

# Poorer prognosis in Taiwanese female ever smokers with stage IV lung adenocarcinoma who were readministered a tyrosine kinase inhibitor

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**Background:** Readministering a second epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) in patients with lung adenocarcinoma with acquired resistance to an initial *EGFR* TKI is a common treatment strategy. However, the prognostic factors for the second *EGFR* TKI are still uncertain.

**Patients and methods:** In this retrospective study, we enrolled patients with stage IV lung adenocarcinoma diagnosed between June 2009 and October 2013 at two university-affiliated hospitals in Taiwan. Basic characteristics including age, sex, smoking status, performance status, *EGFR* mutation status, tumor response, and progression-free survival (PFS) of the second *EGFR* TKI (PFS2) were recorded.

**Results:** A total of 72 patients with stage IV adenocarcinoma with susceptible *EGFR* gene mutations who had been treated with a second *EGFR* TKI were enrolled. Survival analysis using the Kaplan–Meier method and log-rank test showed a significant difference in PFS2 when classifying the patients according to smoking history and sex ( $P=0.0179$ ). When stratifying the patients by sex, a significant difference was found in PFS2 between ever smokers and never smokers in the female (1.87 vs 4.87 months,  $P=0.0081$ ) but not in the male (2.83 vs 2.9 months,  $P=0.9605$ ) patients. A reduced multivariate model developed using the backward variable selection method showed that only ever smoking remained an independent poor prognostic factor for PFS2, and that sex and ever smoking remained independent poor prognostic factors for PFS2 in the female patients (hazard ratio [HR] =3.386, 95% confidence interval [CI]: 1.015–11.298,  $P=0.0473$ ).

**Conclusion:** This study is the first to demonstrate that female ever smokers have a poorer PFS if they have acquired resistance to an initial *EGFR* TKI and receive a second *EGFR* TKI. Further large-scale studies are urgently needed to elucidate the mechanism.

**Keywords:** lung cancer, adenocarcinoma, epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, erlotinib, smoker

## Introduction

Lung cancer is the leading cause of death among patients with malignant tumors worldwide. In 2004, mutations in epidermal growth factor receptor (*EGFR*) that cause oncogene addiction to *EGFR* were discovered in non-small-cell lung cancer (NSCLC), and these mutations have been found to be strongly associated with sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs). Several large Phase III trials have shown that *EGFR* TKIs such as gefitinib and erlotinib can improve the progression-free survival (PFS) of patients with *EGFR*-mutant NSCLC compared to conventional chemotherapy, although no benefit in overall survival (OS) has been observed. However, the average



PFS with *EGFR* TKIs is only ~9–13 months, and acquired resistance to *EGFR* TKIs has been shown to develop.<sup>1–3</sup>

In NSCLC patients with *EGFR* mutations, smoking has been shown to be associated with a shorter PFS than in those who have never smoked, after *EGFR* TKI treatment in many studies. The lack of an established therapeutic option for NSCLC patients who have progressive disease after failure of *EGFR* TKI treatment is still a great challenge for physicians.<sup>4,5</sup> Third-generation *EGFR* TKIs and combination therapies are currently under investigation, and clinical trials are ongoing.<sup>6,7</sup> However, these drugs have yet to be approved by the US Food and Drug Administration. Palliative chemotherapy is an option for patients with acquired *EGFR* TKI resistance. However, the toxicity of antineoplastic agents cannot be tolerated by all patients, and especially the elderly. In 2011, Becker et al demonstrated that retreatment with erlotinib was an option for patients with NSCLC who initially benefited from *EGFR* TKI treatment and then progressed after standard cytotoxic chemotherapy.<sup>8</sup> Several small-scale studies and case reports on retreatment with the same or different *EGFR* TKIs have been published; however, the results have been inconsistent.<sup>8–16</sup> Therefore, we conducted this retrospective study at two university-affiliated hospitals in Taiwan to investigate the effect of retreatment with different *EGFR* TKIs in patients with lung adenocarcinoma harboring sensitizing *EGFR* mutations, and to elucidate the prognostic factors in these patients.

## Patients and methods

### Patient identification

In this retrospective study, patients with stage IV lung adenocarcinoma diagnosed between June 2009 and October 2013 in two university-affiliated hospitals were identified and followed up until September 2014. The diagnosis of lung cancer was confirmed pathologically according to the World Health Organization pathology classification, and tumor staging was determined according to the seventh American Joint Committee on Cancer staging system by a special committee including clinical pulmonologists, medical oncologists, chest surgeons, radiologists, pathologists, and radiation oncologists. Patients were included if they: 1) had adequate tumor specimens for *EGFR* mutation examinations and 2) were treated with gefitinib and erlotinib in two separate periods.

Baseline clinical characteristics were determined by retrospective chart review, including age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status at the beginning of the first TKI treatment and the second TKI treatment, smoking history, and tumor histology. Smoking

history was categorized as current smokers or ever smokers, which included ex-smokers (who had quit  $\geq 5$  years before the diagnosis), and never smokers (<100 lifetime cigarettes).

Mutations in the *EGFR* gene were analyzed using an *EGFR* RGQ kit (Qiagen NV, Venlo, the Netherlands), which utilized amplification refractory mutation specific (ARMS) polymerase chain reactions and Scorpion technology for detection and/or direct sequencing. The detection method was developed and validated by the Division of Molecular Diagnostics, Department of Laboratory Medicine, Kaohsiung Medical University Hospital. An initial treatment response was classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on serial imaging studies using the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Disease control was defined as the best tumor response of CR, PR, or SD that was confirmed and sustained for 8 weeks or longer. The response rate (RR) and disease control rate (DCR) were defined as CR + PR + SD. The durations between the initiation of the first TKI and the second TKI to stopping drug treatment due to disease progression were defined as PFS of the first TKI (PFS1) and PFS of the second *EGFR* TKI (PFS2), respectively. The interval between stopping the first TKI and starting the second TKI was defined as TKI-free interval. OS was defined as the period from starting the second *EGFR* TKI treatment to the date of death.

### Ethics statements

The study protocol was approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUH-IRB-20120278, KMUHIRB-E(II)-20150162). The Institutional Review Board agreed with waiving the need for written informed consent from the participants due to the retrospective nature of this study.

### Statistical analysis

Age, sex, smoking history, *EGFR* gene mutation site (exon 19 or others), performance status when starting TKI treatment, and the initial treatment response to the TKI treatment were summarized and compared between ever smokers and never smokers. Categorical variables and continuous variables were compared using the  $\chi^2$  test (or Fisher's exact test as applicable) and Student's *t*-test, respectively.

Survival times were estimated using the Kaplan–Meier method, with differences between the groups compared using the log-rank test. Cox proportional hazards regression analysis was used to identify the effect of different clinical features on PFS2. After univariate analysis, all variables

were included to obtain an optimal multivariate model to analyze the independent effect of different variables. We also used the backward variable selection method, keeping only variables with a *P*-value less than 0.1, to develop a reduced multivariate model. We also performed stratified analyses in both male and female patients. All statistical analyses were performed using SAS software (version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a two-sided *P*-value less than 0.05.

## Results

### Patient characteristics

A total of 72 patients with stage IV adenocarcinoma with susceptible *EGFR* gene mutations who had been treated with a second *EGFR* TKI were enrolled. The clinical characteristics of the study population, including *EGFR* mutation status and PFS, are summarized in Table 1. There were 55 (76%)

never smokers and 17 (24%) ever smokers. The age was similar between the never smokers (62.0±11.8 years) and ever smokers (60.0±10.1 years), whereas significantly more male patients were ever smokers. Most (96%) patients had received gefitinib as the first *EGFR* TKI and erlotinib as the second *EGFR* TKI, and only three (4%) patients had received erlotinib as the first *EGFR* TKI and gefitinib as the second *EGFR* TKI. The *EGFR* mutation status, initial treatment response to the first *EGFR* TKI, performance status when starting the first and the second *EGFR* TKI, and TKI-free interval were similar between the never smokers and ever smokers, and no significant difference in PFS1 was noted between the never smokers and ever smokers (*P*=0.2027).

### PFS

Survival analysis using the Kaplan–Meier method and log-rank test showed a significant difference in PFS2 when

**Table 1** Characteristics of the study population

Variables	All patients	Never smokers	Ever smokers	P-value
Patients, n (%)	72 (100%)	55 (76%)	17 (24%)	
Age (years), mean ± SD	61.5±11.4	62.0±11.8	60.0±10.1	0.5389
Age, n (%)				
<65 years	46 (64%)	34 (62%)	12 (71%)	0.5106
≥65 years	26 (36%)	21 (38%)	5 (29%)	
Sex, n (%)				
Female	47 (65%)	43 (78%)	4 (24%)	<0.0001
Male	25 (35%)	12 (22%)	13 (76%)	
<i>EGFR</i> gene mutation site, n (%)				
Exon 19	39 (54%)	27 (49%)	12 (71%)	0.1200
Others	33 (46%)	28 (51%)	5 (29%)	
Exon 18	1	0	1	
Exon 21	31	27	4	
Exon 21 + exon 20	1	1	0	
Performance status while starting the first TKI, n (%)				
ECOG score ≤1	61 (85%)	46 (84%)	15 (88%)	1.0000
ECOG score ≥2	11 (15%)	9 (16%)	2 (12%)	
Initial treatment response to the first TKI, n (%)				
Partial response	50 (69%)	39 (71%)	11 (65%)	0.6873
Stable disease	16 (22%)	11 (20%)	5 (29%)	
Progressive disease	6 (8%)	5 (9%)	1 (6%)	
PFS1 (months), median (IQR)	10.2 (5.6–14.9)	9.3 (4.4–14.7)	11.9 (8–15.2)	0.2027
TKI holiday (months), median (IQR)	4.9 (0.6–8.6)	4.6 (0.7–8.9)	6.5 (0.5–7.9)	0.7153
Performance status while starting the second TKI, n (%)				
ECOG score ≤1	45 (63%)	33 (60%)	12 (71%)	0.4306
ECOG score ≥2	27 (38%)	22 (40%)	5 (29%)	
PFS2 (months), median (IQR)	3 (1.9–5.4)	3.2 (2.1–6.4)	2.3 (1.4–3.5)	0.2018
Treatment response to the second TKI, n (%)				
Partial response	3 (4%)	3 (5%)	0 (0%)	0.2968
Stable disease	33 (46%)	27 (49%)	6 (35%)	
Progressive disease	36 (50%)	25 (45%)	11 (65%)	

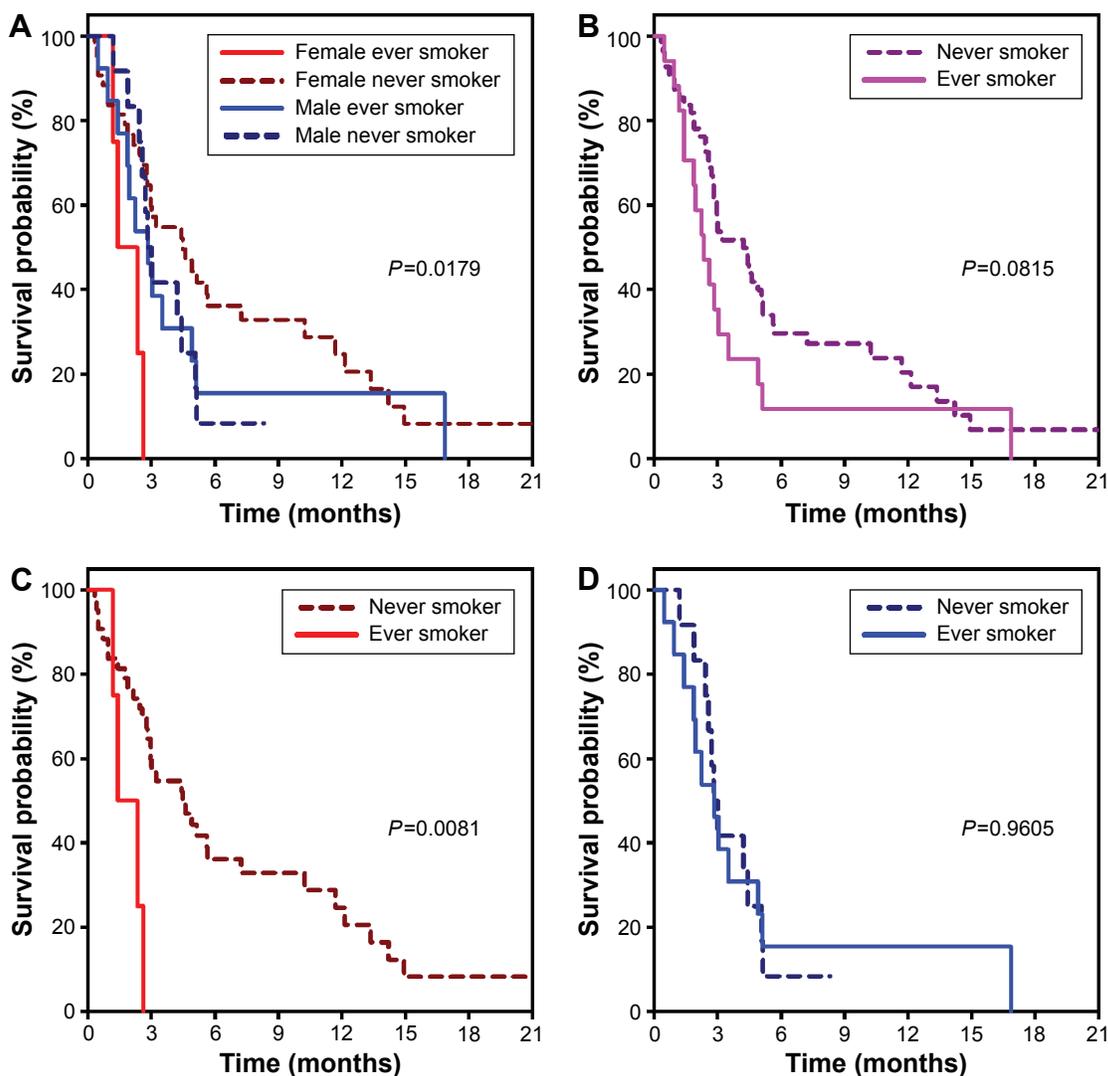
**Notes:** The clinical characteristics of the study population, including *EGFR* mutation status and PFS.

**Abbreviations:** EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS1, progression-free survival of the first TKI; PFS2, progression-free survival of the second *EGFR* TKI; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SD, standard deviation.

classifying the patients according to smoking history and sex ( $P=0.0179$ ) (Figure 1A). In the whole study population, ever smokers had a trend of a worse PFS with the second TKI than the never smokers (median PFS, 2.3 vs 3.2 months;  $P=0.0815$ ) (Figure 1B). When stratifying the patients by sex, a significant difference in PFS2 between ever smokers and never smokers was noted in the female patients (1.87 vs 4.87 months,  $P=0.0081$ ) (Figure 1C), but not in the male patients (2.83 vs 2.9 months,  $P=0.9605$ ) (Figure 1D).

Similarly, univariate Cox regression analysis identified a trend toward a shorter PFS2 in the ever smokers (hazard ratio [HR] =1.657, 95% confidence interval [CI]:

0.930–2.955,  $P=0.0869$ ) and patients having a poorer performance status (ECOG  $\geq 2$ ) when starting the second TKI (HR=1.621, 95% CI: 0.966–2.720,  $P=0.0672$ ) (Table 2). In multivariate analysis including only smoking history and sex, ever smoking was a significant poor prognostic factor for PFS2 (HR =4.721, 95% CI: 1.567–14.224,  $P=0.0058$ ) (Table 3). However, a significant interaction between smoking history and sex was noted ( $P=0.0223$ ), suggesting that the effect of smoking history on PFS2 differed between sexes. In multivariate analysis with the optimal model, ever smoking (HR =4.151, 95% CI: 1.321–13.048,  $P=0.0149$ ) and having an ECOG  $\geq 2$  when starting the second EGFR TKI



**Figure 1** Survival analysis using the Kaplan-Meier method and log-rank test.

**Notes:** When classifying the patients according to smoking history and sex, a significant difference in PFS2 was noted ( $P=0.0179$ ) (A). In the whole study population, ever smokers had a trend of a worse PFS with the second TKI than the never smokers (median PFS, 2.3 vs 3.2 months,  $P=0.0815$ ) (B). When stratifying the patients by sex, a significant difference in PFS2 between ever smokers and never smokers was noted in the female patients (1.87 vs 4.87 months,  $P=0.0081$ ) (C), but not in the male patients (2.83 vs 2.9 months,  $P=0.9605$ ) (D).

**Abbreviations:** TKI, tyrosine kinase inhibitor; PFS, progression-free survival; PFS2, progression-free survival of the second EGFR TKI.

**Table 2** Univariate Cox proportional hazards regression analysis to identify the predictive factors for PFS2

Clinical features	Univariate analysis	
	HR (95% CI)	P-value
Smoking history (ever vs never smoker)	1.657 (0.930–2.955)	0.0869
Sex (male vs female)	1.449 (0.854–2.458)	0.1687
Age ( $\geq 65$ vs $< 65$ years)	0.909 (0.536–1.539)	0.7214
PFS1 ( $> 10$ vs $\leq 10$ months)	1.231 (0.739–2.049)	0.4252
TKI holiday ( $> 5$ vs $\leq 5$ months)	1.185 (0.711–1.973)	0.5151
Performance status when starting the second TKI (ECOG $\geq 2$ vs $\leq 1$ )	1.621 (0.966–2.720)	0.0672

**Notes:** Univariate Cox regression analysis identified a trend toward a shorter PFS2 in ever smokers (HR =1.657, 95% CI: 0.930–2.955,  $P=0.0869$ ) and in patients having a poorer performance status (ECOG  $\geq 2$ ) when starting the second TKI (HR =1.621, 95% CI: 0.966–2.720,  $P=0.0672$ ).

**Abbreviations:** TKI, tyrosine kinase inhibitor; PFS1, progression-free survival of the first TKI; PFS2, progression-free survival of the second EGFR TKI; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

(HR =1.810, 95% CI: 1.017–3.221,  $P=0.0436$ ) were independent poor prognostic factors for PFS2 (Table 3). Furthermore, the reduced multivariate model developed with the backward variable selection method showed that only ever smoking remained an independent poor prognostic factor for PFS2 (HR =3.814, 95% CI: 1.247–11.663,  $P=0.0189$ ) (Table 3). When stratifying the patients by sex, ever smoking remained an independent poor prognostic factor for PFS2 in the female patients (HR =3.386, 95% CI: 1.015–11.298,  $P=0.0473$ ), but not in the male patients (HR =0.828, 95% CI: 0.323–2.127,  $P=0.6955$ ) (Table 4).

## Discussion

The optimal management for patients with acquired resistance to initial EGFR TKI treatment remains unclear. In this study, we found that female ever smokers had a significantly shorter PFS if they had acquired resistance to EGFR TKIs and then received a second EGFR TKI.

Acquired resistance to EGFR TKIs is common among patients with EGFR-mutant lung cancer. Several mechanisms are believed to be responsible for intrinsic and acquired resistance to EGFR TKIs, including secondary EGFR T790M and minor mutations, MET amplification, activation of the MET/HGF axis, acquiring an epithelial-to-mesenchymal transition signature, and transformation from NSCLC to small-cell lung cancer.<sup>4,5</sup> The secondary EGFR mutation, a point mutation in exon 20 (T790M), accounts for approximately half of all cases of acquired resistance to EGFR TKIs. The second-generation irreversible EGFR TKI, afatinib, was developed to overcome the T790M point mutation and has shown good efficacy in vitro. However, no clinical benefit was obtained in patients harboring the T790M mutation who received an EGFR TKI in the LUX-Lung series of trials.<sup>17</sup> Furthermore, several new compounds have been developed to target this point mutation, and clinical trials are currently ongoing.<sup>6,7</sup> Chemotherapy or giving a second EGFR TKI to NSCLC

**Table 3** Multivariate Cox proportional hazards regression analysis to identify the predictive factors for PFS2

Clinical features	Analysis including only smoking history and sex		Maximal model		Reduced model using backward selection	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Smoking history (ever vs never smoker)	4.721 (1.567–14.224)	0.0058	4.151 (1.321–13.048)	0.0149	3.814 (1.247–11.663)	0.0189
Sex (male vs female)	1.681 (0.834–3.389)	0.1462	2.086 (0.990–4.398)	0.0533	1.848 (0.911–3.750)	0.0888
Interaction (smoking history $\times$ sex)	0.196 (0.049–0.794)	0.0223	0.211 (0.048–0.932)	0.0400	0.263 (0.063–1.091)	0.0658
Age ( $\geq 65$ vs $< 65$ years)			1.086 (0.624–1.891)	0.7699		
PFS1 ( $> 10$ vs $\leq 10$ months)			1.401 (0.815–2.406)	0.2221		
TKI holiday ( $> 5$ vs $\leq 5$ months)			0.983 (0.575–1.680)	0.9496		
Performance status when starting the second TKI (ECOG $\geq 2$ vs $\leq 1$ )			1.81 (1.017–3.221)	0.0436	1.734 (0.992–3.031)	0.0535

**Notes:** In multivariate analysis including only smoking history and sex, ever smoking was a significant poor prognostic factor for PFS2 (HR =4.721, 95% CI: 1.567–14.224,  $P=0.0058$ ). However, a significant interaction between smoking history and sex was noted ( $P=0.0223$ ), suggesting that the effect of smoking on PFS2 differed between sexes. In multivariate analysis with the optimal model, ever smoking (HR =4.151, 95% CI: 1.321–13.048,  $P=0.0149$ ) and having ECOG  $\geq 2$  when starting the second EGFR TKI (HR =1.810, 95% CI: 1.017–3.221,  $P=0.0436$ ) were independent poor prognostic factors for PFS2. Furthermore, the reduced multivariate model developed with the backward variable selection method showed that only ever smoking remained an independent poor prognostic factor for PFS2 (HR =3.814, 95% CI: 1.247–11.663,  $P=0.0189$ ).

**Abbreviations:** TKI, tyrosine kinase inhibitor; PFS1, progression-free survival of the first TKI; PFS2, progression-free survival of the second EGFR TKI; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

**Table 4** Multivariate Cox proportional hazards regression analysis to identify the predictive factors for PFS with a second TKI by sex

Clinical features	Female		Male	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Smoking history (ever vs never smoker)	3.386 (1.015–11.298)	0.0473	0.828 (0.323–2.127)	0.6955
Age ( $\geq 65$ vs $< 65$ years)	0.943 (0.465–1.914)	0.8711	1.48 (0.512–4.279)	0.4690
PFS of the first TKI ( $> 10$ vs $\leq 10$ months)	1.184 (0.574–2.441)	0.6472	2.289 (0.786–6.669)	0.1290
TKI holiday ( $> 5$ vs $\leq 5$ months)	0.825 (0.396–1.716)	0.6063	1.392 (0.516–3.754)	0.5139
Performance status when starting the second TKI (ECOG score $\geq 2$ vs $\leq 1$ )	1.941 (0.939–4.010)	0.0733	2.615 (0.734–9.309)	0.1380

**Notes:** When stratifying the patients by sex, ever smoking remained an independent poor prognostic factor for PFS2 in the female patients (HR=3.386, 95% CI: 1.015–11.298,  $P=0.0473$ ), but not in the male patients (HR=0.828, 95% CI: 0.323–2.127,  $P=0.6955$ ).

**Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; PFS2, progression-free survival of the second *EGFR* TKI; TKI, tyrosine kinase inhibitor.

patients with disease progression remains controversial. Conventional chemotherapy given after failure of an initial *EGFR* TKI may also result in a reduction in TKI-resistant clones, leaving TKI-sensitive clones to be further controlled by rechallenge with a second TKI.<sup>15</sup> Starting a second *EGFR* TKI is a generally accepted treatment policy in many settings, especially in patients who refuse chemotherapy, the elderly, or in those with a poor performance status after the first *EGFR* TKI.

The TKI-holiday theory was proposed by Becker et al, who showed a high RR (36%) and DCR (86%) in patients who received a second *EGFR* TKI after a median interval of ~9.5 (3–36) months.<sup>8</sup> They concluded that retreatment with erlotinib was an option for patients with NSCLC who initially benefited from *EGFR* TKI treatment and then experienced recurrence after standard cytotoxic chemotherapy. Sharma et al found that in a human lung cancer cell line (PC9) treated with erlotinib, most cells quickly died; however, a small number of cancer cells persisted. Continued culture of these cells in drug-free media gave rise to drug-sensitive cells (in 9–90 doublings). The authors concluded that altered regulation of chromatin and increased IGF1R activity may be the underlying mechanism for this phenomenon.<sup>18</sup> Since retreatment with an *EGFR* TKI was shown to result in a good DCR by Becker et al,<sup>8</sup> several case reports and case series have been published; however, the results have been inconsistent. According to a review article, the RRs to gefitinib or erlotinib after a drug holiday with the same initial *EGFR* TKI were 21.3% for PR, 34.6% for SD, and 44.1% for PD, and the DCR for the second *EGFR* TKI was 55.9%. The median time to progression ranged from 8 to 29 months for TKI therapy, and 1 to 13 months for progression after the initial TKI to retreatment. The strategy of switching between erlotinib and gefitinib (also called replacement therapy) has also been proposed and evaluated. In one study on replacement therapy after failure of the first *EGFR* TKI, the RRs were 8.2% for PR, 35.0% for SD, and 56.8% for PD.<sup>19</sup> The

results of the current study showed a 4% PR and 46% SD rate in all patients. The RR and DCR appeared to be lower in the ever smokers (0% and 35%, respectively) than in the never smokers (5% and 49%, respectively), but without significance.

The clinical characteristics of lung cancer have an impact on molecular presentations such as *EGFR* mutation status and influence the treatment response in patients with lung cancer. Mitsudomi et al reported that *EGFR* mutations occur more frequently in Asians, females, nonsmokers, and patients with adenocarcinomas.<sup>20</sup> Tobacco smoking is a major risk factor for lung cancer in Asia, with reported prevalence rates of smoking among males and females of 65.1% and 7.1%, respectively. Compared with never smokers, ever smokers were reported to have a higher risk of death from any cause in pooled analyses of all cohorts in 2004, and tobacco smoking has been reported to account for 60.5% of lung cancer-related deaths in Asian men and 16.7% in East Asian women.<sup>21</sup>

In patients with lung cancer harboring *EGFR* mutations, smoking has also been reported to be a poorer prognostic factor when using an *EGFR* TKI as the first-line treatment. Kim et al reported that smokers with more than a 30 pack-year history had a significantly shorter PFS than never smokers (6.4 vs 11.8 months,  $P=0.001$ ) in patients with lung adenocarcinoma, with activating *EGFR* mutations being regarded as an independent poor prognostic factor.<sup>22</sup> Chen et al also showed the never smokers had a significantly longer PFS than smokers.<sup>23</sup> Many hypotheses have been proposed to explain the effect of cigarette smoking on *EGFR* TKI treatment, such as inducing various critical growth regulatory genes (mostly K-ras and TP53) and inducing aberrant *EGFR* phosphorylation resulting in a different *EGFR* conformation and signaling that are resistant to *EGFR* TKIs.<sup>22,23</sup> However, precisely who will benefit from treatment with a second *EGFR* TKI if they have acquired resistance to a first *EGFR* TKI is still uncertain.

Several prognostic factors of second *EGFR* TKIs have been proposed. Hata et al suggested that a higher efficacy of erlotinib

after gefitinib failure can be achieved with proper patient selection criteria, including good performance status, those who benefited from prior gefitinib therapy, and the use of cytotoxic chemotherapies between gefitinib and erlotinib treatment.<sup>14</sup> In addition, Asami et al indicated that a longer duration of prior gefitinib treatment can predict survival in patients with lung adenocarcinoma who subsequently receive erlotinib.<sup>24</sup>

However, in this study, we found that the prior duration of EGFR TKI treatment, response to the first EGFR TKI, and the TKI-free interval were not significant prognostic factors. After careful statistical analysis, we found that female ever smokers had the shortest PFS of all patients receiving a second EGFR TKI compared with female never smokers (1.87 vs 4.87 months,  $P=0.0081$ ) and male ever smokers or male never smokers (2.83 vs 2.9 months). The female patients also had better EGFR TKI response and 1-year PFS rates in a national-wide study in Taiwan.<sup>25</sup> This suggests that female sex has a positive effect on EGFR TKI treatment for NSCLC. However, smoking may have a greater impact than sex on the effect of EGFR TKI treatment in patients with NSCLC harboring EGFR mutations. Indeed, our results demonstrated that female never smokers had a longer PFS than female ever smokers who received second EGFR TKI treatment. A review of all case reports and case series in PubMed disclosed a good response and longer PFS to a second EGFR TKI treatment; however, almost all female ever smokers have been reported to experience no benefits from a second EGFR TKI,<sup>10–13,15,19,26,27</sup> which is consistent with our findings.

There are several limitations to this study. First, the sample size is small, although this retrospective analysis may be the largest study to date enrolling patients with stage IV lung adenocarcinoma who initially harbored EGFR mutations and received a second EGFR TKI. Second, almost no patients had a rebiopsy to determine the reason for acquired resistance. Third, almost all of the patients received gefitinib as the first EGFR TKI and erlotinib as the second EGFR TKI. The prescription of gefitinib in patients with lung adenocarcinoma harboring sensitizing EGFR mutations has been permitted by the National Health Insurance (NHI) Bureau in Taiwan since June 2011, but not erlotinib. Therefore, the majority of our enrolled patients were treated with gefitinib as the first EGFR TKI and erlotinib as the second. In addition, retreatment with the same EGFR TKI is not permitted by the NHI Bureau in Taiwan.

## Conclusion

This study indicates that female ever smokers have a significantly shorter PFS when receiving a second EGFR TKI

if they initially have lung adenocarcinoma harboring EGFR mutations. Based on these findings, we suggest that in clinical practice, female ever smokers should not be candidates for a second EGFR TKI if they have developed acquired resistance to the first EGFR TKI. Furthermore, large-scale studies and bench research should be conducted to elucidate the detailed mechanism in female smokers using rebiopsy specimens.

## Disclosure

The authors report no conflicts of interest in this work.

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