SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 28: 504, 2024

Efficacy analysis of immunotherapy-based combinations for patients with EGFR-mutant advanced non-small cell lung cancer after TKI failure

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Received October 23, 2023; Accepted July 30, 2024

DOI: 10.3892/ol.2024.14637

Abstract. Treatment options for epidermal growth factor receptor (EGFR)-mutant advanced non-small cell lung cancer (NSCLC) following tyrosine kinase inhibitor (TKI) failure are limited, and platinum-based chemotherapy remains the main treatment. The development of effective immunotherapy for this disease has been challenging. In the present study, 37 patients with EGFR-mutant advanced NSCLC who were treated with programmed cell death-1 (PD-1) inhibitor-based combinations after TKI failure were reviewed. The total cohort had a median progression-free survival (mPFS) of 5.2 months (95% CI, 4.077-6.323 months) and a median overall survival (mOS) of 18.3 months (95% CI, 12.932-23.668 months). Patients with Eastern Cooperative Oncology Group performance-status (ECOG-PS) scores of 0 or 1 had longer mPFS than those with ECOG-PS scores of 2 (5.4 vs. 2.4 months; P=0.006). In addition, a PFS benefit was observed in patients with EGFR T790M-negative compared with EGFR T790M-positive tumors (mPFS 6.2 vs. 4.4 months; P=0.041). Patients treated with immunotherapy-based combinations as a front-line therapy had a longer mPFS than those in which the combinations were used as a late-line therapy (6.2 vs. 2.4 months; P<0.001). PD-1 inhibitor combined with chemotherapy and bevacizumab did not show a clear advantage over PD-1 inhibitor combined with chemotherapy alone (mPFS, 6.2 vs. 4.4 months; P=0.681), although it resulted in an improved overall response rate (ORR) and disease control rate. Notably, the 7 patients with a programmed cell death ligand-1 (PD-L1) tumor proportion score of ≥50% had an ORR of 100% and an mPFS of 8.3 months. Therefore, it is suggested that PD-1 inhibitor-based combinations should be a priority treatment option in selective populations, such as those with low ECOG-PS scores, T790M-negative status or high PD-L1 expression in EGFR-mutant NSCLC after TKI failure. The use of immunotherapy and chemotherapy in combination with antiangiogenic agents appears to be a promising combination therapy for such patients.

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Key words: non-small cell lung cancer, EGFR mutation, immunotherapy, efficacy

Introduction

Lung cancer is one of the most common causes of cancer-related deaths worldwide, and was estimated to account for 21% of cancer-related deaths in the United States in 2023 (1). Patients with metastatic lung cancer who are eligible for targeted therapy survive longer than those who are ineligible (2,3). Most patients with advanced non-small cell lung cancer (NSCLC) with an oncogenic mutation of epidermal growth factor receptor (EGFR) benefit significantly from EGFR tyrosine kinase inhibitors (TKIs); however, patients typically progress after 9-13 months of treatment with first- or second-generation EGFR-TKIs (4-8). Among these patients, the resistant EGFR T790M mutation (p.-Thr790Met) is found in 50-60% of tumors (9-12). The third-generation EGFR-TKI osimertinib is effective for treating the T790M mutation, but disease progression occurs after a median time of 10.1 months (13,14).

When osimertinib is used as a first-line therapy or treatment for NSCLC with the resistant T790M mutation in EGFR, the acquired resistance mechanisms are complex, including EGFR-mediated T790M C797S mutation, MET amplification, HER2 amplification and histological transformation; however, the resistance mechanisms in approximately half of cases remain unclear (15-17). The treatment options are limited, and platinum-based chemotherapy is the main treatment option for these patients.

Immunotherapy-based combination therapies are the standard treatment for EGFR/ALK-negative advanced NSCLC. However, clinical trials have indicated that

patients with EGFR-mutant NSCLC have a poor response to anti-programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) single-agent therapy (18-23), and immunotherapy-based combinations may be a potentially effective strategy. Therefore, the present study evaluated the efficacy of immune checkpoint inhibitors (ICIs) combined with chemotherapy with or without bevacizumab in patients with advanced EGFR-mutant NSCLC after TKI failure to inform clinical practice regarding treatment strategies for these patients.

Materials and methods

Patients. The medical records of all patients with lung cancer at Fujian Cancer Hospital (Fuzhou, China) from March 1, 2019 to July 15, 2023 were reviewed. The eligible patients had EGFR-mutant advanced lung adenocarcinoma, with an Eastern Cooperative Oncology Group (ECOG) performance-status score (24) of 0-2 and at least one measurable tumor. Only patients who: i) experienced treatment failure with first-/second-generation EGFR-TKIs who were T790M mutation negative or who experienced treatment failure with a third-generation EGFR-TKI, ii) received ICIs plus chemotherapy with or without bevacizumab therapy, and iii) were stages IVA or IVB according to the 8th TNM classification (25). were included in the study. The study was approved by the Ethics Committee of Fujian Cancer Hospital (approval no. SQ2021-176-01).

Molecular diagnostics. Analysis of EGFR mutations in biopsy specimens or circulating tumor DNA (ctDNA) from all patients was performed by amplification-refractory mutation system (ARMS) PCR using an ADx-ARMS EGFR kit (Amoy Diagnostics Co., Ltd.) or by next-generation sequencing (NGS) at diagnosis. The EGFR T790M mutation was detected in biopsy specimens or ctDNA using the ADx-ARMS EGFR kit or NGS, or by droplet digital PCR (ddPCR) using an EGFR T790M (S-ddPCR) kit (CB240008; Shanghai Yuanqi Biomedical Technology Co., Ltd.) when patients failed first-/second-generation EGFR-TKI treatment. The primer sequences used for ARMS-PCR were as follows: EGFR 19E746_A750del-S, 5'-GTTAAAATTCCCGTCGCTATCAAGACATCT-3'; EGFR 19E746_S752>A-S, 5'-AGAAAGTTAAAATTCCCGTCGCTATCAAGGCTCC-3'; EGFR-L747_S752del-S, 5'-AATTCCCGTCGCTATCAAGGAACC-3'; EGFR-L747_E749del-S, 5'-GTTAAAATTCCCGTCGCTATCAAGGAAGC-3'; EGFR-19-R, 5'-CACAGCAAAGCAGAAACTCACAT-3'; EGFR-21L858R-S, 5'-GCAGCATGTCAAGATCACAGATTTTGGGCG-3'; EGFR-21L861Q-S, 5'-GATCACAGATTTTGGGCTGGCCAAACA-3'; EGFR-21-R, 5'-GTCAGGAAAATGCTGGCTGACCTAAAG-3'; EGFR 20T790M-S, 5'-CCTCACCTCCACCGTGCARCTCATCAT-3'; EGFR-20T790M-R, 5'-GAGCCAATATTGTCTTTGTGTTCCCG-3'; EGFR-18G719A-FR, 5'-TATACACCGTGCCGAACGCACCGGAGG-3'; EGFR-18G719C-FR, 5'-CCGTGCCGAACGCACCGGAGCA-3'; and EGFR-18-FF, 5'-GGAGCCTCTTACACCCAGTGGAGA-3'. ARMS-PCR was carried out using the following thermocycling conditions: Incubation at 95˚C for 10 min, followed by 15 cycles of 95˚C for 40 sec, 64˚C for 40 sec and 72˚C for 30 sec, and then 28 cycles of 93˚C for 40 sec, 60˚C for 45 sec and 72˚C for 30 sec. The primer sequences used for ddPCR were: T790M-F, 5'-GCCGCCTGCTGGCAT-3' and T790M-R, 5'-TGTGTTCCCGGACATAGTCCAG-3'; reference gene primer-F, 5'-ACTACTTGGAGGAGGACCGTCGC-3' and reference gene primer-R, 5'-TTCTGCATGGTATTCTTTCTC-3'. ddPCR was carried out using the following thermocycling conditions: Incubation at 95˚C for 10 min, followed by 40 cycles of 94˚C for 15 sec, 58˚C for 60 sec and 98˚C for 10 min, then a 4˚C hold. A total of 18 specimens underwent NGS performed by Xiamen Spacegen Co., Ltd., including 7 specimens at diagnosis and 11 specimens after the development of first-/second-generation EGFR-TKI resistance. The PD-L1 tumor proportion score (TPS) was measured by immunohistochemistry (Dako28-8; Agilent Technologies, Inc.) in 17 patients after progression on EGFR-TKIs. The immunohistochemistry of PD-L1 expression was carried out using the following procedure: 5-μm sections were cut from each biopsy specimen. Tissue sections were incubated at 60˚C overnight, and incubated 40˚C for 1 h, followed by separation with xylene and ethanol. Tissue sections were treated with PBS at 37˚C for 12 h and subjected to IHC staining. Antigen repair was performed by water bath method at 97˚C for 20 min, and the repair solution was EnVision Flex TRS(pH 6.1); the antibody of PD-L1 (28-8) was diluted at 1:40 to 1:20, used at room temperature for 20 min. EnVision Flex+ was applied for 20 min, with $CuSO_4$ enhanced DAB color development. A Dako AutoStainer Link 48 platform (Agilent Technologies, Inc.) was used for detection.

Treatment regimens and response evaluation. Enrolled patients had received PD-1 inhibitors every 3 weeks, including 200 mg camrelizumab (Jiangsu Hengrui Medicine Co., Ltd.), 200 mg tislelizumab (BeiGene, Ltd.) and 200 or 240 mg toripalimab (Shanghai Junshi Biosciences Co., Ltd.) plus chemotherapy with or without bevacizumab. RECIST version 1.1 was used to evaluate the treatment responses of the patients (26). Progression-free survival (PFS) represented the length of survival from treatment with PD-1 inhibitor and chemotherapy/bevacizumab to progression, and overall survival (OS) represented the survival from treatment with PD-1 inhibitor to death. The response to PD-1 inhibitor-based therapy was defined as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) during the course of therapy. The overall response rate (ORR) was defined as the percentage of patients with a CR or PR: ORR (%)=(CR + PR)/total number of patients x100. The disease control rate (DCR) was defined as the percentage of patients with a CR, PR or SD: DCR (%)=(CR + PR + SD)/total number of patients x100. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTC-AE) v5.0 (27).

Statistical analysis. Kaplan-Meier analysis and the log-rank test were used to compare differences in survival. The ORR and DCR of different subgroups were compared using Fisher's exact tests. In the tests, two-sided $P<0.05$ was considered statistically significant. SPSS version 24.0 (IBM Corp.) statistical software was used to perform all the statistical analyses.

Table I. Characteristics of all patients and clinical response to immunotherapy.

		ORR		DCR		mPFS		
Characteristics	N (%)	n/N (%)	P-value	n/N (%)	P-value	Months	95% CI	P-value
Sex			0.170		1.000			0.929
Male	18 (48.6)	8/18 (44.4)		15/18 (83.3)		5.2	2.665-7.735	
Female	19 (51.4)	4/19 (21.1)		15/19 (78.9)		5.2	3.984-6.416	
Age, years			0.274		1.000			0.315
>60	13 (35.1)	6/13 (46.2)		11/13 (84.6)		4.5	3.080-5.720	
≤60	24 (64.9)	6/24 (25.0)		19/24 (79.2)		5.4	3.245-8.102	
ECOG-PS			1.000		0.156			0.006
0-1	29 (78.4)	10/29 (34.5)		25/29 (86.2)		5.4	2.735-8.065	
2	8 (21.6)	2/8 (25.0)		5/8 (62.5)		2.4	0.321-4.479	
EGFR mutations			0.818		0.223			0.461
19del	18 (48.7)	6/18 (33.3)		15/18 (83.3)		4.6	2.937-6.2637	
21L858R	15 (40.5)	5/15 (33.3)		11/15 (73.3)		4.5	1.452-7.548	
Others	4 (10.8)	1/4 (25.0)		4/4 (100)		5.2	0	
TNM stage			0.306		0.007			0.083
IVA	14 (37.8)	3/14 (21.4)		8/14 (57.1)		3.5	2.100-4.300	
IVB	23 (62.2)	9/23 (39.1)		22/23 (95.7)		5.4	2.894-8.506	
Brain metastases			1.000		0.308			0.734
Present	8 (21.6)	2/8 (25.0)		8/8 (100)		5.2	3.404-6.996	
Absent	29 (78.4)	10/29 (34.5)		22/29 (75.9)		5.2	2.817-7.583	
T790M status (post-TKIs)			0.306		0.390			0.041
Negative	23 (62.2)	9/23 (39.1)		20/23 (87.0)		6.2	3.265-9.135	
Positive	14 (37.8)	3/14 (21.4)		10/14 (71.4)		4.4	2.923-5.877	
Prior EGFR-TKIs			0.239		0.670			
First-generation	11 (29.7)	3/11 (27.3)		10/11 (90.9)		7.1	3.863-10.337	0.068
First/third-generation	14 (37.8)	3/14 (21.4)		10/14 (71.4)		4.4	2.923-5.877	
Third-generation	12 (32.5)	6/12 (50.0)		10/12 (83.3)		5.2	2.314-8.086	
Total duration of previous TKIs, months			1.000		1.000			0.069
≤12	20 (54.1)	6/20 (30.0)		16/20 (80.0)		4.4	2.209-6.591	
>12	17 (45.9)	6/17 (35.3)		14/17 (82.4)		5.4	1.197-9.603	
Line of ICI			0.007		0.016			<0.001
Front-line	26 (70.3)	12/26 (46.2)		24/26 (92.3)		6.2	2.655-9.745	
Late-line	11 (29.7)	0/11 (0)		6/11 (54.5)		2.4	0.309-4.491	
Combination treatment strategy			0.036		0.028			0.681
ICI + C	22 (59.5)	4/22 (18.2)		15/22 (68.1)		4.4	1.826-6.974	
ICI + C + A	15 (40.5)	8/15 (53.3)		15/15 (100)		6.2	3.279-9.121	

ORR, overall response rate; DCR, disease control rate; mPFS, median progression-free survival; ECOG-PS, Eastern Cooperative Oncology Group performance-status; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; TNM, tumor-node-metastasis; ICI, immune checkpoint inhibitor; C, chemotherapy; A, bevacizumab.

Results

Patient population and characteristics. There were 316 patients with EGFR-mutant advanced NSCLC who were treated with EGFR-TKIs from March 1, 2019 to July 15, 2023, of whom 147 had experienced failure when previously treated with TKIs. These included 42 patients who were treated with PD-1 inhibitors after TKI failure. However, 2 patients were lost to follow-up and 3 patients had a ECOG score of 3. Finally, a total of 37 patients with EGFR-mutant advanced NSCLC were included in the study (Fig. 1). The baseline clinicopathological characteristics of these patients are summarized in Table I.

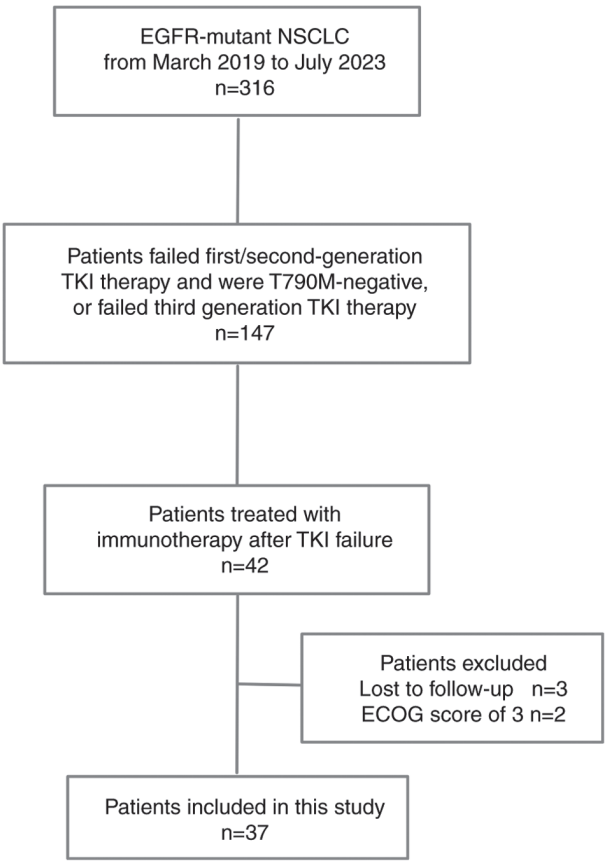

Figure 1. Patient enrollment flow chart. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group.

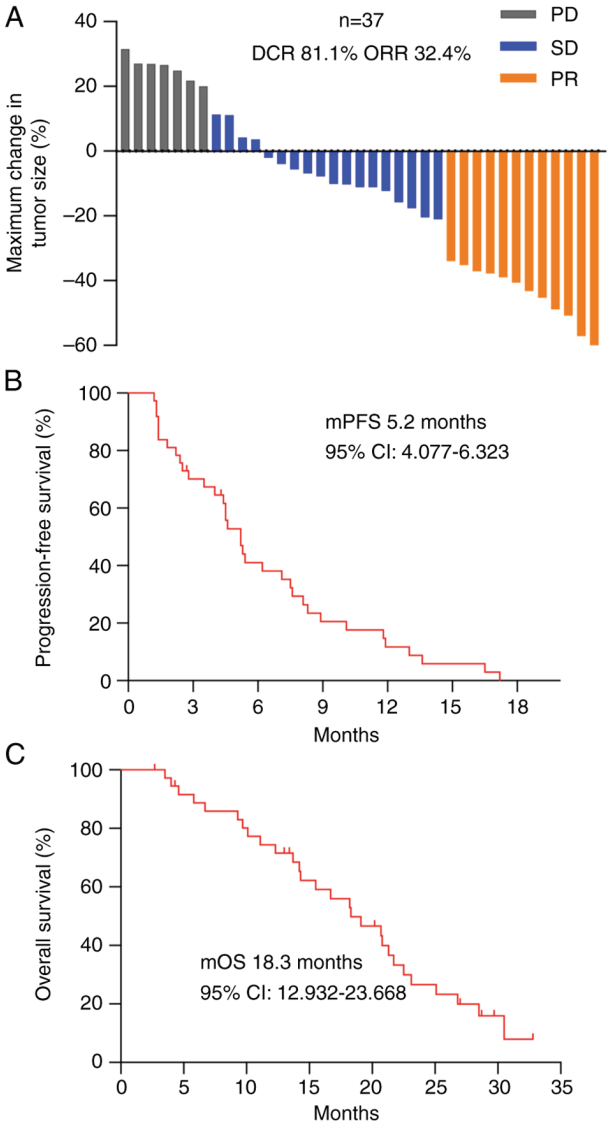

Figure 2. Response to immunotherapy-based combinations in all patients. (A) Treatment response in all patients presented for individual patients, with overall DCR and ORR. Kaplan-Meier curves for (B) mPFS and (C) for mOS. DCR, disease control rate; ORR, overall response rate; PD, progressive disease; SD, stable disease; PR, partial response; mPFS, median progression-free survival; mOS, median overall survival.

The median age was 56 years (range, 32-72 years). A total of 19 patients were female. Most (n=29) patients had an ECOG score of 0 or 1. The EGFR mutation subtypes were EGFR exon 19 deletion mutation (n=18), EGFR exon 21 L858R mutation (n=15) and rare double EGFR rare mutations G719X/L861Q (n=2), G719A/S861I (n=1) and G719X/S861I (n=1). A total of 25 patients received first-generation EGFR-TKIs as first-line treatment, 14 patients acquired the T790M mutation (Table SI) when the disease progressed and were treated with osimertinib, and 12 patients received osimertinib as first-line treatment. The total duration of previous TKI treatment was ≤12 months for 20 patients and >12 months in the remaining 17 patients.

Treatment characteristics. There were 26 patients who immediately received PD-1 inhibitors after TKI failure, which was defined as front-line therapy, and 11 patients who received late-line PD-1 inhibitor therapy because they had received other systemic treatments between EGFR-TKIs and ICI therapy. Regarding the combination treatment strategy, 22 patients were treated with PD-1 inhibitors plus chemotherapy, and the remaining 15 patients were treated with PD-1 inhibitors plus chemotherapy and bevacizumab (Table I).

Overall clinical outcomes. At the last follow-up on January 15, 2024, the median follow-up time was 13.4 months (range, 2.7-32.8 months). The median PFS (mPFS) of all patients was 5.2 months (95% CI, 4.077-6.323 months; Fig. 2B), and the median OS (mOS) was 18.3 months (95% CI, 12.932-23.668 months; Fig. 2C). Disease progression occurred in 94.6% (35/37) of patients, and 75.7% (28/37) of the patients died. Overall, 32.4% (12/37), 48.6% (18/37) and 18.9% (7/37) of the patients exhibited a PR, SD or PD respectively, with a DCR of 81.1% and an ORR of 32.4% (Fig. 2A).

Survival outcomes in selected patient subgroups. Subgroup analyses based on all 37 patients revealed that patients with an ECOG-PS score of 0 or 1 had a similar ORR but longer PFS than those with an ECOG-PS score of 2 (ORR, 34.5 vs. 25.0%, P=1.000; mPFS, 5.4 vs. 2.4 months, P=0.006; Table I, Fig. 3A). The analysis revealed a PFS improvement in EGFR T790M-negative patients, with a median PFS of 6.2 months (95% CI, 3.265-9.135 months), which was longer than that in EGFR T790M-positive patients (4.4 months; 95% CI,

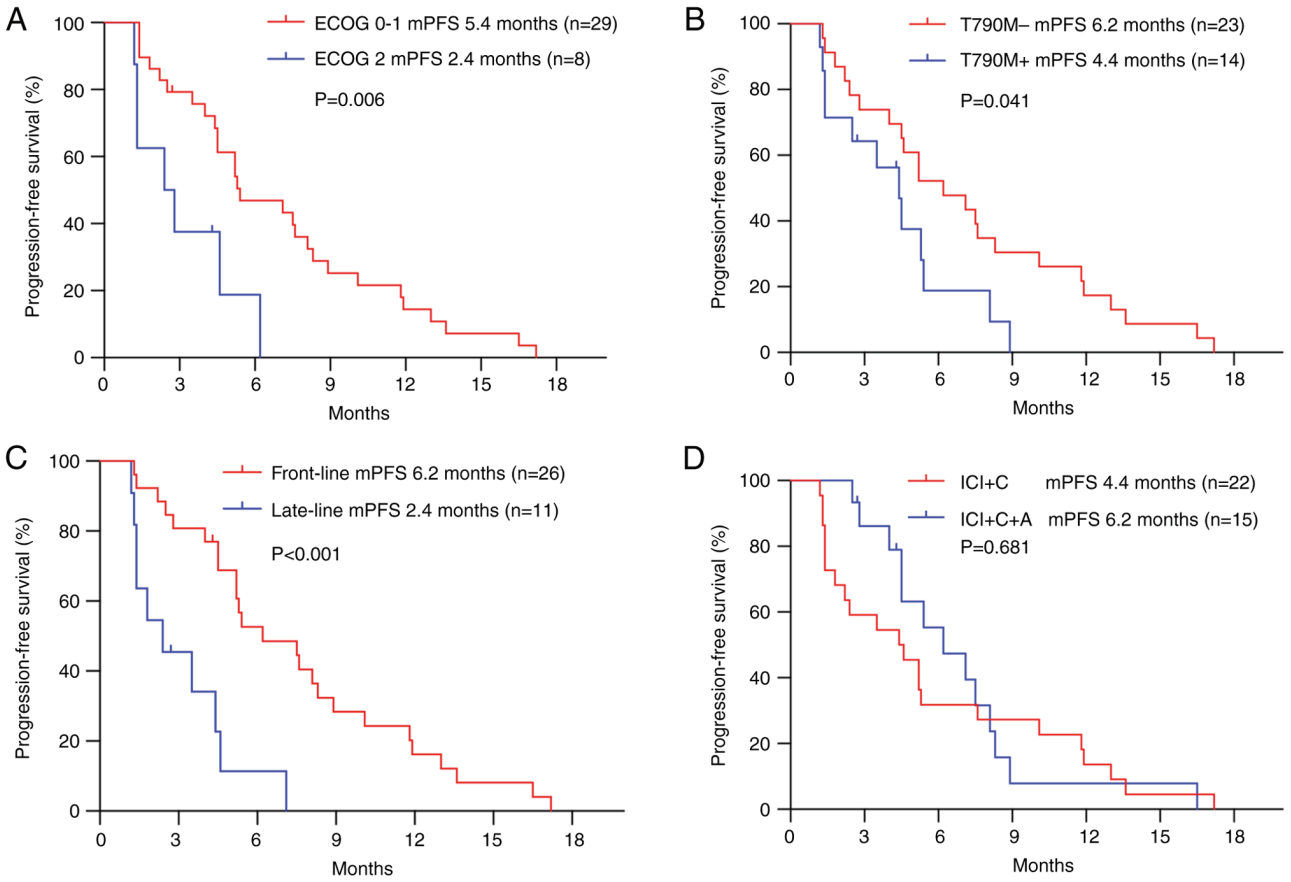

Figure 3. Kaplan-Meier analysis of mPFS in patients according to various factors. Kaplan-Meier analysis according to (A) ECOG performance-status score, (B) T790M status, (C) the line of immunotherapy and (D) combination treatment strategy. mPFS, median progression-free survival; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; C, chemotherapy; A, bevacizumab.

2.923-5.877 months) (P=0.041; Table I; Fig. 3B). The patients treated with ICI-based therapy as front-line therapy showed a higher ORR and longer PFS than those treated with ICI-based therapy as late-line therapy (ORR, 46.2 vs. 0%, P=0.007; mPFS, 6.2 vs. 2.4 months, P<0.001; Table I; Fig. 3C). In the subgroups based on different types of EGFR mutations, TNM stage, the presence or absence of brain metastases, the total duration of previous TKI treatment and the type of ICI-based therapy (with or without bevacizumab), no significant differences in PFS were observed (Table I; Fig. 3D). However, the ORR and DCR of patients treated with ICIs plus chemotherapy and bevacizumab were higher than those of patients treated with ICIs plus chemotherapy (ORR, 53.3 vs. 18.2%, P=0.036; DCR, 100 vs. 68.1%, P=0.028; Table I). Cox multivariate regression analysis revealed that the ECOG-PS score, EGFR T790M status post-EGFR-TKIs and timing of immunotherapy were independent predictors of PFS in patients treated with immunotherapy-based combinations (P<0.05; Table II).

Efficacy according to PD-L1 TPS. The PD-L1 TPS was measured in 45.9% (17/37) of patients with re-biopsy specimens post-EGFR-TKI treatment (Table SII). Four patients were negative for the PD-L1 TPS and 7 patients had a PD-L1 TPS ≥50% (Fig. 4). In these 17 patients, the optimal efficacy was achieved in patients with a PD-L1 TPS ≥50%, with an ORR of 100%, while patients with a PD-L1 TPS <50% had an ORR of only 20% (Fig. 5A). The mPFS was 8.3 months (95% CI, 6.247-10.353 months) for patients with a PD-L1 TPS ≥50%, which was longer than that for patients with a PD-L1 TPS <50% (median PFS, 4.0 months; 95% CI, 2.450-5.550 months) (P=0.050; Fig. 5B). In addition, the mOS was 22.5 months for patients with a PD-L1 TPS ≥50%, which tended to be prolonged compared with that of patients with a PD-L1 TPS <50% (P=0.054; Fig. 5C).

Safety. The median number of PD-1 inhibitor cycles was 6 (range, 1-35). AEs associated with any component of treatment occurred in 28/37 (75.7%) patients. However, no mortalities associated with the treatment occurred. The grade 3 or 4 AEs associated with the treatment were leukopenia in 4/37 (10.8%) patients, as well as fatigue, rash and pneumonitis, each of which occurred in 1/37 (2.7%) of patients (Table III). One patient discontinued immunotherapy due to grade 3 fatigue, and 4 patients discontinued immunotherapy due to grade 2/3 pneumonitis.

Discussion

PD-1/PD-L1 inhibitors have become a standard treatment option for EGFR/ALK-negative advanced NSCLC. The potential of immunotherapy in patients with EGFR mutations, who account for ~50% of Asian patients with NSCLC (28), requires further exploration. In the present study, the effect and safety of PD-1 inhibitors combined with chemotherapy with or

Table II. Univariate and multivariable analyses of covariables associated with progression-free survival in patients treated with immunotherapy.

		Univariate		Multivariate	
Characteristics	N	HR (95% CI)	P-value	HR (95% CI)	P-value
ECOG-PS score					
0-1	29	Ref.	0.010	Ref.	0.017
2	8	3.338 (1.335-8.347)		3.328 (1.245-8.896)	
T790M status post-TKIs					
Negative	24	Ref.	0.048	Ref.	0.021
Positive	13	1.987 (0.918-4.298)		2.166 (1.0064.662)	
Line of immunotherapy					
Front-line	26	Ref.	0.001	Ref.	0.004
Late-line	11	4.465 (1.876-0.628)		2.113 (1.370-3.260)	

HR, hazard ratio; ECOG-PS, Eastern Cooperative Oncology Group performance-status; Ref., reference; TKIs, tyrosine kinase inhibitors.

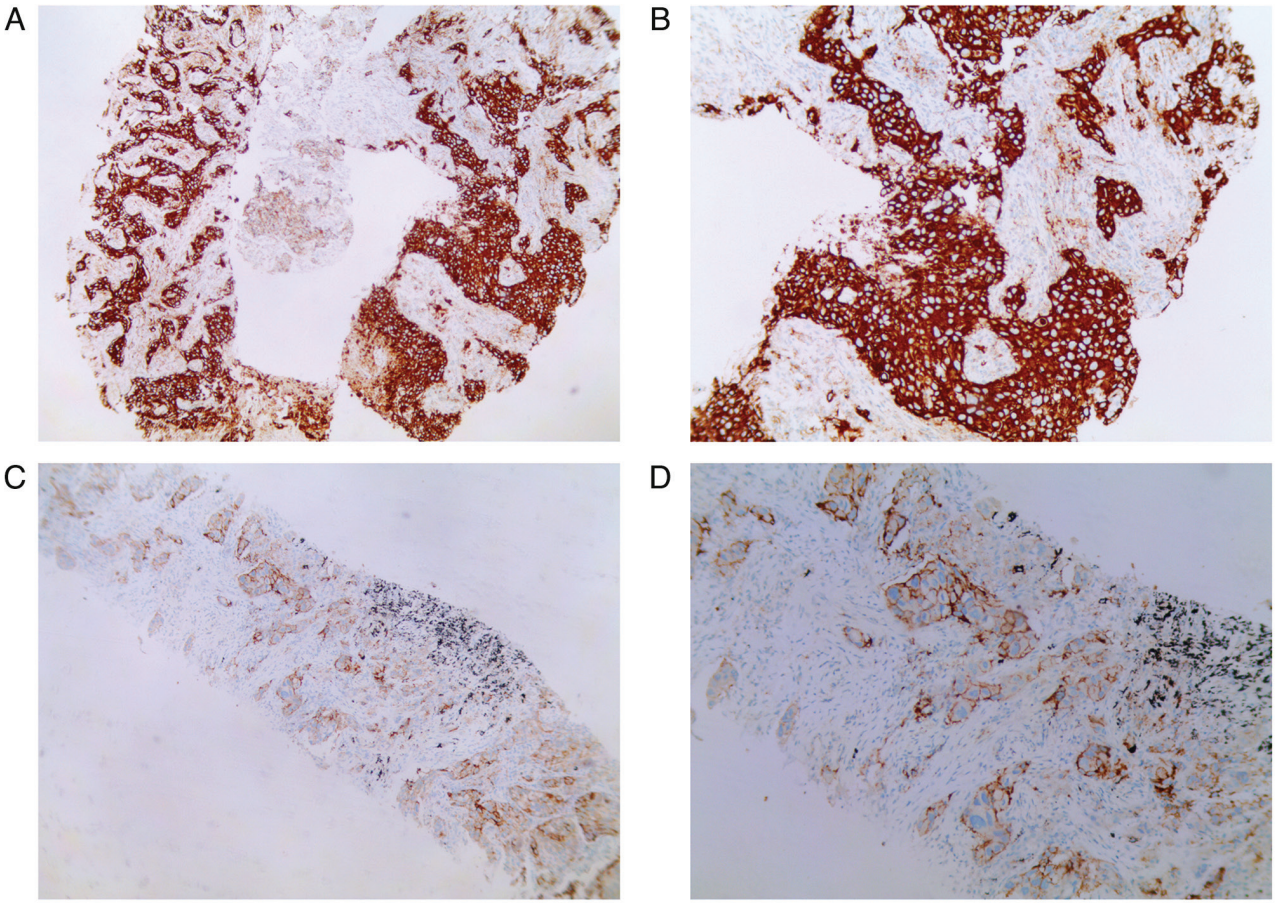

Figure 4. Representative PD-L1 stained tumor images from patients with non-small cell lung cancer obtained by Dako28-8 immunohistochemistry. (A and B) Patient 16 had a PD-L1 TPS of 90%; (A) magnification, x40; (B) magnification, x100. (C and D) Patient 35 had a PD-L1 TPS of 20%; (C) magnification, x40; (D) magnification, x100). PD-L1, programmed cell death ligand-1; TPS, tumor proportion score.

without bevacizumab were evaluated. The results showed that the mPFS of patients receiving PD-1 inhibitor-based combination therapy was 5.2 months, which is similar to that of patients receiving platinum-based double drug chemotherapy as a first-line treatment in advanced NSCLC but longer than that of immune monotherapy reported in previous studies (21,23,29). Data from a multicenter phase II trial of the PD-1 inhibitor toripalimab plus chemotherapy showed an mPFS of 7.0 months when used as a second-line treatment in patients with EGFR-mutant advanced NSCLC after the failure

Table III. Treatment-related adverse events in the 37 patients.

Event	Patients, n (%)	
	All grades	Grade ≥3
Leukopenia	13 (35.1)	4 (10.8)
Fatigue	7 (18.9)	1 (2.7)
Rash	6 (17.1)	1 (2.7)
Nausea	3 (11.5)	-
ALT elevation	5 (13.5)	-
AST elevation	5 (13.5)	-
Pneumonitis	4 (10.8)	1 (2.7)
Capillary proliferation	1 (2.7)	-
Hypertension	1 (2.7)	-
Proteinuria	1 (2.7)	-

ALT, alanine transaminase; AST, aspartate transaminase.

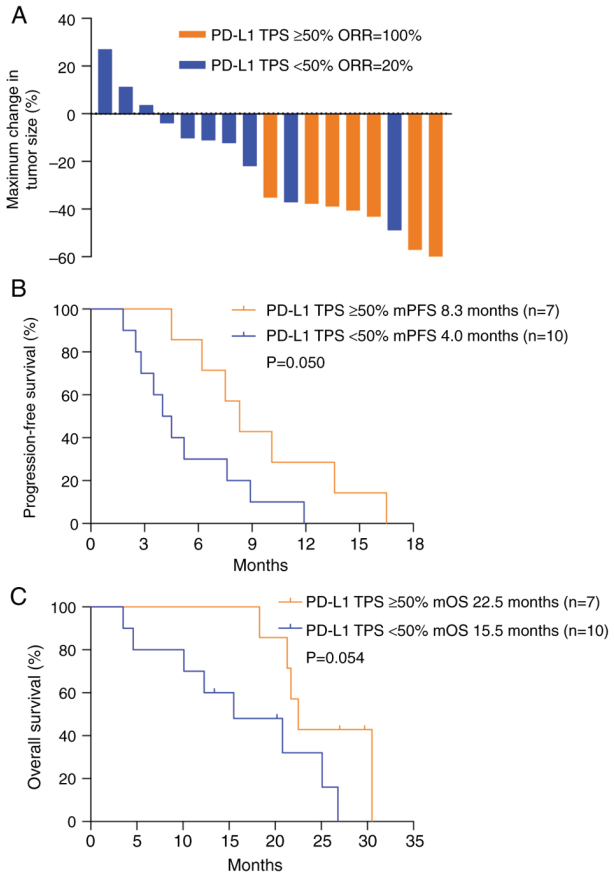

Figure 5. Response to immunotherapy-based combinations according to PD-L1 expression. (A) Treatment response according to PD-L1 expression presented for individual patients, with overall ORR. Kaplan-Meier curves for (B) mPFS and (C) mOS. PD-L1, programmed cell death ligand-1; TPS, tumor proportion score; ORR, overall response rate.

of prior EGFR-TKIs (30). However, in real-world settings, the mPFS was found to be ~5 months for patients treated with these immunotherapy-based combinations (31-35). Unfortunately, the outcome of patients with EGFR-mutant tumors in the IMpower130, CheckMate-722 and KEYNOTE-789 clinical trials also did not suggest an advantage for immunotherapy combined with chemotherapy in TKI-refractory EGFR-mutant NSCLC (36-38). Therefore, the interplay between the tumor immune microenvironment (TME), PD-L1 expression in tumors, tumor mutation burden (TMB) and vascular endothelial growth factor (VEGF) receptor inhibitors may be affecting the efficacy of treatment.

The precise mechanisms underlying the unsatisfactory response to immunotherapy in patients with EGFR-mutant NSCLC remain unclear. The generation of tumor neoantigens, antigen presentation and identification, and activation of T cells have been suggested to impact the effect of immunotherapy (39). The low TMB in patients with EGFR mutations who do non-smoke has been suggested as a potential reason for the poor effect of immunotherapy (40). In addition, low PD-L1 expression may impact the efficacy of immunotherapy in patients with EGFR mutations (19,21). Although chemotherapy can kill tumor cells, increase tumor neoantigen levels and improve the efficacy of immunotherapy (41,42), no survival benefit was observed in patients treated with immunotherapy combined with chemotherapy in previous studies (36,38). Based on the approach of combining immunotherapy with other treatments, the final exploratory analyses of the IMpower 150 trial showed a survival benefit in patient subgroups with EGFR mutations when treated with a combination of atezolizumab, bevacizumab and chemotherapy, even in those patients who had previously been treated with TKIs (43,44). In addition, the ORIENT-31 trial reported the successful use of a PD-1 inhibitor with bevacizumab biosimilar plus chemotherapy (45). However, the use of a PD-1 inhibitor combined with chemotherapy and bevacizumab did not show a clear advantage on mPFS compared with the use of a PD-1 inhibitor combined with chemotherapy alone in the present study, although the ORR and DCR were improved. VEGFs can regulate the TME and stimulate regulatory T cells, thereby improving the efficacy of immunotherapy (46). Therefore, the combination of chemotherapy and immunotherapy with antiangiogenic agents may be a promising treatment strategy for EGFR-mutant advanced NSCLC. However, further clinical studies are necessary to confirm this.

In the present study, a subgroup analysis was performed to evaluate the patients who were more likely to benefit from immunotherapy-based combinations. Patients with an ECOG-PS score of 0 or 1 were found to have an improved response to PD-1 inhibitor-based combination therapy (mPFS, 5.4 months) compared with those with an ECOG-PS score of 2, and EOCG-PS was identified as an independent predictor of PFS in patients treated with immunotherapy-based combinations (P=0.017). T790M mutation status was identified as another independent predictor of the efficacy of immunotherapy-based combinations (P=0.021) in the present study. The T790M-negative patients had an mPFS of 6.2 months, which was longer than the 4.4 months of T790M-positive patients (P=0.041). One possible explanation for this is that T790M-negative tumors are characterized by high PD-L1 expression and a high TMB. Unfortunately, only some of the patients in our study were suitable for PD-L1 testing, and none of the patients underwent TMB testing because of insufficient specimens or the expense of testing after EGFR-TKI

failure. A study by Haratani *et al* (47) indicated that patients with T790M-negative tumors are more likely than those with T790M-positive tumors to benefit from nivolumab after EGFR-TKIs, and suggested that this may be due to high PD-L1 expression in T790M-negative tumors. Similar results were also reported in a IMMUNOTARGET registry study (48). However, prospective clinical trials are required to verify these findings.

The TME contains immune cells and immune factors, and is a key factor affecting the efficacy of immunotherapy. PD-L1 expression and the TME dynamically change with tumor treatment (49). Regrettably, information on the TME was lacking in the present study. However, in a previous study of a lung cancer model with EGFR mutations, it was observed that as EGFR-TKI resistance developed, immune effector cells gradually disappeared, and myeloid-derived suppressor cells continued to proliferate with subsequent increases in IL-10 and chemokine (C-C motif) ligand 2 levels (50). Therefore, the timing of immunotherapy may impact its efficacy. In the present study, front-line PD-1 inhibitor-based combination therapy was associated with a longer PFS than late-line therapy following TKI failure (mPFS, 6.2 vs. 2.4 months; P<0.001). As NSCLC progresses, the TME becomes more complex and less conducive to immunotherapy. Consequently, front-line immunotherapy-based combinations could be recommended for clinical use after TKI failure.

Currently, biomarkers for the efficacy of immunotherapy in EGFR-mutant NSCLC have not been clearly identified. However, PD-L1 is the most important predictor of the efficacy of immunotherapy in patients with NSCLC (51,52). Preclinical evidence suggests that EGFR mutations can upregulate PD-L1 expression (53,54), and EGFR-TKIs may even increase PD-L1 expression in EGFR-mutant tumors (55,56). However, some studies have reported opposite findings (57,58). In the present study, PD-L1 expression was evaluated in 17 patients. Of these, the 7 patients with a PD-L1 TPS ≥50% had an ORR of 100% and a median PFS of 8.3 months, which were improved compared with those of patients with a PD-L1 TPS <50%. The Keynote-010 study revealed the preliminary efficacy of the PD-1 inhibitor pembrolizumab in patients with EGFR-mutant, PD-L1-positive NSCLC (20). In addition, in the ATLANTIC study, durvalumab exhibited greater clinical activity in patients with EGFR-mutant and heavily pretreated NSCLC with ≥25% PD-L1 expression than in those with <25% PD-L1 expression (59). Similarly, the ATTLAS trial showed that patients with EGFR-mutant NSCLC who were PD-L1 positive could benefit from immunotherapy plus chemotherapy and bevacizumab, and that patients with high PD-L1 expression had a longer PFS (60). Further investigations are required to verify the utility of PD-L1 expression as a predictive biomarker of treatment in patients with EGFR mutations.

In conclusion, the treatment options for EGFR-mutant advanced NSCLC after TKI failure are limited. Immunotherapy-based combinations may be a potentially effective strategy, and treatment outcomes are influenced by the TME, the TMB, PD-L1 expression in tumors and prior TKI treatment. In the present study, immunotherapy-based combination therapy was the recommended treatment option for patients with EGFR-mutant advanced NSCLC after TKI failure. In addition, ECOG-PS scores of 0 or 1, T790M-negativity or high PD-L1 expression indicated an improved prognosis for patients with EGFR-mutant NSCLC who experienced tumor progression following EGFR-TKI treatment. Immunotherapy and chemotherapy in combination with antiangiogenic agents appears to be a promising combination therapy for these patients.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Natural Science Foundation of Fujian Province (grant no. 2022J011047), High-level Talent Development Program (grant no. 2024YNG11) and the Innovation of Science and Technology, Fujian Province (grant no. 2021Y0056).

Availability of data and materials

The original NGS data generated in the present study may be found in the SRA under accession number PRJNA1092050. All other data generated in the present study may be requested from the corresponding author.

Authors' contributions

ML and ZH designed the study. CL, JL, SC and LW contributed to data collection and investigation. ML and CL wrote the original draft of the manuscript. ML and ZH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Fujian Cancer Hospital (approval no. SQ2021-176-01). Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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