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Original Research

Non-small cell lung cancer harbouring non-resistant uncommon *EGFR* mutations: Mutation patterns, effectiveness of epidermal growth factor receptor-tyrosine kinase inhibitors and prognostic factors

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KEYWORDS
Non-small cell lung cancer;
EGFR;
Uncommon mutations;
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Abstract ***Introduction:*** Non-small cell lung cancer (NSCLC) harbouring *EGFR* exon 19 deletions or *L858R* mutation usually respond to epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs), whereas *T790M* mutation and exon 20 insertion are frequently resistant to EGFR-TKIs. *EGFR* mutations other than those above are seldom investigated.
Methods: In this multicentre, retrospective study, we enrolled NSCLC patients with non-resistant uncommon *EGFR* mutations, which were defined as mutations other than *L858R*, exon 19 deletions, exon 20 insertions and *T790M*. The mutation patterns, clinical data and treatment outcomes were analysed. Patients were classified as gefitinib/erlotinib and afatinib groups according to the EGFR-TKIs received as the first-line therapy.
Results: A total of 177 patients were identified (177/1983, 8.9%). Sixty-six patients had more than one *EGFR* mutation, including those coexisting with exon 19 deletion or *L858R* mutation. In treatment-naïve patients with advanced stages (n = 72), the objective response rate was 35.8% for gefitinib/erlotinib group and 60.6% for afatinib group ($p = 0.036$). In multivariate analysis, no significant differences were found between gefitinib/erlotinib and afatinib

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groups in median progression-free survival (PFS) and overall survival (OS). Brain metastasis at diagnosis was associated with a shorter PFS (hazard ratio [HR] = 2.49, 95% confidence interval [CI] = 1.29–4.83) and OS (HR = 3.22, 95% CI = 1.41–7.35).
Conclusions: For patients with NSCLC harbouring non-resistant uncommon *EGFR* mutations, afatinib use as the first-line therapy may provide a better treatment response but no survival benefit, as compared with gefitinib or erlotinib. Brain metastasis at diagnosis is associated with a poor prognosis.
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1. Introduction

EGFR mutations as oncogenic drivers are detected in approximately 50% of Asian and 10–20% of Caucasian patients with non-small cell lung cancer (NSCLC) [1,2]. Exon 19 deletions (42–50%) and *L858R* point mutation in exon 21 (32.84–42%) are the most commonly found in NSCLC [3–6]. For patients with advanced NSCLC harbouring exon 19 deletions or *L858R* mutation, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are frequently used as the first-line therapy [7–9].

The *EGFR* mutations other than exon 19 deletions and *L858R* are considered as 'uncommon mutations'. These uncommon mutations are highly heterogenous and account for 6.1–18.2% of *EGFR* mutations, which might be related to different study populations and methods of mutation detection [5,10–14]. NSCLC harbouring exon 20 insertion and *T790M* mutation are resistant to EGFR-TKI therapy [15–22]. As for the other uncommon *EGFR* mutations, *G719X* is the most frequently detected (2–6% of all *EGFR* mutations), followed by *L861Q* (1.3–3.2%), *S768I* (1.3–3%) and *E709X* (<0.5%) [23,24].

Data on treatment effectiveness of EGFR-TKIs in NSCLC patients with non-resistant uncommon *EGFR* mutations are limited [25,26]. The first-generation EGFR-TKIs, gefitinib and erlotinib, were reported to be less effective in patients with *G719X*/*L861Q*/*S768I* mutations than those with exon 19 deletions or *L858R* mutation [27]. Another retrospective study demonstrated a modest effectiveness of the first-generation EGFR-TKIs on NSCLC harbouring *E709X* mutations, with an objective response rate (ORR) of 50% and a median progression-free survival (PFS) of 6.2 months [28]. As for the second-generation EGFR-TKI, a post hoc analysis revealed that afatinib was effective in NSCLC harbouring certain uncommon *EGFR* mutations, including *G719A*, *L861Q* and *S768I* [29].

Most studies on EGFR-TKIs treatment effectiveness for uncommon *EGFR* mutation analysed the patient populations including those received EGFR-TKI as the second-line therapy and beyond. To further clarify the effectiveness of EGFR-TKIs as the first-line therapy in patients with NSCLC harbouring non-resistant uncommon *EGFR* mutations, we conducted a multicentre, retrospective study. The *EGFR* mutation patterns and prognostic factors were also investigated.

2. Material and methods

2.1. Patients

From January 2011 to July 2017, patients diagnosed with histologically proven NSCLC harbouring *EGFR* mutations were screened retrospectively. This multicentre study was conducted at three hospitals, including National Taiwan University Hospital (Taipei, Taiwan) and Far Eastern Memorial Hospital (New Taipei City, Taiwan) in the northern Taiwan and National Taiwan University Hospital Yun-Lin Branch (Yun-Lin County, Taiwan) in the middle Taiwan. This study was approved by Institutional Review Board of these three hospitals.

The non-resistant uncommon *EGFR* mutations were defined as mutations other than *L858R* mutation, in-frame deletions of exon 19, exon 20 insertions and *T790M* mutation. Treatment-naïve patients with advanced NSCLC harbouring non-resistant uncommon mutations, including those coexisting with *L858R* mutation or exon 19 deletions and received EGFR-TKI therapy were included for treatment outcome analysis.

2.2. Clinical data collection and EGFR mutation testing

The medical records were reviewed, and the data were analysed, including age at diagnosis, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, disease stages, histologic types, types of *EGFR* mutation, EGFR-TKI use and treatment outcomes including ORR, disease control rate (DCR), PFS and overall survival (OS). The disease stages were determined according to the American Joint Committee on Cancer staging system, the 7th edition.

The MassARRAY® genotyping (Sequenom, San Diego, CA) and polymerase chain reaction–direct sequencing are the major methods for *EGFR* mutation testing at the National Taiwan University Hospital and Yun-Lin branch of National Taiwan University

Hospital. In the Far Eastern Memorial Hospital, the *EGFR* mutation analyses are performed by the cobas® EGFR Mutation Test (Roche). The *EGFR* mutations data in the reports from other medical institutions or by plasma circulating tumour DNA test were also collected.

The *G719X* denoted that other amino acid residue was substituted for the glycine at position 719. The *E709X* referred to substitutions of the glutamate at position 709 to other residues. Complex uncommon *EGFR* mutations were defined as co-existing two or more distinct uncommon *EGFR* mutations.

2.3. Evaluation of treatment effectiveness

The patients received gefitinib or erlotinib as the first-line therapy were classified as treatment group of gefitinib/erlotinib, whereas those received afatinib as the first-line therapy were classified as afatinib group. The daily doses were 250 mg for gefitinib and 150 mg for erotinib. The daily dose of afatinib was 30 mg or 40 mg, depending on the physician's decisions.

The radiographic image studies during EGFR-TKI treatment period included chest (including the liver and adrenal glands) and brain computed tomography at intervals of 8–12 weeks, chest radiography at intervals of 2–4 weeks or as needed otherwise. These are routine practices at the three hospitals for treatment response evaluation. Those without evaluable follow-up images and with a follow-up period less than 3 months were excluded.

The best treatment responses to EGFR-TKIs were evaluated according to the Response Evaluation Criteria in Solid Tumours, version 1.1 [30], including complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The ORR was defined as the percentage of patients who achieved a CR or PR. The DCR was defined as the percentage of patients who achieved CR, PR, or SD. PFS was defined as the time period from the date of initiation of systemic therapy to the date of disease progression, death or intolerable adverse events occurred. OS was defined as the time period between the date of initiation of EGFR-TKI therapy and the date of death. The second-line therapies and beyond were recorded and analysed, including the crossover rates in the gefitinib/erlotinib group and the afatinib group.

2.4. Statistical analysis

Categorical variables were presented as percentages and were analysed by Chi-square tests. Continuous variables were expressed as medians with range or interquartile ranges (IQRs). PFS and OS were presented as median value with two-sided 95% confidence interval (CI). The differences of PFS and OS between patient groups of gefitinib/erlotinib and afatinib were analysed by a log-rank test and plotted by a Kaplan-Meier method. Multivariate analyses for PFS and OS were performed by using Cox regression models. A two-sided p value < 0.05 was considered statistically significant. All analyses were performed using SPSS 22 (IBM SPSS Statistics Inc. Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 1983 patients with *EGFR*-mutated NSCLC were screened from National Taiwan University Hospital (n = 1489), National Taiwan University Hospital Yun-Lin Branch (n = 91) and Far Eastern Memorial Hospital (n = 403). Among them, 177 had non-resistant uncommon (8.9%).

Most patients had single mutation (n = 111, 62.7%), including *G719X* (n = 55, 31.1%), *L861Q* (n = 45, 25.4%), *S861I* (n = 6, 3.4%), *E709X* (n = 4, 2.3%) and *L747P* (n = 1, 0.6%). Sixty-six patients had NSCLC harbouring more than one *EGFR* mutation (37.3%), including those coexisting with exon 19 deletion or *L858R* mutation (n = 36, 20.3%) and those without (n = 30, 16.9%). Fig. 1 demonstrates the proportions of different non-resistant uncommon *EGFR* mutations. The detail of these *EGFR* mutations was shown in Supplemental Table 1.

Seventy-two patients with advanced stages (stage IIIB or IV) who received EGFR-TKIs as the first-line

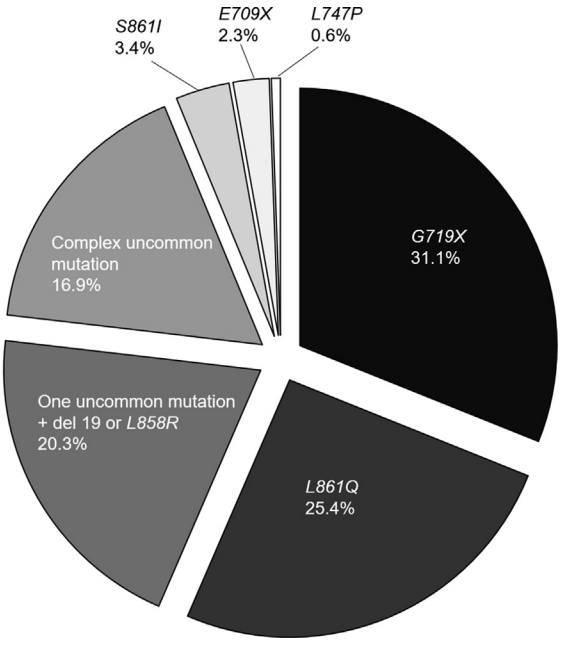

Fig. 1. **Mutation patterns in patients with non-resistant uncommon *EGFR* mutations (n = 177).** Among the patients with one uncommon mutation plus del 19 or *L858R*, one had *G719S,* exon 19 deletion and *L858R* mutations. Del 19 denotes exon 19 deletion.

therapy were included for treatment outcome analysis (Fig. 2). The demographic data were shown in Table 1. The median age at diagnosis were 67 years old. Most patients were female (66.7%), never smokers (75.0%), with ECOG performance status 0–1 (79.2%) and diagnosed with lung adenocarcinoma (97.2%). All patients had stage IV diseases.

There were 39 patients (54.2%) received the first-generation EGFR-TKI therapy, including 26 (36.1%) gefitinib and 13 (18.1%) erlotinib, whereas 33 (45.8%) received afatinib, the second-generation EGFR-TKI. No significant differences in clinical characteristics were found between the treatment groups of gefitinib/erlotinib and afatinib.

3.2. Treatment responses to EGFR-TKIs as the first-line therapy in patients with non-resistant uncommon EGFR mutations

The ORR of gefitinib/erlotinib and afatinib groups were 35.8% and 60.6%, respectively ($p = 0.036$), whereas the DCRs were 84.6% and 90.9%, respectively ($p = 0.421$). Table 2 shows the treatment responses to EGFR-TKIs in patients with different types of non-resistant uncommon *EGFR* mutations. For patients with *L861Q* or complex uncommon *EGFR* mutations, afatinib therapy were associated with a higher ORR (afatinib versus gefitinib/erlotinib: *L861Q*, 60% versus 12.5%, $p = 0.040$; complex uncommon mutation: 83.3% versus 0%, $p = 0.035$). There was no significant difference in DCR between patient groups of gefitinib/erlotinib and afatinib. The median decrease of tumour diameter in percentage for patient groups of gefitinib/erlotinib and afatinib were 26.7% (IQR, 44.0–7.1%) and 34.5% (IQR, 48.7–10.5%), respectively ($p = 0.382$). The tumour diameter changes are demonstrated in Supplemental Fig. 1.

3.3. Survival analysis of patients with non-resistant uncommon EGFR mutations treated with EGFR-TKIs as the first-line therapy

The median PFS in treatment groups of gefitinib/erlotinib and afatinib were 8.8 (95% CI, 4.8–12.8 months) and 12.0 months (95% CI, 9.5–14.5 months), respectively ($p = 0.163$, Fig. 3A). The patients who received afatinib were likely to have a longer median PFS as compared with those received gefitinib or erlotinib, although not statistically significant. The median OS of patient groups of gefitinib/erlotinib and afatinib were 29.0 (95% CI, 22.8–35.2 months) and 27.6 months (95% CI, 2.1–53.1 months), respectively ($p = 0.334$, Fig. 3B).

Nineteen patients had brain metastasis at diagnosis. The median PFS of patients received afatinib were 10.4 months (95% CI, 5.7–15.0 months), which was significantly longer than that of patients received gefitinib or erlotinib (6.2 months, 95% CI, 4.2–8.2 months) (Supplemental Fig. 2, $p = 0.042$). The median OS of patient groups treated with gefitinib/erlotinib and afatinib was 31.3 months (95% CI, 4.3–58.3 months) and 11.6 months (95% CI, 11.3–11.9 months), respectively (Supplemental Fig. 3, $p = 0.665$).

Supplemental Table 2 demonstrated the PFS in patients with subtypes of non-resistant uncommon *EGFR* mutations. No significant difference existed in PFS between the patient groups of gefitinib/erlotinib and afatinib in each subtypes of non-resistant uncommon *EGFR* mutations. Because of the small case numbers, the PFS and OS of patients with *E709X* and *S861I* were not analysed.

Two very rare *EGFR* mutations were found in this study. One 70-year-old female patient had *V689L* and *L858R* mutations. Her disease progressed rapidly, and she passed away after gefitinib therapy for 10 days. Because the follow-up CT was not available, she was not

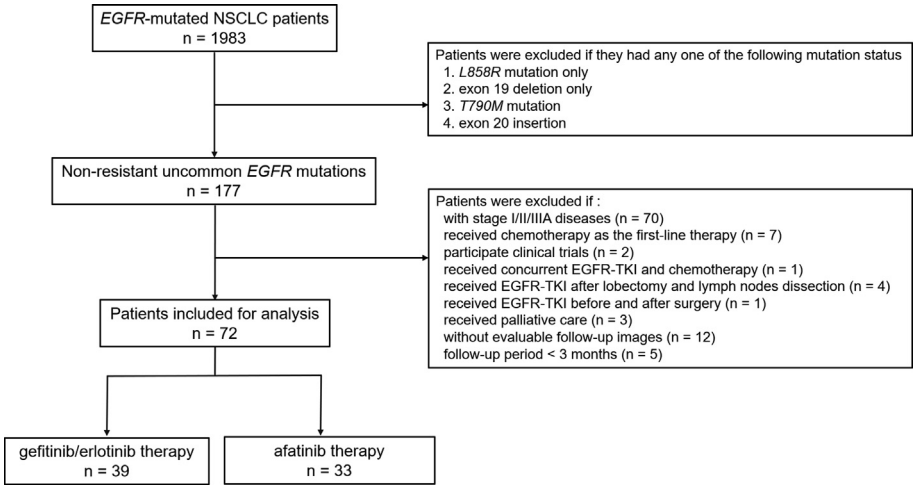

Fig. 2. **Flowchart for patient inclusion.** Non-resistant uncommon *EGFR* mutations indicate uncommon *EGFR* mutations excluding *T790M* mutation and exon 20 insertions. NSCLC, non-small cell lung cancer; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

Table 1
Clinical characteristics of patients with advanced non-small cell lung cancer harbouring non-resistant uncommon *EGFR* mutations and received EGFR-TKIs as the first-line therapy (n = 72).

Characteristics	N (%)	Gefitinib/erlotinib (n = 39)	Afatinib (n = 33)	*p* value
Age, years old				0.085
Median (range)	67 (46–88)	64.4 (46–88)	71.0 (46–87)	
Sex				0.616
Male	24 (33.3)	14 (35.9)	10 (30.3)	
Female	48 (66.7)	25 (64.1)	23 (69.7)	
ECOG performance status				0.504
0–1	57 (79.2)	32 (82.1)	25 (75.8)	
2–4	14 (19.4)	7 (17.9)	7 (21.2)	
Unknown[a]	1 (1.4)	0 (0)	1 (3.0)	
Smoking status				0.495
Never	54 (75.0)	28 (71.8)	26 (78.8)	
Ever	18 (25.0)	11 (28.2)	7 (21.2)	
Histology				0.905
Adenocarcinoma	70 (97.2)	38 (97.4)	32 (97.0)	
Non-adenocarcinoma	2 (2.8)	1[b] (2.6)	1[c] (3.0)	
EGFR mutations				0.247
G719X	25 (34.7)	15 (38.5)	10 (30.3)	
L861Q	18 (25.0)	8 (20.5)	10 (30.3)	
E709X	2 (2.8)	2 (5.1)	0 (0)	
S781I	1 (1.4)	1 (2.6)	0 (0)	
One uncommon mutation plus del 19 or *L858R*	18 (25.0)	11 (28.2)	7 (21.2)	
Complex uncommon mutations	8 (11.1)	2 (5.1)	6 (18.2)	

ECOG, Eastern Cooperative Oncology Group; del 19, exon 19 deletion.
[a] The ECOG performance status was not available.
[b] Carcinoma with rare gland-like differentiation. The immunophenotype is compatible with a non-small cell carcinoma of lung origin.
[c] Poorly differentiated carcinoma.

included for treatment effectiveness analysis. Another 65-year-old man with co-existing *V765M* and exon 19 deletion received afatinib as the first-line therapy. The PFS was 11.2 months, and the OS reached 27.6 months.

3.4. The second-line systemic therapies and beyond

The average number of total lines of systemic treatment for the gefitinib/erlotinib and afatinib groups were 3.0 (range, 1–8) and 2.9 (range, 1–9), respectively ($p = 0.898$). These crossover rates in the gefitinib/erlotinib group (n = 7, 26.9%) and the afatinib group (n = 9, 42.9%) are not significantly different ($p = 0.252$).

Forty-seven patients received the second-line systemic therapies. Most patients received chemotherapies (n = 39, 83.0%), followed by participating clinical trials (n = 5, 10.6%) and EGFR-TKIs (n = 3, 6.4%). Among the patients received chemotherapy, 16 in the gefitinib/erlotinib group and 11 in the afatinib group received platinum-based chemotherapy, including those received platinum plus pemetrexed (15 in the gefitinib/erlotinib group and nine in the afatinib group). For those who received platinum-based chemotherapy, no significant

Table 2
Treatment responses to EGFR-TKIs as the first-line therapy in patients with advanced non-small cell lung cancer harbouring non-resistant uncommon *EGFR* mutations (n = 72).

EGFR mutation	ORR/DCR, %			
	All	Gefitinib/erlotinib	Afatinib	*p* value
G719X (n = 25)	40.0/88.0	26.7/86.7	60.0/90.0	0.096/0.802
L861Q (n = 18)	38.9/88.9	12.5/87.5	60.0/90.0	0.040*/0.867
S768I (n = 1)[a]	100/100	100/100	NA	NA
E709X (n = 2)[b]	0/100	0/100	NA	NA
One uncommon mutation plus del 19 or *L858R* (n = 18)	61.1/88.9	72.7/81.8	42.8/100	0.205/0.231
Complex uncommon mutation (n = 8)[c]	62.5/75.0	0/50.0	83.3/83.3	0.035*/0.346

ORR, objective response rate; DCR, disease control rate; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; del 19, exon 19 deletion; NA, not applicable.
*p value < 0.05.
[a] This patient received gefitinib, with partial response achieved.
[b] One patient received gefitinib therapy and the other received erlotinib, both had stable disease.
[c] One patient with *S768I* and *G719X* mutation received afatinib therapy and had complete remission.

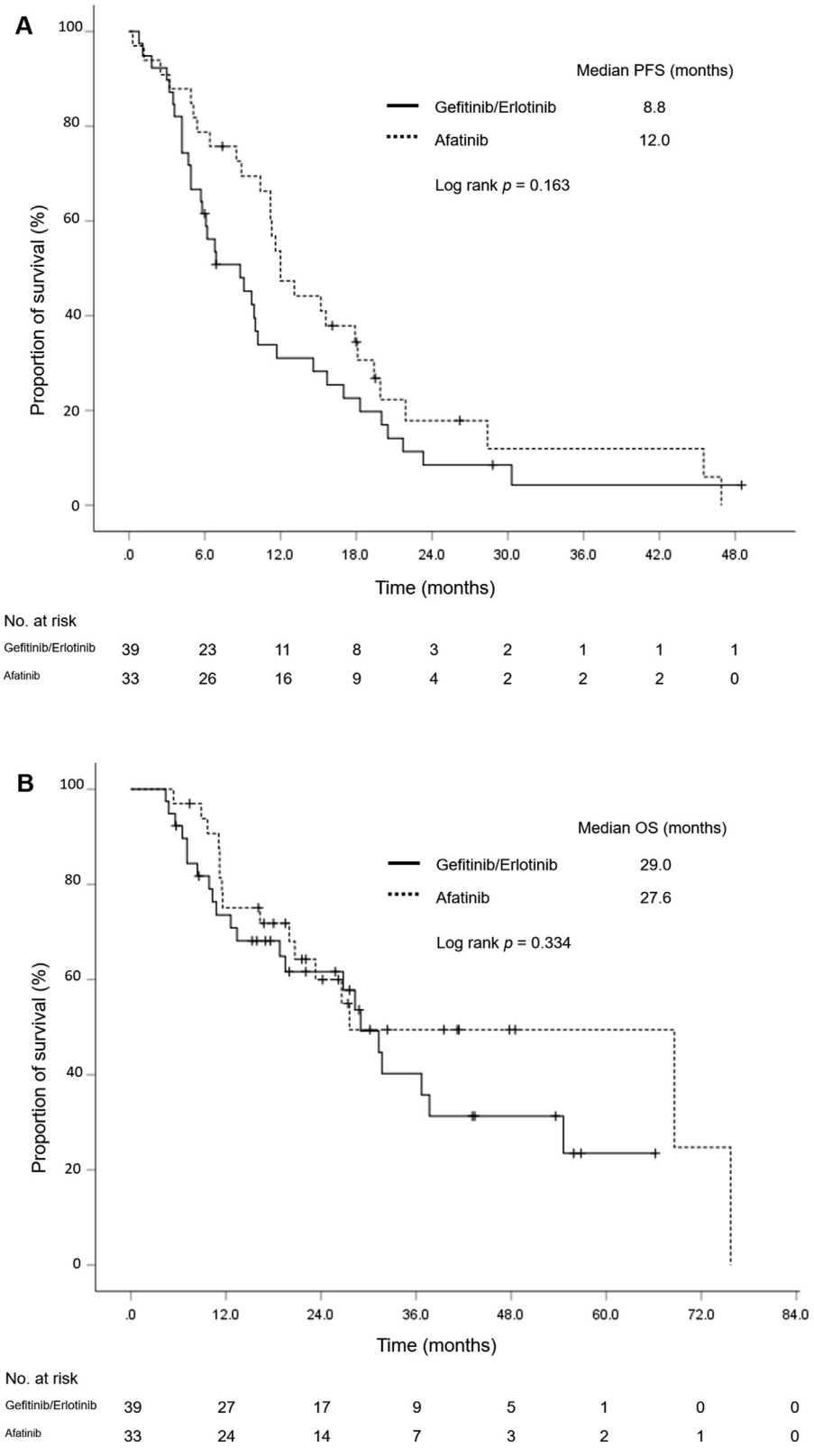

Fig. 3. **Differences between patient groups of gefitinib/erlotinib and afatinib in progression-free survival (A) and overall survival (B).** PFS, progression-free survival; OS, overall survival.

difference was found in median PFS between the gefitinib/erlotinib (5.0 months, 95% CI, 2.4–7.6 months) and afatinib group (3.7 months, 95% CI, 0.8–6.6 months) ($p = 0.943$).

3.5. Prognostic factors for patients with non-resistant uncommon EGFR mutations treated with EGFR-TKIs as the first-line therapy

In multivariate analysis, variables including age, sex, smoking status, ECOG performance status , uncommon *EGFR* mutation coexisting either exon19 deletion or *L858R,* EGFR-TKI therapy and brain metastasis at diagnosis were applied in the Cox regression model. Patients with *EGFR* mutation coexisting either exon 19 deletion or *L858R* mutation had a longer PFS (hazard ratio, HR = 0.35, 95% CI = 0.15–0.79) than those without coexisting exon 19 deletion or *L858R* mutation. Patients with brain metastasis at diagnosis had a shorter PFS (HR = 2.49, 95% CI = 1.29–4.83) and OS (HR = 3.22, 95% CI = 1.41–7.35) than their counter part. No difference in PFS and OS was found between patient groups of gefitinib/erlotinib and afatinib (Table 3).

4. Discussion

This study demonstrated the mutation patterns of NSCLC harbouring non-resistant uncommon *EGFR* mutation. The ORR of advanced NSCLC patients received afatinib as the first-line therapy was significantly higher than those received gefitinib or erlotinib, whereas no significant difference in PFS and OS was found between these two patient groups. Brain metastasis at diagnosis is a poor prognostic factor. To the best of our knowledge, this is the first study on the effectiveness difference between the first-generation and second-generation EGFR-TKIs as the first-line therapy for NSCLC harbouring non-resistant uncommon *EGFR* mutations.

Table 3
Multivariate analyses for prognostic factors in patients with non-resistant uncommon *EGFR* mutations received EGFR-TKIs as the first-line therapy.

Variable	Hazard ratio (95% CI)	
	Progression-free survival	Overall survival
Age (≥70 years old)	0.68 (0.36–1.26)	0.93 (0.41–2.10)
Male sex	1.17 (0.53–2.59)	0.83 (0.24–2.94)
Never-smoker	0.89 (0.37–2.13)	0.41 (0.11–1.54)
ECOG PS ≥ 2	1.20 (0.57–2.50)	1.48 (0.55–3.93)
Uncommon mutation coexisting del 19 or *L858R*[a]	0.35 (0.15–0.79)	0.69 (0.29–1.64)
Afatinib therapy	0.70 (0.42–1.19)	0.72 (0.35–1.46)
Brain metastasis at diagnosis	2.49 (1.29–4.83)	3.22 (1.41–7.35)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; del 19, exon 19 deletion.

[a] Those patients had uncommon mutations without del 19 or *L858R* mutation were used as the reference group.

For NSCLC patients with uncommon *EGFR* mutation, those received the first-generation EGFR-TKIs therapy had a median PFS of 5.0 months [25]. A more recent retrospective study reported a median PFS of 3.6 months in patients with non-classical *EGFR* mutation who received gefitinib or erlotinib [5]. As for patients received afatinib therapy, a combined post hoc analysis demonstrated a median PFS of 10.7 months in NSCLC patients with non-resistant uncommon *EGFR* mutation [29]. Shen *et al.* reported a median PFS of 11.0 months in lung adenocarcinoma patients with non-classical *EGFR* mutation [5]. These studies included previously treated patients. Our study included treatment-naïve patients only and demonstrated a longer PFS as compared with those who received gefitinib or erlotinib therapy and a similar median PFS to those in patients who received afatinib in these studies.

There are few clinical trials comparing the treatment efficacies of the first-generation and the second-generation EGFR-TKI. In the recent LUX-Lung 7 trial (gefitinib versus afatinib), no data on uncommon *EGFR* mutations were reported [31]. A retrospective study showed a longer median PFS in the afatinib group than that of the geftinib/erlotinib group (11.0 versus 3.6 months) [5]. In our study, the PFS in the afatinib group was longer than those in the gefitinib/erlotinib group (12.0 versus 8.8 months), although not statistically significant. Nevertheless, the ORR in the afatinib group is significantly higher than those who received gefitinib/erlotinib group.

Our study demonstrated an ORR of 35.8% and a median PFS of 8.8 months in gefitinib/erlotinib group. In the LUX-Lung 7 trial which enrolled patients with exon 19 deletion and/or *L858R* mutation, the ORR was 56%, and the median PFS reached 10.9 months in the gefitinib group [31]. As for those received afatinib therapy in our study, the ORR was 60.6%, and the median PFS was 12.0 months, which is similar to those in the LUX-Lung 7 trial (ORR 70% and median PFS 11.0 months in the afatinib group) [31]. The NSCLC harbouring non-resistant uncommon mutation may be less sensitive to the first-generation EGFR-TKI as compared with those with common mutation, whereas the treatment effectiveness of afatinib on NSCLC harbouring common and non-resistant uncommon mutation may not be significantly different.

Recently, a retrospective study (n = 306) focused on preventing and treating brain metastases with three EGFR-TKIs in patients with *EGFR*-mutated NSCLC [32]. Most patients (90.5%) had classical *EGFR* mutation [32]. Afatinib tended to provide a better prevention for brain metastasis than gefitinib ($p < 0.001$). For patients with brain metastasis at diagnosis, there were no significant differences in median PFS and OS among the

three EGFR-TKI groups. In our study, afatinib therapy was associated with a significant longer PFS as compared with gefitinib/erlotinib in patients with brain metastasis at diagnosis. Large-scale study on effectiveness of the EGFR-TKIs in NSCLC patients harbouring uncommon *EGFR* mutation and brain metastasis is needed.

In our study, multivariate analysis revealed that uncommon *EGFR* mutation with exon 19 deletion or *L858R* mutation was associated with a better PFS comparing to those without exon 19 deletion or *L858R* mutation. Keam *et al.* reported that the median PFS of NSCLC patients with uncommon *EGFR* mutation plus common mutation received first-generation EGFR-TKIs was longer than those with uncommon *EGFR* mutations alone (8.1 months versus 1.4 months) [33]. In another study by Chiu *et al.*, the median PFS for patients with complex uncommon *EGFR* mutations was longer than single uncommon mutation (11.9 months versus 6.5 months, $p = 0.010$) [27]. Because uncommon *EGFR* mutations is highly heterogenous, further prospective studies are necessary to clarify the effectiveness of EGFR-TKIs on subtypes of uncommon *EGFR* mutations.

In this study, there is no significant difference in crossover rates between the gefitinib/erlotinib and afatinib group. The average number of total lines of systemic treatments are similar in the gefitinib/erlotinib and afatinib group. Among the patients who received chemotherapy as the second-line therapy, most patients (69.0%) received platinum-based chemotherapies. No significant difference was found in median PFS between the gefitinib/erlotinib and afatinib groups for those who received platinum-based chemotherapy. These findings might be the explanation, at least in part, for the lack of survival difference between gefitinib/erlotinib and afatinib group.

There are several limitations in our studies. First, it is a retrospective observational study. The choices of EGFR-TKIs were based on the physician's clinical judgement, which results in a selection bias. Second, the case number is relatively small, which made subgroup analyses difficult. Third, some rare mutation, such as *V717G* and *I719V,* could not be detected by the MassARRAY® genotyping and the cobas® EGFR Test and not analysed in our study. The MassARRAY® genotyping could not detect exon 20 insertion '*A763_Y764 insFQEA'*, which is a non-resistant uncommon *EGFR* mutation. Therefore, those patients with NSCLC harbouring exon 20 insertion '*A763_Y764 insFQEA'* were not identified and investigated.

In conclusion, the use of afatinib as the first-line therapy may provide a better treatment response but no survival benefits as compared with gefitinib or erlotinib for patients with NSCLC harbouring non-resistant uncommon *EGFR* mutations. Brain metastasis at diagnosis is associated with a poor prognosis. Further large-scaled prospective studies on NSCLC harbouring non-resistant uncommon *EGFR* mutation are warranted.

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Conflict of interest statement

Lih-Chyun Chang has no conflict of interest to declare.

Chor-Kuan Lim has no conflict of interest to declare.

Lih-Yu Chang has no conflict of interest to declare.

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Chong-Jen Yu has nothing to disclose related to this work.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.06.025.

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