Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial

Yi-Long Wu, Jin Soo Lee, Sumitra Thongprasert, Chong-Jen Yu, Li Zhang, Guia Ladrera, Vichien Srimuninnimit, Virote Sriuranpong, Jennifer Sandoval-Tan, Yunzhong Zhu, Meilin Liao, Caicun Zhou, Hongming Pan, Victor Lee, Yuh-Min Chen, Yan Sun, Benjamin Margono, Fatima Fuerte, Gee-Chen Chang, Kasan Seetalarom, Jie Wang, Ashley Cheng, Elisna Syahruddin, Xiaoping Qian, James Ho, Johan Kurnianda, Hsingjin Eugene Liu, Kate Jin, Matt Truman, Ilze Bara, Tony Mok

Summary

Background The results of FASTACT, a randomised, placebo-controlled, phase 2 study, showed that intercalated chemotherapy and erlotinib significantly prolonged progression-free survival (PFS) in patients with advanced non-small-cell lung cancer. We undertook FASTACT-2, a phase 3 study in a similar patient population.

Methods In this phase 3 trial, patients with untreated stage IIIB/IV non-small-cell lung cancer were randomly assigned in a 1:1 ratio by use of an interactive internet response system with minimisation algorithm (stratified by disease stage, tumour histology, smoking status, and chemotherapy regimen) to receive six cycles of gemcitabine (1250 mg/m^2 on days 1 and 8, intravenously) plus platinum (carboplatin 5 × area under the curve or cisplatin 75 mg/m^2 on day 1, intravenously) with intercalated erlotinib (150 mg/day on days 15–28, orally; chemotherapy plus erlotinib) or placebo orally (chemotherapy plus placebo) every 4 weeks. With the exception of an independent group responsible for monitoring data and safety monitoring board, everyone outside the interactive internet response system company was masked to treatment allocation. Patients continued to receive erlotinib or placebo until progression or unacceptable toxicity or death, and all patients in the placebo group were offered second-line erlotinib at the time of progression. The primary endpoint was PFS in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT00883779.

Findings From April 29, 2009, to Sept 9, 2010, 451 patients were randomly assigned to chemotherapy plus erlotinib (n=226) or chemotherapy plus placebo (n=225). PFS was significantly prolonged with chemotherapy plus erlotinib versus chemotherapy plus placebo (median PFS 7·6 months [95% CI 7·2–8·3], *vs* 6·0 months [5·6–7·1], hazard ratio [HR] 0·57 [0·47–0·69]; p<0·0001). Median overall survival for patients in the chemotherapy plus erlotinib and chemotherapy plus placebo groups was 18·3 months (16·3–20·8) and 15·2 months (12·7–17·5), respectively (HR 0·79 [0·64–0·99]; p=0·0420). Treatment benefit was noted only in patients with an activating *EGFR* gene mutation (median PFS 16·8 months [12·9–20·4] *vs* 6·9 months [5·3–7·6], HR 0·25 [0·16–0·39]; p<0·0001; median overall survival 31·4 months [22·2–undefined], *vs* 20·6 months [14·2–26·9], HR 0·48 [0·27–0·84]; p=0·0092). Serious adverse events were reported by 76 (34%) of 222 patients in the chemotherapy plus placebo group and 69 (31%) of 226 in the chemotherapy plus erlotinib group. The most common grade 3 or greater adverse events were neutropenia (65 [29%] patients and 55 [25%], respectively), thrombocytopenia (32 [14%] and 31 [14%], respectively), and anaemia (26 [12%] and 21 [9%], respectively).

Interpretation Intercalated chemotherapy and erlotinib is a viable first-line option for patients with non-small-cell lung cancer with *EGFR* mutation-positive disease or selected patients with unknown *EGFR* mutation status.

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Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China (Prof Y-L Wu MD); **Beijing Chest Hospital, Beijing, China** (Prof Y Zhu MD); **Shanghai Lung Tumour Clinical Medical Centre, Shanghai Chest Hospital, Shanghai, China** (Prof M Liao MD); **Shanghai Pulmonary Hospital, Shanghai, China** (C Zhou MD); **Sir Run Run Shaw Hospital, Hangzhou, China** (H Pan MD); **Cancer Centre of Sun Yat-Sen University, Guangzhou, China** (Prof L Zhang MD); **Beijing Cancer Hospital, Beijing, China** (Prof J Wang MD); **Nanjing Gulou Hospital, Jiangsu, China** (X Qian MD); **Chinese Academy of Medical Sciences, Beijing, China** (Y Sun MD); **Queen Mary Hospital, Hong Kong, China** (V Lee FRCR, J Ho MD); **Princess Margaret Hospital, Hong Kong, China** (A Cheng MBBS); **Persahabatan Hospital, Jakarta, Indonesia** (E Syahruddin PhD); **Dokter Soetomo Hospital, Surabaya, Indonesia** (B Margono PhD); **Dr Sardjito Hospital, Yogyakarta, Indonesia** (J Kurnianda SPPD); **National Cancer Centre, Goyang, South Korea** (J S Lee MD); **Philippine General Hospital, Ermita, Manila, Philippines** (J Sandoval-Tan MD); **Lung Centre of the Philippines, Quezon City, Philippines** (G Ladrera MD); **Rizal Medical Center, Pasig City, Philippines** (F Fuerte MD); **National Taiwan University Hospital, Taipei City, Taiwan** (Prof C-J Yu MD);

Introduction

Non-small-cell lung cancer, a leading cause of cancer death, is often diagnosed at advanced stages when treatment options are few.[1] Advances in genetic testing allowed the discovery and clinical application of driver oncogenes, such as activating *EGFR* mutations, as a therapeutic target.[2,3] The results of several randomised studies have established EGFR-tyrosine-kinase inhibitors, specifically erlotinib and gefitinib, as standard first-line treatment for patients with activating *EGFR* mutations.[4–9] However, the practice of personalised medicine requires high-quality tumour samples for analysis and efficient testing facilities, which mean patients might still have unknown *EGFR* mutation status at the time when decisions are made about their first-line treatments.[10,11]

One option is to treat patients with unknown *EGFR* mutations with a combination of chemotherapy and an EGFR-tyrosine-kinase inhibitor. Early concurrent combination studies were designed before the discovery of *EGFR* mutations, and the results of these studies in unselected populations showed that combination

Taipei Veterans General Hospital, School of Medicine, National Yang-Ming Medical University, and Taipei Medical University, Taipei City, Taiwan (Y-M Chen PhD); **Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei and Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan** (G-C Chang MD); **Taipei Medical University Wang Fang Hospital, Taipei City, Taiwan** (H E Liu MD); **Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand** (S Thongprasert MD); **Siriraj Hospital, Bangkok, Thailand** (V Srimuninnimit MD); **Chulalongkorn Hospital, Bangkok, Thailand** (V Sriuranpong MD); **Phramongkutklao Hospital, Bangkok, Thailand** (K Seetalarom MD); **State Key Laboratory of South China, Hong Kong Cancer Institute, Chinese University of Hong Kong, Hong Kong, China** (Prof T Mok MD); **Roche Products Pty, Sydney, NSW, Australia** (M Truman MSc, K Jin MD); **and F Hoffmann-La Roche, Basel, Switzerland** (I Bara MD)

treatment compared with chemotherapy alone did not improve survival.[12–14] An explanation for this lack of efficacy is that G1 cell-cycle arrest caused by EGFR-tyrosine-kinase inhibitors might reduce the cell-cycle phase-dependent activity of chemotherapy.[15] By contrast, preclinical data showed that sequential administration of tyrosine-kinase inhibitors after chemotherapy might be effective.[16,17] To investigate this view, our group completed a randomised phase 2 study (FASTACT, First-line Asian Sequential Tarceva And Chemotherapy Trial) and noted significant improvement in progression-free survival (PFS; hazard ratio [HR] 0·47, 95% CI 0·33–0·68; p=0·0002).[18] Few tumour samples were available for biomarker analysis, thus to what extent activating *EGFR* mutations affected the benefit from this regimen could not be determined.

FASTACT-2 was a phase 3 trial to confirm the phase 2 findings. The primary objective was to compare PFS of the intercalated combination regimen with standard chemotherapy. Biomarker analysis was also undertaken, but these data will be published separately.

Methods

Study design and population

FASTACT-2 was a multicentre, randomised, placebo-controlled, double-blind, phase study of intercalated erlotinib or placebo with gemcitabine and carboplatin or cisplatin followed by maintained erlotinib or placebo in patients with stage IIIB/IV non-small-cell lung cancer. The study was undertaken in 28 centres in China (nine), Hong Kong (four), Indonesia (three), South Korea (one), the Philippines (three), Taiwan (four), and Thailand (four).

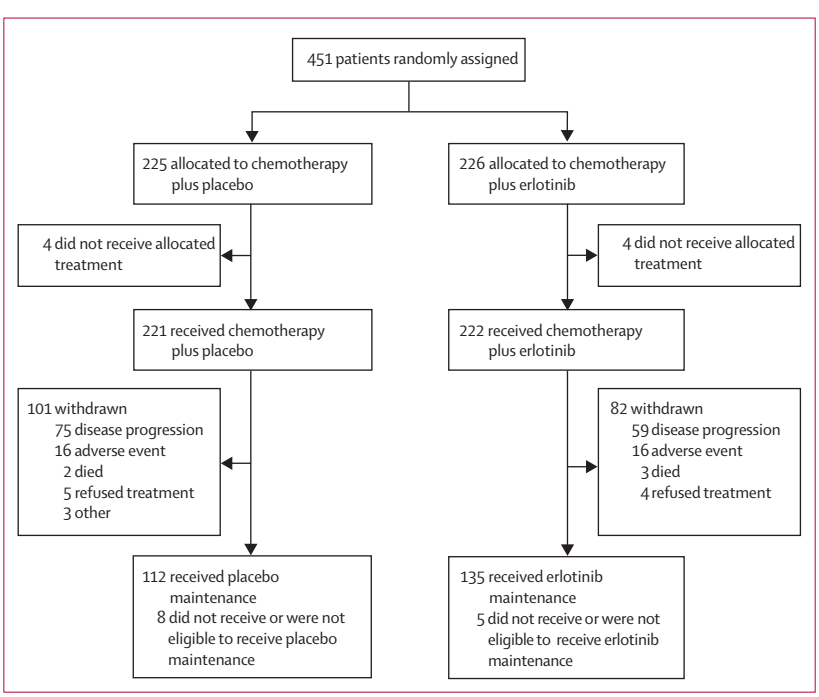

Figure 1: **Trial profile**
Chemotherapy=gemcitabine plus carboplatin or cisplatin.

Patients aged 18 years and older, with stage IIIB/IV non-small-cell lung cancer, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST version 3.0), were eligible. Disease-related exclusion criteria included previous treatment with agents targeting the *HER* axis; previous systemic antitumour treatment; adjuvant or neoadjuvant treatment for non-metastatic disease within 6 months of study treatment; surgery undertaken less than 4 weeks before the study; and localised radiotherapy unless completed more than 4 weeks before the study. General exclusion criteria included brain metastasis (symptomatic or subsequently identified asymptomatic metastases); spinal-cord compression without evidence of stabilisation or treatment; unwillingness to use contraception during the study; women who were pregnant or lactating; women with a positive or no available pregnancy test result at baseline; any unstable illness; and patients known to be HIV positive.

FASTACT-2 was approved by the institutional review board or ethics committee of each participating centre and was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before any study-related procedure.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio by use of a central randomisation programme with a minimisation algorithm. The aim of minimisation was to reduce imbalance between treatment groups within each strata by allocation of patients (using a fairly high probability) to the treatment group that minimised this imbalance. Central randomisation and drug-pack allocation were assigned by use of an interactive internet response system. Everyone outside the company responsible for the interactive internet response system was masked to treatment allocation with the exception of a small independent group that was responsible for monitoring data and safety early in the trial. Patients were stratified by disease stage (IIIB, IV), tumour histology (adeno-carcinoma, other), smoking status (current, former, never), and chemotherapy regimen (gemcitabine plus carboplatin, gemcitabine plus cisplatin).

Procedures

Patients were randomly assigned to receive six cycles of gemcitabine (1250 mg/m² on days 1 and 8 of a 4 week cycle, intravenously) plus platinum (carboplatin 5×area under the curve, intravenously, or cisplatin 75 mg/m² on day 1 of a 4 week cycle, intravenously) with either sequential erlotinib (150 mg/day; chemotherapy plus erlotinib group) or placebo (chemotherapy plus placebo group) on days 15–28 of each cycle. Patients who did not

progress during the six cycles of sequential treatment continued to receive erlotinib or placebo until disease progression, unacceptable toxicity, or death. At disease progression, treatment was unmasked so patients in the chemotherapy only group could crossover to open-label erlotinib, whereas those in the chemotherapy plus erlotinib group could receive further treatment at their investigator's discretion.

Reduction or interruption of dosing of erlotinib due to adverse events could take place at any time. Erlotinib dose was to be reduced initially to 100 mg/day and then to 50 mg/day if necessary. Dosing could be interrupted for a maximum of 2 weeks if clinically indicated.

Tumour response was assessed by use of CT with RECIST every 8 weeks until treatment cessation or disease progression. An independent review committee of clinicians and radiologists masked to treatment assignment reviewed all tumour images and determined tumour response and progression status. Adverse events and clinically significant laboratory abnormalities were monitored and recorded according to the National Cancer Institute Common Terminology Criteria for adverse events (version 3·0). Patients were monitored every 4 weeks during both intercalated and maintenance treatment until 28 days after the last treatment with the study drugs.

Separate consent was required to obtain samples for the predefined biomarker subgroup analysis. Tumour samples (ten to 20 slides for histological procedures; ten slides for cytological procedures) from first diagnosis or from biopsy at least 14 days before the first dose of study drug were needed. *EGFR* mutation analysis was done with the cobas 4800 system (Roche Molecular Diagnostics, Pleasanton, CA, USA). Patients were judged to have activating *EGFR*-mutation-positive disease if one or more of four mutations (exon 19 deletion, or G719X, L858R, or L861Q mutation) were detected. Those with single genomic changes in exon 20 (S768I or T790M) were judged to be resistant to EGFR-tyrosine-kinase inhibitors. Full biomarker analysis included *KRAS*, immunohistochemistries for ERCC1, EGFR, HER2, and HER3, and *EGFR* fluorescence in-situ hybridisation, which will be reported separately.

Correspondence to:
Prof Tony Mok, State Key Laboratory of South China, Hong Kong Cancer Institute, Chinese University of Hong Kong, Shatin, Hong Kong, China
tony@clo.cuhk.edu.hk

	Chemotherapy plus erlotinib group (n=226)	Chemotherapy plus placebo group (n=225)
Age (years; median, range)	59·0 (31·0–96·0)	57·3 (37·0–88·0)
Sex		
Male	132 (58%)	140 (62%)
Female	94 (42%)	85 (38%)
Smoking status		
Current smoker	65 (29%)	66 (29%)
Former smoker	49 (22%)	52 (23%)
Never smoker	112 (50%)	107 (48%)
Stage of disease		
IIIB	21 (9%)	24 (11%)
IV	205 (91%)	201 (89%)
Histological type		
Adenocarcinoma	174 (77%)	168 (75%)
Other	52 (23%)	57 (25%)
ECOG PS		
0	59 (26%)	59 (26%)
1	167 (74%)	165 (74%)*
Chemotherapy regimen		
Gemcitabine and carboplatin	208 (92%)	205 (92%)†
Gemcitabine and cisplatin	18 (8%)	17 (8%)
EGFR mutation status		
Wild type	69 (31%)	67 (30%)
Single resistance mutation‡	2 (<1%)	6 (3%)
Activating *EGFR* mutation‡	49 (22%)	48 (21%)
Unknown	106 (47%)	104 (46%)

Data are number or number (%), unless otherwise indicated. Chemotherapy=gemcitabine plus carboplatin or cisplatin. ECOG=Eastern Cooperative Oncology Group. PS=performance status. *Data missing for one patient. †Data missing for three patients. ‡Single resistance mutation: exon20_INS, S768I, or T790M; activating mutation: exon 19 del, G719X, L858R, or L861Q.

Table 1: **Baseline characteristics of the intention-to-treat population**

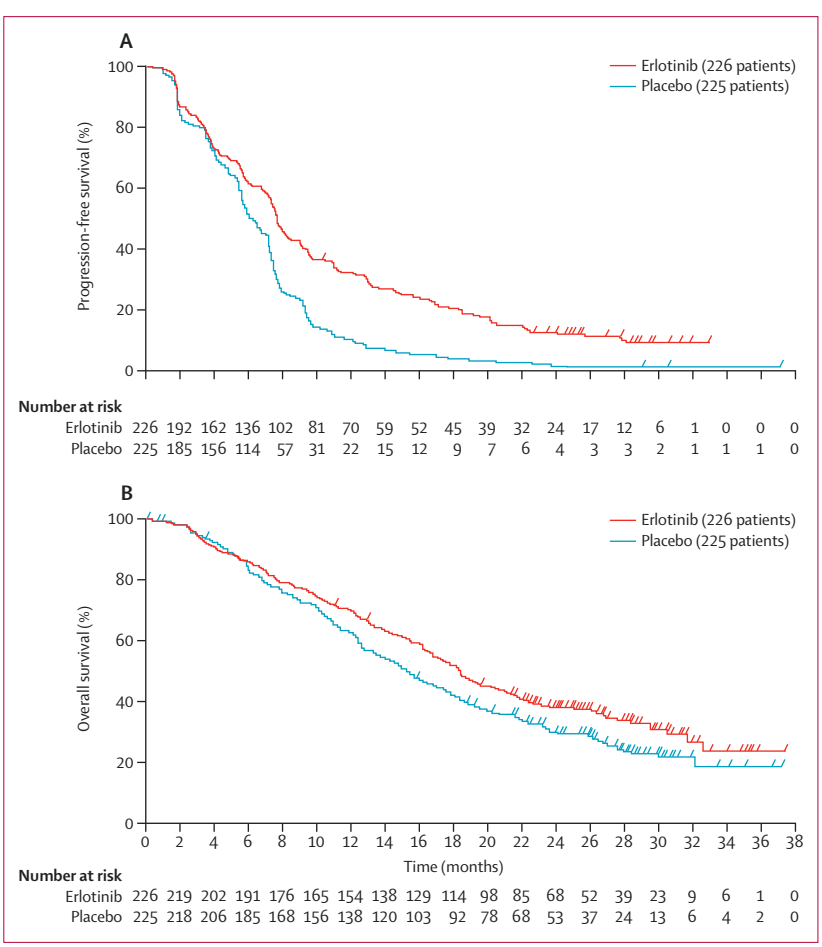

Figure 2: **Kaplan-Meier curve of progression-free survival (A) and overall survival (B) in the intention-to-treat population**

The primary endpoint was investigator-assessed PFS with secondary endpoints of independent review-committee-assessed PFS, overall survival, and PFS and overall survival in subgroups (by histology and smoking status). Other secondary endpoints were the proportion of patients who had an objective response (complete response [CR] + partial response [PR]), duration of response, and quality of life (QoL) according to the Functional Assessment of Cancer Therapy-Lung (FACT-L) and Trial Outcomes Index (TOI). An exploratory objective of the study was assessment of tumour and plasma biomarkers and their correlation with treatment outcomes.

Statistical analysis

The intention-to-treat population comprised all randomly assigned patients. The per-protocol population comprised all randomly assigned patients with no major protocol violations who received at least one dose of study drug, with adequate baseline and follow-up tumour assessment. The safety population comprised all patients who received at least one dose of study drug, with at least one post-baseline safety assessment. Based on a PFS of 5·4 months in the control group,[15] about 379 PFS events were needed to detect a HR of 0·75 (chemotherapy plus erlotinib *vs* chemotherapy plus placebo) at 80% power with a two-sided log-rank test and α level of 5%. Accounting for ineligibility and withdrawal of patients, a total of 450 patients were required.

PFS and overall survival were assessed by use of the Kaplan-Meier method, with treatment effect expressed as HR and two-sided 95% CI. The assumption of proportional hazards was assessed graphically by plotting log-log survival functions between the two treatment groups. No major departures from the assumption were seen. Objective responses were analysed by use of the χ^2 test and were summarised and 95% CI calculated with the Anderson–Hauck method. Safety assessments were analysed descriptively. A sensitivity analysis of the primary endpoint PFS and other secondary endpoints by use of progression data was undertaken with tumour images reviewed by the independent review committee to evaluate tumour response during the study. Statistical analyses were done with SAS (version 8.2).

Primary analysis was undertaken when PFS data reached maturity, about 13 months after the last patient was randomly assigned (data cutoff July 18, 2011). The independent review committee reviewed all tumour assessments done until this date. An updated analysis was undertaken at a cutoff date of June 22, 2012. The results discussed in this report are primarily from this updated analysis.

This trial is registered with ClinicalTrials.gov, number NCT00883779.

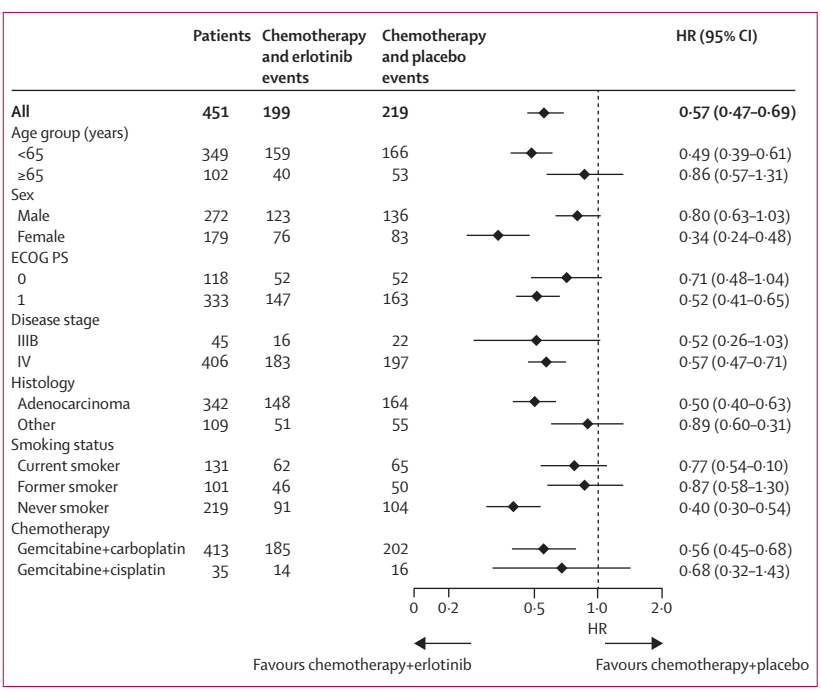

Figure 3: **Forest plot of HRs for progression-free survival by prognostic factors**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. PS=performance status.

	Chemotherapy plus erlotinib group (n=226)	Chemotherapy plus placebo group (n=225)	Odds ratio (95% CI)	p value
Disease control	182 (80·5%, 74·8–85·5)	179 (79·6%, 73·7–84·6)	1·07 (0·66–1·73)	0·7781
Objective response	97 (42·9%, 36·4–49·7)	41 (18·2%, 13·4–23·9)	3·50 (2·25–5·45)	<0·0001
Complete response	3 (1·3%, 0·3–3·8)	1 (0·4%, 0·0–2·5)	2·56 (0·24–26·71)	0·4309
Partial response	94 (41·6%, 35·1–48·3)	40 (17·8%, 13·0–23·4)	3·44 (2·20–5·38)	<0·0001
Stable disease	85 (37·6%, 31·3–44·3)	138 (61·3%, 54·6–67·7)	0·38 (0·26–0·56)	<0·0001
Progressive disease	35 (15·5%, 11·0–20·9)	38 (16·9%, 12·2–22·4)	0·85 (0·51–1·41)	0·5297
Missing	9 (4·0%, 1·8–7·4)	8 (3·6%, 1·5–6·9)	..	..

Data are number (%, 95% CI), unless otherwise indicated. RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2: **Best overall response according to RECIST**

Role of the funding source

This trial was designed, funded, and monitored by F Hoffmann-La Roche. Data were gathered, analysed, and interpreted by F Hoffmann-La Roche, with input from the authors and investigators. All authors and employees of F Hoffmann-La Roche reviewed and commented on the initial draft of the report. The corresponding author had full access to the study data and took full responsibility for the final decision to submit the report for publication.

Results

Between April 29, 2009, and Sept 9, 2010, 451 patients were randomly assigned to receive chemotherapy plus erlotinib (n=226) or chemotherapy plus placebo (n=225). 222 patients in the chemotherapy plus erlotinib group and 221 in the chemotherapy plus placebo group received at least one cycle of intercalated combination treatment. At completion of the combined treatment, 82 and 101 patients had withdrawn from the chemotherapy plus

erlotinib and chemotherapy plus placebo groups, respectively, due to disease progression, adverse events, refusal of treatment, death, or other reasons (figure 1). 16 (7%) of 222 patients in the chemotherapy plus placebo group and 16 (7%) of 226 in the chemotherapy plus erlotinib group discontinued because of adverse events. 55 (24%) of 226 patients required dose reduction or interruption in the chemotherapy plus erlotinib group, whereas 32 (14%) of 222 required dose reduction or interruption in the chemotherapy plus placebo group. Median follow-up was 27·6 months (IQR 24·2–30·1) for the chemotherapy plus placebo group and 28·2 months (24·7–30·5) for the chemotherapy plus erlotinib group.

Table 1 summarises the baseline characteristics of the intention-to-treat population. The demographics were balanced between the two groups. About half the patients were non-smokers and about three-quarters had adenocarcinoma. *EGFR* mutation status was balanced in the two groups.

Investigator-assessed PFS was significantly prolonged in the chemotherapy plus erlotinib group compared with in the chemotherapy plus placebo group (median 7·6 months [95% CI 7·2–8·3] *vs* 6·0 months [5·6–7·1], HR 0·57 [0·47–0·69]; p<0·0001; figure 2A). The median PFS assessed by the independent review committee was 10·0 months (8·7–12·2) for the chemotherapy plus erlotinib group, compared with 7·4 months (7·2–7·9) for the chemotherapy plus placebo group (HR 0·58 [0·46–0·72]; p<0·0001). Median PFS by patients' characteristics is summarised in figure 3, showing that the HR was in favour of erlotinib in all subgroups. The most significant benefit was noted in female patients, never smokers, and patients with adenocarcinoma (figure 3).

Median overall survival was 18·3 months (95% CI 16·3–20·8) for patients in the chemotherapy plus erlotinib group and was 15·2 months (12·7–17·5) for those in the chemotherapy plus placebo group (HR 0·79 [0·64–0·99]; p=0·0420; figure 2B). According to the investigator's assessment, 97 (43%) of 226 patients in the chemotherapy plus erlotinib group and 41 (18%) of 225 patients in the chemotherapy plus placebo group had an objective response (difference 25% [16–33]; p<0·0001). According to the independent review committee, 99 (44%) patients in the chemotherapy plus erlotinib group and 35 (16%) in the chemotherapy plus placebo group had an objective response (difference 28% [20–37]; p<0·0001). Table 2 shows the best overall responses by RECIST. Median duration of response was 5·6 months (IQR 3·7–7·9) for chemotherapy plus placebo group and 11·2 months (5·8–18·5) for chemotherapy plus erlotinib. 145 (64%) patients in the chemotherapy plus placebo group were progression-free at 16 weeks as were 152 (67%) in the chemotherapy plus erlotinib group. Median time to progression was 6·5 months (95% CI 5·7–7·2) for chemotherapy plus placebo and 7·9 months (7·5–9·1) for chemotherapy plus erlotinib.

On disease progression, 79% of the patients in the chemotherapy plus placebo group received an EGFR-tyrosine-kinase inhibitor as second-line treatment and 6% as third-line treatment (table 3). Only 6% of patients in the chemotherapy plus erlotinib group received platinum-based chemotherapy as second-line treatment and 6% as third-line treatment (table 3).

	Second line		Third line	
	Chemotherapy plus erlotinib group (n=226)	Chemotherapy plus placebo group (n=225)	Chemotherapy plus erlotinib group (n=226)	Chemotherapy plus placebo group (n=225)
Systemic treatment (total)	108 (48%)	184 (82%)	50 (22%)	65 (29%)
EGFR tyrosine kinase inhibitor	10 (4%)	178 (79%)	4 (2%)	13 (6%)
Platinum-based doublet chemotherapy	13 (6%)	1 (<1%)	14 (6%)	5 (2%)
Single-agent chemotherapy				
Taxane	43 (19%)	4 (2%)	18 (8%)	22 (10%)
Pemetrexed	45 (20%)	3 (1%)	7 (3%)	22 (10%)
Vinorelbine	1 (<1%)	0	4 (2%)	1 (<1%)
Off-study surgery	2 (<1%)	5 (2%)	..	..
Off-study radiotherapy	40 (18%)	43 (19%)	..	..

Table 3: **Post-study treatment in the second-line and third-line settings**

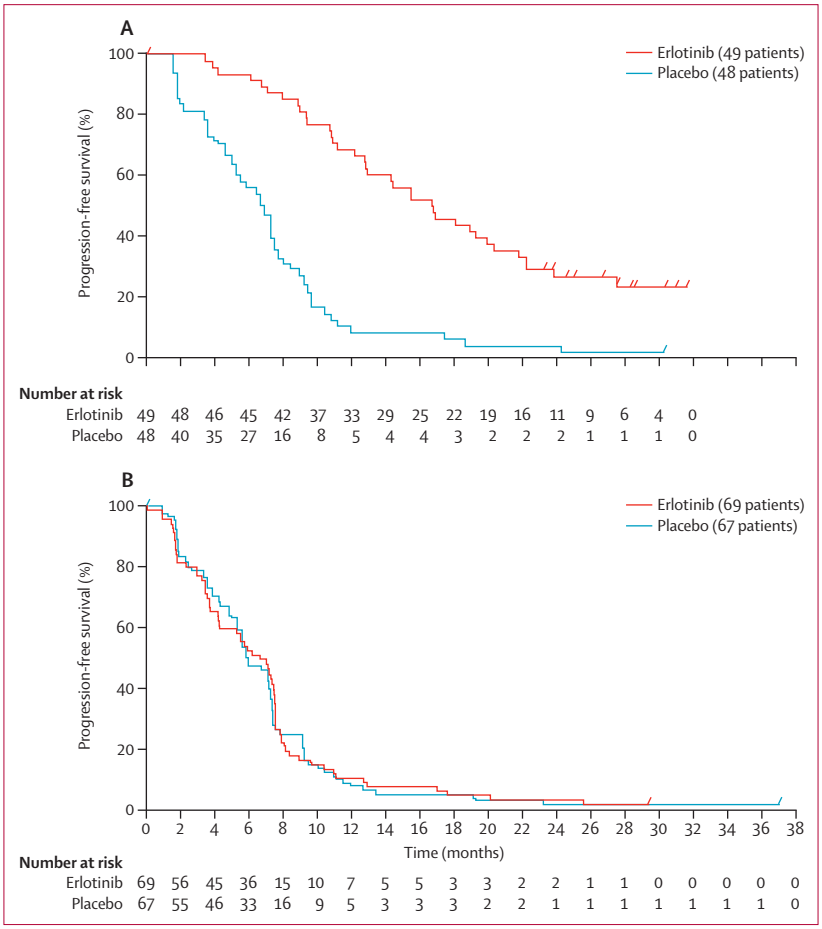

Figure 4: **Kaplan-Meier curve of progression-free survival in patients with activating *EGFR* mutations (A) and *EGFR* wild-type disease (B)**

Tumour samples were available for *EGFR* mutation analysis from 301 (67%) of 451 patients and could be analysed in 283 (63%) patients. *EGFR* mutation status was known for 241 (53%) of 451 patients (table 1). 136 (56%) of 241 patients had *EGFR* wild-type status, eight (3%) had single resistance mutations, and 97 (40%) had *EGFR*-activating mutations (table 1). 210 (47%) of 451 patients had unknown *EGFR* mutation status (table 1).

In patients with tumours with *EGFR*-activating mutations, median PFS was 16·8 months (95% CI 12·9–20·4) in the chemotherapy plus erlotinib group and 6·9 months (5·3–7·6) in the chemotherapy plus placebo group (HR 0·25 [0·16–0·39]; p<0·0001; figure 4A). Median overall survival was 31·4 months (22·2–undefined) in the chemotherapy plus erlotinib group and 20·6 months (14·2–26·9) in the chemotherapy plus placebo group (0·48 [0·27–0·84]; p=0·0092; figure 5A). 41 (85%) of 48 patients in the chemotherapy plus placebo group received an EGFR-tyrosine-kinase inhibitor as subsequent treatment. Objective responses were noted in 41 (84%) of 49 patients with *EGFR*-activating mutations in the chemotherapy plus erlotinib group and seven (15%) of 48 in the chemotherapy plus placebo group (difference 69% [53·5–84·7]; p<0·0001).

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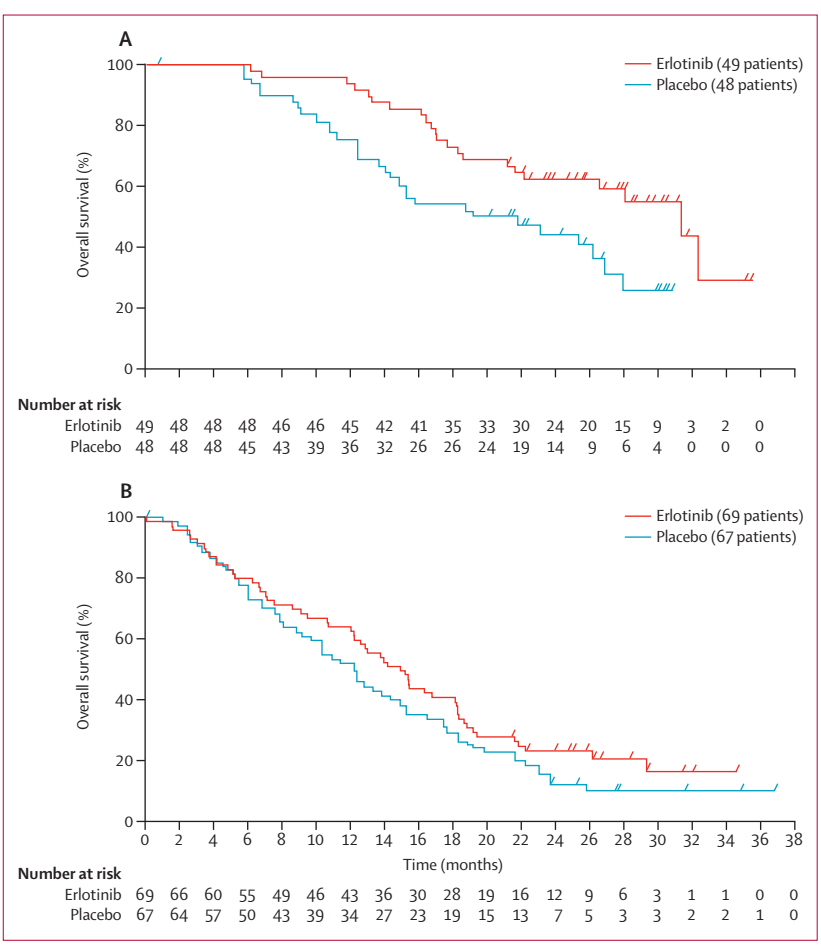

Figure 5: **Kaplan-Meier curves of overall survival in patients with activating *EGFR* mutations (A) and *EGFR* wild-type disease (B)**

No significant difference in PFS was noted in patients with *EGFR* wild-type disease in the chemotherapy plus erlotinib group versus those in the chemotherapy plus placebo group (median PFS 6·7 months [95% CI 4·3 to 7·5], *vs* 5·9 months [5·4 to 7·2], HR 0·97 [0·69 to 1·36]; p=0·8467; figure 4B). Median overall survival in patients with *EGFR* wild-type disease was longer in the chemotherapy plus erlotinib group (14·9 months [12·2 to 18·2] *vs* 12·2 months [8·9 to 14·7], although not significantly so (HR 0·77 [0·53 to 1·11]; p=0·1612; figure 5B). Objective responses were noted in 18 (26%) of 69 patients in the chemotherapy plus erlotinib group and 13 (19%) of 67 patients in the chemotherapy plus placebo group (difference 6·7% [–8·2 to 21·6]; p=0·35). Conversely, PFS was significantly improved in the 210 patients with unknown *EGFR* mutation status, suggesting that a proportion of these patients had *EGFR*-mutation-positive disease (7·1 months [5·6 to 8·2] *vs* 6·0 months [5·5 to 7·1] for chemotherapy plus erlotinib and chemotherapy plus placebo groups, respectively; HR 0·61 [0·46 to 0·82]; p=0·0009). Median overall survival in this group was similar in each randomised group (18·1 months [13·2 to 22·5] and 16·2 months [12·6 to 19·8], respectively; HR 0·93 [0·67 to 1·29]; p=0·64).

We noted more toxicity related to EGFR-tyrosine-kinase inhibitors, including skin rash and diarrhoea, in the chemotherapy plus erlotinib group than in the chemotherapy plus placebo group (appendix). The most commonly reported adverse events of any grade included neutropenia, anaemia, nausea, and rash (table 4). Frequency of treatment-related grade 3 neutropenia was similar in both treatment groups (table 4). Skin toxicity is the most common toxicity related to EGFR-tyrosine-kinase inhibitors but only 5% of patients had grade 3 rash in the chemotherapy plus erlotinib group. Diarrhoea occurred in both groups, but was more common in the chemotherapy plus erlotinib group (table 4). Serious adverse events were reported by 76 (34%) of 222 patients in the chemotherapy plus placebo group and 69 (31%) of 226 in the chemotherapy plus erlotinib group. There were seven deaths from adverse events in the chemotherapy plus placebo group (three were treatment related: gastroenteritis, sepsis, and dyspnoea) and 12 in the chemotherapy plus erlotinib group (three were treatment related: haemoptysis, sepsis, and tubulo-interstitial nephritis). One interstitial-lung-disease-like event occurred in the chemotherapy plus erlotinib group and two in the chemotherapy plus placebo group.

All 451 patients contributed to patient-reported outcome data. Administration rates in the chemotherapy plus erlotinib and chemotherapy plus placebo groups were 98% (222 of 226 patients) and almost 99% (221 of 222 patients), respectively. Figure 6 summarises

	Chemotherapy plus erlotinib group (n=226)				Chemotherapy plus placebo group (n=222)			
	All adverse events	Related adverse events			All adverse events	Related adverse events		
	>10% incidence	Grade 3	Grade 4	Grade 5	>10% incidence	Grade 3	Grade 4	Grade 5
Rash*	140 (62%)	12 (5%)	..	..	72 (32%)	1 (<1%)	..	..
Neutropenia	113 (50%)	48 (21%)	17 (8%)	..	110 (50%)	49 (22%)	6 (3%)	..
Anaemia	100 (44%)	21 (9%)	5 (2%)	..	112 (50%)	21 (9%)	..	..
Nausea	90 (40%)	1 (<1%)	..	..	92 (41%)	..	..	..
Decreased appetite	79 (35%)	1 (<1%)	..	..	92 (41%)	2 (<1%)	..	..
Vomiting	70 (31%)	2 (<1%)	1 (<1%)	..	69 (31%)	1 (<1%)	..	..
Diarrhoea	71 (31%)	3 (1%)	..	..	37 (17%)	2 (<1%)	..	..
Fatigue	56 (25%)	1 (<1%)	..	..	60 (27%)	1 (<1%)	..	..
Thrombocytopenia	53 (23%)	14 (6%)	18 (8%)	..	54 (24%)	12 (5%)	19 (9%)	..
Constipation	48 (21%)	..	..	..	46 (21%)	..	..	..
Insomnia	46 (20%)	..	..	..	37 (17%)	..	..	..
Leucopenia	41 (18%)	15 (7%)	1 (<1%)	..	51 (23%)	14 (6%)	4 (2%)	..
Alopecia	41 (18%)	..	..	..	51 (23%)	..	..	..
Pyrexia	39 (17%)	..	..	..	26 (12%)	..	..	..
Cough	36 (16%)	..	..	..	35 (16%)	..	..	..
Dermatitis acneiform	33 (15%)	2 (<1%)	..	..	12 (5%)	..	..	..
Dry skin	33 (15%)	..	..	..	9 (4%)	..	..	..
Dyspnoea	28 (12%)	1 (<1%)	..	..	32 (14%)	..	..	1 (<1%)
Stomatitis	27 (12%)	..	..	..	8 (4%)	..	..	..
Pruritus	26 (12%)	..	..	..	21 (9%)	..	..	..
Chest pain	24 (11%)	2 (<1%)	..	..	21 (9%)	..	..	..
Mucosal inflammation	25 (11%)	..	..	..	13 (6%)	..	..	..

Data are number (%). Chemotherapy=gemcitabine plus carboplatin or cisplatin. *Includes gemcitabine-related rash.

Table 4: **Summary of the most commonly reported adverse events in the safety population**

the time to symptomatic progression and time to deterioration in TOI and FACT-L. Time to symptomatic progression was slightly prolonged in the chemotherapy plus erlotinib group versus the chemotherapy plus placebo group (7·3 months [95% CI 5·8–10·4] *vs* 6·7 months [5·6–9·0], respectively; HR 0·82 [0·67–1·01]; p=0·065). Significant benefits were noted for time to deterioration in TOI (p=0·015) and time to deterioration in QoL by FACT-L (p=0·012) for the chemotherapy plus erlotinib group: 6·3 months (4·8–9·5) in the chemotherapy plus erlotinib group versus 5·7 months (4·1–6·7) in the chemotherapy plus placebo group.

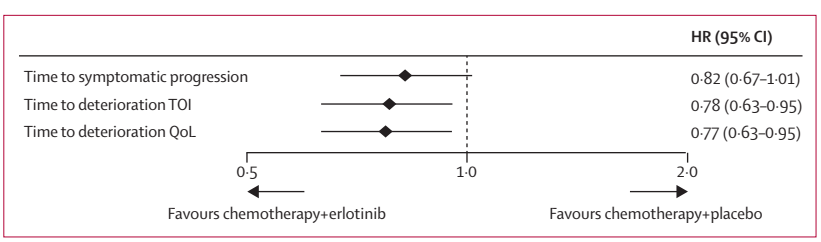

Figure 6: **Forest plot of HRs for time to symptomatic progression, time to deterioration of TOI, and time to deterioration of QoL by Functional Assessment of Cancer Therapy-Lung**
HR=hazard ratio. TOI=Trial Outcomes Index. QoL=quality of life.

Discussion

To the best of our knowledge, this is the first randomised phase 3 trial to show an improvement in efficacy outcomes with an intercalated regimen of chemotherapy and an EGFR inhibitor for patients with advanced non-small-cell lung cancer. The magnitude of PFS improvement was similar to that in the phase 2 FASTACT study.[18]

Several other studies have assessed the use of intercalated regimens in patients with non-small-cell lung cancer. In a randomised phase 2 study, comparison of intercalated single-agent chemotherapy with erlotinib (days 2–16) as second-line treatment in an unselected European population showed significant improvement in overall survival (HR 0·67 [95% CI 0·50–0·93]; p=0·02) and a non-significant improvement in PFS (0·78 [0·59–1·04]; p=0·09).[19] In another randomised study in a clinically selected population of Asian never-smokers, second-line intercalated pemetrexed plus erlotinib was better than single-agent pemetrexed (0·58 [0·39–0·85]; p=0·005) or single-agent erlotinib (0·57 [0·40–0·81]; p=0·002).[20] However, the results of another study that compared an intercalated regimen with erlotinib alone showed no significant difference in 6 month PFS.[21] The results of these studies suggest a potential benefit of intercalated regimens of chemotherapy plus EGFR-tyrosine-kinase inhibitors (panel).

Panel: Research in context

Systemic review

We systemically reviewed PubMed and conference abstracts from the American Society of Clinical Oncology, World Conference on Lung Cancer, American Association for Cancer Research, and European Society for Medical Oncology before starting this trial, searching for reports published in English from 2004 onwards. We searched for relevant publications about "lung neoplasms" and "TKI or tyrosine kinase inhibitor" and "chemotherapy combinations", and data for "single-agent TKI" treatment, before assessing the quality of the evidence, giving greater weight to phase 2 and 3 multicentre trials. Results of three randomised phase 2 studies of intercalated combination of chemotherapy and EGFR-tyrosine-kinase inhibitor (FASTACT,[18] NVALT 10,[22] and S103[23]) suggested an improvement in responses and progression-free survival (PFS) with this type of regimen.

Interpretation

Findings of previous phase 3 studies of concurrent combination of chemotherapy and EGFR-tyrosine-kinase inhibitor in unselected populations did not show any treatment benefit; however, retrospective biomarker analysis was only available in a small fraction of patients. Sequential intercalated combination regimens of chemotherapy and EGFR-tyrosine-kinase inhibitors (FASTACT,[18] NVALT 10,[22] and S103[23]) have shown improvement in responses and PFS, specifically in patients with adenocarcinoma. Again, however, there was a lack of substantial biomarker analysis in these randomised phase 2 studies. FASTACT-2 is the first randomised phase 3 study of this approach with translational biomarker analysis in more than 50% of the study population. Results of FASTACT-2 show that the sequential intercalated erlotinib and chemotherapy regimen improved overall survival and PFS. The benefit in terms of higher numbers of responses and prolonged PFS with an intercalated combination is greater in patients with *EGFR*-mutation-positive disease. This combination is also the first to result in significant improvement in overall survival compared with treatments in previous phase 3 studies of single-agent EGFR-tyrosine-kinase inhibitor (IPASS,[4] First-SIGNAL,[8] NEJ,[7] WJTOG,[24] OPTIMAL,[25] and EURTAC[6]), which did not show OS benefit. Although we recommend *EGFR* mutation testing should be implemented wherever possible, this combination offers a new treatment option for patients with unknown *EGFR* status. Using this intercalated combination, treatment outcomes are potentially better than those with the standard chemotherapy regimen that patients with unknown EGFR status would otherwise receive.

Patients with *EGFR*-mutation-positive disease derived benefit from the combination treatment, whereas those with wild-type disease did not. However, tumour samples with known *EGFR* mutation results were available in only 53% of the intention-to-treat population (table 1). Activating *EGFR* mutations were found in 40% of patients (table 1), as expected in an Asian population.[26] The specific benefit of intercalated treatment is suggested by the high tumour response rate (84%) and early separation of the Kaplan-Meier survival curves in this subgroup. PFS, overall survival, and the proportion of patients who had a RECIST-defined response compare favourably with the findings of other phase 3 studies of first-line EGFR-tyrosine-kinase inhibitor treatment for non-small-cell lung cancer (table 5).

Maintenance treatment with EGFR-tyrosine-kinase inhibitors has been shown to improve PFS. The PFS benefit achieved in FASTACT-2 is likely due to both the intercalated regimen and maintenance EGFR-tyrosine-kinase inhibitor; the extent of benefit noted here is in agreement with data reported in the SATURN trial and INFORM trials.[29,30] The current study is, to the best of our knowledge, the first to report significant prolongation of overall survival in patients with *EGFR*-mutation-positive non-small-cell lung cancer. Median overall survival of the patients in the control group with activating *EGFR* mutation is similar to the overall survival of patients with similar mutation status receiving first-line EGFR-tyrosine-kinase inhibitors.[4–7] This similarity is explained by the 85% crossover rate of the control group to second-line or third-line EGFR-tyrosine-kinase inhibitors. However, the 11-month improvement in median overall survival in patients with EGFR activating mutations in the chemotherapy plus erlotinib group compared with similar patients in the

	Patient population and mutation status	EGFR tyrosine-kinase inhibitors	n	Median PFS (months)	Median overall survival (months)	Proportion of patients with an objective response (%)	Proportion of patients who achieved disease control (%)
WJTOG 3405[9,24]	*EGFR*-mutation-positive patients	Gefitinib	86	9·2	36·0	NR	93·1
NEJ002[7]	*EGFR*-mutation-positive patients	Gefitinib	115	10·8	30·5	73·7	NR
OPTIMAL[5,25,27]	*EGFR*-mutation-positive patients	Erlotinib	83	13·7	22·7 (60% maturity)	83	96
EURTAC[6]	*EGFR*-mutation-positive patients	Erlotinib	86	10·4	19·3	58	NR
LUX-Lung 3[28]	*EGFR*-mutation-positive patients	Afatinib	230	11.1	..	56	NR
FASTACT-2	*EGFR*-mutation-positive patients	Erlotinib	97	16·8	31·4	83·6	NR
IPASS[4]	Overall population	Gefitinib	609	5·7	18·6	43·0	NR
First-SIGNAL[8]	Overall population	Gefitinib	159	5·8	22·3	55	NR
FASTACT-2	Overall population	Erlotinib	226	7·6	18·5	42·9	NR

PFS=progression-free survival. NA=not applicable. NR=not reported.

Table 5: **Efficacy outcomes from clinical trials evaluating EGFR tyrosine-kinase inhibitors in the first-line treatment of non-small-cell lung cancer**

chemotherapy and placebo group cannot be entirely attributed to the 15% of patients in the control group who were not exposed to EGFR-tyrosine-kinase inhibitor. This improvement suggests that the intercalated combination of chemotherapy and erlotinib might have maximised the treatment effect of these agents in patients with *EGFR*-mutation-positive tumours.

The main difference between first-line EGFR-tyrosine-kinase inhibitor, maintenance EGFR-tyrosine-kinase inhibitor, and the FASTACT strategy is the timing of exposure to chemotherapy and EGFR-tyrosine-kinase inhibitor, which might explain the improvement in PFS and overall survival. This sequential approach might have avoided the G1 arrest by erlotinib, thus optimising the cell-cycle phase-dependent activity of chemotherapy.[15] Recent advances in sequencing technologies have indicated that intratumour and intertumour genomic heterogeneity exists; patients with tumours positive for *EGFR* mutations might also have wild-type cell colonies.[31] *EGFR* and *KRAS* heterogeneity has also been reported.[32] Early exposure to chemotherapy might control tumour growth through *EGFR* wild-type cells in patients who were clinically assessed to have *EGFR*-mutation-positive disease. This theory is also indirectly supported by an exploratory analysis of the OPTIMAL (CTONG0802) study.[25] In OPTIMAL, median overall survival of patients exposed to chemotherapy and erlotinib (in any line of treatment) was 30·4 months compared with 20·7 months in patients exposed to erlotinib only and 11·7 months in patients exposed to chemotherapy only.[25] The merit of intercalated chemotherapy and EGFR-tyrosine-kinase inhibitor for patients with known *EGFR* mutations should further be explored in a randomised study with pemetrexed or cisplatin as the backbone chemotherapy and EGFR-tyrosine-kinase inhibitor monotherapy as the control. The sequential approach of FASTACT-2 gave similar efficacy results as those in the TRIBUTE and TALENT studies, with about half the overall amount of erlotinib.[13,14]

Patients with *EGFR* wild-type non-small-cell lung cancer did not benefit from this intercalated regimen. The slight, but insignificant, difference in overall survival noted between groups is probably explained by differences in exposure to second-line chemotherapy. However, the intercalated regimen caused a minimal increase in toxicities. Haematological and gastrointestinal toxicities were similar between the intercalated and control groups, whereas skin rash was higher in the intercalated group. The 4 weekly gemcitabine and platinum regimen seems to be associated with a lower frequency of tumour response in this study than that seen in 3 weekly regimens, but the median PFS of 6·0 months is similar to that noted with 3 weekly regimens.[6,33,34]

The standard treatment for patients with an activating *EGFR* mutation is first-line single-agent EGFR-tyrosine-kinase inhibitor.[5,6] Front-line *EGFR* mutation testing should be the standard, but this might vary between different health-care systems and countries. In a study of 987 cases of non-small-cell lung cancer in China, the take-up rate of *EGFR* mutation testing was only 10%.[10] This low rate could be explained by inadequate tumour sample, lack of testing technology, or lack of facilities. The intercalated combination of chemotherapy and EGFR-tyrosine-kinase inhibitor could be a new treatment option for this patient group with unknown *EGFR* mutation status. Benefit is higher in patients with the mutations, but there is no detrimental effect for patients without mutations, similar to subgroup analyses in the TRIBUTE and INTACT trials.[12,14] By use of this intercalated combination, treatment outcomes are potentially better than the standard chemotherapy regimen that the patient would otherwise receive. We would suggest that the regimen be considered for patients with an unknown mutation status in whom clinical parameters are suggestive of a high incidence of *EGFR* mutations.

Contributors

All authors contributed to drafting or revising of the report and all authors had final approval of the report. VL, VSrim, C-JY, JSL, TM, ST, IB, KJ, and Y-LW contributed to study design. VSriu, JW, XQ, YS, YZ, VL, KS, LZ, HP, ML, Y-MC, FF, GL, JS-T, VSrim, G-CC, C-JY, BM, JK, TM, HEL, ST, CZ, CT, JH, Y-MC, KJ, ES, and Y-LW contributed to data gathering, including enrolment of patients. JW, XQ, YS, YZ, VL, LZ, ML, G-CC, C-JY, JSL, TM, ST, CZ, MT, IB, JH, AC, KJ, and Y-LW contributed to data analysis and interpretation.

Conflicts of interest

VL received honoraria from Eli Lilly. TM has consulted for AstraZeneca, Boehringer Ingelheim, F Hoffmann-La Roche, Eli Lilly, Pfizer, Bristol-Myers Squibb, AVEO, Beigene, Johnson & Johnson, Merck Serono, Taiho, and GlaxoSmithKline; he also received payment for speaking from AstraZeneca, Boehringer Ingelheim, F Hoffmann-La Roche, Eli Lilly, Pfizer, Bristol-Myers Squibb, AVEO, Merck, Taiho, and GlaxoSmithKline. LZ received research support from AstraZeneca, Eli Lilly, F Hoffmann-La Roche, and Avantis. MT is a paid contractor for F Hoffmann-La Roche and owns stocks in the company. IB is an employee of F Hoffmann-La Roche. JH received honoraria from Boehringer Ingelheim, Pfizer, Merck Sharp and Dome, F Hoffmann-La Roche, Eli Lilly, and AstraZeneca. KJ is an employee of F Hoffmann-La Roche. Y-LW received honoraria from F Hoffmann-La Roche, AstraZeneca, Eli Lilly, Sanofi, and Pfizer. The other authors declare that they have no conflicts of interest.

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