Received: 27 October 2023 | Revised: 11 April 2024 | Accepted: 20 April 2024

DOI: 10.1002/hsr2.2114

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Efficacy of cross-line anti-programmed death 1/programmed cell death-ligand 1 antibody in the treatment of advanced nonsmall cell lung cancer: A retrospective study

Xiang Zhao | Yuan Cheng | Cuiyan Guo | Ligong Nie | Qi Zhang | Meng Zhang | Kunyan Sun | Guangfa Wang

Department of Respiratory and Critical Care Medicine, Peking University First Hospital, Beijing, China

Correspondence
Yuan Cheng, Department of Respiratory and Critical Care medicine, Peking University First Hospital, Beijing 100034, China.
Email: softsnake@bjmu.edu.cn

Funding information
Beijing Municipal Natural Science Foundation, Grant/Award Number: L222151; National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital), Grant/Award Number: 2023IR48; Beijing Xisike Clinical Oncology Research Foundation, Grant/Award Number: Y-HS202202-0073

Abstract

Background and Aims: Immune checkpoint inhibitors (ICIs) across multiple treatment lines have not yet been evaluated comprehensively. The purpose of this research was to investigate whether or not continuous cross-line ICIs therapy is effective in treating non-small cell lung cancer (NSCLC).

Methods: We conducted a retrospective investigation into the medical histories of 47 patients diagnosed with advanced NSCLC and treated with ICIs at the Peking University First Hospital between January 2018 and June 2022.

Results: Due to the progression of their disease, 14 patients were given the same ICIs, 5 patients were given different ICIs, and 6 patients discontinued taking ICIs altogether. The objective response rates were 7.140% in the ICIs cross-line treatment group, 0% in the replacement of ICIs treatment group, and 0% in the discontinuation of ICIs treatment group. The disease control rates were 64.260% in the ICIs cross-line treatment group, 60% in the replacement of ICIs treatment group, and 0% in the discontinuation of ICIs treatment group. The average overall survival durations of the three groups were 24.020 (95% confidence interval [CI]: 17.061–30.979), 31.643 (95% CI: 23.513–39.774), and 7.997 (95% CI: 3.746–12.247) months, respectively ($p = 0.003$). The median second progression-free survival (PFS2) durations of the three groups were 4.570 (95% CI: 3.276–5.864), 3.530 (95% CI: 0.674–6.386), and 1.570 (95% CI: 0–4.091) months, respectively ($p = 0.091$).

Conclusions: Cross-line ICIs cannot improve the prognosis and PFS2 of patients with NSCLC, but compared to discontinuing ICIs, OS may be prolonged. A few patients may benefit from prolonged ICIs therapy.

KEYWORDS

advanced nonsmall cell lung cancer, cross-line therapy, immune checkpoint inhibitors, immune-related adverse events, prognosis

1 | INTRODUCTION

According to the current guidelines, monotherapy or combination therapy with programmed death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) is currently the standard first-line treatment for advanced non-small cell lung cancer (NSCLC) with driver mutation-negative patients.[1] The majority of patients have not benefited from treatment (primary drug resistance), and some responders relapse after a time of response, even though the fact that cancer immunotherapies have an unprecedentedly high sustained response rate (acquired drug resistance).[2] Therapeutic strategies following the progression of first-line immunotherapies are currently a clinical challenge. In the clinical setting, some oncologists continue to use PD-1 in combination with other posttreatment methods or change the type of PD-1/PD-L1. However, once patients progress from first-line PD-1/PD-L1 treatment, it is unclear whether they can continue to benefit from same type of PD-1/PD-L1 treatment. In previous studies of metastatic melanoma and lymphoma, it is effective to continue to use the same type of immune checkpoint inhibitors (ICIs) after tumor progression.[3] There is no study exploring the benefits of cross-line use of same ICIs in subsequent second-line or later-line therapies in NSCLC patients. Therefore, this study aimed to explore whether the cross-line use of ICIs has clinical benefits and whether there are some clinical predictors of their efficacy.

2 | METHODS

2.1 | Study design and population

In this retrospective, single-center cohort study, we reviewed the medical records of patients receiving immunotherapy for advanced lung cancer in the Department of Respiratory Medicine, Peking University First Hospital from January 2018 to June 2022. The inclusion criteria were as follows: (1) histopathologically confirmed NSCLC , stage IIIB or above; (2) age 18–80 years; (3) Eastern Cooperative Oncology Group performance status score <2 points; and (4) tumor progression during/after anti-PD-1/PD-L1 therapy. The exclusion criteria were as follows: (1) NSCLC patients with driver oncogenes, like EGFR/ALK/ROS-1; (2) a lack of baseline or follow-up data and discontinuation of ICIs treatment for personal reasons or immune-related adverse events (irAEs). We defined cross-line therapy as the continued administration of the same ICIs in patients who were previously treated with ICIs after tumor progression. We defined the continued ICIs treatment group as the continued administration of the same ICIs or different ICIs in patients who were previously treated with ICIs after tumor progression. Patients were categorized into ICIs cross-line treatment group, replacement of ICIs treatment group, and discontinuation of ICIs treatment group. The following data were collected: age and sex, cancer stage, previous and subsequent treatments, start time of the first and second ICIs treatments, type of ICIs, duration of the first and second ICIs treatments, adverse events according to common terminology criteria, best response to the first and second ICIs therapies (as defined by the Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria), and reasons for discontinuation. This study was approved by the Ethics Committee of Peking University First Hospital.

2.2 | Outcomes and follow-up

Patients diagnosed with advanced NSCLC after first-line ICIs therapy may continue, replace, or discontinue the ICIs as second-line therapy after tumor progression. Second progression-free survival (PFS2) and overall survival (OS) were used to observe any statistically significant differences between the three groups. PFS2 was defined as the time from the adjustment of the second-line treatment regimen after immunotherapy progression to disease recurrence or death due to any cause. OS was defined as the duration from the commencement of ICIs treatment and death from any cause. The patients were monitored until the date of death or the date of the last follow-up (June 1, 2022).

2.3 | Evaluation criteria for efficacy and adverse reactions

According to the RECIST criteria, outcomes were categorized as clinical complete remission (CR) that is, complete disappearance of all lesions; partial remission (PR) that is, a reduction of at least 30% in the overall length and width of the lesions from their baseline measurements; or stable disease (SD) that is, reduction of the sum of the length and diameter of the baseline lesions. The Common Terminology Evaluation Criteria for Adverse Events 4.0 was applied to the analysis of adverse responses.

2.4 | Statistical analysis

Data were compared using a t-test for normally distributed variables represented as means ± standard deviations (SDs). Non-normally distributed data are summarized as medians and interquartile ranges (IQRs) and were compared using the Mann–Whitney test. The Pearson $\chi 2$ test or Fisher exact test was utilized to compare differences in the effective rate and clinical benefit rate between the groups, and the Kaplan–Meier method was utilized to analyze OS and PFS2. Log-rank univariate and multivariate Cox proportional hazards model analyses of survival differences were performed. SPSS 27.0 software and Prism 9.0 was utilized for statistical processing. In all analyses, using a two tailed test with $p < 0.05$ was regarded as statistically significant.

3 | RESULTS

3.1 | Patient characteristics

We collected the medical records of 47 patients receiving ICIs for advanced NSCLC in the Department of Respiratory Medicine, Peking

University First Hospital from 2018 to 2022 and excluded 22 cases (Figure 1). The ICIs cross-line treatment group included 14 patients who continued to use the same type of ICIs as the second-line treatment. In the ICIs cross-treatment group, 10 patients were treated with pembrolizumab, two patients were treated with nivolumab, one patient was treated with tislelizumab, and one patient was treated with camrelizumab. The replacement of ICIs treatment group included five patients who received different ICIs as second-line treatment. In the replacement of ICIs treatment group, initial durvalumab was changed to pembrolizumab after disease progression for one case, initial nivolumab was changed to tislelizumab after disease progression for one case, initial pembrolizumab was changed to durvalumab after disease progression for one case, and initial pembrolizumab was changed to camrelizumab after disease progression for one case. Furthermore, one patient was initially treated with sintilimab and subsequently switched to pembrolizumab as the disease progressed; another patient was treated with chemotherapy and relapsed following targeted maintenance. The discontinuation of ICIs treatment group included six patients who discontinued ICIs as second-line treatment. In the discontinued ICIs treatment group, three patients received pembrolizumab, two patients received nivolumab, and one patient received camrelizumab. The features of the patients are outlined in Table 1. The first-line and second-line treatment for all patients are shown in Supplementary Table 1.

3.2 | Outcome

The objective response rates (ORRs) were 7.14% (CR: 0, PR: 1, SD: 8, PD: 5) in the ICIs cross-line treatment group, 0% (CR: 0, PR: 0, SD: 3, PD: 2) in the replacement of ICIs treatment group, and 0% (CR: 0, PR: 0, SD: 0, PD: 6) in the discontinuation of ICIs treatment group. The disease control rates (DCRs) were 64.26% (CR: 0; PR: 1; SD: 8; PD: 5) in the ICIs cross-line treatment group, 60% (CR: 0; PR: 0; SD: 3; PD: 2) in the replacement of ICIs treatment group, and 0% (CR: 0; PR: 0; SD: 0; PD: 6) in the discontinuation of ICIs treatment group (Table 2).

The average OS durations of the three groups were 24.020 (95% confidence interval [CI]: 17.061–30.979), 31.643 (95% CI: 23.513–39.774), and 7.997 (95% CI: 3.746–12.247) months, respectively ($p = 0.003$). There was no corresponding survival time when the cumulative survival rate was 50%; hence, the average OS was used instead of the median (Figure 2). The median PFS2 durations of the three groups were 4.57 (95% CI: 3.276–5.864), 3.53 (95% CI: 0.674–6.386), and 1.57 (95% CI: 0–4.091) months, respectively ($p = 0.091$) (Figure 3). However, after disease progression, regardless of whether the same ICIs were continued or different ICIs substituted, the average OS and median PFS times were longer than those of patients with discontinued ICIs, although this difference was not statistically meaningful.

We also compared the OS and PFS2 of continued ICIs treatment group and discontinuation of ICIs treatment group. The average OS durations of the two groups were 26.494 (95% confidence interval [CI]: 19.973–33.016) and 7.997 (95% CI: 3.746–12.247) months, respectively ($p = 0.001$) (Figure 4). There was no corresponding survival time when the cumulative survival rate was 50%; hence, the average OS was used instead of the median. The median PFS2 durations of the two groups were 4.50 (95% CI: 3.236–5.764), and 1.57 (95% CI: 0–4.091) months, respectively ($p = 0.039$) (Figure 5).

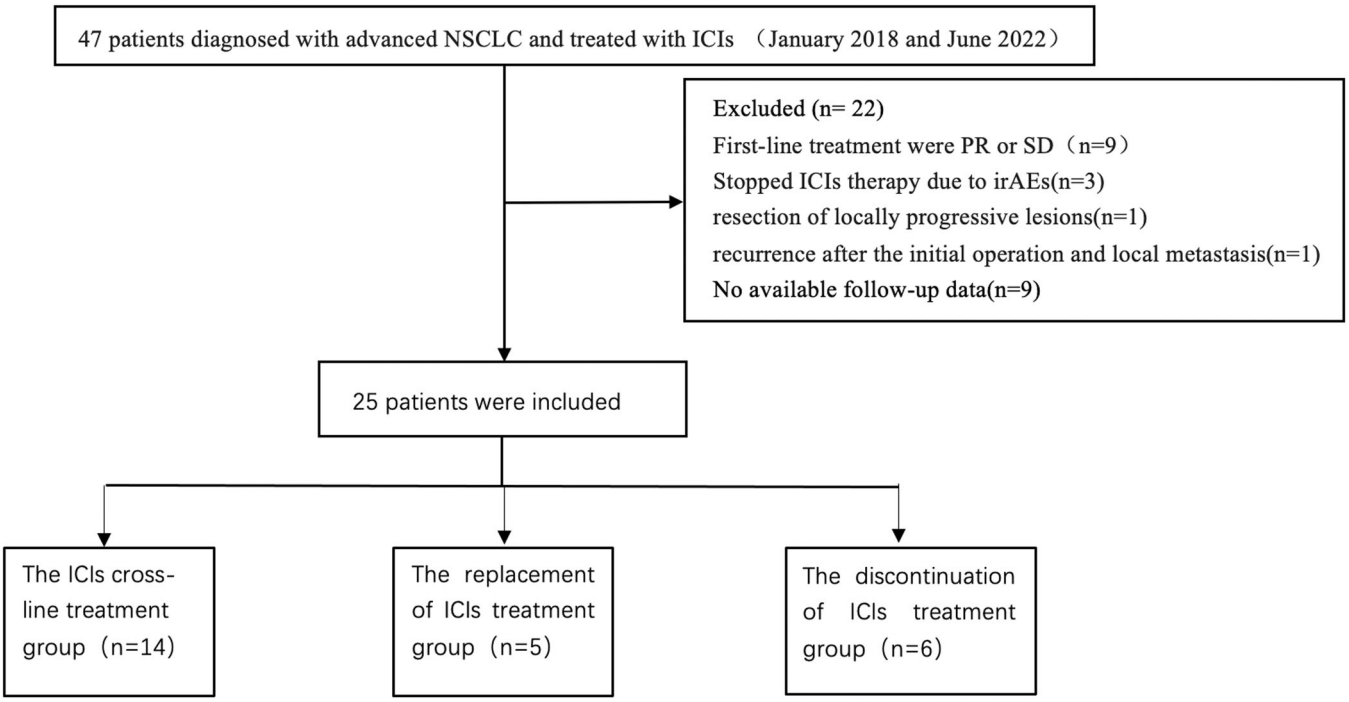

FIGURE 1 Flow diagram of the study cohort.

TABLE 1 Baseline and characteristics of patients.

Patient characteristics	Cross-line ICIs ($n = 14$)	Replacing ICIs ($n = 5$)	Discontinue ICIs ($n = 6$)	p
Median age (years)	64 [40–80]	62 [46–70]	64.5 [49–70]	0.845
Sex (male/female)	(9/5)	(3/2)	(5/1)	0.643
Smoking history	10 (71.4%)	3 (60.0%)	6 (100%)	0.252
Brinkman Index (kg/m^2)	22.1 [20.0, 24.5]	24.9 [23.3, 26.6]	23.0 [21.0, 26.8]	0.162
Histopathology				0.829
Adenocarcinoma	5 (35.7%)	3 (60.0%)	2 (33.3%)	
Squamous	7 (50.0%)	2 (40.0%)	3 (50.0%)	
Other	2 (14.3%)	0 (0%)	1 (16.7%)	
Performance status				0.789
0	12 (86.1%)	5 (100%)	6 (100%)	
1	1 (7.14%)	0 (0%)	0 (0%)	
2	1 (7.14%)	0 (0%)	0 (0%)	
PD-L1 Expression				0.500
TPS ≥ 50%	2 (14.29)	0 (0%)	0 (0%)	
1% ≤ TPS < 50%	0 (0%)	1 (20.0%)	1 (16.7%)	
<TPS 1%	3 (21.4%)	0 (0%)	1 (16.7%)	
Unmeasurable	9 (64.29%)	4 (80.0%)	4 (66.6%)	
Clinical staging				0.089
Stage IIIB	1 (7.1%)	2 (40.0%)	0 (0%)	
Stage IV	13 (92.9%)	3 (60.0%)	6 (100%)	

Abbreviations: ICIs, immune checkpoint inhibitor; TPS, tumor proportion score.

TABLE 2 The ORR, DCR, PFS, and OS of three groups.

	ORR	DCR	PFS (average)	OS (median)
ICIs cross-line treatment group	7.140%	64.260%	24.020	4.570
Replacement of ICIs treatment group	0%	60%	31.643	3.530
Discontinuation of ICIs treatment group	0%	0%	7.997	1.570

In the log-rank univariate analysis of OS and PFS2, the duration of ICIs treatment was related to OS ($p = 0.011$) (Table 3).

3.3 | Immune-related adverse events

In total, 25 patients in the three groups were evaluated for adverse reactions. In the ICIs cross-line treatment group, one patient had immune liver injury and grade 1 pneumonitis, and one patient had thyroiditis. The incidence rate of irAEs in this group was 14.3% (2/14). In the replacement of ICIs treatment group, one patient had grade 1 pneumonitis and another patient had adrenocortical dysfunction. The incidence rate of irAEs in this group was 40% (2/5). In the discontinuation of ICIs treatment group, one patient had adrenocortical dysfunction, and the incidence rate of irAEs in this group was 12.5% (1/6). These irAEs occurred during pembrolizumab treatment. None of the individuals died of irAEs.

4 | DISCUSSION

We retrospectively analyzed 25 patients, and the ORR, DCR, median PFS2, and average OS of the ICIs cross-line treatment group were 7.140%, 64.260%, 4.570 months, and 24.020 months, respectively. The ORR, DCR, median PFS2, and average OS of the replacement of ICIs treatment group were 0%, 60%, 3.530 months, and 31.463 months, respectively. The ORR, DCR, median PFS2, and average OS of the discontinuation of ICIs treatment group were 0%, 0%, 1.570 months, and 7.997 months, respectively. Therefore, cross-line ICIs or replacement ICIs groups showed a trend of prolongation of PFS2 and OS as compared with discontinuation of ICIs treatment group, although the difference was not statistically significant.

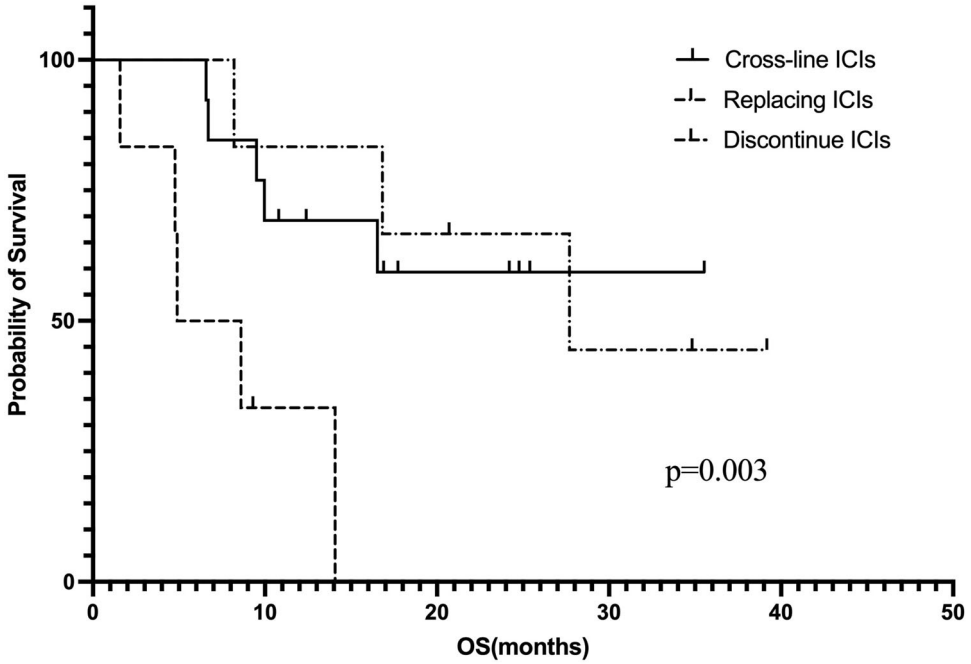

FIGURE 2 Kaplane-Meier curves demonstrating the OS of the ICIs cross-line treatment group, the replacement of ICIs treatment group.

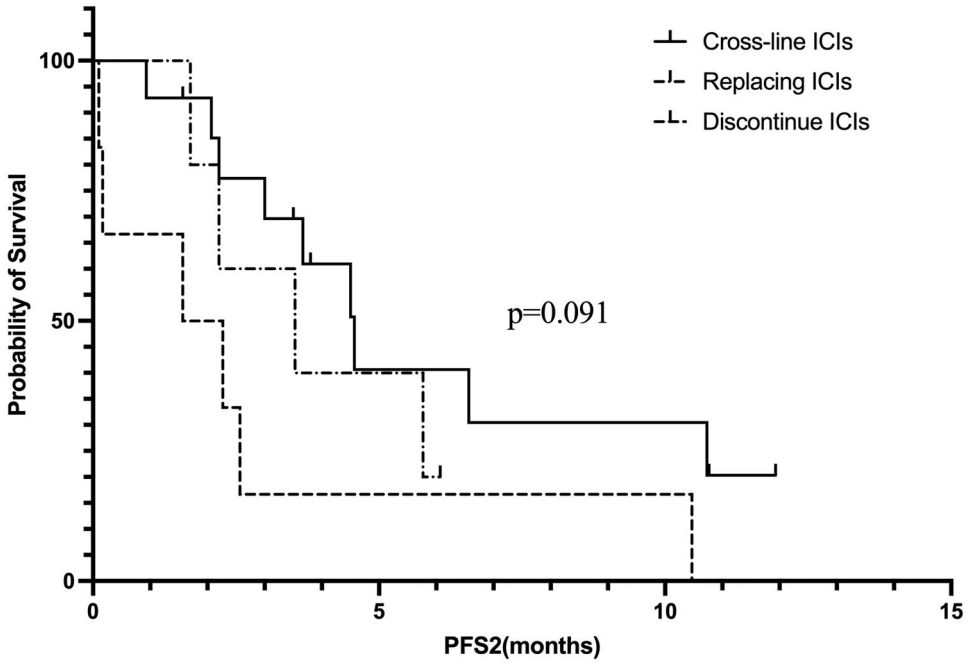

FIGURE 3 Kaplane-Meier curves demonstrating the PFS2 of the ICIs cross-line treatment group, the replacement of ICIs treatment group.

Treatment with PD-1 inhibitors has been demonstrated to be successful as a first-line therapy for advanced NSCLC.[1] However, the treatment strategy following the progress of first-line immunotherapy is currently a clinical challenge. There is no consensus about deciding whether to continue to use the same kind of ICIs or to replace it. Several studies have reported limited data regarding retreatment with ICIs.[4–8] There is insufficient data to determine if the type of ICIs should be changed at the time of re-administration. The follow-up data of certain clinical trials and retrospective investigations indicated that certain patients may benefit from the cross-line usage of ICIs following illness progression or recurrence. Retreatment with the same anti-PD-L1 antibody is effective in treating multiple tumor types, with eight patients showing favorable clinical responses.[4] One retrospective study from Japan showed 14 patients

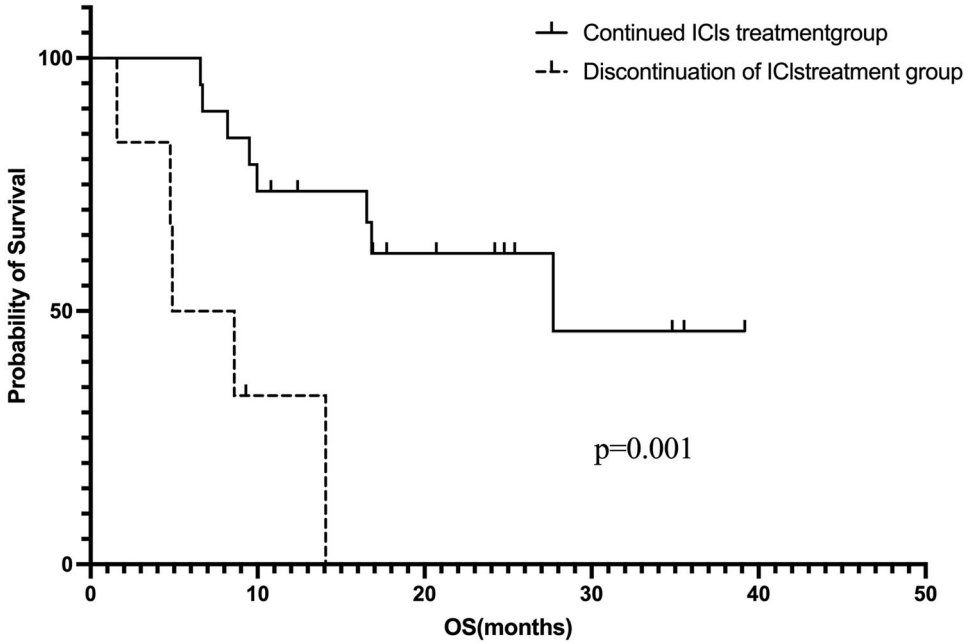

FIGURE 4 Kaplan-Meier curves demonstrating the OS of the ICIs treatment group and discontinuation of ICIs treatment group.

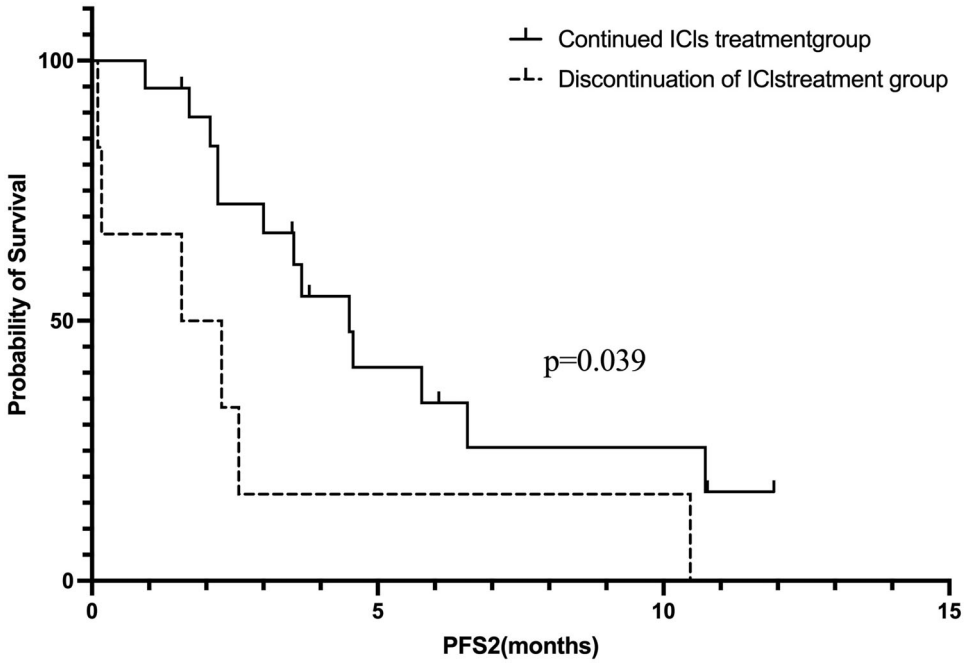

FIGURE 5 Kaplane-Meier curves demonstrating the PFS2 of the ICIs treatment group and discontinuation of ICIs treatment group.

with ICIs rechallenge, a total of 8 patients with the same type of ICIs, and 6 patients with different ICIs. Median progression-free survival (PFS) was 1.5 months (95% CI: 0.8–2.6) and median overall survival (OS) was 6.5 months (95% CI: 1.4–19.0). The ORR was 7.1%, and the DCR was 21.4%.[5] The following studies included cross-line treatment and replacement of ICIs, which is defined as rechallenge. According to the findings of Fujita et al., the ORR, DCR, and PFS of pembrolizumab rechallenge following the progression of nivolumab were, respectively, 8.3%, 41.7%, and 3.1 months for a group of 12 NSCLC patients.[6] In addition, the ORR, DCR, and PFS of atezolizumab in 18 patients with NSCLC who had previously been treated with anti-PD-1 antibodies (nivolumab and pembrolizumab) were 0%, 38.9%, and 2.9 months, respectively. In addition, patients who had been treated with anti-PD-1 antibodies in the past experienced only a limited benefit from subsequent atezolizumab treatment.[7] Yuki Katayama et al. the ORR, DCR, PFS, and OS were 2.9%, 42.9%%, 2.7

TABLE 3 Univariate analysis of influence factors for OS and PFS.

	Univariate analysis of OS		Univariate analysis of PFS2	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (≥50)	0.038 (0–43.291)	0.334	1.420 (0.405–4.974)	0.584
Sex (male)	0.536 (0.147–1.957)	0.345	0.828 (0.293–2.339)	0.722
Smoking History	0.709 (0.193–2.612)	0.606	0.844 (0.278–2.559)	0.765
Brinkman Index (≥22)	0.801 (0.245–2.616)	0.801	0.575 (0.204–1.621)	0.295
Histopathology				
Adenocarcinoma	Reference	0.723	Reference	0.726
Squamous	0.432 (0.097-2.708)	0.432	1.290 (0.337–4.943)	0.832
Other	0.683 (0.135-3.454)	0.645	0.864 (0.226–3.312)	0.832
Performance status				
0	Reference	0.889	Reference	0.450
1	/	0.965	/	0.962
2	/	0.963	/	0.957
Clinical staging (IV)	(0–24.766)	0.288	0.859 (0.195–3.785)	0.840
PD-L1 expression				
≥TPS 50%	Reference	0.978	Reference	0.958
1% ≤ TPS < 50%	/	0.989	/	0.987
< TPS 1%	1.249 (0.157–9.905)	0.834	1.312 (0.290–5.943)	0.724
Unmeasurable	1.390 (0.295–6.552)	0.677	1.389 (0.370–5.216)	0.627
ALB ≥ 35	0.878 (0.241–3.195)	0.843	0.700 (0.229–2.144)	0.533
hsCRP≥8	0.915 (0.247–3.386)	0.915	1.273 (0.481–3.370)	0.627
NLR	0.965 (0.729–1.278)	0.805	1.017 (0.806–1.282)	0.889
LMR	1.062 (0.908–1.241)	0.452	0.981 (0.853–1.128)	0.786
PLR	0.997 (0.991–1.002)	0.233	0.997 (0.993–1.001)	0.108
ICIs treatment duration				
<3 months	Reference	0.014	Reference	0.070
3–6 months	/	0.919	10 (2.295–43.574)	0.002
≥6 months	10.142 (2.131–48.271)	0.004	2.337 (0.784–6.967)	0.128

months, and 7.5 months, respectively, in 35 NSCLC patients with ICI rechallenge.[8] OS and PFS2 durations were longer in the cross-line treatment or replacement of ICIs group than in the discontinuation of ICIs group, but the difference was not statistically significant. The OS and PFS2 of the patients who continued to use ICIs were significantly longer than those who discontinued using ICIs in our study.

Current countermeasures for drug resistance include changing chemotherapy regimens, combining adjuvant therapy, antiangiogenic therapy, radiation therapy, and combining tumor microenvironment-modulating drugs or other forms of the immune checkpoint blockade.[9] When a patient develops primary or adaptive resistance to one type of ICI, it does not imply that other ICI target-related pathways are ineffective. If ICIs with other targets such as CTLA-4 or LAG3 are used, they can effectively promote the activation of T cells and maintain the tumor-infiltrating lymphocyte activation state. For example, when a PD-L1 monoclonal antibody is effective initially and subsequently acquires resistance, the addition of other ICIs may also reactivate T cells and synergistically delay T cell exhaustion.[10] Individuals with acquired resistance continue to express PD-L1 and PD-1, indicating that they have to infiltrate T cells with an activated phenotype, and patients experiencing relapse may regain a therapeutic response after discontinuation of ICIs or following chemotherapy.[11,12] To summarize, cross-line therapy may be beneficial with or without other treatments. DNA damaging agents, when combined with the same ICIs with chemotherapy, can promote cancer cell immunogenicity by enhancing neoantigen complexes,

inducing immune cell death, and altering the cytokine milieu in the tumor microenvironment, thus leading to PD-L1 activation in tumor cells, redistribution, and enhanced expression. However, when the same ICIs are combined with antiangiogenic drugs, they exhibit immunomodulatory effects in the tumor microenvironment, reverse the immunosuppression caused by tissue hypoxia and immunosuppressive cells, and enhance dendritic cell maturation and T cell transport and function.[13] Several immune checkpoints, including CTLA-4, TIGIT, LAG3, and TIM3, are still under early investigation.[14,15] The choice of treatment regimen after immunotherapy resistance is still in the exploratory stage, and there is no conclusion on the best regimen. Therefore, further clinical studies are warranted.

The clinical benefit of cross-line ICIs therapy is limited compared with initial ICIs treatment. Nevertheless, some NSCLC patients in our study benefited from cross-line ICIs therapy. Thus, it is necessary to elucidate predictive clinical factors for ICIs responders' retreatment in NSCLC patients. Patients who had a high level of PD-L1 expression (Tumor Proportion Score [TPS] ≥ 50%) showed a superior response to treatment in earlier big clinical studies.[16] Two retrospective studies on patients with lung cancer also demonstrated the efficacy of retreatment. In one research, pembrolizumab replaced nivolumab in three advanced NSCLC patients with high PD-L1 expression (TPS ≥ 80%). Anti-PD-1 antibody retreatment may be beneficial for patients who have extremely high levels of PD-L1 expression (TPS ≥ 80%).[6] Another study reported that patients who had a favorable response to the initial ICIs treatment benefited from the retreatment with ICIs −10 patients with cross-line therapy and one patient were initially receiving nivolumab, which were replaced with pembrolizumab for these patients.[17] However, in our cohort, PD-L1 expression was not available in some of the patients. Based on our only data, PD-L1 expression was not associated with PFS and OS (Supplementary Table 2). PD-L1 expression correlates with response to first-line ICIs treatment, however, a conclusion about the relationship between PD-L1 expression and the effect of the cross-line use of ICIs could not be drawn because of the small sample size of the current study. PD-L1 expression results by immunohistochemistry are affected by biopsy methods, intratumoral heterogeneity, type of cytological samples and fixatives, and other factors at the time of detection. A single biomarker is unlikely to predict response to ICIs treatment. Tumor mutational burden (TMB), tumor-infiltrating lymphocytes, and tumor infiltrating myeloid-derived suppressor cells (MDSC) may be used as a predictor of the efficacy of immunotherapy. However, TMB and the percentages of PD-L1positive MDSC are correlated with disease stage or clinical outcome. TMB may be heterogeneous within the tumor, and high TMB does not guarantee response to immune checkpoint inhibitors.[18–20] At present, there are no clinical characteristics or biomarkers that can predict the response of cross-line therapy, which needs to be explored.

Other studies showd that blood neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) levels at baseline may be good predictors of the ICIs rechallenge treatment response.[8] Patients with normal albumin levels were found to have a significant 0.50-fold reduced risk of death, using the clinical reference value as a cutoff.[21] C-reactive protein (CRP) was positively correlated with the mortality of patients with NSCLC, no matter what stage of cancer.[22] Alifano et al. Showed that compared with stage III/IV cancer patients and undetectable CRP levels in stage I/II cancer patients, a CRP level>20 mg/L was significantly associated with poor survival.[23] In NSCLC patients treated with ICIs, high pretreatment NLR and pretreatment PLR are associated with poor survival. LMRs with low pretreatment and posttreatment LMR were also associated with unsatisfactory survival outcomes.[24] However, We discovered that high-sensitivity CRP, NLR, and PLR were not linked with PFS2 and OS in our univariate analysis.[22–24] We were unable to identify any reliable clinical factors. There were a few variables with statistical significance ($p < 0.05$) in the univariate analysis; therefore, multivariate analysis of the Cox model could not be performed. This may be related to the small sample size in this retrospective study.

Regarding safety, the administration of various ICIs induced the recurrence of irAEs that occurred during the first therapy with ICIs. Four of 10 patients who experienced irAEs during the first ICIs therapy relapsed during the second ICIs therapy. Most irAEs during the rechallenge therapy were manageable.[25]

The current study had several limitations. First, it had a small sample size and a retrospective design, which made statistical analysis difficult. Second, a possible selection bias may have existed because the ICIs rechallenge was based on the physician's discretion. There were also differences in the number of chemotherapy protocols and their administration for each patient.

5 | CONCLUSIONS

The cross-line use of anti-PD-1/PD-L1 antibody showd a trend of improvement in PFS2 and OS, and its safety is reliable; however, the benefit to the patients is limited. We did not find a meaningful clinical predictor of post-line anti-PD-1/PD-L1 treatment benefit. A prospective study with a large sample size is needed in the future.

AUTHOR CONTRIBUTIONS

Xiang Zhao: Data curation; formal analysis; investigation; methodology; project administration; resources; software; validation; visualization; writing—original draft; writing—review and editing. **Yuan Cheng**: Data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—original draft; writing—review and editing. **Cuiyan Guo**: Data curation; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Ligong Nie**: Data curation; formal analysis; project administration; resources; supervision; validation; writing—review and editing. **Qi Zhang**: Conceptualization; data curation; formal analysis; methodology; resources; software; supervision; validation; visualization. **Meng Zhang**: Methodology; project administration;

resources; software; supervision; validation. **Kunyan Sun**: Data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation. **Guangfa Wang**: Investigation; methodology; project administration; software; supervision; validation; visualization.

ACKNOWLEDGMENTS

This study is supported by Beijing Municipal Natural Science Foundation (L222151), National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital) (2023IR48), and Beijing Xisike Clinical Oncology Research Foundation (Y-HS202202-0073).

CONFLICT OF INTEREST STATEMENT

All authors have read and approved the final version of the manuscript had full access to all of the data in this study and Yuan Cheng takes complete responsibility for the integrity of the data and the accuracy of the data analysis. All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

TRANSPARENCY STATEMENT

The lead author Yuan Cheng affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Xiang Zhao https://orcid.org/0000-0003-3551-1671
Yuan Cheng https://orcid.org/0000-0002-9763-7424
Cuiyan Guo https://orcid.org/0000-0002-6291-9915
Kunyan Sun https://orcid.org/0000-0003-1258-8940

REFERENCES

1. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2022;20(5):497-530.
2. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168(4):707-723.
3. Nomura M, Otsuka A, Kondo T, et al. Efficacy and safety of retreatment with nivolumab in metastatic melanoma patients previously treated with nivolumab. *Cancer Chemother Pharmacol*. 2017;80(5):999-1004.
4. Bernard-Tessier A, Baldini C, Martin P, et al. Outcomes of long-term responders to anti-programmed death 1 and anti-programmed death ligand 1 when being rechallenged with the same anti-programmed death 1 and anti-programmed death ligand 1 at progression. *Eur J Cancer*. 2018;101:160-164.
5. Watanabe H, Kubo T, Ninomiya K, et al. The effect and safety of immune checkpoint inhibitor rechallenge in non-small cell lung cancer. *Jpn J Clin Oncol*. 2019;49(8):762-765.
6. Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. *Cancer Chemother Pharmacol*. 2018;81(6):1105-1109.
7. Fujita K, Uchida N, Yamamoto Y, et al. Retreatment with Anti-PD-L1 antibody in advanced non-small cell lung cancer previously treated with Anti-PD-1 antibodies. *Anticancer Res*. 2019;39(7):3917-3921.
8. Katayama Y, Shimamoto T, Yamada T, et al Retrospective efficacy analysis of immune checkpoint inhibitor rechallenge in patients with Non-Small cell lung cancer. *J Clin Med*. 2019;9(1):102. doi:10.3390/jcm9010102IF
9. Prelaj A, Pircher CC, Massa G, et al. Beyond first-line immunotherapy: potential therapeutic strategies based on different pattern progressions: oligo and systemic progression. *Cancers*. 2021;13(6):1300.
10. Shi H, Lan J, Yang J. Mechanisms of resistance to checkpoint blockade therapy. *Adv Exp Med Biol*. 2020;1248:83-117.
11. Kim TK, Vandsemb EN, Herbst RS, Chen L. Adaptive immune resistance at the tumour site: mechanisms and therapeutic opportunities. *Nat Rev Drug Discov*. 2022;21(7):529-540.
12. O'Donnell JS, Teng MWL, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. *Nat Rev Clin Oncol*. 2019;16(3):151-167.
13. Ramjiawan RR, Griffioen AW, Duda DG. Anti-angiogenesis for cancer revisited: is there a role for combinations with immunotherapy? *Angiogenesis*. 2017;20(2):185-204.
14. Leighl NB, Redman MW, Rizvi N, et al. Phase II study of durvalumab plus tremelimumab as therapy for patients with previously treated anti-PD-1/PD-L1 resistant stage IV squamous cell lung cancer (Lung-MAP substudy S1400F, NCT03373760). *J Immunother Cancer*. 2021;9(8):e002973.
15. Niu J, Maurice-Dror C, Lee DH, et al. First-in-human phase 1 study of the anti-TIGIT antibody vibostolimab as monotherapy or with pembrolizumab for advanced solid tumors, including non-small-cell lung cancer. *Ann Oncol*. 2022;33(2):169-180.
16. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550.
17. Niki M, Nakaya A, Kurata T, et al. Immune checkpoint inhibitor rechallenge in patients with advanced non-small cell lung cancer. *Oncotarget*. 2018;9(64):32298-32304.
18. Munari E, Mariotti FR, Quatrini L, et al. PD-1/PD-L1 in cancer: pathophysiological, diagnostic and therapeutic aspects. *Int J Mol Sci*. 2021;22(10):5123.
19. Pepe F, Pisapia P, Gristina V, et al. Tumor mutational burden on cytological samples: a pilot study. *Cancer Cytopathol*. 2021;129(6):460-467.
20. Satturwar S, Girolami I, Munari E, Ciompi F, Eccher A, Pantanowitz L. Program death ligand-1 immunocytochemistry in lung cancer cytological samples: a systematic review. *Diagn Cytopathol*. 2022;50(6):313-323.
21. Sun H, Hu P, Shen H, et al. Albumin and neutrophil combined prognostic grade as a new prognostic factor in non-small cell lung cancer: results from a large consecutive cohort. *PLoS One*. 2015;10(12):e0144663.
22. Yang JR, Xu JY, Chen GC, et al. Post-diagnostic c-reactive protein and albumin predict survival in Chinese patients with non-small cell lung cancer: a prospective cohort study. *Sci Rep*. 2019;9(1):8143.
23. Alifano M, Falcoz PE, Seegers V, et al. Preresection serum c-reactive protein measurement and survival among patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2011;142(5):1161-1167.
24. Liu N, Mao J, Tao P, Chi H, Jia W, Dong C. The relationship between NLR/PLR/LMR levels and survival prognosis in patients with non-small cell lung carcinoma treated with immune checkpoint inhibitors. *Medicine*. 2022;101(3):e28617.

25. Kitagawa S, Hakozaki T, Kitadai R, Hosomi Y. Switching administration of anti-PD-1 and anti-PD-L1 antibodies as immune checkpoint inhibitor rechallenge in individuals with advanced non-small cell lung cancer: case series and literature review. *Thorac Cancer*. 2020;11(7):1927-1933.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhao X, Cheng Y, Guo C, et al. Efficacy of cross-line anti-programmed death 1/programmed cell death-ligand 1 antibody in the treatment of advanced nonsmall cell lung cancer: a retrospective study. *Health Sci Rep*. 2024;7:e2114. doi:10.1002/hsr2.2114