Original Article

Efficacy and safety of anti-programmed cell death protein 1 antibody combination therapy in patients with advanced experienced epidermal growth factor receptor-tyrosine kinase inhibitor-resistant lung adenocarcinoma: a retrospective cohort study

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Background: The effectiveness of combining anti-programmed cell death protein 1 (PD-1) and chemotherapy has been evaluated as superior to that of chemotherapy alone in the patients with advanced epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI)-resistant non-small cell lung cancer (NSCLC). In this study the efficacy and safety of anti-PD-1 combination therapy were evaluated retrospectively in patients who experienced EGFR-TKI-resistant with advanced lung adenocarcinoma (LUAD), with the goal of providing helpful guidance for clinical application.

Methods: The clinical results of patients with incurable LUAD who received anti-PD-1 antibody combined with or without anti-angiogenic or chemotherapy after EGFR-TKI therapy failure were collected. The efficacy was calculated based on the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). The efficacy of the regimes was compared according to treatment groups and programmed cell death ligand 1 (PD-L1) expression.

Results: The final analysis included a total of 43 patients with advanced EGFR-mutant LUAD. The overall cohort had an ORR of 23.3%, median PFS (mPFS) of 6.5 months, and median OS (mOS) of 10.6 months. No notable distinction was observed in mPFS and mOS among patients receiving three types of anti-PD-1 antibody combination therapies. Patients with positive PD-L1 expression showed a longer mPFS compared to patients with negative PD-L1 expression. No statistical difference was detected in terms of mPFS between the use of immune combination chemotherapy and immune combination anti-angiogenic therapy in the PD-L1 positive subgroup, and PFS was prolonged regardless of the PD-L1 expression status being positive or negative in the population receiving immune combination chemotherapy. Treatment-related adverse events (TRAEs) of grade 3 or higher were observed in 16.3% of patients, including chemotherapy-containing immunotherapy. No deaths resulting from immune-related adverse events (irAEs) were reported, and only 1 patient receiving immunotherapy plus chemotherapy had to discontinue treatment due to irAEs.

Conclusions: Combination immunotherapy is feasible in post-TKI resistant individuals with LUAD harboring EGFR mutations. Immune combination chemotherapy and immune combination anti-angiogenic therapy have equivalent efficacy in the PD-L1 positive population. PD-L1 expression can be used as a

reference for screening candidates for combination immunotherapy.

Keywords: Anti-programmed cell death protein 1 combination therapy (anti-PD-1 combination therapy); epidermal growth factor receptor-tyrosine kinase inhibitor resistance (EGFR-TKI resistance); lung adenocarcinoma (LUAD)

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Introduction

The use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is a prevailing initial treatment for advanced EGFR-mutated non-small cell lung cancer (NSCLC); although it has displayed remarkable efficacy (1,2), the acquired resistance and progression of disease are ineluctable (3-5). Resistance to EGFR-TKIs can occur in three forms: first- and second-generation resistance, third-generation resistance at first line, and third-generation resistance at second and above line. Chemotherapy is considered the principal approach for managing EGFR-TKI resistance, but its effectiveness is suboptimal (6-9). These findings underscore the necessity for new therapeutic strategies. To address this issue, several immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) have been approved by the U.S. Food and Drug Administration for the therapeutic intervention of advanced NSCLC. Among these ICIs are nivolumab and pembrolizumab (10,11). However, the application of immunotherapy is controversial in the EGFR-TKI-resistant population; certain clinicians have recommended exploring ICIs-based combination therapy as a possible alternative (12,13), especially given the lackluster results yielded by ICI monotherapy.

Previous research conducted by our team has revealed that the combination of ICIs and an anti-angiogenic agent contributes to a surge in the duration of response, especially in cases of EGFR-TKI resistance (14). Hence, we aimed to assess the safety and effectiveness of varied immune-combination therapies in patients with advanced EGFR-TKI-resistant lung adenocarcinoma (LUAD). We present this article in accordance with the TREND reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1399/rc).

Highlight box

Key findings

- Immune combination chemotherapy and immune combination anti-angiogenic therapy have equivalent efficacy in the treatment of programmed cell death ligand 1 positive patients with advanced epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI)-resistant lung adenocarcinoma (LUAD).

What is known and what is new?

- The effectiveness of combining immune checkpoint inhibitors and chemotherapy has been evaluated as superior to that of chemotherapy alone in patients with advanced EGFR-TKI-resistant non-small cell lung cancer.
- This study compared the efficacy of immunotherapy with or without anti-angiogenic or chemotherapy in the advanced EGFR-TKI-resistant LUAD patients.

What is the implication, and what should change now?

- This data may provide theoretic groundwork for avoiding unnecessary chemotherapy in EGFR-resistant patients and also highlight the role of programmed cell death protein 1 pathway inhibitors in immune combination therapy.

Methods

Patient selection and procedures

The tumor tissue samples and clinical treatment data of stage IV LUAD patients who visited The First Affiliated Hospital of Anhui Medical University between January 2020 and June 2022 were analyzed retrospectively in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University (No. Quick-PJ 2023-04-34). The requirement for informed consent was waived due to the retrospective nature of this study. The study enrolled individuals between the ages of 18 and 75, with locally advanced or metastatic LUAD (stages III B–C or IV) according to the American Joint Committee on Cancer Staging Manual, eighth edition.

Participants with EGFR sensitizing mutations confirmed by tumor histology, cytology, or circulating tumor DNA (ctDNA), including exon 19 deletions (E19del) and exon 21 L858R missense mutations (L858R) were eligible. In addition, participants were required to have experienced disease progression after receiving EGFR-TKI conforming to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Disease progression was defined as follows: (I) progression following treatment with first- or second-generation EGFR-TKIs, and either having a negative EGFR Thr790Met (T790M) mutation status confirmed by tissue samples or receiving third-generation EGFR-TKI as first-line treatment; (II) progression following treatment with first- or second-generation EGFR-TKI, and having been treated with third-generation EGFR-TKIs for at least 6 months. Participants who progressed after third-generation treatment did not require re-biopsy. Additional inclusion criteria consisted of at least 1 measurable lesion (in accordance with RECIST 1.1), Eastern Cooperative Oncology Group performance status (ECOG-PS) 0 or 1, and an estimated life span of at least 3 months.

Patients who had small cell lung cancer (SCLC) histology or symptomatic metastasis of the central nervous system were excluded from the study. Those who had previously undergone systemic anti-tumor therapy, including cytotoxic chemotherapy, except for EGFR-TKIs for advanced NSCLC, immunotherapy (such as anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4) antibodies, or agents that affect T-cell co-stimulation and other immune checkpoints, were also excluded.

Patients who met all the inclusion and exclusion criteria had their medical histories collected retrospectively, including information on the generation of EGFR-TKIs resistance, the use of ICIs and combined treatments, EGFR mutation detection results, and PD-L1 expressions.

Efficacy and safety

RECIST 1.1 was used to evaluate tumor response. The data of objective response rate [ORR; the combination of complete response (CR) and partial response (PR) rates], disease control rate [DCR; the combination of CR, PR, and stable disease (SD) rates], progression-free survival (PFS), and overall survival (OS) were analyzed. Immunohistochemistry (IHC) was used to analyze expression PD-L1 using the Dako 22C3 (Monoclonal Mouse Anti-Human PD-L1, Clone 22C3; Dako, Carpenteria, CA, USA) on the available tumor biopsy samples. Efficacy rates were compared according to treatment groups (anti-PD-1 antibody combined with or without anti-angiogenic or chemotherapy) and PD-L1 expression. Safety and tolerability were assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 throughout the study.

Statistical analysis

Medians (ranges) were used to summarize continuous data, frequencies (percentages) were used for categorical data. PFS and OS were evaluated using the Kaplan-Meier method. All significance tests were two-sided, with a P value <0.05. Statistical analyses were conducted using the software SPSS 26.0 (IBM Corp., Armonk, NY, USA), as well as GraphPad Prism version 9 (GraphPad Software Inc., San Diego, CA, USA) and the Hiplot platform (https://hiplot.com.cn/).

Results

Patient characteristics

Over the course of January 2020 to June 2022, there were 43 patients who participated in this study. In the screening with a cut-off value of 1% of PD-L1 tumor proportion score (TPS), 14/20 (70.0%) patients were reported positive, and more specifically, 4/6 (66.7%) patients received immunotherapy combined with chemotherapy, 8/10 (80.0%) patients received immunotherapy combined with antiangiogenic, 2/4 (50.0%) patients received immunotherapy in combination with antiangiogenic and chemotherapy. In the study, the presence of brain metastases at baseline was reported in nearly one-third of participants. *Table 1* provides an overview of the baseline demographic and clinical features.

Treatment distribution

In this study, 39.6% (17/43) of cases received immunotherapy in combination with antiangiogenic and chemotherapy, whereas 30.2% (13/43) received immunotherapy in combination with only antiangiogenic therapy, and the remaining 30.2% (13/43) received immunotherapy combined with only chemotherapy. Sintilimab (51.2%) and camrelizumab (48.8%) were the main anti-PD-1 drugs, which have been approved for NSCLC treatment

Table 1 Baseline characteristics of study populations

Characteristics	Patients (N=43)
Sex	
Male	27 (62.8)
Female	16 (37.2)
Age (years)	61 [32–75]
Histology	
Adenocarcinoma	43 (100.0)
Smoking status	
Current or former smoker	9 (20.9)
Never smoked	34 (79.1)
EGFR mutation	
Edel19	22 (51.2)
L858R	21 (48.8)
PD-L1 expression	
Positive	14 (32.6)
Negative	6 (14.0)
Not reported	23 (53.5)
The generation of EGFR-TKIs resistance	
First generation	15 (34.9)
Second generation	2 (4.7)
Third generation as first-line treatment	3 (7.0)
Third generation as second or above-line treatment	23 (53.5)
Brain metastases	13 (30.2)

Data are shown as n (%) or median [range]. EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand 1; TKIs, tyrosine kinase inhibitors.

in China (15,16). As for chemotherapy, the proportions of pemetrexed-platinum-based chemotherapy and paclitaxel-platinum-based chemotherapy were similar, at 53.8% and 46.2%, respectively. With respect to the anti-angiogenic drugs, anlotinib predominated (76.9%) in immune combination with an anti-angiogenic strategy, whereas bevacizumab was mainly used in immune combination with anti-angiogenic plus chemotherapy (82.4%).

Survival of EGFR-TKI-resistant patients

All 43 patients were evaluated for treatment efficacy: the overall ORR was 23.3% and the overall DCR was 90.7%. Among the 43 samples whose dates of PFS or OS were available, the median PFS (mPFS) and OS (mOS) were 6.5 and 10.6 months, respectively. No significant differences were detected in terms of the mPFS between anti-PD-1 antibody combined with anti-angiogenic drugs and chemotherapy, anti-PD-1 antibody combined with chemotherapy, and anti-PD-1 antibody combined with anti-angiogenic therapy (6 *vs.* 6.5 *vs.* 11.8 months, respectively, P=0.48, *Figure 1A*). Additionally, no statistically significant difference was observed in terms of mOS in above-mentioned 3 anti-PD-1 antibody combination therapies (8.2 *vs.* 11.8 *vs.* 10.9 months, respectively, P=0.12, *Figure 1B*).

To assess the prognostic significance of PD-L1 expression, PFS and OS were analyzed according to the expression of PD-L1. In the overall cohort, patients with positive PD-L1 expression (mPFS 7.5 months) showed an improved PFS prognosis compared to those with negative PD-L1 expression (mPFS 5.25 months, *Figure 2A*), but the difference was not significant (P=0.62; log-rank test), similar results were also observed in terms of OS (12.45 *vs.* 5.50 months, respectively, P=0.26; log-rank test, *Figure 2B*). Furthermore, in the PD-L1 positive subgroup, no statistically significant difference was observed in terms of PFS between the use of immune combination chemotherapy and immune combination anti-angiogenic therapy (7.55 *vs.* 7.50 months, respectively, P=0.59; log-rank test, *Figure 2C*). Besides, in the population receiving immune combination chemotherapy, there was a trend towards prolonged PFS regardless of the PD-L1 expression status being positive or negative (7.55 *vs.* 7.80 months, respectively, P=0.44; log-rank test, *Figure 2D*).

Safety

Table 2 shows the immune-related adverse events (irAEs) observed in all study participants. Of the 43 patients, 26 (60.5%) experienced at least 1 irAE. Among these patients, 7 (16.3%) experienced irAEs that were grade 3–4, whereas 3 (7.0%) reported severe cases. Immune hepatitis and myelosuppression were the most typically reported irAEs, with incidence rates of 30.2% and 27.9%, respectively. As shown in *Table 2*, in different immunotherapy regimens, the incidence of treatment-related adverse events (TRAEs) was relatively high in anti-PD-1 antibody combined with chemotherapy (with or without anti-angiogenic therapy), specifically, fatigue (23.1%), reactive cutaneous capillary endothelial proliferation (46.2%) and immune hepatitis

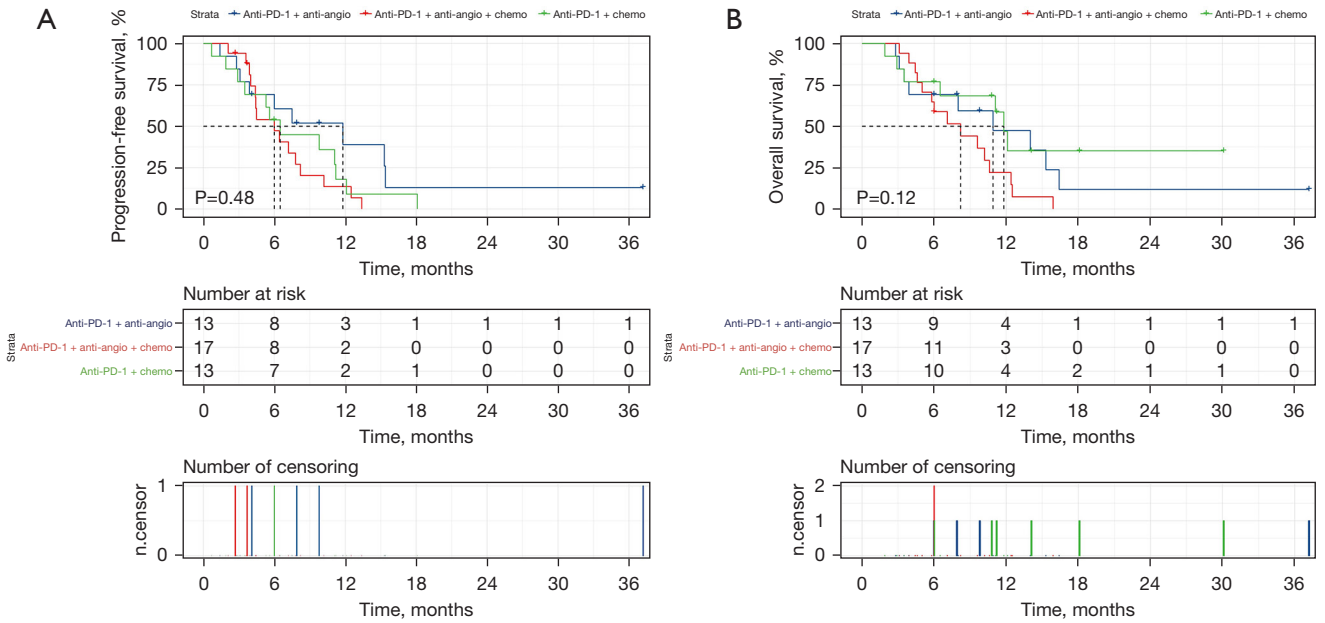

Figure 1 PFS (A) and OS (B) curves of overall populations in three anti-PD-1 antibody combination therapies (months). The log-rank test was used to compare survival differences among groups. Anti-PD-1 + anti-angio, anti-PD-1 antibody in combination with anti-angiogenic therapy; anti-PD-1 + anti-angio + chemo, anti-PD-1 antibody in combination with antiangiogenic and chemotherapy; anti-PD-1 + chemo, anti-PD-1 antibody in combination with chemotherapy; PFS, progression-free survival; OS, overall survival; PD-1, programmed cell death protein 1.

(46.2%) predominated in immune combination with chemotherapy, whereas immune combination with anti-angiogenic plus chemotherapy was mainly manifested in myelosuppression (41.2%).

Only 1 patient was unable to receive anti-PD-1 therapy due to severe immune pneumonitis. Throughout the observation period, the causes of death were disease progression and respiratory failure. It is noteworthy that none of the patients died as a result of an irAE.

Discussion

EGFR-TKIs are regarded as the first option for NSCLC patients with EGFR mutations. However, although they can lead to ORRs, progression of the disease, and certain resistance often accompanies their use (17-19). Due to the challenges associated with the use of EGFR-TKIs, ICIs have garnered attention as an important area of research for improving survival rates among patients with advanced NSCLC who lack driver gene mutations (20-22). Research results have been inconsistent concerning the potency of immunotherapy in treating EGFR-TKI-resistant NSCLC. EGFR mutation is associated with an uninflamed phenotype and weak immunogenicity in the extracranial lesions (23). The efficacy of ICIs as a single therapy has proven to be unsatisfactory for patients with EGFR mutations, given that ICI combination therapies have been promoted by several studies, and some preclinical studies have provided a novel and powerful rationale for immune combination therapy (24,25). The results of ORIENT-31 demonstrated a significant increase in tumor control period when sintilimab was combined with bevacizumab, pemetrexed, and cisplatin compared with pemetrexed and cisplatin alone. Furthermore, the combination therapy was well-tolerated overall (26). However, in the ultimate analysis of the KEYNOTE-789 (NCT03515837) trial, although there was a slight improvement in OS for progressive disease following TKI therapy for metastatic non-squamous NSCLC patients receiving pembrolizumab combined with pemetrexed and platinum chemotherapy compared to the pemetrexed and platinum chemotherapy only group, these improvements did not reach statistical significance according to pre-specified statistical values. Such divergent results are thought-provoking. Although benefits were observed in the PFS/OS when immunotherapy was combined with anti-angiogenic therapy plus chemotherapy,

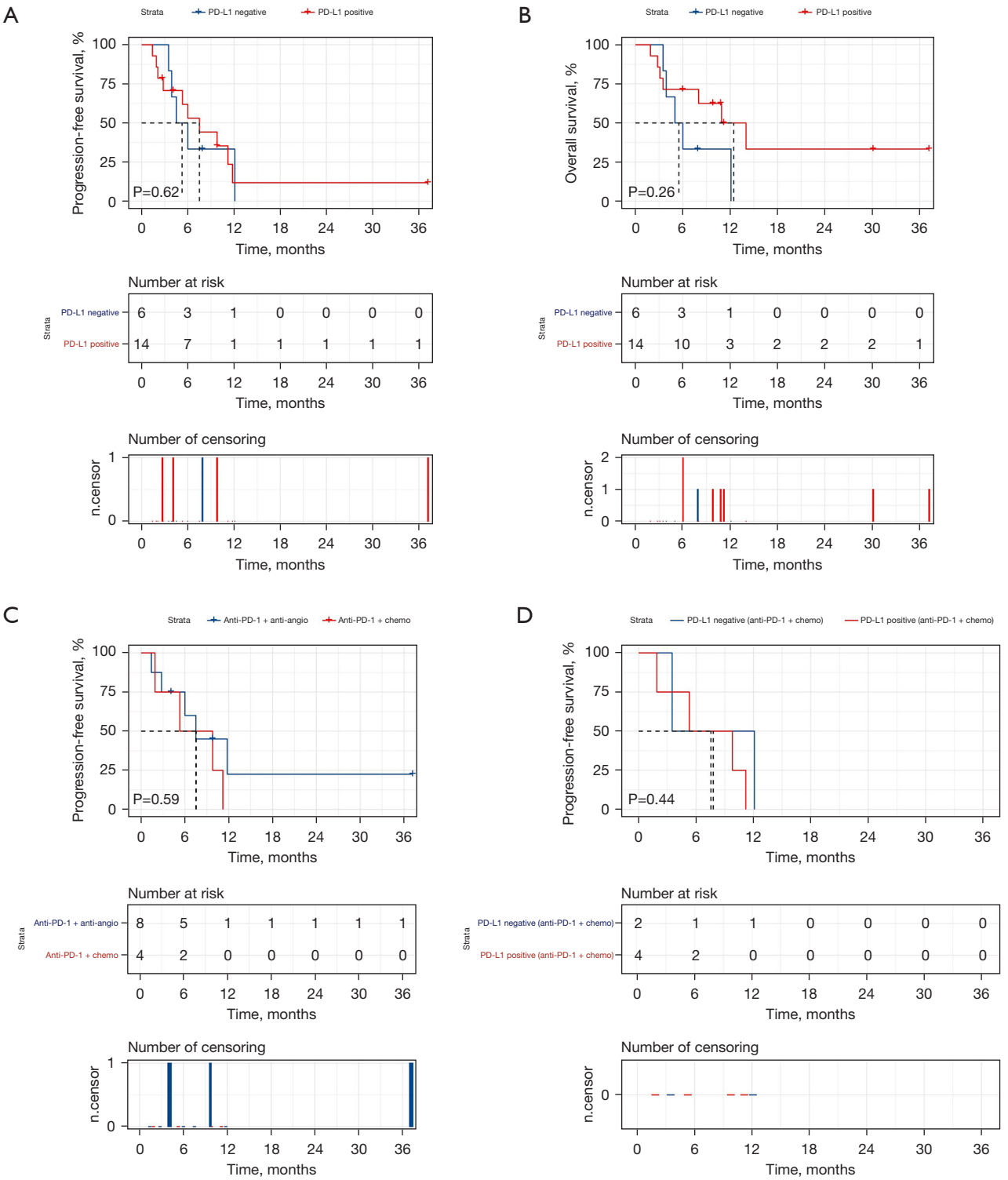

Figure 2 PFS and OS according to treatment group and PD-L1 expression. PFS (A) and OS (B) curves of overall populations according to PD-L1 expression (months). (C) PFS curves of PD-L1 positive populations according to treatment group (months). (D) PFS curves of patients receiving immune combination chemotherapy according to PD-L1 expression (months). The log-rank test was used to compare survival differences among groups. Anti-PD-1 + anti-angio, anti-PD-1 antibody in combination with anti-angiogenic therapy; anti-PD-1 + chemo, anti-PD-1 antibody in combination with chemotherapy; PD-L1, programmed death ligand 1; PFS, progression-free survival; OS, overall survival.

Table 2 Treatment-related adverse effects

Adverse events	All patients (N=43), n (%)		Anti-PD-1 + chemo (N=13), n (%)		Anti-PD-1 + anti-angio (N=13), n (%)		Anti-PD-1 + anti-angio + chemo (N=17), n (%)	
	Any grades	Grade 3–4	Any grades	Grade 3–4	Any grades	Grade 3–4	Any grades	Grade 3–4
irAEs leading to interruption	3 (7.0)	3 (7.0)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	1 (5.9)	1 (5.9)
irAEs leading to discontinuation	1 (2.3)	1 (2.3)	1 (7.7)	1 (7.7)	0	0	0	0
irAEs requiring steroids	2 (4.7)	2 (4.7)	1 (7.7)	1 (7.7)	0	0	1 (5.9)	1 (5.9)
Treatment-related deaths	0	0	0	0	0	0	0	0
TRAEs								
Fatigue	5 (11.6)	0	3 (23.1)	0	1 (7.7)	0	1 (5.9)	0
Rash	2 (4.7)	0	0	0	1 (7.7)	0	1 (5.9)	0
Pruritus	2 (4.7)	0	0	0	1 (7.7)	0	1 (5.9)	0
Diarrhea	2 (4.7)	0	1 (7.7)	0	0	0	1 (5.9)	0
Nausea	3 (7.0)	0	1 (7.7)	0	1 (7.7)	0	1 (5.9)	0
Decreased appetite	3 (7.0)	0	1 (7.7)	0	1 (7.7)	0	1 (5.9)	0
RCCEP	10 (23.3)	0	6 (46.2)	0	2 (15.4)	0	2 (11.8)	0
Immune pneumonitis	1 (2.3)	1 (2.3)	1 (7.7)	1 (7.7)	0	0	0	0
Immune cystitis	0	0	0	0	0	0	0	0
Urinary tract infection	2 (4.7)	0	1 (7.7)	0	0	0	1 (5.9)	0
Immune hepatitis	13 (30.2)	0	6 (46.2)	0	2 (15.4)	0	5 (29.4)	0
Myelosuppression	12 (27.9)	3 (7.0)	5 (38.5)	2 (15.4)	0	0	7 (41.2)	1 (5.9)
Hypothyroidism	5 (11.6)	0	1 (7.7)	0	3 (23.1)	0	1 (5.9)	0

PD-1, programmed cell death protein 1; anti-PD-1 + chemo, anti-PD-1 antibody in combination with chemotherapy; anti-PD-1 + anti-angio, anti-PD-1 antibody in combination with anti-angiogenic therapy; anti-PD-1 + anti-angio + chemo, anti-PD-1 antibody in combination with antiangiogenic and chemotherapy; irAEs, immune-related adverse events; TRAEs, treatment-related adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation.

especially for patients with EGFR mutations, the comparison among different immune combination therapies had not been assessed, emphasizing the need to further investigate whether the PFS/OS are different between chemotherapy and anti-angiogenesis therapy.

In this study, no statistical difference was observed in terms of mPFS between the use of immune combination chemotherapy and immune combination anti-angiogenic therapy in the PD-L1 positive subgroup. This data may provide theoretic groundwork for avoiding unnecessary chemotherapy in EGFR-resistant patients and also highlights the importance of PD-1 pathway inhibitors in immune combination therapy. Moreover, the PFS was prolonged regardless of the PD-L1 expression status being positive or negative in the population receiving immune combination chemotherapy, which provides some treatment options for patients who were not screened for PD-L1 expression.

In addition, no notable distinction was observed in mPFS and mOS among patients receiving three anti-PD-1 antibody combination therapies. Patients with positive PD-L1 expression showed an improved median PFS compared to those with negative PD-L1 expression. Similar results have been reported in other studies, showing that PD-1 pathway inhibitors are effective in EGFR-mutant patients with high expression of PD-L1 (27,28). Regarding safety, our results align with the established safety profiles of either ICIs or the combined therapy, and no novel safety signals were detected. Grade 3 or higher TRAEs were observed in 16.3% of patients, inclusive of TRAEs in immunotherapies

that contained chemotherapy.

Due to the small sample size and retrospective setting, no significant results were found when compared mPFS and mOS among patients receiving 3 anti-PD-1 antibody combination therapies. These results need to be further strengthened by extending coverage or partnering with multiple institutions to increase the number of eligible patients.

Conclusions

Our study indicated that combination immunotherapy is feasible in post-TKI resistant individuals with LUAD harboring EGFR mutations. Immune combination chemotherapy and immune combination anti-angiogenic therapy have equivalent efficacy in the PD-L1 positive population. PD-L1 expression can be used as a reference for screening patient suitability for combination immunotherapy which suggests the potential for further improvement in patient prognosis.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1399/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1399/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1399/coif). All authors thank Shanghai Tengyun Biotechnology Co., Ltd. for developing the Hiplot Pro platform (https://hiplot.com.cn/) and providing technical assistance and valuable tools for data analysis and visualization for free. All authors report that this research was supported by the Department of Science and Technology of Anhui Province (No. 2022e07020044) and the Chinese Thoracic Oncology Group (CTONG) (No. CTNOG-YC20220113). The authors have no other 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 the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University (No. Quick-PJ 2023-04-34). The requirement for informed consent was waived due to the retrospective nature of this study.

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