Original Article

Comparison of the effectiveness of alectinib versus crizotinib followed by alectinib in patients with ALK-positive advanced non-small-cell lung cancer in real-world setting and in the ALEX study

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Background: Alectinib has been established as a standard of care for patients with treatment-naive anaplastic lymphoma kinase-rearranged (ALK-positive) advanced non-small-cell lung cancer (NSCLC); however, it has rarely been compared with the sequential approach (crizotinib followed by alectinib) in China. This study aimed to compare real-world alectinib upfront data with either real-world sequential approach data or clinical trial first-line alectinib data.

Methods: The patients who received alectinib in the real-world setting were monitored from August 2016 to November 2020. The patients' characteristics were well balanced using the inverse probability of treatment weighting (IPTW) method. Real-world progression-free survival (rwPFS), real-world overall survival (rwOS), and real-world intracranial progression-free survival (rwiPFS) were calculated. To compare the effectiveness of alectinib in real-world setting with that in the ALEX study, data from the ALEX study were analyzed.

Results: This study included 311 patients who were divided into three groups: alectinib group (n=102), sequential group (n=63), and alectinib group in ALEX (n=146). The rwPFS and rwOS were similar between the alectinib and sequential groups. However, alectinib group was associated with a lower risk of central nervous system progression than sequential group. Compared with alectinib group in ALEX, the alectinib group in the real world had a significantly longer PFS [hazard ratio (HR), 0.57; 95% confidence interval (CI): 0.37–0.89; P=0.01] and OS (HR, 0.42; 95% CI: 0.21–0.82; P=0.01) after IPTW.

Conclusions: Our real world data suggested that sequential group was associated with a higher risk of progression in the brain than the alectinib upfront treatment. However, both treatments had similar survival in advanced ALK-positive NSCLC. Patients with advanced ALK-positive NSCLC in the real-world setting had significantly improved outcomes than those in the ALEX study.

Keywords: Anaplastic lymphoma kinase (ALK); non-small-cell lung cancer (NSCLC); real world data; alectinib

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Introduction

Over the past two decades, molecular targeted therapies for non-small-cell lung cancer (NSCLC) have remarkably improved outcomes. For a small proportion (3–7%) (1,2) of patients with advanced NSCLC harboring anaplastic lymphoma kinase (ALK) alterations, the median survival exceeds 5 years (3-5). The apparent prolongation of survival is due to the continuous development of new drugs. Next-generation ALK tyrosine kinase inhibitors (TKIs) are more potent (6-10) and central nervous system (CNS)-penetrant (3,4,11-14) compared with crizotinib, the first-generation ALK TKI.

Highlight box

Key findings

- We found that crizotinib followed by alectinib was associated with a higher risk of progression in the brain than the alectinib upfront treatment in the advanced anaplastic lymphoma kinase-rearranged (ALK+) non-small-cell lung cancer (NSCLC) patients in the real-world setting.
- Both treatments had similar survival in advanced ALK+ NSCLC in the real-world setting.

What is known and what is new?

- The ALEX study has confirmed that in the first-line treatment of advanced ALK+ NSCLC, alectinib is superior to crizotinib in both systemic and intracranial efficacy.
- There are few studies that apply scientific statistical methods to compare the difference in efficacy between sequential treatment with crizotinib followed by alectinib and first-line alectinib treatment, either in clinical trials or real-world data (RWD). This article applies the inverse probability of treatment weighting method to compare the differences in systemic and intracranial efficacy between sequential crizotinib followed by alectinib treatment and first-line alectinib treatment in the real world, and compares the RWD with the ALEX study.

What is the implication and what should change now?

- The study once again confirmed the efficacy and front-line application value of alectinib in RWD. However, with the release of the CROWN data, the role of this study may lie in providing RWD on progression-free survival (PFS), intracranial PFS, and overall survival for the application of alectinib in advanced ALK+ NSCLC, providing a basis for clinical doctors' treatment decisions.

The phase III ALEX study (6) (NCT02075840) showed that alectinib was better than crizotinib at treating advanced ALK-positive (ALK+) NSCLC. However, there is no ongoing or currently planned randomized trial comparing alectinib and crizotinib followed by alectinib (C + A) for patients with ALK+ NSCLC. Therefore, this study aimed to compare alectinib upfront real world data (A RWD) and C + A RWD. The hazard ratios (HRs) of A RWD *vs.* C + A RWD were calculated for real-world outcomes, including real-world progression-free survival (rwPFS), overall survival (rwOS), and intracranial progression-free survival (rwiPFS). Furthermore, the study aimed to compare A RWD and alectinib trial data (A ALEX) in the first-line setting. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-898/rc).

Methods

Study population

A national retrospective study of patients with advanced ALK+ NSCLC receiving alectinib was conducted between August 1, 2016, and November 17, 2020, at nine sites in China. The last follow-up date was March 4, 2023. All the patients in the real-world setting received alectinib as first- or second-line treatment. Among the patients, 63 had previously received crizotinib. Tumor response assessments were performed every 8–12 weeks with Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Peking University Cancer Hospital (No. 2018KT115-GZ01) and individual consent for this retrospective analysis was waived. ALEX data from the data contributor Roche were available through Vivli (https://search.vivli.org/).

Statistical analysis

Propensity score weighting [inverse probability of treatment weighting (IPTW)] was employed to form

Table 1 Unadjusted patient characteristics by treatment group

Characteristic	ALEC RWD (n=102)	CRIZ + ALEC RWD (n=63)	SMD	ALEC ALEX (n=146)	SMD
Age (years)	50.5 (41.0, 58.0)	50.0 (43.5, 57.5)	0.084	58.0 (49.0, 64.8)	0.653
Sex			0.030		0.040
Male	42 (41.2)	25 (39.7)		63 (43.2)	
Female	60 (58.8)	38 (60.3)		83 (56.8)	
ECOG PS			0.246		0.294
0	44 (43.1)	26 (41.3)		43 (29.5)	
1	51 (50.0)	28 (44.4)		93 (63.7)	
2	7 (6.9)	9 (14.3)		10 (6.8)	
Smoking			0.039		0.558
Never	86 (84.3)	54 (85.7)		88 (60.3)	
Former/current	16 (15.7)	9 (14.3)		58 (39.7)	
Histology			0.246		0.319
Adenocarcinoma	99 (97.1)	63 (100.0)		130 (89.0)	
Others	3 (2.9)	0 (0.0)		16 (11.0)	
Stage at initial diagnosis			0.440		0.263
IIIB	9 (8.8)	0 (0.0)		4 (2.7)	
IV	93 (91.2)	63 (100.0)		142 (97.3)	
CNS metastases			0.416		0.078
Yes	36 (35.3)	35 (55.6)		57 (39.0)	
No	66 (64.7)	28 (44.4)		89 (61.0)	

Age is presented as mean (IQR); other data are presented as n (%). ALEC, alectinib; CNS, central nervous system; CRIZ, crizotinib; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; RWD, real-world data; SMD, standardized mean difference.

comparable cohorts of patients on the basis of pretreatment characteristics. The covariates were defined with clinical judgment and known confounders from previous literature (6-10), including age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG), histology, disease stage, and brain metastasis (BM). Survival curves were generated using the Kaplan-Meier method for unadjusted or IPTW-adjusted cohorts. The curves for different treatment groups were compared using the IPTW-adjusted log-rank test and a Cox proportional hazards model with a robust variance estimator following IPTW adjustment. All analyses were conducted using the R software version 4.3.2.

In the A RWD group, rwPFS was defined as the time from the initiation of alectinib to disease progression or death, whichever occurred first. In the C + A RWD group, it was defined as the time from the initiation of crizotinib to disease progression plus the time from the initiation of alectinib to disease progression or death, whichever occurred first. Furthermore, rwOS was defined as the time from the initiation of ALK TKI to death and rwiPFS as the time from the initiation of ALK TKI to intracranial disease progression or death, whichever occurred first.

Results

Demographic and clinical characteristics

This study included 311 patients who were divided into three groups: A RWD (n=102), C + A RWD (n=63), and A ALEX (n=146). Compared with the A RWD group, the C + A RWD group had a greater proportion of patients with adenocarcinoma [63 (100%) *vs.* 99 (97.1%)], advanced

Table 2 IPTW adjusted patient characteristics by treatment group

Characteristic	ALEC RWD (ESS =90.2)	CRIZ + ALEC RWD (ESS =62.7)	SMD	ALEC RWD (ESS =97.4)	ALEC ALEX (ESS =146.8)	SMD
Age (years)	50.0 (41.3, 58.0)	50.0 (42.7, 57.5)	0.009	52.0 (47.0, 60.0)	52.9 (44.0, 61.0)	0.089
Sex			0.007			0.034
Male	38.0 (42.1)	26.6 (42.4)		40.5 (41.6)	63.5 (43.3)	
Female	52.3 (57.9)	36.1 (57.6)		56.9 (58.4)	83.3 (56.7)	
ECOG PS			0.007			0.051
0	36.0 (39.9)	25.3 (40.3)		32.9 (33.7)	47.5 (32.3)	
1	44.0 (48.8)	30.4 (48.5)		56.9 (58.4)	89.1 (60.7)	
2	10.2 (11.3)	7.1 (11.2)		7.7 (7.9)	10.2 (7.0)	
Smoking			0.017			0.088
Never	75.6 (83.8)	52.2 (83.2)		72.6 (74.5)	103.6 (70.6)	
Former/current	14.6 (16.2)	10.5 (16.8)		24.8 (25.5)	43.1 (29.4)	
Histology			<0.001			0.008
Adenocarcinoma	90.2 (100.0)	62.7 (100.0)		90.1 (92.5)	135.4 (92.2)	
Others	0.0 (0.0)	0.0 (0.0)		7.3 (7.5)	11.4 (7.8)	
Stage at initial diagnosis			<0.001			0.095
IIIB	0.0 (0.0)	0.0 (0.0)		5.1 (5.2)	4.9 (3.3)	
IV	90.2 (100.0)	62.7 (100.0)		92.3 (94.8)	141.9 (96.7)	
CNS metastases			0.004			0.065
Yes	42.0 (46.6)	29.4 (46.8)		35.0 (36.0)	57.4 (39.1)	
No	48.2 (53.4)	33.4 (53.2)		62.4 (64.0)	89.4 (60.9)	

Age is presented as mean (IQR); other data are presented as ESS (%). ALEC, alectinib; CNS, central nervous system; CRIZ, crizotinib; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IPTW, inverse probability of treatment weighting; IQR, interquartile range; RWD, real-world data; SMD, standardized mean difference.

cancer [stage IV, 63 (100%) *vs.* 93 (91.2%)], baseline BMs [35 (55.6%) *vs.* 36 (35.3%)], and high ECOG PS [ECOG PS of 2, 9 (14.3%) *vs.* 7 (6.9%)] (*Table 1*). After weighting, sufficient balance (standardized mean difference <0.1) was achieved for all covariates (*Table 2*). Compared with the A RWD group, the A ALEX group had a greater proportion of patients who were elder (mean age, 58.0 *vs.* 50.5 years), with ECOG PS 1 patients (63.7% *vs.* 50.0%) and with advanced cancer (stage IV, 97.3% *vs.* 91.2%) as well as a smaller proportion of patients with never-smokers (60.3% *vs.* 84.3%) and adenocarcinoma (89.0% *vs.* 97.1%). Sufficient balance was achieved for all covariates after weighting, and the distributions of propensity weights almost completely overlapped.

Treatment effectiveness

A RWD *vs.* C + A RWD

Disease progression or death occurred in 61 patients during a median follow-up of 29.9 months (A RWD) and 32.1 months (C + A RWD), and 26 deaths occurred during a median follow-up of 32.4 months (A RWD) and 44.8 months (C + A RWD). No significant difference was observed in rwPFS and rwOS between the A RWD and C + A RWD groups [median rwPFS: 50.6 *vs.* 42.8 months; median rwOS: not reached (NR) *vs.* NR]. The unadjusted HRs were 0.87 [95% confidence interval (CI): 0.52–1.45; P=0.59] for disease progression or death and 0.80 (95% CI: 0.36–1.82; P=0.59) for death (*Figure 1A*,*1B*). The adjusted

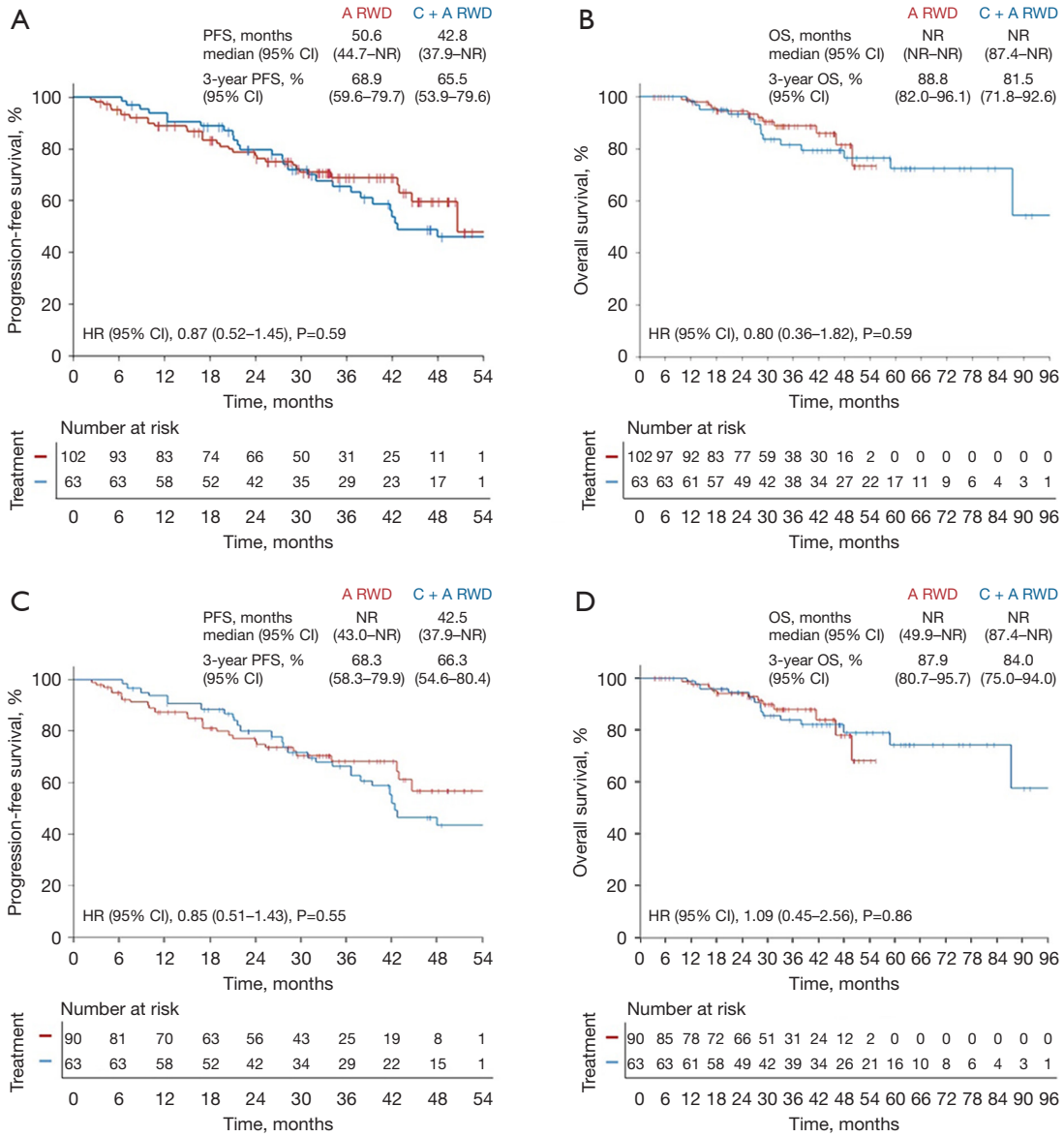

Figure 1 PFS and OS between the A RWD and C + A RWD groups before (A,B) and after (C,D) IPTW adjustment. A, alectinib as the first-line treatment; C + A, crizotinib as the first-line treatment, followed by alectinib, at the time of progression; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NR, not reached; OS, overall survival; PFS, progression-free survival; RWD, real-world data.

HRs for rwPFS and rwOS in the A RWD (n=90) and C + A RWD (n=63) groups were 0.85 (95% CI: 0.51–1.43; P=0.55) and 1.09 (95% CI: 0.45–2.56; P=0.86), respectively (*Figure 1C*,*1D*). After IPTW adjustment, the median rwPFS was NR months (95% CI: 43.0–NR) in the A RWD group and 42.5 months (95% CI: 37.9–NR) in the C + A RWD group, with 3-year rwPFS rates of 68.3% and 66.3%, respectively (*Figure 1C*). Furthermore, the median rwOS was NR months (95% CI: 49.9–NR) in the A RWD group and NR months (95% CI: 87.4–NR) in the C + A RWD group, with 3-year rwOS rates of 87.9% and 84.0%, respectively (*Figure 1D*).

Intracranial efficacy between A RWD and C + A RWD

The A RWD group exhibited longer rwiPFS than the C + A RWD group, with the proportions of patients without

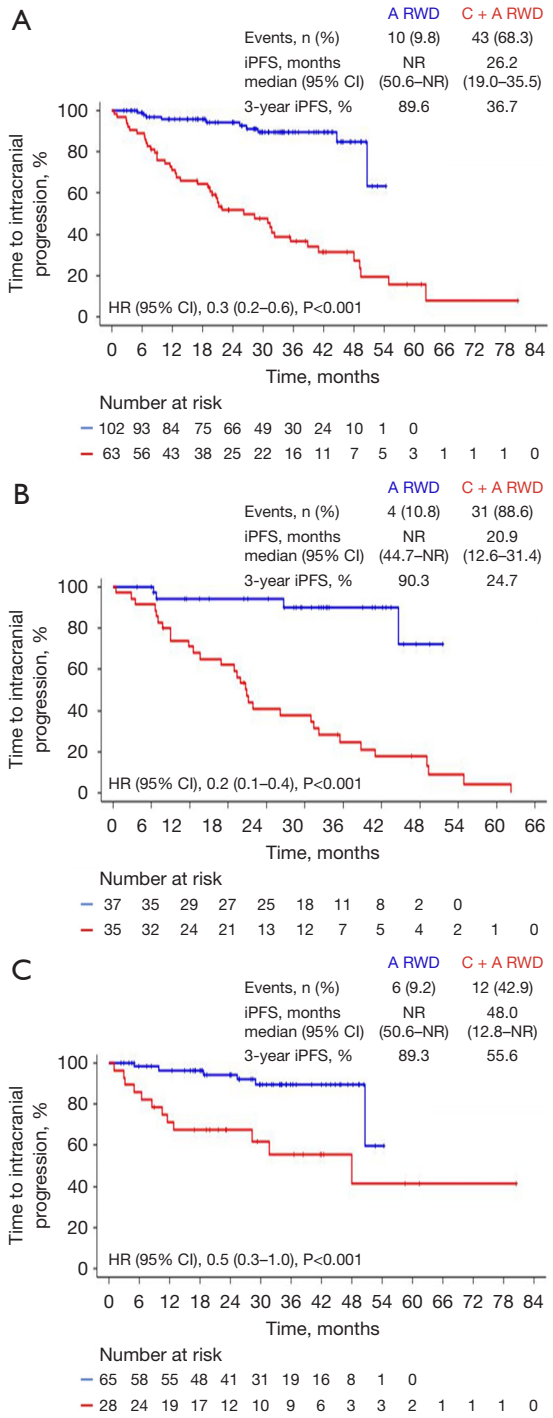

Figure 2 Intracranial PFS between the A RWD and C + A RWD groups (A) and patients with (B) and without (C) baseline BMs. A, alectinib as the first-line treatment; BMs, brain metastases; C + A, crizotinib as the first-line treatment, followed by alectinib, at the time of progression; CI, confidence interval; HR, hazard ratio; iPFS, intracranial PFS; NR, not reached; PFS, progression-free survival; RWD, real-world data.

3-year intracranial progression being 89.6% and 36.7%, respectively (*Figure 2A*). Among 72 patients with baseline BMs (measurable and non-measurable), the median rwiPFS was NR months (95% CI: 44.7–NR) in the A RWD group and 20.9 months (95% CI: 12.6–31.4) in the C + A RWD group, with 3-year rwiPFS rates of 90.3% and 24.7%, respectively (*Figure 2B*). Similar results were observed in patients without baseline BMs (*Figure 2C*). At 3 years, the probability of being free of intracranial progression in patients without baseline BMs and treated with A was 89.3% and that in those treated with C + A was 55.6%.

In the A RWD group, 4 (10.8%) of 37 patients with baseline BMs and 6 (9.2%) of 65 patients without baseline BMs had progression of preexisting BMs or developed a new intracranial lesion at the time of analysis. Contrarily, in the C + A RWD group, 31 (88.6%) of 35 patients with baseline BMs and 12 (42.9%) of 28 patients without baseline BMs had intracranial progression.

A RWD *vs.* A ALEX

A RWD was associated with a significantly lower risk of death than A ALEX (*Figure 3*). The HRs for OS in the A RWD (n=102) and A ALEX (n=146) groups before and after IPTW were 0.35 (95% CI: 0.18–0.67; P=0.001) (*Figure 3B*) and 0.42 (95% CI: 0.21–0.82; P=0.01) (*Figure 3D*), respectively. After IPTW adjustment, the median PFS was 50.6 months (95% CI: 42.8–NR) in the A RWD group and 34.9 months (95% CI: 22.4–NR) in the A ALEX group, with 3-year PFS rates of 66.1% and 48.5%, respectively (*Figure 3C*). The median OS was NR months (95% CI: 49.9–NR) in the A RWD group and NR months (95% CI: NR–NR) in the A ALEX group, with 3-year OS rates of 86.8% and 69.3%, respectively (*Figure 3D*).

Discussion

This study provided critical real-world evidence on the comparative effectiveness of alectinib upfront versus sequential crizotinib-alectinib therapy in advanced ALK+ NSCLC, particularly highlighting alectinib's superior CNS protective efficacy. By applying the IPTW method to balance baseline characteristics, the study strengthened the validity of observational comparisons and bridged gaps between clinical trial data and real-world practice.

For the RWD, the PFS and OS were similar in the A RWD and C + A RWD groups. Contrarily, for intracranial effectiveness, upfront treatment with alectinib was found to be associated with a clinically meaningful lower risk of

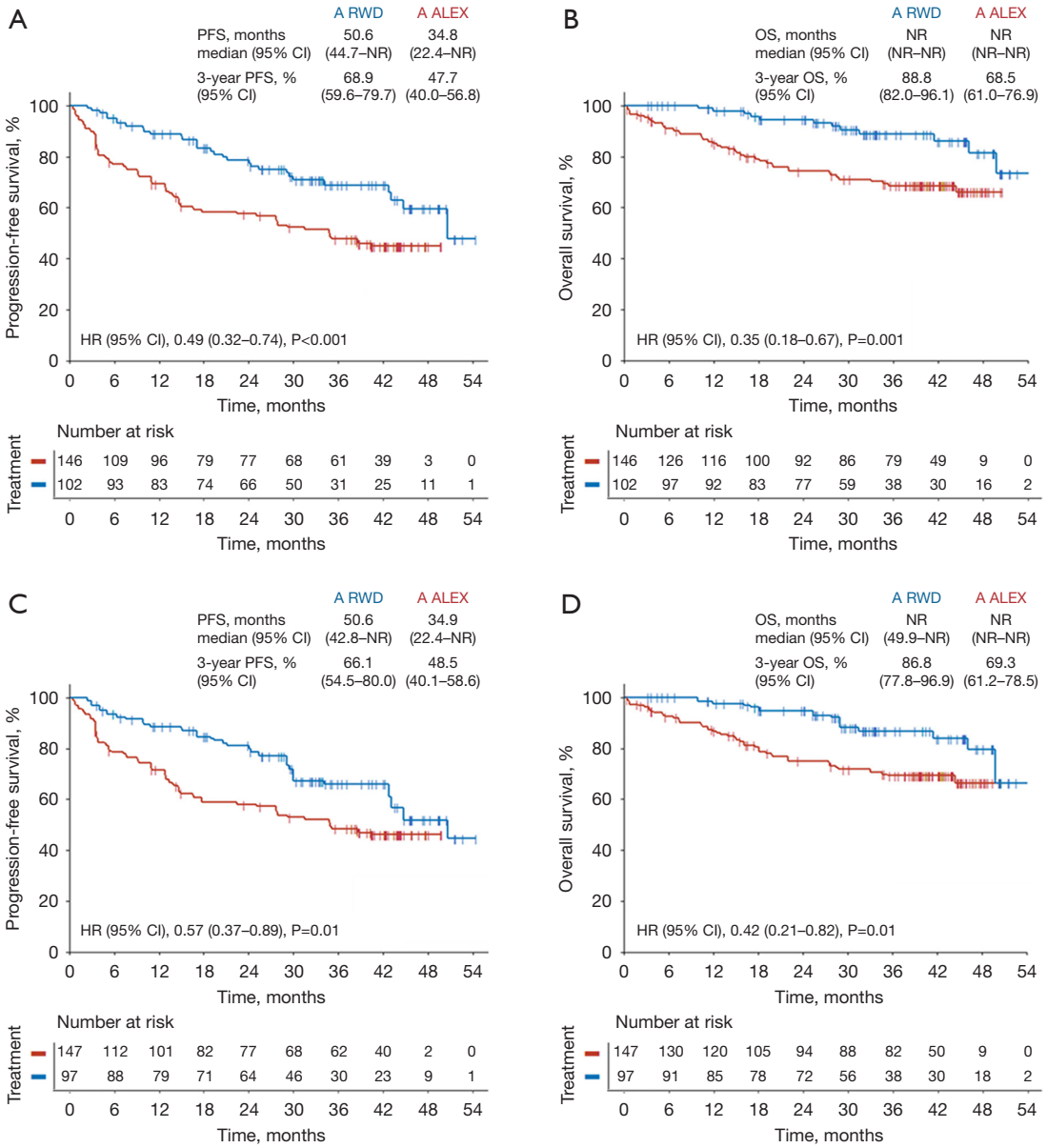

Figure 3 PFS and OS between the A RWD and A ALEX groups before (A,B) and after (C,D) IPTW adjustment. A, alectinib as the first-line treatment; ALEX, ALEX study; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NR, not reached; OS, overall survival; PFS, progression-free survival; RWD, real-world data.

brain progression or death than the sequential treatment approach, consistent with the findings of previous studies on alectinib (3,11,12). Although there are many studies comparing crizotinib and alectinib as first-line treatments in terms of efficacy (5,15), studies comparing alectinib with C + A at the time of progression are scarce. The WJOG9516L study (16) reported that the time-to-treatment failure of the C + A group was significantly longer than that of the A upfront group, but the baseline characteristics in both group were not well statistically matched. Similarly, Song *et al.* (17) compared sequential therapy with crizotinib and a second-generation ALK TKI and direct therapy of second-generation ALK TKI regimens in terms of efficacy. However, the risk of bias in nonrandomized studies can pose a threat to their validity even when employing statistical methods to mitigate confounding factors due to

the lack of treatment randomization. In this comparative effectiveness study, we employed IPTW to balance the differences between the groups. Our RWD indicated that C + A was associated with a higher risk of progression in the brain than alectinib upfront treatment. However, both treatments had similar survival in advanced ALK+ NSCLC, which is consistent with previous reports.

BMs remain a common and important clinical challenge for patients with ALK-rearranged NSCLC. The pooled prevalence of BMs was 34.9% (nine studies, 782 patients, 95% CI: 23.4–47.3%) in patients with ALK+ NSCLC, which was the highest among common genomic alterations, and the pooled incidence of new BM was 0.12 per year (18), suggesting the need for effective therapies that not only treat established BMs but also prevent the development of new BMs. In the ALEX study, the 1-year cumulative incidence of CNS progression was 9.4% with alectinib *vs.* 41.4% with crizotinib (6). In our study, the cumulative incidence of CNS progression at 1 year was 4.3% and 28.9% in the A RWD and C + A RWD groups, respectively. In the C + A RWD group, 45% of the patients developed BMs as an initial progression. Contrarily, in the A RWD group, only five patients (15%) developed BMs. Alectinib was associated with a 70% lower risk of intracranial progressive disease or death than crizotinib (HR, 0.3; 95% CI: 0.2–0.6; P<0.001), indicating the favorable CNS protective effect of alectinib. Furthermore, cost-effectiveness analysis of the management of CNS metastases in advanced ALK+ NSCLC revealed that alectinib could reduce BM-related healthcare resource utilization and costs in the Spanish healthcare setting (19).

In this study, the absence of OS differences between upfront alectinib and sequential C + A in our study aligned with findings from the J-ALEX and ALTA-1L trials, where crossover to second-generation TKIs was permitted. In contrast, the OS benefit observed in the ALEX trial likely stemmed from its prohibition of crossover, limiting post-crizotinib options. This underscored the importance of subsequent therapy availability in real-world settings, where sequential strategies might achieve comparable survival to upfront second-generation TKIs.

We compared the efficacy of alectinib between the A RWD and A ALEX groups. The possible causes of better survival in the A RWD group than in the A ALEX group are as follows: (I) differences in the baseline characteristics of the enrolled patients, such as race, complications, and nutritional status; (II) economical condition: alectinib was approved for ALK+ advanced NSCLC in China in August 2018 but was not included in the health insurance until 2020. Before 2020, the cost of alectinib was up to RMB 300,000 per year, which is expensive for patients with an average financial status; (III) local treatments: 17.6% of the patients in the A RWD group underwent radiotherapy or surgery in the chest or other metastatic sites before or during alectinib treatment, whereas in the ALEX study, 17.8% of the patients previously received CNS treatments and other radical local treatments were forbidden during alectinib treatment; (IV) in the ALEX study, only two thirds of crizotinib patients received another treatment at progression while in our RWD all crizotinib patients received alectinib as the next line of treatment.

There are some limitations in this study. (I) Retrospective design and selection bias. While IPTW was employed to balance baseline characteristics, the retrospective nature of this study inherently introduced risks of unmeasured confounding (e.g., undocumented comorbidities, or variations in supportive care). For instance, patients in the sequential (C + A) group were required to have received alectinib after crizotinib progression, which might select for a population with better overall health or slower disease biology, potentially inflating the observed survival outcomes. Additionally, the exclusion of patients who discontinued treatment due to toxicity or non-compliance could further bias results toward favorable efficacy estimates. (II) Heterogeneity in real-world *vs.* clinical trial settings. Comparisons between the real-world alectinib cohort and the ALEX trial population were constrained by fundamental differences in study design and data collection. (III) Limited follow-up and maturity of survival data. The median follow-up for the alectinib group (29.9 months) and sequential group (32.1 months) remained relatively short given the prolonged survival typical of ALK+ NSCLC. Consequently, median OS was not reached in either group, and long-term outcomes (e.g., 5-year survival) remained uncertain. Furthermore, the sequential group, treated earlier [2016–2020], had longer follow-up (44.8 months) than the alectinib group (32.4 months), potentially introducing time-related biases in survival comparisons. (IV) Generalizability of findings. The study was conducted exclusively in China, where regional treatment practices (e.g., later adoption of alectinib due to cost barriers before 2020) and genomic heterogeneity (e.g., ALK fusion variants prevalent in Asian populations) might limit extrapolation to other global cohorts. For example, the high proportion of never-smokers (84.3% in A RWD *vs.* 60.3% in A ALEX) could influence both toxicity profiles and efficacy outcomes. (V) Statistical Adjustments and Residual Confounding.

Although IPTW balanced measurable covariates (e.g., age, ECOG PS, brain metastases), unmeasured confounders such as socioeconomic status, access to palliative care, or genetic subtyping (e.g., EML4-ALK variants) were not accounted for. Moreover, the small sample size of the sequential group (n=63) reduced statistical power to detect subtle differences in outcomes, particularly for subgroup analyses (e.g., patients with baseline brain metastases).

Conclusions

Our RWD indicated that C + A was associated with a higher risk of progression in the brain than alectinib upfront treatment. However, both treatments had similar survival in advanced ALK+ NSCLC. Patients with advanced ALK+ NSCLC in the real-world setting had significantly improved outcomes than those in the ALEX study.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-898/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-898/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-898/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 the Medical Ethics Committee of Peking University Cancer Hospital (No. 2018KT115-GZ01) and individual consent for this retrospective analysis was waived.

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