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Epidermal growth factor receptor tyrosine kinase inhibitors for non-small cell lung cancer harboring uncommon *EGFR* mutations: Real-world data from Taiwan

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Abstract

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the standard treatment for patients with non-small cell lung cancer (NSCLC) harboring *EGFR* mutations. This study aimed to evaluate the efficacy of EGFR-TKIs and prognostic factors for patients with NSCLC harboring uncommon *EGFR* mutations, which account for 10% of *EGFR* mutations.

Methods: A total of 230 treatment-naive patients with NSCLC harboring uncommon *EGFR* mutations treated with first-line EGFR-TKIs between 2011 and 2018 at four hospitals (belonging to four institutions, Linkou, Kaohsiung, Keelung, and Chiayi, of the Chang Gung Memorial Hospital) in Taiwan were retrospectively reviewed. Their clinicopathological characteristics, adverse events (AEs), objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were collected. Univariate and multivariate analyses were performed to identify potential prognostic factors for PFS.

Results: Overall, patients who received afatinib ($n = 62$) had better PFS (median: 6.4 vs. 5.9 months, $p = 0.022$) and OS (median: 13.4 vs. 13.0 months, $p = 0.008$) than those who received gefitinib/erlotinib ($n = 124$), although no significant differences were observed for ORR (46.8% vs. 35.5%, $p = 0.137$) or DCR (59.7% vs. 58.9%, $p = 0.916$). Patients who received afatinib showed significantly higher ORR (58.3% vs. 31.3%, $p = 0.027$) but not DCR compared with gefitinib/erlotinib for major uncommon mutations. Afatinib trended toward better PFS and OS for major uncommon mutations and compound mutations. No EGFR-TKIs were effective for most NSCLC patients with exon 20 insertions. Performance status, metastasis of the liver and pleura, and dose reduction were independent prognostic factors for PFS.

Conclusion: Afatinib demonstrated better survival outcomes than gefitinib/erlotinib for NSCLC patients harboring major *EGFR* uncommon mutations and compound mutations. Performance status and metastatic sites may be useful for predicting PFS for major uncommon mutations and compound mutations.

KEYWORDS
afatinib, erlotinib, gefitinib, lung cancer, uncommon mutation

INTRODUCTION

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), including the first-generation (1G) TKIs, gefitinib and erlotinib[1–4]; second-generation (2G) TKIs, afatinib and dacomitinib[5–8]; and the third-generation (3G) TKI, osimertinib,[9,10] have become first-line treatments for patients with advanced non-small cell lung cancer (NSCLC) harboring activating *EGFR* mutations.[11,12] Among known *EGFR* mutations, the exon 19 deletion and the exon 21 L858R mutation account for approximately 90% of all *EGFR* mutations in NSCLC and are typically referred to as common or classical mutations.[13] In nearly all early trials of 1G/2G EGFR-TKIs, all *EGFR* mutations, both common and uncommon mutations, including the T790M mutation, were enrolled. Due to the disparate sensitivities observed in response to EGFR-TKIs between common and uncommon mutations and the large degree of heterogeneity among uncommon mutations, later studies, such as the LUX-Lung 7[7] and FLAURA trials,[10] only enrolled patients with common mutations.

Although uncommon mutations account for 10% of *EGFR* mutations, these mutations are heterogeneous and display various responses to EGFR-TKIs. Uncommon mutations can be divided into the T790M mutation, exon 20 insertions, major uncommon mutations (G719X, L861Q, and S768I), compound mutations, and others.[14] The T790M and exon 20 insertions are generally considered resistant to EGFR-TKIs, although osimertinib is effective against the T790M mutation. Afatinib is the only Food and Drug Administration (FDA)-approved EGFR-TKI for the treatment of uncommon, nonresistant mutation (L861Q, G719X, and S768I), based on a post hoc analysis of the LUX-Lung 2, 3, and 6 trials.[15]

As only a few studies with limited case numbers have examined the activity of different EGFR-TKIs in NSCLC patients harboring uncommon mutations,[16,17] the current study aimed to compare the effects of first-line 1G/2G EGFR-TKIs for the treatment of patients with NSCLC harboring uncommon *EGFR* mutation, other than de novo T790M.

METHODS

Patients and data collection

Patient data were obtained from the Cancer Registry System using the Chang Gung Research Database.[18,19] NSCLC patients harboring *EGFR* mutations and treated with first-line EGFR-TKIs from January 2011 to January 2018 from four institutions (Linkou, Kaohsiung, Keelung, and Chiayi) of the Chang Gung Memorial Hospital (CGMH) were retrospectively reviewed. The mutation status was retrospectively reviewed, and those patients with NSCLC harboring uncommon *EGFR* mutations were enrolled in the current study. Patients treated with concurrent chemotherapy, concurrent bevacizumab, second-line systemic treatment, or neoadjuvant treatments were excluded.

The clinicopathological features, including age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS) score, location of metastases, *EGFR* mutation, tumor response, and subsequent treatment, were obtained. In addition, adverse events (AEs), graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4, AE-related dose adjustments, and AE-related drug discontinuations were recorded. The last follow-up time point in the study was May 2021.

This study was approved by the Institutional Review Board of CGMH (201901395B0C501). Patient consent to participate was not required due to the retrospective nature of this study.

Classification of uncommon *EGFR* mutations

Various classification schemes exist for uncommon *EGFR* mutations. This study classified uncommon *EGFR* mutations based on the largest mutation study, reported by Yang et al.[14] First, tumors with de novo T790M mutations were excluded. Tumors with exon 20 insertions, with or without other *EGFR* mutations, were classified as "exon 20 insertions." Tumors with more than one *EGFR* mutation other than the exon 20 insertion were classified as "compound mutations." According to the mutational composition, compound mutations were subclassified as either with or without major uncommon mutations and with or without common mutations (L858R or exon 19 deletion). Tumors containing the L861Q, G719X, or S768I mutations were classified as "major uncommon mutations." Tumors with unclassified mutations were classified as "others" (Figure 1).

Treatment and response evaluation

Patients were treated with first-line EGFR-TKIs until disease progression or intolerable toxicity. The tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors 1.1 criteria. The best clinical tumor response based on radiological findings was recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Any tumor response that was not assessed before death or discontinuation due to intolerance was recorded as "not assessed (NA)." Progression-free survival (PFS) was defined as the duration from the first day of EGFR-TKI treatment until the first radiological evidence of disease progression; the last dose of EGFR-TKI owing to toxicity, loss of patient follow-up, or patient preference; death; or last follow-up. Patients who experienced no progression and no death during treatment were censored during the PFS analysis. Patients who experienced radiological progression or death within 1 month after EGFR-TKI

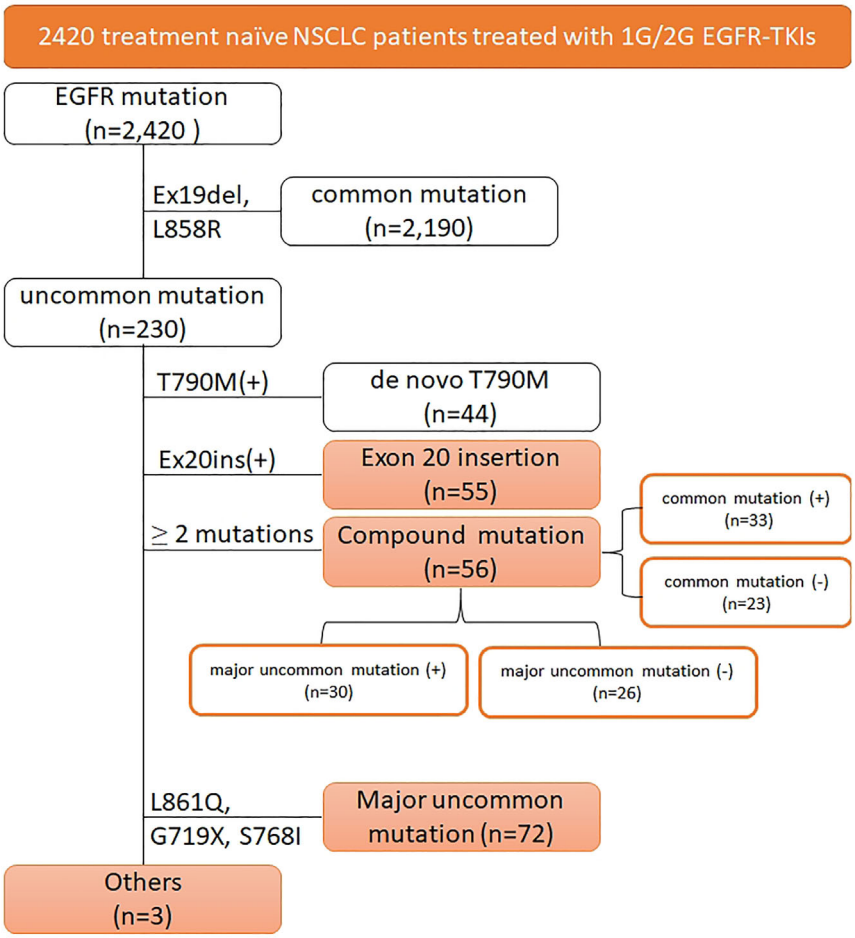

FIGURE 1 Flow chart showing patient selection in the current study. Overall, 2420 patients had *EGFR* mutations, consisting of 2190 common mutations (exon 19 deletions (Ex19del, L858R) and 230 uncommon mutations. A total of 44 de novo T790M cases were excluded from the current study, resulting in the inclusion of 186 patients with uncommon mutations, which were divided into exon 20 insertions (Ex20ins, $n = 55$), compound mutations (≥2 mutations, $n = 56$), major uncommon mutations (L861Q, G719X, or S768I, $n = 72$), and others ($n = 3$). Compound mutations were subgrouped according to whether they included common mutations or major uncommon mutations

discontinuation and who received no sequential treatment were counted as an event. OS was defined as the duration from the first day of EGFR-TKI treatment until the date of death or last follow-up. Patients who did not experience death were censored during survival curve analysis.

Statistical analysis

PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate analysis was performed to evaluate possible prognostic factors, including age, sex, ECOG PS, smoking history, histology, and the location of metastases. Multivariate regression included all factors from the univariate analyses with a significant effect at $p < 0.05$, except for clinical response as it was the most significant factor that largely influenced the impact of other factors in the univariate analyses. The results are presented as the hazard ratio (HR) and 95% confidence interval (CI) according to Cox regression analyses. IBM SPSS Statistics for Windows (version 23.0) was used to perform all statistical analyses, and $p < 0.05$ was considered statistically significant. Survival curves were plotted by SPSS and a forest plot was created using R statistical software (R version 4.0.5, R Core Team, 2021, R Foundation for Statistical Computing) with packages (http://www.r-project.org/).

RESULTS

Classification of *EGFR* mutations

A total of 2420 patients with *EGFR* mutation–positive NSCLC who were treated with frontline EGFR-TKIs were reviewed. Among them, 2190 patients (90.5%) had common mutations, and 230 had uncommon mutations (9.5%). Forty-four patients had de novo T790M mutations (1.8%), and the remaining 186 (7.7%) patients with uncommon mutations other than T790M were included in the current study.

Among uncommon mutations other than the T790M mutation, 55 (29.6%) patients had exon 20 insertions, 56 (30.1%) patients had compound mutations, 72 (38.7%) patients had major uncommon mutations, and three (1.6%) had other mutations. Among those patients with compound mutations, 33 (58.9%) patients had a concurrent common mutation, and 30 (53.6%) patients had a concurrent major uncommon mutation. The details of mutation classifications in patients are summarized in Figure 1.

TABLE 1 Patient characteristics ($n = 186$)

Characteristics	N (%)	Gefitinib/erlotinib ($n = 124$)	Afatinib ($n = 62$)	*p*-value
Age (years)				0.540
Median (range)	68 (43–94)	70.5 (43–94)	65.5 (46–88)	
Sex				0.526
Male	75 (40.3)	52 (41.9)	23 (37.1)	
Female	111 (59.7)	72 (58.1)	39 (62.9)	
ECOG performance status				0.060
0–1	137 (73.7)	86 (69.4)	51 (82.3)	
2–4	49 (26.3)	38 (30.6)	11 (17.7)	
Smoking				0.237
No	128 (68.8)	83 (66.9)	45 (72.6)	
Yes	48 (25.8)	36 (29.0)	12 (19.4)	
Unknown	10 (5.4)	5 (4.0)	5 (8.1)	
Histology				0.553
Adenocarcinoma	184 (98.9)	122 (98.4)	62 (100.0)	
Adenosquamous	2 (1.1)	2 (1.6)	0	
EGFR mutation				0.292
G719X	35 (18.8)	24 (19.4)	11 (17.7)	
S768I	3 (1.6)	2 (1.6)	1 (1.6)	
L861Q	34 (18.3)	22 (17.7)	12 (19.4)	
With major uncommon mutation	30 (16.1)	19 (15.3)	11 (17.7)	
Without major uncommon mutation	26 (14.0)	22 (17.7)	4 (6.5)	
Exon 20 insertion	55 (29.6)	32 (25.8)	23 (37.1)	
Others	3 (1.6)	3 (2.4)	0	
EGFR mutation				0.597
Major uncommon mutation				
G719X	35 (18.8)	24 (19.4)	11 (17.7)	
S768I	3 (1.6)	2 (1.6)	1 (1.6)	
L861Q	34 (18.3)	22 (17.7)	12 (19.4)	
Compound mutation				
With common mutation	33 (17.7)	25 (20.2)	8 (12.9)	
Without common mutation	23 (12.4)	16 (12.9)	7 (11.3)	
Exon 20 insertion	55 (29.6)	32 (25.8)	23 (37.1)	
Others	3 (1.6)	3 (2.4)	0	
Lung metastasis				0.060
Yes	81 (43.5)	48 (38.7)	33 (53.2)	
No	105 (56.5)	76 (61.3)	29 (46.8)	
Liver metastasis				0.108
Yes	22 (11.8)	18 (14.5)	4 (6.5)	
No	164 (88.2)	106 (85.5)	58 (93.5)	
Brain metastasis				>0.999
Yes	57 (30.6)	38 (30.6)	19 (30.6)	
No	129 (69.4)	86 (69.4)	43 (69.4)	
Bone metastasis				0.755
Yes	87 (46.8)	57 (46.0)	30 (48.4)	
No	99 (53.2)	67 (54.0)	32 (51.6)	
Pleural metastasis				0.461
Yes	77 (41.4)	49 (39.5)	28 (45.2)	

(Continues)

TABLE 1 (Continued)

Characteristics	N (%)	Gefitinib/erlotinib ($n = 124$)	Afatinib ($n = 62$)	*p*-value
No	109 (58.6)	75 (60.5)	34 (54.8)	
Adrenal metastasis				0.427
Yes	7 (3.8)	6 (4.8)	1 (1.6)	
No	179 (96.2)	118 (95.2)	61 (98.4)	
Distant lymph node metastasis				0.857
Yes	17 (9.1)	11 (8.9)	6 (9.7)	
No	169 (90.9)	113 (91.1)	56 (90.3)	

Note: Values are presented as n (%).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor.

TABLE 2 Dose adjustment and clinical response ($n = 186$)

Characteristic Dose reduction	N (%)	Gefitinib/erlotinib ($n = 124$)	Afatinib ($n = 62$)	*p*-value <0.0001
Yes	40 (21.5)	10 (8.1)	30 (48.4)	
No	146 (78.5)	114 (91.9)	32 (51.6)	
Discontinuation				0.219
Yes	12 (6.5)	6 (4.8)	6 (9.7)	
No	174 (93.5)	118 (95.2)	56 (90.3)	
Response				0.303
PR	73 (39.2)	44 (35.5)	29 (46.8)	
SD	37 (19.9)	29 (23.4)	8 (12.9)	
PD	42 (22.6)	28 (22.6)	14 (22.6)	
N/A	34 (18.3)	23 (18.5)	11 (17.7)	

Note: Values are presented as n (%). EGFR, epidermal growth factor; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 3 Objective response rate (ORR) and disease control rate (DCR) for gefitinib/erlotinib and afatinib

	Gefitinib/erlotinib ($n = 124$)		Afatinib ($n = 62$)		*p*-value	
Mutation	ORR	DCR	ORR	DCR	ORR	DCR
Major uncommon ($n = 72$)	15/48 (31.3)	32/48 (66.7)	14/24 (58.3)	17/24 (70.8)	0.027	0.721
G719X	9/24 (37.5)	18/24 (75.0)	6/11 (54.5)	8/11 (72.7)	0.467	>0.999
S768I	1/2 (50.0)	1/2 (50.0)	0/1 (0)	0/1 (0)	>0.999	>0.999
L861Q	5/22 (22.7)	13/22 (59.1)	8/12 (66.7)	9/12 (75.0)	0.025	0.465
Compound ($n = 56$)	25/41 (61.0)	32/41 (78.0)	9/15 (60.0)	11/15 (73.3)	0.947	0.730
With major uncommon	13/19 (68.4)	16/19 (84.2)	7/11 (63.6)	8/11 (72.7)	>0.999	0.641
Without major uncommon	12/22 (54.5)	16/22 (72.7)	2/4 (50.0)	3/4 (75.0)	>0.999	>0.999
With common mutation	16/25 (64.0)	19/25 (76.0)	4/8 (50.0)	6/8 (75.0)	0.681	>0.999
Without common mutation	9/16 (56.3)	13/16 (81.3)	5/7 (71.4)	5/7 (71.4)	0.657	0.621
Exon 20 insertion ($n = 55$)	3/32 (9.4)	8/32 (25.0)	6/23 (26.1)	9/23 (39.1)	0.143	0.263
Others ($n = 3$)	1/3 (33.3)	1/3 (33.3)	0	0	N/A	N/A
Overall ($n = 186$)	44/124 (35.5)	73/124 (58.9)	29/62 (46.8)	37/62 (59.7)	0.137	0.916

Note: Values are presented as n (%).
Abbreviations: N/A, not assessed.

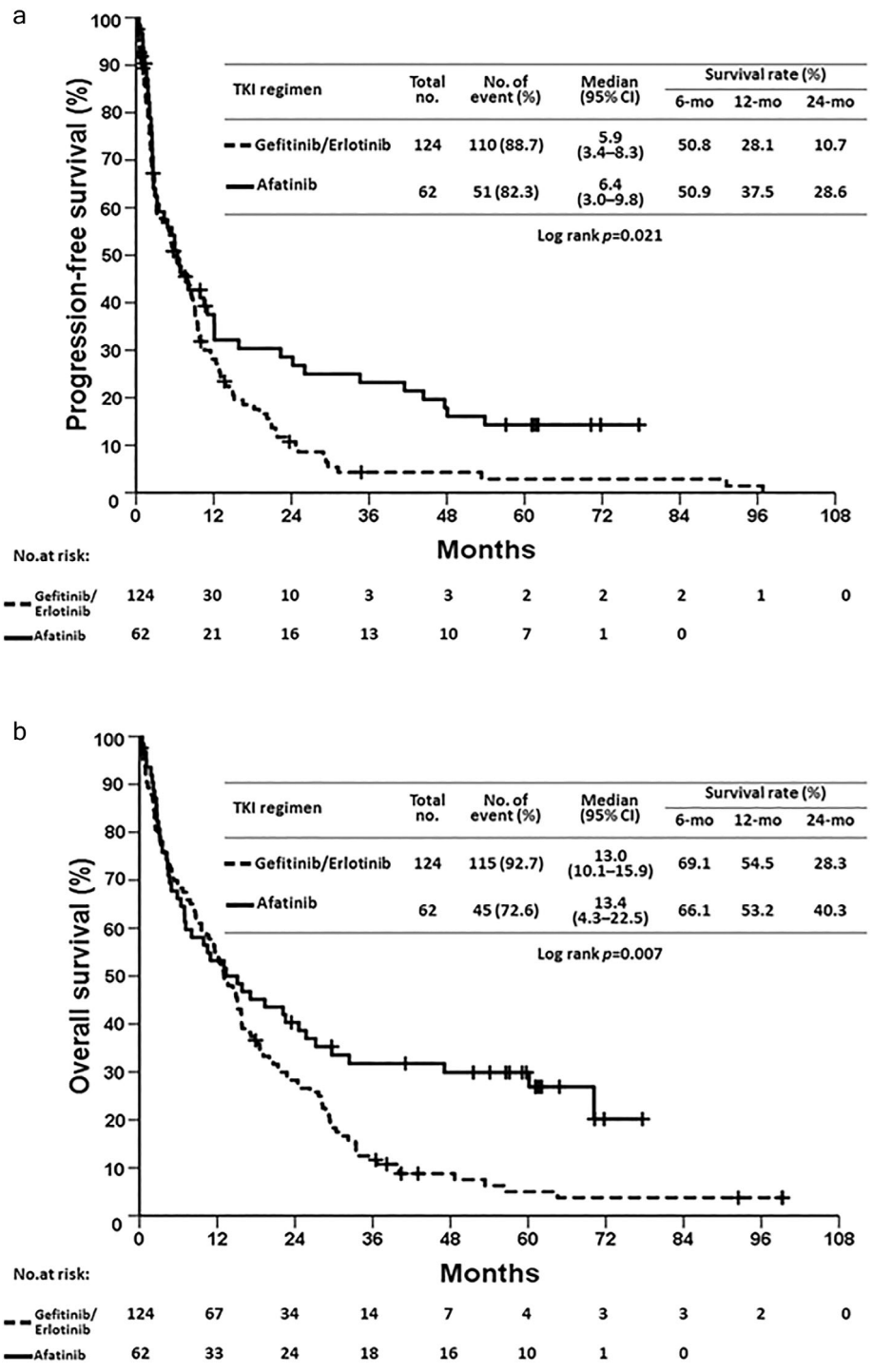

FIGURE 2 Kaplan–Meier curves of progression-free survival (PFS; a) and overall survival (OS; b) among 186 patients with uncommon mutations treated with either afatinib or gefitinib/erlotinib. The survival curves between each treatment were compared using the log-rank test. Patients treated with afatinib had better PFS ($p = 0.021$) and OS ($p = 0.007$) than those treated with gefitinib/erlotinib

Patient characteristics

A total of 186 patients with uncommon mutations were included in the current study. The patient characteristics are shown in Table 1. All patients were treated with either 1G EGFR-TKIs ($n = 124$, including 96 given gefitinib and 28 given erlotinib) or afatinib ($n = 62$). Except for dose reduction (48.4% for afatinib vs. 8.1% for 1G EGFR-TKIs, $p < 0.001$), no significant differences were observed between the two treatment groups.

Overall, the median age was 68 years, range 43–94 years, and 111 (59.7) were female. Most patients were classified as ECOG PS of 0–1 ($n = 137$, 73.7%), never smokers ($n = 128$, 68.8%), with adenocarcinoma ($n = 184$, 98.9%), and stage IV disease ($n = 185$, 99.5%). Bone ($n = 87$, 46.8%) was the most common metastatic site, followed by lung ($n = 81$, 43.5%), pleura ($n = 77$, 41.4%), and brain ($n = 57$, 30.6%).

Overall, 40 (21.5%) experienced dose reduction due to AEs and 12 (6.5%) experienced drug discontinuations due to AEs (Table 2).

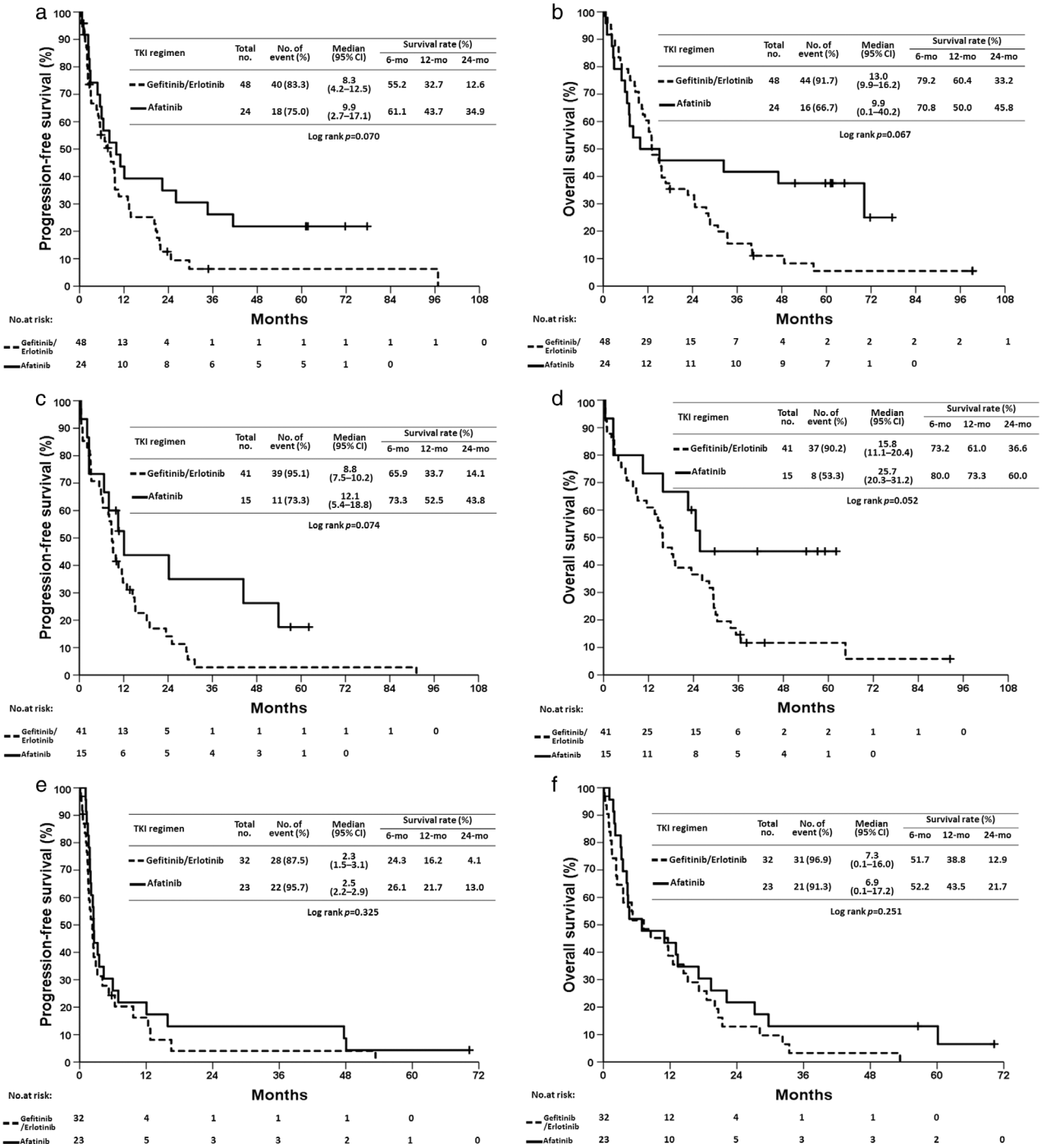

FIGURE 3 Kaplan–Meier curves of progression-free survival (PFS; a, c, and e) and overall survival (OS; b, d, and f) among patients with major uncommon mutations (a and b), compound mutations (c and d), and exon 20 insertions (e and f) treated with either afatinib or gefitinib/erlotinib. The survival curves between each treatment were compared using the log-rank test

Clinical efficacy of EGFR-TKIs against uncommon *EGFR* mutations

The overall ORR and DCR were 39.2 and 59.1%, respectively. The ORRs were 31.3, 61.0, and 9.4% for major uncommon mutations, compound mutations, and exon 20 insertions, respectively (Table 3).

Compared with 1G EGFR-TKIs for the treatment of all uncommon mutations, afatinib ($n = 62$) was associated with better PFS (median PFS: 6.4 vs. 5.9 months, HR: 0.67, 95% CI: 0.48–0.94, $p = 0.022$, Figures 2a and 4a, Supplementary Table S1) and OS (median OS: 13.4 vs. 13.0 months, HR: 0.62, 95% CI: 0.44–0.88, $p = 0.008$, Figures 2b and 4b, Supplementary Table S2) than gefitinib/erlotinib ($n = 124$),

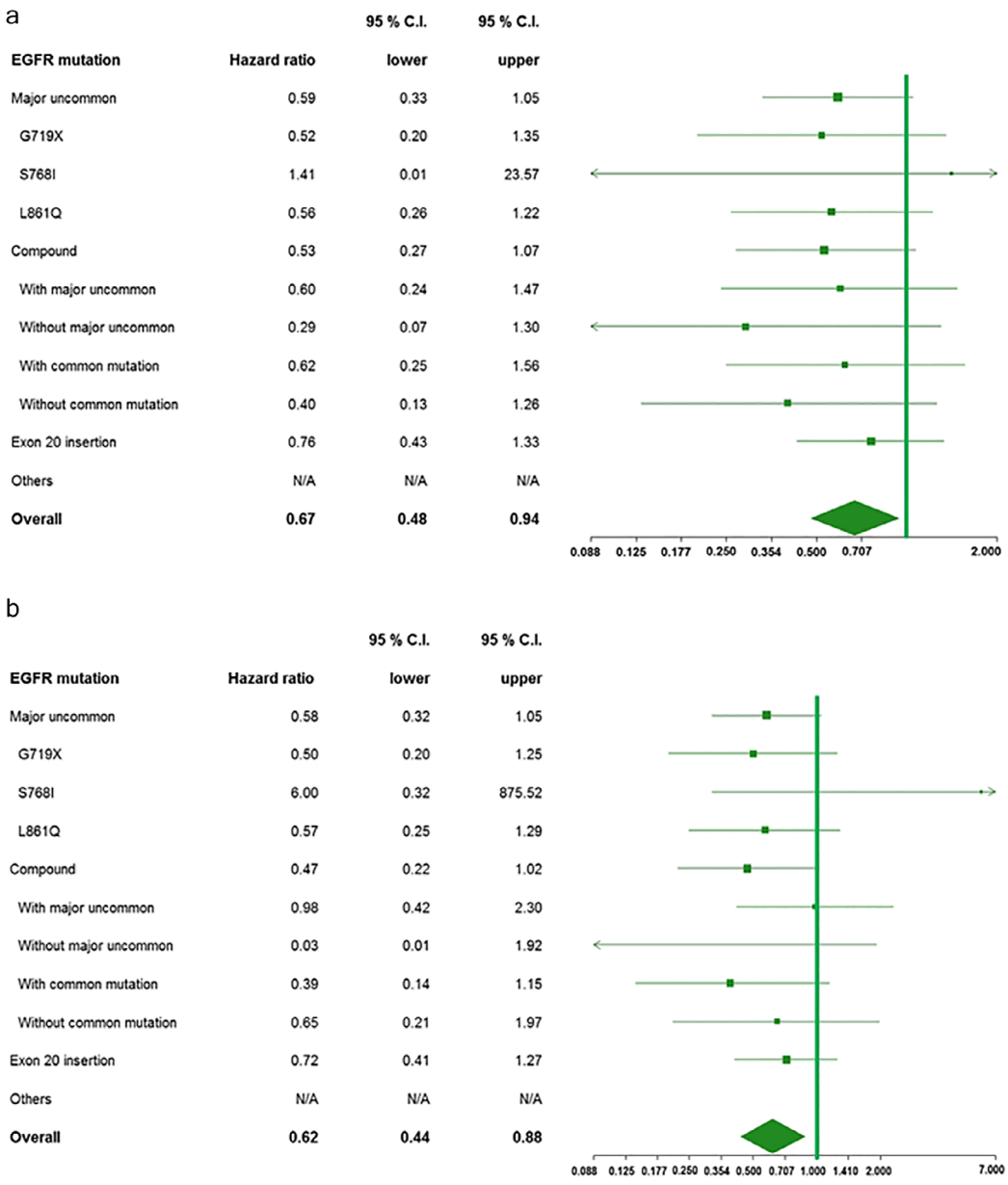

FIGURE 4 Forest plots of subgroup analyses for afatinib versus gefitinib/erlotinib for different genetic alterations in terms of progression-free survival (PFS; a) and overall survival (OS; b)

although no significant differences were observed for ORR (46.8% vs. 35.5%, $p = 0.137$) or DCR (59.7% vs. 58.9%, $p = 0.916$; Table 3).

Based on mutation patterns, uncommon mutations were divided into four groups: major uncommon mutations ($n = 48$), compound mutations ($n = 41$), exon 20 insertions ($n = 32$), and others ($n = 3$). Afatinib had significantly higher ORR than gefitinib/erlotinib (58.3% vs. 31.3%, $p = 0.027$) but no significant difference was observed in DCR (70.8% vs. 66.7%, $p = 0.721$) for major uncommon mutation. Patients with major uncommon mutations treated with afatinib trended toward longer PFS (median PFS: 9.9 vs. 8.3 months, log-rank $p = 0.070$, Figure 3a) and OS (median OS: 9.9 vs. 13.0 months, log-rank $p = 0.067$, Figure 3b) than those treated with gefitinib/erlotinib, although significance was not achieved for either outcome.

However, both afatinib and gefitinib/erlotinib had similar ORR (61% vs. 60%, $p = 0.947$) and DCR (73.3% vs. 78%, $p = 0.730$) for compound mutations.

Patients with compound mutations treated with afatinib trended toward longer PFS (median PFS: 12.1 vs. 8.8 months, $p = 0.074$, Figure 3c) and OS (median OS: 25.7 vs. 15.8 months, $p = 0.052$, Figure 3d) than those treated with gefitinib/erlotinib, although significance was not achieved for either outcome.

For treatment of exon 20 insertions, afatinib had higher ORR (26.1% vs. 9.1%, $p = 0.143$) and DCR (39.1% vs. 25%, $p = 0.263$) than gefitinib/erlotinib, but these differences were not significant. Patients with exon 20 insertions treated

TABLE 4 Univariate and multivariate for progression-free survival (PFS; excluding patients with exon 20 insertion and other mutations)

		Univariate			Multivariate	
Characteristic	**Total No.**	**No. of events (%)**	**Median (95% CI)**	***p*-value**	**Hazard ratio (95% CI)**	***p*-value**
Age (years)				0.362	–	
<70	60	49 (81.7)	10.6 (7.6–13.6)			
≥70	68	59 (86.8)	8.1 (5.9–10.2)			
Sex				0.008		
Male	52	50 (96.2)	6.7 (3.3–10.0)		1	
Female	76	58 (66.3)	10.6 (7.8–13.4)		0.81 (0.48–1.38)	0.444
ECOG performance status				0.007		
0–1	93	78 (83.9)	9.6 (7.0–12.2)		0.58 (0.37–0.91)	0.017
2–4	35	30 (85.7)	6.7 (0.3–13.0)		1	
Smoking				<0.001		
No	93	73 (88.5)	10.5 (7.7–13.4)		0.68 (0.38–1.21)	0.193
Yes	35	35 (100.0)	6.4 (4.1–8.6)		1	
Histology				0.717	–	
Adenocarcinoma	181	156 (86.2)	6.3 (4.5–8.2)			
Adenosquamous	2	2 (100.0)	2.8 (−)			
EGFR mutation				0.860	–	
Major uncommon	72	58 (80.6)	8.3 (5.0–11.7)			
Compound	56	50 (89.3)	9.1 (6.8–11.4)			
Dose reduction				<0.001		
Yes	26	18 (69.2)	21.8 (14.3–29.4)		0.49 (0.27–0.88)	0.017
No	102	90 (88.2)	8.0 (5.7–10.3)		1	
Discontinuation				0.325	–	
Yes	10	4 (40.0)	10.6 (−)			
No	118	104 (88.1)	8.6 (6.8–10.4)			
Lung metastasis				0.062	–	
Yes	55	45 (91.8)	9.1 (7.5–10.8)			
No	73	63 (86.3)	8.3 (5.5–11.2)			
Liver metastasis				<0.0001		
Yes	12	10 (83.3)	2.0 (0.1–4.1)		1	
No	116	98 (84.5)	9.5 (7.8–11.1)		0.35 (0.17–0.72)	0.004
Brain metastasis				0.199		
Yes	34	30 (88.2)	5.2 (0.7–9.7)			
No	94	78 (83.0)	9.1 (7.5–10.8)			
Bone metastasis				0.022		
Yes	52	44 (84.6)	6.0 (3.2–8.7)		1	
No	76	64 (84.2)	10.5 (96.7–14.3)		0.70 (0.46–1.06)	0.091
Pleural metastasis				0.012		
Yes	45	44 (97.8)	6.7 (3.3–10.0)		1	
No	83	64 (77.1)	9.5 (7.4–11.5)		0.59 (0.40–0.89)	0.011
Adrenal metastasis				0.246	–	
Yes	5	4 (80.0)	5.2 (2.3–8.1)			
No	123	104 (84.6)	9.1 (7.7–10.5)			
Distant lymph node metastasis				0.347	–	
Yes	12	10 (83.3)	4.6 (0.1–12.6)			
No	116	98 (84.5)	9.1 (7.4–10.8)			
TKI regimens				0.009		

(Continues)

TABLE 4 (Continued)

Characteristic	Total No.	Univariate			Multivariate	
		No. of events (%)	Median (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Gefitinib/erlotinib	89	79 (88.8)	8.6 (6.8–10.4)		1	
Afatinib	39	29 (74.4)	10.5 (6.0–15.0)		0.77 (0.46–1.28)	0.311
Response				<0.0001	–	
PR	63	50 (79.4)	11.5 (9.2–13.8)			
SD	29	26 (89.7)	13.8 (2.1–25.5)			
PD	17	17 (100.0)	2.1 (1.8–2.4)			
N/A	19	15 (88.9)	2.1 (0.8–3.4)			

Note: Values are presented as n (%).

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor; N/A, not assessed; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

with afatinib has similar PFS (median PFS: 2.5 vs. 2.3 months, $p = 0.325$, Figure 3e) and OS (median OS: 6.9 vs. 7.3 months, $p = 0.251$, Figure 3f) compared with those treated with gefitinib/erlotinib.

Subgroup analyses for PFS (Figure 4a, Supplementary Table S1) and OS (Figure 4b, Supplementary Table S2) demonstrated that afatinib showed better PFS and OS than gefitinib/erlotinib in all mutation subgroups, although significance was not achieved for any subgroup due to limited cases.

Influence of TKIs and other variables on PFS

Due to the limited number of other mutations and the poor response observed for exon 20 insertions, only major uncommon mutations and compound mutations were included in the univariate and multivariate analyses. Common AEs are summarized in Supplementary Table S3. Patients treated with afatinib experienced more diarrhea, skin lesions, and paronychia than those treated with gefitinib/erlotinib. In the univariate regression, TKI type; sex; smoking status; ECOG PS; dose reduction; metastasis to the liver, bone or pleura; and clinical tumor response were individually associated with PFS.

In the multivariate regression, ECOG PS of 0–1 (vs. 2–4; adjust HR [AHR]: 0.58, 95% CI: 0.37–0.91, $p = 0.017$), no liver metastasis (AHR: 0.35, 95% CI: 0.17–0.72, $p = 0.004$), no pleural metastasis (AHR: 0.59, 95% CI: 0.40–0.89, $p = 0.011$), and dose reduction due to AEs (AHR: 0.49, 95% CI: 0.22–0.88, $p = 0.017$) were independent prognostic factors for PFS. In addition, dose reduction (AHR: 0.56, 95%: 0.29–1.09, $p = 0.088$) trended toward better PFS than no dose reduction, although this did not reach significance (Table 4).

The AEs of paronychia and skin lesions were found to be associated with PFS (Supplementary Table S4). After adjusting by potential confounding factors, including TKI type, sex, smoking status, ECOG PS, dose reduction, metastasis to the liver, bone, or pleura, the AE of paronychia (grade 1/2 vs. 0, AHR: 0.38, 95% CI: 0.22–0.66, $p < 0.001$) and the AE of skin lesions (grade 1/2 vs. 0, AHR: 0.46, 95% CI: 0.29–0.71, $p < 0.001$; grade 3 vs. 0, AHR: 0.21, 95% CI: 0.07–0.59, $p = 0.003$) were independent factors that were associated with PFS (Supplementary Table S4).

DISCUSSION

In the current study, the efficacies of EGFR-TKIs for NSCLC harboring uncommon *EGFR* mutations were retrospectively investigated. Both gefitinib/erlotinib and afatinib were active against major uncommon mutations and compound mutations, and afatinib showed numerically longer PFS and OS than gefitinib/erlotinib. Although most EGFR-TKIs were not effective for exon 20 insertions, some patients benefited from treatment with afatinib. Furthermore, no liver metastasis, no bone metastasis, no pleural metastasis, and AEs of paronychia and skin lesions were independent favorable prognostic factors for PFS in patients with major uncommon mutations and compound mutations.

The current study was compatible with a previous study examining a database of 693 cases,[14] which reported that afatinib demonstrated activity against major uncommon mutations, compound mutations, other uncommon mutations, and some exon 20 insertions. In a pooled analysis of 44 patients, the ORR of 1G EGFR-TKIs was 41% for uncommon mutations, which was similar to the ORR observed for 1G EGFR-TKIs in the current study.[20] In the current study, we aimed to compare the efficacy of different EGFI-TKIs for the treatment of uncommon mutations. Afatinib demonstrated significantly higher ORR for the treatment of major uncommon mutations and trended toward better PFS and OS in the treatment of major uncommon mutations and compound mutations. In line with a previous study by Chang et al.,[21] who reported on 177 Taiwanese patients with nonresistant uncommon mutations (T790M and exon 20 insertions were excluded), afatinib demonstrated higher ORR (60.6% vs. 35.8%, $p = 0.036$) than gefitinib/erlotinib, although no significant differences in PFS and OS were

identified by multivariate analysis.[21] Only brain metastasis was identified as an independent factor by Chang et al., whereas the current study identified more metastatic sites, including liver, bone, and pleural metastases, as independent prognostic factors. Another cohort examining 135 Korean patients who harbored uncommon *EGFR* mutations reported that afatinib was associated with nonsignificantly better PFS (15.1 vs. 7.7 months, $p = 0.165$) and significantly better OS (34.6 vs. 15.5 months, $p = 0.032$) than 1G EGFR-TKIs.

For the treatment of exon 20 insertions, afatinib showed an ORR of 26.1%, which was compatible with a previous report of afatinib in 693 uncommon mutations, which resulted in an ORR of 24.4% for treatment-naïve exon 20 mutations,[14] indicating that afatinib might benefit some patients with exon 20 mutations. Recently, more specific inhibitors were developed for the treatment of exon 20 mutations, such as mobocertinib (TAK-788)[22] and amivantamab (JNJ-372),[23] which showed better activity than afatinib, and amivantamab was recently approved by the US FDA in May 2021. However, afatinib may represent one possible option for treatment in patients with exon 20 insertions, particularly if specific inhibitors are unavailable in daily practice.

In the current study, we identified several independent prognostic factors, including dose reduction, metastasis to the liver, and pleura. Multiple metastases indicate a high tumor burden, which is associated with increased resistance to EGFR-TKIs.[24,25] Although various metastatic sites have been reported as risk factors in previous studies examining common mutations, only brain metastasis has previously been reported as a specific risk factor for uncommon mutations.[21] By contrast, the current study identified metastases to the liver and pleura as independent predictors of PFS. In addition, dose reduction was previously reported as a prognostic factor for PFS in patients with NSCLC harboring common mutations,[26] but this is the first report of it being a prognostic factor for uncommon mutations. Although skin rash AEs were reported to be a prognostic factor for PFS in NSCLC associated with common mutation,[27] no such reports have previously been reported for uncommon mutations. In addition, an association between paronychia and survival has not been specifically mentioned in previous studies[28]; therefore, this study may be the first report to identify the severity of paronychia to be associated with PFS, particularly in patients with uncommon mutations.

As a retrospective study, bias is an inevitable risk of the current study. Some patients were lost to follow-up, resulting in missing details, such as tumor response and PFS. PFS was censored if the date of progression was unknown. However, the survival data can be obtained accurately from the cancer registration system in Taiwan. As a result, median PFS and OS were close or the same, although the case numbers were limited. In addition, the classification of uncommon mutations is not currently formalized, particularly for the major uncommon mutations and compound (complex) mutations, which might make comparisons with other studies difficult.[14,17,21] Furthermore, although chemotherapy may show efficacy similar to that of EGFR-TKIs for patients with uncommon mutations, particularly in the exon 20 insertion, patients receiving EGFR-TKIs may gain additional benefits from TKIs compared to those undergoing chemotherapy without EGFR-TKIs. As this cohort of patients was treated with first-line EGFR-TKIs, the efficacy of chemotherapy in patients with uncommon mutations cannot be compared with these results.

In conclusion, afatinib demonstrated better activity than 1G EGFR-TKIs, although no significance was achieved due to the limited number of cases. Multiple metastases and AEs may predict treatment outcomes for major uncommon mutations and compound mutations.

AUTHOR CONTRIBUTIONS

Conceptualization, J.W.-C.C. and C.-E.W.; methodology, C.-F.C., C.-H.S.K. and P.-C.H.; formal analysis, C.-E.W. F.-Y. F. and C.-F.C.; investigation, C.-E.W., C.-F.C., C.-H.S. K. and P.-C.H.; data curation, C.-T.Y., C.-Y.H. and C.-E.W.; writing–original draft preparation, C.-Y.H. and C.-E.W.; writing–review and editing, J.W.-C.C. and C.-E.W.; validation, C.-T.Y., C.-Y.H. and C.-E.W.; supervision, J.W.-C.C. and C.-E.W. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

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