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Original Research

Comparative analysis of alectinib and brigatinib in real-world treatment of advanced NSCLC with ALK rearrangements

Kyuhwan Kim, Kyu Yean Kim, Hye Seon Kang, Ah Young Shin, Sung Kyoung Kim, Chan Kwon Park, Sang Haak Lee, Seung Joon Kim, Jeong Uk Lim and Chang Dong Yeo

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Correspondence to:
Jeong Uk Lim
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 07345, Republic of Korea
cracovian@catholic.ac.kr

Chang Dong Yeo
Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Eunpyeong St Mary's Hospital, College of Medicine, The Catholic University of Korea, 1021, Tongil-ro, Eunpyeong-gu, Seoul 03312, Republic of Korea
brainyeo@catholic.ac.kr

Kyuhwan Kim
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Department of Internal Medicine, Armed Forces Goyang Hospital, Goyang, Republic of Korea

Kyu Yean Kim
Division of Pulmonary, Critical Care Medicine, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu-si, Republic of Korea

Hye Seon Kang
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon-si, Republic of Korea

Abstract

Background and objectives: This study aimed to compare the efficacy of the second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) alectinib and brigatinib in the treatment of advanced non-small-cell lung cancer (NSCLC) with ALK rearrangements based on real-world data.

Design and methods: We conducted a multicenter retrospective study using the Clinical Data Warehouse from seven university hospitals affiliated with the Catholic Medical Center. Patients diagnosed with ALK-positive advanced NSCLC and treated with alectinib or brigatinib were included. Key outcomes such as time to discontinuation (TTD), duration of response (DOR), overall survival (OS), and objective response rate (ORR) were analyzed.

Results: A total of 143 patients were included (107 treated with alectinib, 36 with brigatinib). Alectinib was more frequently used as a first-line treatment (71% vs 44.4% for brigatinib, $p = 0.008$). Prior crizotinib treatment was more frequent in the brigatinib group (52.8% vs 22.4% for alectinib, $p < 0.001$). The best ORR was similar between the groups (84.1% for alectinib vs 83.3% for brigatinib, $p = 0.518$). The median TTD was 57.8 months (95% confidence interval (CI): 29.0–86.7) for alectinib and 39.6 months (95% CI: 21.7–57.4) for brigatinib ($p = 0.462$). No significant differences were observed in intracranial TTD, intracranial DOR, or OS between the groups. Prior crizotinib treatment significantly shortened TTD for second-generation TKIs ($p = 0.025$), but the overall TKI treatment duration did not show a significant difference between patients who received frontline second-generation ALK TKIs and those who received second-generation ALK TKIs sequentially after crizotinib.

Conclusion: Alectinib and brigatinib demonstrated comparable efficacy in ALK-positive advanced NSCLC. Undergoing crizotinib followed by a second-generation TKI was not significantly different from initiating a second-generation TKI without prior crizotinib in terms of outcomes.

Plain language summary

A real-world comparison of Alectinib and Brigatinib for treating advanced lung cancer

This study compares two medications, alectinib and brigatinib, used to treat advanced non-small cell lung cancer (NSCLC) in patients with specific genetic changes called ALK rearrangements. A total of 143 patients were included in the study. Of these, 107 were treated with alectinib and 36 with brigatinib. The results showed that both alectinib and brigatinib had similar effects. There was no significant difference in the overall response to treatment or survival rates between the two drugs. However, the study found that

Ah Young Shin
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Republic of Korea

Sung Kyoung Kim
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon-si, Republic of Korea

Chan Kwon Park
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Sang Haak Lee
Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Seung Joon Kim
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Postech-Catholic Biomedical Engineering Institute, Songeui Multiplex Hall, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

patients who had previously been treated with crizotinib before switching to one of these drugs had shorter treatment durations, but when whole duration of crizotinib followed by alectinib/brigatinib was counted, no significant difference was seen.

Keywords: alectinib, anaplastic lymphoma kinase, brigatinib, carcinoma, non-small-cell lung

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Introduction

Anaplastic lymphoma kinase (ALK) rearrangements are found in approximately 3%–8% of patients with non-small-cell lung cancer (NSCLC) and are a driver of oncogenic transformation.[1–3] Crizotinib, the first approved ALK tyrosine kinase inhibitor (TKI) for metastatic ALK mutation-positive NSCLC, became the standard treatment by demonstrating greater efficacy compared to chemotherapy.[4,5] However, most patients eventually develop resistance to treatment and experience disease progression, particularly in the central nervous system (CNS).[6] This resistance can result from limited CNS penetration, secondary mutations in the ALK kinase domain, amplification of the ALK fusion gene, and activation of alternative signaling pathways.[7,8]

To overcome these issues, newer ALK TKIs with enhanced CNS activity and greater potency against resistance mutations have been developed. Alectinib and brigatinib are among these advanced ALK TKIs, exhibiting high CNS activity and differing selectivity against resistance mutations in ALK.[9–11] In clinical studies of patients with ALK-positive NSCLC who progressed on crizotinib, the median progression-free survival (PFS) ranged from 8.1 to 10.9 months with alectinib[10,12] and from 14.7 to 16.8 months with brigatinib.[13,14] The ALTA-3 trial, which compared the efficacy and safety of brigatinib versus alectinib, showed no superiority for either drug in terms of PFS in crizotinib-pretreated ALK-positive NSCLC.[15] The ALINA trial demonstrated impressive outcomes for alectinib in resectable ALK-positive NSCLC, with the median disease-free survival (DFS) not yet reached.[16] Current NCCN guidelines recommend second-generation ALK TKIs such as alectinib and brigatinib, as well as the third-generation ALK TKI lorlatinib, as preferred options for first-line treatment of advanced NSCLC with ALK translocation.[17]

Another question is whether using crizotinib as the first-line treatment, followed by a second-generation ALK TKI is superior to using a second-generation ALK TKI as the first-line treatment. Trials comparing crizotinib and alectinib have shown that alectinib has superior outcomes in patients with ALK-positive advanced NSCLC.[18] A meta-analysis also demonstrated that second-generation ALK TKIs improve overall survival (OS).[19] Real-world data include patients who initially received crizotinib and later switched to a second-generation ALK TKI, making it clinically meaningful to compare these two treatment strategies.

This study aimed to analyze real treatment data, focusing on brigatinib and alectinib in ALK+ advanced NSCLC patients, based on retrospective data from multicenter studies.

Methods

Patient selection

This multicenter retrospective study was conducted across seven university hospitals affiliated with the Catholic Medical Center (CMC) in Korea. To access and extract patient information, we utilized the Clinical Data Warehouse (CDW) platform, which integrates clinical data from the seven affiliated CMC hospitals and distributes this data to researchers. For this study, we utilized a database containing over 15 million fully anonymized electronic medical records.

The study population comprised patients diagnosed with ALK-positive advanced NSCLC and treated with either alectinib or brigatinib. ALK

positivity was histologically confirmed through immunohistochemistry, fluorescence in situ hybridization, or next-generation sequencing. Patients were included if they were adults aged 18 years or older diagnosed with lung cancer, as indicated by the International Classification of Diseases, 10th Revision (ICD-10) code starting with C34. They must have been treated between December 1, 2017, and December 13, 2022, and prescribed one of the following treatments: crizotinib, alectinib, brigatinib, or lorlatinib.

Patients were excluded if they were diagnosed with ALK-negative advanced NSCLC or if they were treated solely with crizotinib for ALK-positive advanced NSCLC. In addition, patients without first-response evaluation results were excluded. Cases where data extraction was incomplete, making it difficult to perform a proper evaluation, were also excluded.

Efficacy assessments

Clinical data were retrospectively collected from the CDW. The collected clinical factors included age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, pathology, stage (American Joint Committee on Cancer Staging Manual, 8th Edition) and metastatic sites at the initiation of palliative treatment, presence of intracranial involvement, and administration of crizotinib or lorlatinib.

Treatment outcomes were evaluated based on several key metrics. Time to discontinuation (TTD) was defined as the time from the initiation of ALK TKI therapy to discontinuation. Disease progression at the time of drug discontinuation was also examined. Duration of response (DOR) refers to the time from achieving complete or partial response to discontinuation of the drug due to disease progression. OS was the time from initiation of second-generation ALK TKI therapy to death from any cause. OS from the start of any initial TKI treatment after ALK diagnosis was also analyzed. In addition, evaluations were conducted for the objective response rate (ORR) and intracranial ORR. Clinical responses were assessed according to RECIST version 1.1 criteria. Response evaluations were performed every two to three treatment cycles using thoracic or abdominal/pelvic computed tomography scans and/or brain magnetic resonance imaging. Safety data were also collected and analyzed.

Our primary goal was to compare the treatment outcomes of alectinib and brigatinib in ALK-positive NSCLC patients through the evaluation of TTD and OS. In addition, we assessed intracranial TTD, intracranial OS, DOR, and ORR. Frontline second-generation ALK TKIs and the efficacy of sequential second-generation ALK TKIs following crizotinib administration were also analyzed. Analyses were conducted on the TTD of second-generation ALK TKIs in patients with and without prior crizotinib exposure. In addition, to compare overall treatment durations, the TTD of frontline second-generation ALK TKIs and the treatment duration of sequential second-generation ALK TKIs following crizotinib administration were analyzed using Kaplan–Meier curves. In this analysis, the event for sequential second-generation ALK TKIs following crizotinib administration was defined as discontinuation of the second-generation ALK TKI.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental File).

Statistical methods

We employed descriptive statistics to present baseline patient data. The relationships between categorical variables were evaluated using the Chi-square or Fisher's exact test. Correlations between continuous and categorical data points were analyzed using the *t*-test. Kaplan–Meier plots were used to assess patient survival times, and the log-rank test was applied to evaluate differences in event timing. Both univariate and multivariate analyses using Cox proportional hazard models were performed to assess hazard ratios (HRs). In all statistical evaluations, a p-value less than 0.05 was considered statistically significant. All calculations were performed using SPSS version 23 Armonk, NY: IBM Corp.

Results

General characteristics

The study included 143 patients with ALK-positive advanced NSCLC who were treated with either alectinib ($n = 107$) or brigatinib ($n = 36$; Figure 1). At the cutoff date, the median follow-up time was 34.5 months (95% confidence interval (CI), 30.2–37.9) for the alectinib group and

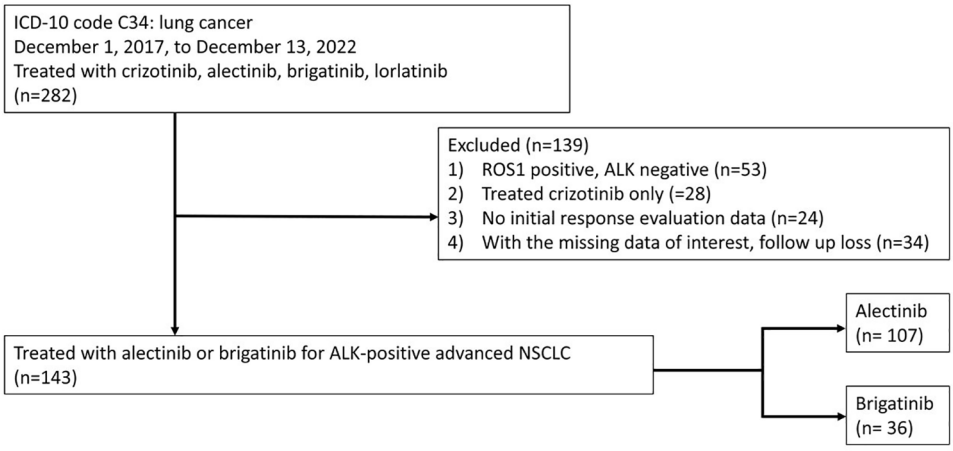

Figure 1. Flowchart of patient selection.
ALK, anaplastic lymphoma kinase; ICD-10, International Classification of Diseases 10th Revision; NSCLC, non-small-cell lung cancer.

41.1 months (95% CI, 36.2–52.2) for the brigatinib group. The mean patient age was 62.2 ± 12.5 years for alectinib and 60.4 ± 12.3 years for brigatinib ($p = 0.460$). The sex distribution between the groups was similar ($p = 0.334$), with most patients being female. Most patients were never smokers (72.9% for alectinib, 69.4% for brigatinib; $p = 0.777$). ECOG performance status was primarily 0 or 1 in both groups ($p = 0.426$). Adenocarcinoma was the predominant pathology (96.3% for alectinib, 94.4% for brigatinib; $p = 0.642$). The distribution of metastatic sites, including brain ($p = 0.328$), bone ($p = 0.847$), liver ($p = 1.000$), and intrathoracic metastasis ($p = 0.307$), showed no significant difference between the groups. Alectinib was used as the first-line therapy in 71.0% of cases, while brigatinib was used in 44.4% ($p = 0.008$). Prior crizotinib treatment was more frequent in the brigatinib group (52.8% vs 22.4%; $p < 0.001$). The proportion of patients who underwent lorlatinib after progression was similar between the groups, with 18.7% in the alectinib group and 13.9% in the brigatinib group ($p = 0.618$; Table 1).

Outcomes

The best ORR was 84.1% for alectinib and 83.3% for brigatinib, with no significant difference between the groups ($p = 0.518$; Table 2). The median TTD was 57.8 months (95% CI, 29.0–86.7) for alectinib and 39.6 months (95% CI, 21.7–57.4) for brigatinib. The log-rank test for TTD showed no significant difference between the groups ($p = 0.462$). The median DOR was 54.8 months (95% CI, 23.6–86.0) for alectinib and 43.8 months (95% CI, 14.3–73.4) for brigatinib, with no significant difference between the groups ($p = 0.926$; Figure 2).

The intracranial best ORR was 86.0% for alectinib and 88.9% for brigatinib, with no significant difference between the groups ($p = 0.118$; Table 3). The median intracranial TTD and DOR were not achieved in either the alectinib or brigatinib group. The mean intracranial TTD was 42.3 months (95% CI, 35.1–49.5) for alectinib and 38.5 months (95% CI, 27.8–49.2) for brigatinib ($p = 0.894$). The mean intracranial DOR was 42.3 months (95% CI, 35.4–49.2) for alectinib and 38.3 months (95% CI, 27.7–49.0) for brigatinib ($p = 0.846$). The log-rank tests for intracranial TTD and intracranial DOR showed no significant differences between the groups (Figure 3). The median OS for the alectinib group was 61.8 months (95% CI, 49.2–74.4), while the brigatinib group did not reach the median OS. The mean OS for the brigatinib group was 47.9 months (95% CI, 42.4–53.3). The OS between the alectinib and brigatinib groups showed no significant difference ($p = 0.384$; Figure 4).

When analyzing the effect of prior crizotinib treatment, TTD for second-generation ALK TKIs was significantly lower in patients with prior crizotinib exposure before second-generation ALK TKIs ($p = 0.025$). The mean TTD for patients without prior crizotinib treatment ($n = 100$) was 42.3 months (95% CI, 37.7–46.8), compared to a

Table 1. Comparison of clinical characteristics.

Clinical features	Alectinib	Brigatinib	Total	*p*-Value
Patients, *n* (%)	107	36	143	
Age, mean ± SD	62.2 ± 12.5	60.4 ± 12.3	61.8 ± 12.4	0.460
Sex				0.334
Male	43 (40.2)	18 (50.0)	61 (42.7)	
Female	64 (59.8)	18 (50.0)	82 (82.0)	
Smoking status				0.777
Never smoker	78 (72.9)	25 (69.4)	103 (72.0)	
Ex-smoker	19 (17.8)	6 (16.7)	25 (17.5)	
Current smoker	10 (9.3)	5 (13.9)	15 (10.5)	
ECOG				0.426
0	68 (63.6)	25 (69.4)	93 (65.0)	
1	28 (26.2)	10 (27.8)	38 (26.6)	
2	11 (10.3)	1 (2.8)	12 (8.4)	
Recurrence after complete resection	23 (21.5)	8 (22.2)	31 (21.7)	1.000
Pathology				0.642
Adenocarcinoma	103 (96.3)	34 (94.4)	137 (95.8)	
Squamous cell carcinoma	4 (3.7)	2 (5.6)	6 (4.2)	
Stage at palliative treatment				0.593
III	10 (9.3)	2 (5.6)	12 (8.4)	
IVA	45 (42.1)	18 (50.0)	63 (44.1)	
IVB	52 (48.6)	16 (44.4)	68 (47.6)	
Metastatic site				
Brain	43 (40.2)	11 (30.6)	54 (37.8)	0.328
Bone	44 (41.1)	14 (38.9)	58 (40.6)	0.847
Liver	13 (12.1)	4 (11.1)	17 (11.9)	1.000
Intrathoracic metastasis	69 (64.5)	27 (75.0)	96 (67.1)	0.307
Second-generation ALK TKI				
*N*th line				0.008
1	76 (71.0)	16 (44.4)	92 (64.3)	
2	27 (25.2)	15 (41.7)	42 (29.4)	
3	4 (3.7)	5 (13.9)	9 (6.3)	
Underwent prior crizotinib	24 (22.4)	19 (52.8)	43 (30.1)	<0.001
Underwent lorlatinib after progression	20 (18.7)	5 (13.9)	25 (17.5)	0.618

ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; SD, standard deviation; TKI, tyrosine kinase inhibitor.

Table 2. Best objective response to alectinib and brigatinib.

Parameters	Alectinib ($n=107$)	Brigatinib ($n=36$)	Total ($n=143$)	*p*-Value
Best objective response rate, *n* (%)	90 (84.1)	30 (83.3)	120 (83.9)	0.518
CR	4 (3.7)	1 (2.8)	5 (3.5)	
PR	86 (80.4)	29 (80.6)	115 (80.4)	
SD	8 (7.5)	5 (13.9)	13 (9.1)	
PD	9 (8.4)	1 (2.8)	10 (7.0)	
Not evaluable	0	0	0	

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

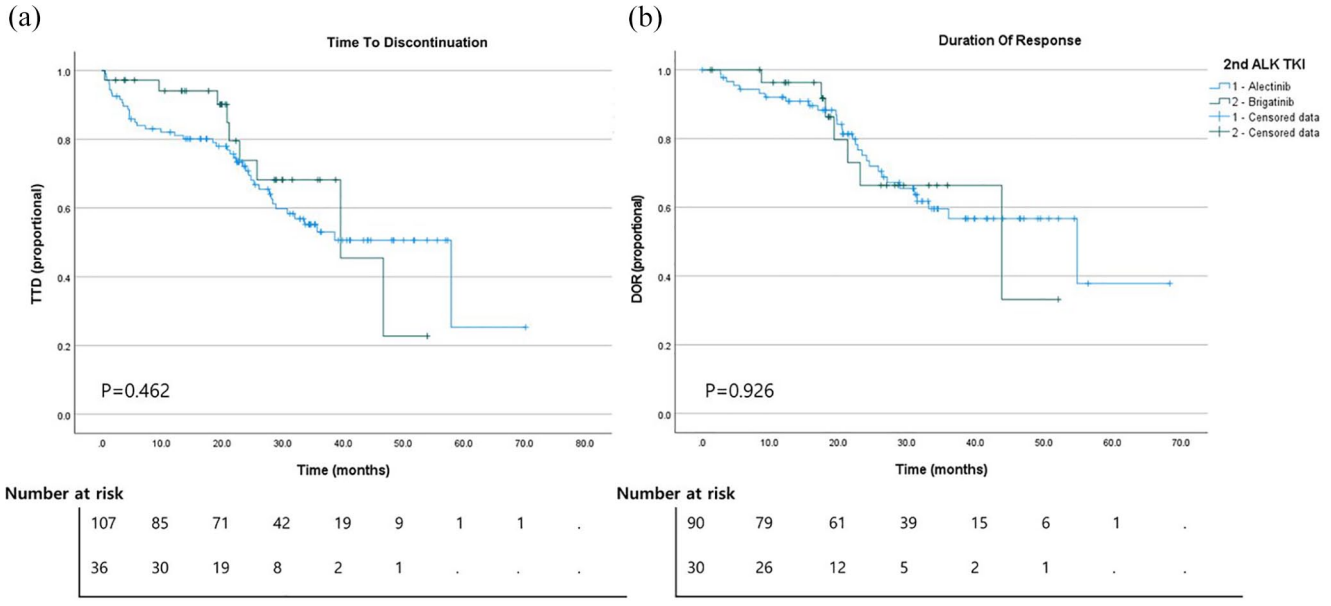

Figure 2. Comparison of TTD and DOR between alectinib and brigatinib. Kaplan–Meier curves comparing (a) TTD between alectinib and brigatinib and (b) DOR between alectinib and brigatinib.
ALK, anaplastic lymphoma kinase; CI, confidence interval; DOR, duration of response; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

median TTD of 28.3 months (95% CI, 14.5–42.1) for patients with prior crizotinib treatment ($n=43$). However, the overall TKI treatment duration between patients who received frontline second-generation ALK TKIs and those who received second-generation ALK TKIs sequentially after crizotinib showed no significant difference ($p=0.516$). The mean treatment duration for patients receiving frontline second-generation ALK TKIs ($n=100$) was 42.3 months (95% CI, 37.7–46.8), while the mean treatment duration for those receiving second-generation ALK TKIs sequentially after crizotinib ($n=40$) was 54.3 months (95% CI, 45.969–62.501). In addition, when comparing the OS from the start of TKI treatment in ALK-positive NSCLC patients based on prior crizotinib exposure, no significant difference was observed between the two groups

Table 3. Comparison of intracranial objective response rate.

Parameters	Alectinib ($n=47$)	Brigatinib ($n=18$)	Total ($n=65$)	p-Value
Intracranial best objective response rate	37 (86.0)	16 (88.9)	53 (86.9)	0.118
CR	18 (41.9)	3 (16.7)	21 (34.4)	
PR	19 (44.2)	13 (72.2)	32 (52.5)	
SD	5 (11.6)	1 (5.6)	6 (9.8)	
PD	1 (2.3)	1 (5.6)	2 (3.3)	
Not evaluable	4	0	4	

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

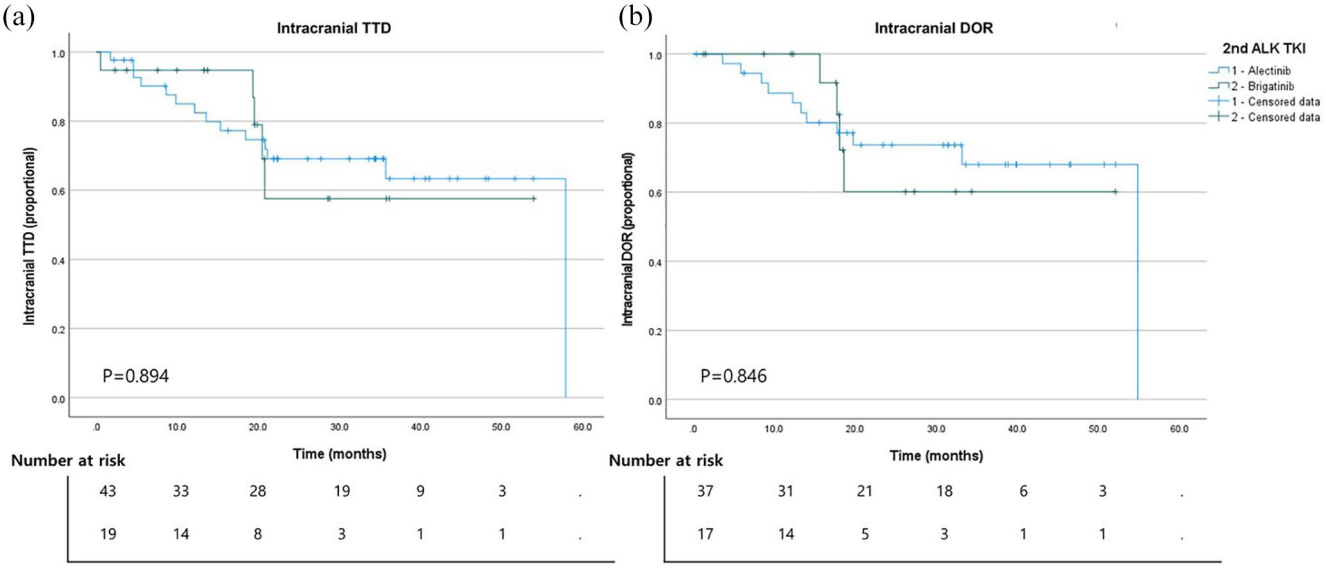

Figure 3. Comparison of intracranial TTD and DOR between alectinib and brigatinib. Kaplan–Meier curves comparing (a) intracranial TTD between alectinib and brigatinib and (b) intracranial DOR between alectinib and brigatinib.
ALK, anaplastic lymphoma kinase; CI, confidence interval; DOR, duration of response; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

($p=0.710$). The mean OS for patients without prior crizotinib treatment ($n=100$) was 61.3 months (95% CI, 54.2–68.2), while the mean OS for patients with prior crizotinib treatment ($n=43$) was 69.7 months (95% CI, 60.8–78.4; Figure 5).

Cox regression analyses were conducted to identify clinical variables affecting TTD and OS in patients treated with alectinib or brigatinib. In the univariate analysis, significant factors for TTD were ECOG performance status 2 (HR 3.333, 95% CI 1.449–7.665; $p=0.005$), stage IVB at diagnosis (HR 2.143, 95% CI 1.223–3.755; $p=0.008$), second-line or later treatment (HR 1.766, 95% CI 1.021–3.052; $p=0.042$), and liver metastasis (HR 2.458, 95% CI 1.229–4.917; $p=0.011$). In the multivariate analysis, ECOG performance status 2 (HR 2.464, 95% CI 1.031–5.888; $p=0.042$) and second-line or later treatment (HR 1.984, 95% CI 1.123–3.505; $p=0.018$) remained significant (Table 4).

In the univariate analysis for OS, significant factors were ECOG performance status 2 (HR 6.332, 95% CI 2.634–15.221; $p<0.001$), stage

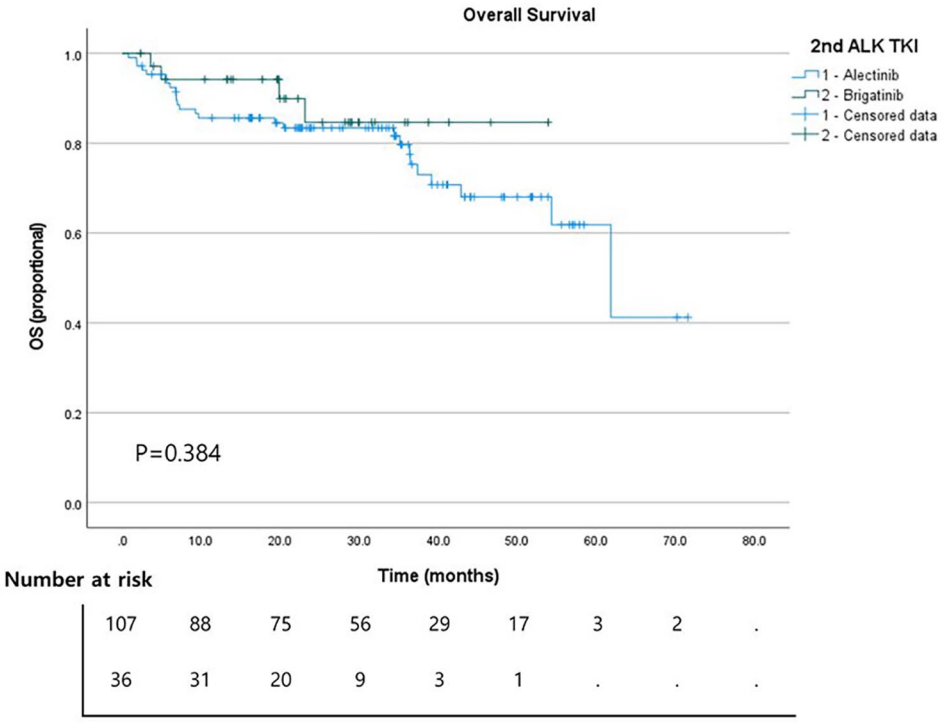

Figure 4. Comparison of OS between alectinib and brigatinib.
ALK, anaplastic lymphoma kinase; CI, confidence interval; OS, overall survival; TKI, tyrosine kinase inhibitor.

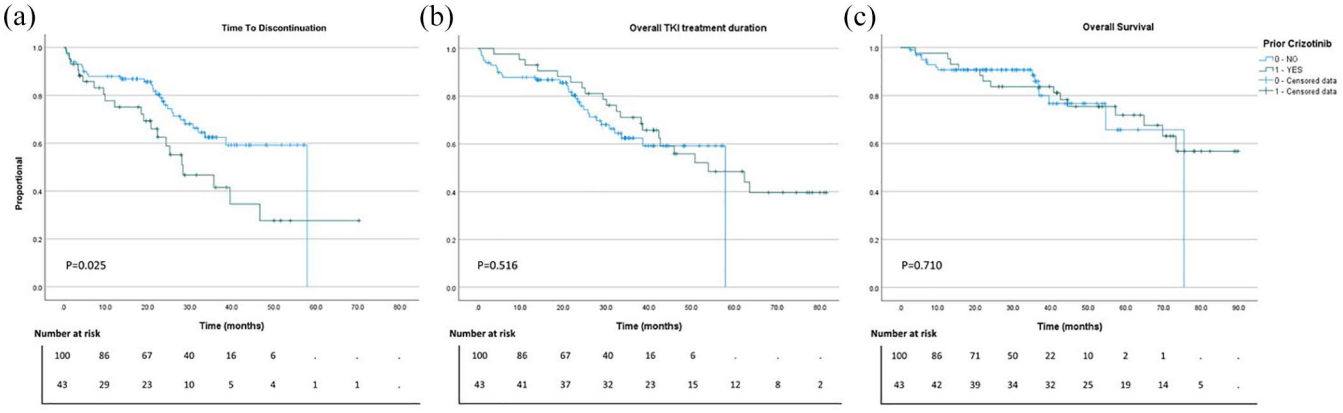

Figure 5. Kaplan–Meier curves according to prior crizotinib treatment. Kaplan–Meier curves comparing (a) TTD of second-generation ALK TKIs according to prior crizotinib treatment, (b) overall TKI treatment duration between first-line crizotinib to second-line alectinib or brigatinib discontinuation, frontline alectinib or brigatinib, and (c) OS from the start of TKI treatment in ALK-positive NSCLC based on prior crizotinib treatment.
ALK, anaplastic lymphoma kinase; CI, confidence interval; OS, overall survival; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

IVB at diagnosis (HR 2.273, 95% CI 1.058–4.886; $p=0.035$), ever smoking (HR 2.1, 95% CI 1.001–4.102; $p=0.050$), second-line or later therapy (HR 2.241, 95% CI 1.076–4.668; $p=0.031$), and liver metastasis (HR 2.988, 95% CI 1.267–7.046; $p=0.012$). In the multivariate analysis, ECOG performance status 2 (HR 8.722, 95% CI 3.302–23.037; $p<0.001$), ever smoking (HR 4.203, 95% CI 1.518–11.642; $p=0.006$), and second-line or later therapy (HR 4.002, 95% CI 1.742–9.196; $p=0.001$) remained significant (Table 5).

Table 4. Univariate and multivariate analyses of the clinical variables affecting TTD patients receiving alectinib or brigatinib.

Parameters	Number	Univariate		*p*-Value	Multivariate		*p*-Value
		Hazard ratio	95% CI		Hazard ratio	95% CI	
Sex							
Male	61	Reference			Reference		
Female	82	0.998	0.573–1.739	0.994	0.891	0.504–1.575	0.692
Age	143	1.002	0.982–1.023	0.836	1.007	0.985–1.029	0.554
Smoking status							
Never smoker	103	Reference					
Ever smoker	40	1.568	0.874–2.811	0.131			
ECOG							
0	93	Reference			Reference		
1	38	1.519	0.812–2.840	0.190	1.289	0.678–2.450	0.438
2	12	3.333	1.449–7.665	0.005	2.464	1.031–5.888	0.042
Stage at diagnosis							
III + IVA	75	Reference			Reference		
IVB	68	2.143	1.223–3.755	0.008	1.71	0.935–3.126	0.084
Second-generation ALK TKI							
Alectinib	107	Reference					
Brigatinib	36	0.763	0.370–1.572	0.436			
*N*th line							
1	92	Reference			Reference		
⩾2	51	1.766	1.021–3.052	0.042	1.984	1.123–3.505	0.018
Brain metastasis	54	1.547	0.897–2.667	0.117			
Bone metastasis	58	1.643	0.951–2.839	0.075			
Liver metastasis	17	2.458	1.229–4.917	0.011	2.045	0.966–4.329	0.062

ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

Toxicity profile

Treatment-related adverse events (AEs) were compared between the alectinib and brigatinib groups (Table 6). Total AEs occurred in 91.3% of patients in the alectinib arm and 100% in the brigatinib arm. The most frequently reported AEs for alectinib were anemia (35%), liver function test (LFT) elevation (34%), total bilirubin elevation (33%), and creatinine elevation (11.7%). For brigatinib, the most common AEs were LFT elevation (75%), anemia (25%), creatinine elevation (25%), and headache (13.9%). Dose reduction was reported in 31.4% of patients in the alectinib arm and 23% in the brigatinib arm. Pneumonitis was reported in 4.9% of patients in the alectinib arm and 2.8% in the brigatinib arm. Dose interruptions occurred in 15.2% and 8.8% of patients in the alectinib and

Table 5. Univariate and multivariate analyses of the clinical variables affecting OS patients receiving alectinib or brigatinib.

Parameters	Number	Univariate		*p*-Value	Multivariate		*p*-Value
		Hazard ratio	95% CI		Hazard ratio	95% CI	
Sex							
Male	61	Reference			Reference		
Female	82	0.912	0.442–1.879	0.803	1.286	0.503–3.287	0.600
Age	143	1.008	0.980–1.037	0.577	1.019	0.985–1.053	0.276
Smoking status							
Never smoker	103	Reference			Reference		
Ever smoker	40	2.1	1.001–4.102	0.050	4.203	1.518–11.642	0.006
ECOG							
0	93	Reference			Reference		
1	38	1.828	0.761–4.390	0.177	2.205	0.868–5.599	0.096
2	12	6.332	2.634–15.221	<0.001	8.722	3.302–23.037	<0.001
Stage at diagnosis							
III + IVA	75	Reference			Reference		
IVB	68	2.273	1.058–4.886	0.035	2.036	0.882–4.701	0.096
Second-generation ALK TKI							
Alectinib	107	Reference					
Brigatinib	36	0.625	0.215–1.818	0.388			
*N*th line							
1	92	Reference			Reference		
⩾2	51	2.241	1.076–4.668	0.031	4.002	1.742–9.196	0.001
Brain metastasis	54	1.681	0.818–3.455	1.681			
Bone metastasis	58	1.939	0.945–3.978	0.071			
Liver metastasis	17	2.988	1.267–7.046	0.012	2.109	0.827–5.379	0.118

ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; TKI, tyrosine kinase inhibitor.

brigatinib arms, respectively. Permanent discontinuation occurred in only one case in the alectinib arm, which was due to LFT elevation.

Discussion

The present study compared patients who underwent treatment with alectinib or brigatinib and further assessed the outcomes of these patient groups. The results showed that the alectinib and brigatinib groups did not exhibit a marked difference in their outcomes. In addition, crizotinib followed by a second-generation TKI was not significantly different from initiating a second-generation TKI without prior crizotinib in terms of outcomes.

Table 6. Comparison of safety profiles between alectinib and brigatinib groups.

Adverse event[a]	Alectinib	Brigatinib	*p*-Value
Any adverse events	94 (91.3%)	36 (100.0%)	0.067
Elevated blood pressure	0 (0%)	1 (2.8%)	0.090
Blurred vision	0 (0%)	1 (2.8%)	0.090
Eosinophilia	1 (1%)	0 (0%)	0.553
Headache	5 (4.9%)	5 (13.9%)	0.074
Hearing problems	1 (1%)	0 (0%)	0.553
Peripheral neuropathy	4 (3.9%)	2 (5.6%)	0.671
Thrombocytopenia	1 (1%)	1 (2.8%)	0.433
Bradycardia	2 (1.9%)	0 (0%)	0.400
Dizziness	3 (2.9%)	1 (2.8%)	0.967
Constipation	10 (9.7%)	1 (2.8%)	0.185
Oral mucositis	2 (1.9%)	3 (8.3%)	0.076
Dermatitis	6 (5.8%)	3 (8.3%)	0.599
Diarrhea	5 (4.9%)	1 (2.8%)	0.598
Nausea or vomiting	4 (3.9%)	0 (0%)	0.230
Poor appetite	6 (5.8%)	2 (5.6%)	0.952
Anemia	36 (35%)	9 (25%)	0.272
Creatinine elevation	12 (11.7%)	4 (11.1%)	0.930
Creatine phosphokinase elevation	1 (1%)	9 (25%)	<0.001
Bilirubin elevation	34 (33%)	<0.001	<0.001
Aspartate aminotransferase/alanine aminotransferase elevation	35 (34%)	27 (75%)	<0.001
Pneumonitis	5 (4.9%)	1 (2.8%)	0.650
Edema	5 (4.9%)	4 (11.1%)	0.149
Dose reduction	33 (31.4%)	8 (23.5%)	0.308
Dose interruption	16 (15.2%)	3 (8.8%)	0.344
Permanent discontinuation	1 (1%)	0 (0%)	0.568

[a]The grades of adverse events were not provided.

In the present study, the alectinib and brigatinib groups did not show significant differences in baseline clinical characteristics, except that a significantly higher proportion of patients received brigatinib as a second or later line of treatment. Despite enrolling patients during the same observation period, the proportion of patients who underwent prior crizotinib was higher in the

brigatinib group. This is thought to be due to clinicians' preference for using alectinib as a first-line treatment.

Initiating alectinib or brigatinib as first-line treatment is not inferior in terms of treatment outcomes compared to sequential crizotinib followed by a second-generation ALK TKI. In the present study, the overall TKI treatment duration did not show a significant difference between patients who received frontline second-generation ALK TKIs and those who received second-generation ALK TKIs sequentially after crizotinib. Nevertheless, considering that second-generation TKIs show superior outcomes in advanced NSCLC with ALK translocations,[18] initiating crizotinib treatment for patients, especially with brain metastases, may not be an option of priority. A meta-analysis that included 12 randomized controlled trials demonstrated that second-generation ALK TKIs significantly improved OS (HR 0.72, 95% CI 0.57–0.90, $p = 0.004$) and showed better intracranial response in patients with brain metastases.[19] Crizotinib has limited penetration across the blood–brain barrier, leading to suboptimal efficacy against CNS metastases.[20,21] Clinical studies, such as the ALEX and ALTA-1L trials, showed that second-generation ALK inhibitors like alectinib and brigatinib significantly reduce the risk of CNS progression compared to crizotinib.[18,22] These findings suggest that crizotinib is less suitable for patients with brain metastases, with second-generation ALK inhibitors being the preferred option. The recent version of the NCCN guidelines indicates that alectinib, brigatinib, and lorlatinib are the preferred options for advanced NSCLC with ALK translocation, while crizotinib is useful only in certain circumstances.[17] Crizotinib may be considered in cases involving mesenchymal–epithelial transition (MET) co-mutations, as its dual activity against MET and ALK may provide clinical benefits.[23] Alternatively, it could be an option in situations where second- or third-generation ALK TKIs are not available; however, second- and third-generation ALK TKIs are generally regarded as the preferred options.

The ECOG score, smoking history, and line of treatment at the time second-generation TKIs were prescribed were independent predictors of OS. The significantly worse outcomes observed in ever smokers with lung cancer are likely due to several factors, including impaired pulmonary function,[24,25] an increased likelihood of comorbidities,[26] and a higher mutation burden.[27] In a study by Zheng et al., ever-smokers exhibited significantly shorter median OS (23.5 months; 95% CI, 11.5–35.5) compared to never-smokers (40.7 months; 95% CI, 33.1–47.2) among those receiving first-line ALK TKI treatment. This disparity may be attributed to factors, tumor mutation burden, and co-occurring genetic alterations such as TP53 mutations, which are known to predict poorer prognosis.[28,29]

Caution is necessary when interpreting CNS-related outcomes. Despite a lack of statistical significance, the alectinib group showed a tendency toward higher CNS-related treatment responses compared to the brigatinib arm. However, brigatinib patients more frequently received radiotherapy for CNS lesions, indicating a potential difference in disease burden between the two groups. Prior studies comparing alectinib and brigatinib have also reported no significant differences in CNS-related outcomes.[30] The ALTA-3 trial demonstrated intracranial ORRs of 73% and 68% in the brigatinib and alectinib arms, respectively.[15] Prospective studies are necessary to validate the efficacy against intracranial metastatic lesions.

The safety profiles of alectinib and brigatinib observed in this study showed significant overlap in key AEs with historical data from clinical trials, such as the ALEX trial and the ALTA-1L trial.[18,22] For alectinib, our study similarly identified LFT elevation, anemia, and bilirubinemia as the most common AEs, though their prevalence was higher in our study. In addition, dose reductions were reported more frequently, while dose interruptions were lower in the alectinib arm compared to historical data. Brigatinib demonstrated a significantly high frequency of creatine phosphokinase elevation, consistent with findings from the ALTA-1L trial. However, our study revealed generally higher AE rates for brigatinib, such as LFT elevation, anemia, and headache, likely due to a higher proportion of patients receiving brigatinib as a second-line or later therapy, suggesting that the patients may have been in poorer overall condition.

The rates of pneumonitis, though low in both groups (4.9% for alectinib and 2.8% for brigatinib), are noteworthy and warrant clinician awareness. Despite the comparatively higher incidence of AEs in both groups, permanent treatment discontinuations were rare, with only one case reported in the alectinib group, suggesting that AEs were generally manageable with

supportive care and dose modifications. However, the retrospective nature of this study imposes certain limitations, such as the absence of AE grading, potential underestimation of subjective symptoms, and the confounding effects of prior lines of therapy.

The present study has several limitations. First, the relatively small sample size, particularly in the brigatinib group ($n = 36$), reduces the statistical power of the study. This issue is especially pronounced in analyses of intracranial outcomes, where the brigatinib group included only 18 patients. The lack of statistical significance in these results should not be misinterpreted as evidence of equivalence.

Second, the observational and retrospective design of the study exacerbates this limitation. The absence of randomization and differences in the baseline characteristics—such as prior crizotinib exposure and treatment line—introduce potential biases that are difficult to fully adjust for in the analysis.

Third, there is potential selection bias in patients receiving second-line alectinib or brigatinib after crizotinib. These patients may represent a healthier subset capable of undergoing subsequent therapy. Ideally, subgroup analyses separating frontline and second-line treatments would be performed to address this bias. However, the limited sample size in this study posed challenges to conducting such analyses, complicating direct comparisons between frontline second-generation ALK TKIs, and sequential treatments following crizotinib.

Given these limitations, while the study suggests comparable efficacy between alectinib and brigatinib, these findings should be interpreted with caution, especially regarding intracranial outcomes. Larger, prospective studies with sufficient statistical power are required to validate these results and clarify clinically meaningful differences.

Conclusion

This multicenter, real-world study found no significant differences in TTD or OS between alectinib and brigatinib in ALK-positive advanced NSCLC. Despite comparable efficacy, the study's small sample size and retrospective design limit definitive conclusions. Larger prospective studies are needed to confirm these findings and evaluate safety profiles to guide TKI selection in both first-line and post-progression settings.

Declarations

Ethics approval and consent to participate

This study protocol was approved by the Institutional Review Board (IRB) of the Catholic University (Approval No. SC23WISE0014). Since anonymized clinical data were utilized, informed consent was waived.

Consent for publication

Not applicable.

Author contributions

Kyuhwan Kim: Data curation; Methodology; Software; Writing – original draft.

Kyu Yean Kim: Data curation.

Hye Seon Kang: Data curation; Writing – review & editing.

Ah Young Shin: Data curation; Resources.

Sung Kyoung Kim: Data curation; Resources.

Chan Kwon Park: Data curation; Resources.

Sang Haak Lee: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision.

Seung Joon Kim: Data curation; Resources.

Jeong Uk Lim: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Chang Dong Yeo: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID iD

Jeong Uk Lim https://orcid.org/0000-0001-8364-2380

Supplemental material

Supplemental material for this article is available online.

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