Efficacy of dacomitinib in patients with non-small cell lung cancer carrying complex *EGFR* mutations: a real-world study

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Background: Dacomitinib is a first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring common epidermal growth factor receptor (*EGFR*) mutations; however, clinical evidence of its activity on NSCLC with complex *EGFR* mutations is limited.

Methods: Patients harboring complex (common mutations co-existing with uncommon mutations), or common (comparison cohort) *EGFR* mutations, who were treated with dacomitinib, were retrospectively evaluated in the Chinese National Cancer Center and the China PLA hospital between August 2019 and August 2021.

Results: In total, 72 patients with NSCLC harboring complex (C+U group, n=18) or common (C group, n=54) *EGFR* mutations and being treated with dacomitinib were enrolled. In the C+U group, 16 cases (88.9%) harbored L858R mutations co-existing with uncommon mutations located from exon 18 to exon 25 of *EGFR* (mostly E709X), and two cases harbored exon 19 deletion co-existing with G724S or K754E. Among the 15 evaluable patients, the objective response rate (ORR) was 40% (6/15), and the disease control rate (DCR) was 73.3% (11/15). The median progression-free survival (PFS) was 7.5 months [95% confidence interval (CI), 4.4–10.6 months]. Except for the application line of dacomitinib (P=0.039), no significant statistical differences were found in other characteristics and adverse events between the two groups. The Kaplan-Meier method revealed no significant differences in PFS (P=0.889) and overall survival (OS) (P=0.703). However, the stratified analysis found worse PFS in the C+U group than that observed in the C group when receiving 1st and ≥3rd line dacomitinib treatment, while its OS was worse than that of group C when receiving ≥3rd line treatment. Furthermore, in a multivariate analysis, complex mutation status was an independent prognostic factor for OS (P=0.038) in the entire cohort.

Conclusions: This study indicated a worse response and prognosis of patients with NSCLC harboring complex *EGFR* mutations than those harboring common *EGFR* mutations when treated with dacomitinib. Further studies and data are needed to confirm this conclusion.

Keywords: Dacomitinib; non-small cell lung cancer (NSCLC); complex epidermal growth factor receptor mutations (complex EGFR mutations); efficacy

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Introduction

The most common mutations on the epidermal growth factor receptor (*EGFR*) gene in non-small cell lung cancer (NSCLC) are called "common mutations", and include exon 19 deletion (19Del) (49–72%) and L858R (28–43%) (1). They have shown a remarkable response to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) which include first-generation TKI (gefitinib, erlotinib), second generation TKI (afatinib, dacomitinib), and third-generation TKI (osimertinib), while other mutations (10–20%) on *EGFR* are called "uncommon mutations" or "rare mutations", with a significant heterogenic response to EGFR-TKIs (1-5). Some uncommon mutations, including G719X, S768I, and L861Q, are also called "major uncommon mutations" and are sensitive to different generations of TKIs, especially afatinib. In comparison, T790M and exon 20 insertion mutations are insensitive to most listed TKIs (except for osimertinib) (2,6-8). Compound mutations are defined as the coexistence of two or more *EGFR* mutations, regardless of these being common or uncommon mutations, and they are associated with poor prognosis in patients that carry them (9). With the improvement of molecular detection technologies, the proportion of the identified compound mutations has been increased significantly up to 26% (9,10). However, studies on compound mutations are limited due to the numerous permutations between common and uncommon mutations and the variety of uncommon mutation types. These studies are primarily retrospective and have divergent findings, thus leading to a lack of clinical data to confirm and help physicians make decisions for clinical practice (4,5).

As an irreversible, highly selective, second-generation EGFR-TKI, dacomitinib can inhibit signaling from all members of the human EGFR family. The ARCHER 1,050 study demonstrated significantly improved progression-free survival (PFS) [14.7 *vs.* 9.2 months, hazard ratio (HR) 0.59; 95% confidence interval (CI), 0.47–0.74; P<0.0001] of dacomitinib over gefitinib, leading to its approval as a new standard first-line treatment in patients with *EGFR*-positive NSCLC (11). In addition, a few published studies have indicated that dacomitinib has potential applications in patients harboring uncommon mutations (12,13), although no conclusive evidence has been presented thus far.

Therefore, to evaluate the efficacy of dacomitinib, we retrospectively analyzed 18 patients with NSCLC harboring complex *EGFR* mutations by focusing only on complex mutations that include a common mutation and an uncommon mutation. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1841/rc).

Methods

Patient eligibility and data collection

Patients were enrolled from the outpatient department of the Chinese PLA General Hospital and the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, and the Peking Union Medical College. Eligible patients met the following requirements: (I) cytologically or histologically confirmed diagnosis of NSCLC; (II) unresectable stage III patients who refused to receive chemoradiotherapy or stage IV patients; (III) harbored common *EGFR* mutations (19del or L858R, set as C group) or complex *EGFR* mutations (including a common mutation and an uncommon mutation, set as C+U group) excluding exon 20 insertion mutations and T790M; and (IV) tumor tissue or cell-free DNA were available from plasma, pleural effusion, or cerebrospinal fluid samples and were tested using next-generation sequencing (NGS) which was performed by qualified third-party genetic testing companies that had been accredited by the College of American Pathologists (CAP) before dacomitinib treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Boards of the Chinese PLA General Hospital and the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital (No. 18-070 and 1648). The Research Ethics Boards waived the need for informed consent as this was a retrospective study.

Treatment and efficacy/toxicity evaluation

All patients were treated with dacomitinib alone in a multi-line setting. The physician determined the starting dose based on the patient's condition. In general, the starting dose was 45 mg for patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 and weight ≥60 kg; 30 mg for patients with a PS of 1 and weight ≤60 kg; 30 mg for patients with a PS of 1 and weight ≥60 kg, with an increase to 45 mg if the patient had a good tolerance; and 15 mg for patients with PS ≥2. Imaging

evaluation included chest computed tomography (CT) scans and brain magnetic resonance imaging (MRI), performed every 1–2 months after drug administration. Objective tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines (14). The objective response was divided into two categories: complete response (CR) and partial response (PR), while disease control included CR, PR, and stable disease (SD) combined. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

Categorical variables were reported as numbers and percentages. The chi-square test was used for comparison between different groups. The data cut-off date was September 21, 2021, when the disease status of the patients was confirmed. PFS was defined as the time from dacomitinib administration to disease progression or death from any cause. Overall survival (OS) was defined as the time from dacomitinib administration to death from any cause. Patients who were lost to follow-up were judged to be censored and the last determinable time of survival was used as the time of termination of follow-up. The relationship between various variables and survival was evaluated using the Kaplan-Meier method. Differences between survival curves were tested for statistical significance using log-rank tests. To reduce the effect of confounding factors, stratified analyses of clinical characteristics that differed significantly between the two groups were conducted. Significant prognostic predictors for patients identified by univariate analyses were further assessed by multivariate analyses using the Cox proportional hazards regression model. Statistical analyses were performed, and analytic graphs were created using GraphPad Prism 8 software (GraphPad Software, San Diego, CA, USA). An α value of 0.05 was used as the examination standard.

Results

Baseline characteristics

In total, 72 patients with NSCLC harboring complex *EGFR* mutations (C+U group, n=18) or common *EGFR* mutations (C group, n=54), who were treated with dacomitinib, were enrolled in two medical centers between August 2019 and August 2021. The baseline characteristics of the two

cohorts are displayed in *Table 1*. For the C+U group, there were 12 women (66.7%) and 6 men (33.3%), with a median age of 68 years (range, 50–81 years). More than 70% of the patients were non-smokers, and adenocarcinoma was the histologic type detected in all patients. More than half of the patients (55.6%, 10/18) received dacomitinib as the first-line treatment, and nearly 70% of patients received it at a dosage of 30 mg. The L858R was the most frequent mutation (88.9%, 16/18) in complex *EGFR* mutations (*Table 1*). The ECOG PS of the 18 patients ranged from 0 to 2, and most patients (77.8%, 14/18) had PS ≤1. Except for the application line of dacomitinib, no significant statistical differences between the C and C+U groups were found in other characteristics, including age, sex, smoking history, histology, disease stage, and common mutation status (*Table 1*). More patients in the C+U group received dacomitinib as the first-line treatment than those in the C group (55.6% *vs.* 25.9%, P=0.039).

Genetic profiling

Tumor tissue or cell-free DNA from plasma, pleural effusion, or cerebrospinal fluid samples before dacomitinib treatment were tested using the NGS method in all patients. *Figure 1* shows the three-dimensional distribution of uncommon mutations in complex mutations and the corresponding number of cases of the C+U group. *Figure 2* shows the details of uncommon mutations, common mutations, and accompanying mutations. Sixteen patients (88.9%) harbored L858R co-existing with rare mutations located in exon 18 to exon 25 of *EGFR* (mostly E709X in exon 18), and two harbored 19del co-existing with G724S or K754E. The most common concomitant mutations were detected in *TP53* (tumor protein p53), *CDK4/6* (cyclin-dependent kinase 4/6), and *STK11* (serine/threonine kinase 11) genes (*Figure 2*). In the C group, the most common mutation was also L858R (75.9%, 41/54), and the most common accompanying mutations were *TP53*, *PI3KCA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) point mutations, *MET* (MET proto-oncogene, receptor tyrosine kinase), and *EGFR* amplification (Figure S1).

Efficacy/toxicity evaluation

Among the 15 evaluable patients (3 patients could not be evaluated due to lack of target lesions) in the C+U group, 6 (40%), 5 (33.3%) and 4 (26.7%) had PR, SD, and *de novo*

Table 1 Baseline characteristics

Characteristics	C group (n=54)	C+U group (n=18)	P value#
Age (years), n (%)			0.586
≤60	28 (51.9)	8 (44.4)	
>60	26 (48.1)	10 (55.6)	
Gender, n (%)			0.219
Female	27 (50.0)	12 (66.7)	
Male	27 (50.0)	6 (33.3)	
Smoking history, n (%)			0.248
Yes	20 (37.0)	4 (22.2)	
No	34 (63.0)	14 (77.8)	
Histology, n (%)			1.000
AC	52 (96.3)	18 (100)	
Others	2 (3.7)	0 (0)	
Disease stage, n (%)			0.942
III	3 (5.6)	1 (5.6)	
IV	41 (75.9)	13 (72.2)	
Recurrence	10 (18.5)	4 (22.2)	
Common *EGFR* mutation status, n (%)			0.402
19del	13 (24.1)	2 (11.1)	
L858R	41 (75.9)	16 (88.9)	
Brain metastases, n (%)			0.584
Yes	25 (46.3)	7 (38.9)	
No	29 (53.7)	11 (61.1)	
Tumor burden, n (%)			0.715
≥3 metastatic organs	8 (14.8)	4 (22.2)	
<3 metastatic organs	46 (85.2)	14 (77.8)	
Therapies given prior to dacomitinib			<0.001
None	14 (25.9)	10 (55.6)	
Targeted therapy only	17 (31.5)	6 (33.3)	
Chemotherapy only	0 (0)	2 (11.1)	
Targeted therapy/chemotherapy	23 (42.6)	0 (0)	
Dacomitinib application line, n (%)			0.039
1	14 (25.9)	10 (55.6)	
2	11 (20.4)	4 (22.2)	
≥3	29 (53.7)	4 (22.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	C group (n=54)	C+U group (n=18)	P value[#]
Dacomitinib dosage, n (%)*			0.797
15 mg	9 (16.7)	3 (16.7)	
30 mg	29 (53.7)	12 (66.7)	
45 mg	16 (29.6)	3 (16.7)	
ECOG PS, n (%)*			0.304
0	9 (16.7)	5 (27.8)	
1	40 (74.1)	9 (50.0)	
≥2	5 (9.3)	4 (22.2)	

*, percentages might add up to more than 100% due to rounding; [#], the chi-square test was used for the comparison. C group, common mutations group; C+U group, common mutations combined with uncommon mutations group; AC, adenocarcinoma; others, including adenosquamous carcinoma and squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status.
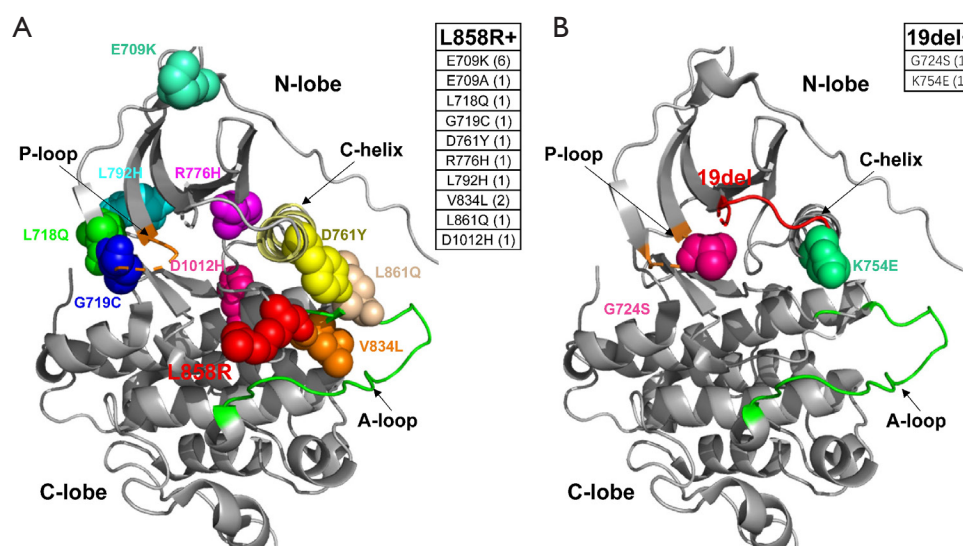
Figure 1 Three-dimensional distribution of uncommon mutations in the C+U group and corresponding number of cases (n=18). We labeled all the uncommon mutation sites co-existing with L858R (A) or 19del (B) carried by the patients in the C+U group in the spatial structure of epidermal growth factor receptor-kinase domain (PDB:4I23). The graph was remodeled in PyMOL software. C+U, common mutations combined with uncommon mutations.

resistance to dacomitinib with PD as the best response, respectively. The objective response rate (ORR) was 40% (6/15) and the disease control rate (DCR) was 73.3% (11/15) (*Figure 2A*). At the data cut-off date, the median PFS (mPFS) was 7.5 months (95% CI, 4.4–10.6 months), and the median follow-up duration was 8.6 months (95% CI, 3.4–13.8 months) in the C+U group. The PFS was mature in 11 (61.1%) patients, and the tumors of seven

patients were still under control (*Figure 2B*). In contrast, among the 48 evaluable patients (6 patients could not be evaluated due to lack of target lesions) in the C group, the ORR was 33.3% (16/48), and the DCR was 77.1% (37/48) (Figure S1). At the data cut-off date, the mPFS was 6.1 months (95% CI, 4.3–7.9 months), and the median follow-up duration was 10.5 months (95% CI, 8.1–12.9 months) in the C group. However, there were no significant
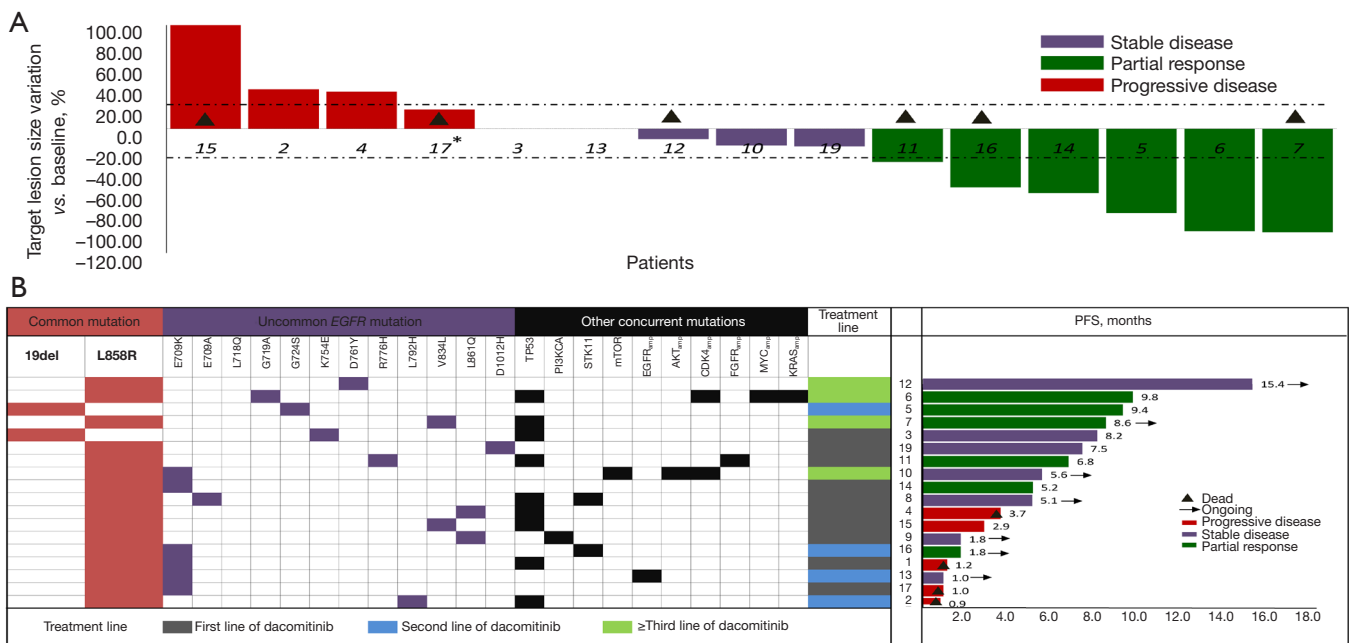
Figure 2 Best change in total target lesion size, genetic profile, and progression-free survival in the C+U group by patient (n=15). (A) Treatment responses of dacomitinib in 15 evaluable patients are shown in the waterfall plot. Patients with brain metastases are marked with black triangles. *, this patient also received whole brain radiotherapy. Dashed lines represent 20% progression (progressive disease) and 30% tumor regression (partial response). (B) The genetic profile (left panel) and progression-free survival (right panel) in the C+U group by patient (n=18) were displayed. The case numbers in *Figure 1* and *Figure 2* correspond to each other. C+U, common mutations combined with uncommon mutations. amp, amplication; PFS, progression-free survival.

differences in ORR (P=0.636) (*Figure 3*), DCR (P=0.765) (*Figure 3*), PFS (P=0.889) (*Figure 4*), and OS (P=0.703) (*Figure 4*) between the C and C+U groups.

All patients had grade 1–2 adverse effects (AEs), but no grade 4–5 treatment-emergent AEs occurred. No significant differences were found in grade 1–3 AEs between the C and C+U groups (*Table 2*). In the C+U group, only one patient required a dosage reduction from 45 to 15 mg due to intolerable grade 3 rash, and one patient had a dosage increase from 30 to 45 mg due to good tolerance. In the C group, 2 patients required a dosage reduction from 45 to 15 mg due to intolerable grade 3 diarrhea or rash, and 3 patients had a dosage increase from 30 to 45 mg due to good tolerance.

Survival analysis

Stratified analyses
Given the significant differences of baseline characteristics in the application line of dacomitinib between the C and C+U groups, we conducted stratified analyses on ORR,

DCR, PFS, and OS based on different application lines. The total ORR (33.3% *vs.* 40.0%, P=0.636) and the DCR (77.1% *vs.* 73.3%, P=0.089) of the C group were not significantly different compared with those of the C+U group (*Figure 3*). However, stratified results showed that the ORR gradually decreased as the application line moved back. The C+U group showed a worse treatment response than the C group in all application line subgroups (*Figure 3A*), although the difference was not statistically significant. Patients in the C+U group receiving third-line dacomitinib had a significantly lower DCR than those in the C group (P=0.040) (*Figure 3B*). In the survival analysis, both the PFS (P=0.889) (*Figure 4A*) and OS (P=0.703) (*Figure 4B*) of the C group were not significantly different compared with those of the C+U group. However, stratified analyses demonstrated that the PFS of the C+U group was worse than that of the C group when receiving first-line (P=0.047) (*Figure 4*) or ≥ third-line (P=0.018) (*Figure 4*) dacomitinib treatment, and the OS of the C+U group was worse than that of the C group when receiving ≥ third-line treatment (P=0.003) (*Figure 4*).
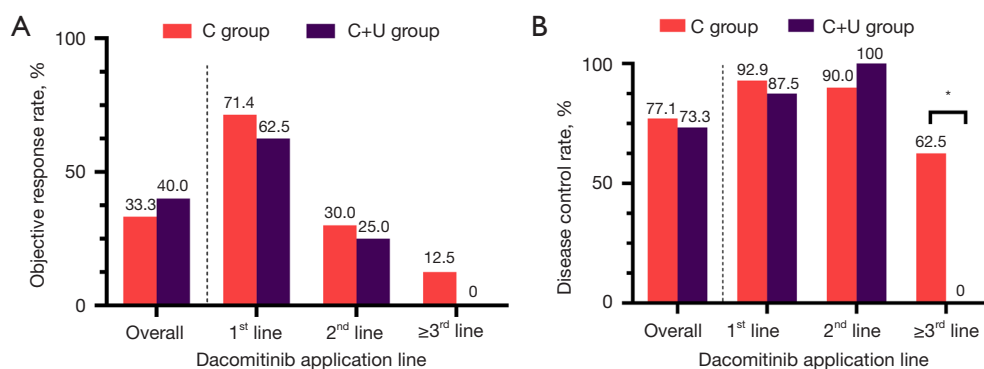
Figure 3 Stratified analyses of objective response rate and disease control rate of the whole cohort (n=72). The objective response rate (P=0.636) as well as disease control rate (P=0.089) of the C group was not significantly different compared with the C+U group. However, the C+U group showed a worse treatment response than the C group in all application line subgroups (A), although the differences were not statistically significant. Patients in the C+U group receiving third-line dacomitinib had a significantly lower disease control rate than those in the C group (P=0.040) (B). *, this indicates a statistically significant difference between the two groups. Comparisons between the two groups were made using the chi-square test. C+U, common mutations combined with uncommon mutations.

Univariate and multivariate analyses

To determine the effect of the compound mutation status on prognosis, we conducted univariate and multivariate analyses (*Table 3*) for the whole cohort (C group plus C+U group). In the univariate analysis, age (P=0.037), smoking status (P=0.033), total tumor burden (P=0.011), and administration of dacomitinib (P<0.001) were all statistically significant prognostic factors for PFS, while only the application line of dacomitinib (P<0.001) was a statistically significant prognostic factor for OS. In the multivariate analysis, smoking status (HR =2.541, 95% CI: 1.069–6.040; P=0.035), brain metastases (HR =0.467, 95% CI: 0.232–0.946; P=0.035), and application line of dacomitinib (HR =5.049, 95% CI: 1.694–15.050; P=0.004) were independent predictors of PFS, whereas only smoking status (HR =5.971, 95% CI: 1.118–31.888; P=0.037) and compound mutation status (HR =5.405, 95% CI: 1.096–26.316; P=0.038) were independent predictors of OS (*Table 3*).

Discussion

According to previous studies, the incidence of complex *EGFR* mutations can be as high as 26%, which may be attributed to the progressive improvements in detection technology (4,9,10). Based on the combination mode and the incidence of different types of uncommon mutations, complex *EGFR* mutations can be roughly divided into the following four main types: (I) a combination of uncommon and common mutations (such as E709K + L858R) (C+U

group in our study), (II) double major uncommon mutations (such as G719X + S768I), (III) major uncommon mutations combined with non-major uncommon mutations (such as G719X + R108K), and (IV) double common mutations (such as 19del + L858R) (1,3,15-18). In our study, we focused on the first type of complex *EGFR* mutations. To the best of our knowledge, there are only a few reports on the efficacy of dacomitinib on treating complex *EGFR* mutations, and the influence of complex mutations on prognosis remains elusive. Our study revealed that patients with NSCLC harboring uncommon mutations combined with common mutations (C+U group) were less responsive to treatment with dacomitinib than those harboring common mutations (C group).

Currently, EGFR-TKIs have the best therapeutic outcomes for common mutations, with the outcomes for uncommon mutations being generally inferior to common mutations (19,20), except for some sensitive major uncommon mutations (including G719X, L861Q, and S768I) (21). Compound mutations imply the presence of heterogeneous clones (both primary and secondary) within the tumor and heterogeneity in the therapeutic response. It is taken for granted that the primary clone determines the outcome of treatment, but according to previous studies (22,23), the treatment response does not depend exclusively on the primary clone but mainly on the concomitant mutations (secondary clone). When a common or major uncommon mutation is combined with a sensitive uncommon mutation (such as L858R + G719C, G719C +
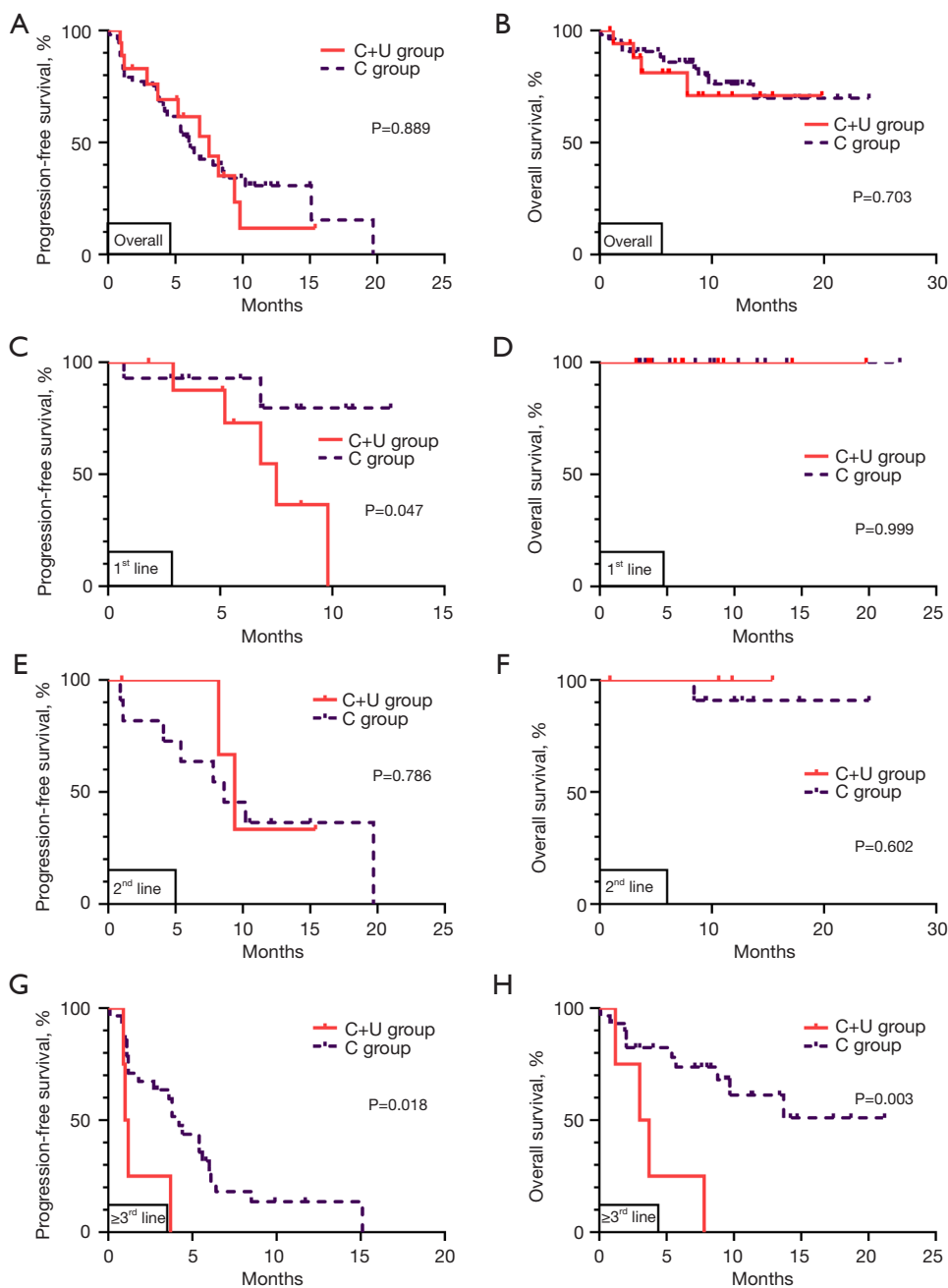
Figure 4 Stratified analyses of progression-free survival and overall survival of the whole cohort (n=72). In the survival analysis, the progression-free survival (P=0.889) (A) as well as OS (P=0.703) (B) of the C group was not significantly different compared with the C+U group. However, the progression-free survival of the C+U group was worse than that of the C group when receiving 1st (P=0.047) (C) or ≥3rd (P=0.018) (G) line dacomitinib treatment, and the OS of the C+U group was worse than that of group C when receiving ≥3rd line treatment (P=0.003) (H). C+U, common mutations combined with uncommon mutations; OS, overall survival.

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Table 2 Treatment-emergent AEs (n=72)

AEs	G1			G2			G3		
	C group	C+U group	P value[#]	C group	C+U group	P value[#]	C group	C+U group	P value[#]
Diarrhea	23 (42.6%)	11 (61.1%)	0.831	7 (13.0%)	4 (22.2%)	0.668	1 (1.9%)	0	0.736
Rash	22 (40.7%)	7 (38.9%)		11 (20.4%)	5 (27.8%)		4 (7.4%)	2 (11.1%)	
Oral mucositis	15 (27.8%)	4 (22.2%)		7 (13.0%)	2 (11.1%)		1 (1.9%)	1 (5.6%)	
Dry skin	12 (22.2%)	4 (22.2%)		4 (7.4%)	3 (16.7%)		0	0	
Paronychia	9 (16.7%)	5 (27.8%)		11 (20.4%)	2 (11.1%)		1 (1.9%)	0	

Data are n (%). There were no grade 4–5 treatment-emergent AEs. [#], the chi-square test was employed for the comparative analysis. AEs, adverse events; C group, common mutations group; C+U group, common mutations combined with uncommon mutations group.

S768I), the therapeutic effect is not necessarily affected (19). However, when it is combined with a resistant uncommon mutation (such as L858R + Q787R, L858R + H870R, and G719C + E709K), the therapeutic effect is generally diminished (22).

Keam *et al.* (19) found no significant difference in ORR (74.8% *vs.* 68.8%) and mPFS (11.9 *vs.* 8.1 months) between the common mutations group (n=16) and the group of combined uncommon and common mutations (n=16) who received either gefitinib or erlotinib. However, Hata *et al.* (24) revealed that patients who mainly received gefitinib harboring 19del and L858R had a better ORR (86%, 6/7) than those that carried uncommon mutations combined with common mutations (40%, 2/5). No statistical significance was detected (P=0.222), although the mPFS was longer in the former group (16.5 *vs.* 3.8 months) (P=0.046). By comparing NSCLC patients harboring common *EGFR* mutations (n=97), Tan *et al.* (3) revealed that treatment outcomes of patients harboring uncommon mutations combined with common mutations (n=52, similar to the first complex mutations type defined in our study), complex uncommon mutations (n=22, as the combination of the second and third complex mutations types defined in our study), and uncommon mutations treated with first-line gefitinib/erlotinib/icotinib or afatinib were significantly different (ORR: 76.3%, 61.5%, 54.5%, and 50.0%, P=0.023; mPFS: 13.3, 14.7, 8.1, and 6.0 months, P=0.004). We speculate that these conflicting results may arise from the study size and treatment context (e.g., number of lines treated) in the different studies.

In our study, contrary to the results of Tan *et al.* (3), patients in the C group harboring 19del or L858R had a better ORR (71.4%, 10/14) than those in the C+U group (62.5%, 5/8), although not statistically significant (P=0.665).

In addition, the mPFS was also longer in the C group (not reached *vs.* 7.5 months; P=0.047). This suggests that the treatment disadvantages caused by uncommon mutations in the C+U group cannot be reversed by second-generation TKI dacomitinib. Besides, an *in vitro* study by Nishino *et al.* showed that, several uncommon *EGFR* mutations (including L718Q, L718V, L792H, and L792F) combined with L858R could lead to various responses when dacomitinib were administrated on Ba/F3 cells, and most combinations had worse responses than the single L858R did (25). Nevertheless, previous studies suggested that the second-generation TKI, afatinib, showed superior efficacy over gefitinib/erlotinib/icotinib in patients harboring uncommon mutations combined with common mutations (ORR: 100% *vs.* 54.5%, P=0.017; mPFS: not reached *vs.* 13.6 months, P=0.032) (1,3,17). Another point we should mention is that, in addition to second-generation TKI, limited evidence showed that the third-generation TKI osimertinib also had promising efficacy for *EGFR* uncommon mutations (2). However, the efficacy of osimertinib for compound *EGFR* mutations warrants more data to confirm.

Recently, several studies have shown that dacomitinib is potentially effective in *EGFR*-positive NSCLC with central nervous system metastasis, with the ORR ranging from 87.5–92.9% and DCR of 100% (26-29). Peng *et al.* demonstrated that a patient with brain metastases harboring G719A achieved an objective response, indicating a potential therapeutic effect in NSCLC patients harboring uncommon mutations with brain metastases (26). It is worth mentioning that, in our study, we did not observe any significant differences in the ORR (40% *vs.* 42.9%, P=0.893), DCR (90% *vs.* 71.4%, P=0.234), or mPFS (10.2 *vs.* 6.8 months, P=0.721) in NSCLC patients with brain metastases between the C and C+U groups. This shows

Table 3 Univariate and multivariate analyses of PFS and OS in the whole cohort (n=72)

| Variables | n | Univariate analysis* | | | | Multivariate analysis# | | | | | |
| | | PFS (months) | | OS (months) | | PFS (months) | | | OS (months) | | |
		Median	P value	Average	P value	HR	95% CI	P value	HR	95% CI	P value
Complex mutation status											
C group/C+U group	54/18	7.5/6.1	0.889	18.8/15.3	0.702				5.405	1.096–26.316	0.038
Age											
≤60/>60 years	36/36	8.2/5.4	0.037	20.8/14.4	0.152						
Gender											
Male/female	33/39	6.0/7.5	0.230	19.2/15.5	0.927						
Smoking											
No/yes	48/24	7.5/5.4	0.033	20.2/14.9	0.076	2.541	1.069–6.040	0.035	5.971	1.118–31.888	0.037
ECOG PS											
0–1/2–4	63/9	6.8/6.0	0.118	19.2/9.8	0.144						
Disease stage											
III+IV/recurrence	58/14	6.0/9.8	0.121	18.5/16.9	0.460						
Tumor burden											
<3/≥3 metastatic organs	60/12	7.5/3.7	0.011	19.4/9.9	0.142						
EGFR mutation subtypes											
19del/L858R	15/57	6.4/6.8	0.412	19.5/17.4	0.850						
Brain metastases						2.141	1.057–4.329	0.035			
No/yes	40/32	8.5/5.6	0.206	17.8/17.8	0.459						
Initial dosage of dacomitinib			0.719		0.906						
15 mg	12	4.2		13.9							
30 mg	44	7.5		19.2							
45 mg	16	6.1		18.0							
Treatment line of dacomitinib			<0.001		<0.001			0.004			
1st line	24	9.8		11.3		–	–	–			
2nd line	15	9.4		12.5		1.336	0.427–4.182	0.618			
≥3rd line	33	3.8		10.7		5.049	1.694–15.050	0.004			

All variables were included in the multivariate analysis, but only statistically significant results were demonstrated. Set variables before the "/" as reference. *, the log-rank test was employed for the comparative analysis. #, the cox's proportional hazards regression model was used to analyze the influencing factors of PFS and OS. C group, common mutations group; C+U group, common mutations combined with uncommon mutations group; PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status.

that dacomitinib still has a good intracranial control ability in a population harboring a combination of common and uncommon mutations. To our knowledge, this is the first study to report the benefits of dacomitinib in this subset of patients.

An interesting finding in our study is that in the C+U group, the proportion of L858R is significantly higher than that of 19del. In fact, the previous study conducted by Hong *et al.* suggested that, compared with patients with 19del, those with L858R were more likely to incorporate other concomitant mutations and had worse survival (30). Wu *et al.* (1) reported that L858R was the predominant subtype contained in the complex EGFR mutation, which could possibly explain the phenomenon in our study. Besides, the *TP53* mutation rate was 18.5% as we calculated in the C group, which was indeed relatively lower than that reported by other scholars (~ more than 30%) (31), we thought that this may contributed to the heterogeneity of the gene testing panels and the relatively small number of the study population.

The wide application of highly sensitive NGS technology and the liquid-based mutation detection analysis in clinical practice can identify a broader spectrum of uncommon *EGFR* mutations. Determining the precise treatment based on these mutations is the next challenge we must embrace.

A limitation of this study is the small sample size of the C+U group, which may make the comparison with the C group not strongly convincing. Second, as this is not a multi-center study, selection bias cannot be avoided. Therefore, our data should be interpreted with caution. Furthermore, the resistance mechanisms of dacomitinib have not been investigated thus far.

In conclusion, through limited cases, this real-world study revealed a worse response and prognosis of patients with NSCLC harboring complex *EGFR* mutations than those harboring common *EGFR* mutations when treated with dacomitinib. Nevertheless, according to the limited available evidence and our study results, second-generation *EGFR*-TKI dacomitinib is optional for this subset of patients, especially for those with brain metastases.

Acknowledgments

Footnote

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