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Clinical outcomes of EGFR-TKIs in advanced squamous cell lung cancer

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We aimed to explore the treatment efficacy of first-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for lung squamous cell carcinoma (SCC) patients and identify potential beneficial subgroups of EGFR-mutated lung SCC patients in this study. Between February 1st, 2013 and December 1st, 2021, 657 advanced lung SCC patients were enrolled at Zhejiang Cancer Hospital. Amplification refractory mutation system PCR or next-generation sequencing were used to detect gene abnormality. Clinicopathological features were analyzed by chi-square test and the clinical results of lung SCC patients who received first-generation EGFR-TKI were analyzed by the Kaplan-Meier method. Lung SCC patients harboring EGFR mutation accounted for 11.0% in this study. Of 657 lung SCC patients, the median PFS and OS of 116 patients who received targeted therapy were 3.6 months and 16.2 months, patients treated with targeted therapy had similar OS to patients without targeted therapy (p=0.839). Of 110 lung SCC patients who received first-generation EGFR-TKI, EGFR-mutated patients had long PFS (p=0.000) but similar OS (p=0.472) than patients with EGFR wide type. EGFR-mutated SCC patients who received first-generation EGFR-TKI as a first-line benefit are equal to patients who received first-generation EGFR-TKI as the second line or beyond according to similar PFS (p=0.311) and OS (p=0.721) between them. In addition, there was also no significant difference in PFS (p=0.376) and OS (p=0.205) between patients with exon 19 deletion and L858R point mutation. Lung SCC patients harboring EGFR mutation received first-generation EGFR-TKI had better clinical survival than patients with EGFR wide type.

Key words: epidermal growth factor receptor, exon 19 deletion, L858R mutation, lung squamous cell cancer

Lung cancer is a major cause of death worldwide, especially in developing countries like China [1]. Lung squamous cell carcinoma (SCC) accounts for 30% of lung cancer and is associated with smoking [2, 3]. Epidermal growth factor receptor (EGFR) is the most common gene involved in lung adenocarcinomas, which is relatively uncommon in lung SCCs, and the prevalence of EGFR mutations in SCC patients has been reported to be about 1–5% [4, 5].

Improvements in the treatment of lung SCCs have been slower when compared with that for lung adenocarcinomas. Platinum-doublet chemotherapy is presently the standard first-line choice, with a modest clinical efficacy for advanced lung SCC patients [6]. Immunotherapy alone or combined with chemotherapy, depending on the expression level of programmed death 1, can also be a treatment for lung SCC patients [7–10]. The second-line treatments include docetaxel monotherapy, immune checkpoint inhibitors, and chemotherapy, combined with anti-angiogenic therapy [10, 11]. With the development of targeted therapy, several clinical trials and retrospective analyses have recently reported the efficacies of EGFR-tyrosine kinase inhibitors (TKIs) for the treatment of lung SCC patients. The phase III BR.21 trial recruited 222 lung SCC patients and showed that erlotinib had a more favorable progression-free survival (PFS) and overall survival (OS) than the placebo. However, no clinical data were reported for 42 Asian patients in this trial [12, 13]. Song et al. enrolled 102 lung SCC patients, who received gefitinib or erlotinib, and found that the median PFS was 1.93 months, and four patients with EGFR mutations had a longer PFS than patients with wild-type EGFR, who had a median PFS of 8.0 months [14]. The phase III LUX-Lung 8 trial enrolled 67 Chinese lung SCC patients, to determine the treatment efficacy of an EGFR-TKI, which showed that the median PFS and OS of patients treated with erlotinib

were 1.9 and 6.8 months, respectively [12–16]. However, the sample size of this study was inadequate, so the clinical efficacy of first-generation EGFR-TKIs for lung SCC patients still remains unclear, and therefore requires large-scale cohorts for validation.

In the present study, we retrospectively enrolled advanced lung SCC patients receiving targeted and non-targeted therapies, and also enrolled lung SCC patients with EGFR mutations or wild-type EGFR. We aimed to determine the clinical outcomes of first-generation EGFR-TKIs for lung SCC patients, and to identify potential beneficial subgroups of lung SCC patients harboring EGFR mutations. To the best of our knowledge, this was the largest sample size of lung SCC patients receiving first-generation EGFR-TKIs.

Patients and methods

Patients. From February 2013 to December 2021, we retrospectively enrolled 657 stage III/IV lung SCC patients at the Zhejiang Cancer Hospital, with 72 being mutated EGFR lung SCC patients. Of the 657 lung SCC patients, we divided them into two groups: the targeted therapy group (116/657) and the non-targeted therapy group (541/657). All patients were followed-up with computed tomography, and the responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) [17]. This study adhered to the ethical standards of Zhejiang Cancer Hospital (IRB-2022-64) and the Declaration of Helsinki, and written informed consent was waived due to the retrospective nature of the study.

Gene mutations. All patients in this study were confirmed as SCC using a histopathological examination. Gene abnormalities, including wild-type EGFR, deletion of exon 19, the L858R mutation, the G719X mutation, and other gene mutations, were analyzed by amplification refractory mutation system PCR (ARMS-PCR) and next-generation sequencing (NGS) before treatment with EGFR-TKIs. EGFR was genotyped by ARMS-PCR method with the AmoyDx Human EGFR Gene 29 Mutations Detection kit with fluorescence polymerase chain reaction (PCR) (Amoy Diagnostics, Xiamen, China), and the primers used to verify the EGFR mutation in ARMS-PCR are described in Supplementary Table S1. NGS was used to detect gene abnormalities, which was in accordance with the College of American Pathologists (CAP) guidelines [18, 19].

Statistical analysis. Patient clinicopathological differences between wild-type EGFR and mutated EGFR were identified using the χ^2 test. The endpoints of this study were the objective response rate (ORR), PFS, and OS. ORR was defined as the sum of the complete response (CR) and partial response (PR). PFS was defined as the period from the start of EGFR-TKI treatment to disease progression. OS was defined as the time from the initial diagnosis to the last follow-up or death from any cause. PFS and OS were analyzed using the Kaplan-Meier method. All analyses were conducted using Prism 8.0 software for Windows (GraphPad, San Diego, CA, USA). The Cox proportional hazards model was used to identify independent parameters, which affected the PFS and OS. A two-sided value of $p<0.05$ was regarded as statistically significant. The last follow-up time was December 1, 2021, and the median follow-up time was 12.4 months (range: 1.0–79.6 months).

Results

Patient characteristics. A total of 657 advanced lung SCC patients were enrolled in this study, with 72 harboring EGFR mutations, which accounted for 11.0% of the advanced lung SCC patients. Of the 657 lung SCC patients, 541 patients were treated with non-targeted therapy and 116 patients were treated with targeted therapy. Of the 116 patients with targeted therapy, 52 involved EGFR sensitive mutation patients, 57 involved wild-type EGFR, and seven patients harbored other gene abnormalities. In addition, only 110 patients were treated with first-generation EGFR-TKIs, which included 55 patients with wild-type EGFR, 51 patients with sensitive EGFR mutations, and four patients with other gene mutations. The details of these patients are listed in Table 1.

Of the 106 mutated EGFR or wild-type EGFR lung SCC patients treated with first-generation EGFR-TKIs, the median age was 61 years (range: 28–83 years). We next compared the characteristic differences between them and found that

Table 1. The 657 advanced lung SCC patients in this study.

Total	Targeted therapy 116	Non-targeted therapy 541
Gene examination	116	541
ARMS-PCR	62	520
NGS	54	21
EGFR sensitive mutation	52	15
19 deletion	29	6
L858R mutation	23	9
Other gene abnormality	7	12
G719X mutation	2	1
S768I mutation	1	0
PIK3CA mutation	1	2
HER2 mutation	1	0
MET mutation	1	0
Exon 20 insertion	1	0
ALK fusion	0	3
RET fusion	0	1
ROS-1 fusion	0	2
TP53 mutation	0	3
Gene wild type	57	514
Gefitinib	7	0
Erlotinib	2	0
Icotinib	101	0
Afatinib	5	0
Osimertinib	1	0

Abbreviations: SCC-squamous cell carcinoma; EGFR-epidermal growth factor receptor; EGFR-TKI-epidermal growth factor receptor tyrosine kinase inhibitor; ARMS-PCR-Amplification refractory mutation system PCR; NGS-next-generation sequencing

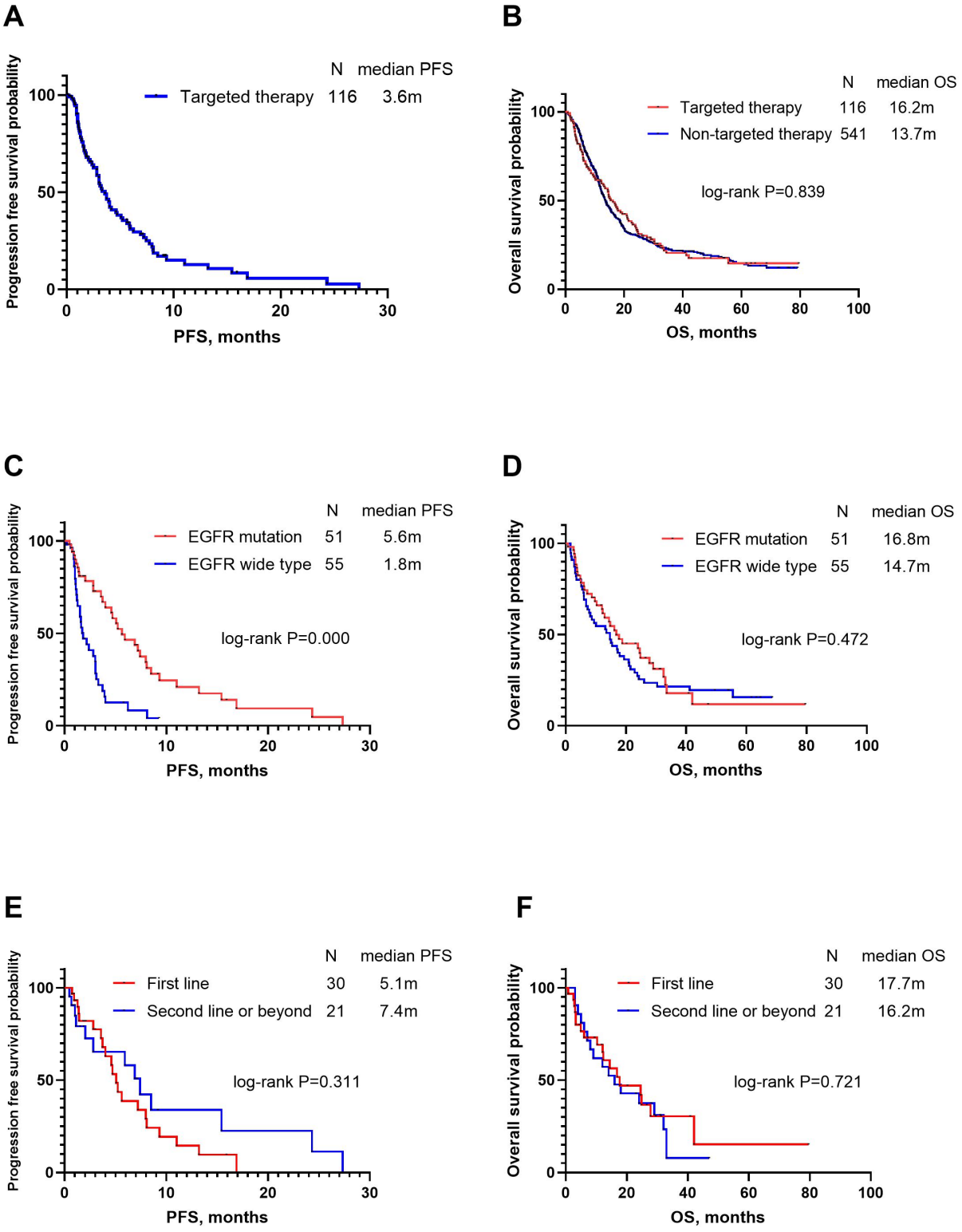

Figure 1. A) The progression-free survival (PFS) of lung squamous cell carcinoma (SCC) patients receiving targeted therapy. B) Survival difference in the overall survival (OS) between lung SCC patients with targeted therapy and non-targeted therapy. C) Survival difference in the PFS between epidermal growth factor receptor (EGFR)-mutated patients and wild-type EGFR patients. D) Survival difference in the OS between mutant EGFR patients and wild-type EGFR patients. E) Survival difference in the PFS between mutant EGFR patients receiving EGFR-TKIs using different-line treatments. F) Survival difference in the OS between mutated EGFR patients receiving EGFR-TKIs as different-line treatments.

lung SCC patients harboring EGFR mutations were more common in males, non-smoking patients, and brain metastasis patients. The patient details are listed in Table 2.

Efficacy. Of the 657 lung SCC patients, 541 were treated with non-targeted therapy, and 116 were treated with targeted therapy. The median PFS and OS of 116 patients receiving targeted therapy were 3.6 months [95% confidence interval (CI): 2.85–4.29) (Figure 1A) and 16.2 months (95% CI: 13.40–19.00, respectively)]. The median OS of 541 non-targeted therapy patients was 13.7 months (95% CI: 12.40–15.00). We next compared the survival difference in OS between patients with non-targeted and targeted therapies and found that targeted therapy patients had a similar OS as non-targeted therapy patients (p=0.839, Figure 1B).

Of the 116 patients receiving targeted therapy, only 110 patients were treated with first-generation EGFR-TKIs (including gefitinib, erlotinib, and icotinib). The best ORR was PR in this study. The ORR, median PFS, and OS of 110 patients were 7.3%, 3.3 months (95% CI: 2.43–4.17), and 15.4 months (95% CI: 11.75–19.05), respectively. We divided 110 patients into two groups: the wild-type EGFR group (55/110) and the EGFR mutation group (51/110), with the remaining patients having other gene mutations (4/110). The ORR, median PFS, and OS of wild-type EGFR patients were 3.6%, 1.8 months (95% CI: 1.04–2.57), and 14.7 months (95% CI: 8.47–20.86), respectively. The median ORR, PFS, and OS of EGFR mutation patients were 11.8%, 5.6 months (95% CI: 3.09–8.17), and 16.8 months (95% CI: 7.29–26.24), respectively. Mutated EGFR patients had a longer PFS than wild-type EGFR patients (p=0.000, Figure 1C), and the difference in OS between them was not significant (p=0.472, Figure 1D).

Of the 51 mutated EGFR lung SCC patients receiving first-generation EGFR-TKIs, the ORR, median PFS, and OS of patients (30/51) receiving EGFR-TKIs as first-line treatments were 6.7%, 5.1 months (95% CI: 4.15–5.98), and 17.7 months (95% CI: 4.01–31.39), respectively. The ORR, median PFS, and OS of EGFR-mutated lung SCC patients (21/51) receiving EGFR-TKIs as second-line treatment or beyond were 9.5%, 7.4 months (95% CI: 4.96–9.91), and 16.2 months (95% CI: 7.38–25.02). There was no significant difference between them in PFS (p=0.311, Figure 1E) and OS (p=0.721, Figure 1F).

Of the 51 lung SCC patients harboring EGFR sensitive mutations, the ORR, median PFS, and OS of patients with 19 deletions (29/51) were 6.9%, 5.9 months (95% CI: 2.68–9.18), and 14.8 months (95% CI: 8.82–20.85), respectively. The ORR, median PFS, and OS of patients with the L858R point mutation (22/51) were 18.2%, 5.6 months (95%CI: 0.13–11.14), and 24.6 months (95% CI: 16.70–32.44), respectively. There was no significant difference between them in PFS (p=0.376) and OS (p=0.205, Table 3).

Independent factors affecting the PFS and OS. The outcomes of univariate and multivariate analyses for PFS and OS of 106 mutated EGFR or wild-type EGFR lung SCC patients treated with first-generation EGFR-TKIs are shown in Tables 4 and 5. We found that the EGFR mutation types affected the PFS, and patients with EGFR mutations had a longer PFS than patients with wild-type EGFR (hazard ratio (HR), 0.345; 95% CI: 0.203–2.432; p=0.000; Figure 2A). The factors affecting the OS using univariate analysis included liver metastasis, and patients with liver metastases had a shorter OS than patients without metastases (HR: 1.958; 95% CI: 1.006–3.810; p=0.048; Figure 2B).

Table 2. Clinicopathological features between lung SCC patients with mutated EGFR or wild-type EGFR when receiving first-generation EGFR-tyrosine kinase inhibitors.

Items	EGFR wild-type	EGFR mutation	p-value
Sex			
Male	48 (87.3)	27 (52.9)	0.000
Female	7 (12.7)	24 (47.1)	
Age			
<60	22 (40.0)	28 (54.9)	0.125
≥60	33 (60.0)	23 (45.1)	
Smoking status			
Yes	45 (81.8)	20 (39.2)	0.000
No	10 (18.2)	31 (60.8)	
PS			
0–1	49 (89.1)	44 (86.3)	0.659
2	6 (10.9)	7 (13.7)	
Stage			
IIIB	14 (25.5)	13 (25.5)	0.997
IV	41 (74.5)	38 (74.5)	
Brain metastasis			
Yes	5 (9.1)	39 (76.5)	0.043
No	50 (90.9)	12 (23.5)	
Liver metastasis			
Yes	8 (14.5)	3 (5.9)	0.144
No	47 (85.5)	48 (94.1)	
Bone metastasis			
Yes	15 (27.3)	17 (33.3)	0.497
No	40 (72.7)	34 (66.7)	
Pleura metastasis			
Yes	20 (36.4)	17 (33.3)	0.744
No	35 (63.6)	34 (66.7)	

Abbreviations: SCC-squamous cell carcinoma; EGFR-epidermal growth factor receptor

Discussion

In this study, lung SCC patients harboring EGFR mutations accounted for 11.0%, and mutated EGFR lung SCC patients treated with first-generation EGFR-TKIs had a longer PFS, but the similar OS, as patients with wild-type EGFR. Mutated EGFR SCC patients receiving first-generation EGFR-TKIs as a first-line treatment had a similar PFS and OS as patients receiving first-generation EGFR-TKI as a second-line or beyond treatment. In addition, lung SCC patients harboring L858R mutations or exon 19 deletions also had a similar clinical efficacy when treated with first-generation EGFR-TKIs. To the best of our knowledge, this was the largest sample size of lung SCC patients receiving first-generation EGFR-RKI. In addition, we further identi-

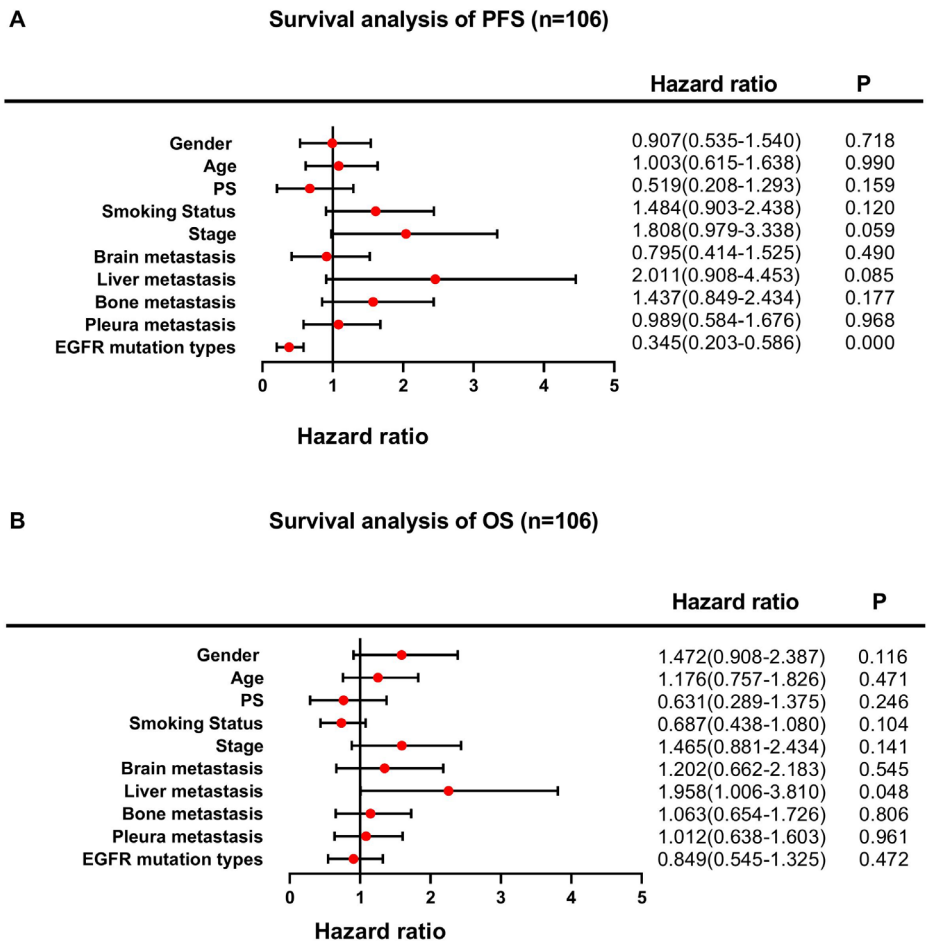

Figure 2. A) Cox regression analysis of the progression-free survival in mutated epidermal growth factor receptor (EGFR) or wild-type EGFR patients receiving first-generation EGFR-tyrosine kinase inhibitors (TKIs). B) Cox regression analysis of the overall survival of mutated EGFR or wild-type EGFR patients receiving first-generation EGFR-TKIs.

Table 3. The treatment efficacy of first-generation EGFR-TKIs in lung SCC patients.

Items	N	ORR	PFS	95% CI	p-value	OS	95% CI	p-value
Patients	110	7.3%	3.3	2.43–4.17	–	15.4	11.75–19.05	–
Mutation types								
EGFR wide type	55	3.6%	1.8	1.04–2.57	0.000	14.7	8.47–20.86	0.472
EGFR mutation	51	11.8%	5.6	3.09–8.17		16.8	7.29–26.24	
EGFR-TKI treatment line								
First	30	6.7%	5.1	4.15–5.98	0.311	17.7	4.01–31.39	0.721
Second or beyond	21	9.5%	7.4	4.96–9.91		16.2	7.38–25.02	
EGFR mutation								
19 deletion	29	6.9%	5.9	2.68–9.18	0.376	14.8	8.82–20.85	0.205
L858R point mutation	22	18.2%	5.6	0.13–11.14		24.6	16.70–32.44	

Abbreviations: SCC-squamous cell carcinoma; EGFR- epidermal growth factor receptor; EGFR-TKI-epidermal growth factor receptor tyrosine kinase inhibitor; PFS- progression-free survival; OS-overall survival; ORR- objective response rate

fied potential beneficial subgroups of mutated EGFR lung SCC patients receiving first-generation EGFR-TKIs.

The median PFS and OS of lung SCC patients treated with targeted therapy were 3.6 months and 16.2 months, respectively, which showed a similar OS as the patients treated with non-targeted therapy. The phase III BR.21 trial recruited 222 lung SCC patients receiving erlotinib, with a median PFS and OS of 2.3 months and 5.6 months, respectively [12]. Song

et al. recruited 102 relapsed lung SCC patients receiving gefitinib or erlotinib and found that the median PFS was 1.93 months [14]. The clinical data of first-generation EGFR-TKI from these studies were consistent with the results of the present study. We, therefore, concluded that lung SCC patients benefited from first-generation EGFR-TKIs.

Lung SCC patients harboring EGFR mutations had a longer PFS and similar OS as the wild-type EGFR patients. Liu et al. conducted a pooled analysis and reported that the ORR, PFS, and OS of mutated EGFR SCC patients treated with first-generation EGFR-TKIs were 39.1%, 5.6 months, and 15.0 months, respectively. They also enrolled 44 mutated EGFR SCC patients receiving first-generation EGFR-TKIs, with the ORR, PFS, and OS of 43.2%, 5.1 months, and 17.2 months, respectively; however, they did not characterize potential subtypes of EGFR mutations [20]. Zhuang et al. reported similar outcomes [21]. Liang et al. recruited 78 EGFR-mutated SCC patients receiving icotinib as first-line or beyond therapies and reported that the median PFS and OS were 12.7 months and 18.5 months, respectively [22]. We obtained similar outcomes, with the median PFS and OS of lung SCC patients with EGFR mutations being 5.6 months and 16.8 months, respectively. In addition, Xu et al. enrolled 29 EGFR-mutant SCC patients and reported that mutated EGFR patients treated with first-generation EGFR-TKIs had a longer PFS than patients with wild-type EGFR (3.94 vs. 1.94 months, p=0.004). The median OSs of patients with mutated EGFR and wild-type EGFR were 18.04 months and 14.03 months, respectively [23]. Chang et al. recruited 45 mutant EGFR SCC patients and found that the median PFS of 38 patients receiving EGFR-TKIs (including two patients receiving afatinib) was 8.0 months, with patients with mutated EGFR having a longer OS than patients without an EGFR mutation (22.8 vs. 18.6 months, p=0.377) [24]. We also obtained similar results. However, the clinical outcomes from our study included a larger sample size of lung SCC patients receiving first-generation EGFR-TKIs, and we also further validated the potential benefit of EGFR-mutated SCC patients receiving first-generation EGFR-TKIs.

In this study, mutated EGFR lung SCC patients receiving EGFR-TKIs as first-line treatment had a similar PFS and OS as patients receiving EGFR-TKI as second-line or beyond treatments. In addition, patients with exon 19 deletions also had a similar PFS and OS as patients with L858R mutations. Jin et al. recruited 28 EGFR-mutated SCC patients and reported that the median PFS of patients treated with EGFR-TKIs (including three patients with afatinib and one patient with osimertinib) was 4.6 months, and there was no significant difference in the PFS between exon 19 deletions and the L858R mutation (5.4 vs. 6.8 months, respectively; p=0.550) [25]. We also obtained similar results. Patients with exon 19 deletions had a similar PFS and OS as patients with L858R mutations, so we further characterized the difference in the OS between patients with exon 19 deletions and L858R mutations. We also found that mutated EGFR lung SCC patients receiving first-generation EGFR-TKI as first-line treatment benefited equally as patients receiving first-generation EGFR-TKIs, which showed unremarkable PFS and OS differences in this study, and which was consistent with the results of previous studies. These results showed that EGFR-TKI could also be a choice for lung SCC patients who were unable to tolerate chemotherapy and could not benefit from immunotherapy due to low expression levels of PD-L1, especially for patients harboring EGFR mutation.

There were some limitations in this study. First, the clinical data were obtained retrospectively and could influence the outcomes. Second, the sample size of lung SCC patients in this study was not adequate. Third, lung SCC patients were enrolled in this study from a single center, which could have involved bias in sample or survival analysis.

In conclusion, lung SCC patients harboring EGFR mutations accounted for 11.0% in this study. EGFR-mutated lung SCC patients treated with first-generation EGFR-TKIs had a longer PFS and similar OS as patients with wild-type EGFR. In addition, mutated EGFR lung SCC patients receiving first-generation EGFR-TKI as first-line treatment had a similar PFS and PS as patients treated with first-generation EGFR-TKIs as second-line or beyond treatments. Patients with exon 19 deletions also had a similar PFS and OS as patients with L858R mutations. With the discovery of afatinib, the difference in treatment efficacies between first-generation EGFR-TKIs and second-generation EGFR-TKIs remains unclear and needs to be further validated by prospective or retrospective studies with larger sample size.

Supplementary information is available in the online version of the paper.

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Clinical outcomes of EGFR-TKIs in advanced squamous cell lung cancer

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Supplementary Information

Supplementary Table S1. Primers and probes sequences.

Primers	Sequence
E-18-M1-S10-tag	gccagcAGCCCTCAGTAGCGAAGCACAAAAAGATCAAAGTGCTGGC
E-18-M2-S10-tag	tcagcacAGCCCTCAGTAGCGAAGCAAATTCAAAAAGATCAAAGTGCTGA
E-18-M3-S10-tag	acagcacttAGCCCTCAGTAGCGAAGCAATTCAAAAAGATCAAAGTGCTGT
E-19-M2-S10-tag	AGCCCTCAGTAGCGAAGCAAGTTAAAATTCCCGTCGCTATCAAGAC
E-19-M3-S10-tag	AGCCCTCAGTAGCGAAGCATTCCCGTCGCTATCAAGGAATCG
E-19-M4-S15-tag	AGCCCTCAGTAGCGAAGCAAAATTCCCGTCGCTATCAAAA
E-19-M9-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGTTCC
E-19-M10-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGAGC
E-19-M12-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGAAGC
E-19-M13-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGAATCTC
E-19-M14-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGAACC
E-19-M16-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGAACAG
E-19-M17-S10-tag	AGCCCTCAGTAGCGAAGCACCCGTCGCTATCAAGGAATCATC
E-20-M1-S11-tag	atgatgagAGCCCTCAGTAGCGAAGCACCACCGTGCAGCTCATCAT
E-20-M2-10-tag	aaggccatcAGCCCTCAGTAGCGAAGCAGAAGCCTACGTGATGGCCTT
E-20-M3-S10-tag	gtggtgggAGCCCTCAGTAGCGAAGCAGTGGACAACCCCCACCAC
E-20-M4-S10-tag	AGCCCTCAGTAGCGAAGCAATGGCCAGCGTGGACGGT
E-20-M5-S10-tag	AGCCCTCAGTAGCGAAGCACTACGTGATGGCCAGCGTGGCCAGTGTG
E-21-M1-D-F6-tag	cgcccAGCCCTCAGTAGCGAAGCATGTCAAGATCACAGATTTTGGGCG
E-21-M2-S11-tag	tctttggAGCCCTCAGTAGCGAAGCACAGATTTTGGGCTGGCCAAAGA
E-18-R10-tag	AGCCCTCAGTAGCGAAGCATCTGGGCTCCCCACCAGAC
E-19-R3-tag	AGCCCTCAGTAGCGAAGCACAGCTGCCAGACATGAGAAAAG
E-20-R10-tag	AGCCCTCAGTAGCGAAGCACCAGTTGAGCAGGTACTGGGAG
E-20-M2-R-tag	cttcGCAAGCCCTCAGTAGCGAATCCAGGAGGCAGCCGAAG
E-21-R10-tag	AGCCCTCAGTAGCGAAGCAGGAAAATGCTGGCTGACCTAAAG
T-primer	AGCCCTCAGTAGCGAAGCA
E-2-S10	GCACGAGTAACAAGCTCACG
E-2-R10	GATCATAATTCCTCTGCACATAGGTAA
E-2-S10-tag	AGCCCTCAGTAGCGAAGCAGCACGAGTAACAAGCTCACG
E-2-R10-tag	AGCCCTCAGTAGCGAAGCAGATCATAATTCCTCTGCACATAGGTAA
Probe	**Sequence**
E-18-P-C	FAM-5'CGTGCGTTCGGCACGGTGTATAAGGTATACAC3' –Tamra
E-19-P-C	FAM-5'CTCACATCCTCGATGTGAGTTTCTGCTTTGCAGAAA-3' -Tamra
E-20-P-C	FAM-5'AGCCGACCTTCGGCTGCCTCCTGGAGGC3'-Tamra
E-20-M2-P-C	FAM-5'-ctCACGGTGGAGGTGAGGCAGATGtgc-3'-BHQ2
E-21-P-C	FAM-5'TAAGGAGCCTCCTTACTTTGCCTCCTTCTGCAAAG3' – Tamra