Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

James C-H Yang, Lecia V Sequist*, Sarayut Lucien Geater, Chun-Ming Tsai, Tony Shu Kam Mok, Martin Schuler, Nobuyuki Yamamoto, Chong-Jen Yu, Sai-Hong I Ou, Caicun Zhou, Daniel Massey, Victoria Zazulina, Yi-Long Wu*

Summary

Background Most patients with non-small-cell lung cancer tumours that have *EGFR* mutations have deletion mutations in exon 19 or the Leu858Arg point mutation in exon 21, or both (ie, common mutations). However, a subset of patients (10%) with mutations in *EGFR* have tumours that harbour uncommon mutations. There is a paucity of data regarding the sensitivity of these tumours to EGFR inhibitors. Here we present data for the activity of afatinib in patients with advanced non-small-cell lung cancer that have tumours harbouring uncommon *EGFR* mutations.

Methods In this post-hoc analysis, we used prospectively collected data from tyrosine kinase inhibitor-naive patients with *EGFR* mutation-positive advanced (stage IIIb–IV) lung adenocarcinomas who were given afatinib in a single group phase 2 trial (LUX-Lung 2), and randomised phase 3 trials (LUX-Lung 3 and LUX-Lung 6). Analyses were done in the intention-to-treat population, including all randomly assigned patients with uncommon *EGFR* mutations. The type of *EGFR* mutation (exon 19 deletion [del19], Leu858Arg point mutation in exon 21, or other) and ethnic origin (LUX-Lung 3 only; Asian *vs* non-Asian) were pre-specified stratification factors in the randomised trials. We categorised all uncommon mutations as: point mutations or duplications in exons 18–21 (group 1); de-novo Thr790Met mutations in exon 20 alone or in combination with other mutations (group 2); or exon 20 insertions (group 3). We also assessed outcomes in patients with the most frequent uncommon mutations, Gly719Xaa, Leu861Gln, and Ser768Ile, alone or in combination with other mutations. Response was established by independent radiological review. These trials are registered with ClinicalTrials.gov, numbers NCT00525148, NCT00949650, and NCT01121393.

Findings Of 600 patients given afatinib across the three trials, 75 (12%) patients had uncommon *EGFR* mutations (38 in group 1, 14 in group 2, 23 in group 3). 27 (71·1%, 95% CI 54·1–84·6) patients in group 1 had objective responses, as did two (14·3%, 1·8–42·8) in group 2 and two (8·7%, 1·1–28·0) in group 3. Median progression-free survival was 10·7 months (95% CI 5·6–14·7) in group 1, 2·9 months (1·2–8·3) in group 2; and 2·7 months (1·8–4·2) in group 3. Median overall survival was 19·4 months (95% CI 16·4–26·9) in group 1, 14·9 months (8·1–24·9) in group 2, and 9·2 months (4·1–14·2) in group 3. For the most frequent uncommon mutations, 14 (77·8%, 95% CI 52·4–93·6) patients with Gly719Xaa had an objective response, as did nine (56·3%, 29·9–80·2) with Leu861Gln, and eight (100·0%, 63·1–100·0) with Ser768Ile.

Interpretation Afatinib was active in non-small-cell lung cancer tumours that harboured certain types of uncommon *EGFR* mutations, especially Gly719Xaa, Leu861Gln, and Ser768Ile, but less active in other mutations types. Clinical benefit was lower in patients with de-novo Thr790Met and exon 20 insertion mutations. These data could help inform clinical decisions for patients with non-small-cell lung cancer harbouring uncommon *EGFR* mutations.

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Graduate Institute of Oncology, National Taiwan University and National Taiwan University Hospital, Taiwan (Prof J C-H Yang MD); **Massachusetts General Hospital Cancer Center, Boston, MA, USA** (L V Sequist MD); **Internal Medicine, Faculty of Medicine, Prince of Songkla University, Thailand** (S L Geater MD); **Department of Chest Medicine, Taipei Veterans General Hospital and School of Medicine National Yang-Ming University, Taipei, Taiwan** (Prof C-M Tsai MD); **Clinical Oncology, The Chinese University of Hong Kong, Hong Kong** (Prof T S K Mok MD); **West German Cancer Center, Department of Medical Oncology, University Hospital Essen, Germany and German Cancer Consortium (DKTK), Heidelberg, Germany** (Prof M Schuler MD); **Third Department of Internal Medicine, Wakayama Medical University, Japan** (Prof N Yamamoto MD); **Department of Internal Medicine, National Taiwan University and National Taiwan University Hospital, Taiwan** (Prof C-J Yu MD); **Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA** (S-H I Ou MD); **Shanghai Pulmonary Hospital, Shanghai, China** (Prof C Zhou MD); **Clinical Development and Medical Affairs** (V Zazulina MD), **Boehringer Ingelheim** (D Massey MSc), **Bracknell, UK;**

Introduction

Drugs that target the EGFR or the wider ERBB tyrosine kinase receptor family are the standard of care for patients with *EGFR*-mutant, non-small-cell lung cancer tumours.[1–7] The clinical benefit of first-line therapy with erlotinib and gefitinib compared with platinum-based combination chemotherapy in this patient population has been noted in several phase 3 trials.[1–5] Afatinib, an irreversible ERBB family blocker, was recently approved in the USA, Europe, and several other countries worldwide for first-line treatment of non-small-cell lung cancer tumours with *EGFR* mutations following results of two large randomised controlled trials[6,7] that showed that afatinib treatment resulted in improved objective responses and progression-free survival compared with platinum-based chemotherapy. Additionally, in pre-specified analyses of two independent phase 3 trials, compared with chemotherapy, afatinib significantly improved overall survival in patients with exon 19 deletions but did not improve overall survival in patients

and Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, China (Prof Y-L Wu MD)

*These authors contributed equally to this work.

Correspondence to: Prof Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, 510080, China
syylwu@live.cn

Panel: Research in context

Evidence before the study

We searched PubMed for articles published between Jan 1, 2004, and Dec 31, 2014, using the search string "uncommon *EGFR* mutations OR rare *EGFR* mutations AND NSCLC". Of 150 articles, 19 examined the sensitivity of uncommon *EGFR* mutations to EGFR tyrosine kinase inhibitors, either in vitro or in vivo. These studies reported that Gly719Xaa and Leu861Gln mutations confer sensitivity to first-generation, reversible EGFR tyrosine kinase inhibitors in some but not all cases, while Thr790Met and exon 20 insertion mutations generally conferred resistance to EGFR tyrosine kinase inhibitors. However, most of these studies did not prospectively analyse treatment effects in a clinical trial setting, and were restricted to analysis of a few patients.

Added value of this study

To the best of our knowledge, this is the largest analysis of prospective clinical trial data of patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations after treatment with an irreversible ERBB family blocker or chemotherapy. Afatinib showed activity in patients with point mutations or duplications in exons 18–21, suggesting that this group of uncommon mutations can be categorised as sensitising *EGFR* mutations. However, similar to first-generation, reversible EGFR tyrosine kinase inhibitors, afatinib did not provide clinical benefit to patients harbouring de-novo Thr790Met or exon 20 insertion mutations, and results of an exploratory analysis showed that chemotherapy might be a preferable first-line option for patients with these mutations.

Implications of all the available evidence

Data from our study suggest that afatinib is a treatment option for patients with some uncommon *EGFR* mutations. Performing larger randomised trials in patients with uncommon *EGFR* mutations is unlikely in view of the small population size and genetic diversity of these tumours; although limitations exist (eg, inclusion of patients treated beyond progression), a global registry might be more feasible to obtain additional data for these particular patients.

with Leu858Arg mutations,[8] suggesting that different *EGFR* mutations should be studied independently.

The two most common *EGFR* mutations, del19 and the Leu858Arg point mutation in exon 21, account for roughly 90% of all mutation-positive, non-small-cell lung cancer tumours and are sensitive to drugs that target EGFR.[1,8,9] The remaining 10% of *EGFR* mutation-positive cases are a heterogeneous group of molecular alterations within exons 18–21 (ie, uncommon mutations) with variable responses to EGFR-targeted drugs, which have not been prospectively studied in detail.[10] Results of retrospective studies and case reports of erlotinib and gefitinib show inconsistent responses in patients with uncommon *EGFR* mutations.[11–18] Therefore, a clearer understanding of how patients with uncommon *EGFR* mutations respond to ERBB family inhibitors is needed. Here, we describe the activity of afatinib in patients with uncommon *EGFR* mutations in the LUX-Lung clinical trials programme, with data from the non-randomised phase 2 LUX-Lung 2 (LL2) study and the phase 3 randomised LL3 and LL6 trials.[6,7,19]

Methods

Study design and participants

We combined individual data from adult patients (aged ≥18 years) with advanced (stage IIIb–IV) lung adenocarcinomas with uncommon *EGFR* mutations in LL2, LL3, and LL6. The study design, eligibility criteria, and primary results of these three clinical trials of afatinib in *EGFR* mutation-positive patients with non-small-cell lung cancer have been published elsewhere.[6,7,19] All patients in this series were prospectively diagnosed and treated, and tumour responses were independently reviewed. Briefly, LL2 was a single-group phase 2 trial done in Taiwan and the USA, which included patients with *EGFR* mutation-positive lung adenocarcinoma with at least one measurable tumour lesion (by CT or MRI), Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, life expectancy of 3 months or longer, and who had received no previous treatment for advanced disease or progressed after one previous chemotherapy regimen.[19] Both LL3[6] and LL6[7] were phase 3 trials in treatment-naive patients with advanced adenocarcinoma of the lung harbouring *EGFR* mutations who had ECOG performance status of 0 or 1, life expectancy of 3 months or longer, and at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST [version 1.1]). LL3 was a worldwide study, whereas LL6 was done in China, South Korea, and Thailand. Exclusion criteria for all three trials included diagnosis of any other cancers at screening or within the past 5 years (excluding non-melanoma skin cancer and in-situ cervical cancer); pre-existing interstitial lung disease; active brain metastases; clinically relevant (past or present) cardiovascular abnormalities (eg, poorly controlled arrhythmia, unstable angina, congestive heart failure of New York Heart Association classification of 3) or myocardial infarction less than 6 months before randomisation (LL3 and LL6 only); significant or recent acute gastrointestinal disorders (with diarrhoea as a major symptom); cardiac left ventricular function with resting ejection fraction of less than 50%; known HIV carrier or presence of active hepatitis B or C infection.

All trials were done in accordance with the Declaration of Helsinki and Good Clinical Practice, and all study protocols were approved by the ethics committees of all participating centres. All patients provided written informed consent.

Randomisation

For the randomised trials, eligible patients were randomly assigned (2:1) to receive afatinib or chemotherapy, stratified by *EGFR* mutation type (ie, del19 mutations, Leu858Arg mutations, or other [all other single or complex] mutations) and ethnic origin (Asian *vs* non-Asian; LL3 only). Within each strata, a block size of three was used. Randomisation was done at Boehringer Ingelheim with a validated random-number generating system, and was verified by a trial-independent statistician. Randomisation was implemented centrally with an interactive voice-web response system. Access to the randomisation schedule was prohibited for individuals directly involved in trial conduct and analysis. There was no randomisation between doses in any of the three studies.

Procedures

Patients in the LL2 trial originally received 50 mg afatinib once a day as the recommended starting dose (the first 99 patients [77%] of the 129 treated); however, the starting dose was subsequently reduced for newly enrolled patients to 40 mg once a day because durable responses and improved tolerability were reported in patients who underwent dose reductions to 40 mg in the first part of the study. Treatment continued until disease progression, intolerable adverse events, or withdrawal of consent. Tumours in LL2 were assessed by CT scan or MRI at baseline, week 4, week 8, week 12, and every 8 weeks thereafter.

Patients in the LL3 and LL6 trials were randomly assigned (2:1) to receive first-line 40 mg afatinib once a day (starting dose per protocol) or up to six cycles of intravenous pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) once every 21 days in LL3 or gemcitabine (1000 mg/m²; days 1 and 8) plus cisplatin (75 mg/m²; day 1) once every 21 days in LL6. Patients receiving afatinib in the two randomised trials were allowed to increase their dose to 50 mg after the first course of treatment if it was well tolerated, or reduce to lower doses (by 10 mg decrements) if treatment-related grade 3 or prolonged grade 2 adverse events occurred. Treatment continued until disease progression, intolerable adverse events, or withdrawal of consent. Tumours were assessed by CT or MRI in 6-week intervals for the first 48 weeks, and in 12-week intervals thereafter until disease progression or initiation of new anticancer treatment.

EGFR mutations were identified prospectively by direct sequencing in LL2 and by central testing with a validated test kit (TheraScreen *EGFR* 29 [TheraScreen29]; Qiagen, Manchester, UK) in LL3 and LL6. In LL2, exons 18–21 amplified by PCR and analysed bidirectionally by direct sequencing for the presence of somatic mutations according to previously described methods.[19] All mutations were confirmed by several independent PCR analyses. Allele-specific quantitative real-time PCR for the two most common activating mutations (del19 and Leu858Arg) was undertaken in cases that were deemed inadequate for direct sequencing (ie, insufficient sample or quality), based on review by a molecular pathologist or for specimens with a high percentage of normal cells (<50% tumour cells). TheraScreen29, used in LL3 and LL6, is designed to detect 29 *EGFR* mutations against a background of wild-type genomic DNA; the mutations detectable include 19 different deletions in exon 19, Leu858Arg substitution in exon 21, three specific insertions in exon 20 (2307_2308ins9, 2319_2320insCAC, 2310_2311insGGT), and several point mutations (Leu861Gln [exon 21], Gly719Ser [exon 18], Gly719Ala [exon 18], Gly719Cys [exon 18], Thr790Met [exon 20], and Ser768Ile [exon 20]). Direct sequencing used in LL2 allowed for the detection of additional uncommon *EGFR* mutations (ie, not limited to the 29 identifiable with the TheraScreen29 test). If both Leu858Arg and del19 were detected in the same sample, the patient was allocated to the stratification category Leu858Arg. In other instances

	Afatinib			Chemotherapy
	LUX-Lung 2 (n=23)*	LUX-Lung 3 (n=26)†	LUX-Lung 6 (n=26)†	LUX-Lung 3 and LUX-Lung 6 total (n=25)
Age (years)	64·0 (35–86)	58·0 (42–82)	57·0 (30–79)	61·0 (31–73)
Sex				
Women	13 (57%)	15 (58%)	16 (62%)	14 (56%)
Men	10 (43%)	11 (42%)	10 (38%)	11 (44%)
Smoking status				
Never smoked	13 (57%)	17 (65%)	17 (65%)	21 (84%)
Ex-smoker	9 (39%)	7 (27%)	8 (31%)	4 (16%)
Current smoker	1 (4%)	2 (8%)	1 (4%)	0 (0%)
Ethnic origin				
Caucasian	3 (13%)	8 (31%)	0 (0%)	3 (12%)
Asian	20 (87%)	17 (65%)	26 (100%)	22 (88%)
Other	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Stage (AJCC 6.0)				
IIIB (wet)	1 (4%)	1 (4%)	0 (0%)	1 (4%)
IV	22 (96%)	25 (96%)	26 (100%)	24 (96%)
ECOG performance status				
0	14 (61%)	13 (50%)	5 (19%)	11 (44%)
1	9 (39%)	13 (50%)	21 (81%)	14 (56%)
Line of therapy				
First-line	10 (43%)	26 (100%)	26 (100%)	25 (100%)
Second-line	13 (57%)	0 (0%)	0 (0%)	0 (0%)
Mutation status				
Group 1‡	11 (48%)	9 (35%)	18 (69%)	18 (72%)
Group 2§	1 (4%)	11 (42%)	2 (8%)	3 (12%)
Group 3¶	11 (48%)	6 (23%)	6 (23%)	4 (16%)

Data are n (%) or median (range). AJCC=American Joint Committee on Cancer. ECOG=Eastern Cooperative Oncology Group. *Four patients received 40 mg afatinib per day as the starting dose; the remaining 19 patients received 50 mg afatinib per day as the starting dose. †All patients received 40 mg afatinib per day as the starting dose. ‡Consists of patients with all point mutations or duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and rare others). §Consists of patients with de-novo Thr790Met mutations. ¶Consists of patients with exon 20 insertions.

Table 1: **Baseline characteristics of patients with uncommon *EGFR* mutations**

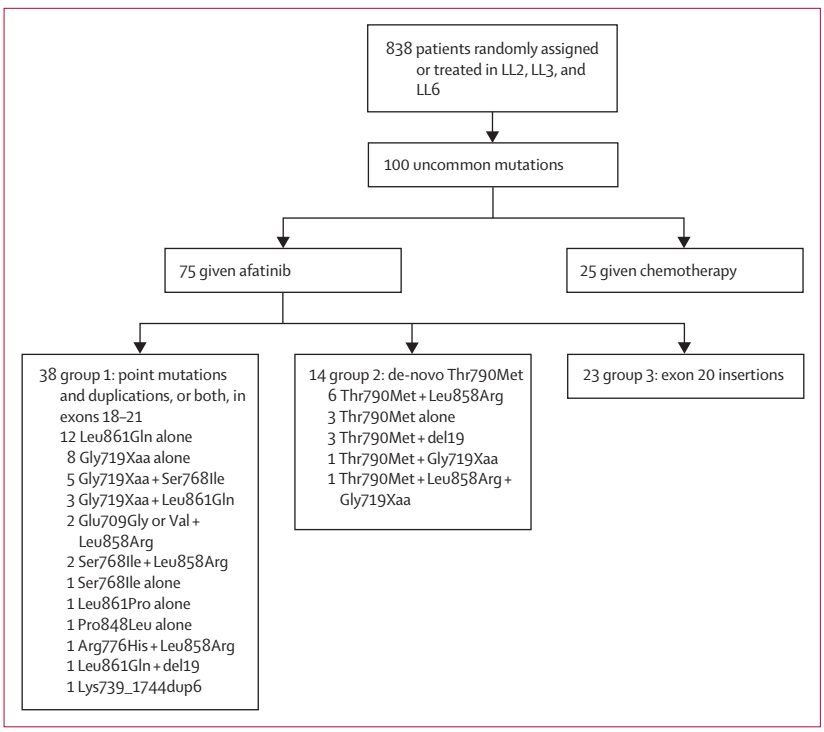

Figure 1: **Subgroups of uncommon mutations**
LL2=LUX-Lung 2. LL3=LUX-Lung 3. LL6=LUX-Lung 6.

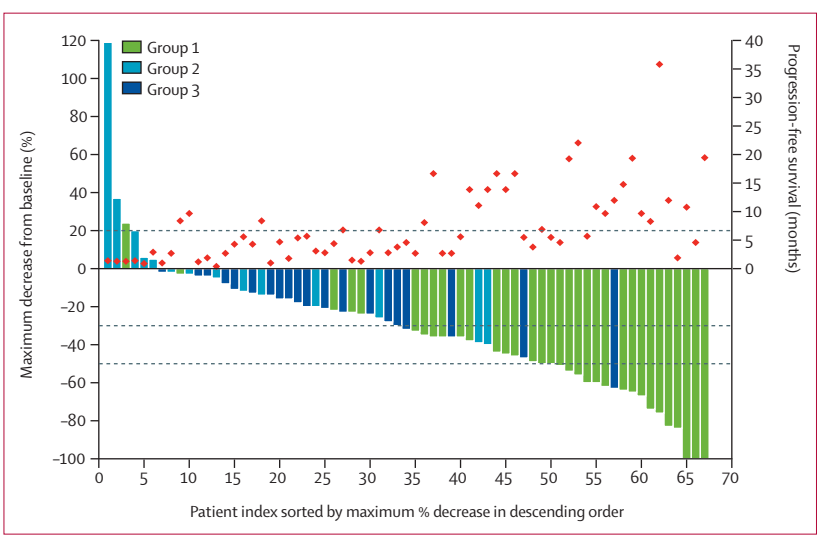

Figure 2: **Tumour shrinkage per independent review**
67 patients were included (eight had insufficient data). Group 1=point mutations or duplications in exons 18–21; Group 2=de-novo Thr790Met mutations; Group 3=exon 20 insertions.

when more than one mutation was detected, the patient was allocated to the stratification category "other".

Outcomes

The primary endpoint in LL2 was objective response (independent review); secondary endpoints included disease control, time to and duration of objective response, tumour shrinkage, progression-free survival, and overall survival. The primary endpoint of both LL3 and LL6 was progression-free survival (by independent review), with objective response, disease control, and overall survival as secondary endpoints. Other secondary endpoints included patient-reported outcomes and safety.

This post-hoc analysis focused on the activity of afatinib in uncommon mutations that were categorised into three cohorts: point mutations and duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and other point mutations alone or in combination with each other; group 1), de-novo Thr790Met mutation in exon 20 (alone or in combination with other mutations; group 2), or exon 20 insertions (group 3). Thr790Met and exon 20 insertion mutations were divided into separate groups because they have been previously shown to confer resistance and decreased sensitivity to EGFR tyrosine kinase inhibitors.[14,20] An additional analysis looked at outcomes in a subgroup of patients, mainly from group 1, with the mutation types Gly719Xaa (exon 18), Leu861Gln (exon 21), and Ser768Ile (exon 20), alone or in combination with other mutations as this group of point mutations represents about half of the uncommon mutations in *EGFR* that are associated with non-small-cell lung cancer.[9,21]

Tumour response was assessed with RECIST by a central independent radiology review prospectively as part of the original study design.

Statistical analysis

Detailed statistical analyses of the individual trials have been previously published.[6,7,19] This post-hoc, intention-to-treat analysis included all randomly assigned and entered patients with an uncommon *EGFR* mutation. For each mutation group, the proportions of patients that achieved objective response (complete response or partial response) and disease control (complete response, partial response, or stable disease) were calculated along with exact Clopper-Pearson 95% CIs. Median duration of response, progression-free survival, and overall survival were calculated with corresponding 95% CIs, estimated with Kaplan-Meier methods. No formal statistical comparisons were done because of the small patient numbers. Median duration of follow-up for progression-free survival and overall survival were calculated with the reverse Kaplan-Meier method. Statistical analyses were done with SAS (version 9.4).

The ongoing LL2, LL3, and LL6 trials are registered with ClinicalTrials.gov, numbers NCT00525148, NCT00949650, and NCT01121393.

Role of the funding source

JC-HY and Boehringer Ingelheim designed the LL2 and LL3 studies; LVS designed LL3 and YLW designed LL6, together with Boehringer Ingelheim. JC-HY and Boehringer Ingelheim designed and analysed this post-hoc study. Boehringer Ingelheim managed the clinical trial database and coordinated the development of the

	Objective response	Duration of response (months)	Disease control	Progression-free survival (months)	Overall survival (months)
Group 1 (n=38)*	27 (71·1%, 54·1–84·6)	11·1 (4·1–15·2)	32 (84·2%, 68·7–94·0)	10·7 (5·6–14·7)	19·4 (16·4–26·9)
Group 2 (n=14)†	2 (14·3%, 1·8–42·8)	8·2 (4·1–12·4)	9 (64·3%, 35·1–87·2)	2·9 (1·2–8·3)	14·9 (8·1–24·9)
Group 3 (n=23)‡	2 (8·7%, 1·1–28·0)	7·1 (4·2–10·1)	15 (65·2%, 42·7–83·6)	2·7 (1·8–4·2)	9·2 (4·1–14·2)

Data are n (%, 95% CI) or median (95% CI). *Consists of patients with all point mutations or duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and rare others). †Consists of patients with de-novo Thr790Met mutations. ‡Consists of patients with exon 20 insertions.

Table 2: **Response to treatment with afatinib in patients with uncommon mutations**

report. JC-HY, LVS, and Y-LW retained full access to the study data and were involved in preparation of the manuscript draft. All authors were involved in the development of the manuscript.

Results

Patients were screened between Aug 21, 2007, and June 4, 2009, for LL2; between Aug 17, 2009, and Feb 28, 2011, for LL3; and between April 27, 2010, and Nov 16, 2011, for LL6. The overall frequency of patients with uncommon *EGFR* mutations was 18% (23/129) for LL2, 11% (37/345) for LL3, and 11% (40/364) for LL6. 75 (13%) of 600 patients (129 in LL2, 229 in LL3, 242 in LL6) given afatinib across the three trials harboured uncommon *EGFR* mutations and were therefore included in this post-hoc study; this frequency is in line with that reported (about 10%)[9] for uncommon mutations in patients with non-small-cell lung cancer harbouring *EGFR* mutations.

Table 1 shows baseline patient demographic and clinical characteristics of patients with uncommon *EGFR* mutations. All of the patients in LL3 and LL6 and all but 13 patients in LL2 received afatinib in the first-line setting. 13 of 23 patients from LL2 received afatinib after treatment with chemotherapy. Across the three trials, four (17%) of 23 patients started at 40 mg in LL2, 25 (96%) of 26 patients started at 40 mg in LL3 (one patient started at 50 mg because of a protocol deviation), and 26 (100%) of 26 patients started at 40 mg in LL6. There were no significant demographic differences in patients with uncommon mutations compared with patients with del19 and Leu858Arg mutations (appendix).

Across the three trials, patients with uncommon mutations given afatinib were divided into three cohorts: group 1 (n=38), group 2 (n=14), and group 3 (n=23; figure 1). Of those with group 1 mutations, the most common mutations were Leu861Gln alone (n=12), Gly719Xaa alone (n=8), and Gly719Xaa plus either Ser768Ile (n=5) or Leu861Gln (n=3).

Afatinib was associated with decreases in tumour size, and this decrease was associated with an increase in progression-free survival (figure 2). One patient with a Gly719Xaa mutation (group 1) had a complete response. The other two patients with 100% tumour shrinkage had K739_1744dup6 and Leu858Arg+Glu709Gly/Val mutations. More patients with group 1 mutations had an objective response or achieved disease control than did those with group 2 or 3 mutations (table 2). Median duration of response was longer in patients with group 1 mutations than in the other two groups (table 2).

	Mutation	Objective response	Progression-free survival (months)	Overall survival (months)
Gly719Xaa (n=18)	Gly719Xaa (n=8) Gly719Xaa+Thr790Met (n=1) Gly719Xaa+Ser768Ile (n=5) Gly719Xaa+Leu861Gln (n=3) Gly719Xaa+Thr790Met+Leu858Arg (n=1)	14 (77·8%, 52·4–93·6)	13·8 (6·8–NE)	26·9 (16·4–NE)
Leu861Gln (n=16)	Leu861Gln (n=12) Leu861Gln+Gly719Xaa (n=3) Leu861Gln+Del19 (n=1)	9 (56·3%, 29·9–80·2)	8·2 (4·5–16·6)	17·1 (15·3–21·6)
Ser768Ile (n=8)	Ser768Ile (n=1) Ser768Ile+Gly719Xaa (n=5) Ser768Ile+Leu858Arg (n=2)	8 (100·0%, 63·1–100·0)	14·7 (2·6–NE)	NE (3·4–NE)

Data are n (%, 95% CI) or median (95% CI). NE=not estimable. Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

Table 3: **Activity of afatinib in specific compound uncommon mutations**

We did a separate analysis of patients with tumours that harbour Gly719Xaa, Leu861Gln, and Ser768Ile mutations, which formed the majority of uncommon mutations. Of note, two patients in group 2 also had Gly719Xaa mutations and were included in this analysis of specific uncommon mutations (table 3). Objective responses were most common in patients with Ser768Ile mutations, followed by those with Gly719Xaa (table 3).

See Online for appendix

For all patients with uncommon mutations (n=100), the median duration of follow-up was 19·2 months (IQR 8·2–19·4) for progression-free survival and 34·7 months (32·4-39·2) for overall survival. For all patients with rare mutations who received afatinib, median progression-free survival and median overall survival was substantially longer for patients in group 1 than it was for those in groups 2 and 3 (table 2 and figure 3). Patients with Gly719Xaa mutations had a substantially longer median progression-free survival and median overall survival than did those with Leu861Gln mutations; median progression-free survival was longest for patients with Ser768Ile mutations, for whom median overall survival was not estimable (table 3).

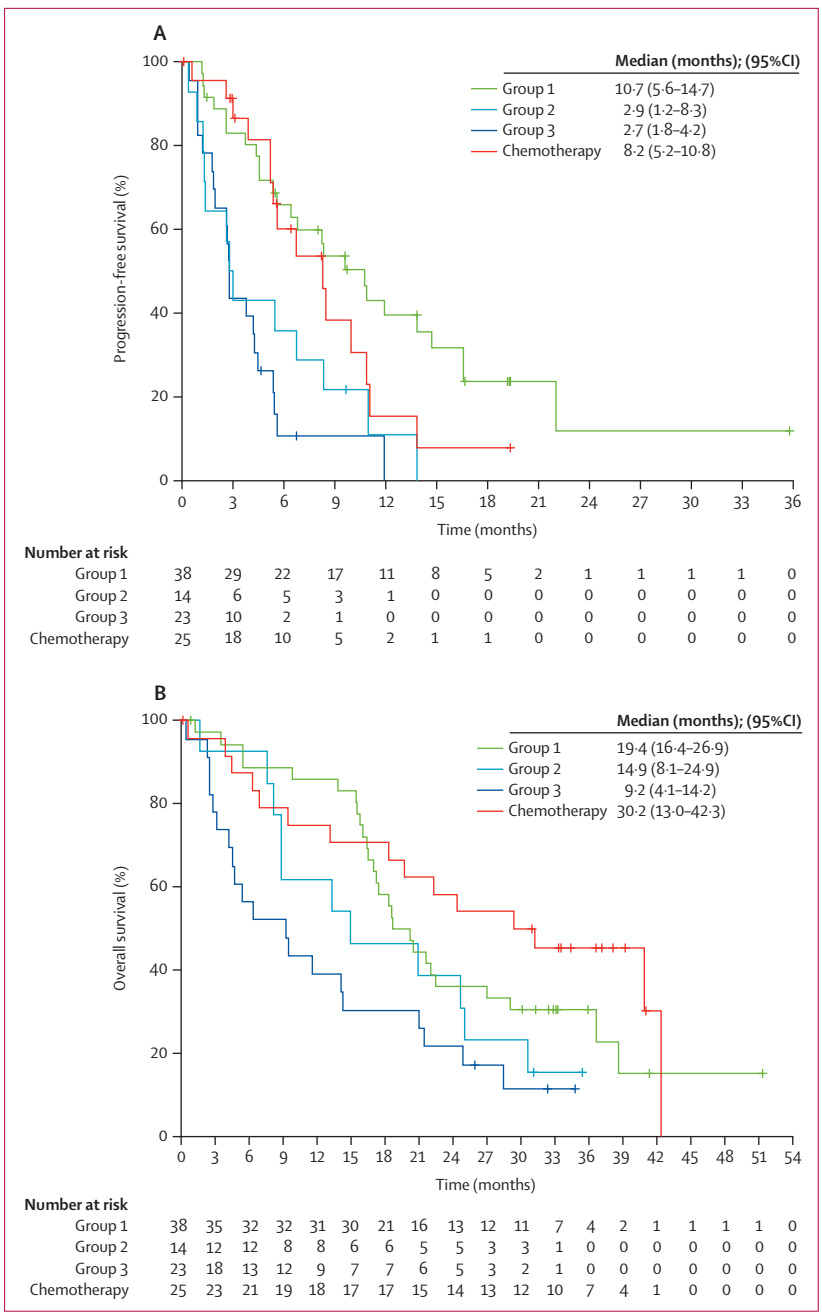

Figure 3: **Kaplan-Meier plot of progression-free survival (A) and overall survival (B)**
Group 1=point mutations or duplications in exons 18–21; Group 2=de-novo Thr790Met mutations; group 3=exon 20 insertions.

In group 2, six patients had a Thr790Met mutation in addition to a Leu858Arg mutation. These patients had a longer median progression-free survival (7·5 months [95% CI 0·8–11·0]) and median overall survival (22·9 months [95% CI 8·7–NE]) than the overall group 2 (Thr790Met) cohort. By contrast, for the three patients with a Thr790Met mutation in addition to a del19 mutation, median progression-free survival (1·2 months [95% CI 0·3–3·0]) and median overall survival (8·1 months [7·5–24·6]) were shorter than in the overall group 2 cohort.

Of all 25 patients with uncommon *EGFR* mutations receiving chemotherapy, objective responses were noted in six (24·0%, 95% CI 9·4–45·1) patients, median progression-free survival was 8·2 months (95% CI 5·2–10·8), and median overall survival was 30·2 months (95% CI 13·0–42·3; figure 3). A further exploratory analysis of patients given chemotherapy who had mutations that fell into the same mutation groups 1 (n=18), 2 (n=3), and 3 (n=4) as defined for those treated with afatinib was also done (appendix). Median progression-free survival and median overall survival was longer for group 1 patients treated with chemotherapy than for patients in the other two groups (appendix).

Of the patients with the most frequent uncommon mutations treated with chemotherapy, four (30·8%, 95% CI 9·1–61·4) of 13 with with Gly719Xaa mutations, none (0·0%, 0·0–52·2) of five with Leu861Gln mutations, and two (33·3%,4·3–77·7) of six with Ser768Ile had objective responses. The longest median progression-free survival was noted for five patients with Leu861Gln mutations (11·9 months [95% CI, 8·4–NE]), whose median overall survival was not estimable at the time of the analysis. For patients with tumours harbouring Gly719Xaa or Ser768Ile mutations, median progression-free survival was 5·6 months (95% CI 3·0–11·1) and 3·8 months (0·5–NE) months, respectively, while median overall survival was 30·2 months (3·8–40·8) and 18·9 months (0·5–40·8), respectively.

At the time of analysis, 71 (95%) of 75 patients given afatanib had stopped treatment and 48 of these patients had started other systemic anti-cancer treatments. Across all subsequent lines of treatment, 42 (59%) of 71 patients received chemotherapy and 14 (20%) patients received an EGFR tyrosine kinase inhibitor. Of the 17 patients who received subsequent treatments in the chemotherapy group, 12 (48%) of 25 were given an EGFR tyrosine kinase inhibitor and eight (32%) were given additional chemotherapy.

Discussion

In this study, we examined the clinical response to afatinib in patients with uncommon *EGFR* mutations, defined as any mutation other than del19 or Leu858Arg. We found a high degree of molecular heterogeneity in this uncommon *EGFR* mutation population and, for the purposes of this analysis, we grouped them into three distinct cohorts based on the previously described[9] differences in sensitivity to EGFR tyrosine kinase inhibitors: point mutations or duplications in exons 18–21, de-novo Thr790Met mutations in exon 20, and insertion mutations in exon 20 (appendix). The best response to afatinib was noted in patients with point mutations or duplications in exons 18–21. These results suggest that this group of uncommon mutations could be categorised as receptive to EGFR inhibitors and

support the use of afatinib in these patients but not in those patients with group 2 or 3 mutations.

A set of pre-specified analyses of LL3 and LL6, which compared afatinib with chemotherapy in patients with the del19 mutation or Leu858Arg mutation, showed that afatinib significantly improved overall survival compared with chemotherapy in patients with the del19 mutation, but not in those with Leu858Arg mutations.[8] Our data suggest that in patients with uncommon *EGFR* mutations who were given afatinib, overall survival varied between different mutation subgroups (table 2). However, no formal statistical comparisons between patients with common versus uncommon *EGFR* mutations were done due to high molecular heterogeneity and the relatively small size of the uncommon mutation subgroups.

Objective responses to afatinib were least common in patients with exon 20 insertions (group 3), similar to findings with gefitinib and erlotinib,[12–14] and consistent with preclinical data.[22,23] This suggests that EGFR family inhibitors as a whole may be an ineffective treatment option for this patient population. Mechanistic studies of exon 20 insertion mutations show important differences compared with common *EGFR* mutations. Unlike common *EGFR* mutations, exon 20 insertion mutations do not affect the ATP-binding pocket required for kinase activity but instead form a wedge at the end of the C-helix that promotes active kinase conformation but does not increase the affinity for EGFR tyrosine kinase inhibitors.[24] Because patients with exon 20 insertions treated with afatinib have an objective response of less than 10% and a median progression-free survival of 2·7 months, chemotherapy might be a better first-line treatment option for this cohort. These findings confirm that a large unmet need exists for patients with exon 20 insertions.

We noted a wide range of responses within the subset of patients with de-novo Thr790Met mutations (group 2), which might reflect variation in Thr790Met allelic frequency. Although data for variations in Thr790Met allelic frequency for the three patients with de-novo Thr790Met mutation alone (rather than in combination with other mutations) were not collected, previous reports[25,26] have shown that patients with tumours with even small allelic frequencies of Thr790Met mutations (detected by techniques such as next generation sequencing), respond to EGFR inhibitors, but have a shorter progression-free survival than patients without detectable Thr790Met.[25,26] Conversely, patients with high allelic frequencies of Thr790Met mutations rarely respond to EGFR tyrosine kinase inhibitors. Additionally, the presence or absence of another mutation affects the response to EGFR inhibitors. For example, both progression-free survival and overall survival were longer in patients with both Thr790Met and Leu858Arg mutations than in patients with the Thr790Met and del19 mutations in our analysis, representing a juxtaposition of the typical results recorded in cancers with these mutations that are negative for Thr790Met.[27–30] However, patient numbers in each subgroup were small, and results of these subanalyses should be interpreted with caution; overall, afatinib was not highly active in patients with de-novo Thr790Met mutations, and chemotherapy might be a preferable first-line treatment option for these patients. This is an active area of clinical investigation.

High afatinib activity was recorded in patients with the uncommon *EGFR* mutations Gly719Xaa, Leu861Gln, and Ser768Ile; these are the three most frequently detected types of uncommon *EGFR* mutations in lung adenocarcinoma.[9,21] However, the scarce clinical data available regarding the activity of reversible EGFR inhibitors in tumours that harbour these three mutations are inconclusive, anecdotal, and mostly retrospective; findings of gefitinib from case reports are mixed.[15,16] Although findings of an earlier study had originally shown that several of these *EGFR* point mutations (Gly719Cys and Leu861Gln) conferred sensitivity to gefitinib,[17] gefitinib was recently characterised in the NEJ002 trial as being ineffective against both Gly719Xaa and Leu861Gln.[18] By contrast with the NEJ002 findings, investigators of a previous retrospective analysis that sought to characterise the effectiveness of gefitinib and erlotinib in tumours with uncommon *EGFR* mutations noted that objective responses associated with Gly719 and Leu861 mutations were more frequent than for tumours with other uncommon mutations.[14]

A limitation of this study is the small size of the uncommon *EGFR* mutation cohort, which required us to combine patients from three trials. Furthermore, the molecular heterogeneity of the uncommon mutations population and numeric imbalances within genetic subgroups limits the ability to formally compare the 25 patients who received chemotherapy and the 75 patients who received afatinib, especially because different outcomes were associated with each mutation group, and different chemotherapy regimens were used in each trial. Moreover, any statistical comparisons between patients given afatinib and those given chemotherapy for each mutation group are unlikely to be informative in view of the small number of patients within each group, especially in the subgroups given chemotherapy. Therefore, data were summarised on an individual patient basis, categorising the mutations or double-mutant cases into post-hoc groups. For completeness, patients receiving chemotherapy were also categorised into the same post-hoc mutation groups as patients given afatinib; however, no biological differences were expected to underpin response to chemotherapy in view of its cytotoxic mode of action. Our findings show that it is important to assess uncommon *EGFR* mutations independently or appropriately grouped, and not as a whole group (ie, uncommon) because mutation-specific responses may not be identified and activity in certain mutations might be masked by a lack of response in others. Finally, although 84% of the patient population in this study were Asian, results of LL3 (in which 28% of the

population were non-Asian) suggest that the presence of an *EGFR* mutation is the main biological determinant of response to afatinib, which takes precedence over demographic or baseline characteristics (eg, ethnic origin, age, and sex).[6] The higher percentage of Asian patients in this study reflects the higher incidence of *EGFR* mutations in Asians than in non-Asians.

In summary, afatinib showed activity in patients with non-small-cell lung cancer tumours that contained the more frequently reported types of uncommon *EGFR* mutations. However, we noted poor activity for patients with de-novo Thr790Met and exon 20 insertion mutations, for whom treatment with chemotherapy might be considered rather than EGFR inhibitors. Although these data should be interpreted with caution because of the small number of patients assessed in this study, these data might inform therapeutic options for patients with non-small-cell lung cancer with uncommon *EGFR* mutations.

Contributors

JC-HY contributed to the scientific literature search, accrual and treatment of patients, study design, oversight, and supervision, and data acquisition, analysis, and interpretation. LVS contributed to accrual and treatment of patients, study design, oversight, and supervision, and data interpretation. SLG contributed to data acquisition. C-MT and NY contributed to accrual and treatment of patients and data acquisition and interpretation. TSKM contributed to study design and data interpretation. MS contributed to provision of study material, patient accrual, and data acquisition, analysis, and interpretation. C-JY contributed to data acquisition and interpretation. S-HIO contributed to patient accrual and data interpretation. CZ contributed to data acquisition, analysis, and interpretation. DM contributed to study design and data analysis and interpretation. VZ contributed to the literature search and data acquisition, analysis, and interpretation. Y-LW contributed to study conception and design, data analysis and interpretation, and study oversight and supervision. All authors were involved in the drafting and reviewing of the manuscript, and provided approval for submission.

Declaration of interests

JC-HY received honoraria from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Clovis Oncology, Eli Lilly, Innopharma, Merck Serono, MSD, Novartis, Ono Pharmaceuticals, Pfizer, and Roche/Genentech. He also reports receiving an institutional fee for advisory board participation from Takeda and a grant from Boehringer Ingelheim. LVS reports non-compensated consulting for AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Genentech, Novartis, Merrimack, and Taiho. C-MT received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Pfizer, and Roche. TSKM received honoraria from Amgen, AstraZeneca, AVEO, Bayer, BioMarin, BMS, Boehringer Ingelheim, Clovis Oncology, Eisai, Eli Lilly, Janssen, Merck Serono, Novartis, Pfizer, Roche, and Taiho, and received a grant from AstraZeneca. MS received honoraria from AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis, and Pfizer, and reports that his institution received grants from Boehringer Ingelheim and Novartis. DM is an employee of Boehringer Ingelheim. VZ is an employee of Boehringer Ingelheim. Y-LW received honoraria from Roche, AstraZeneca, Eli Lily, Sanofi, and Pfizer. All other authors declare no competing interests.

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References

1 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361:** 947–57.

2 Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; **362:** 2380–88.

3 Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013; **24:** 54–59.

4 Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12:** 735–42.

5 Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13:** 239–46.

6 Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31:** 3327–34.

7 Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15:** 213–22.

8 Yang JCH, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for *EGFR* mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; **16:** 141–51.

9 Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* 2007; **7:** 169–81.

10 Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol* 2014; **25:** 126–31.

11 Yang CH, Yu CJ, Shih JY, et al. Specific *EGFR* mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naive non-small-cell lung cancer receiving first-line gefitinib monotherapy. *J Clin Oncol* 2008; **26:** 2745–53.

12 Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic *EGFR* mutations. *J Clin Oncol* 2008; **26:** 2442–49.

13 De Pas T, Toffalorio F, Manzotti M, et al. Activity of epidermal growth factor receptor-tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring rare epidermal growth factor receptor mutations. *J Thorac Oncol* 2011; **6:** 1895–901.

14 Wu JY, Yu CJ, Chang YC, Yang CH, Shih JY, Yang PC. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res* 2011; **17:** 3812–21.

15 Asahina H, Yamazaki K, Kinoshita I, Yokouchi H, aka-Akita H, Nishimura M. Non-responsiveness to gefitinib in a patient with lung adenocarcinoma having rare EGFR mutations S768I and V769L. *Lung Cancer* 2006; **54:** 419–22.

16 Masago K, Fujita S, Irisa K, et al. Good clinical response to gefitinib in a non-small cell lung cancer patient harboring a rare somatic epidermal growth factor gene point mutation; codon 768 AGC > ATC in exon 20 (S768I). *Jpn J Clin Oncol* 2010; **40:** 1105–09.

17 Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.

18 Watanabe S, Minegishi Y, Yoshizawa H, et al. Effectiveness of gefitinib against non-small-cell lung cancer with the uncommon EGFR mutations G719X and L861Q. *J Thorac Oncol* 2014; **9:** 189–94.

19 Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol* 2012; **13:** 539–48.

20 Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005; **2:** e73.

21 Kobayashi S, Canepa HM, Bailey AS, et al. Compound EGFR mutations and response to EGFR tyrosine kinase inhibitors. *J Thorac Oncol* 2013; **8:** 45–51.

22 Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol* 2012; **13:** e23–e31.

23 Greulich H, Chen TH, Feng W, et al. Oncogenic transformation by inhibitor-sensitive and -resistant *EGFR* mutants. *PLoS Med* 2005; **2:** e313.

24 Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med* 2013; **5:** 216ra177.

25 Su KY, Chen HY, Li KC, et al. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non-small-cell lung cancer. *J Clin Oncol* 2012; **30:** 433–40.

26 Costa C, Molina MA, Drozdowskyj A, et al. The impact of EGFR T790M mutations and BIM mRNA expression on outcome in patients with EGFR-mutant NSCLC treated with erlotinib or chemotherapy in the randomized phase III EURTAC trial. *Clin Cancer Res* 2014; **20:** 2001–10.

27 Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 2005; **23:** 2513–20.

28 Riely GJ, Pao W, Pham D, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. *Clin Cancer Res* 2006; **12:** 839–44.

29 Jackman DM, Yeap BY, Sequist LV, et al. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res* 2006; **12:** 3908–14.

30 Kim DW, Lee SH, Lee JS, et al. A multicenter phase II study to evaluate the efficacy and safety of gefitinib as first-line treatment for Korean patients with advanced pulmonary adenocarcinoma harboring EGFR mutations. *Lung Cancer* 2011; **71:** 65–69.

EGFR mutations and EGFR tyrosine kinase inhibitors

In 2004, three groups independently noted that the presence of activating mutations in patients with advanced non-small-cell lung cancer made tumours sensitive to EGFR tyrosine kinase inhibitors.[1] Since then, nine randomised trials including almost 1800 patients have been done, which have compared chemotherapy with tyrosine kinase inhibitors for first-line treatment of a subpopulation of patients with advanced non-small-cell lung cancer tumours that contained these mutations.[2]

In most studies, patients were only eligible for inclusion if they had a deletion in exon 19 or the Leu858Arg mutation in exon 21 of EGFR—ie, the most common *EGFR* mutations in this subset of patients. Retrospective data suggest that rare mutations, with the exception of Gly719Xaa and Leu861Gln, are more strongly associated with smoking habits, worse prognosis, and decreased responsiveness to EGFR inhibitors than are common mutations.[3-6]

Because preclinical data suggest that afatinib can irreversibly inhibit all ERBB family receptor tyrosine kinases, it was thought that the drug could be effective for patients with rare mutations, especially for patients with tumours that had the Thr790Met mutation.[7] Hence, in LUX-Lung 3 and LUX-Lung 6,[8,9] investigators randomly assigned patients with all types of *EGFR* mutations to treatment with afatinib or chemotherapy. Researchers stratified for *EGFR* mutation type (del19 *vs* Leu858Arg *vs* other uncommon mutations) in both studies and by ethnic origin in LUX-Lung 3 only.

In the recently published joint analysis[10] of overall survival, the hazard ratio for the overall population was 0·91 (95% CI 0·75–1·11; p=0·37) and 0·81 (0·66–0·99; p=0·037) when the 78 patients with rare mutations were excluded. In view of these findings, it could be postulated that patients with tumours with rare mutations respond differently to afatinib compared with patients with common mutations, and patients with these rare mutations might respond better to chemotherapy treatment than to afatinib. However, the study of mechanisms related to activation of EGFR suggested that rare mutations represent a heterogeneous mixture of activating and inhibiting mutations.[3,5,6] In *The Lancet Oncology*, Yang and colleagues[11] now report the activity of afatinib in patients with these rare mutations. In this post-hoc analysis of patients from LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6, patients with rare mutations were given afatinib (n=75) or chemotherapy (n=25). The investigators divided patients harbouring rare *EGFR* mutations into three groups according to their biological sensitivity to afatinib: group 1 included patients with mutations thought to be more sensitive to EGFR inhibitors, whereas groups 2 and 3 included patients with mutations likely to be resistant to afatinib.

Although limited by the small sample size, the present analysis seems to confirm the hypothesis that response to treatment varies based on the *EGFR* mutation present. In particular, data from this study suggest that group 1 mutations confer a better prognosis than other rare mutations. However, a possible limitation of this approach is the method used to detect the different mutations. In LUX-Lung 2,[12] patients were screened with direct sequencing, which allowed the detection of a higher number of mutations (albeit with lower sensitivity) compared with the TheraScreen test used in LUX-Lung 3 and LUX-Lung 6. This disparity could have caused investigators to potentially underestimate the types and the frequency of the mutations detected and the effects recorded. However, Yang and colleagues[11] were unable to establish whether the differences in patient outcomes in each group were due to the intrinsic biological differences conferring different prognosis or whether the effect establishes a true differential response to afatinib.

After almost 10 years of studies and meta-analyses on EGFR tyrosine kinase inhibitors, several questions remain. It is still unclear what method is the best to detect the presence of mutations and the biological significance of the presence of mutations in a very low percentage of cells. It is now clear that various mutations in *EGFR* respond differently to treatment; however, is it also possible to personalise treatment based on which *EGFR* mutation is present? Currently, data required to answer this question are only available for the common exon 19 deletion mutation and the Leu858Arg mutation. Data derived from indirect meta-analyses suggest that various EGFR inhibitors have a similar effect on progression-free survival in patients with the exon 19 deletion, but insufficient data are

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available for overall survival. The results of LUX-Lung 7 (NCT01466660), a phase 2 randomised trial comparing afatinib with gefitinib, could help to answer this question. Results for Leu858Arg are still inconclusive because progression-free survival is higher in patients given all EGFR inhibitors versus chemotherapy, with the notable exception of afatanib. Even less is known about rare mutations, but the data from this current study—although patient numbers are too small to draw definite conclusions—suggest that chemotherapy could be the best first-line treatment for some of these patients, and that the decision of whether to offer chemotherapy or EGFR tyrosine kinase inhibitors should be discussed with each patient on the basis of toxicity profiles and all available data.

*Valter Torri, Massimo Broggini, Marina Chiara Garassino**
IRCCS Istituto di Ricerche Farmacologiche Mario Negri (IRFMN), Milan, Italy (VT, MB); Thoracic Oncology, Medical Oncology Department 1, Fondazione IRCCS Istituto Nazionale dei Tumori, 20129 Milano (MCG)
marina.garassino@istitutotumori.mi.it

MCG has served on advisory boards for Boeheringer Ingelheim and Eli Lilly. VT and MB declare no competing interests.

1 Tomida S, Yatabe Y, Yanagisawa K, Mitsudomi T, Takahashi T. Throwing new light on lung cancer pathogenesis: updates on three recent topics. *Cancer Sci* 2005; **96:** 63–68.

2 Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst* 2013; **105:** 595–605.

3 Arrieta O, Cardona AsF, Corrales L, et al. The impact of common and rare EGFR mutations in response to EGFR tyrosine kinase inhibitors and platinum-based chemotherapy in patients with non-small cell lung cancer. *Lung Cancer* 2015; **87:** 169–75.

4 Baek JH, Sun J-M, Min YJ, et al. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small cell lung cancer except both exon 19 deletion and exon 21 L858R: A retrospective analysis in Korea. *Lung Cancer* 2015; **87:** 148–54.

5 Keam B, Kim DW, Park JH, et al. Rare and complex mutations of epidermal growth factor receptor, and efficacy of tyrosine kinase inhibitor in patients with non-small cell lung cancer. *Int J Clin Oncol* 2014; **19:** 594–600.

6 Lohinai Z, Hoda MA, Fabian K, et al. Distinct epidemiology and clinical consequence of classic versus rare EGFR mutations in lung adenocarcinoma. *J Thorac Oncol* 2015; **10:** 738–46.

7 Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008; **27:** 4702–11.

8 Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31:** 3327–34.

9 Wu Y-L, Zhou C, Hu C-P, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15:** 213–22.

10 Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; **16:** 141–51.

11 Yang JC-H, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol* 2015; published online June 5. http://dx.doi.org/10.1016/S1470-2045(15)00026-1

12 Yang JC-H, Shih J-Y, Su W-C, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol* 2012; **13:** 539–48.