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Safety and efficacy of alectinib versus crizotinib in alk-positive non-small cell lung cancer: An update meta-analysis

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Abstract: Our study aimed to evaluate the efficacy and toxicity of alectinib compared with crizotinib and provide a reference for clinical use of ALK-TKI, systematically. We searched articles published update till October, 2021 based on the electronic databases，including PubMed, EMBASE and Cochrane Library. All trials analyzed the summary odds ratios (ORs) of the interesting outcomes. Three RCTs, including six studies were included. The pooled hazard ratio (HR) =0.33 (95%CI=0.21–0.51, P<0.00001) shown that the alectinib group achieved significant progress-free survival (PFS) superiority than crizotinib, consistent with those for the with (P=0.001) or without (P<0.00001) measurable CNS lesions at baseline. Also, the regimen of the alectinib did achieved benefit in the ORR (OR=2.07, 95%CI=1.41-3.06, P=0.0002) than crizotinib. Due to the limited data, the pool result of the difference of overall survival (OS) was without statistically significant (P=0.35). With regard to the safety, grade 3 to 5 adverse events were less frequent with alectinib than crizotinib (OR=0.53, 95%CI=0.31-0.90, P=0.02). As compared with crizotinib, alectinib demonstrated better PFS efficacy and comparable safety as a first-line treatment for advanced ALK-positive Non-Small Cell Lung Cancer (NSCLC). OS data remain immature, further trials with long-term survival rate have future to look forward to.

Keywords: Alectinib; Crizotinib; NSCLC; Meta-analysis

INTRODUCTION

Over the last few years, the development of several anaplastic lymphoma kinase (ALK) inhibitors has completely changed the therapeutic strategies of advanced NSCLC with ALK-rearranged and showed significant efficacy superiority for patients (Sgambato, 2018).

Crizotinib, as the first ALK inhibitor, was approved for ALK-positive NSCLC patients and has significantly improved the prognosis relative to standard chemotherapy in advanced patients (Solomon, 2014; Nishio, 2018). However, progression also occurs in patients with ALK-positive NSCLC receiving crizotinib due to the acquired resistance within the first year of therapy (Solomon, 2014; Nishio, 2018). Various mechanisms have been reported as contributing to crizotinib resistance (Dagogo-Jack, 2016; Harada, 2021). Additionally, crizotinib has poor accumulation in the central nervous system (CNS) because of the poor penetration of the blood-brain barrier (Costa, 2011; Metro, 2015; Okimoto, 2019). It is necessary to develop next-generation ALK inhibitors that can against the acquired drug resistance and CNS progression.

Alectinib, a second-generation ALK inhibitor, has identifiable to be a more potent and selective anti-tumour activity that could bypass crizotinib resistance (Zhou, 2019). Preclinical researches had shown that alectinib had high penetration into the CNS. Improvements in PFS and better tolerability were also observed in previous trials that compare alectinib with crizotinib (Hida, 2017; Nakagawa, 2020; Camidge. 2019; Peters, 2017). While, the superiority of final OS failed to achieve in the J-ALEX study, which has been reported in 2021 ASCO (Yoshioka, 2021).

Whether the alectinib can completely replace the crizotinib as first-line option for NSCLC with ALK-rearranged. We conducted this update meta-analysis to clarify the efficacies and toxicity of alectinib relative to crizotinib in ALK-positive NSCLC and provide some references for the clinical use of alectinib with the latest data.

MATERIALS AND METHODS

Search strategy

Two reviewers separately performed a systematic screening process by the PubMed, Embase, Cochrane database update till October, 2021 to identify all the eligible researches. The following key words and relevant Medical Subject Heading (MeSH) terms were used: ‘anaplastic lymphoma kinase-positive’, ‘non-small-cell lung cancer’, ‘alectinib’ and ‘crizotinib’. The reference lists and materials were also reviewed to detect other literature.

Eligibility criteria

Studies associated with the following criteria were included in current study: (1) patients: articles that enrolled patients with ALK-positive NSCLC; (2) intervention: research that focused on comparing alectinib versus crizotinib; (3) design: randomized controlled trials (RCTs); (4) outcomes : PFS, OS, ORR, AEs; we just include the latest data in multiple reports.

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Data extraction
Two authors independently extracted the following data from each trial. Disagreement was settled through discussion to reach a consensus. From each of the eligible studies, the main categories were based on the following: the trial's name; publication year; mean age of the participants; treatment regimen; number of patients; and interested finding of each treatment.

Quality evaluation
We choose the risk of bias items (ROBI) for RCTs recommended by The Cochrane Handbook for Systematic Reviews of Interventions. The process was performed by two reviewers separately; differences were resolved through discussion.

Data synthesis and analysis
To examine the heterogeneity of included trial and determine the model for analysis (random-effect model or fixed-effect model), we conducted the I^2 tests and Chi-squared (Higgins, 2002). Studies with $I^2 \geq 50\%$ was considered to indicate moderate and high heterogeneity, $I^2 < 50\%$ was thought to have low heterogeneity, respectively (Higgins, 2003). Only when there was low heterogeneity among studies, the fixed-effects model was used.

Otherwise, the random effects model was used. Results with a P value less than 0.05 were considered statistically significant. Statistical analyses were performed using Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). Results of this current study were demonstrated in forest plots.

RESULTS

Overview of literature search and study characteristics
A total of 337 articles were retrieved initially for evaluation. After the preliminary screening of the abstracts and titles, 11 studies were further evaluated in more detail, but 5 studies were then excluded because fail to meet the inclusion criteria.

Finally, a total of 6 researches were included (Zhou, 2019; Hida, 2017; Nakagawa, 2020; Camidge, 2019; Peters, 2017; Yoshioka, 2021). The overview of literature search is shown in fig. 1. The primary characteristics of the eligible articles is present in the table 1.

All included articles in our analysis were represented moderate quality at least. Fig. 2 and fig. 3 presented the summary of the quality assessment process.

Clinical and methodological heterogeneity
OS of alectinib versus crizotinib
Due to the limited data of OS, we only combined the OR from 2 studies. As shown in fig. 4, the difference in OS between alectinib and crizotinib was not statistically significant (OR=0.82, 95%CI=0.54-1.25, P=0.35).

ORR of alectinib versus crizotinib
The fixed-effects model yielded a pooled OR of studies (P=0.38, $I^2 = 0\%$). As shown in fig. 4, there is significant statistical difference of ORR when comparing the two groups (OR=2.07, 95%CI=1.41-3.06, P=0.0002).

AEs of alectinib versus crizotinib
As shown in fig. 4, results showed that alectinib did not reach a statistically significant level than crizotinib in terms of the adverse effects (OR=0.64, 95% CI=0.20-2.01, P=0.44). In addition, no formal statistical difference was found for adverse events leading to treatment discontinuation (OR=0.70, 95%CI=0.42-1.18, P=0.18), dose interruption (OR=0.61, 95%CI=0.25-1.49, P=0.28) and the serious adverse event (OR=0.92, 95%CI=0.54-1.57, P=0.76). While, grade 3 to 5 adverse events were less frequent with alectinib than crizotinib (OR=0.53, 95% CI=0.31-0.90, P=0.02) and the differences were statistically significant.

PFS of alectinib versus crizotinib
The random effect model was used for merging, since there is high degree of the heterogeneity across the three trials. The pooled data demonstrated that alectinib has shown superior PFS compared with crizotinib (OR=0.33, 95% CI=0.21-0.51, P<0.00001) (fig. 5).

Among patients with (OR=0.18, 95%CI=0.06-0.51, P=0.001) (fig. 5) or without (OR=0.41, 95%CI=0.31-0.55, P<0.00001) (fig.5) measurable CNS lesions at baseline, the pooled analysis revealed that alectinib did also have significantly longer PFS versus the crizotinib group and the differences were both statistically significant.

DISCUSSION

The current standard first-line treatments for ALK-positive NSCLC patients is crizotinib (Solomon, 2014). While, many ALK-positive NSCLC patients experience the CNS progressionin patients receiving crizotinib within the first year (Costa, 2011; Costa, 2015; Zhang, 2015). Subsequently, it has now been supplanted by more potent second-generation ALK inhibitors based on several randomized, phase 3 studies, resulting that second-generation ALK inhibitors were superior to crizotinib as first-line therapy (Camidge, 2019; Camidge, 2018).

Results of this update meta-analysis confirmed that alectinib has superior PFS than crizotinib in ALK-positive NSCLC patients. This consistency was also observed in patients with/without measurable CNS lesions at baseline. Also, the regimen of the alectinib did achieved benefit in the objective response rate.

Since crizotinib has poor activity against brain metastasis, the CNS is the most frequent relapse site during crizotinib treatment (Costa, 2015).

Table 1: The Primary characteristics of the eligible studies in more detail

Trail	J-ALEX		ALESIA		ALEX	
Author	Nakagawa *et al*		Caicun Zhou *et al*		T. Mok *et al*	
Reference	15-17		18		19-20	
Year	2017/2020/2021		2019		2017/2020	
Intervention	alectinib	crizotinib	alectinib	crizotinib	alectinib	crizotinib
Sample size	103	104	152	151	152	151
Age (years)	61	59.5	50.5	51.1	56.3	53.8
Interesting outcomes	PFS,PFS*,PFS#, OS, ORR, AEs, sAEs		PFS,PFS*,PFS#, ORR, AEs, sAEs		PFS,PFS*,PFS#, OS, ORR, AEs, sAEs	

*Brain metastases at baseline (-), #Brain metastases at baseline (+), AEs: adverse events

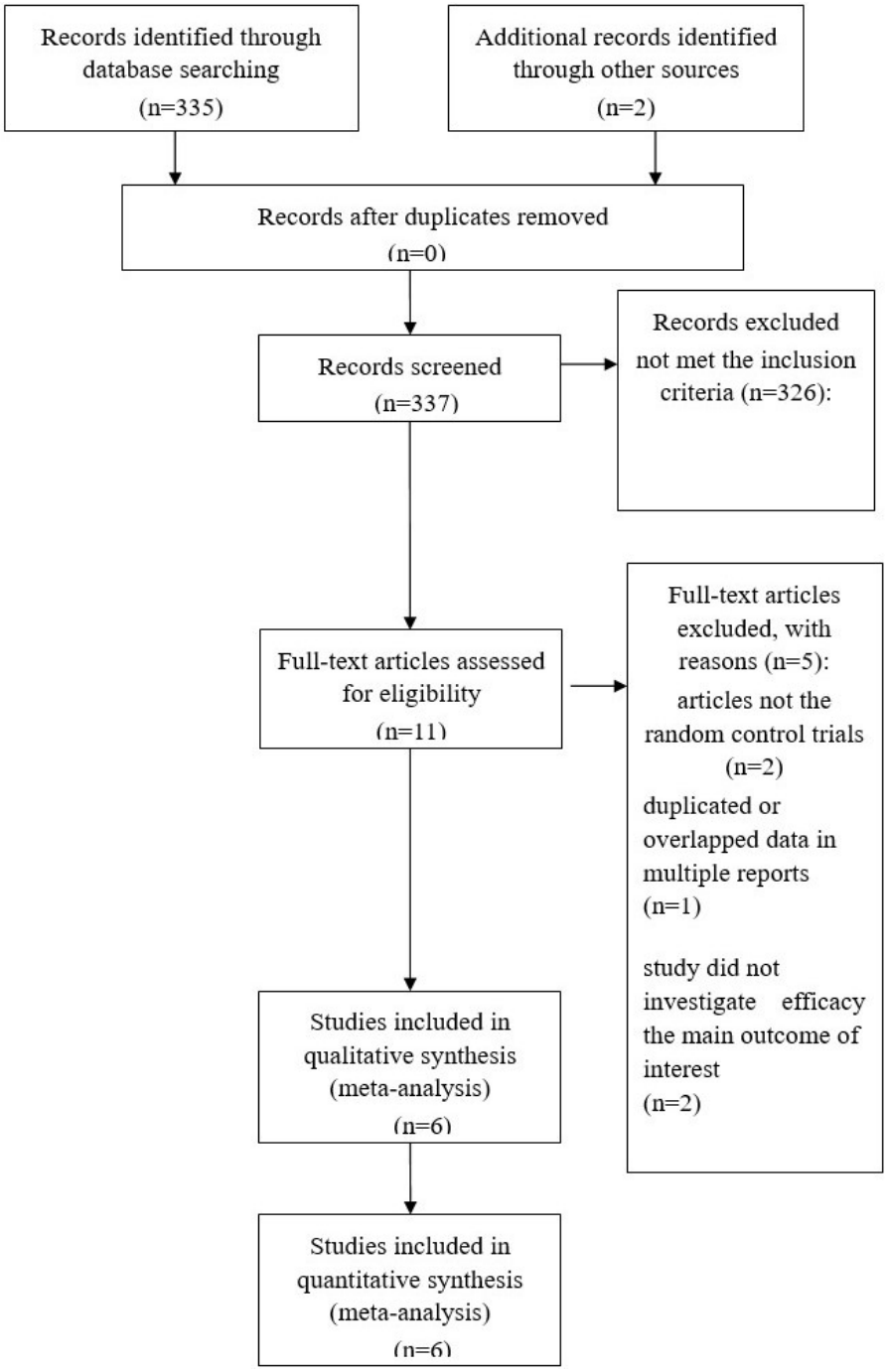

Fig. 1: PRISMA flow chart of selection process to identify studies eligible for pooling

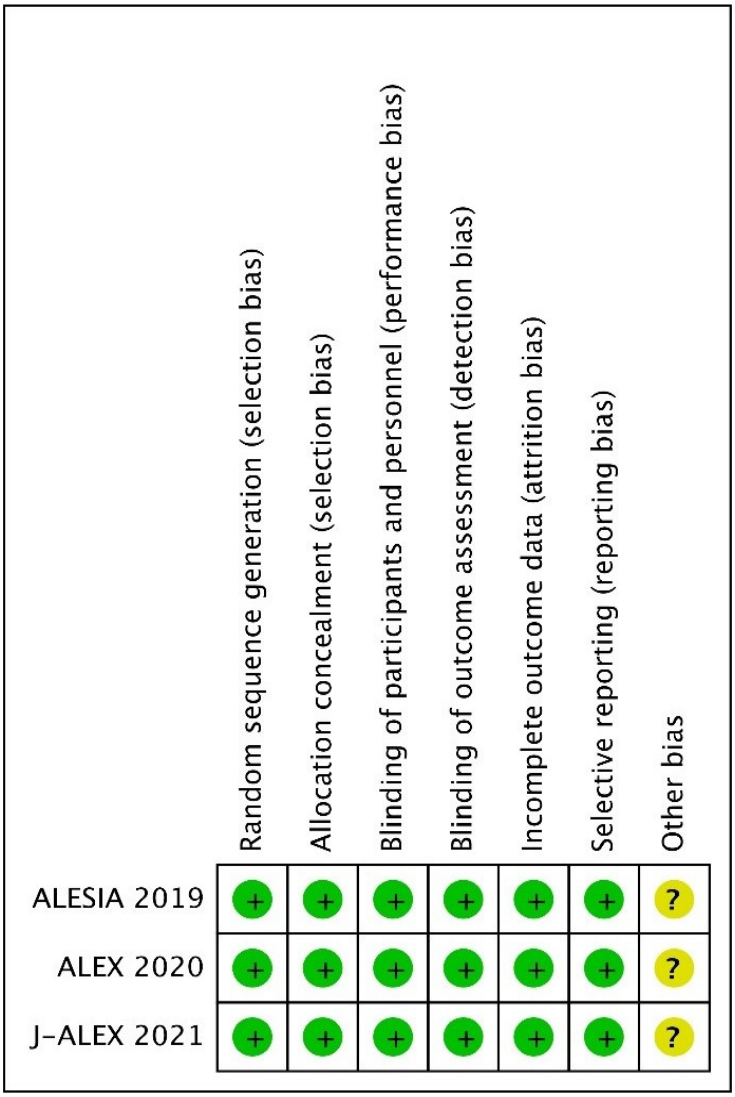

Fig. 2: Methodological quality assessment for each included study

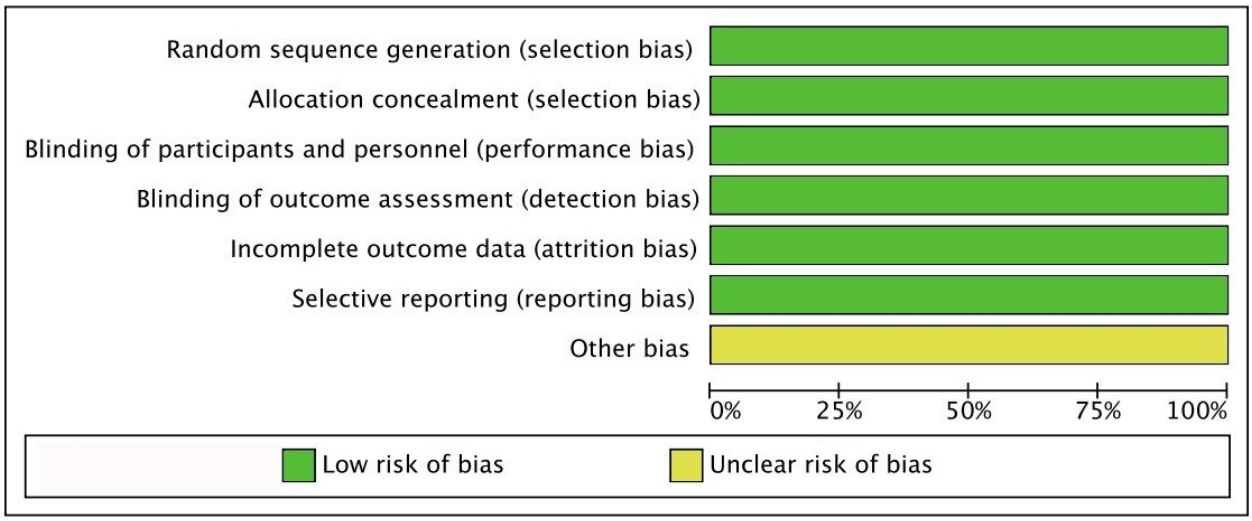

Fig. 3: Quality assessment summary for included studies

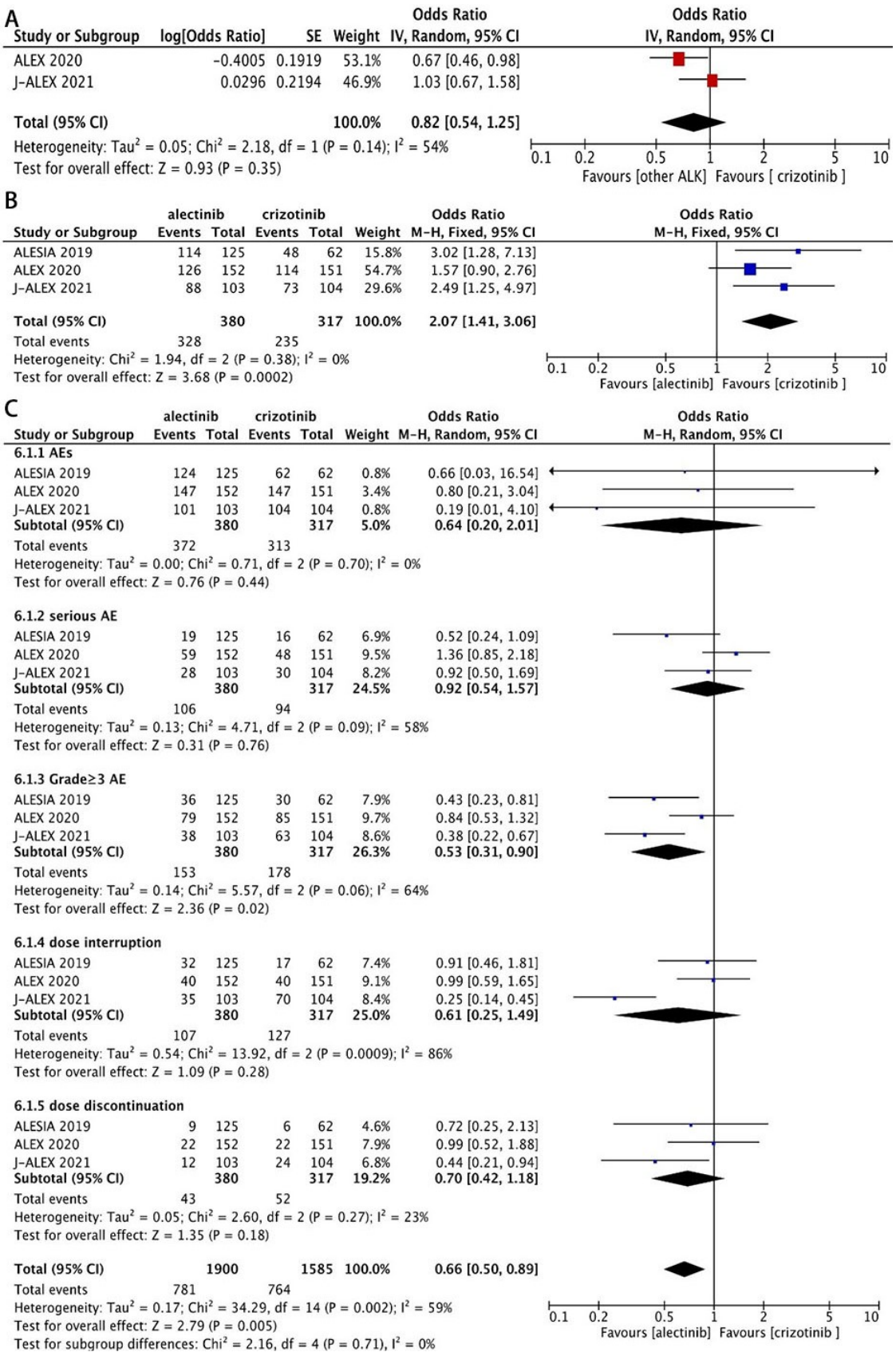

Fig. 4: Pooled analysis of OS, ORR, AEs of alectinib versus crizotinib. a OS; b ORR; c AEs

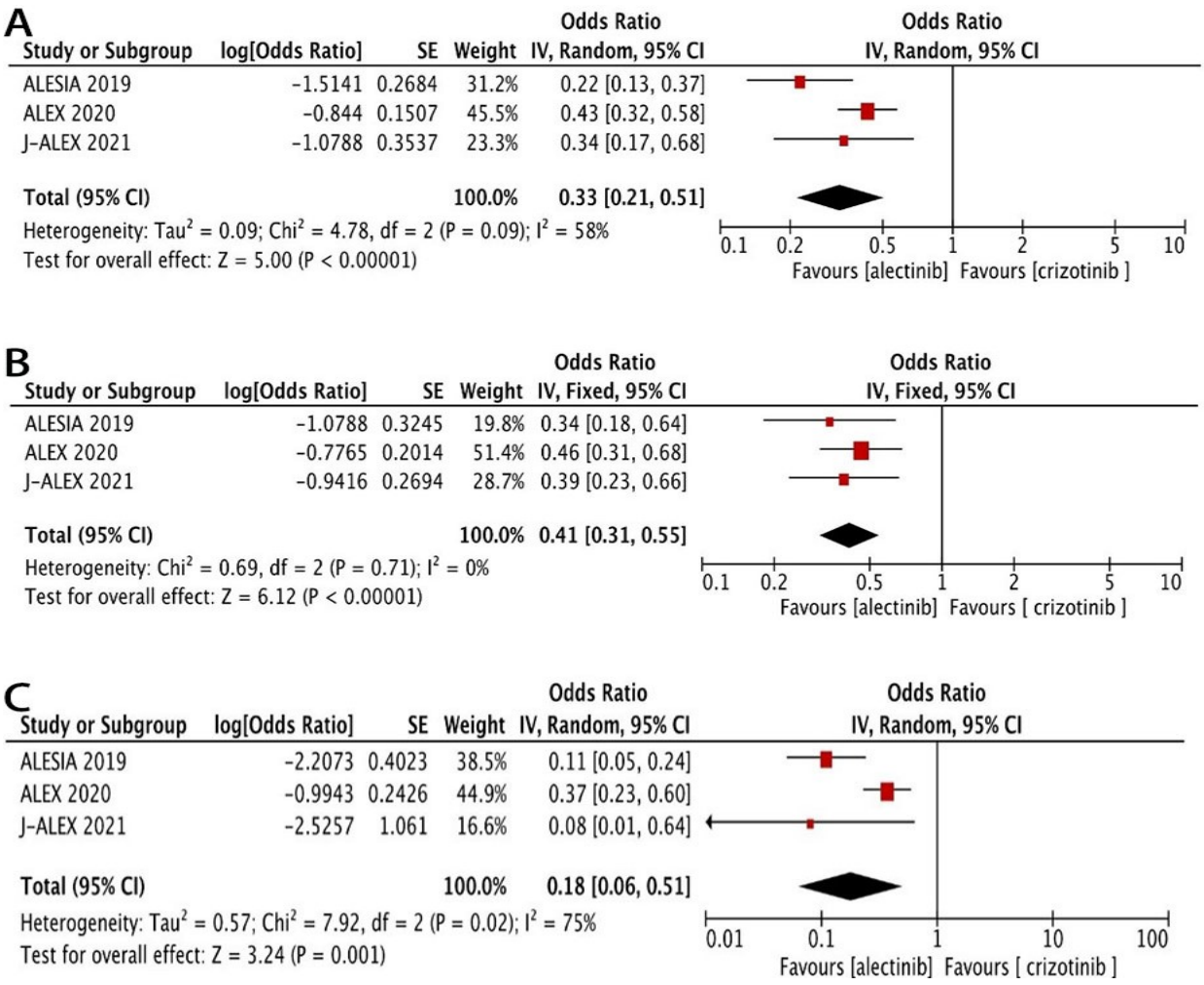

Fig. 5: Pooled analysis of PSF of alectinib versus crizotinib. a PSF; b PFS among patients with measurable CNS lesions at baseline; c PFS among patients without measurable CNS lesions at baseline

Unlike crizotinib, alectinib is a CNS penetrant. The blood–brain barrier (BBB) product the CNS from harboring potentially harmful substance, contributing to CNS homeostasis. BBB active P-glycoprotein, a key drug efflux transporter of the adenosine triphosphate (ATP) that recognized to be significant for drug response and disposition (Silverman, 1999; Fromm, 2000; Litman, 2001). In pre-clinical investigations, alectinib has superior penetration efficacy into the CNS and was not transported out by P-glycoprotein (Toyokawa, 2015). Potential "bypass" mechanisms through activation of other receptor tyrosine kinases (Toyokawa, 2015) also contributing to targeting of crizotinib resistance.

Use of next-generation ALK inhibitors as salvage treatment is feasible, but their impact on OS is still unclear. The odds ratio for OS in our analysis did not reach significance difference. Lacking of OS benefit to date is likely due to the fact that in those included trials patients receiving crizotinib experienced progress disease (PD) earlier than those treated with alectinib. As a result, more patients in the crizotinib group received at least one post-progression anticancer sooner than the alectinib arm. Additionally, most patients assigned to crizotinib received alectinib as a post-progression therapy. Thus, we can make a bold assumption that although no statistical difference was found OS at this stage, but the trend of improvement with alectinib will likely persist.

Safety results from our analysis reveal that alectinib showed a comparable safety profile compared with crizotinib, but grade ≥3 AEs were more frequent with crizotinib than with alectinib. Fewer gastrointestinal AEs, especially the nausea and diarrhea, were reported in the alectinib group than the crizotinib group. However, it still has prominent liver damage and myalgia, which will provide some references for the clinical use of alectinib.

Limitations of our study include the imbalance existed among included studies due to different quality and the varying definition, which may have an effect on the findings of our meta-analysis. In addition, due to the

limited data of OS data to analysis. More high-quality researches with further data are strongly in-needed to clarify this issue.

CONCLUSION

Results from this update meta-analysis show consistency with previous clinical investigations and build on existing evidence supporting the fact that alectinib listed as the preferred option than crizotinib as the front-line option for patients with ALK-positive non-small-cell lung cancer. Although the final OS data is limited, the result seems to be a positive trend for OS favoring alectinib if treatment crossover had not been allowed.

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