BRIEF REPORT

Brief Report: Real-World Treatment Patterns and Clinical Outcomes for Patients With Advanced ALK-Rearranged NSCLC in British Columbia

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ABSTRACT

Introduction: EML4-ALK rearrangements represent an oncogenic driver alteration in 5% of NSCLC cases. We aim to better understand real-world treatment patterns and outcomes of *ALK* fusion-positive (ALK+) patients with advanced-stage NSCLC.

Methods: We performed a retrospective population-based chart review of ALK+ patients with locally advanced or metastatic NSCLC in British Columbia (BC), Canada. Patients diagnosed from January 2014 to May 2023 were identified through the BC Cancer Genetics Laboratory database, and data were collected up to December 2023.

Results: A total of 216 patients with stage IIIB, IIIC, or IV ALK+ lung NSCLC were identified. Median age was 60 (range: 24–91) years, 151 (68.9%) had never smoked, and 95 (43.9%) were Asian. The median overall survival was 49.4 months with median follow-up time of 55.4 months. Majority of the cohort (n = 198, 91.7%) received palliative systemic therapy, all of which included at least one ALK tyrosine kinase inhibitor (TKI). The most common first-line regimen was alectinib (n = 97, 49.0%) followed by crizotinib (n = 84, 42.4%); only four and one patient received lorlatinib and brigatinib first line, respectively. Alectinib was frequently prescribed overall, with 80.3% of patients receiving it in any treatment line. Time to treatment discontinuation was significantly longer ($p < 0.0001$) on first-line alectinib at 22.9 months as compared with 10.9 months for crizotinib.

Conclusions: Patients with ALK+ advanced NSCLC in BC have durable responses to ALK TKIs. Despite approval of all ALK TKIs for first-line use since 2021, alectinib is largely the favored agent in BC. Further real-world investigations can refine treatment strategies and shape policies around ALK TKIs for patients with ALK+ NSCLC.

Keywords: NSCLC; Targeted therapy; ALK; Real-world; Treatment sequencing

Introduction

Lung cancer is the most lethal cancer worldwide. *ALK* fusion-positive (ALK+) lung cancers account for approximately 5% of all NSCLC cases and are more common in younger never or light smokers.[1] These patients with ALK+ lung cancer tend to present with adenocarcinoma subtype and are more likely to present with brain metastases at diagnosis as compared with other lung cancer subtypes.[1,2]

The first ALK tyrosine kinase inhibitor (TKI), crizotinib, received Health Canada approval for advanced-stage ALK+ NSCLC in 2012. Since then, second-

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generation (ceritinib, alectinib, brigatinib) and third-generation (lorlatinib) ALK TKIs have been successively approved and moved into earlier line settings.[3] Before this, sequencing treatment with multiple ALK TKIs in the second-line setting and beyond was available through expanded access programs as newer targeted therapies were approved.[3] Real-world studies have also reported median overall survival (OS) of approximately seven years for patients receiving sequential ALK TKIs.[4]

In June 2021, Health Canada authorized lorlatinib in the first-line setting for ALK+ patients with locally advanced or metastatic NSCLC. In April 2022, the Canadian Agency for Drugs and Technologies in Health recommended reimbursement of ALK TKI only in the first-line setting in the context of a publicly funded universal health care system. Consequently, previous access to treatment sequencing approaches accessed through industry-sponsored patient access programs became limited to first-line therapy only, whereas OS data on lorlatinib and brigatinib for treatment-naive ALK+ patients are still immature.[5,6]

Given the evolving landscape of drug approval and access to *ALK*-targeted therapies, we conducted a population-based review evaluating treatment patterns and clinical outcomes for patients with ALK+ advanced-stage NSCLC in British Columbia, Canada.

Materials and Methods

We performed a retrospective chart review of electronic medical records of ALK+ patients diagnosed from January 1, 2014, to May 1, 2023. Eligible patients were identified through the Provincial British Columbia (BC) Cancer Genetics Laboratory database on the basis of *ALK*-positive results identified through FISH, NGS, IHC, or a combination of methods. Equivocal immunohistochemistry results were confirmed with fluorescence in situ hybridization. Patients with a diagnosis of unresectable locally advanced or metastatic NSCLC were included unless they had fewer than two visits at the BC Cancer Agency.

Data abstraction of patient demographics, treatment, and toxicity information concluded on December 1, 2023. The study protocol was approved by the BC Cancer Research Ethics Board Accession Number H23-01707.

Survival analysis was conducted among patients who received at least one line of systemic therapy. Data for time to treatment discontinuation (TTD) and OS data were obtained. TTD was defined as time from starting to ending a treatment or death, and OS was defined as time from NSCLC diagnosis to time of death. Median follow-up time was calculated with censored patients.

Statistical analyses were performed using R 4.3.0 (R Core Team, Vienna, Austria). Kaplan-Meier curves were created for both TTD and OS and compared by log-rank test for statistical significance. Subgroup analysis was conducted by Cox proportional hazards model and expressed as hazard ratios and 95% confidence intervals (CIs).

Results

Baseline Characteristics

Among this large real-world cohort of 216 patients with advanced ALK+ NSCLC, 95 (43.9%) were Asian, 125 (57.9%) were female, and the median age was 60 (range: 24–91) years. Most of these patients have never smoked (n = 147, 68.1%) and have adenocarcinoma (n = 209, 96.7%). Furthermore, most patients had stage IV disease (n = 170, 78.7%), and 65 (30.1%) presented with brain metastases at diagnosis or recurrence. Other patient and disease characteristics are summarized in Table 1.

Treatment Patterns

Of 198 patients who received systemic therapy in the palliative setting (91.7% of our cohort), all individuals received at least one line of ALK TKI. For first-line treatment, 49.0% of this cohort received alectinib (n = 97), 42.4% received crizotinib (n = 84), and 5.6% received platinum-based chemotherapy (n = 11) (Table 2). Of the 65 patients with brain involvement at baseline, 35.4% (n = 23) received first-line crizotinib and 46.2% (n = 30) received first-line alectinib. Among these patients, 73.9% (n = 17 of 23) first-line crizotinib patients versus only 46.7% (n = 14 of 30) first-line alectinib patients received cranial irradiation.

Alectinib was also the most favored second-line drug choice, prescribed 45.5% in this setting, primarily for patients who progressed on first-line crizotinib. In total, 80.3% of ALK+ patients with advanced NSCLC received alectinib (n = 159 of 198) at some point during their treatment course (Table 2). Ceritinib, brigatinib, and lorlatinib were more frequently prescribed second line and beyond in treatment trajectory (10.6%, 18.2%, and 22.2% of the cohort, respectively) (Fig. 1*A*).

Regarding lines of systemic therapy, 46.5% (n = 92), 18.9% (n = 37), and 20.2% (n = 40) of ALK+ patients received one, two, and three lines of therapy, respectively. The remaining 14.6% of patients (n = 29) received four or more lines of therapy. In terms of the number of lines of ALK TKI treatment, the median was one, with 51.5% (n = 102) receiving one, 21.7% (n = 43) receiving two, and 19.2% (n = 38) receiving three or more ALK TKIs (Table 2, Fig. 1*A*).

Prescribing patterns of first-line ALK TKIs in this cohort were as follows: crizotinib was predominantly prescribed until June 2018, but since Health Canada

Table 1. Patient and Tumor Characteristics of Patients With ALK-Positive Advanced and Metastatic NSCLC in British Columbia Diagnosed From January 2014 to May 2023

Characteristics	n (%)
Number of patients	216
Median age at diagnosis (range)	60 (24-91)
Sex	
Female	125 (57.9)
Male	91 (42.1)
Ethnicity	
White	112 (51.9)
East Asian	80 (37.0)
South Asian	15 (6.9)
Other (African, Hispanic, Indigenous, Middle Eastern)	9 (4.2)
Smoking status	
Never	147 (68.1)
Former (<10 pack-years)	32 (14.8)
Former (≥10 pack-years)	19 (8.8)
Current (<10 pack-years)	2 (0.9)
Current (≥10 pack-years)	11 (5.1)
Unknown	5 (2.3)
Prior malignancy	
Yes	40 (18.5)
No	170 (78.7)
Unknown	6 (2.8)
Family history of cancer (first or second degree)	
Yes	91 (42.1)
No	112 (51.9)
Unknown	13 (6.0)
Family history of lung cancer	
Yes	36 (16.7)
No	167 (77.3)
Unknown	13 (6.0)
Performance status (ECOG)	
0	40 (18.5)
1	123 (56.9)
2	32 (14.8)
3	9 (4.2)
Unknown	12 (5.6)
Histology	
Adenocarcinoma	209 (96.7)
Adenosquamous	1 (0.5)
Squamous	5 (2.3)
Large cell neuroendocrine	1 (0.5)
PD-L1 status	
<1%	20 (9.3)
1%-49%	43 (19.9)
>50%	94 (43.5)
Unknown	59 (27.3)
Stage at initial diagnosis	
I	8 (3.7)
II	8 (3.7)
III	30 (13.9)
IV	170 (78.7)
Sites of metastases	
Bone	99 (45.8)
Brain	95 (44.0)
Pleura	101 (46.8)
Adrenal gland	27 (12.5)
Liver	51 (20.5)
Brain metastasis at baseline	
Yes	65 (30.1)
No	151 (69.9)

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.

approval and availability of second- and third-generation ALK-targeted therapies, alectinib has been most frequently prescribed. Among this cohort, only four patients were treated with first-line lorlatinib and one received brigatinib first line (Fig. 1*B*).

Toxicity

In the first-line setting, dose adjustments occurred for 8.3% (n = 7 of 84) and 15.5% (15 of 97) for patients receiving crizotinib and alectinib, respectively. The most common reason underlying the change in treatment lines was clinical and radiographic progression of disease (n = 176, 78.6%). Rate of central nervous system (CNS) failure was higher from first-line crizotinib at 28.6% (n = 24 of 84) as compared with first-line alectinib at 8.2% (n = 8 of 97). Other reasons for treatment discontinuation included toxicity (n = 42, 18.8%) and other reasons such as starting cytotoxic chemotherapy before receiving an ALK+ result (n = 6, 2.7%). Among all ALK TKIs, 18.0% (n = 18 of 97) of patients on crizotinib required early treatment discontinuation, primarily because of gastrointestinal intolerance including nausea and vomiting. In comparison, rates of treatment discontinuation because of adverse effects were 14.3% for ceritinib (3 of 21), 13.6% for lorlatinib (6 of 44), 7.5% for alectinib (12 of 159), and 7.9% for platinum-based chemotherapy (3 of 38). Reported adverse side effects were primarily neurologic (hallucinations, psychosis) for lorlatinib as compared with hepatic (transaminitis, hyperbilirubinemia) or renal (renal insufficiency) for alectinib.

Clinical Outcomes

Median TTD, a real-world end point that has been found to closely correlate with progression-free survival (PFS), was 22.9 months (95% CI: 18.07–45.5) for alectinib and 10.9 months for crizotinib (95% CI: 7.49–16.0) (Fig. 2*A*). Subgroup analyses by age, sex, race, prior malignancy, Eastern Cooperative Oncology Group (ECOG) performance status, and brain metastasis at diagnosis consistently found prolonged TTD from first-line alectinib compared with crizotinib (Fig. 2*B*). There were only five patients who received other ALK TKIs in

Table 2. Treatment History in Patients With *ALK*-Positive Advanced or Metastatic NSCLC in British Columbia

Prior Curative Intent Treatment	n (%)
Surgery	25 (11.6)
Adjuvant chemotherapy	14 (6.5)
Chemoradiation	15 (6.9)
Radiation	6 (2.8)
Palliative radiation	117 (54.2)
Palliative systemic therapy	198 (91.7)
Within those who received systemic therapy	
ALK TKI	198 (100)
Crizotinib	97 (49.0)
Alectinib	159 (80.3)
Brigatinib	36 (18.2)
Ceritinib	21 (10.6)
Lorlatinib	44 (22.2)
Chemotherapy	38 (19.2)
Chemotherapy + immunotherapy	2 (1.0)
Immunotherapy	8 (4.0)
First-line treatment	
Crizotinib	84 (42.4)
Alectinib	97 (49.0)
Brigatinib	1 (0.5)
Lorlatinib	4 (2.0)
Chemotherapy	11 (5.6)
Chemotherapy + immunotherapy	1 (0.5)
Median number of treatment lines (range)	1 (1-7)
Median number of ALK TKI lines (range)	1 (1-5)
Reason for changing to another line of treatment	
Progressive disease	176 (78.6)
Toxicity	42 (18.8)
Crizotinib	18/97 (18.6)
Ceritinib	3/21 (14.3)
Alectinib	12/159 (7.5)
Lorlatinib	6/44 (13.6)
Carboplatin + pemetrexed	3/38 (7.9)
Other (ALK+ result, CAP approval for another drug)	6 (2.7)

ALK+, *ALK* fusion-positive; CAP, Compassionate Access Program; TKI, tyrosine kinase inhibitor.

the first-line setting, limiting the ability to perform outcome analyses for those agents.

Median OS for the entire cohort was 49.4 months (95% CI: 43.3–94.6) from a median 55.4 months of follow-up period. At a median follow-up of 81.4 months for patients treated with crizotinib first line, the median OS was 44.6 months (95% CI: 30.7–80.3). In comparison, for patients treated with first-line alectinib, at a median follow-up of 39.0 months, median OS has not yet been reached (Fig. 2*C*). Presence of brain metastases at baseline did not influence OS in this cohort overall or within first-line crizotinib and first-line alectinib groups (Supplementary Fig. 1*A*), likely because of widespread use of ALK TKIs (91.7% of patients) and their CNS activity. Poor ECOG score (≥2) was associated with significantly worse TTD and OS in this ALK+ patient cohort ($p = 0.0022$, $p = 0.0003$) (Supplementary Fig. 1*B*).

Discussion

We report results from a large retrospective cohort of 216 ALK+ patients with advanced or metastatic NSCLC in BC, Canada. Similar to other real-world studies, patients were relatively younger (median age 60 y), more likely female, and predominantly never or light former smokers.[1]

Treatment sequencing regimens were diverse across ALK+ patients in BC, with some receiving up to five lines of ALK TKI therapy during a period when there was access to multiple sequential targeted therapies through patient access programs for new ALK TKIs that became available between 2012 and 2019.[3] This cohort dates back to 2014 and captures the shift in first-line systemic treatment prescribing patterns from crizotinib to alectinib promptly on the approval of first-line alectinib in June 2018.[3] Despite Health Canada approval of lorlatinib first line in June 2021 and lorlatinib having substantially better PFS in ALK TKI-naive patients compared with alectinib in non-Asian subgroups from network meta-analysis,[7] lorlatinib was prescribed to only four patients after April 2022, when publicly funded access to multiple ALK TKIs became limited across Canada. Since April 2022, alectinib remains the first-line drug of choice for ALK+ patients in BC. This pattern of practice may be due to a combination of reasons, including physician familiarity with prescribing first-line alectinib, immaturity of long-term survival data for lorlatinib, and greater frequency of severe adverse side effects with lorlatinib as compared with alectinib.[8,9]

To our knowledge, this is the first account of prescribing pattern of ALK TKIs over time in a real-world setting and reveals how prescribing practices may or may not be influenced by policy. TTD for first-line crizotinib (10.9 mo) and first-line alectinib (22.9 mo) was comparable to PFS reported in the ALEX trial at 10.9 months and 34.8 months, respectively.[10] Approximately half of the alectinib-treated population in our cohort have not yet progressed; thus, their TTD is predicted to increase as data mature. Similar to other real-world reports,[4,11] presence of brain metastases at diagnosis did not affect OS, lending to the CNS efficacy of multiple ALK TKIs.

Adverse events were most common with crizotinib, followed by lorlatinib, and then alectinib, and aligns with previous reports,[8,12] revealing the consistency of our large Canadian cohort with other real-world reports. A strength of this study is the prolonged overall median follow-up time of 55.4 months, representing a population with follow-up that exceeds many previous real-world analyses on ALK TKIs.[9,11]

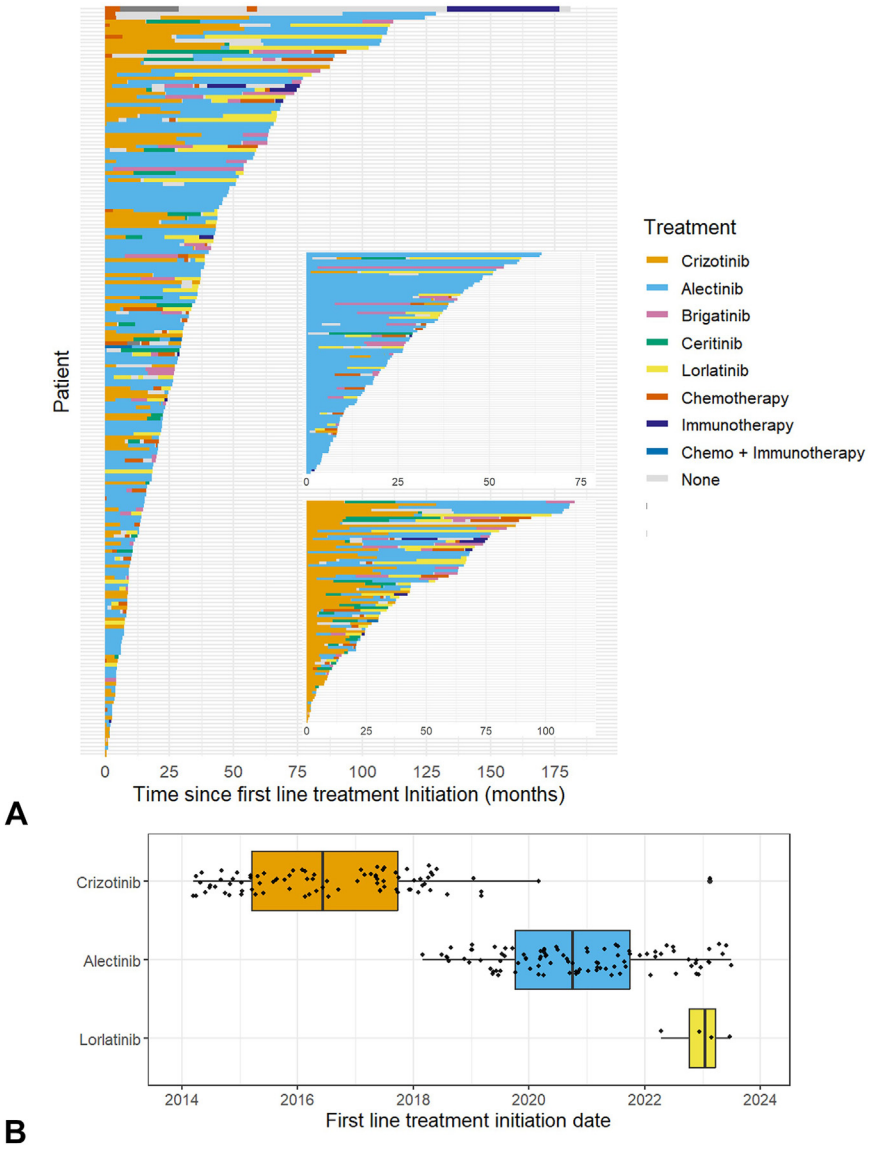

Figure 1. Sequencing treatment patterns and first-line prescribing practices in British Columbia for ALK+ patients. (*A*) Sequencing treatment patterns of individual ALK+ patients over time beginning from initiation of first-line of systemic therapy. Subplots on the right depict less variable patterns in patients who received first-line alectinib (top) than first-line crizotinib (bottom). (*B*) Dates of first-line treatment initiation of different ALK TKIs over time reveal dominance of alectinib from June 2018 to present. Brigatinib was not included in the graph because it was prescribed first-line only once in February 2023. ALK+, *ALK* fusion-positive; TKI, tyrosine kinase inhibitor.

The heterogeneity of treatment among this cohort makes it difficult to determine an optimal treatment sequence; however, alectinib remains favored as a first-line treatment option for ALK+ patients receiving palliative therapy in BC, with 80.3% receiving alectinib therapy at some point in their treatment regimen. Median OS of this cohort at 49.4 months is comparable with other Canadian real-world investigations at 48.5 and 54.0 months.[11,13] Nevertheless, this does not translate to one ALK TKI being suitable for all patients, as 8.6% of patients (n = 17) who started on ALK TKI first line experienced progression in less than 6 months, indicating potential preexisting resistance on an individual level. ECOG score was more than or equal to two for seven of these patients; otherwise, there were no significant clinicopathologic features between this subset of patients compared with the rest of the cohort.

One limitation of this study is the potential for selection bias, as both the study cohort and covariates are determined retrospectively. Furthermore, the reported prescribing patterns are influenced by the unique context of treatment access and coverage under a publicly funded health care system, limiting their generalizability to other settings. Another drawback is the lack

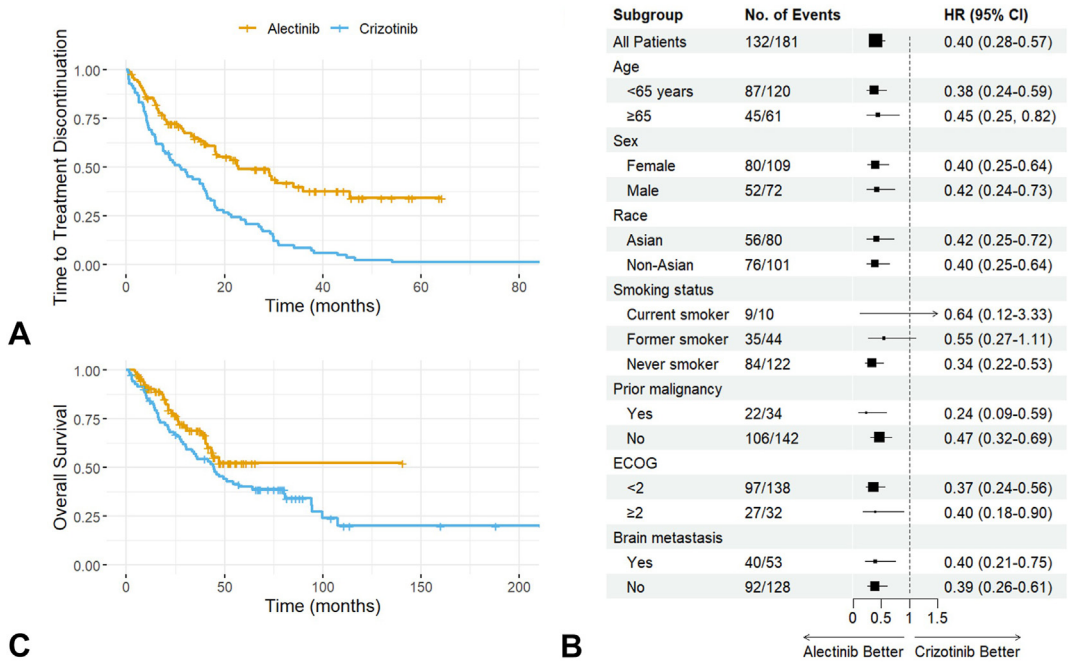

Figure 2. Survival analysis on first-line crizotinib versus first-line alectinib in ALK-positive patients with advanced or metastatic NSCLC in the real-world setting. (*A*) Time to treatment discontinuation is significantly longer in alectinib than crizotinib patients first-line at 22.9 months and 10.9 months, respectively ($p < 0.0001$). (*B*) Subgroup analysis of time to treatment discontinuation reveals consistent superiority of alectinib compared with crizotinib independent of age, sex, race, smoking status, prior malignancy, ECOG performance status, and brain metastasis at baseline. (*C*) Median overall survival trends toward significance in favor of first-line alectinib than crizotinib ($p = 0.43$). ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

of long-term follow-up in patients receiving first-line lorlatinib. Real-world investigations in the coming years will be fruitful to compare first-line lorlatinib with alectinib and crizotinib for ALK+ NSCLC patients. In addition, different variants of EML4-ALK have been found to have different risks of progression in response to ALK TKI.[7] Studying EML4-ALK variant testing before first-line or subsequent-line treatment selection in different health care settings could determine whether treatment strategies can be optimized on an individualized level.

Conclusion

ALK TKI treatment sequencing approaches have been common in BC and ALK TKIs are well tolerated by patients with ALK+ advanced NSCLC. Second-generation ALK TKI alectinib was found to have longer TTD and trended toward greater OS than crizotinib in the first-line setting, consistent with ALEX, the randomized controlled trial on these agents.

Alectinib was predominantly prescribed in the first-line setting in the past five years, and data on other later generation ALK TKIs, brigatinib and lorlatinib, were limited in the first-line setting. Prescribing practices do not always align with policies and directly affect patient outcomes as a result. The rapid evolution of targeted therapies, ever-changing guidelines under universal health care, and variable time to treatment resistance between individuals in the ALK+ NSCLC space require further controlled trials and real-world investigations to define optimal treatment strategies and policies.

CRediT Authorship Contribution Statement

Peiyao Wang: Data curation, Formal analysis, Investigation, Visualization, Writing—original draft.

Curtis Hughesman: Data curation, Writing—review and editing. Stephen Yip: Data curation, Writing—review and editing.

William W. Lockwood: Conceptualization, Writing—review and editing.

Sophie Sun: Conceptualization, Investigation, Supervision, Writing—original draft.

Disclosure

Dr. Yip is a member of advisory boards and has received honoraria from Amgen, AstraZeneca, Bayer, Janssen, and Roche. Dr. Sun is a member of advisory boards or has consulted for AstraZeneca, Bristol Myers Squibb, Merck, Novartis, Pfizer, and Takeda. These relations did not affect this work. Ms. Wang, Drs.

Lockwood and Hughesman have no conflicts of interest to declare.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100697.

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