ORIGINAL RESEARCH

Final overall survival analysis from the phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with *ALK*-positive non-small-cell lung cancer ☆

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Background: Mature progression-free survival (PFS) data from the phase III J-ALEX study showed superiority for alectinib versus crizotinib [hazard ratio (HR) 0.37, 95% confidence interval (CI) 0.26-0.52; median PFS 34.1 versus 10.2 months, respectively] in advanced *ALK* (anaplastic lymphoma kinase)-positive non-small-cell lung cancer (NSCLC). Overall survival (OS) data were immature (HR 0.80, 99.8799% CI 0.35-1.82) at the time of data cut-off (30 June 2018). We report final OS data after ≥5 years of follow-up.

Patients and methods: ALK inhibitor naive Japanese patients who were chemotherapy naive or had received one prior chemotherapy regimen were enrolled. Patients were randomized to receive alectinib 300 mg ($n = 103$) or crizotinib 250 mg ($n = 104$) twice daily until progressive disease, unacceptable toxicity, death, or withdrawal. The primary endpoint was independent review facility-assessed PFS, with OS (not fully powered) as a secondary endpoint.

Results: Median duration of OS follow-up was 68.6 months with alectinib and 68.0 months with crizotinib. Treatment with alectinib did not prolong OS relative to crizotinib (HR 1.03, 95.0405% CI 0.67-1.58; $P = 0.9105$). Five-year OS rates were 60.9% (95% CI 51.4-70.3) with alectinib and 64.1% (95% CI 54.9-73.4) with crizotinib. In total, 91.3% ($n = 95/104$) of crizotinib-treated patients and 46.6% ($n = 48/103$) of alectinib-treated patients received at least one subsequent anticancer therapy. After study drug discontinuation, 78.8% of patients in the crizotinib arm switched to alectinib, while 10.7% of patients in the alectinib arm switched to crizotinib as a first subsequent anticancer therapy. Patients randomized to crizotinib tended to switch treatment earlier than those randomized to alectinib.

Conclusion: Final OS analysis from J-ALEX did not show superiority of alectinib to crizotinib; this result was most likely confounded by treatment crossover. Alectinib remains a standard of care for the treatment of patients with advanced *ALK*-positive NSCLC.

Key words: alectinib, *ALK*-positive NSCLC, crizotinib, J-ALEX, overall survival

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INTRODUCTION

Alectinib, a highly selective anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), is a preferred first-line therapy for patients with advanced *ALK*-positive non-small-cell lung cancer (NSCLC).[1,2] The randomized, multicenter, open-label, phase III J-ALEX study compared the efficacy and safety of alectinib, at the approved Japanese dose of

300 mg twice daily (b.i.d.), with crizotinib in Japanese patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC.[3] The approved Japanese dose for alectinib, 300 mg twice daily (b.i.d.), was used in J-ALEX based on data from the Japanese AF-001JP study, while the approved dose for alectinib outside of Japan is 600 mg b.i.d.[4,5] At the time of the primary endpoint analysis (data cut-off: 3 December 2015), alectinib demonstrated superior progression-free survival (PFS) relative to crizotinib according to an independent review facility [IRF; hazard ratio (HR) 0.34, 99.7% confidence interval (CI) 0.17-0.71, stratified log-rank $P < 0.0001$].[3] Analysis of the central nervous system (CNS) efficacy of alectinib in J-ALEX showed that alectinib prolonged the time to progression of CNS metastases and prevented the development of new CNS lesions in patients without baseline CNS disease.[6]

Mature PFS data from J-ALEX (data cut-off: 30 June 2018) continued to demonstrate superiority in IRF-assessed PFS for alectinib versus crizotinib (HR 0.37, 95% CI 0.26-0.52; median PFS 34.1 versus 10.2 months with crizotinib).[7] Overall survival (OS) data remained immature with 30.1% of events recorded in the alectinib arm and 31.7% of events in the crizotinib arm (HR 0.80, 99.8799% CI 0.35-1.82).[7] The J-ALEX study was closed at the clinical data cut-off date of 30 June 2018, and OS follow-up and data collection of subsequent treatment were continued after the close of the study. Here, we report the final OS analysis of J-ALEX after at least 5 years of follow-up from the last patient.

METHODS

Study design and patients

The design of the J-ALEX study (JapicCTI-132316; JO28928) has been described previously.[3] ALK inhibitor naive Japanese patients with advanced *ALK*-positive NSCLC, who were chemotherapy naive or had received one prior chemotherapy regimen were enrolled. Key eligibility criteria included age ≥20 years; stage IIIB, IV, or recurrent *ALK*-positive NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; and at least one investigator-assessed measurable lesion according to RECIST version 1.1. Patients with treated or asymptomatic brain metastases were also eligible. *ALK* positivity was confirmed centrally by immunohistochemistry and FISH, or by RT-PCR, using tissue or cell samples.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice in Japan. The study protocol was reviewed by the institutional review board from the perspective of ethical, scientific, and medical validity. All patients provided written informed consent prior to any study-related procedures.

Treatment

Patients were randomized 1:1 via an interactive web response system to receive oral alectinib 300 mg or oral crizotinib 250 mg b.i.d. until progressive disease (PD), unacceptable toxicity, death, or withdrawal. Randomization

was stratified according to ECOG performance status (0/1 versus 2); treatment line (first versus second); and clinical stage (IIIB/IV versus recurrent). Treatment crossover between arms after study drug discontinuation was permitted. Patients initially randomized to the crizotinib arm who withdrew due to PD, prior to the approval of alectinib in Japan, were permitted to receive alectinib during the study.

Endpoints

The primary study endpoint was PFS as assessed by an IRF. Secondary endpoints included OS, objective response rate, duration of response, time to response, time to progression of brain metastases in patients who presented with them at baseline, time to onset of brain metastases in patients who did not present with them at baseline, health-related quality of life, safety, and pharmacokinetics. IRF-assessed PFS was defined as the time from randomization to confirmation of PD assessed by the IRF or death, whichever occurred first. OS was defined as the time from randomization to death from any cause.

Statistical analyses

A sample size of 200 patients was planned primarily to detect a clinically meaningful difference in IRF-assessed PFS, assuming an enrollment period of 44 months. The study was not fully powered primarily for the endpoint of OS, but it was estimated that 150 OS events would provide 70% statistical power for a superiority hypothesis, under a targeted HR of 0.667.[3] The final analysis of OS was planned to be conducted when 150 events have accrued or when the sponsor decides to terminate the trial, whichever occurs first. In this study, superiority in OS could be tested in a hierarchical fashion only if the null hypothesis for the superiority in PFS was rejected. Multiplicity by multiple analysis, including two formal interim analyses of OS, was adjusted by O'Brien and Fleming-type alpha spending function. The Kaplan-Meier methodology was used to estimate time to event endpoints. A stratified Cox regression model using the stratification factors for randomization was used to estimate the HR and its CI of OS between treatment arms. Efficacy analyses were carried out on the intent-to-treat population, which comprised all randomized patients.

RESULTS

Baseline characteristics

Patients were enrolled between November 2013 and August 2015. In total, 207 patients were randomized to receive alectinib ($n = 103$) or crizotinib ($n = 104$).[3] Baseline patient characteristics were generally balanced, but there was a greater proportion of patients who presented with brain metastases at baseline in the crizotinib arm ($n = 29/104$, 27.9%) compared with the alectinib arm ($n = 14/103$, 13.6%; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100527). However, this
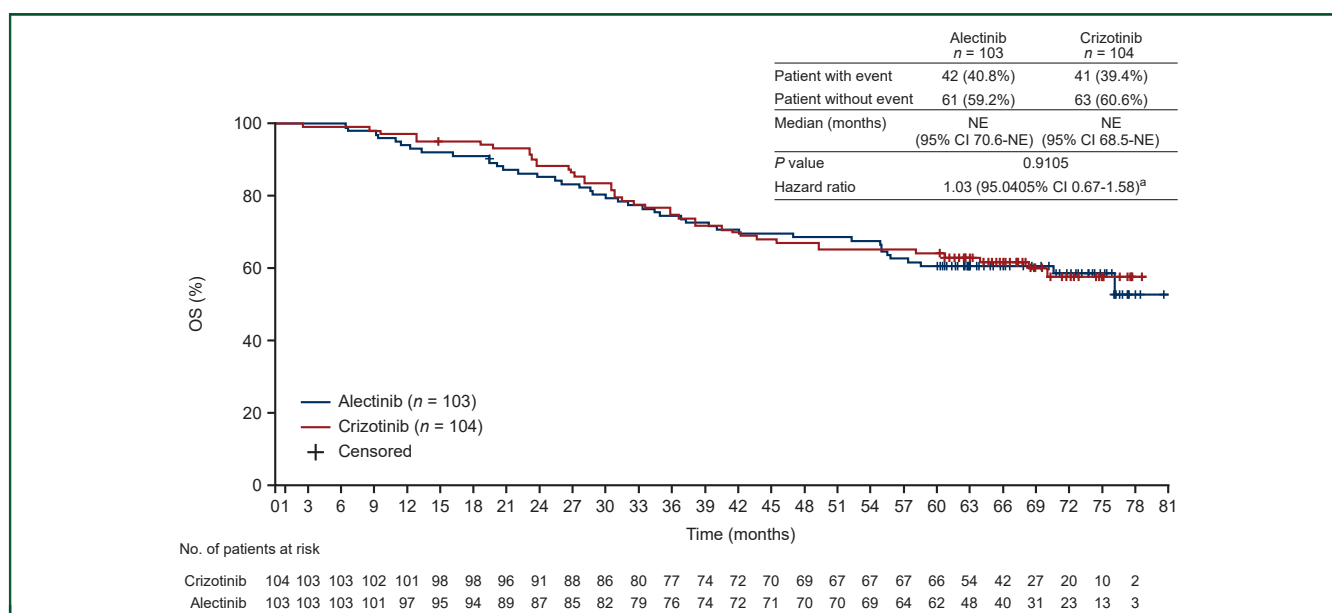
Figure 1. Final OS in the ITT population.
CI, confidence interval; ITT, intent to treat; NE, not estimable; OS, overall survival.
[a]The O'Brien—Fleming rejection boundary was $P < 0.049595$ for the final OS analysis.

imbalance did not impact the conclusion from the primary analysis.[3]

Efficacy

At the time of the final OS analysis in late 2020, when a minimal follow-up duration of 5 years for each patient was reached, the median duration of follow-up was 68.6 months (range 6-81) with alectinib and 68.0 months (range 2-79) with crizotinib. In total, 42 death events (40.8%) were recorded in the alectinib arm and 41 (39.4%) in the crizotinib arm. Superiority in OS of alectinib to crizotinib was not demonstrated (HR 1.03, 95.0405% CI 0.67-1.58, $P = 0.9105$); median OS was not reached in either treatment arm (Figure 1). The 5-year OS rate was 60.9% (95% CI 51.4-70.3) with alectinib and 64.1% (95% CI 54.9-73.4) with crizotinib. Subgroup analyses for OS were generally consistent with the results for all patients (Figure 2).

Subsequent therapies

Overall, 91.3% ($n = 95/104$) and 46.6% ($n = 48/103$) of patients received one or more subsequent anticancer therapies in the crizotinib and alectinib arms, respectively, most commonly an ALK TKI. Access to other next-generation ALK TKIs occurred in 25.2% of patients in the alectinib arm and 82.7% of patients in the crizotinib arm (Table 1). After study drug discontinuation, 78.8% ($n = 82/104$) of patients originally randomized to receive crizotinib switched over to alectinib, while 10.7% ($n = 11/103$) of patients randomized to receive alectinib switched over to crizotinib. Subsequent anticancer therapies in patients that discontinued first treatment due to lack of efficacy are summarized in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100527. A further 56.7% ($n = 59/104$) of patients in the crizotinib arm and 37.9% ($n = 39/$

103) of patients in the alectinib arm received a second subsequent anticancer therapy (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100527).

Patients were permitted to change from their initial treatment to a subsequent treatment for various reasons, including PD (i.e. after study drug discontinuation, termed 'treatment switching'). Patients in the crizotinib arm tended to have their treatment switched earlier than those in the alectinib arm (Figure 3). In a non-randomized subset of patients who had their treatment switched, OS following the first treatment switch was more favorable in the crizotinib arm than in the alectinib arm (Figure 4).

DISCUSSION

In this final OS analysis of the J-ALEX study, prolongation of OS in the alectinib arm (at the approved Japanese dose of 300 mg b.i.d.) was not observed relative to the crizotinib arm. However, OS at this final analysis was not fully powered because the number of events was 83, which is approximately half of the planned number of 150 events. The final OS analysis was planned to be conducted when 150 events had accrued or when the sponsor decided to terminate the trial, whichever occurred first. Although the OS data had not reached 150 events, the sponsor decided to conduct the final OS analysis after at least 5 years of follow-up from the last patient was completed, as it was assumed that it would take a long period until 150 events accrued as the survival rate of each TKI arm was greater than was estimated. A 5-year follow-up from the last patient enrollment was considered as a relevant and substantial follow-up period for this analysis in advanced NSCLC. In addition, a greater proportion of patients in the crizotinib arm had their initial treatment switched compared with the alectinib arm. The majority (82.7%) of
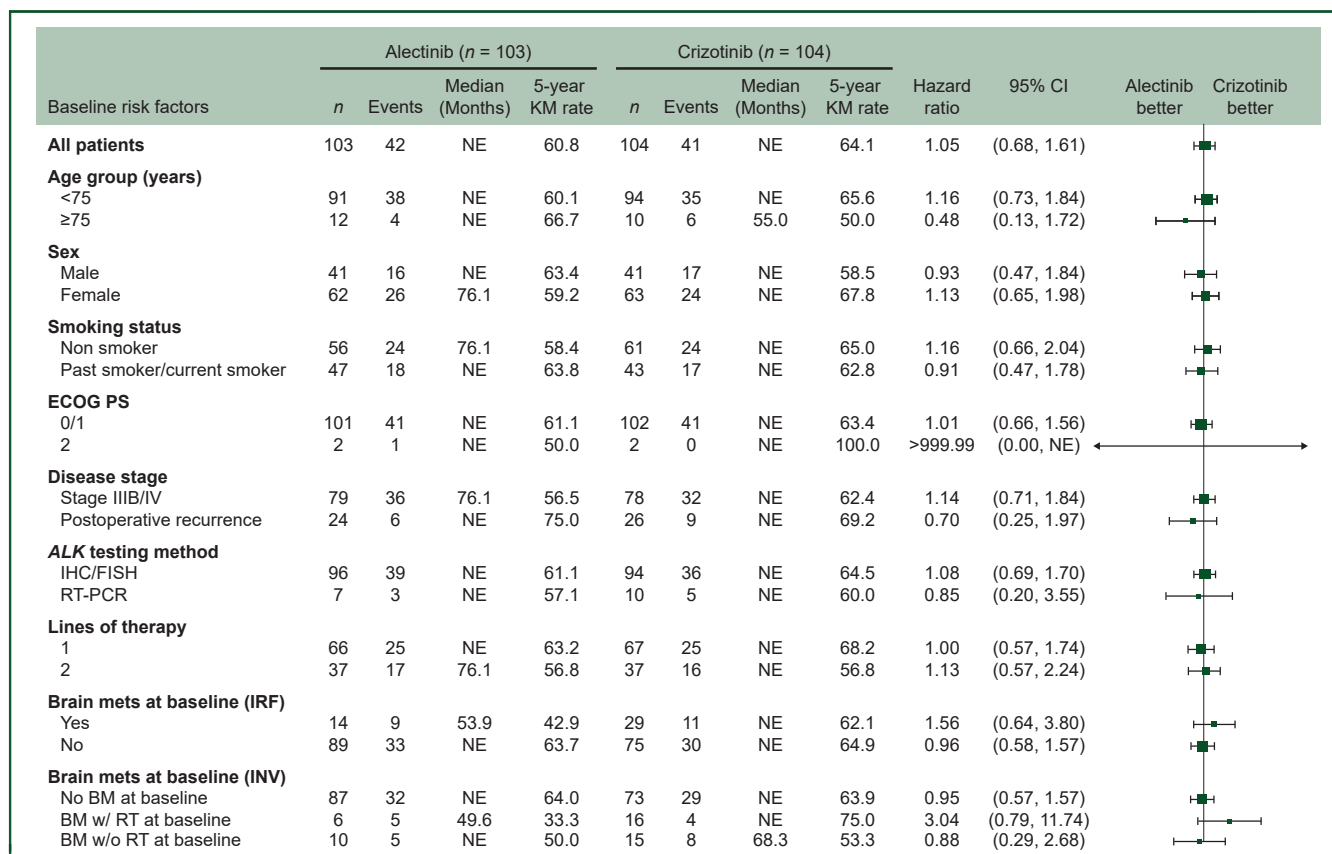
Baseline risk factors	Alectinib (n = 103)				Crizotinib (n = 104)				Hazard ratio	95% CI	Alectinib better Crizotinib better
	n	Events	Median (Months)	5-year KM rate	n	Events	Median (Months)	5-year KM rate			
All patients	103	42	NE	60.8	104	41	NE	64.1	1.05	(0.68, 1.61)	
Age group (years)											
<75	91	38	NE	60.1	94	35	NE	65.6	1.16	(0.73, 1.84)	
≥75	12	4	NE	66.7	10	6	55.0	50.0	0.48	(0.13, 1.72)	
Sex											
Male	41	16	NE	63.4	41	17	NE	58.5	0.93	(0.47, 1.84)	
Female	62	26	76.1	59.2	63	24	NE	67.8	1.13	(0.65, 1.98)	
Smoking status											
Non smoker	56	24	76.1	58.4	61	24	NE	65.0	1.16	(0.66, 2.04)	
Past smoker/current smoker	47	18	NE	63.8	43	17	NE	62.8	0.91	(0.47, 1.78)	
ECOG PS											
0/1	101	41	NE	61.1	102	41	NE	63.4	1.01	(0.66, 1.56)	
2	2	1	NE	50.0	2	0	NE	100.0	>999.99	(0.00, NE)	
Disease stage											
Stage IIIB/IV	79	36	76.1	56.5	78	32	NE	62.4	1.14	(0.71, 1.84)	
Postoperative recurrence	24	6	NE	75.0	26	9	NE	69.2	0.70	(0.25, 1.97)	
***ALK* testing method**											
IHC/FISH	96	39	NE	61.1	94	36	NE	64.5	1.08	(0.69, 1.70)	
RT-PCR	7	3	NE	57.1	10	5	NE	60.0	0.85	(0.20, 3.55)	
Lines of therapy											
1	66	25	NE	63.2	67	25	NE	68.2	1.00	(0.57, 1.74)	
2	37	17	76.1	56.8	37	16	NE	56.8	1.13	(0.57, 2.24)	
Brain mets at baseline (IRF)											
Yes	14	9	53.9	42.9	29	11	NE	62.1	1.56	(0.64, 3.80)	
No	89	33	NE	63.7	75	30	NE	64.9	0.96	(0.58, 1.57)	
Brain mets at baseline (INV)											
No BM at baseline	87	32	NE	64.0	73	29	NE	63.9	0.95	(0.57, 1.57)	
BM w/ RT at baseline	6	5	49.6	33.3	16	4	NE	75.0	3.04	(0.79, 11.74)	
BM w/o RT at baseline	10	5	NE	50.0	15	8	68.3	53.3	0.88	(0.29, 2.68)	

Figure 2. OS subgroup analysis.
BM, brain metastases; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IRF, independent review facility; INV, investigator-assessed; KM, Kaplan-Meier; Mets, metastases; NE, not estimable; OS, overall survival; RT, radiotherapy; w/, with; w/o, without.

patients in the crizotinib arm received an ALK TKI, including 78.8% of patients who received alectinib as a first subsequent treatment. Patients initially randomized to

Table 1. First subsequent anticancer therapies after alectinib or crizotinib

Patients, n (%)	Alectinib (n = 103)	Crizotinib (n = 104)
Receiving at least one treatment	48 (46.6)	95 (91.3)
ALK TKI	26 (25.2)	86 (82.7)
Alectinib	0 (0)	82 (78.8)
Crizotinib	11 (10.7)	0 (0)
Brigatinib	6 (5.8)	1 (1.0)
Lorlatinib	4 (3.9)	3 (2.9)
Ceritinib	5 (4.9)	0 (0)
Chemotherapy	18 (17.5)	7 (6.7)
Pemetrexed	13 (12.6)	5 (4.8)
Carboplatin	8 (7.8)	2 (1.9)
Cisplatin	5 (4.9)	3 (2.9)
Paclitaxel	1 (1.0)	2 (1.9)
Tegafur	2 (1.9)	0 (0)
Docetaxel	1 (1.0)	0 (0)
Zoledronic acid	1 (1.0)	0 (0)
VEGF inhibitor (bevacizumab)	4 (3.9)	1 (1.0)
Cancer immunotherapy (nivolumab)	2 (1.9)	0 (0)
RANKL inhibitor (denosumab)[a]	2 (1.9)	2 (1.9)

ALK, anaplastic lymphoma kinase; RANKL, receptor activator of nuclear factor kappa-B ligand; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
[a]Administered as part of supportive care.

receive crizotinib tended to have their treatment switched earlier than those randomized to receive alectinib mainly due to earlier determination of PD with crizotinib. In addition, the proportion of patients receiving more than one subsequent anticancer therapy was higher in the crizotinib arm relative to the alectinib arm.

Although patient characteristics at change of treatment may vary from those at baseline, patients in the crizotinib arm who had their treatment switched demonstrated a numerically longer OS from the initial treatment switch than those in the alectinib arm who switched treatment. These findings suggest that the OS results from J-ALEX may have been confounded by the crossover of a large proportion of patients (78.8% in the crizotinib arm received alectinib as first subsequent anticancer therapy). This was also observed in a phase II prospective analysis in patients with *ALK*-positive NSCLC treated with alectinib following PD on crizotinib.[8] Despite OS in J-ALEX being similar in the alectinib and crizotinib arms, superior PFS for alectinib in J-ALEX has been previously reported and the frequency of adverse events (AEs), such as gastrointestinal toxicity, was lower with alectinib than with crizotinib.[3]

In the phase III, randomized, global ALEX study, the globally approved alectinib dose of 600 mg b.i.d. demonstrated a clinically meaningful improvement in OS versus crizotinib in patients with treatment-naïve, advanced *ALK*-
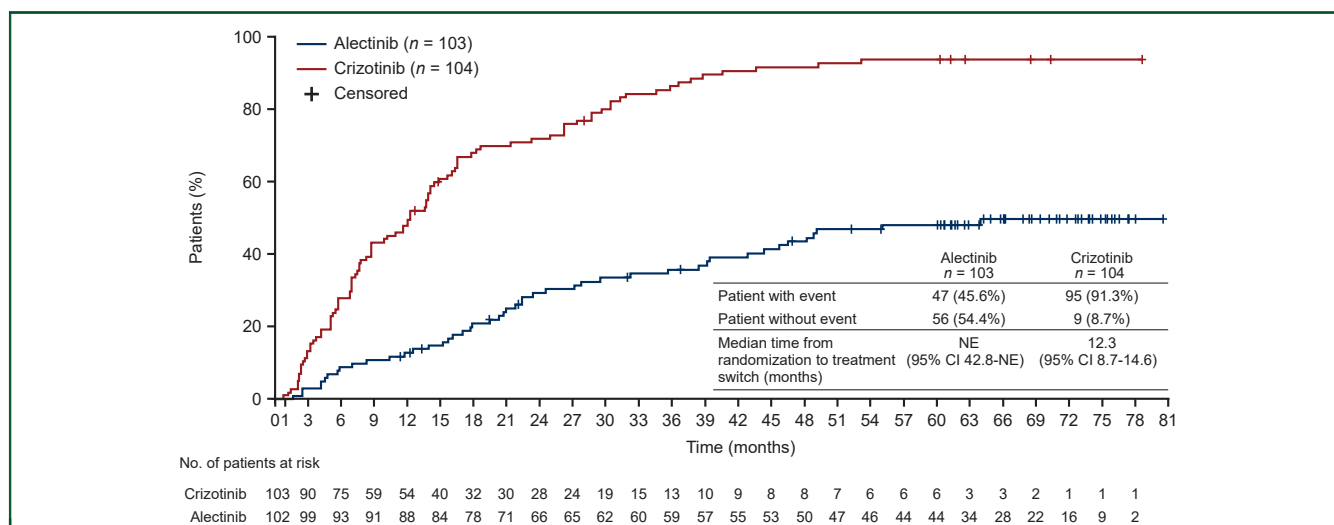
Figure 3. Time from randomization to first treatment switch.
CI, confidence interval; NE, not estimable.

positive NSCLC; 5-year OS rates were 62.5% with alectinib and 45.5% with crizotinib.[9] OS data remain immature with 37% of required events recorded. Median OS in ALEX was not reached with alectinib and was 57.4 months with crizotinib (stratified HR 0.67, 95% CI 0.46-0.98).[9] At data cut-off, 55.3% patients in the alectinib arm and 75.5% patients in the crizotinib arm experienced PD. Access to other next-generation ALK TKIs occurred in 38.1% patients who progressed in the alectinib arm of ALEX, and in 53.5% patients who progressed in the crizotinib arm.[9] In this study, 82.7% ($n = 86/104$) of patients in the crizotinib arm and 25.2% ($n = 26/103$) of patients in the alectinib arm received other ALK TKIs as the first subsequent anticancer therapy after study drug discontinuation. It is interesting to note that 38.8% ($n = 40/103$) of patients in the alectinib arm and 76.9% ($n = 80/104$) patients in the crizotinib arm experienced treatment discontinuation due to the lack of efficacy,

and access to other ALK TKIs occurred in 35.0% ($n = 14/40$) and 91.3% ($n = 73/80$) of patients who progressed in the alectinib arm and crizotinib arm, respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100527). It should also be noted that a lower dose of alectinib than the globally approved dose was used in J-ALEX. However, a population pharmacokinetic and exposure-response analysis demonstrated that alectinib 300 mg b.i.d. dose can be bridged to the 600 mg b.i.d. dose.[10] Taken together, this suggests that the difference in the frequency of other next-generation ALK TKIs, including alectinib in the crizotinib arm, being used as subsequent therapies may have had a greater impact on the OS result than the difference in dose between the ALEX and J-ALEX studies.

The next-generation ALK TKIs, brigatinib and lorlatinib, are more effective than crizotinib in the treatment of
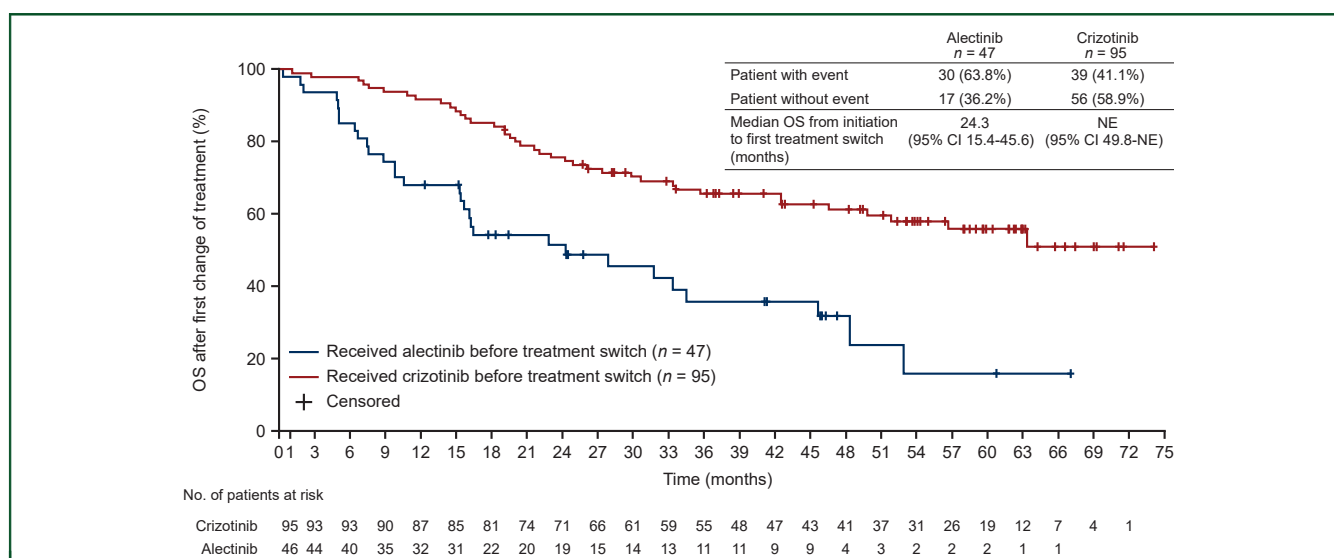
Figure 4. OS from initiation of first treatment switch in patients receiving subsequent therapies.
CI, confidence interval; NE, not estimable; OS, overall survival.

advanced *ALK*-positive NSCLC, with suggested activity against broader resistant mutations, indicating that they may also be effective against alectinib-resistant populations.[11] Indeed, lorlatinib (median PFS 5.5 months[12]) or brigatinib (median PFS 7.3 months[13]) have demonstrated efficacy in patients who have progressed on alectinib. Both agents are approved in the first-line treatment setting, but AEs such as increased blood creatine phosphokinase with brigatinib and neurocognitive effects with lorlatinib have been widely reported.[11] These findings could support the use of alectinib as initial therapy, followed by newer ALK TKIs once alectinib resistance develops. Therefore, alectinib may be considered a preferred first-line treatment option from the perspective of AE management and acquired resistance follow-up.

Results of the J-ALEX study suggest that alectinib contributes to the long-term survival of patients with advanced *ALK*-positive NSCLC, with median OS not reached in either treatment arm, and 5-year OS rates of approximately 60%. Published 5-year OS rates in patients with advanced NSCLC receiving other agents are considerably lower than in J-ALEX.

The superior efficacy of alectinib relative to crizotinib in advanced *ALK*-positive NSCLC can be partially explained by its greater CNS activity. For reference, CNS activity data from J-ALEX for the clinical cut-off date of 30 June 2018 are provided in Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2022.100527. Previous results from J-ALEX showed that alectinib prolonged the time to progression of CNS metastases in patients who presented with them at baseline and delayed the onset of new CNS lesions in patients who did not present with them at baseline.[6] Similar findings were reported in the global ALEX study.[14] The high CNS protection activity of alectinib was also reported in a retrospective analysis in select patients with advanced *ALK*-positive NSCLC failing crizotinib treatment; patients receiving alectinib experienced a lower incidence of CNS progression than those receiving ceritinib (cause-specific HR 0.10, 95% CI 0.01-0.78).[15]

Conclusion

In the J-ALEX study, alectinib resulted in long-term survival in patients with advanced *ALK*-positive NSCLC, although prolongation of OS was not observed relative to the crizotinib arm, possibly due to treatment crossover. Median OS was not reached in either treatment arm, with 5-year OS rates of approximately 60%, and the study was not powered primarily for OS. These findings suggest that alectinib remains a preferred standard of care for the treatment of patients with advanced *ALK*-positive NSCLC.

DATA SHARING

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). For further details on Chugai's Data Sharing Policy and how to request access to related clinical study documents, see here (www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html).

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