Original Article

Pembrolizumab for the better treatment of EGFR-mutant T790M-negative advanced lung adenocarcinoma patients than dual treatment of pemetrexed plus platinum after tyrosine kinase inhibitor treatment failure

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Background: The treatment of lung cancer patients, especially those with epidermal growth factor receptor (EGFR)-mutant T790M-negative adenocarcinoma, after first- or second-line tyrosine kinase inhibitor (TKI) treatment failure is challenging due to the poor prognosis and limited effectiveness of platinum two-drug chemotherapy or chemotherapy plus anti-angiogenesis therapy. It is well-known that pembrolizumab monotherapy exhibits low toxicity and long-term survival, but it is unknown in these patients.

Methods: From September 2018 to March 2021, 460 patients in Jiangmen Central Hospital were included and 82 patients with disease progression in lung adenocarcinoma who remained T790M-negative on the second biopsy were screened. Two groups were divided according to treatment status, and simple random sampling was performed to obtain 32 cases respectively. The safety of the patients was subsequently evaluated by telephone follow-up.

Results: The objective response rate (ORR) and disease control rate (DCR) in the pembrolizumab group were 15.63% and 53.13%. In the chemotherapy group, the ORR was 8.33% and the DCR was 25% (P<0.05). In the pembrolizumab group, the progression-free survival (PFS) [14.65 months, 95% confidence interval (CI): 13.03 to 16.28] was significantly higher than that of the control group (9.54 months, 95% CI: 8.43 to 10.65) (P<0.05). In the univariate analysis, programmed cell death protein 1 ligand (PD-L1) expression, smoking status, gender, and whether first-line chemotherapy was associated with survival. In the multivariate analysis, gender [P=0.001; hazard ratio (HR) 10.98, 95% CI: 2.49–46.67], first-line chemotherapy (P=0.037; HR 4.5, 95% CI: 1.1–4.81), and PD-L1 expression (P=0.039; HR 0.16, 95% CI: 0.04–0.68) were correlated with patient survival. Grade 3 or grade 4 treatment-related adverse events were not found in the pembrolizumab group, while 2 cases of grade 3 or 4 treatment-related adverse events occurred in the control group.

Conclusions: In advanced lung adenocarcinoma patients with EGFR-mutant T790M-negative after TKI treatment, pembrolizumab had a higher ORR and PFS. Pembrolizumab in women with first-line chemotherapy and PD-L1 ≥25% of those patients may have a good response and a low rate of adverse reactions. A multicenter, prospective, evidence-based study of pembrolizumab salvage therapy in those patients is warranted for posterior line treatment.

Keywords: Lung cancer; PD1; epidermal growth factor receptor mutation (EGFR mutation); pembrolizumab

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Introduction

Lung cancer is a malignant tumor with a low survival rate at the advanced stage. Lung cancer accounts for the highest proportion of all male and female deaths, and nearly a quarter of all deaths are caused by lung cancer (1). The discovery of oncogenic driver genes such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and proto-oncogene 1 receptor tyrosine kinase (ROS1) has opened a new era of targeted therapy for lung cancer. Treatment with EGFR-tyrosine kinase inhibitors (TKIs) is associated with higher response rates and higher survival in EGFR mutation-positive patients (2). Due to the high EGFR mutation rate in Asian, non-smoking, and female adenocarcinoma patients, the survival rate is prolonged, and the quality of life is greatly improved after TKI treatment (3). National Comprehensive Cancer Network (NCCN) guidelines recommend first-line TKI therapy for patients with EGFR gene mutation, which has become the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR-sensitive mutation (4). However, some patients were given first-line chemotherapy before TKI medical decision. EGFR driver gene-positive patients are recommended to receive first-line chemotherapy according to the Chinese Society of Clinical Oncology (CSCO) guidelines, and it is also recommended to switch to EGFR-TKI therapy after completing conventional chemotherapy (including maintenance therapy) or change to targeted therapy after discontinuation of chemotherapy (grade 2A evidence) (5). Previous studies have shown that the survival time of advanced lung cancer patients with EGFR mutation can be improved after first-line platinum double-drug chemotherapy plus targeted therapy, especially for patients with exon 19 mutation (6-8). Nevertheless, acquired resistance to targeted therapies is inevitable and ultimately leads to treatment failure. TKI treatment will cause drug resistance in patients, leading to a second biopsy. If next-generation sequencing (NGS) still shows EGFR mutation without T790M mutations, platinum two-drug chemotherapy and targeted anti-angiogenesis therapy can be used in treatment, but the effect is limited because of the substantial hematotoxicity, cardiotoxicity and nephrotoxicity, and poor prognosis. Immunotherapy has dramatically improved the survival of NSCLC patients with lower toxic effects in the last decade. However, the application of immunotherapy to patients with EGFR-mutant T790M-negative adenocarcinoma after first- or second-line TKI treatment failure is still unknown. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-671/rc).

Methods

General information

Between September 1, 2018, and March 1, 2021, 82 patients with EGFR-mutant T790M-negative lung adenocarcinoma after first- or second-line TKI treatment failure were screened from 460 patients and finally divided into two groups. By simple random sampling, 32 cases were obtained in the 42 case pembrolizumab group and 32 samples were obtained in the 40 cases chemotherapy group. The inclusion criteria were as follows: (I) patients aged 18–65 years were diagnosed with lung adenocarcinoma after drug resistance by pathology or cytology; (II) EGFR mutation was previously treated with platinum-containing two-drug chemotherapy or first-generation targeted drugs, excluding first-line combination therapy; (III) patients with EGFR mutation and no T790M mutation or co-mutation detected by secondary biopsy NGS; (IV) patients with at least one measurable lesion defined by the Response Evaluation Criteria in Solid Tumors (RECIST); (V) Eastern Cooperative Oncology Group (ECOG) PS score of 0–1; (VI) those with no contraindications for immunotherapy and chemotherapy, with sufficient functional reserves of major organs. The exclusion criteria were as follows: patients with poorly controlled hypertension, bleeding tendency, or ischemic cardiovascular disease, along with severe liver or kidney dysfunction. In the immunotherapy group, 32 patients were selected to receive pembrolizumab monotherapy, while in the control chemotherapy group, 32

patients were given pemetrexed plus platinum-containing double drug treatment. In the immunotherapy group, the median age was 58.30±2.31 years, ranging from 51 to 70 years. There were 10 males and 22 females. The performance status (PS) score was 0 in 22 cases and 1 in 10 cases. The expression of PD-L1 <25% in 26 cases and PD-L1 ≥25% in 6 cases. There were 18 cases in stage III and 14 cases in stage IV. There were 19 exons 19 deletion mutations and 13 L858R mutations in exons 21. There were 9 smokers and 23 non-smokers. First-line chemotherapy was administered in 21 cases and first-line targeted therapy was administered in 11 cases. 32 patients in the control chemotherapy group were treated with pemetrexed plus platinum, including 49–69 years old with a median age of 56.40±3.42 years old. There were 17 males and 15 females. The PS score was 0 in 18 cases and 1 in 14 cases. The expression of PD-L1 <25% in 22 cases and PD-L1 ≥25% in 10 cases. There were 20 stage III cases and 12 stage IV cases. There were 14 exon 19 deletion mutations and 18 exon 21 L858R mutations. There were 17 smokers and 15 non-smokers. First-line chemotherapy was administered in 18 cases and first-line targeted therapy was administered in 14 cases.

Preoperative biochemical routine tests, chest CT, PET (bone scan and isotope pulmonary perfusion imaging), lung function tests, and chest radiography were performed. All enrolled patients received at least 4 cycles of chemotherapy and more than 4 cycles of immunotherapy and followed up to evaluate their efficacy until disease progression with death or unacceptable adverse reactions occurred up to March 1, 2021. Lost data of follow-up as a truncated value. The study was approved by ethics board of Jiangmen Central Hospital [No. (2018)50]. Informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Design

The immunotherapy group received pembrolizumab 200 mg/time, with continuous intravenous infusion for 20 min, and 21 days was a treatment cycle. The efficacy was evaluated once every 2 treatments cycles. The control group received pemetrexed plus platinum two-drug chemotherapy: pemetrexed 500 mg/m^2, intravenous drops on the first day for 21 days as a treatment cycle, and the efficacy was evaluated once every 2 treatment cycles. According to imaging examinations, RECIST 1.1 was used to evaluate the efficacy (9), which was divided into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response rate (ORR) was the sum of CR and PR. The disease control rate (DCR) was the sum of CR, PR, and SD. Progression-free survival (PFS) was the time interval from receiving pembrolizumab or chemotherapy to disease progression or death, or the time interval from withdrawal to PD with unacceptable adverse reactions. The ORR, DCR, PFS, and adverse reactions in the 2 groups were observed. Lung cancer staging was based on TNM 8th edition (10). Adverse reactions were graded I-IV according to the Common Terminology Criteria for Adverse Events 4.0 (CTCAE 4.0) of the US National Cancer Institute (11).

Statistical analysis

Baseline characteristics in this study were described by applying descriptive statistics. All calculations included calculating the means ± 95% confidence intervals (95% CIs). SPSS 24.0 statistical software was used for statistical analysis. The R×C Chi-square test or Fisher's exact probability method was used for counting data. The Kaplan-Meier method was used for survival analysis and single-factor analysis, and the log-rank test was used to compare survival times between the 2 groups. The Cox proportional risk regression model was used for multivariate analysis. Tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

A total of 460 patients in Jiangmen Central Hospital were included for NGS testing. Activating EGFR mutations were detected in 252 of 460 patients (54.78%). Two hundred and twenty-two had deletion in exon19 or L858R mutations patients were treated with EGFR-TKI or EGFR-TKI after platinum-containing dual drugs in first-line. Among the Two hundred and twenty-two patients who received EGFR-TKI in first-line or second-line, 151 were recognized as having PD during EGFR-TKI treatment, whereas 71 were not recognized as CR, PR, or SD. Among 151 patients, 64 patients were received a second biopsy and NGS, and 49 patients were excluded for a variety of reasons.82 patients were screened who had no change in pathological findings, and still with EGFR mutation T790M-negative. According to the treatment plans. Those patients were divided into 42 cases of pembrolizumab and 40 cases of chemotherapy, followed by simple random sampling, with

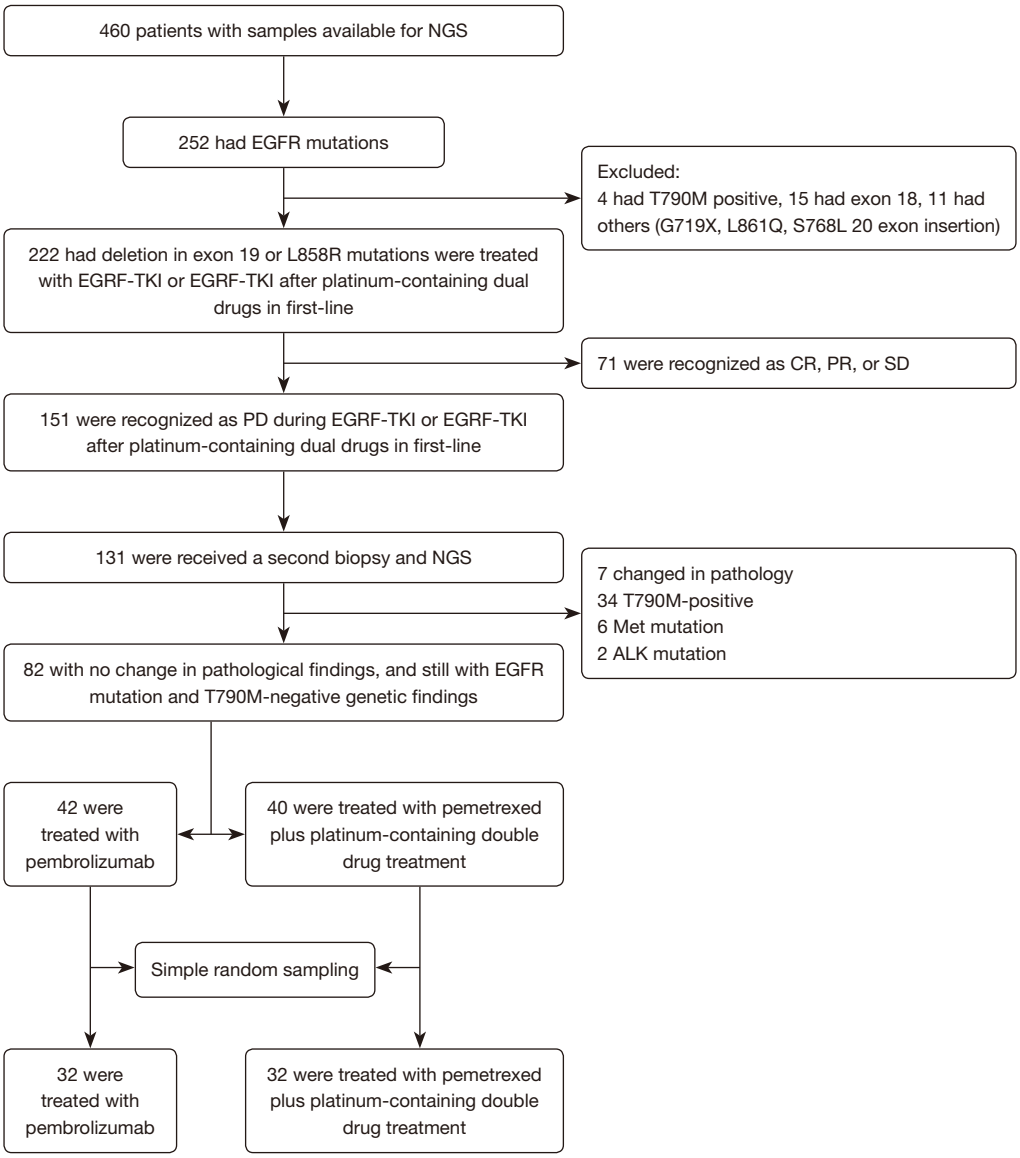

Figure 1 Flowchart of patients' selection. NGS, next-generation sequencing; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Met, mesenchymal-epithelial transition; ALK, anaplastic lymphoma kinase.

32 cases each (*Figure 1*). The baseline characteristics of the 2 groups are shown in (*Table 1*), and there was no difference between the 2 groups (P>0.05).

In terms of objective responses, in the pembrolizumab group, there was 1 case of CR, 4 cases of PR, 12 cases of SD, and 15 cases of PD. The ORR and DCR were 15.63% and 53.13%, respectively. In the chemotherapy group, there were no cases of CR, 2 cases of PR, 6 cases of SD, and 24 cases of PD among the 32 patients. The ORR was 8.33% and the DCR was 25% (P<0.05).

PFS between the 2 groups was compared by the Kaplan-Meier survival curve method after 8–27 months of TKI-targeted treatment resistance. PFS was 14.65 months (95% CI: 13.03 to 16.28) in the pembrolizumab treatment group and 9.54 months (95% CI: 8.43 to 10.65) in the chemotherapy group. The log-rank test showed a significant difference in survival rate between the 2 groups, and the survival rate of the pembrolizumab treatment group was

Table 1 Baseline characteristics of the pembrolizumab and chemotherapy groups after TKI first- or second-line treatment resistance

Variables	Treatment with pembrolizumab	Platinum-based chemotherapy	P value
Age, years			0.309
≥65	15	11	
<65	17	21	
Sex			0.076
Male	10	17	
Female	22	15	
Mutation			0.211
Del19	19	14	
L858R	13	18	
Grade			0.611
III	18	20	
IV	14	12	
Smoker			0.121
No	23	17	
Yes	9	15	
PS			0.302
0	22	18	
1	10	14	
PD-L1			0.248
≥25%	6	10	
<25%	26	22	
Them in first-line			0.442
Yes	21	18	
No	11	14	

TKI, tyrosine kinase inhibitor; PD-L1, programmed cell death protein 1 ligand; PS, performance status.

significantly higher than that of the chemotherapy group (P<0.05) (*Figure 2*).

Univariate and multivariate analyses were performed for lung adenocarcinoma patients treated with pembrolizumab after first- or second-line TKI failure. In the univariate analysis, PD-L1 expression, smoking status, gender, and whether first-line chemotherapy was associated with survival (*Figure 3*). In the multivariate analysis, gender (P=0.001; HR 10.98, 95% CI: 2.49–46.67), first-line

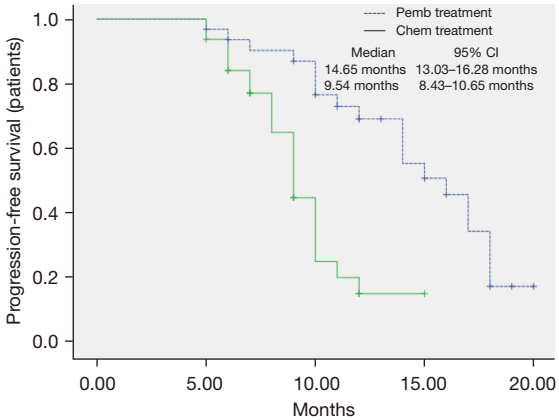

Figure 2 Survival analysis of lung cancer patients with EGFR resistance treated with pembrolizumab and chemotherapy. EGFR, epidermal growth factor receptor; PD-L1, programmed cell death protein 1 ligand; CI, confidence interval.

chemotherapy (P=0.037; HR 4.5, 95% CI: 1.1–4.81), and PD-L1 expression (P=0.039; HR 0.16, 95% CI: 0.04–0.68) were correlated with patient survival (*Table 2*).

Grade 3 or grade 4 treatment-related adverse events were not found in the immunotherapy treatment group. There were 3 cases of fatigue, 2 cases of skin rash, 2 cases of gamma-glutamyl transferase elevation, 1 case of diarrhea, and 1 case of transfusion reaction. Two cases of grade 3 or 4 treatment-related adverse events occurred in the control group, including 3 cases related to the treatment of bone marrow suppression, 3 cases of elevated transaminase, and 5 cases of gastrointestinal reactions such as vomiting.

Discussion

EGFR mutations are present in 30–50.9% of Asian patients with NSCLC (12,13). For patients with advanced lung cancer with EGFR mutation, EGFR-TKIs can be clinically targeted for precise and individualized treatment. Compared with chemoradiotherapy alone, the survival was prolonged and the adverse reactions were relatively mild. However, many patients were often found drug resistant to EGFR-TKIs within 1 year, leading to tumor progression (13-15). In the real world, mutation of exon 20 of EGFR (T790M positive) after acquired resistance of EGFR-TKIs in Asian patients is the common type, with an incidence up to 50%. If T790M positive is detected in a second test after acquired resistance, third-generation targeting has a good effect (16). However, EGFR mutation and T790M negative

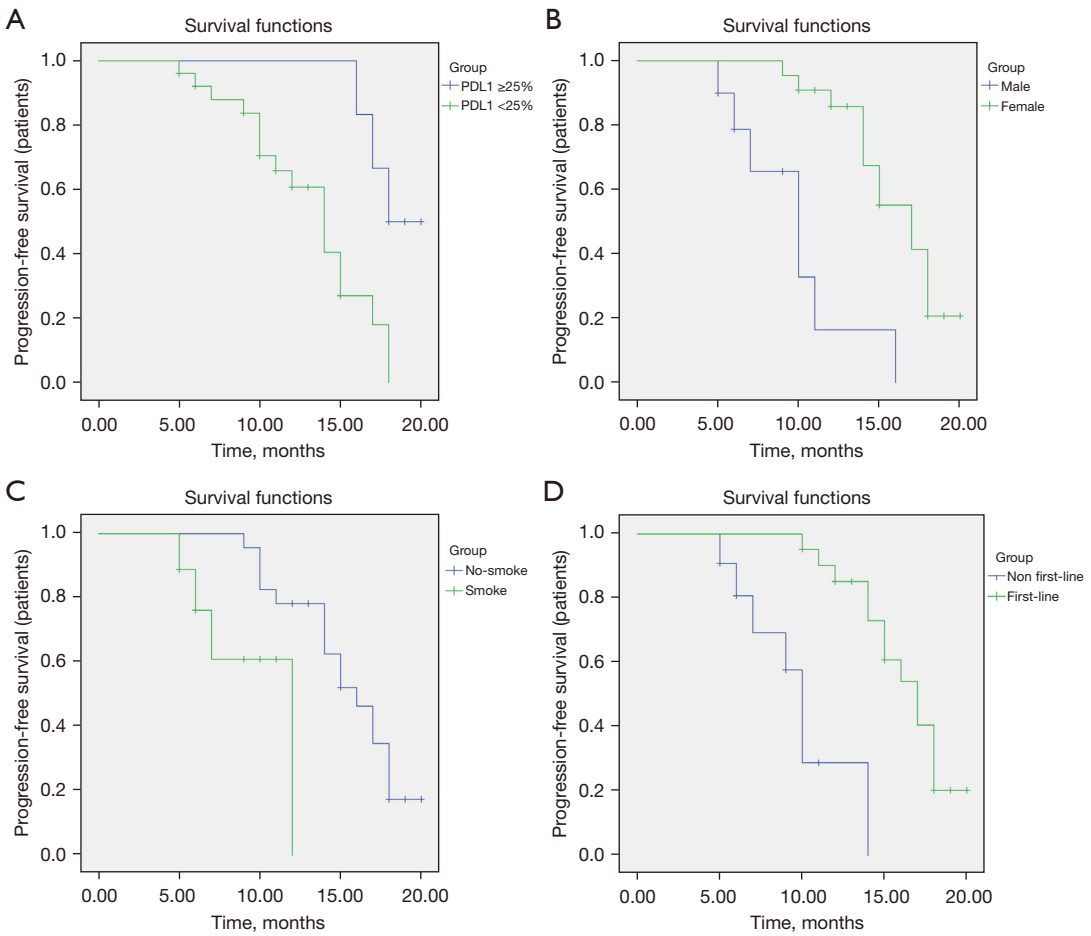

Figure 3 Univariate analysis of lung cancer patients with TKI progression treated with pembrolizumab. (A) Single-factor analysis of the effect of PD1 expression on survival; (B) single-factor analysis of the effect of gender on survival; (C) single-factor analysis of the effect of smoking on survival; (D) single-factor analysis of the effect of first-line chemotherapy on survival. TKI, tyrosine kinase inhibitor; PD1, programmed cell death protein 1.

patients still account for a part of the proportion. After drug resistance, T790M negative patients can be treated with platinum two-drug chemotherapy or chemotherapy plus anti-angiogenesis therapy, but the survival time is short and the effect is limited.

Tumor immunotherapy with immune checkpoint inhibitors, mainly including cytotoxic T-lymphocyte-associated antigen (CTLA-4) and anti-PD-1/PD-L1 antibodies is a hot field. Immune checkpoint inhibitors have significant lasting effects in the treatment of NSCLC patients (17). Previous study has shown that EGFR mutation in NSCLC patients mostly belongs to the immune desert type or immune immunity type, with fewer CD8 positive cells infiltrating the immune microenvironment, and more inhibitory regulatory T cells (Tregs) or macrophages, and overexpression of IL2 is involved in immunosuppression (18). In addition, EGFR mutations are associated with low response rates to PD-1 pathway blockade in NSCLC patients who often have poor antigenicity (19). The expression of PD-L1 in EGFR mutant patients was lower than that in EGFR wild-type patients (20). Patients with EGFR mutation showed a lack of T cell infiltration and a reduced PDL1+/CD8+ TIL ratio, while T cell infiltration PD-L1+/CD8+TIL ratio and tumor mutational burden (TMB) was lower than EGFR wild-type (20). EGFR-mutated NSCLC tumors lack T cell infiltration and have a more immunosuppressive tumor microenvironment, which may lead to a negative feedback response to PD-1/PD-L1 inhibitors (21,22). Therefore, patients with EGFR mutation are not suitable

Table 2 Univariate and multivariate Cox analysis of patients receiving pembrolizumab for TKI treatment progression in lung adenocarcinoma

Covariates	Univariate analysis		Multivariate analysis	
	PFS (95% CI)	P value	HR (95% CI)	P value
Smoker		0.011	0.38 (0.07–2.14)	0.273
No	15.44 (13.98–16.90)			
Yes	9.70 (7.31–12.09)			
Chemotherapy in first-line		<0.001	4.50 (1.10–4.81)	0.037
Yes	16.25 (14.91–17.59)			
No	9.83 (7.62–12.05)			
PS		0.258		
0	15.40 (12.75–18.05)			
1	13.61 (11.88–15.33)			
Age, years		0.287		
<65	15.41 (13.75–17.08)			
≥65	13.31 (10.50–16.11)			
Mutation		0.176		
Exon 19	15.50 (13.87–17.13)			
L858R	12.75 (9.69–15.82)			
Grade		0.331		
III	15.43 (13.56–17.29)			
IV	13.25 (10.78–15.72)			
Sex		<0.001	10.78 (2.49–46.67)	0.001
Male	8.63 (5.92–10.88)			
Female	16.10 (14.68–17.52)			
PD-L1		0.006	0.16 (0.04–0.68)	0.039
≥25%	18.50 (17.21–19.79)			
<25%	13.19 (11.54–14.83)			

TKI, tyrosine kinase inhibitor; PD-L1, programmed cell death protein 1 ligand; PS, performance status; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival.

for immunotherapy.

Now no large prospective studies of patients in immunotherapy after first- or second-line EGFR-TKI resistance were given. The KEYNOTE 789 trial is still being conducted to explore drug resistance in patients treated with EGFR-TKIs failure. Results of the ATLANTIC study were updated to explore the efficacy and safety of durvalumab monotherapy in the third-line and back-line treatment of patients with advanced NSCLC, including EGFR mutation-positive patients. The results showed that patients with EGFR mutation had an overall survival (OS) of 16.1 months, which was better than the chemotherapy group alone, revealing that immunotherapy can play an important role in the back-end treatment of patients with EGFR mutation (23). EGFR mutation-positive T790M-negative NSCLC patients with acquired resistance to EGFR-TKIs may be more likely to benefit from nivolumab treatment than chemotherapy, which attributes to high PD-L1 expression levels (24). NSCLC patients with EGFR-TKI mutations can not only benefit

from the direct tumor-killing effect, but also indirectly benefit from the immune enhancement after EGFR-TKI treatment. Both gefitinib-sensitive and drug-resistant cells were shown to be inhibited by PD-1 blockade, this suggests that upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC, it implies that optional immune targeted therapy for NSCLC patients with EGFR mutation (25). Pembrolizumab treatment of EGFR-mutant T790M-negative advanced lung adenocarcinoma patients after first- or second-line tyrosine kinase inhibitor treatment failure had better efficacy, which may be due to changes immune mechanisms and the microenvironment after chemotherapy, leading T lymphocytes having an enhanced ability to recognize TKI-treatment resistant tumors (26).

Both mutations and activation of EGFR can increase PD-L1 expression. This implies that patients with EGFR mutations resistant to EGFR-TKIs may also have high levels of PD-L1 (27). PD-1 inhibitors have shown anti-tumor activity against NSCLC. Multivariate analysis of PD-L1 expression in NSCLC suggests that EGFR mutation and adenocarcinoma histology were significantly associated with PD-L1 expression. The expression of PD-L1 in EGFR mutation was also significantly higher than that of wild-type EGFR. The EGFR inhibitor erlotinib downregulated the expression of PD-L1 in EGFR mutations and adenocarcinoma histology cells, but not in the wild-type EGFR cells, suggesting that PD-L1 expression is increased the EGFR signaling pathway by initiating EGFR mutation (28). PD-1 blockade alleviates tumor burden by eliminating tumor cells and reducing the level of tumor-promoting cytokines and the number of immunosuppressive cells (29). In this study, T790M-negative patients with TKI resistance and PD-L1 ≥25% could benefit from immunotherapy with Pembrolizumab, indicating that PD-L1 expression is still an important indicator of immunotherapy efficacy.

The expression of PD-L1 in the females is higher than that in males, males in immunotherapy have a better response than females in previous studies (30,31). But in our study, the immunotherapy group have a better response than the chemotherapy group in female patients, though the expression of PD-L1 was higher in female patients than in normal people, which may be due to the higher rate of EGFR mutation in female patients. The sensitive EGFR mutation has an inherent correlation with the increase of PD-L1. The use of EGFR-TKIs could reduce the expression of PD-L1, but when drug resistance occurs, the expression of PD-L1 increases again. Phosphatidylinositol-3 kinase/protein kinase B (PI3K/AKT) and mitogen-activated ERK/extracellular signal-regulated kinase (MEK/ERK), which EGFR downstream signaling pathway, is reactivated by other pathways (32). Alternatively, sex hormones may activate other pathways in the back line of female patients, which may provide theoretical basis for immunotherapy of anti-PD-1/PD-L1 treatment in the backline of drug resistance to EGFR-TKIs (33).

Tumor mutation burden may be higher in patients with a history of heavy smoking. The expression of PD-L1 was found to be higher in non-smokers than smokers. In immunotherapy, smoking is better than non-smoking in previous studies (34,35). pembrolizumab was given after TKI resistance, Univariate analysis showed that non-smokers were beneficial. It could be that most female patients with EGFR mutations were non-smokers or light-smokers with low PDL1 expression and poor immunotherapy effect. However, PDL1 and TMB increased again after drug resistance, so immunotherapy benefited. In the multivariate analysis, no benefit was highlighted, which may be due to the small number of cases or the influence of bias factors.

Targeted therapies typically have rapid and impressive response rates but moderate PFS, while immunotherapy can achieve durable tumor control but with a lower response rate (36). After drug resistance to targeted therapy, pembrolizumab monotherapy has achieved good efficacy, thus bringing greater benefits to patients with lung adenocarcinoma. Pembrolizumab in women with first-line chemotherapy and PD-L1 ≥25% of those patients may have a good response and low rate of adverse reactions in EGFR-mutant T790M-negative advanced lung adenocarcinoma patients after TKI treatment failure.

This study was an exploratory post-hoc analysis, not a strict randomized controlled trial, with a limited sample size in each group, incomplete baseline balance of patients, and a limited level of evidence. Although PD-L1 expression of EGFR mutation patients in each group after drug resistance was presented in the analysis, PD-L1 was not analyzed before drug resistance, so there was still bias. Therefore, a multicenter, prospective, evidence-based study of pembrolizumab salvage therapy in patients with EGFR-positive NSCLC who do not have T790M mutations after chemotherapy and TKI resistance is warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-671/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-671/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-671/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 ethics board of Jiangmen Central Hospital [No. (2018)50]. Informed consent was taken from all the patients.

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