afatinib (50 mg per day) or placebo; all patients received best supportive care. Randomisation was done in blocks of three and was stratified by sex and baseline ECOG performance status (0–1 *vs* 2). Investigators, patients, and the trial sponsor were masked to treatment assignment. The primary endpoint was overall survival (from date of randomisation to death), analysed on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT00656136.

Findings Between May 26, 2008, and Sept 21, 2009, we identified 697 patients, 585 of whom were randomly allocated to treatment (390 to afatinib, 195 to placebo). Median overall survival was 10·8 months (95% CI 10·0–12·0) in the afatinib group and 12·0 months (10·2–14·3) in the placebo group (hazard ratio 1·08, 95% CI 0·86–1·35; p=0·74). Median progression-free survival was longer in the afatinib group (3·3 months, 95% CI 2·79–4·40) than it was in the placebo group (1·1 months, 0·95–1·68; hazard ratio 0·38, 95% CI 0·31–0·48; p<0·0001). No complete responses to treatment were noted; 29 (7%) patients had a partial response in the afatinib group, as did one patient in the placebo group. Subsequent cancer treatment was given to 257 (68%) patients in the afatinib group and 153 (79%) patients in the placebo group. The most common adverse events in the afatinib group were diarrhoea (339 [87%] of 390 patients; 66 [17%] were grade 3) and rash or acne (305 [78%] patients; 56 [14%] were grade 3). These events occurred less often in the placebo group (18 [9%] of 195 patients had diarrhoea; 31 [16%] had rash or acne), all being grade 1 or 2. Drug-related serious adverse events occurred in 39 (10%) patients in the afatinib group and one (<1%) patient in the placebo group. We recorded two possibly treatment-related deaths in the afatinib group.

Interpretation Although we recorded no benefit in terms of overall survival with afatinib (which might have been affected by cancer treatments given after progression in both groups), our findings for progression-free survival and response to treatment suggest that afatinib could be of some benefit to patients with advanced lung adenocarcinoma who have failed at least 12 weeks of previous EGFR tyrosine-kinase inhibitor treatment.

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Introduction

Of patients diagnosed with advanced lung adenocarcinoma, those with activating EGFR mutations treated with first-line erlotinib or gefitinib generally have a high objective response rate (complete or partial response) and long progression-free survival and overall survival.[1–3] Nonetheless, all patients' treatment eventually fails. Like other cancers driven by mutant kinases, such as chronic myeloid leukaemia and gastrointestinal stromal tumours, acquired resistance to EGFR tyrosine-kinase inhibitors (TKIs) is most commonly characterised by the so-called gatekeeper mutation, T790M.[1–3]

Afatinib (previously called BIBW2992; Boehringer-Ingelheim Pharma GmbH, Ingelheim, Germany)[4,5] is an irreversible ErbB-family blocker, the preclinical in-vitro and in-vivo activity profile of which includes EGFR mutant models with activating EGFR mutations, including the most common mutations, L858R and deletion-19, and the exon 20 gatekeeper T790M mutations, albeit at lower potency.[4,6] Thus, we undertook this phase 2b/3 study of afatinib in patients with lung adenocarcinoma who had

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Articles

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received at least one platinum-based chemotherapy regimen, and at least 12 weeks of previous erlotinib or gefitinib treatment, a group for whom few, if any, approved treatment options are available and who we reasoned could potentially benefit from treatment that targets EGFR mutations known to be less sensitive to erlotinib and gefitinib. Patients did not need to have been tested for EGFR mutation status to enter the study, because repeat biopsy was not deemed feasible in this large, international study, and to obtain archival tumour tissue for all patients would be challenging. Instead, the requirement for at least 12 weeks of previous EGFR-TKI treatment served as an enrichment strategy for patients with EGFR mutations and acquired resistance.

Methods

Study design and patients

LUX-Lung 1 was a randomised, double-blind, multicentre, phase 2b/3 trial comparing afatinib plus best supportive care with placebo plus best supportive care, done in 86 centres in 15 countries (from three continents: Asia [China, Hong Kong, Korea, Singapore, Taiwan, Thailand], Europe [Belgium, Germany, France, Italy, The Netherlands, UK, Spain], and North America [Canada, USA]). Eligible patients had pathologically confirmed stage IIIB (with pleural effusion) or stage IV adenocarcinoma with measurable disease, had failed one or two lines of chemotherapy (including adjuvant chemotherapy), and had disease progression after at least 12 weeks of previous treatment with erlotinib or gefitinib. Tumour stage was judged according to the TNM classification system by the International Union Against Cancer (UICC) 6th edition. Patients were eligible if they were aged 18 years or older and had an Eastern Cooperative Oncology Group [ECOG] performance status of 0–2 and a life expectancy of 3 months or longer, having not received these EGFR-TKIs for at least 14 days before the first dose of the study drug. Exclusion criteria included the following: active brain metastases, pregnant or nursing women, heart disease or dysfunction, serious gastrointestinal disorders, serious active infection, and abnormal liver, renal, and haematological function.

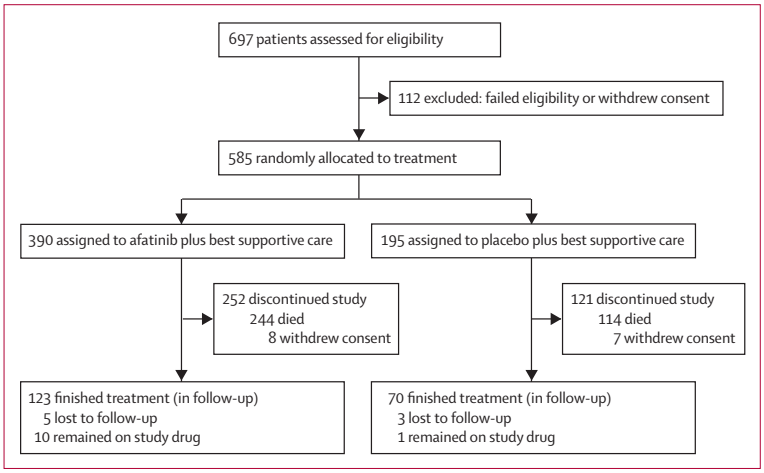

Figure 1: **Trial profile**

	Afatinib plus best supportive care (n=390)	Placebo plus best supportive care (n=195)
Age (years)	58 (30–85)	59 (32–82)
Sex		
Male	159 (41%)	78 (40%)
Female	231 (59%)	117 (60%)
ECOG performance status		
0	92 (24%)	53 (27%)
1	268 (69%)	127 (65%)
2	30 (8%)	15 (8%)
Ethnic origin		
White	121 (31%)	72 (37%)
Eastern Asian	227 (58%)	110 (56%)
Other Asian	38 (10%)	12 (6%)
Other	4 (1%)	1 (<1%)
Clinical stage (at screening)		
IIIB	15 (4%)	6 (3%)
IV	375 (96%)	189 (97%)
Smoking history		
Never-smoker	245 (63%)	121 (62%)
Ex-smoker (since >1 year before diagnosis) with <15 pack-years	27 (7%)	13 (7%)
Current or other ex-smoker	118 (30%)	61 (31%)
Number of lines of previous chemotherapy		
1	231 (59%)	119 (61%)
2	156 (40%)	74 (38%)
>2	3 (<1%)	2 (1%)
Previous platinum-based regimen	387 (99%)	195 (100%)
Previous EGFR-TKI		
Erlotinib only	215 (55%)	108 (55%)
Gefitinib only	152 (39%)	79 (41%)
Both	23 (6%)	8 (4%)
Duration of previous EGFR-TKI treatment		
Median duration (weeks)	42 (9–370)	44 (9–311)
<12 weeks	3 (<1%)	1 (<1%)
12 weeks to <24 weeks	75 (19%)	34 (17%)
24 weeks to <36 weeks	88 (23%)	38 (19%)
36 weeks to <48 weeks	50 (13%)	30 (15%)
48 weeks or more	174 (45%)	92 (47%)
Duration between end of previous EGFR-TKI treatment and randomisation		
Median duration (weeks)	5 (1–160)	4 (2–170)
<4 weeks	146 (37%)	84 (43%)
4 weeks to <8 weeks	78 (20%)	39 (20%)
8 weeks to <12 weeks	34 (9%)	15 (8%)
12 weeks or more	130 (33%)	56 (29%)
Unknown	2 (<1%)	1 (<1%)

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	Afatinib plus best supportive care (n=390)	Placebo plus best supportive care (n=195)
(Continued from previous page)		
Best response to previous EGFR-TKI treatment		
Complete or partial response	178 (46%)	85 (44%)
Stable disease	177 (45%)	97 (50%)
Progressive disease	15 (4%)	4 (2%)
Unknown	20 (5%)	9 (5%)
Systemic treatment between end of previous EGFR-TKI treatment and randomisation	104 (27%)	39 (20%)
Response (complete or partial response) or long duration (≥48 weeks) with previous EGFR-TKI treatment	257 (66%)	134 (69%)
Patients meeting Jackman criteria* of acquired resistance	133 (34%)	81 (42%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. *Complete or partial response or stable disease for more than 6 months with previous EGFR tyrosine-kinase inhibitor (TKI) treatment, short interval (≤4 weeks) from stopping previous EGFR-TKI treatment, and no intervening chemotherapy.[13]

Table 1: **Baseline characteristics**

The study protocol, designed in accordance with the Declaration of Helsinki, was approved by institutional review boards at participating centres. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly allocated in a two-to-one ratio to receive afatinib plus best supportive care or placebo plus best supportive care, stratified by sex and baseline ECOG performance status (0–1 *vs* 2). The randomisation sequence was generated by an independent team from the trial sponsor with a validated computer system (clinical trial supply system). This team was not involved in the rest of the trial. The randomisation sequence was then implemented centrally via an interactive voice response system. Patients were randomly allocated to treatment in block sizes of three. Investigators, patients, and the trial sponsor were masked to block size and treatment assignments.

Procedures

Patients received best supportive care in addition to continuous oral daily dosing of the study drug with a starting dose of 50 mg afatinib or placebo until progression or undue adverse events. If patients had drug-related adverse events (grade ≥3, assessed with National Cancer Institute Common Terminology Criteria [version 3.0]) or grade 2 diarrhoea, nausea, or vomiting for 7 or more consecutive days despite best supportive care, treatment with the study drug was paused for up to 14 days. After treatment interruption and recovery to grade 1 or lower, treatment with the study drug was restarted with the dose reduced by 10 mg; this dose reduction could be repeated in case of the occurrence of further adverse events. However, after a third occurrence, treatment with the study drug was discontinued.

EGFR mutation results, if available, from local laboratories were recorded, and all available archival tumour samples were analysed by a central laboratory (Genzyme, Cambridge, MA, USA) with PCR amplification of exons 18–21 with bidirectional direct sequencing, and all mutations confirmed in duplicate. Additionally, serum samples obtained at screening were frozen (at –80°C) and later analysed for mutations with the Therascreen (EGFR-29) kit (Qiagen, Gaithersburg, MD, USA).

Safety assessments included adverse-event assessments, haematological tests, and biochemical tests of serum samples, all of which were done every 28-day cycle (twice during cycles one and two). Left ventricular ejection fraction was measured by echocardiogram or radionucleotide scan every three cycles to monitor for possible cardiac toxicity.

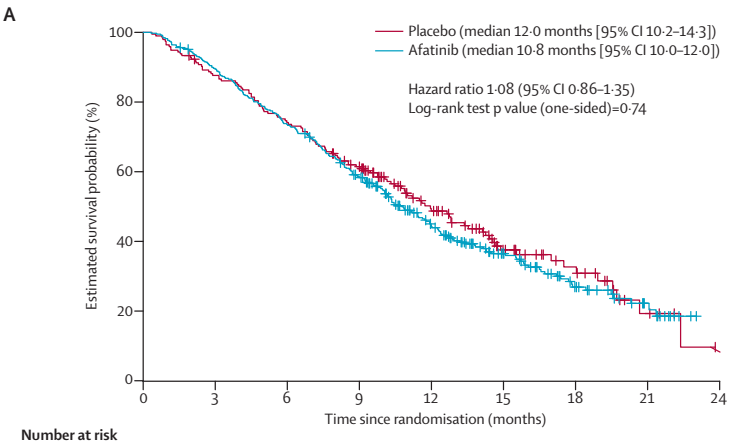
Tumour assessments were done by CT or MRI scans of patients' chest to pelvis at screening, at weeks 4, 8, and 12, and at 8-week intervals thereafter. Although both methods were available, almost all tumour assessments were with CT scans of the chest and abdomen. Brain imaging or bone scans were done as needed. Independent review (BioClinica, Newtown, PA, USA) consisted of two primary radiologist reviewers and a third for adjudication. Final review was by an oncologist and the adjudicator, with integration of radiological assessment with clinical information.

Health-related quality-of-life (HRQoL) benefits were assessed with the self-administered cancer-specific European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-C30,[7] the lung cancer-specific EORTC QLQ-LC13.[8]

	n	EGFR mutation positive in all assessable patients	EGFR mutation positive in assessable patients in the afatinib group	EGFR mutation positive in assessable patients in the placebo group
All patients meeting entry criteria	585	96/141 (68%)	62/93 (67%)	34/48 (71%)
Duration of previous EGFR-TKI treatment				
<24 weeks	113	8/24 (33%)	6/17 (35%)	2/7 (29%)
≥24 weeks	472	88/117 (75%)	56/76 (74%)	32/41 (78%)
≥48 weeks	266	60/72 (83%)	38/46 (83%)	22/26 (85%)
Complete or partial response with previous EGFR-TKI treatment	263	58/66 (88%)	42/46 (91%)	16/20 (80%)
Complete or partial response with previous EGFR-TKI treatment or duration of treatment ≥48 weeks	391	86/103 (83%)	55/66 (83%)	31/37 (84%)

Data are number positive/number tested by optional tissue testing (either local or central laboratory; %). TKI=tyrosine-kinase inhibitor.

Table 2: **Analysis of key subgroups for EGFR mutation positivity by tissue testing**



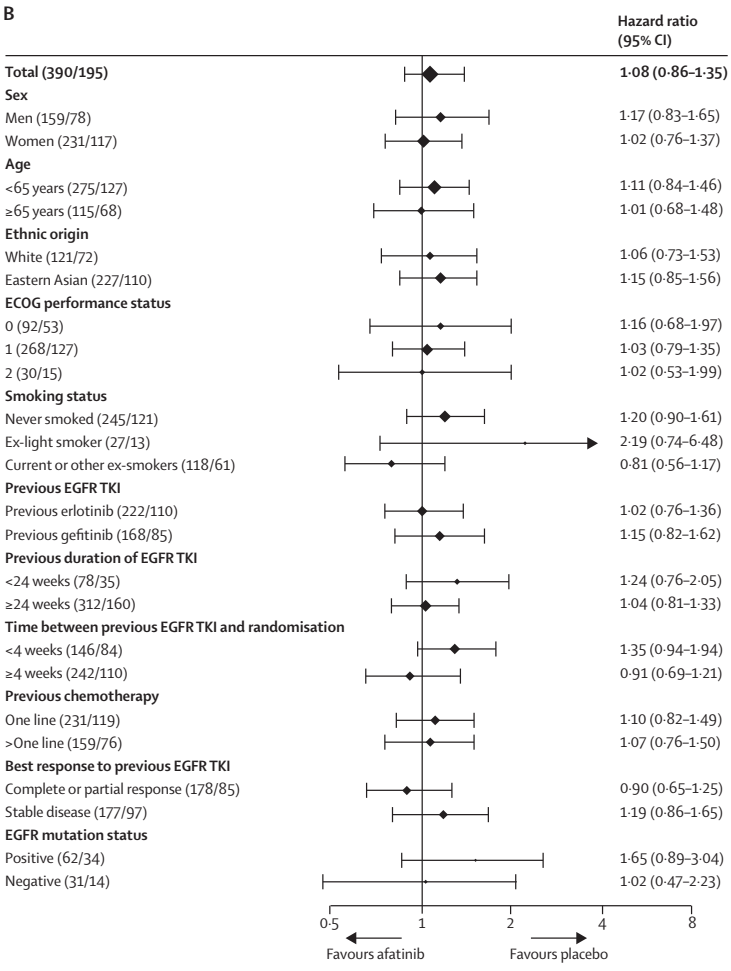


***Figure 2*: Overall survival**
(A) Kaplan-Meier curve for all patients at primary analysis (358 events). (B) Forest plot for subgroup analyses. ECOG=Eastern Cooperative Oncology Group.

Statistical analysis

We did a planned analysis at the end of phase 2b based on objective response rate by an independent data monitoring committee. The requirement of having three or more responses (irrespective of confirmation) in the first 40 afatinib-treated patients was met (ten responses were recorded), and the study proceeded to full phase 3 accrual.

The primary endpoint of this study was overall survival. The key assumption that led to the selection of this primary endpoint was that the survival in the control group in this trial was expected to be short and similar to the 4·7-month control median overall survival in the second-line and third-line non-small-cell lung cancer (NSCLC) phase 3 trial of erlotinib.[9] The primary analysis was predefined, planned to take place after 359 events had occurred. Secondary endpoints included progression-free survival, objective response rate (using Response Evaluation Criteria in Solid Tumors version 1.0), response duration, safety, and health-related quality of life. Statistical analyses were done by intent to treat.

Overall survival was calculated from the date of randomisation to death. Patients alive at analysis were censored at the last contact date. We compared overall survival between treatment groups using a one-sided, α=0·025, log-rank test, stratified by baseline ECOG performance status (0–1 *vs* 2) and sex. We needed 560 patients with 359 events to have a 90% power at the one-sided 0·025 significance level to reject the null hypothesis, given a true overall survival hazard ratio (HR) of 0·70 (eg, 6·7 months *vs* 4·7 months median). We calculated median overall survival from the Kaplan-Meier estimates and 95% CIs using Greenwood's SE estimate. We estimated the HR for overall survival from the Cox proportional hazard model stratified by ECOG performance status and sex.

We measured progression-free survival from start of treatment to disease progression or death, whichever occurred first; we censored at the last imaging date if no progression or death. We analysed progression-free survival in much the same way as we analysed overall survival. We calculated the duration of objective response in much the same way that we calculated progression-free survival, but only for patients who showed objective response and the calculation was started from when the objective response was first recorded. Similarly, duration of disease control was calculated only for patients who showed disease control and started from the date of randomisation. We calculated median duration of response and disease control using Kaplan-Meier estimates with 95% CIs.

The analysis of HRQoL focused on three most commonly expected NSCLC-related symptoms—ie, cough (Q1 of LC13), dyspnoea (Q3 and Q5 of LC13), and pain (Q9 and Q19 of C30). Scoring of the symptoms followed the EORTC scoring algorithm.[10] The proportion of patients who were classified as improved (≥10-point increase from baseline score), stable, or worsened

(≥10-point decrease from baseline score) were calculated and compared between treatment groups.

To explore the possible effect of cancer treatments after progression on overall survival, we did two analyses. The first was a prespecified inverse probability of censoring weighted Cox model.[11,12] Patients who had taken subsequent cancer treatment were censored at the time of such treatment. We calculated the probability of censoring taking into account important prognostic factors (eg, sex, ethnic origin, smoking history) and post-randomisation variables (eg, time to response and ECOG performance status over time). The second was a post-hoc subgroup analysis in patients who did not take any subsequent systemic cancer treatments compared with those who did.

Several subgroup variables were prespecified to explore treatment effects on overall survival, progression-free survival, and objective response rate between subgroups—eg, demographics (eg, age, sex, ECOG performance status), baseline disease characteristics (eg, EGFR mutation status), features of previous treatment with a EGFR TKI (eg, duration, best response). We also explored two post-hoc subgroup variables: patients clinically enriched for EGFR mutations (best response to previous EGFR TKI was complete or partial response, duration of previous EGFR TKI ≥48 weeks, or both) and those meeting the resistance criteria to EGFR TKIs described by Jackman and colleagues (these criteria were published after enrolment was complete).[11,12] We used SAS version 9.2 for statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT00656136.

Role of the funding source

The trial sponsor collected and analysed the data. The trial was designed by the trial sponsor; the design was finalised in collaboration with JC-HY and VAM. JC-HY and VAM wrote the paper, which was approved by all authors. The investigators interpreted the data independently. The corresponding author had full access to all the data and final responsibility to submit for publication.

Results

Between May 26, 2008, and Sept 21, 2009, we randomly allocated 585 patients to receive either afatinib plus best supportive care (390 patients) or placebo plus best supportive care (195 patients; figure 1). A summary of best supportive care in this trial is shown in the appendix. Baseline characteristics were much the same between the two groups (table 1). Most patients (361 [62%] of 585) were from Asian countries and around two-thirds (387 of 585) were Asian by ethnic origin. Most patients were never-smokers (table 1).

All patients had received previous EGFR-TKI treatment, with most having a short duration between the end of their treatment and randomisation, and more than half having received such treatment for more than 36 weeks (table 1). Just less than half of all patients had had a response (complete or partial response) to previous EGFR-TKI treatment (table 1).

At screening, knowledge of a patient's mutational status was not mandatory. Of the 141 patients with tissue results from archival material, 96 were positive for EGFR mutations (table 2), 76 (79%) of whom had one of the common mutations (L858R in exon 21 or deletion in exon 19). Eight patients (four in the placebo group and four in the afatinib group) had T790M mutations on archival tissue (according to local testing; usually obtained at diagnosis rather than after progression when receiving erlotinib or gefitinib). Seven of these patients had a co-existing del19 (six patients) or L858R (one patient) mutation. Tests of serum samples gave a much lower positivity rate than did tests of tissue samples, which

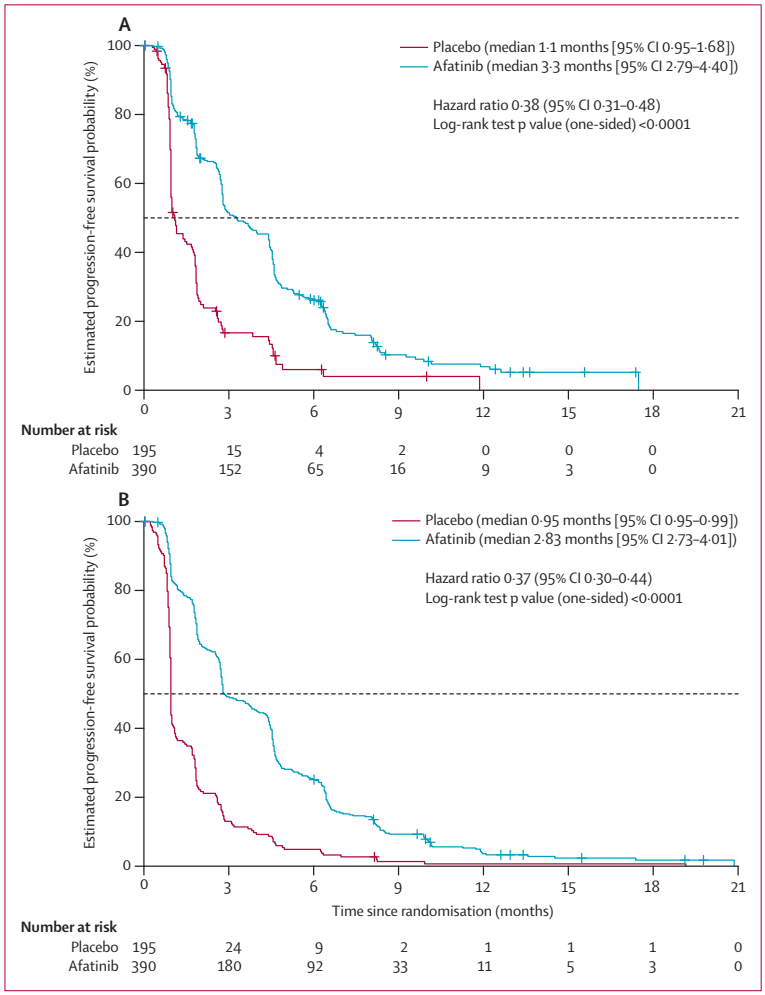


Figure 3: **Kaplan-Meier curves for progression-free survival**
For all patients by (A) independent review and (B) investigator assessment.

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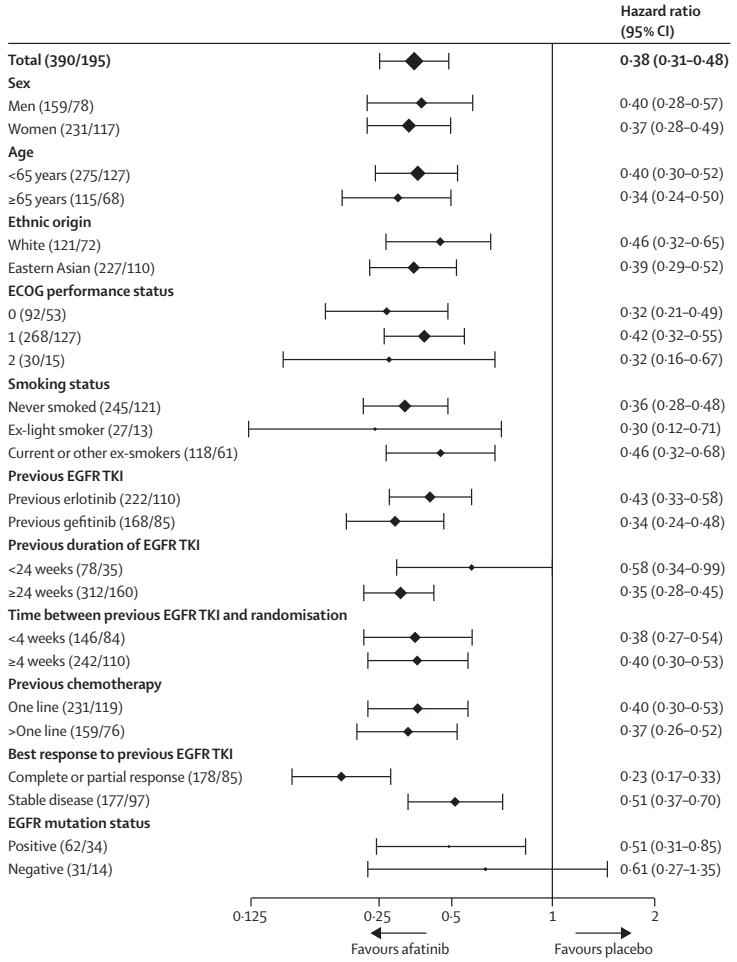

Figure 4: **Progression-free survival, by subgroup (independent review)**

	Afatinib plus best supportive care (n=390)		Placebo plus best supportive care (n=195)	
	Independent review	Investigator assessment	Independent review	Investigator assessment
Objective responses (all partial responses)				
Confirmed	29 (7%)*	42 (11%)†	1 (<1%)	1 (<1%)
Irrespective of confirmation	52 (13%)‡	68 (17%)‡	1 (<1%)	1 (<1%)
Stable disease for ≥8 weeks	198 (51%)	194 (50%)	35 (18%)	41 (21%)
Disease control (partial response+stable disease) for ≥8 weeks	227 (58%)§	236 (61%)§	36 (18%)	42 (22%)

*p=0·0071 compared with placebo. †p=0·0019 compared with placebo. ‡p=0·0002 compared with placebo. §p<0·0001 compared with placebo.

Table 3: **Objective response rate and disease control**

made interpretation of results difficult because of the high rate of presumed false-negatives (data not shown). Most patients who had complete or partial response to previous EGFR-TKI treatment had an EGFR mutation, in keeping with other studies,[13,14] with the proportion of patients with EGFR mutations increasing with duration of previous EGFR-TKI treatment (table 2).

We did our primary analysis when 358 events were reached, on July 8, 2010, after the database had been locked and cleaned. There was no significant difference in overall survival between the two groups: median overall survival was 10·8 months (95% CI 10·0–12·0) in the afatinib group and 12·0 months (10·2–14·3) in the placebo group (HR 1·08, 95% CI 0·86–1·35; one-sided p=0·74; figure 2). There was no evidence of a difference between treatment groups when analysed by subgroup (figure 2).

By both independent and investigator assessment, median progression-free survival was longer in the afatinib group than it was in the placebo group (figure 3). The longer progression-free survival with afatinib was seen in all but one (EGFR mutation negative) of the prespecified subgroups (figure 4).

Confirmed objective responses were noted in 29 (7%) patients treated with afatinib by independent review and in 42 (11%) patients by investigator assessment (table 3). Median response duration was 24 weeks (95% CI 16·1–40·0) by independent assessment and 20 weeks (16·1–24·1) by investigator assessment. Most responses were first noted at the week 4 and week 8 scans. By contrast, we recorded one partial response in the placebo group. 205 (53%) of the 390 patients who received afatinib had tumour burden decreases below baseline compared with 36 (18%) of the 195 patients given placebo (appendix). Confirmed disease control was noted in 227 (58%) patients treated with afatinib group by independent review and 236 (61%) by investigator assessments (table 3), with a median duration of disease control of 23 weeks (95% CI 20·0–27·4) by independent assessment and 20 weeks (19·9–22·9) by investigator assessment.

For the 96 patients who had EGFR mutation-positive tumour tissue, progression-free survival was longer for those patients who received afatinib than it was for those who received placebo by independent review (median 3·3 months [95% CI 2·6–4·4] *vs* 1·0 month [0·95–1·2]; HR 0·51 [95% CI 0·31–0·85]; p=0·009). By contrast, there was no difference in progression-free survival between treatment groups for the 45 patients who were EGFR mutation-negative (median 2·8 months [1·8–4·6] *vs* 1·8 months [0·9–4·7]; HR 0·61 [95% CI 0·27–1·35]; p=0·22; appendix). Interaction between treatment and EGFR mutation status was not statistically significant, possibly because of the small sample sizes. Both the proportion of patients with an objective response and the overall survival findings were much the same in patients with or without EGFR mutations (figure 2; response data not shown).

We analysed various subgroups of patients, defined clinically on the basis of benefit of previous EGFR-TKI treatment. The effect of afatinib on progression-free

survival and overall survival improvment was greatest in subgroups with the highest EGFR mutation rates (table 4 and appendix). For the post-hoc subgroup analysis of patients who met Jackman and colleagues' criteria[13] of acquired resistance (133 [34%] patients in the afatinib group, 81 [42%] in the placebo group), median progression-free survival by independent review for afatinib was 4·5 months (95% CI 2·73–4·73) compared with 1·0 month (0·95–1·71) for placebo (appendix). Waterfall plots of maximal tumour reduction for these patients were similar to those of the general study population (appendix), as was overall survival (data not shown).

A greater proportion of patients in the placebo group received further cancer treatment after disease progression than did those in the afatinib group, although this difference was not statistically significant (table 5), with such treatment coverage in both groups higher than in first-line NSCLC studies.[15–18] Most of these therapies were systemic (mainly chemotherapy with, for example, pemetrexed or docetaxel, but also EGFR-TKIs, which were twice as commonly used in the placebo group than they were in the afatinib group). The proportion of patients who received two or more subsequent treatment regimens was larger in the placebo group than it was in the afatinib group (table 5).

The prespecified inverse probability of censoring weighted Cox model, in which patients who had taken subsequent cancer treatment were censored at the time of such treatment, showed favourable results for afatinib in terms of overall survival (HR 0·64, 95% CI 0·43–0·95; p=0·028). Furthermore, we did a post-hoc exploratory analysis of overall survival for patients who did not receive any subsequent treatment, and the results favoured afatinib (figure 5). For patients receiving at least one subsequent systemic therapy, we noted no difference between treatments (figure 5).

Because a large proportion of patients (227 [39%] of 585 patients) were still alive at the time of primary analysis, we did a post-hoc analysis in February, 2012 (analysing 501 [86%] of 585 possible events), which also showed no difference in overall survival between groups (median overall survival was 10·9 months [10·0–12·3] with afatinib and 11·7 months [10·1–14·1] with placebo; HR 1·01, 95% CI 0·84–1·22; p=0·54; appendix).

Compared with placebo, a greater proportion of patients in the afatinib group had clinically meaningful improvements in the three prespecified NSCLC-related HRQoL items: cough (163 [46%] of 356 patients *vs* 42 [25%] of 171 patients; χ^2 test p<0·0001), dyspnoea (181 [51%] of 356 patients *vs* 62 [36%] of 171 patients; p<0·006), and pain (179 [50%] of 359 patients *vs* 55 [32%] of 171 patients; p<0·0001). More details are available elsewhere.[19]

Adverse events that occurred with at least a 10% higher incidence in the afatinib group than in the placebo group were diarrhoea, rash or acne, stomatitis, nail effect (mainly paronychia), expistaxis, pruritis, and decreased appetite (table 6). Diarrhoea and rash or acne were the most common adverse events (table 6). Overall, 150 (38%) of 390 patients receiving afatinib needed a dose reduction because of an adverse event, with 80 (21%) patients requiring a dose reduction because of diarrhoea and 59 (15%) because of rash or acne. However, only 14 patients discontinued afatinib treatment because of diarrhoea and seven patients discontinued their treatment because of rash or acne. There were 70 patients in the afatinib group who had an adverse event that required treatment discontinuation, 30 of whom had drug-related events. For all other adverse events, the occurrence of grade 3 events was 6% or fewer (table 6), and the rates of drug discontinuation for these events were 1·5% or fewer.

	N	EGFR mutation positivity rate (n/N [%])*	Progression-free survival (hazard ratio† [95% CI])	Overall survival (hazard ratio‡ [95% CI])
All patients	585	96/141 (68%)	0·38 (0·31–0·48)	1·08 (0·86–1·35)
Duration of previous EGFR-TKI treatment				
<24 weeks	113	8/24 (33%)	0·58 (0·34–0·99)	1·24 (0·76–2·05)
≥24 weeks	472	88/117 (75%)	0·35 (0·28–0·45)	1·04 (0·81–1·33)
≥48 weeks	266	60/72 (83%)	0·31 (0·22–0·44)	1·00 (0·72–1·40)
Previous EGFR-TKI treatment (complete or partial response) (prespecified)	263	58/66 (88%)	0·23 (0·17–0·33)	0·90 (0·65–1·25)
Previous EGFR-TKI treatment (complete or partial response or duration ≥48 weeks) (post-hoc)	391	86/103 (83%)	0·28 (0·21–0·36)	0·90 (0·69–1·18)

TKI=tyrosine-kinase inhibitor. *By optional tissue testing (either local or central laboratory); †By independent review. ‡At primary analysis.

Table 4: **Analysis of key subgroups for EGFR-mutation positivity**

	Afatinib group (N=380)	Placebo (N=194)
Any	257 (68%)	153 (79%)
Chemotherapy	230 (61%)	135 (70%)
Pemetrexed	136 (36%)	92 (47%)
Docetaxel	81 (21%)	51 (26%)
Vinorelbine	55 (15%)	37 (19%)
Other	101 (26%)	51 (26%)
EGFR tyrosine-kinase inhibitor	46 (12%)	46 (24%)
Anti-angiogenesis agent	17 (4%)	12 (6%)
Radiotherapy	35 (9%)	27 (14%)
Number of subsequent systemic treatment regimens		
One or more	246 (63%)	148 (76%)
Two or more	108 (28%)	86 (44%)*
Three or more	40 (10%)	31 (16%)
Four or more	7 (2%)	11 (6%)

Data are n (%); denominators are the number of patients who discontinued the study drug in both treatment groups. *p<0·0001 by Fisher's exact test compared with afatinib group.

Table 5: **Subsequent cancer treatment after discontinuation of study drug**

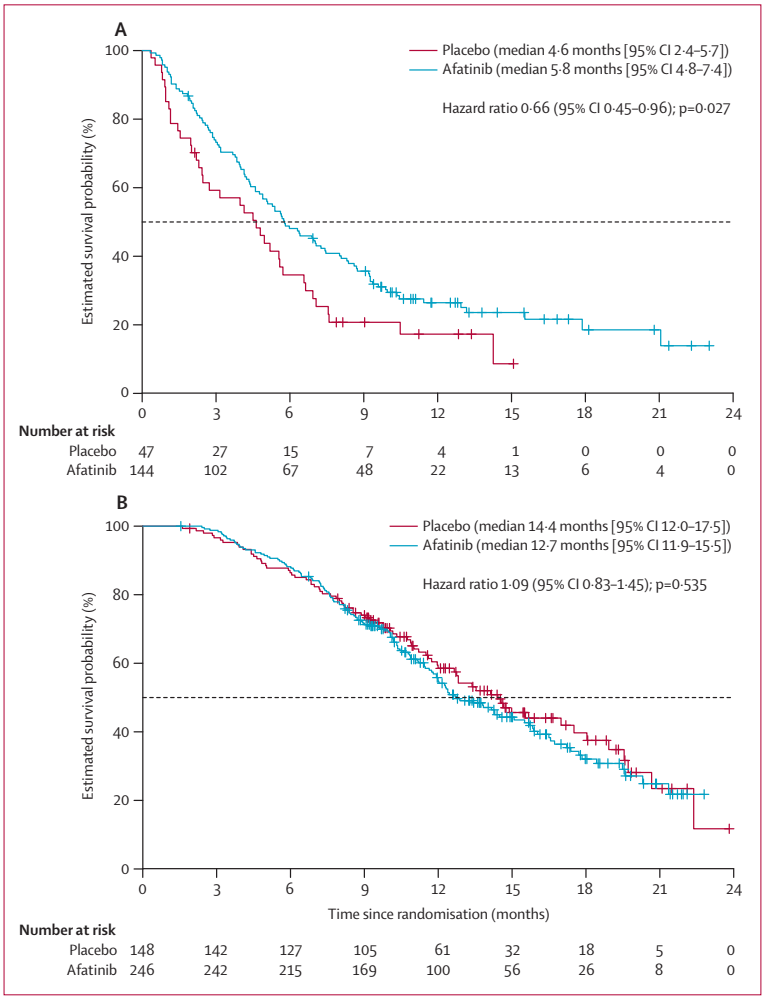

Figure 5: **Overall survival patients with no subsequent systemic therapy (A) and those with at least one subsequent systemic therapy (B)**

Drug-related serious adverse events occurred in 39 (10%) of 390 patients in the afatinib group and one (<1%) of 195 patients in the placebo group (pulmonary embolism); diarrhoea was the most common serious adverse event in the afatinib group, occurring in 17 (4%) patients. Evidence of serious drug-related renal insufficiency was reported for nine (2%) patients in the afatinib group, and was generally associated with diarrhoea and dehydration; patients generally responded to hydration, suggesting a prerenal cause. There were two deaths deemed possibly related to afatinib: heart failure after hospitalisation for a pulmonary infection in one patient and acute renal and hepatic failure in another. We recorded no cases of possible interstitial lung disease that were deemed to be drug related, although there was a fatal exacerbation of pre-existing pneumonitis in one patient treated with afatinib. No patient had substantial left ventricular ejection fraction changes.

Discussion

The lack of effective therapies in patients with EGFR-positive NSCLC after the development of acquired resistance to erlotinib or gefitinib is a major clinical problem.[20,21] This study, in the third-line and fourth-line setting, failed to show a difference between groups in its primary endpoint, overall survival, although our progression-free survival findings were promising (panel). Afatinib had a clear biological effect, with confirmed partial responses seen in about 7–11% of patients and substantially prolonged median progression-free survival for those treated with afatinib compared with those given placebo, particularly in the post-hoc subset of patients who met the most stringent criteria for true acquired resistance.[13] The activity of afatinib in this subgroup (in which the interval between end of previous EGFR-TKI treatment and start of the study treatment was ≤4 weeks) suggests that the effect of afatinib is not merely a result of re-exposure to another EGFR-TKI.[22]

One of the difficulties in the development of effective treatments for acquired resistance to erlotinib or gefitinib includes the presence of multiple resistance mechanisms.[3] These include the development of the EGFR T790M mutation (which is present in 50–60% of such patients), amplification of the MET tyrosine kinase, PI3K mutations, epithelial–mesenchymal transition, and transformation to a small-cell carcinoma morphological entity. Several other targeted drugs have been studied alone or in combination in patients who received previous erlotinib or gefitinib. In general, responses to treatment are rare and progression-free survival, when reported, is short.[3] For phase 2 studies with entry criteria almost identical to this study with previous failure of erlotinib or gefitinib and with an enrichment strategy for patients with EGFR mutations, experimental approaches with XL-647, dasatinib, neratinib, and the combination of cetuximab plus erlotinib showed objective response rates ranging from 0% to 3%.[23–26]

The improvement in progression-free survival with afatinib compared with placebo shown here was coupled with improvements in lung-cancer-related symptoms. Afatinib had manageable adverse events. Rash or acne and diarrhoea, predictable class effects, were the most commonly observed adverse events and occurred at grade 3 in 17% and 14% of patients, respectively. However, few patients discontinued afatinib because of these adverse events, suggesting that the best-supportive-care measures and dose reductions were effective in allowing patients who benefited from afatinib to continue with their treatment.

The improvement in progression-free survival with afatinib, relative to placebo, was greater in patients with EGFR mutations than it was in those without such

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	Afatinib group (n=390)						Placebo group (n=195)					
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea*	339 (87%)	148 (38%)	125 (32%)	66 (17%)	0	0	18 (9%)	18 (9%)	0	0	0	0
Rash or acne*†	305 (78%)	120 (31%)	129 (33%)	56 (14%)	0	0	31 (16%)	25 (13%)	6 (3%)	0	0	0
Stomatitis*†	237 (61%)	148 (38%)	77 (20%)	12 (3%)	0	0	5 (3%)	5 (3%)	0	0	0	0
Nail effect*†	153 (39%)	82 (21%)	51 (13%)	20 (5%)	0	0	2 (1%)	1 (<1%)	1 (<1%)	0	0	0
Decreased appetite*	119 (31%)	72 (18%)	33 (8%)	14 (4%)	0	0	22 (11%)	11 (6%)	10 (5%)	1 (<1%)	0	0
Fatigue†	115 (29%)	61 (16%)	31 (8%)	23 (6%)	0	0	43 (22%)	23 (12%)	17 (9%)	3 (2%)	0	0
Nausea	91 (23%)	64 (16%)	19 (5%)	8 (2%)	0	0	39 (20%)	30 (15%)	9 (5%)	0	0	0
Vomiting	78 (20%)	48 (12%)	21 (5%)	9 (2%)	0	0	26 (13%)	21 (11%)	4 (2%)	1 (<1%)	0	0
Epistaxis*	73 (19%)	68 (17%)	5 (1%)	0	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Pruritus*	71 (18%)	52 (13%)	18 (5%)	1 (<1%)	0	0	11 (6%)	10 (5%)	1 (<1%)	0	0	0
Dry skin	61 (16%)	44 (11%)	16 (4%)	1 (<1%)	0	0	14 (7%)	14 (7%)	0	0	0	0
Dyspnoea	58 (15%)	19 (5%)	21 (5%)	15 (4%)	2 (<1%)	1 (<1%)	26 (13%)	7 (4%)	9 (5%)	9 (5%)	0	1 (1%)
Ocular effect†	52 (13%)	35 (9%)	15 (4%)	2 (<1%)	0	0	4 (2%)	4 (2%)	0	0	0	0
Cough	51 (13%)	36 (9%)	12 (3%)	3 (<1%)	0	0	37 (19%)	23 (12%)	9 (5%)	5 (3%)	0	0
Constipation	40 (10%)	27 (7%)	12 (3%)	1 (<1%)	0	0	23 (12%)	14 (7%)	9 (5%)	0	0	0
Rhinorrhoea	40 (10%)	35 (9%)	5 (1%)	0	0	0	2 (1%)	2 (1%)	0	0	0	
Back pain	28 (7%)	14 (4%)	13 (3%)	1 (<1%)	0	0	22 (11%)	11 (6%)	7 (4%)	4 (2%)	0	0
Fever	39 (10%)	29 (7%)	8 (2%)	1 (<1%)	0	0	7 (4%)	7 (4%)	0	0	0	0
Decreased weight	36 (9%)	22 (6%)	13 (3%)	1 (<1%)	0	0	2 (1%)	1 (<1%)	1 (<1%)	0	0	0
Hypokalaemia	34 (9%)	20 (5%)	3 (<1%)	8 (2%)	3 (<1%)	0	4 (2%)	3 (2%)	1 (<1%)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	29 (7%)	17 (4%)	7 (2%)	5 (1%)	0	0	0	0	0	0	0	0
Pain in arms or legs	27 (7%)	15 (4%)	11 (3%)	1 (<1%)	0	0	4 (2%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0
Chest pain	26 (7%)	14 (4%)	12 (3%)	0	0	0	13 (7%)	8 (4%)	3 (2%)	2 (1%)	0	0
Productive cough	8 (2%)	8 (2%)	0	0	0	0	13 (7%)	11 (6%)	2 (1%)	0	0	0
Pain in upper abdomen	25 (6%)	14 (4%)	11 (3%)	0	0	0	8 (4%)	5 (3%)	3 (2%)	0	0	0
Lip effect†	23 (6%)	14 (4%)	8 (2%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Anaemia	22 (6%)	4 (1%)	9 (2%)	8 (2%)	1 (<1%)	0	3 (2%)	0	2 (1%)	1 (<1%)	0	0
Dysgeusia	22 (6%)	18 (5%)	4 (1%)	0	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Headache	20 (5%)	15 (4%)	3 (<1%)	2 (<1%)	0	0	9 (5%)	8 (4%)	0	1 (<1%)	0	0
Insomnia	17 (4%)	11 (3%)	6 (2%)	0	0	0	10 (5%)	7 (4%)	3 (2%)	0	0	0

*Events with at least 10% higher incidence in the afatinib group than in the placebo group. †Group term of closely related adverse events.

Table 6: **Adverse events with at least 5% incidence in one group**

mutations, although these analyses were limited by the sample size, because provision of archival tumour tissue was not mandatory in this trial. Subset analyses were also prespecified to include subgroups of patients with a response to previous EGFR-TKI treatment or with a long duration of previous EGFR-TKI treatment because such patients have been reported to have a very high rate of EGFR mutations,[13,14] as substantiated in this trial. For such subgroups, afatinib's effect on progression-free survival seemed to be associated with the degree of enrichment for EGFR mutations: in subgroups with a high (80–90%) likelihood of EGFR mutations, afatinib showed greater benefits in terms of progression-free survival than in those with a lower likelihood of EGFR mutations. Similar findings, in terms of median progression-free survival, were reported in a phase 2 single-arm study of afatinib in Japan[27] with almost identical entry criteria to this study, and for which the study population had a high degree of enrichment for EGFR mutations (85% positivity based on tissue testing).

We selected overall survival as the primary endpoint, with the assumption at the time the trial was designed being that overall survival would be short and that there would be little post-progression treatment. Contrary to these assumptions, the median overall survival for placebo (about 1 year) was longer than anticipated, and, to our knowledge, unprecedented in a trial of pretreated patients with NSCLC. The median overall survival reported in the Zephyr trial of vandetanib versus placebo in unselected pretreated patients with NSCLC was about 8 months.[28] Patients with EGFR mutations live longer and might respond better to chemotherapy than do patients with no such mutation.[3,17] In this trial, subsequent cancer therapies, which are believed to be potential confounders of an overall survival endpoint,[29] included chemotherapy and EGFR-TKIs, both of which

Panel: Research in context

Systematic review

We did a systematic review before starting this trial. We searched Medline and abstracts from major cancer conferences using keywords "NSCLC", "gefitinib", "erlotinib", and "chemotherapy", looking for phase 2 or phase 3 studies in patients with non-small-cell lung cancer (NSCLC) after chemotherapy and EGFR tyrosine-kinase inhibitor failure. We retrieved no prospective studies, only anecdotal case reports. No available evidence suggests that any therapy substantially extends survival or provides clinical benefit in patients previously treated with EGFR tyrosine-kinase inhibitors with EGFR-mutation-positive NSCLC. Because of the high unmet medical need in this population of patients, we thought it appropriate to do this trial. Encouraging preclinical data and the activity of afatinib seen in phase 1 trials provided further support.

Interpretation

To our knowledge, this is the only reported randomised trial of any drug in pretreated patients with non-small-cell lung cancer with previous chemotherapy failure and acquired resistance to previous EGFR tyrosine-kinase inhibitors. We noted no improvement in overall survival with afatinib plus best supportive care versus placebo plus best supportive care. However, the median overall survival of 12 months was much longer than previously reported for refractory NSCLC, and most patients received a range of subsequent therapies. The improvement in progression-free survival with afatinib compared with placebo, plus benefits in quality of life, are clinically meaningful. Our findings also have important implications for future trial designs in this treatment setting and provide a framework for future statistical assumptions and scientific hypotheses.

were given to a greater proportion of patients in the placebo group than those in the afatinib group, although these differences were not statistically significant. Subsequent EGFR-TKI treatment is relevant because evidence exists that patients can continue to have some benefit from an EGFR-TKI after disease progression.[22,30] Consistent with the potential confounding effects of subsequent cancer therapies, a post-hoc analysis of patients not given any subsequent systemic cancer therapy suggested an overall survival benefit with afatinib.

A range of confounding variables potentially contributed to the absence of an overall survival difference in this trial, especially the imbalance between groups in subsequent cancer treatment. In first-line EGFR mutation-positive NSCLC, afatinib is reported to have a much higher level of activity.[31] Enrolment of two first-line, phase 3 NSCLC trials of patients with EGFR mutations comparing afatinib with chemotherapy has been completed (NCT00949650, NCT01121393). The results of these two trials could provide for the first time confirmatory evidence of the efficacy of an irreversible ErbB-family blocker in this setting.

Contributors

VAM contributed to study design and data analysis and interpretation. VH contributed to study design, and data collection, analysis, and interpretation. JC contributed to study design and data interpretation. Y-MC contributed to data collection and interpretation. KP contributed to data collection, analysis, and interpretation. SW-K and W-CS contributed to patient accrual and data collection. CZ contributed to data collection and interpretation. MW contributed to patient accrual. YS contributed to data analysis and interpretation. DSH and LC contributed to study design, and data collection, analysis, and interpretation. E-HT contributed to patient accrual and data collection. T-YC contributed to patient accrual and data collection. MS contributed to study design and data collection, analysis, and interpretation. XJC contributed to study design and data analysis and interpretation. RML contributed to data analysis and interpretation. JC-HY contributed to study design, patient accrual, and interpretation of data. All authors contributed to writing, critical review, and final approval to submit the paper for publication.

Conflicts of interest

VAM has received honoraria from Boehringer Ingelheim, Clovis Oncology, Astellas, and Genentech—he working at Memorial Sloan-Kettering Cancer Center during the design, conduct, and analysis of the trial, but is now an employee of Foundation Medicine (a private company that does not receive any financial backing from Boehringer Ingelheim). VH has participated in advisory boards for Boehringer Ingelheim. JC has received fees for speaking and consulting from AstraZeneca, Boehringer Ingelheim, and Roche; travel to the ASCO, ESMO, and IASLC congresses was funded by AstraZeneca, Boehringer Ingelheim, and Roche. KP has been an adviser for Boehringer Ingelheim. CZ has received honoraria for participating in advisory boards for Boehringer Ingelheim, Lilly, and Roche Pharmaceuticals. LC has received honoraria from Boehringer Ingelheim for participating in advisory boards. MS, XJC, and RML are employees of Boehringer Ingelheim. JC-HY is an advisory board member for Boehringer Ingelheim and has received honoraria from Boehringer Ingelheim (before February, 2009). All other authors declare that they have no conflicts of interest.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

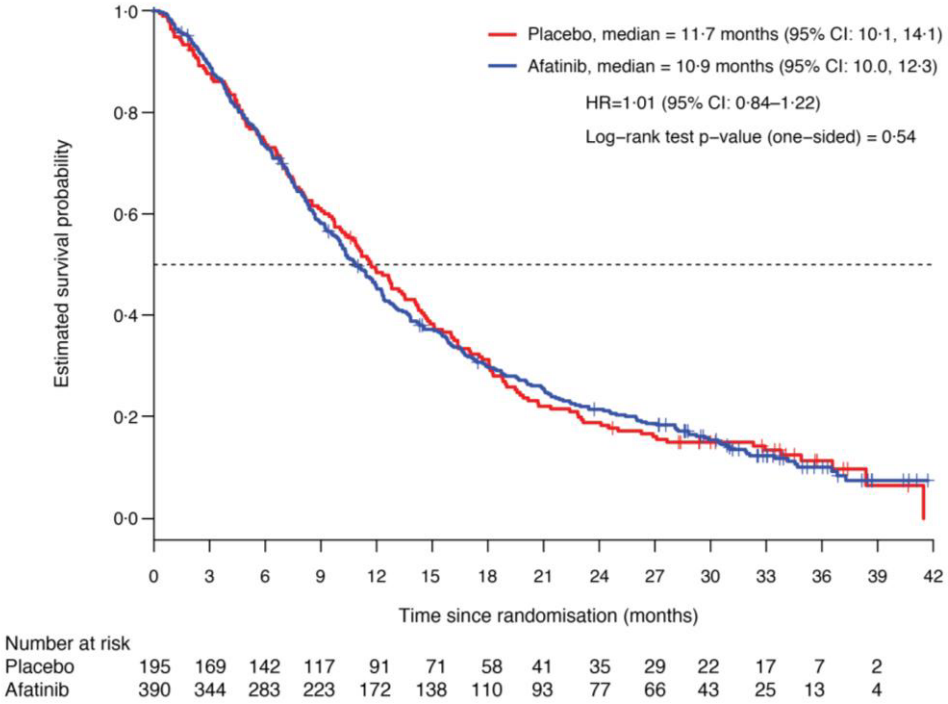
Supplement to: Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012; published online March 26. DOI:10.1016/S1470-2045(12)70087-6.

LUX-Lung 1: a phase 2b/3, randomised trial of afatinib plus best supportive care (BSC) versus placebo plus BSC in advanced, metastatic non-small cell lung cancer patients following failure of 1–2 lines of chemotherapy and erlotinib or gefitinib

Supplemental table 1: **Summary of Best Supportive Care (BSC)**

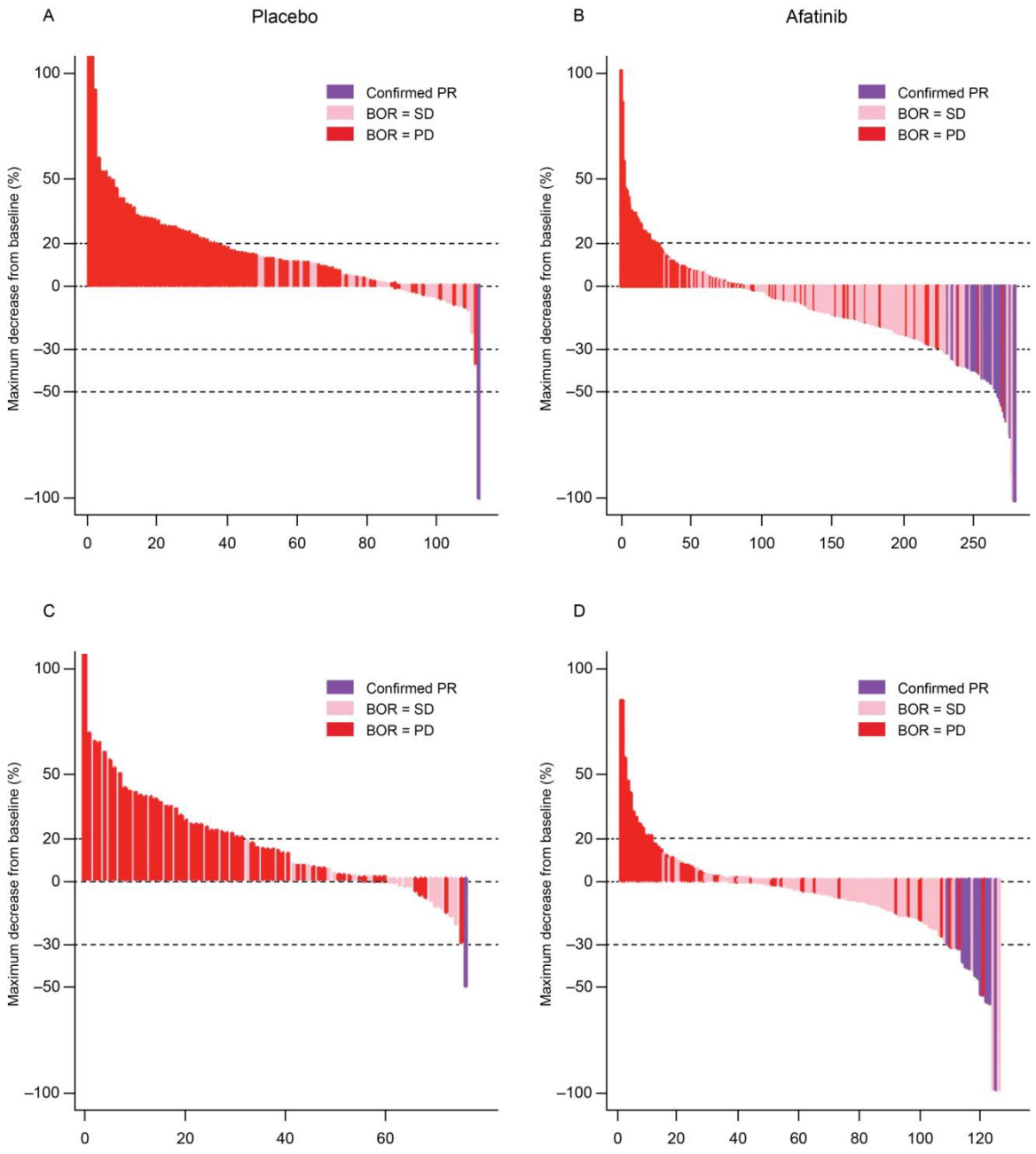
Best Supportive Care (BSC)	Afatinib, n=390 (%)	Placebo, n=195 (%)
Corticosteroids (Excluding for skin conditions)	102 (26·2)	35 (18·0)
Corticosteroids for skin and nails	49 (12·56)	9 (4·62)
Other Treatments for Skin, Nails, and other Cutaneous Conditions	76 (19·49)	8 (4·10)
Analgesics Narcotic	39 (10·00)	12 (6·15)
Analgesics Non−Narcotic	21 (5·38)	11 (5·64)
Treatment for Stomatits and Mucositis	38 (9·74)	2 (1·03)
Anorexia Treatment	27 (6·92)	6 (3·08)
Respiratory Therapy (includes bronchodialators, inhaled cortico−steroids, cough treatment)	22 (5·64)	8 (4·10)
Psychotherapy (includes treatment for insomnia)	16 (4·10)	10 (5·13)
Nutritional Support−Oral/NG	18 (4·62)	7 (3·59)
Nutritional Support−Parenteral	19 (4·87)	4 (2·05)
Palliative Radiation	17 (4·36)	6 (3·08)
Supplemental Oxygen	15 (3·85)	5 (2·56)
Anti−Emetics	16 (4·10)	3 (1·54)
Antibiotics	14 (3·59)	3 (1·54)
Transfusion−RBC	11 (2·82)	3 (1·54)
Anti−depressant/anti−anxiety	8 (2·05)	2 (1·03)
Physical Therapy	4 (1·03)	3 (1·54)
GI Support	6 (1·54)	0
Thoracentesis	3 (0·77)	2 (1·03)
Ulcer Prevention and Heartburn Treatment	1 (0·26)	1 (0·51
Pleurodesis	1 (0·26)	0
Erythropoiesis−stimulating agent	1 (0·26)	0
Other	113 (29·0)	28 (14·4)

Supplemental figure 1: **Updated OS (February 2012)**



OS=overall survival; CI=confidence interval; HR=hazard ratio·

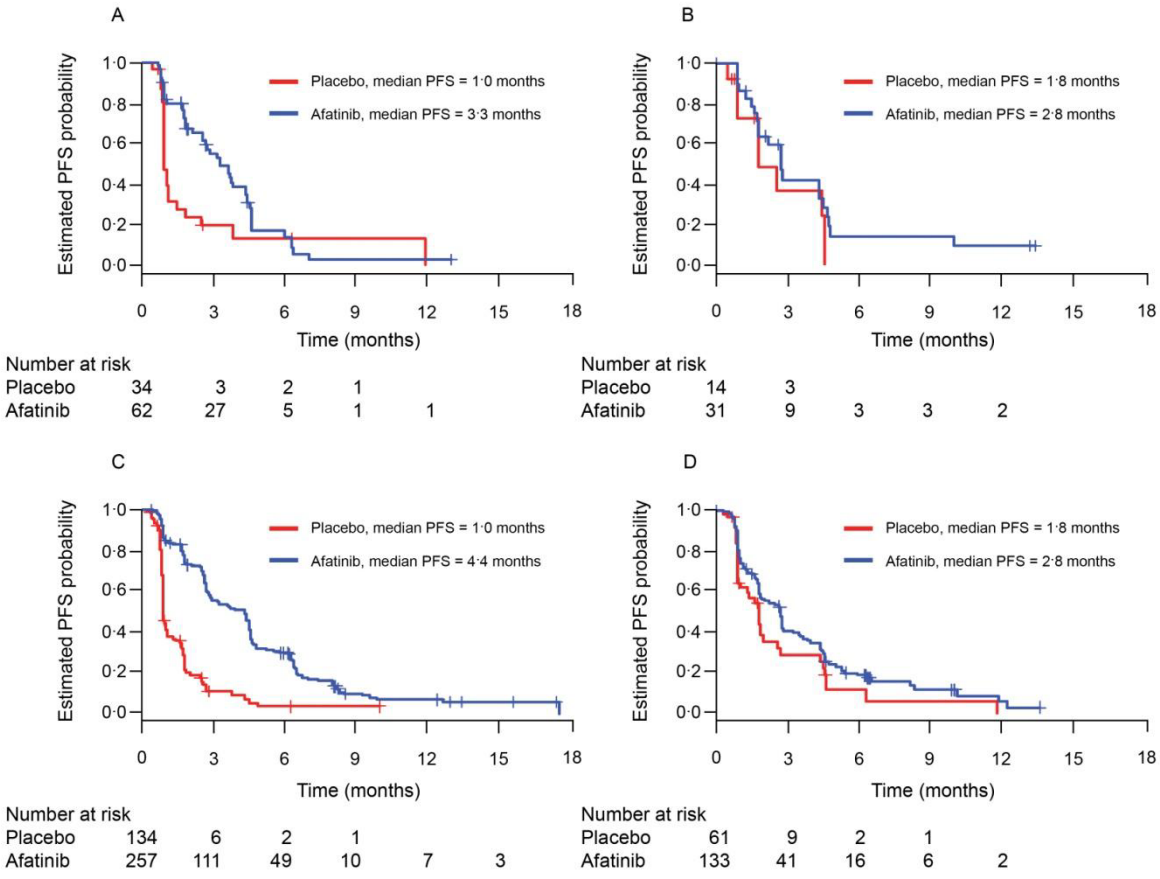
Supplemental figure 2: **Maximum decrease in tumour size from baseline (independent review)· (A) Placebo: all patients, (B) Afatinib: all patients, (C) Placebo: patients meeting Jackman criteria of acquired resistance, and (D) Afatinib: patients meeting Jackman criteria of acquired resistance**



PR=partial response; BOR=best overall response; SD=stable disease; PD=progressive disease

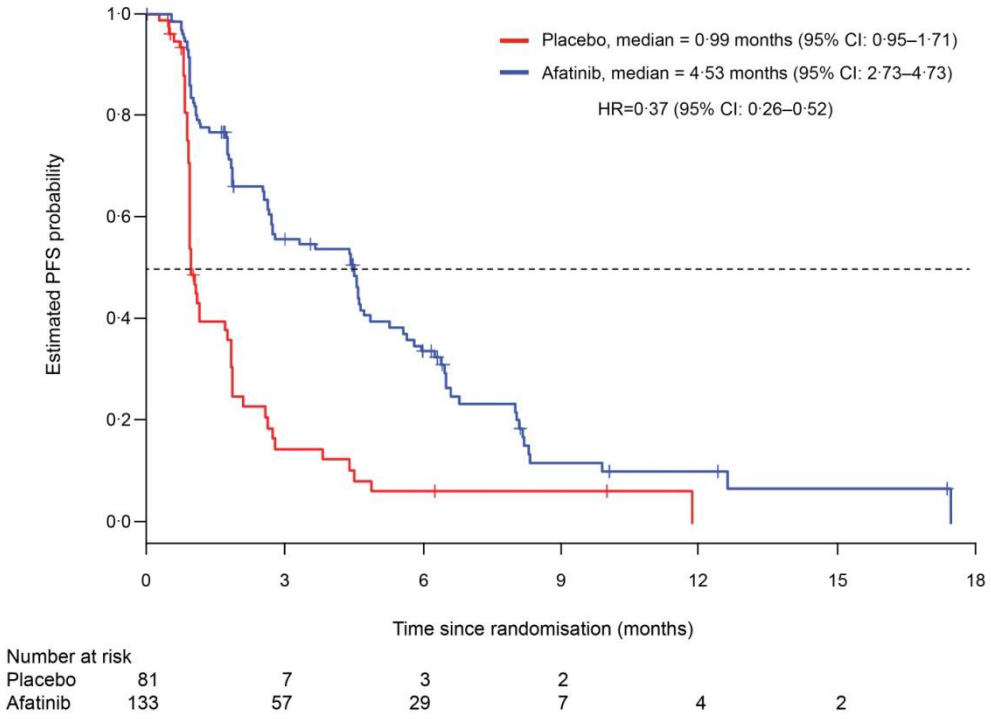
Footnote: Jackman criteria (Jackman et al· J Clin Oncol 2010;28(2):357-60)
Best response to prior EGFR TKI = CR/PR OR (best response = SD but prior EGFR TKI duration > 26 weeks) AND duration between end of prior EGFR TKI and randomisation <= 4 weeks AND no systemic treatment between end of prior EGFR TKI and randomisation

Supplemental figure 3: **PFS (independent review) for key subgroups regarding EGFR mutations· (A) PFS for patients with tumours having EGFR mutations (n=96; based on tissue testing), (B) PFS for patients with tumours without EGFR mutations (n=45; based on tissue testing), (C) PFS for patients in a large subgroup (n=391, 67% of all patients) highly enriched for EGFR mutations (83% positivity): patients had CR/PR to prior EGFR TKI and/or treated for ≥48 weeks with prior EGFR-TKI, and (D) PFS for patients in the subgroup complementary to Panel C: no response to prior EGFR-TKI and <48 weeks of treatment with prior EGFR-TKI (n=194; 33% of all patients); this subgroup had a much lower EGFR mutation positivity rate (25%) than the overall study population (67%)**



PFS=progression-free survival; EGFR=epidermal growth factor receptor; CR=complete response; PR=partial response; TKI=tyrosine kinase inhibitor

Supplemental figure 4: **PFS by independent review for the subgroup of patients meeting the Jackman criteria of acquired resistance (n=214)**



PFS=progression-free survival; CI=confidence interval; HR=hazard ratio·

Footnote: Jackman criteria (Jackman et al· J Clin Oncol 2010;28(2):357-60)
Best response to prior EGFR TKI = CR/PR OR (best response = SD but prior EGFR TKI duration > 26 weeks) AND duration between end of prior EGFR TKI and randomisation <= 4 weeks AND no systemic treatment between end of prior EGFR TKI and randomisation

Appendix I· List of trial investigators

- Belgium (L Bosquée, P Germonpré, J Vansteenkiste, J Van Meerbeeck and P Vuylsteke)
- Canada (N Blais, Q Chu, V Hirsh, G Liu, J Laskin and S Sun)
- China (C Bai, M Hou, G Jiang, H Pan, Y Sun, J Wang, M Wang, Y Wu and C Zhou)
- France (J Cadranel, B Lebeau, J Mazières, D Moro-Sibilot, M Perol, V Westeel and G Zalcman)
- Germany (D Atanackovic, N Frickhofen, C Manegold, M Reck, C-P Schneider, M Schuler, M Sebastian and J von Pawel)
- Hong Kong (T Mok)
- Italy (L Crinò, F De Marinis, F Grossi, S Novello, D Pozzessere and A Santoro)
- Korea (DS Heo, J Kim, S-W Kim, Y-C Kim, J-S Lee and K Park)
- The Netherlands (H Groen, W Pieters and E Smit)
- Singapore (E-H Tan)
- Spain (C Camps, P Garrido, JL González-Larriba, R Hitt, J Sanchez Torres, N Viñolas and GL Vivanco)
- Taiwan (G-C Chang, T-Y Chao, Y-M Chen, T-C Hsia, H-P Kuo, W-C Su, C-M Tsai, and JC-H Yang)
- Thailand (V Sriuranpong, P Sunpaweravong and S Thongprasert)
- UK (D Dunlop, M O'Brien, A Price, E Rankin and J Spicer)
- USA (D Adkins, I Ahmed, D Bradford, J Brittel, V Charu, H Chun, W Harker, D Irwin, C Leichman, T Malpass, V Miller, C Puccio, M Saltzman and J Thropay)