Potential for afatinib as an optimal treatment for advanced non-small cell lung carcinoma in patients with uncommon *EGFR* mutations

Ichidai Tanaka[a]*, Masahiro Morise[a], Yuta Kodama[a], Akira Matsui[a], Naoya Ozawa[a], Sachiko Ozone[a], Daiki Goto[a], Ayako Miyazawa[a], Tetsunari Hase[a], Naozumi Hashimoto[a], Mitsuo Sato[b], and Yoshinori Hasegawa[a]

[a]Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

[b]Department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan

*Correspondence: Ichidai Tanaka; Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

E-mail: ichidai@med.nagoya-u.ac.jp

Tel: 052-744-2167

Fax: 052-744-2176

Word count: (excluding references): 965

Number of tables: 3

Number of figures: 1

Dear Editor,

Uncommon *epidermal growth factor receptor (EGFR)* mutations in non-small lung cancer (NSCLC) are a heterogeneous group of genetic alterations that produce variable responses to EGFR-tyrosine kinase inhibitor (TKI) in patients with most of the evidence of the responses to EGFR-TKIs being based on small case studies or single case reports [1-3]. Several studies have demonstrated that patients with uncommon *EGFR* mutations respond poorly to first-generation EGFR-TKIs, such as gefitinib and erlotinib, compared to patients with common *EGFR* mutations [2-5]. Among the rare subtypes, the two highest frequency mutations, G719X in exon18 and L861Q in exon21, have been recognized as being relatively sensitizing mutations; the objective overall response rate and the median progression-free survival (PFS) have been reported to be around 40–70% and 4.0–9.0 months, respectively [1, 6, 7]. Due to the similar efficiency obtained by platinum-doublet chemotherapy, the therapeutic strategy for advanced NSCLC patients with uncommon *EGFR* mutation has been inconsistent. Recently, a second-generation EGFR-TKI, afatinib, has shown superior efficacy over the first-generation EGFR-TKIs in NSCLC patients with common *EGFR* mutations [8, 9]. Furthermore, a post-hoc analysis of the Lux-Lung -2, -3, and -6 trials showed that afatinib was active in NSCLC patients with uncommon *EGFR* mutations, and that the median PFS in the patients with G719X in exon 18 or L861Q in exon 21 were 13.8

months or 8.2 months, respectively [10]. These results indicate that afatinib could be an optimal treatment option for the patients with uncommon *EGFR* mutations. However, there have been no reports that show the superiority of afatinib over the first-generation EGFR-TKIs in a cohort study.

Here, we conducted a retrospective analysis of patients treated with EGFR-TKIs in our cohort and evaluated the efficacy of afatinib with respect to clinical outcomes in advanced NSCLC patients with uncommon *EGFR* mutations and compared it to the efficacy of the first-generation EGFR-TKIs. Clinical data between January 2004 and Jun 2018 were assessed from patients with stage III, IV, or recurrent NSCLC, harboring *EGFR* mutations who received treatment with EGFR-TKIs (N = 177) at Nagoya University hospital. Uncommon *EGFR* mutations were defined as any mutation other than short in-frame deletions of exon 19 and the L858R point mutation in exon 21, and were observed in 18 patients (10.2%). Patient characteristics were not statistically significant differences between the patients with common *EGFR* mutations and those with uncommon *EGFR* mutation (Table 1). The most frequent mutation in the group of uncommon *EGFR* mutations was L861Q in exon 21 (N = 7 [4.0%]) and the second most frequent mutation was G719A in exon 18 (N = 5 [2.8%]). Among the 18 patients with uncommon *EGFR* mutations, 8 patients had received afatinib and 10 patients had received the first-generation EGFR-TKIs (Table 2). There were no statistically significant differences in the patients' clinical characteristics comparing the two groups. The best overall responses (ORRs) in the afatinib group and the first-

generation EGFR-TKIs were 75.0% (N = 6/8) and 40.0% (N = 4/10), respectively (Table 3). The PFS in the afatinib group were significantly longer than those in the first-generation EGFR-TKIs group (P = 0.0481; Fig.1A), with median PFS of 17.1 and 5.5 months, respectively. To evaluate the efficacy of afatinib in patients with *EGFR* mutations, we also analyzed 159 patients with common *EGFR* mutations in this cohort. Among them, 11 patients had received afatinib. The patient characteristics were not statistically different between the afatinib and first-generation EGFR-TKIs groups (data not shown). The ORRs in the afatinib group and the first-generation EGFR-TKIs group were 63.6% (7/11) and 47.1% (66/138), respectively (Table 3). The median PFS (14.0 vs 11.0 months) was also longer in the afatinib group than in the first-generation *EGFR*-TKIs group; however, these differences did not reach statistical significance (P = 0.6136; Fig.1B).

In this retrospective analysis, the ORR and PFS found in the first-generation *EGFR*-TKIs group were consistent with previous reports, and the efficacy of afatinib showed a statistically significant superiority over the first-generation *EGFR*-TKIs in patients with uncommon *EGFR* mutations. The ORR of the 8 patients treated with afatinib was 75.0%, which is similar to the result of the post-hoc analysis in the Lux-Lung trails which showed that the ORR of patients with the G719X mutations in exon 18 or L861Q in exon 21 were 77.8% and 56.3%, respectively [10]. However, the median PFS in our cohort was somewhat longer than one seen from the post-hoc analysis of the Lux-Lung trails [10]. This difference might be due to the limitations of a small

case study, racial differences, and the various follow-up terms used to evaluate the responses in a retrospective analysis. The successful establishment of a therapeutic strategy for uncommon *EGFR* mutations is limited by the low frequency and the heterogeneity of the various alterations. Furthermore, patients with low frequency *EGFR* mutations have not been included in the majority of pivotal clinical trials for *EGFR*-TKI treatment. These limitations make it hard to accumulate any reliable evidence; therefore, sharing information from even single case report or small case studies, is crucial for patients with uncommon *EGFR* mutations. Our results suggest that afatinib is an optimal treatment for patients with advanced NSCLC who harbor uncommon *EGFR* mutations. Further large-scale studies are urgently needed to address this issue.

Funding

This research did not receive any specific grant from Funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statements

Dr. Hase has received research founding from Boehringer Ingelheim; Dr. Hasegawa reported receiving grant from Boehringer Ingelheim., Pfizer Inc., Astellas Pharma Inc., ONO PHARMACEUTICAL CO., Shionogi & Co., AstraZeneca, Sanofi K.K., TEIJIN LIMITED, MSD

K.K., Meiji Seika Pharma Co., DAIICHI SANKYO COMPANY, LIMITED., GlaxoSmithKline K.K., Otsuka Pharmaceutical Co., KYORIN Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Novartis Pharma K. K., Kyowa Hakko Kirin Co., Eli Lilly Japan K.K., Chugai Pharmaceutical Co. that was paid to Nagoya University.

References

[1] J.Y. Wu, C.J. Yu, Y.C. Chang, C.H. Yang, J.Y. Shih, P.C. Yang, 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. 17 (2011) 3812–3821.

[2] Z. Lohinai, M.A. Hoda, K. Fabian, G. Ostoros, E. Raso, T. Barbai, J. Timar, I. Kovalszky, M. Cserepes, A. Rozsas, V. Laszlo, M. Grusch, W. Berger, W. Klepetko, J. Moldvay, B. Dome, B. Hegedus, Distinct epidemiology and clinical consequence of classic versus rare EGFR mutations in lung adenocarcinoma, J. Thorac. Oncol. 10 (2015) 738–746.

[3] G. Galli, G. Corrao, M. Imbimbo, C. Proto, D. Signorelli, M. Ganzinelli, N. Zilembo, M. Vitali, F. de Braud, M.C. Garassino, G. Lo Russo, Uncommon mutations in epidermal growth factor receptor and response to first and second generation tyrosine kinase inhibitors: A case series and literature review, Lung Cancer 115 135–142.

[4] Y.M. Chen, C.H. Lai, H.C. Chang, T.Y. Chao, C.C. Tseng, W.F. Fang, C.C. Wang, Y.H. Chung, Y.H. Wang, M.C. Su, K.T. Huang, H.C. Chen, M.C. Lin, The impact of clinical parameters on progression-free survival of non-small cell lung cancer patients harboring EGFR-mutations receiving first-line EGFR-tyrosine kinase inhibitors, Lung Cancer 93 (2016) 47–54.

[5] B. Klughammer, W. Brugger, F. Cappuzzo, T. Ciuleanu, T. Mok, M. Reck, E.H. Tan, P. Delmar, G. Klingelschmitt, A.Y. Yin, O. Spleiss, L. Wu, D.S. Shames, Examining treatment outcomes with erlotinib in patients with advanced non-small cell lung cancer whose tumors harbor uncommon EGFR mutations, J. Thorac. Oncol. 11 (2016) 545–555.

[6] N. Sutiman, S.W. Tan, E.H. Tan, W.T. Lim, R. Kanesvaran, Q.S. Ng, A. Jain, M.K. Ang, W.L. Tan, C.K. Toh, B. Chowbay, EGFR mutation subtypes influence survival outcomes following first-line gefitinib therapy in advanced Asian NSCLC patients, J. Thorac. Oncol. 12 (2017) 529–538.

[7] G.M. O'Kane, P.A. Bradbury, R. Feld, N.B. Leighl, G. Liu, K.M. Pisters, S. Kamel-Reid, M.S. Tsao, F.A. Shepherd, Uncommon EGFR mutations in advanced non-small cell lung cancer, Lung Cancer 109 (2017) 137–144.
[8] K. Park, E.H. Tan, K. O'Byrne, L. Zhang, M. Boyer, T. Mok, V. Hirsh, J.C. Yang, K.H. Lee, S. Lu, Y. Shi, S.W. Kim, J. Laskin, D.W. Kim, C.D. Arvis, K. Kolbeck, S.A. Laurie, C.M. Tsai, M. Shahidi, M. Kim, D. Massey, V. Zazulina, L. Paz-Ares, 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 (2016) 577–589.
[9] L. Paz-Ares, E.H. Tan, K. O'Byrne, L. Zhang, V. Hirsh, M. Boyer, J.C. Yang, T. Mok, K.H. Lee, S. Lu, Y. Shi, D.H. Lee, J. Laskin, D.W. Kim, S.A. Laurie, K. Kolbeck, J. Fan, N. Dodd, A. Marten, K. Park, Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial, Ann. Oncol. 28 (2017) 270–277.
[10] J.C. Yang, L.V. Sequist, S.L. Geater, C.M. Tsai, T.S. Mok, M. Schuler, N. Yamamoto, C.J. Yu, S.H. Ou, C. Zhou, D. Massey, V. Zazulina, Y.L. Wu, 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. 16 (2015) 830–838.

Table 1. Clinical characteristics of 177 lung cancer patients with *EGFR* mutations

Characteristic	Total	Common mutation n (%)	Uncommon mutation n (%)	P‡
Total	177	159 (89.8)	18 (10.2)	
Median Age (Range)	66.3	66.3 (35-87)	70.5 (52-87)	0.2406
Gender				
Male	67	62 (92.5)	5 (7.5)	0.4465
Female	110	97 (88.2)	13 (11.8)	
Smoking status*				
Current	19	19 (100.0)	0 (0.0)	0.2586
Former	50	45 (90.0)	5 (10.0)	
Never	104	91 (87.5)	13 (12.5)	
PS				
0	86	75 (87.2)	11 (12.8)	0.4816
1	71	65 (91.5)	6 (8.5)	
≥2	20	19 (95.0)	1 (5.0)	
Stage				
IIIA	4	4 (100.0)	0 (0.0)	0.0008
IIIB	9	5 (55.5)	4 (45.5)	
IV	104	99 (95.2)	5 (4.8)	
Recurrence	60	51 (85.0)	9 (15.0)	
Subtype				
Adenocarcinoma	171	154 (90.1)	17 (9.9)	0.4762
Squamous cell carcinoma	3	3 (100.0)	0 (0.0)	
Adenosquamous cell carcinoma	1	1 (100.0)	0 (0.0)	
NSCLC	2	1 (50.0)	1 (50.0)	

‡P values were calculated by T-Test, Fisher's exact test or Chi-square test.

*Information was not available for 4 cases

Table 2. Clinical characteristics of 18 lung cancer patients with uncommon *EGFR* mutations

Characteristic	Total	EGFR-TKI		P‡
		Gefitinib/Erlotinib n (%)	Afatinib, n (%)	
Total	18	10 (55.5)	8 (44.4)	
Median Age (Range)	70.5	70.0 (52-79)	73.0 (61-87)	0.0560
Gender				
Male	5	3 (60.0)	2 (40.0)	0.8139
Female	13	7 (53.8)	6 (46.2)	
Smoking status				
Former	5	2 (40.0)	3 (60.0)	0.4101
Never	13	8 (61.5)	5 (38.5)	
PS				
0	11	5 (45.5)	6 (54.5)	0.4597
1	6	4 (66.7)	2 (33.3)	
≥2	1	1 (100.0)	0 (0.0)	
Stage				
IIIB	4	3 (75.0)	1 (25.0)	0.1634
IV	5	1 (20.0)	4 (80.0)	
Recurrence	9	6 (66.7)	3 (33.3)	
Subtype				
Adenocarcinoma	17	9 (52.9)	8 (47.1)	0.3574
NSCLC	1	1 (100.0)	0 (0.0)	
EGFR mutation status				
Ex18:G719A	5	2 (40.0)	3 (60.0)	
Ex18:G719C	1	0 (0.0)	1 (100.0)	
Ex19:K574E	1	1 (100.0)	0 (0.0)	
Ex19:L747-S752del	1	1 (100.0)	0 (0.0)	
Ex19:L746-E749delA750VT751S	1	1 (100.0)	0 (0.0)	
Ex21:L861Q	7	4 (57.1)	3 (42.9)	
Ex21:L858R + T790M	1	1 (100.0)	0 (0.0)	
Ex18:G719A and Ex21:L861Q	1	0 (0.0)	1 (100.0)	

‡P values were calculated by T-Test, Fisher's exact test or Chi-square test.

Table 3. response to EGFR-TKIs in patients with uncommon *EGFR* mutations

	Common mutation				Uncommon mutation			
	Gefitinib or Erlotinib‡		Afatinib		Gefitinib or Erlotinib		Afatinib	
	N=138	%	N=11	%	N=10	%	N=8	%
Best response								
PR	65	47.1	7	63.6	4	40.0	6	75.0
SD	45	32.9	3	27.3	4	40.0	2	25.0
PD	28	20.0	1	9.1	2	20.0	0	0.0
ORRs	66	47.1	7	63.6	4	40.0	6	75.0
DCRs	112	80.0	10	90.9	8	80.0	8	100.0

PR; partial response, SD; stable disease, PD; progression disease,

ORR; overall response rate, DCR; disease control rate

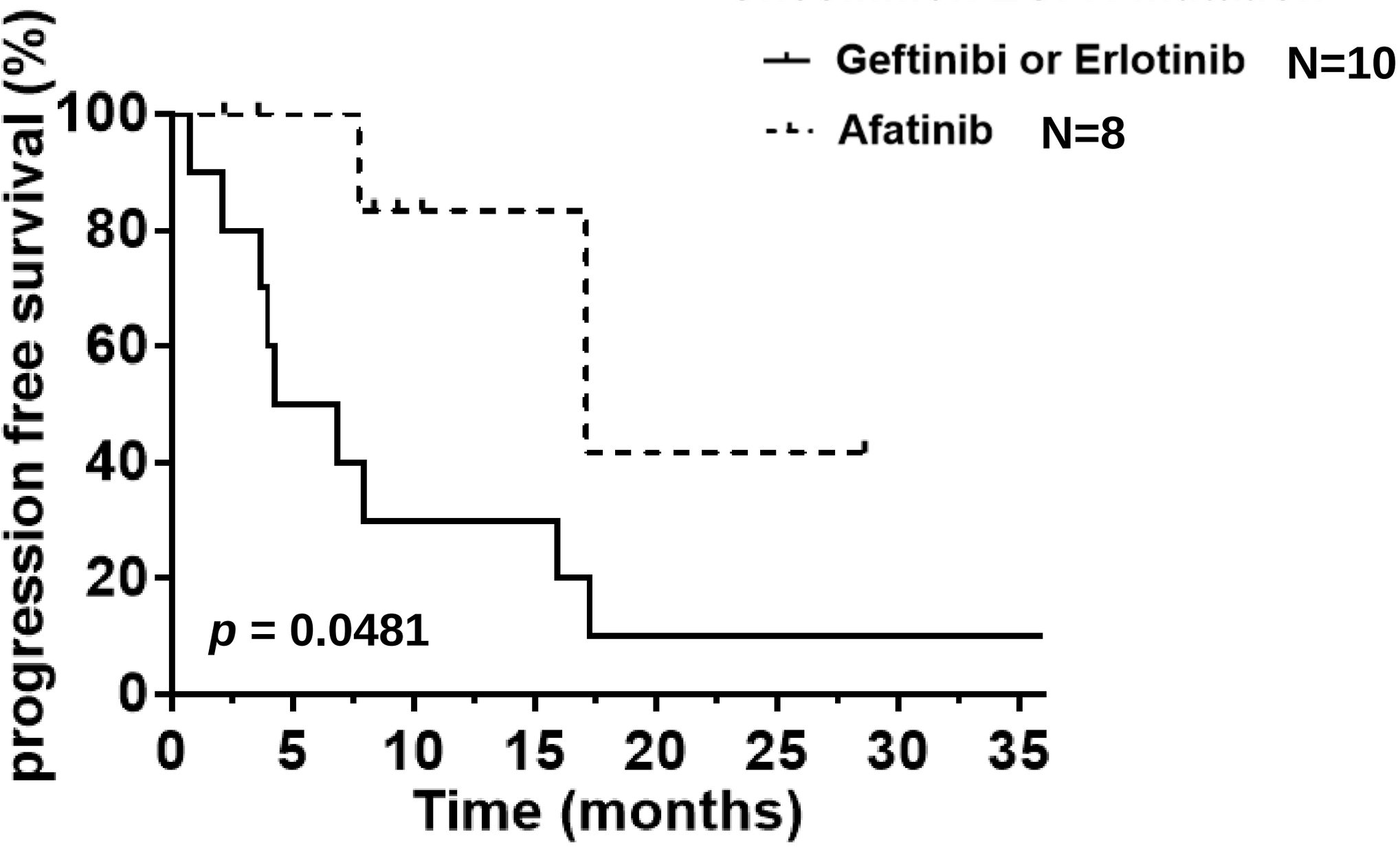
‡10 patients were not evaluated

Figure legends

Fig. 1. Kaplan-Meier plot of progression-free survival (PFS) in the patients with uncommon *EGFR* mutations (A) and common *EGFR* mutations (B). PFS was defined as the time from the start of first-line TKI treatment to disease progression or death, whichever was earlier, and data were censored at the last follow-up date. The log-rank test was implemented to analyze the differences between the patient groups.

Figure 1

1A



1B