The efficacy and safety of PD-1 inhibitors for EGFR-mutant non-small cell lung cancer after tyrosine kinase inhibitor failure: a retrospective real-world cohort study

Chunyang Zhou[1#^], Zijian Wang[2#], Chengrui Fu[3#], Hengmin Tao[4], Chengxin Liu[3,5^]

[1]Department of Radiation Oncology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, China; [2]College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China; [3]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, China; [4]Department of Head and Neck Radiotherapy, Shandong Provincial ENT Hospital, Shandong University, Jinan, China; [5]Cheeloo College of Medicine, Shandong University, Jinan, China

Contributions: (I) Conception and design: C Liu, H Tao; (II) Administrative support: C Liu, H Tao; (III) Provision of study materials or patients: C Liu; (IV) Collection and assembly of data: C Zhou, Z Wang; (V) Data analysis and interpretation: C Zhou, Z Wang, C Fu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hengmin Tao. Department of Head and Neck Radiotherapy, Shandong Provincial ENT Hospital, Shandong University, Jinan, China. Email: jnradiotherapy@163.com; Chengxin Liu. Cheeloo College of Medicine, Shandong University, Jinan 250012, China; Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China. Email: lwtdzyyx@163.com.

Background: Acquired drug resistance to various tyrosine kinase inhibitor (TKI) inevitably develops in almost all epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC). The present study aimed to evaluate the efficacy and safety of programmed cell death protein 1 (PD-1) inhibitors for such patients after TKI failure and further explore the subpopulation that exhibited the most benefit.

Methods: A total of 102 EGFR-mutant NSCLC patients who received PD-1 inhibitors after developing resistance to EGFR-TKIs were included in the study. The primary endpoints were progression-free survival (PFS) and grade 3–5 adverse events (AEs), while the secondary endpoints were overall survival (OS), disease control rate (DCR) and subgroup analyses.

Results: All the 102 patients received 2 or more lines of immunotherapy. The overall median PFS was 4.95 months [95% confidence interval (CI): 3.91–5.89 months]. The $EGFR^{L858R}$ group showed a significant PFS benefit compared with the $EGFR^{D19}$ group (6.4 *vs.* 3.5 months, P=0.002), and likewise for the DCR between the 2 groups ($EGFR^{L858R}$ *vs.* $EGFR^{D19}$ group: 84.3% *vs.* 66.7%, P=0.049). In addition, median PFS in the $EGFR^{T790M}$-negative group (6.47 months) was significantly longer than the $EGFR^{T790M}$-positive group (3.20 months) (P=0.003). The overall OS was 10.70 months (95% CI: 8.92–12.48 months), without a prognostic factor. There was a trend towards improved PFS and OS with combination therapy. The incidence of grade 3–5 treatment-related AEs was 19.6%, while the incidence of grade 3–5 immune-related AEs (irAEs) was 6.9%. Treatment-related AEs were similar in different mutation subtypes. The incidence of grade 3–5 irAEs was higher in the $EGFR^{D19}$ group (10.3%) compared with the $EGFR^{L858R}$ group (5.9%), and likewise in the $EGFR^{T790M}$-negative group (10%) compared with the $EGFR^{T790M}$-positive group (2.6%).

Conclusions: After EGFR-TKI failure, PD-1 inhibitors provided better survival in advanced NSCLC for the $EGFR^{L858R}$ subgroup and $EGFR^{T790M}$-negative subgroup, and there was a trend towards improved outcomes with combination therapy. In addition, toxicity was well tolerated. Our real-world study increased the population size and obtained a similar survival outcome compared from clinical trials.

^ ORCID: Chunyang Zhou, 0000-0003-3535-440X; Chengxin Liu, 0000-0003-2962-0820.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) accounting for 80% of all lung cancers (1). Epidermal growth factor receptor (EGFR)-mutant lung cancers represent a distinct subset of NSCLC, which has broad clinical heterogeneity. The mutation rate varies greatly by region and is up to 40% in Eastern Asia and 11–16% in the West (2). EGFR-tyrosine kinase inhibitors (TKIs) have shown great treatment efficacy for advanced EGFR-mutant NSCLC and are recommended as first-line treatment in the National Comprehensive Cancer Network (NCCN) guidelines (3-5). However, acquired drug resistance to various EGFR-TKIs inevitably develops in almost all such patients. Patients often experience disease progression after about a year of treatment with first- and second-generation EGFR-TKIs (5-7). For these patients, third-generation EGFR-TKI osimertinib can be used in those who have a secondary Thr790Met point mutation in exon 20 of the EGFR gene mutation ($EGFR^{T790M}$). However, drug resistance arises again at an average of 10 months (8).

Highlight box

Key findings

- PD-1 inhibitors provided better survival in some types of EGFR-mutant NSCLC.

What is known and what is new?

- Immune checkpoint inhibitors have yielded significant treatment progress in patients with driver oncogenes wild-type advanced NSCLC.
- After EGFR-TKI failure, PD-1 inhibitors provided better survival in advanced NSCLC in the $EGFR^{L858R}$ subgroup and $EGFR^{T790M}$-negative subgroups, and there was a trend towards improved outcomes with combination therapy.

What is the implication, and what should change now?

- PD-1 inhibitors could be approved for patients with advanced NSCLC in the $EGFR^{L858R}$ subgroup and $EGFR^{T790M}$-negative subgroup after EGFR-TKI failure.

Although osimertinib exhibits superior progression-free survival (PFS) as initial treatment in advanced EGFR-mutant NSCLC, acquired resistance invariably develops with a median PFS of 19 months (9). At present, there is no unified treatment after acquired resistance of EGFR-TKIs in NSCLC. This has long been an important unmet clinical need, especially in East Asia, and a novel treatment strategy is urgently needed.

Immune checkpoint inhibitors (ICIs) have yielded significant treatment progress in patients with driver oncogenes wild-type advanced NSCLC, although previous clinical evidence has revealed that ICIs failed to improve survival benefits in EGFR-mutant advanced NSCLC (10-12). However, a recent preclinical study found that driver oncogenes could upregulate programmed death-ligand 1 (PD-L1) expression in NSCLC (13), and several clinical trials, including ATLANTIC (14), PROLUNG (15), and IMpower150 (16), have shown more encouraging results for ICIs in EGFR-mutant NSCLC. However, the feasibility of immunotherapy remains controversial. Considering that there are few patients qualified for the inclusion criteria in conventional clinical trials, and the prospective head-to-head comparison between multiple ICIs' regimens was highly unlikely. Our real-world study had the advantages of including broader populations, increasing efficiency, and reflecting the actual use of drugs in clinical setting. We collected the clinical records of EGFR-mutant NSCLC patients who received immunotherapy after EGFR-TKI failure at our institution to further explore the efficacy and safety of programmed cell death protein 1 (PD-1) inhibitors and the subpopulation that exhibited the most benefit. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6272/rc).

Methods

Patients

We designed a retrospective cohort study, collected the medical records of patients with advanced NSCLC at

Shandong Cancer Hospital between October 1, 2018 and December 31, 2020. A total of 102 patients met the following inclusion criteria: (I) stage IIIC or IV NSCLC; (II) EGFR-activating mutation with tissue or plasma sample; (III) radiological disease progression after at least 1 line of EGFR-TKI therapy (patients with $EGFR^{T790M}$-positive must have had radiological progression after osimertinib); (IV) received at least 2 cycles of PD-1 inhibitors; (V) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and (VI) at least 1 measurable lesion evaluated according to the modified immune Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapeutics (iRECIST). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (No. SDTHEC202201100829). Individual consent for this retrospective analysis was waived.

Data collection

The following clinicopathological data were collected from the medical records of the patients: sex; age at diagnosis; pathological type; tumor-node-metastasis (TNM) stage; ECOG score; smoking history; EGFR mutation type; PD-L1 expression (PD-L1 expression was assessed at the time of disease progression, immediately before the initiation of ICIs); metastatic sites before ICIs; ICI treatment line; ICI treatment regimen; time until disease progression; time until death; adverse effects (AEs); laboratory tests such as routine blood tests, liver and renal function, tumor biomarkers, myocardial zymogram, and thyroid function; and imaging examinations.

Treatment

The physician determined which ICI treatment regimen patients received. All patients were treated with a 3-week treatment plan, and their treatment efficacy and tolerance were evaluated every 2 cycles. The treatment was continued until disease progression, unacceptable serious AEs, death, or any other reason was observed.

Evaluation of efficacy and safety

The effectiveness of the treatment was evaluated according to iRECIST in terms of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The duration of response (DOR) was defined as the time between the date of first response (CR or PR) and the date of first documented event of progression or death. PFS refers to the duration from the first treatment to progression or death, while overall survival (OS) refers to the duration from the first treatment to death or the last follow-up. AEs were divided into grades 1–5 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. We collected the highest grade if more than 1 patient suffered the same AE during treatment. The primary endpoints were PFS and grade 3–5 AEs, while the secondary endpoints were OS, disease control rate (DCR), and subgroup analyses in different mutation subtypes and different therapeutic subgroups.

Statistical analysis

Qualitative data were summarized according to frequency and percentage. The χ^2 test was used for the comparison of categorical variables. The median PFS, OS, and DOR were estimated by the Kaplan-Meier method and compared by the log-rank test in subgroups. Patients without progression or death at the time of analysis were censored at the last follow-up. To respect the real-world data, we do not strictly balance the baseline characteristics between groups. Hazard ratios (HR) and associated 95% confidence intervals (CIs) were estimated by a stratified Cox proportional-hazards model. To avoid the influence of confounding factors, factors with a P value less than 0.1 in univariate analysis were included in multivariate analysis. Multivariate survival analysis was performed by Cox proportional hazards model to evaluate the independent prognostic factors associated with survival. All statistical analyses were performed using SPSS version 26 and GraphPad Prism version 9.2 (GraphPad Prism was used for Kaplan-Meier method and log-rank test; SPSS for other analyses). All two-sided P values less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 102 patients with advanced NSCLC who received PD-1 inhibitors after EGFR-TKI failure were included in the study (*Table 1*). The follow-up time was 36 months. The median age of the population was 53 years (range, 36–80 years). There were 55 (53.9%) females and 47

Table 1 Patient characteristics at baseline

Characteristics	Patients (N=102) (%)
Age (years)	
<60	72 (70.6)
≥60	30 (29.4)
Sex	
Female	55 (53.9)
Male	47 (46.1)
Histology	
Adenocarcinoma	98 (96.1)
Adenosquamous carcinoma	3 (2.9)
Squamous cell carcinoma	1 (1.0)
Stage	
IIIB–C	3 (2.9)
IV	99 (97.1)
Smoking history	
Never	82 (80.4)
Yes	20 (19.6)
Driver mutation	
Exon 19 del	39 (38.2)
Exon 21 L858R	51 (50.0)
T790M positive alone	4 (3.0)
Uncommon	8 (8.8)
T790M mutation	
Positive	39 (38.2)
Negative	30 (29.4)
Unknown	33 (32.4)
Amount of metastatic disease	
0–2	79 (77.5)
3–5	23 (22.5)
Sites of metastatic disease	
Bone	71 (69.6)
Brain	42 (41.2)
Lung	41 (40.2)
Liver	22 (21.6)
Adrenal gland	10 (9.8)
PD-L1 level	
<1%	10 (9.8)
1–49%	25 (24.6)
50–100%	18 (17.6)
Unknown	49 (48.0)
ICI treatment regimen	
IM	10 (9.8)
I + A	22 (21.6)
I + C	49 (48.0)
I + A + C	21 (20.6)
ICI treatment line	
Line 2	34 (33.3)
Line 3 or more	68 (66.7)

PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitor; IM, immune monotherapy; I, immune checkpoint inhibitors; A, antiangiogenic drug; C, chemotherapy.

(46.1%) males in this study. Most patients were stage IV (97.1%), adenocarcinoma (96.1%), nonsmokers (80.4%), and treated with 3 or more lines of immunotherapy (66.7%). Metastatic disease in the bone, brain, lung, liver, and adrenal gland were observed in 71 (69.6%), 42 (41.2%), 41 (40.2%), 22 (21.6%), and 10 (9.8%) patients, respectively. While 79 (77.5%) patients had 0–2 metastases, 23 (22.5%) patients had 3–5 metastases. Ten (9.8%) patients received ICI monotherapy (IM), 22 (21.6%) patients received ICIs combined with antiangiogenesis drugs (I + A), 49 (48.0%) patients received ICIs combined with chemotherapy (I + C), and 21 (20.6%) patients received the above 3 drugs in combination (I + A + C). Initial genetic detection revealed the most common EGFR mutation type was $EGFR^{L858R}$ (n=51), followed by $EGFR^{D19}$ (n=39), uncommon sensitive mutation (n=8), and $EGFR^{T790M}$-positive alone (n=4). After first-line EGFR-TKI failure, 65 patients underwent genetic testing again. Secondary $EGFR^{T790M}$-positive mutation was found in 18 $EGFR^{D19}$ patients, 13 $EGFR^{L858R}$ patients, and 4 uncommon sensitive mutation patients. Thus, there were 39 $EGFR^{T790M}$-positive patients, 30 $EGFR^{T790M}$-negative patients, and 33 patients with unknown status. A total of 43 patients were screened for PD-L1 expression level before

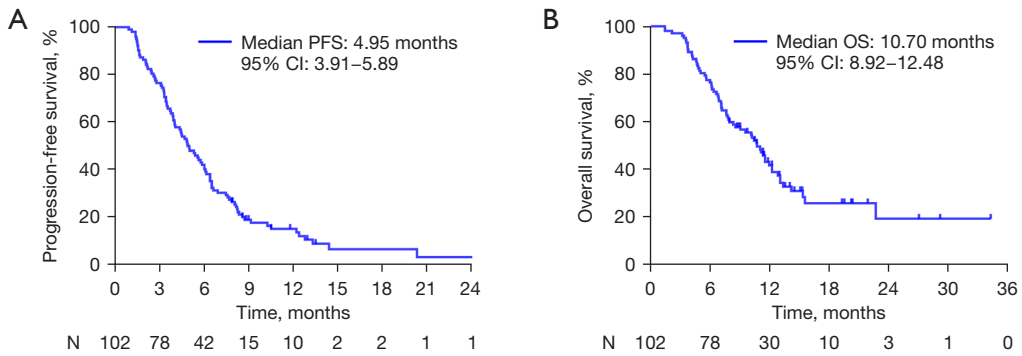

Figure 1 The overall survival curve of patients. (A) The overall PFS curve of patients. (B) The overall OS curve of patients. PFS, progression-free survival; OS, overall survival. N, number of patients.

the initiation of ICIs, 10 (9.8%) of whom had a level of 0%, 25 (24.6%) patients had 1–49%, and 18 (17.6%) patients had 50–100%.

PFS

A total of 91/102 (89.2%) patients had disease progression. The overall median PFS was 4.95 months (95% CI: 3.91–5.89 months) (*Figure 1A*). We used Cox univariate analysis to analyze the influence of baseline factors and found that liver metastasis (P=0.045), $EGFR^{T790M}$ mutation (P=0.002), and driver mutation [P (21L858R *vs.* 19del) =0.004] were significantly associated with PFS (*Table 2*).

To further eliminate interference from multiple influences, factors with P<0.1 in univariate analysis were included in multivariate analysis. We found that patients with $EGFR^{L858R}$ had significantly longer PFS than those with $EGFR^{D19}$ (P=0.004), and patients who were $EGFR^{T790M}$-negative had significantly longer PFS than those who were $EGFR^{T790M}$-positive (*Table 2*). These results suggested that EGFR mutation subtypes were independent prognostic factors of PFS. Although there was no statistical difference between different ICI treatment regimens, a trend towards improved PFS was observed with combination therapy. The median PFS of the IM, I + A, I + C, and I + A + C groups was 3.9, 4.7, 5.0, and 6.1 months, respectively (Table S1).

OS

A total of 66/102 (64.7%) patients died at the last follow-up. The median OS in all patients was 10.70 months (95% CI: 8.92–12.48 months) (*Figure 1B*). Univariate analysis found that liver metastasis (P=0.033) was significantly associated with OS, while multivariate analysis showed no factors significantly related with OS (*Table 3*). Meaningfully, the Kaplan-Meier method showed that the median OS of patients with liver metastases was significantly shorter than for patients without liver metastases (7.28 *vs.* 11.33 months, P=0.024, Figure S1). Therefore, baseline liver metastasis might be a poor prognostic factor of survival outcome. In addition, there was a trend towards improved OS with ICI combination therapy, with median OS of the IM, I + A, I + C, and I + A + C groups of 6.0, 9.0, 11.3, and 11.5 months, respectively (Table S1).

Survival analysis of patients with different EGFR mutation subtypes

We divided the patients into 2 groups according to mutation subtype, with 39 patients in the $EGFR^{D19}$ group and 51 patients in the $EGFR^{L858R}$ group. The baseline characteristics of the 2 groups are shown in *Table 4*. There was a statistically significant difference in the PD-L1 level factor between the 2 groups because the tissue sample of nearly half the patients was insufficient for PD-L1 testing after genetic detection. There were no statistically significant differences between the 2 groups in other baseline characteristics, indicating that no large selection bias existed. For data integrity, we analyzed the original data without modification. The median PFS was 6.40 months (95% CI: 5.64–7.17 months) in the $EGFR^{L858R}$ group and 3.50 months (95% CI: 2.81–4.19 months) in the $EGFR^{D19}$ group, with a significant PFS benefit (P=0.002, *Figure 2A*). The median OS of the $EGFR^{D19}$ and $EGFR^{L858R}$ groups was 10.20 (95% CI: 5.69–14.71) and 11.50 (95% CI: 5.69–14.71) months,

Table 2 Univariate and multivariate analyses for covariables associated with progression-free survival

Characteristics	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age	<60 *vs.* ≥60 years	1.208 (0.761–1.919)	0.422		
Sex	Female *vs.* male	1.190 (0.784–1.803)	0.413		
Smoking history	Yes *vs.* no	0.898 (0.528–1.526)	0.690		
Line	Line 2 *vs.* line 3 or more	0.642 (0.409–1.009)	0.055	0.777 (0.478–1.263)	0.308
Lung metastasis	Yes *vs.* no	0.836 (0.547–1.280)	0.411		
Brain metastasis	Yes *vs.* no	1.168 (0.767–1.779)	0.470		
Liver metastasis	Yes *vs.* no	1.661 (1.012–2.727)	0.045*	1.598 (0.931–2.743)	0.089
Bone metastasis	Yes *vs.* no	1.236 (0.783–1.952)	0.363		
Adrenal gland metastasis	Yes *vs.* no	0.812 (0.406–1.626)	0.556		
Amount of metastatic disease	3–5 *vs.* 0–2	1.066 (0.653–1.741)	0.798		
T790M mutation	Positive *vs.* negative	2.342 (1.384–3.964)	0.001*	2.197 (1.245–3.876)	0.007*
	Unknown *vs.* negative	1.167 (0.683–1.993)	0.692	1.044 (0.598–1.824)	0.879
Driver mutation	21L858R *vs.* 19del	0.517 (0.331–0.807)	0.004*	0.510 (0.323–0.805)	0.004*
	T790M alone *vs.* 19del	3.072 (1.076–8.775)	0.036*	1.362 (0.441–4.208)	0.591
	Uncommon *vs.* 19del	0.601 (0.252–1.433)	0.239	0.579 (0.239–1.401)	0.225
PD-L1 level	1–49% *vs.* <1%	0.804 (0.377–1.715)	0.573		
	≥50% *vs.* <1%	0.980 (0.453–2.116)	0.958		
	Unknown *vs.* <1%	0.555 (0.275–1.121)	0.101		
Treatment	I + A *vs.* IM	0.982 (0.448–2.152)	0.965		
	I + C *vs.* IM	0.926 (0.446–1.925)	0.837		
	I + A + C *vs.* IM	0.825 (0.369–1.845)	0.639		

*, represents a statistically significant difference. PD-L1, programmed death-ligand 1; I, immune checkpoint inhibitors; A, antiangiogenic drug; IM, immune monotherapy; C, chemotherapy; HR, hazard ratio; CI, confidence interval.

respectively, which had no significant difference (P=0.065, *Figure 2B*). The DCR of the $EGFR^{L858R}$ group presented a significant benefit compared with the $EGFR^{D19}$ group (84.3% *vs.* 66.7%, P=0.049, Table S2). The DOR of the 2 groups was similar ($EGFR^{D19}$ *vs.* $EGFR^{L858R}$ 6.9 *vs.* 7.1 months, P=0.952, Table S2).

Meanwhile, we performed survival analysis between the $EGFR^{T790M}$-negative group and $EGFR^{T790M}$-positive group. The $EGFR^{T790M}$-negative group (6.47 months, 95% CI: 4.25–8.54) showed a significant PFS benefit compared with the $EGFR^{T790M}$-positive group (3.20 months, 95% CI: 2.51–4.01) (P=0.003, Figure S2A). The median OS of the 2 groups showed a trend towards improved outcomes but without significant difference (13.3 *vs.* 7.6 months, P=0.098, Figure S2B).

Safety

Treatment-related adverse events are summarized in *Table 5*. Grade 1–2 AEs occurred in 74.5% (n=76) of patients, and grade 3–4 AEs occurred in 18.6% (n=19). The main grade 1–2 treatment-related AEs were anemia (37.3%), fatigue (25.5%), decreased platelet count (17.6%), decreased white blood cells (16.7%), and decreased neutrophil count (14.7%). The main grade 3–4 treatment-related AEs were decreased white blood cells (7.8%), decreased neutrophil count (6.9%), and anemia (2.9%). The main grade 1–2 immune-related AEs (irAEs) were 10 (9.8%) cases of cardiotoxicity, 9 (8.8%) cases of hepatotoxicity, and 8 (7.8%) cases of hypothyroidism. The overall incidence of grade 3–5 irAEs was 6.9%, including 3 cases of hepatotoxicity,

Table 3 Univariate and multivariate analyses for covariables associated with overall survival

Characteristics	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age	<60 *vs.* ≥60 years	0.910 (0.548–1.511)	0.715		
Sex	Female *vs.* male	1.512 (0.922–2.480)	0.101		
Smoking history	Yes *vs.* no	0.574 (0.292–1.126)	0.106		
Line	Line 2 *vs.* line 3 or more	0.827 (0.484–1.412)	0.486		
Lung metastasis	Yes *vs.* no	0.786 (0.475–1.300)	0.348		
Brain metastasis	Yes *vs.* no	1.373 (0.841–2.240)	0.205		
Liver metastasis	Yes *vs.* no	1.818 (1.051–3.146)	0.033*	1.741 (0.990–3.061)	0.054
Bone metastasis	Yes *vs.* no	1.561 (0.898–2.713)	0.114		
Adrenal gland metastasis	Yes *vs.* no	0.984 (0.448–2.162)	0.968		
Amount of metastatic disease	3–5 *vs.* 0–2	1.188 (0.666–2.118)	0.560		
T790M mutation	Positive *vs.* negative	1.663 (0.888–3.114)	0.112		
	Unknown vs. negative	1.220 (0.632–2.356)	0.554		
Driver mutation	21L858R *vs.* 19del	0.601 (0.354–1.018)	0.058	0.632 (0.372–1.076)	0.091
	T790M alone *vs.* 19del	1.093 (0.330–3.616)	0.884	1.012 (0.263–3.003)	0.850
	Uncommon *vs.* 19del	0.732 (0.281–1.904)	0.522	0.730 (0.280–1.901)	0.519
PD-L1 level	1–49% *vs.* <1%	1.196 (0.467–3.065)	0.709		
	≥50% *vs.* <1%	1.157 (0.443–3.022)	0.766		
	Unknown *vs.* <1%	0.824 (0.342–1.988)	0.667		
Treatment	I + A *vs.* IM	0.797 (0.338–1.883)	0.606		
	I + C *vs.* IM	0.696 (0.317–1.531)	0.368		
	I + A + C *vs.* IM	0.771 (0.321–1.850)	0.560		

*, represents a statistically significant difference. PD-L1, programmed death-ligand 1; I, immune checkpoint inhibitors; A, antiangiogenic drug; IM, immune monotherapy; C, chemotherapy; HR, hazard ratio; CI, confidence interval.

Table 4 Patient characteristics for 2 EGFR-mutated types

Characteristics	Exon 19 del (N=39) (%)	Exon 21 L858R (N=51) (%)	P
Age (years)			0.102
<60	32 (82.1)	34 (66.7)	
≥60	7 (17.9)	17 (33.3)	
Sex			0.966
Female	22 (56.4)	29 (56.9)	
Male	17 (43.6)	22 (43.1)	
Histology			0.722
Adenocarcinoma	38 (97.4)	49 (96.1)	
Adenosquamous carcinoma	1 (2.6)	2 (3.9)	

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	Exon 19 del (N=39) (%)	Exon 21 L858R (N=51) (%)	P
Stage			0.847
IIIB–C	1 (2.6)	1 (2.0)	
IV	38 (97.4)	50 (98.0)	
Smoking history			0.702
Never	34 (87.2)	43 (84.3)	
Yes	5 (12.8)	8 (15.7)	
T790M mutation			0.120
Positive	18 (46.2)	13 (25.5)	
Negative	10 (25.6)	19 (37.3)	
Unknown	11 (28.2)	19 (37.2)	
Amount of metastatic disease			0.651
0–2	29 (74.4)	40 (78.4)	
3–5	10 (25.6)	11 (21.6)	
Sites of metastatic disease			
Bone	27 (69.2)	36 (70.6)	0.889
Brain	21 (53.8)	19 (37.3)	0.116
Lung	12 (30.8)	22 (43.1)	0.230
Liver	10 (25.6)	9 (17.6)	0.357
Adrenal gland	5 (12.8)	5 (9.8)	0.652
PD-L1 level			0.037
<1%	8 (20.5)	1 (2.0)	
1–49%	9 (23.1)	14 (27.5)	
50–100%	5 (12.8)	9 (17.6)	
Unknown	17 (43.6)	27 (52.9)	
ICI treatment regimen			0.607
IM	5 (12.8)	5 (9.8)	
I + A	8 (20.5)	12 (23.5)	
I + C	16 (41.0)	26 (51.0)	
I + A + C	10 (25.6)	8 (15.7)	
ICI treatment line			
Line 2	12 (30.8)	17 (33.3)	0.796
Line 3 or more	27 (69.2)	34 (66.7)	

*, represents a statistically significant difference. PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitor; IM, immune monotherapy; I, immune checkpoint inhibitors; A, antiangiogenic drug; C, chemotherapy.

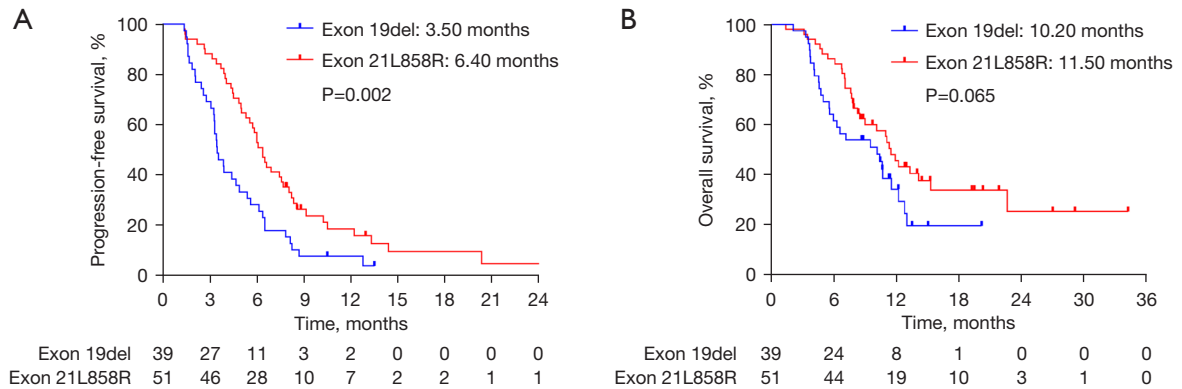

Figure 2 Comparison of survival curve between EGFR^{D19} and EGFR^{L858R} groups. (A) The PFS curve of EGFR^{D19} and EGFR^{L858R} groups. (B) The OS curve of EGFR^{D19} and EGFR^{L858R} groups. PFS, progression-free survival; EGFR, epidermal growth factor receptor; OS, overall survival.

3 cases of cardiotoxicity, and 1 case of pneumonitis. Among them, the 1 case of pneumonitis and 1 case of cardiotoxicity led to discontinuation, and 1 grade 5 irAE, autoimmune myocarditis, occurred in a 70-year-old male. The incidence of treatment-related AEs were similar in different mutation subtypes, age groups, and treatment regimens, while the incidence of grade 3–5 irAEs was less in the EGFR^{L858R} group, EGFR^{T790M}-positive group, patients <60 years group, and the IM and I + A + C groups (Table S3). Overall, the most common treatment-related AEs occurred in the blood system, while the most common irAEs occurred in the endocrine system. Cardiotoxicity, an uncommon but fatal irAE, occurred in 10 patients in our study, which highlighted the need for clinicians to monitor patients carefully and manage AEs in a timely manner.

Discussion

In the present retrospective real-world study, we evaluated the efficacy and safety of PD-1 inhibitors for EGFR-mutant NSCLC after TKI failure and further investigated the subpopulation that exhibited the most benefit. The median PFS and OS of all patients was 4.95 and 10.7 months, respectively. The EGFR^{L858R} group had a significant PFS benefit compared with the EGFR^{D19} group, and likewise the EGFR^{T790M}-negative group compared with the EGFR^{T790M}-positive group. CT18, a multicenter phase-II trial with a similar intention has recently been published (17). The study enrolled 40 EGFR-mutant-advanced patients who had experienced first-line EGFR-TKI failure and did not harbor the T790M mutation. All patients received ICIs combined with chemotherapy (toripalimab plus carboplatin and pemetrexed). The median PFS and OS was 7.0 and 23.5 months, respectively, and the incidence of grade 3–5 irAEs was 7.5%, showing promising antitumor activity with acceptable safety profiles as a second-line setting for patients with EGFR-mutant NSCLC. In addition to some consistent results, such as the similar PFS, the superior outcomes for the EGFR^{L858R} subgroup, and the similar incidence of grade 3–5 irAEs, our real-world retrospective study had a unique advantage compared with the CT18 trial. Firstly, we increased the population size and found that EGFR^{T790M}-positive patients could not obtain appreciable benefit from PD-1 inhibitors after third-generation TKI failure. Secondly, our study was the first prospective or retrospective study to include a head-to-head comparison among 4 different ICI treatment regimens. In addition, we aimed to reflect the actual use of drugs in our real-world study. We await the results of some ongoing phase-III trials, such as Keynote-789, in this setting.

The different survival outcomes among varying mutation subtypes were consistent with findings reported previously (18-20). This is likely due to difference in tumor mutation burden (TMB), a biomarker which has positive correlation with increased efficacy of immunotherapy (21). One study found TMB was significantly higher in patients in the EGFR wild-type group compared with the EGFR-mutant group. Among EGFR-mutant subtypes, TMB in the EGFR^{L858R} group was higher than the EGFR^{D19} group, and the initial TMB of EGFR^{T790M}-positive patients trended towards being lower (22). In addition, another study found that high TMB correlates with improved PFS, DOR, and

Table 5 Treatment-related adverse events

Adverse event	Grade 1–2, n (%)	Grade 3-4, n (%)	Grade 5, n (%)
Any	76 (74.5)	19 (18.6)	1 (1.0)
Led to discontinuation	0	2 (2.0)	0
Led to death	0	0	1 (1.0)
Anemia	38 (37.3)	3 (2.9)	0
Platelet count decreased	18 (17.6)	2 (2.0)	0
White blood cell decreased	17 (16.7)	8 (7.8)	0
Neutrophil count decreased	15 (14.7)	7 (6.9)	0
Hypoalbuminemia	10 (9.8)	0	0
Fatigue	26 (25.5)	2 (2.0)	0
Anorexia	8 (7.8)	1 (1.0)	0
Nausea	7 (6.9)	1 (1.0)	0
Vomiting	5 (4.9)	0	0
Diarrhea	4 (3.9)	0	0
Constipation	2 (2.0)	0	0
Fever	1 (1.0)	0	0
Immune-related adverse events			
Any	29 (28.4)	6 (5.9)	1 (1.0)
Cardiotoxicity	10 (9.8)	2 (2.0)	1 (1.0)
Hepatotoxicity	9 (8.8)	3 (2.9)	0
Hypothyroidism	8 (7.8)	0	0
Hyperthyroidism	3 (2.9)	0	0
Hypoparathyroidism	2 (2.0)	0	0
Adrenal insufficiency	2 (2.0)	0	0
Pneumonitis	2 (2.0)	1 (1.0)	0
Nephrotoxicity	1 (1.0)	0	0
Rash	1 (1.0)	0	0

objective response rate (ORR) to immunotherapy (23). Although it is unclear what is driving the difference in TMB between these alleles, for patients with high TMB, treatment with PD-1 inhibitors after EFGR-TKI failure could be more effective.

After acquired resistance of EGFR-TKIs, for patients with asymptomatic or isolated lesion progression, definitive local therapy for limited lesions and continued osimertinib are recommended (4). Patients with systemic progression could try gene testing again and be treated with corresponding targeted drugs according to mutation type, such as MET amplification, secondary EGFR mutations including C797S and L718Q mutation, HER2 amplification, and BRAF V600, among others (24-26). For patients without an appropriate gene target, a beneficial systemic treatment option is needed. Platinum-based chemotherapy is currently the main subsequent systemic treatment and can maintain median PFS within 4–5 months (27).

A retrospective study found that PD-1 inhibitor could achieve good efficacy in EGFR-mutant NSCLC patients with PD-L1 overexpression. The ORR of 17 patients with the above characteristics was 29.4% after PD-1 inhibitor

treatment, and the median OS was 26.4 months (28). However, some clinical studies showed that immune monotherapy could not improve the survival outcomes in pretreated advanced EGFR-mutant NSCLC compared with chemotherapy (29-33).

Recently, the IMPOWER150 trial's (34) final analyses were published of the EGFR-mutation subgroup with TKI failure. There was a trend towards improved median OS in the atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) arm (29.4 months) versus the BCP arm (18.1 months), with an HR of 0.60 (95% CI: 0.31–1.14), as well as in median PFS (10.2 *vs.* 6.9 months; HR 0.61; 95% CI: 0.36–1.03). No trend for median OS was noted between the ACP arm and BCP arm (19.0 *vs.* 18.1 months, HR =1.0, 95% CI: 0.57–1.74), suggesting bevacizumab was an important component of these arms. Another phase II prospective study (35) enrolled 40 advanced EGFR-mutation NSCLC patients after EGFR-TKI failure. All patients received the modified regimen of IMPOWER150 (atezolizumab/carboplatin/pemetrexed/bevacizumab) to tailor to the needs of East Asian patients, and similar efficacy was achieved (median PFS: 9.4 months, median OS: not reached), with a much more favorable toxicity profile compared with that of the IMPOWER150 trial. The results of ORIENT-31 phase III trial also supported the combination of PD-1 inhibitors, antiangiogenic therapy, and chemotherapy compared with chemotherapy. These encouraging results showed the combination of PD-1 inhibitors, antiangiogenic therapy, and chemotherapy were effective for such patients. According to our results, although there was no statistical difference between different ICI treatment regimens, there was a trend towards improved PFS and OS with combination therapy, especially the triple-drug combination of PD-1 inhibitors, antiangiogenic therapy, and chemotherapy. These results suggested a combination of immunotherapy, antiangiogenic therapy, and chemotherapy could bring more survival benefits.

Liver metastases have been shown to be a poorer prognostic factor in NSCLC than metastases to other sites (36). Patients with baseline liver metastases have been found to receive only minimal therapeutic benefit from immune monotherapy (37). Our study revealed the same results, with median PFS and OS in liver metastatic patients of 3.5 and 6.8 months, respectively, significantly shorter than patients without liver metastases. However, the IMPOWER150 trial achieved an exciting result in the baseline liver metastases subgroup. Improved PFS was observed with ABCP versus the BCP arm (8.2 *vs.* 5.4 months; HR 0.41, 95% CI: 0.26–0.62), as well as improved OS (ABCP *vs.* BCP: 13.2 *vs.* 9.1 months; HR 0.68, 95% CI: 0.45–1.02). However, there was no PFS or OS benefit in the ACP arm compared with the BCP arm (34,38). These results highlighted that the I + A + C regimen might be a potential new treatment option for liver metastatic patients with poor prognostic outcomes.

The overall incidence of grade 3–5 irAEs was 6.9%, which was similar to the AEs in NSCLC patients without driver mutations (39-41). Interestingly, pneumonitis was the most common irAE in NSCLC patients without driver mutations. However, we found immunotherapy resulted in a high rate of cardiotoxicity and thyroid toxicity in patients with EGFR-mutant advanced NSCLC. These results highlighted that clinicians should monitor irAEs carefully and manage them in time. Additionally, a large-cohort study is needed to validate the phenomenon.

Conclusions

The present study was limited by its retrospective nature, including the small number of enrolled cases, recall bias, loss of follow-up bias, data heterogeneity, and so on. Nevertheless, our real-world study presented some meaningful results. After EGFR-TKI failure, immunotherapy provided better survival in the advanced NSCLC $EGFR^{L858R}$ subgroup and $EGFR^{T790M}$-negative subgroup, and there was a trend towards improved outcomes with immune combination therapy. In addition, toxicity was well tolerated.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6272/rc

Data Sharing Statement: Available at https://atm.amegroups.

com/article/view/10.21037/atm-22-6272/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6272/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (No. SDTHEC202201100829). Individual consent for this retrospective analysis was waived.

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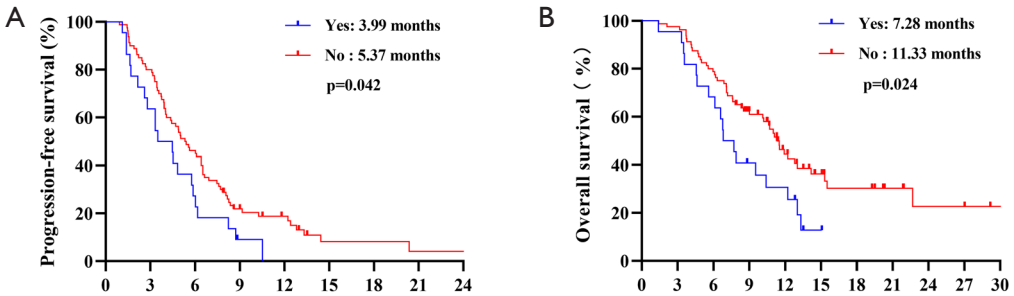

Figure S1 Comparison of survival curve between liver metastasis and without liver metastasis groups. (A) The progression-free survival curve of liver metastasis and without liver metastasis groups. (B) The overall survival curve of liver metastasis and without liver metastasis groups.

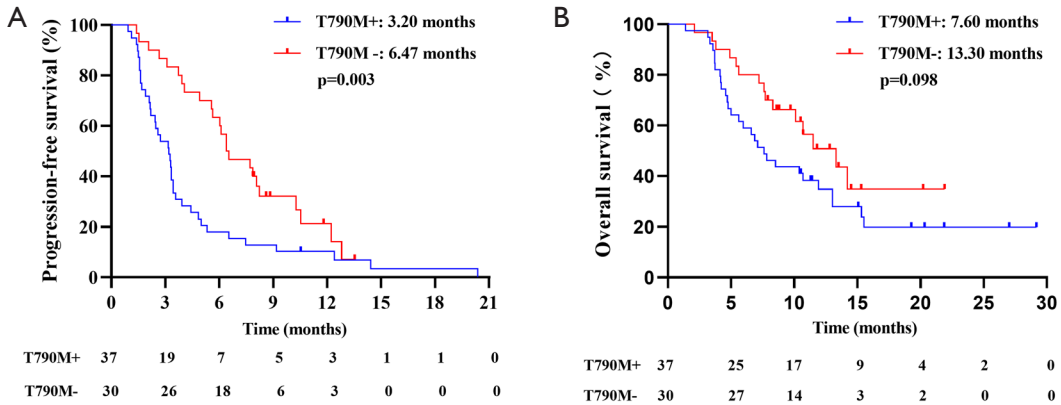

Figure S2 Comparison of survival curve between $EGFR^{T790M}$-positive and $EGFR^{T790M}$-negative groups. (A) The progression-free survival curve of $EGFR^{T790M}$-positive and $EGFR^{T790M}$-negative groups. (B) The overall survival curve of $EGFR^{T790M}$-positive and $EGFR^{T790M}$-negative groups.

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Table S1 Median PFS and OS in different treatment subgroups

Variable	mPFS (months, 95% CI)	P value	mOS (months, 95% CI)	P value
ICI treatment regimen		0.946		0.837
IM	3.93 (1.56–6.31)		5.97 (3.57–15.26)	
I+A	4.70 (2.98–6.42)		9.03 (6.55–11-51)	
I+C	5.00 (2.44–7.56)		11.33 (6.81–15.85)	
I+A+C	6.10 (3.857–8.343)		11.50 (9.17–13.83)	

PFS, progression-free survival; OS, overall survival; I, immune checkpoint inhibitors; IM, immune monotherapy; A, antiangiogenic drug; C, chemotherapy; ICI: immune checkpoint inhibitors; CI: confidence interval.

Table S2 Tumor response of patients for 2 EGFR-mutated types

Variable	Exon 19 del (N = 39)	Exon 21 L858R (N = 51)	P value
Best overall response—N (%)			
Complete response	0 (0)	0 (0)	
Partial response	5 (12.8%)	14 (27.5%)	
Stable disease	21 (53.8%)	29 (56.8%)	
Progressive disease	13 (33.3%)	8 (15.7%)	
Disease control rate	66.7%	84.3%	0.049*
Time to response—M[†]			
Median	1.4	1.4	0.950
Range	—	1.3–1.5	
Duration of response—M[†]			
Median	6.9	7.1	0.952
Range	6.0–7.7	6.4–7.7	

EGFR = epidermal growth factor receptor, N = number, M = month, disease control rate = the patients who had complete response or partial response, time to response = the time from immunotherapy beginning to the date of first documented complete or partial response, duration of response = the time between the date of first response and the date of first documented event of progression or death. [†]Results were calculated with the use of the Kaplan–Meier method. *represents a statistically significant difference.

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Table S3 Adverse events in different groups

Adverse events	Treatment-related adverse events		Immune-related adverse events	
	All grades	Grade 3–5	All grades	Grade 3–5
Driver mutation				
Exon 19 del	82.1%	17.9%	33.3%	10.3%
Exon 21 L858R	72.5%	17.6%	33.3%	5.9%
T790M mutation				
Positive	79.5%	17.9%	28.2%	2.6%
Negative	73.3%	16.7%	30.0%	10.0%
Age				
<60	73.6%	15.3%	29.2%	5.6%
≥60	83.3%	23.3%	36.7%	10.0%
ICI treatment regimen				
IM	50.0%	0.0%	10.0%	0.0%
I+A	72.7%	13.6%	50.0%	13.6%
I+C	81.6%	26.5%	30.6%	8.2%
I+A+C	81.0%	14.3%	23.8%	0.0%

ICI: immune checkpoint inhibitors; I, immune checkpoint inhibitors; IM, immune monotherapy; A, antiangiogenic drug; C, chemotherapy.

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