Cancer Chemotherapy and Pharmacology (2019) 83:817–825
https://doi.org/10.1007/s00280-019-03790-w

ORIGINAL ARTICLE

Re-challenge of afatinib after 1st generation EGFR-TKI failure in patients with previously treated non-small cell lung cancer harboring EGFR mutation

Ou Yamaguchi[1] · Kyoichi Kaira[1] · Atsuto Mouri[1] · Ayako Shiono[1] · Kosuke Hashimoto[1] · Yu Miura[1] · Fuyumi Nishihara[1] · Yoshitake Murayama[1] · Kunihiko Kobayashi[1] · Hiroshi Kagamu[1]

Received: 4 January 2019 / Accepted: 29 January 2019 / Published online: 13 February 2019

Abstract

Background Re-challenge of erlotinib after gefitinib failure is reported to yield some benefit in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation. However, little is known about the re-challenge of afatinib after 1st generate on EGFR tyrosine kinase inhibitor (TKI) failure.

Methods From May 2015 to August 2018, 62 patients with advanced NSCLC harboring sensitive *EGFR* mutation received afatinib after gefitinib and/or erlotinib failure at our institution was included in our retrospective study.

Results The overall response rate (ORR) and disease control rate (DCR) of afatinib as re-challenge were 17.0% and 79.2%, respectively. The median time on treatment of 1st generation EGFR-TKI (1st TKI) was 14 months. By multivariate analysis, smoking, performance status (PS), and time on treatment of 1st TKI with more than 10 months were confirmed to be independent prognostic factors predicting a worse progression-free survival (PFS), and significant prognostic markers for overall survival (OS) were PS and time on treatment of 1st TKI with more than 10 months, especially in patients with exon 19 deletion.

Conclusions Re-challenge of afatinib was identified as one of the therapeutic options after 1st TKI failure in the patients with advanced NSCLC harboring *EGFR* mutation when the time of treatment by prior 1st TKI is more than 10 months.

Keywords Afatinib · Re-challenge · EGFR mutation · EGFR-TKI

Introduction

Lung cancer is a neoplasm associated mostly with dismal outcomes in the affected patients. In particular, advanced non-small cell lung cancer (NSCLC) is considered as a chemo-resistant neoplasm, and the survival of the patients is known to be extremely short, even after systemic chemotherapy. Recently, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) have been developed that render the advanced NSCLC harboring *EGFR* mutation sensitive [1–3]. Currently, there are three types of EGFR-TKIs: 1st generation EGFR-TKIs (1st TKI) such as gefitinib or erlotinib, 2nd generation EGFR-TKIs (2nd TKI) such as afatinib, and 3rd generation EGFR-TKIs (3rd TKI) such as osimertinib; these are widely used in the NSCLC patients [1–3]. According to the recent clinical trials, osimertinib is identified as a more effective EGFR-TKI than the 1st TKI [3]. The 2nd TKIs, such as afatinib or dacomitinib, also yield a better survival benefit compared to the 1st TKI [4, 5]. Unfortunately, no comparison between 2nd TKI and 3rd TKI has been performed yet because of lack of clinical studies. To prolong survival after EGFR-TKI failure, there is no established sequence of the types of EGFR-TKIs to be used subsequently. The therapeutic role of re-challenge with EGFR-TKIs as a subsequent treatment against NSCLC patients harboring *EGFR* mutations remains unclear. Although some reports have described the usefulness of re-challenge with another 1st TKI after the failure of one 1st TKI [6–8], little is known about the effectiveness of afatinib re-challenge after 1st TKI failure in actual clinical practice.

✉ Kyoichi Kaira
kkaira1970@yahoo.co.jp

[1] Department of Respiratory Medicine Comprehensive Cancer Center, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan

A previous clinical trial (Lux-Lung 1) has described the therapeutic potential of afatinib treatment in patients with advanced pulmonary adenocarcinoma, who had progressed after at least 12 weeks of treatment of the 1st TKI, compared to placebo [9]. The results of this study suggest that afatinib can be beneficial in terms of progression-free survival (PFS) and response to treatment in such patients. The re-challenge of afatinib in Japanese patients with NSCLC yielded an overall response rate (ORR) of 8.2% and a median PFS of 4.4 months, as seen in the Lux-Lung 4 trial [10]. Considering that the efficacy of gefitinib re-challenge achieved a median PFS of 2.0–3.4 months [6–8], the re-challenge of afatinib seems to show a better efficacy after the 1st TKI failure [10]. In the recent reports, it has been suggested that re-administration of EGFR-TKI seems to improve its efficacy based on the previous EGFR-TKI-free interval [11, 12]. However, it remains unknown the type of patients receiving 1st TKI that may get a meaningful survival benefit from the sequential treatment of afatinib, as TKI re-challenge.

Recently, Oda et al. reported a phase II study of EGFR-TKI re-administration with afatinib against patients with advanced NSCLC harboring a sensitive non-T790M *EGFR* mutation [13]. In this study, the ORR, disease control rate (DCR), median PFS, and median overall survival (OS) were 17%, 84%, 4.2 months, and 11.6 months, respectively. The results of this study suggested that the re-challenge of afatinib after the 1st TKI failure yielded modest activity, and is one of the valid treatment options in patients with non-T790M *EGFR* mutation. However, this prospective study had a limited sample size ($n = 12$), and thus, the clinical significance of afatinib re-challenge could not be proved.

Based on this background, we retrospectively examined the clinical significance of EGFR-TKI re-challenge in patients with advanced NSCLC harboring sensitive *EGFR* mutation that received afatinib after gefitinib and/or erlotinib treatment failure.

Methods

Patient eligibility and data collection

The patient selection for this retrospective analysis is defined as follows: histologically proven advanced NSCLC at stage III, IV, or in recurrence after operation; age > 20 years; *EGFR* mutation; disease progression on gefitinib and/or erlotinib, followed by afatinib treatment; availability of ORR data of afatinib according to the response evaluation criteria in solid tumors (RECIST). Patients were excluded if they had any of the following: a concomitant serious illness, such as myocardial infarction in the previous 3 months, uncontrolled angina pectoris, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia, or lung disease; infection or other diseases contraindicating chemotherapy; pregnancy or breast-feeding. This study was approved by the institutional ethics committee of the Saitama Medical University International Medical Center.

Treatment and efficacy evaluation

Afatinib was orally administered daily. The starting dose of afatinib was chosen by the chief physician. Complete blood cell count, differential count, routine chemistry measurements, physical examination, and toxicity levels were evaluated. Acute toxicity was graded according to the CTCAE version 4.0. Tumor response was evaluated according to the RECIST criteria ver. 1.1 [14].

Statistical analysis

Statistical significance was indicated by $p < 0.05$. Fisher's exact test was used to examine the association between two categorical variables. The Kaplan–Meier method was used to estimate survival as a function of time, and survival differences were analyzed through the log-rank test. PFS was defined as the time from the initial administration of afatinib to tumor recurrence or death from any cause, whereas overall survival (OS) was defined as the time from the initial administration of afatinib to death from any cause. Time of treatment was defined as the time from the administration of the first dose of 1st TKI to that of the last dose of 1st TKI. If both gefitinib and erlotinib were administered prior to afatinib to one patient, the combined time of treatment with gefitinib as well as erlotinib was used as the time of treatment for the patient [15]. Statistical analyses were performed using GraphPad Prism 4 (Graph Pad Software, San Diego, CA, USA) and JMP 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics

Sixty-four patients with advanced NSCLC harboring sensitive *EGFR* mutation received afatinib after gefitinib and/or erlotinib treatment failure, at Saitama Medical University International Medical Center from May 2015 to August 2018. Of 64 patients, 2 were excluded because of inadequate medical information. A total of 62 patients ($n_{\text{males}} = 25$, $n_{\text{females}} = 37$; median age = 69 years; age range = 31–82 years) were eligible for the analysis. The patient characteristics are listed in Table 1. Totally, 28 patients had a smoking history, and clinical staging revealed 43 patients at stage IV, and 19 patients with recurrence after surgical resection. The histology consists of all patients with adenocarcinoma. *EGFR* mutation analysis revealed 35 patients with deletion of exon

Table 1 Patient's demographics on re-challenge of afatinib

Variables	$N=62$
Median age years (range)	69 (31–82 years)
Gender	
Male/female	25/37
Smoking	
Yes/no	28/34
ECOG PS	
0–1/2–3	42/20
BSA	
≦1.5/> 1.5	43/19
EGFR mutation status	
Del 19/L858R/G719A/L861Q/Other	35/19/1/2/5
Histological type	
Adenocarcinoma	62
Disease stage at the initiation of prior EGFR-TKI	
IV/recurrence after surgical resection	43/19
Median time between last administration of prior EGFR-TKI and initiation of afatinib	
Days (range)	121 (1–1005 days)
Initial dosage of afatinib	
40/30/20 mg/body	46/9/7
Dose reduction of afatinib	
Yes/no	37/25
Treatment line of afatinib median line (range)	3 (2–7)
Cytotoxic regimens before afatinib	
CBDCA + PTX/PEM-based regimens/DTX-based regimens	5/32/8
The initial EGFR-TKI before afatinib	
Gefitinib/erlotinib/gefitinib and erlotinib	23/11/29
Sequential treatment after afatinib	
Osimertinib/nivolumab/pembrolizumab	8/10/1

ECOG eastern cooperative oncology group, *PS* performance status, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *BSA* body surface area, *CBDCA* carboplatin, *PTX* paclitaxel, *PEM* pemetrexed, *DTX* docetaxel

19, 19 patients with L858R (exon 21), and 2 patients with other mutations. As the 1st TKI before afatinib treatment, 23 patients were treated with gefitinib, 11 patients with erlotinib, and 29 patients received both gefitinib and erlotinib as a sequential treatment. The median administration period of the 1st TKI in patients who received single agent gefitinib or erlotinib ($n=34$), or both drugs ($n=29$) was 18 months and 20 months, respectively ($p=0.96$).

Treatment delivery and response rate of afatinib

Afatinib was administered orally once a day at a dose of 40, 30, or 20 mg/kg of body weight, according to the judgment of chief physician. Out of 62 patients, 40 mg, 30 mg, or 20 mg initial dose of afatinib was started in 46 (74%), 9 (15%), and 7 (11%) patients, respectively. The dose reduction of afatinib had to be performed in 37 (59%) patients, and the median treatment line in the initiation of afatinib was 3, ranging from 2 to 7 lines. Since 9 of 62 patients had no evaluable target lesion, the ORR for afatinib was assessed in 53 patients, according to the RECIST criteria. Among 53 patients, 9 achieved PR (partial response), with an ORR of 17.0% (95% CI 8.1–29.8%). Thirty-two patients achieved SD (stable disease), and 12 had PD (progressive disease). The DCR was 79.2% (95% CI 65.9–89.2%). The ORRs of afatinib re-challenge in patients who received single agent gefitinib or erlotinib ($n=29$), or both drugs ($n=19$) as prior 1st TKI were 17.2% (95% CI 5.8–35.8%) and 21.1% (95% CI 6.1–45.6%), respectively, ($p>0.99$). Moreover, the ORRs of afatinib re-challenge in the patients treated with 40 mg ($n=37$), or 30 mg and 20 mg ($n=16$) initial dose of afatinib were 10.8% (95% CI 3.0–25.4%), and 31.3% (11.0–58.7%), respectively, ($p=0.11$), and those in patients with exon 19 deletion or L858R were 14.2% and 14.2%, respectively.

Survival analysis of afatinib and time on treatment of the 1st TKI

The median PFS and OS rates after afatinib administration were 194 days and 551 days, respectively. Of all patients, 54 developed recurrence, and 42 died after afatinib treatment. The time of treatment with 1st TKI ranged from 1 to 136 months, and the median time was 14 months. The median times of treatment with 1st TKI, such as gefitinib or erlotinib, or with both agents combined were 18 months (ranging from 1 to 97 months) and 26 months (ranging from 6 to 136 months), respectively ($p = 0.96$). For survival analysis, the cut-off values of time of treatment were defined as 6, 8, 10, 12, 14, and 20 months. The median time from the last dose of 1st TKI to the initial dose of afatinib was 42 days, ranging from 1 to 1005 days, and the cut-off values for that were defined as 4, 6, and 12 months. Univariate analysis revealed that smoking, performance status (PS), and time of treatment with the 1st TKI were significant prognostic factors for PFS. The PS and time of treatment with the 1st TKI were

Table 2 Univariate survival analysis according to different variables

Variables	*N* = 62	PFS				OS			
		Median (days)	HR	95% CI	*p* value	Median (days)	HR	95% CI	*p* value
Age									
≦69/> 69 years	35/27	174/194	1.12	0.64–1.92	0.15	572/485	1.42	0.76–2.65	0.26
Gender									
Male/female	25/37	144/209	136	0.91–3.03	0.09	532/587	0.96	0.51–1.81	0.92
Smoking									
Yes/no	94/213	213/94	0.44	0.24–0.82	**< 0.01**	572/551	0.91	0.49–1.68	0.75
ECOG PS									
0–1/2–3	42/20	227/73	0.43	0.23–0.83	**0.01**	778/153	0.32	0.15–0.67	**< 0.01**
BSA									
≦1.5/>1.5	43/19	168/227	0.77	0.43–1.39	0.39	501/904	0.74	0.38–1.45	0.39
EGFR mutation status									
Del 19/L858R	35/19	174/168	0.99	0.54–1.81	0.98	754/505	0.59	0.28–1.24	0.12
Time on treatment of prior EGFR-TKI									
≦6/>6 months	7/55	60/195	0.19	0.05–0.66	**< 0.01**	145/587	0.21	0.05–0.78	**0.02**
≦8/>8 months	11/51	94/195	0.33	0.13–0.84	**0.02**	389/587	0.32	0.11–0.98	**0.04**
≦10/>10 months	16/46	73/222	0.41	0.19–0.87	**0.02**	389/587	0.36	0.14–0.87	**0.02**
≦12/>12 months	17/45	85/209	0.43	0.21–0.91	**0.02**	389/587	0.42	0.18–0.96	**0.04**
≦14/>14 months	22/40	73/238	0.36	0.18–0.71	**< 0.01**	389/667	0.34	0.16–0.72	**< 0.01**
≦20/>20 months	32/30	109/256	0.45	0.25–0.81	**< 0.01**	532/754	0.63	0.34–1.17	0.14
Time from prior EGFR-TKI to afatinib									
≦4/>4 months	39/23	168/209	0.63	0.36–1.11	0.11	505/704	0.68	0.36–1.26	0.22
≦6/>6 months	42/20	194/191	0.71	0.40–1.24	0.22	532/704	0.78	0.41–1.46	0.44
≦12/>12 months	52/10	194/134	0.60	0.29–1.21	0.15	551/704	0.82	0.37–1.76	0.61
Cytotoxic agent between prior EGFR-TKI and afatinib									
Yes/no	31/31	194/164	0.73	0.42–1.27	0.26	532/704	0.53	0.28-1.00	0.05
Initial dosage of afatinib									
40/20 or 30 mg	46/16	171/238	1.22	0.67–2.21	0.52	551/667	1.21	0.59–2.43	0.61
Disease stage at the initiation of prior EGFR-TKI									
IV/recurrence after surgical resection	43/19	174/194	1.46	0.83–2.03	0.19	551/587	1.42	0.76–2.67	0.29
Treatment line of afatinib									
≦3/>3 lines	33/29	213/168	0.66	0.38–1.13	0.11	572/551	1.02	0.55–1.86	0.95
Numbers of initial EGFR-TKI before afatinib									
1/2	36/26	209/156	0.59	0.34–1.03	0.05	667/437	0.59	0.32–1.09	0.08

Bold indicates statistically significant difference

ECOG eastern cooperative oncology group, *PS* performance status, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *BSA* body surface area

identified as significant predictors for OS (Table 2). According to the results of the univariate log-rank test, we screened variables with a cut-off value of $p < 0.05$, and selected PS, smoking history, and time of treatment with the 1st TKI. We also carried out a multivariate analysis based on different cut-off values of time of treatment with the 1st TKI, and identified 10 months as an appropriate value for predicting favorable OS and PFS (Table 3). Therefore, through multivariate analysis, smoking, PS, and 10 months time of treatment were confirmed to be independent prognostic factors predicting better PFS, and PS and time of treatment were identified as significant prognostic markers for OS (Table 4). Figure 1 shows the Kaplan–Meier survival curves based on time of treatment, time from 1st TKI to afatinib, and EGFR mutation status. Figure 2 shows the forest plot of PFS and OS according to the time of treatment of 1st TKI for each variable. As compared to a lower time of treatment, more than 10 months, time of treatment was significantly linked to better PFS in patients with smoking, exon 19 deletions, *EGFR* mutations, treatment line, time from the last administration of 1st TKI to the initiation of afatinib, or the dosage of afatinib (Fig. 2a); and gave a significantly better OS related to gender, BSA (body surface area), and time from 1st TKI to afatinib treatment (Fig. 2b).

Discussion

This is a retrospective study to assess the efficacy and outcome of afatinib treatment after the failure of 1st TKI. We found that re-challenge with afatinib as the 2nd TKI is useful to improve patient survival, if time of treatment with the 1st TKI is more than 10 months, which is an independent factor for predicting a favorable prognosis upon afatinib re-challenge. Moreover, afatinib re-challenge might contribute to a significant prolongation of PFS in patients with *EGFR* mutations, especially exon 19 deletions. Interestingly, the ORR and DCR of afatinib re-challenge were 17.0% and 79.2%, respectively. The efficacy of re-challenge with 2nd TKI seemed to be higher than that with 1st TKI. We suggest that the re-challenge with afatinib could be one of the therapeutic options after EGFR-TKI failure in patients with more than 10 months time of treatment with the 1st TKI. Since this is a

Table 3 Multivariate analysis according to different cut-off values in time on treatment of prior EGFR-TKI

Different variables	*p* value in multivariate survival analysis according to different cut-off values of time on treatment of prior EGFR-TKI					
PFS	≦6/>6 (months)	≦8/>8 (months)	≦10/>10 (months)	≦12/>12 (months)	≦14/>14 (months)	≦20/>20 (months)
Smoking	<0.01	0.01	<0.01	<0.01	<0.01	0.01
ECOG PS	0.01	0.01	<0.01	<0.01	<0.01	0.01
Time on treatment of prior EGFR-TKI	0.05	0.04	0.01	0.02	<0.01	0.06
OS	≦6/>6 (months)	≦8/>8 (months)	≦10/>10 (months)	≦12/>12 (months)	≦14/>14 (months)	≦20/>20 (months)
Smoking	0.30	0.20	0.24	0.33	0.39	0.25
ECOG PS	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Time on treatment of prior EGFR-TKI	0.05	0.10	0.03	0.04	<0.01	0.42

ECOG eastern cooperative oncology group, *PS* performance status, *PFS* progression-free survival, *OS* overall survival, *EGFR* epidermal growth factor receptor; *TKI* tyrosine kinase inhibitor

Table 4 Multivariate analysis using selected different variables

Selected variables	PFS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Smoking						
Yes/no	0.39	0.21–0.72	**<0.01**	0.66	0.33–1.32	0.24
ECOG PS						
0–1/2–3	0.66	0.51–0.89	**<0.01**	0.56	0.40–0.80	**<0.01**
Time on treatment of prior EGFR-TKI						
≦10/> 10 months	0.65	0.47–0.92	**0.01**	0.65	0.46–0.96	**0.03**

ECOG eastern cooperative oncology group, *PS* performance status, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor

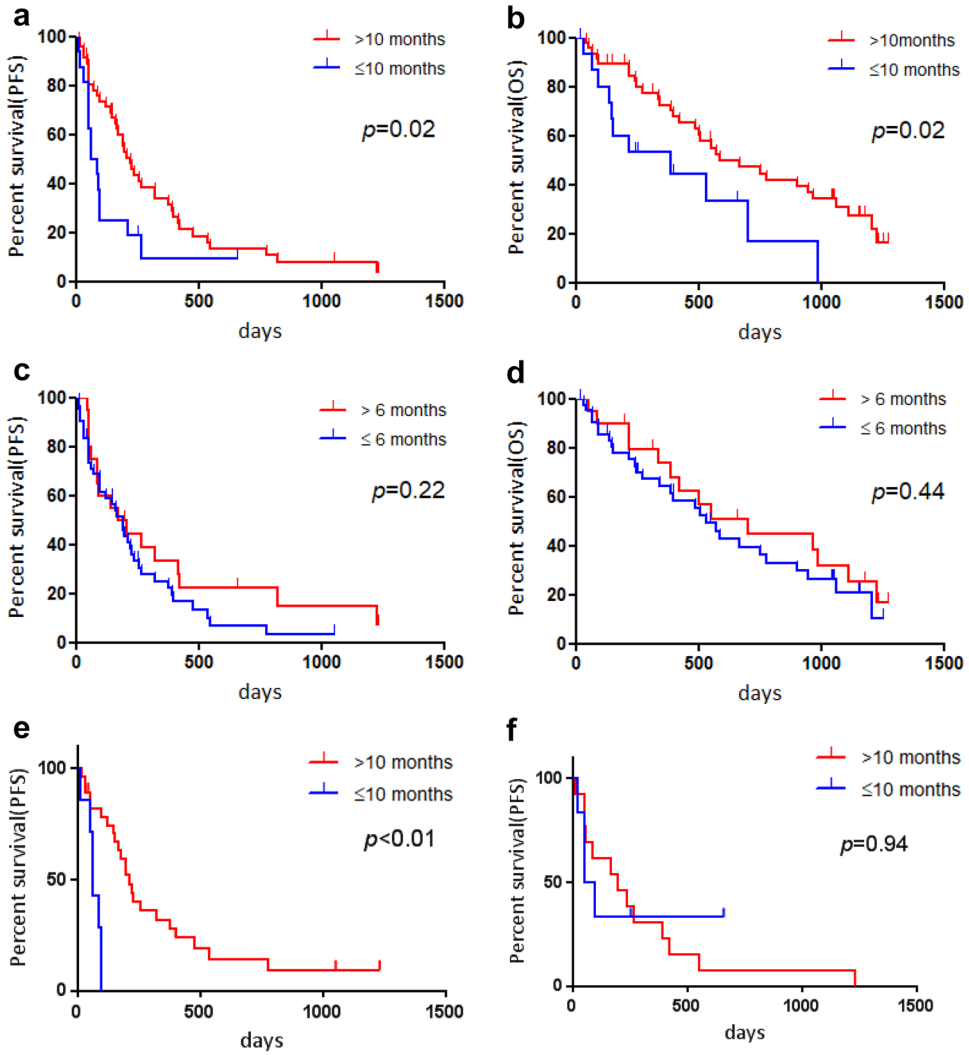

Fig. 1 Kaplan–Meier survival curves according to time on treatment of the previous 1st TKI, time from the last dose of 1st TKI to the initial dose of afatinib and *EGFR* mutation status. The patients having time on treatment with more than 10 months of the previous 1st TKI achieved a significantly longer PFS ($p=0.02$) (**a**) and OS ($p=0.02$) (**b**) than those with less than 10 months. The median PFS and OS in patients with time on treatment with more than 10 months and less than 10 months was 229 days and 73 days, respectively, and 587 days and 389 days, respectively. A statistically significant difference in the PFS ($p=0.22$) (**c**) and OS ($p=0.44$) (**d**) was observed in the patients between more than and less than 6 months regarding the time from the last dose of 1st TKI to the initial dose of afatinib. In the analysis according to *EGFR* mutation status, PFS was significantly longer in the patients with time on treatment with more than 10 months of previous 1st TKI than in those with less than 10 months (**e**) in patients with exon 19, *EGFR* mutation ($p<0.01$) (**f**), but not different among patients according to the time on treatment using cut-off values of 10 months in patients with previous exon 21 L858R *EGFR* mutation

retrospective analysis, further investigation is warranted to confirm the results of our study through a prospective trial.

Afatinib is the 2nd TKI, orally administered as an irreversible inhibitor of the ErbB family of tyrosine kinases, having a different mechanism of tumor regression than the 1st TKI. Although the Lux-Lung 4 study has reported the efficacy of afatinib in patients with NSCLC that experienced disease progression after 1st TKI failure, 85% of all patients were treated with afatinib within 4 weeks of 1st TKI failure; the study also included 17.7% patients with *EGFR* wild type [10]. The results of the Lux-Lung 4 study are expected to elucidate the clinical benefit of afatinib re-challenge after the prior EGFT-TKI failure. However, the study did not analyze the efficacy of afatinib re-challenge based on the administration period of the previous 1st TKI, and therefore, the established markers for predicting the outcome after the administration of afatinib remain unclear. Similarly, the study did not discuss the prognosis of afatinib re-challenge after 1st TKI failure in patients with non-T790M *EGFR* mutation [13].

Cho et al. have documented the clinical efficacy of re-challenge with erlotinib following gefitinib failure as a

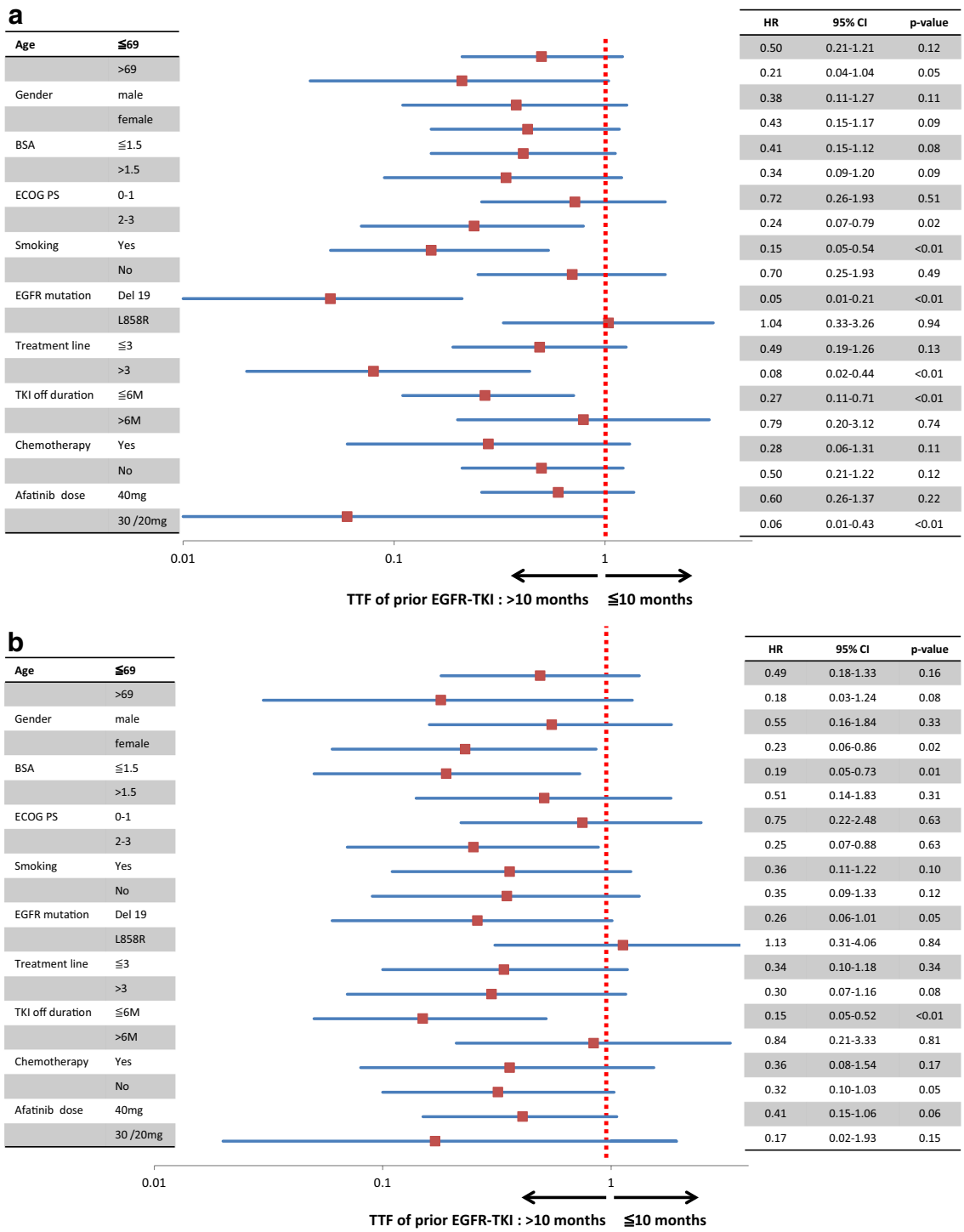

Fig. 2 Forest plot of 5-year PFS (**a**) and OS (**b**) rates according to time on treatment using cut-off values of 10 months in each variables

salvage treatment for advanced NSCLC, and concluded that the patients with > 4 months PFS during the previous gefitinib therapy displayed a significantly longer PFS with erlotinib than those with < 4 months PFS with gefitinib [16]. The previous studies demonstrated that erlotinib after failure of gefitinib may produce clinical benefit against patients who had a PFS of more than 6 months during gefitinib treatment or a long SD on prior gefitinib therapy [12, 16, 17].

Although it is unknown why the duration of the previous EGFR-TKI treatment is linked to the prediction of duration of re-treatment, the reasons, such as different sensitivity of 1st TKI, and presence of sensitive or resistant mutations are presumed [18–20]. Considering these findings, it can be suggested that the duration of maintenance with the previous 1st TKI could affect the efficacy of 2nd TKI, as a re-treatment after 1st TKI failure. To our knowledge, this is the first study to examine the effectiveness of afatinib as a re-challenge based on the treatment duration of prior 1st TKI; however, the exact mechanism remains unknown. In particular, we discovered that the therapeutic efficacy of afatinib as re-challenge was significantly higher in patients with exon 19 deletions than those with L858R located in exon 21. According to the previous clinical trial, patients with exon 19 deletions are more sensitive to afatinib [21]. The data regarding *EGFR* mutation status should also be considered to select afatinib as one of the therapeutic options for EGFR-TKI re-challenge.

There are some limitations to this study. First, our approach is a retrospective investigation, and the sample size is limited to prove the optimal role of afatinib re-challenge as a treatment option. Second, the initial dose of afatinib differs according to the judgment of chief physician. Yang et al. demonstrated that the dose adjustment of afatinib is necessary to reduce the adverse events without affecting the therapeutic efficacy [22]. In the present study, no statistically significant difference in the efficacy of afatinib was observed in patients with or without the initial dose reduction. However, the ORR of afatinib re-challenges with 30 or 20 mg dosage (31.3%) seemed to be higher than those administered initially with 40 mg afatinib (10.8%). Therefore, the initial dose of 30 or 20 mg may be reasonable for the initiation of afatinib re-challenge. Finally, the treatment pattern of 1st TKI was either single agent gefitinib or erlotinib, or usage of both the drugs. However, our analysis revealed no significant difference in the efficacy and outcome of afatinib in the patients receiving one or two 1st TKI. We believe that the administration period of prior 1st TKI is important to affect the efficacy of afatinib re-challenge, but not the number of prior 1st TKIs.

In conclusion, the re-challenge of afatinib was identified as one of the therapeutic options after 1st TKI failure, when the duration of prior 1st TKI is > 10 months, regardless of the time from the last dose of 1st TKI to the initial dose of afatinib. We found that the re-challenge of afatinib yielded an ORR of 17.0%, PFS of 6 months, and an OS of 18 months. Compared to the other treatment options, such as cytotoxic agents or immunotherapy, re-challenge of afatinib after 1st TKI failure may be suitable for the patients harboring sensitive *EGFR* mutation that have some survival benefits from the 1st TKI therapy. Further study is warranted to elucidate the clinical benefit of 2nd TKI such as afatinib as re-challenge after osimertinib as 3rd generation TKI in a prospective matter.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest OY, AM, KK, and HK have received research grants and a speaker honorarium from Boehringer Ingelheim Company. All remaining authors have declared no conflicts of interest.

References

1. Maemondo M, Inoue A, Kobayashi K et al (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380–2388
2. Sequist LV, Yang JC, Yamamoto N et al (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31:3327–3334
3. Soria JC, Ohe Y, Vansteenkiste J et al (2018) Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378:113–125
4. Park K, Tan EH, O'Byrne K et al (2016) Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 17:577–589
5. Wu YL, Cheng Y, Zhou X et al (2017) Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 18:1454–1466
6. Asahina H, Oizumi S, Inoue A et al (2010) Phase II study of gefitinib re-administration in patients with advanced non-small cell lung cancer and previous response to gefitinib. Oncology 79:423–429
7. Koizumi T, Agatsuma T, Ikegami K et al (2012) Prospective study of gefitinib readministration after chemotherapy in patients with advanced non-small-cell lung cancer who previously responded to gefitinib. Clin Lung Cancer 13:458–463
8. Oh IJ, Ban HJ, Kim KS et al (2012) Retreatment of gefitinib in patients with non-small cell lung cancer who previously controlled to gefitinib: a single-arm, open-label, phase II study. Lung Cancer 77:121–127
9. Miller VA, Hirsh V, Cadranel J et al (2012) Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 13:528–538
10. Katakami N, Atagi S, Goto K et al (2013) LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 31:3335–3341
11. Tomizawa Y, Fujita Y, Tamura A et al (2010) Effect of gefitinib re-challenge to initial gefitinib responder with nonsmall cell lung cancer followed by chemotherapy. Lung Cancer 68:269–272
12. Kaira K, Naito T, Takahashi T et al (2010) Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer. Lung Cancer 68:99–104
13. Oda N, Hotta K, Ninomiya K et al (2018) A phase II trial of EGFR-TKI readministration with afatinib in advanced non-small-cell

lung cancer harboring a sensitive non-T790M EGFR mutation: Okayama Lung Cancer Study Group trial 1403. Cancer Chemother Pharmacol 82:1031–1038
14. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumour: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
15. Hochmair MJ, Morabito A, Hao D et al (2018) Sequential treatment with afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: an observational study. Future Oncol 14:2861–2874
16. Cho KM, Keam B, Kim TM et al (2015) Clinical efficacy of erlotinib, a salvage treatment for non-small cell lung cancer patients following gefitinib failure. Korean J Intern Med 30:891–898
17. Cho BC, Im CK, Park MS et al (2007) Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol 25:2528–2533
18. Wong AS, Soong R, Seah SB et al (2008) Evidence for disease control with erlotinib after gefitinib failure in typical gefitinib-sensitive Asian patients with non-small cell lung cancer. J Thorac Oncol 3:400–404
19. Choong NW, Dietrich S, Seiwert TY et al (2006) Gefitinib response of erlotinib-refractory lung cancer involving meninges–role of EGFR mutation. Nat Clin Pract Oncol 3:50–57
20. Zhang Z, Lee JC, Lin L et al (2012) Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. Nat Genet 44:852–860
21. Yang JC, Wu YL, Schuler M et al (2015) 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 16:141–151
22. Yang JC, Sequist LV, Zhou C et al (2016) Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials. Ann Oncol 27:2103–2110