Original Article

Treatment of metastatic ALK-positive non-small cell lung cancer: real-world outcomes in a single center study

Caroline Kamali[1,2], Georgios Tsakonas[1,2], Per Hydbring[1], Kenbugul Jatta[1], Anders Berglund[3], Kristina Viktorsson[1], Rolf Lewensohn[1,2], Luigi De Petris[1,2], Simon Ekman[1,2]^

[1]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [2]Theme Cancer, Medical Unit Head, and Neck, Lung and Skin Cancer, Thoracic Oncology Center, Karolinska University Hospital, Stockholm, Sweden; [3]EpiStat AB, Uppsala, Sweden

Contributions: (I) Conception and design: C Kamali, S Ekman; (II) Administrative support: C Kamali, S Ekman; (III) Provision of study materials or patients: C Kamali, L De Petris, S Ekman; (IV) Collection and assembly of data: C Kamali; (V) Data analysis and interpretation: C Kamali, A Berglund, L De Petris, S Ekman; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Simon Ekman, MD, PhD. Department of Oncology-Pathology, Karolinska Institutet, Theme Cancer, J6:20, Visionsgatan 4, S-171 64 Solna, Stockholm, Sweden; Theme Cancer, Medical Unit Head, and Neck, Lung and Skin Cancer, Thoracic Oncology Center, Karolinska University Hospital, Stockholm, Sweden. Email: simon.ekman@ki.se.

Background: Rearrangement in anaplastic lymphoma kinase (*ALK*) occurs in 4–7% of non-small cell lung cancer (NSCLC) cases. Despite improved survival with tyrosine kinase inhibitors (TKIs), treatment resistance remains challenging. This retrospective study analyzed advanced ALK-positive NSCLC patients, focusing on clinical aspects, treatments, resistance, and outcomes.

Methods: Patients diagnosed between January 2009 and December 2021 who received at least one ALK-TKI line at the Karolinska University Hospital, were included. We evaluated crizotinib or 2nd generation ALK-TKI effectiveness in first-line treatment and lorlatinib in subsequent lines. Overall survival (OS) was defined as from the date of advanced lung cancer diagnosis until the date of last follow-up (April 22, 2022) or the date of death from any cause. Progression-free survival (PFS), from the date of starting ALK-TKI until the date of progression, death, or last follow-up. Resistance mechanisms were assessed through re-biopsies utilizing next-generation sequencing (NGS).

Results: Out of 160 eligible patients, 10 were excluded. Median follow-up was 54.0 months from diagnosis and 45.0 months from initial ALK-TKI treatment. Crizotinib showed a median PFS of 8.0 months and a median OS of 35.0 months. Second generation ALK-TKIs demonstrated a median PFS of 52.0 months [OS was not reached (NR)]. Overall, the median OS was 65.0 months. Poor prognostic factors included male sex, thromboembolism, crizotinib treatment, and chronic obstructive pulmonary disease (COPD)/asthma. Rebiopsies in 18 cases revealed secondary ALK mutations in 8 patients, correlating with a shorter median PFS in subsequent ALK-TKI treatment (1.0 *vs.* 7.0 months).

Conclusions: This comprehensive study, spanning over a decade, provides crucial insights into the clinical characteristics, treatment patterns, and resistance mechanisms of advanced ALK-positive NSCLC, where median OS exceeds 5 years. Re-biopsies during treatment are essential for advancing our understanding of resistance mechanisms and the tumor dynamics evolving during ALK-TKI therapy.

Keywords: Advanced non-small cell lung cancer (advanced NSCLC); anaplastic lymphoma kinase (ALK); tyrosine kinase inhibitor (TKI); real-world data; long-term survival outcomes

Submitted May 03, 2024. Accepted for publication Sep 06, 2024. Published online Nov 12, 2024.
doi: 10.21037/tlcr-24-396
View this article at: https://dx.doi.org/10.21037/tlcr-24-396

^ ORCID: 0000-0002-8343-6226.

Introduction

Rearrangement in the anaplastic lymphoma kinase (*ALK*) gene is a driving oncogenic event causing non-small cell lung cancer (NSCLC) and is detected in approximately 4–7% of all cases (1). There are more than 90 different *ALK* fusion partners described where echinoderm microtubule-associated protein-like 4 (*EML4*) is the most common one and accounts for 80% of the *ALK* fusions (2). At least 15 different *EML4-ALK* variants have been identified where variants 1, 2, and 3a/b have been reported to represent 33%, 10%, and 29% of the cases, respectively (3). These patients are often younger with light or never smoking history and adenocarcinoma histology (4). They are at higher risk of developing brain metastasis which affects up to 60% of the patients during the disease (5).

Targeted therapy with tyrosine kinase inhibitors (TKIs) has significantly improved survival for advanced *ALK*-positive lung cancer patients, replacing the previous standard of care with conventional systemic chemotherapy due to improved response rates and clinical outcomes (6). The first ALK-TKI approved was crizotinib which showed a significantly better response rate and progression-free survival (PFS) compared to chemotherapy (7). However, many patients develop brain metastases due to the drug's limited penetration into the central nervous system (CNS) (8). Today, the 2nd generation ALK-TKIs alectinib, ceritinib, and brigatinib are all approved in the first-line setting with better penetration in the brain (9-11). In a substantial fraction of patients, patients develop drug resistance due to secondary *ALK* kinase domain mutations leading to clinical relapse, these "on-target" mutations include C1156Y, L1196M, G1269A, and G1202R (12,13). Other resistance mechanisms described are the occurrence of "bypass signaling" or "off-target" genetic aberrations, such as in epidermal growth factor receptor (*EGFR*) and Kirsten rat sarcoma virus (*KRAS*) (14). Lorlatinib is a third-generation ALK-TKI that is also indicated in first-line but is also designed to overcome secondary resistance mutations within the *ALK* tyrosine kinase domain (15). The introduction of these drugs has prolonged the median overall survival (OS) for patients with metastatic ALK-positive NSCLC to over 7 years (16,17).

Even though several drugs provide impressive results, the most effective sequential treatment strategy is yet to be known. In this retrospective study, we aimed to analyze the real-life cohort of Swedish patients with advanced ALK-positive NSCLC treated at Karolinska University Hospital in Stockholm to evaluate the roles of different ALK-TKIs when used in the first line and to identify potential unmet needs of these treatments. Evaluation of resistance mechanisms was also performed on re-biopsies using next-generation sequencing (NGS). Our study provides a comprehensive picture of clinical characteristics, treatment pathways, and outcomes of real-life *ALK*-rearranged NSCLC patients with advanced disease in clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-396/rc).

Highlight box

Key findings

- This retrospective study provides valuable insights into the real-world clinical experience and outcomes of patients treated with anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors (TKIs), offering guidance for the optimization of treatment strategies.
- The median overall survival was 65.0 months for patients treated with ALK-TKI as first-line treatment. Poor prognostic factors identified included: male gender, thromboembolism, crizotinib as initial treatment, and chronic lung disease.

What is known and what is new?

- While clinical trials play a pivotal role in advancing cancer therapies, they often fall short in addressing the myriad complexities surrounding patient outcomes and treatment resistance.
- Our comprehensive analysis of clinicopathologic and molecular characteristics, treatment patterns, and discontinuation reasons after progression on initial ALK-TKI provides practical insights into the challenges faced during treatment. The identification of specific resistance mechanisms, including secondary ALK kinase domain mutations and off-target genetic aberrations, highlights the need for personalized therapeutic approaches to overcome resistance.

What is the implication, and what should change now?

- The findings emphasize the need for continued research into personalized and sequential treatment strategies to enhance long-term survival outcomes in this patient population.
- Access to ALK-TKIs with good central nervous system penetration and tolerability, is important to achieve prolonged survival. Re-biopsies during treatment are crucial for enhancing our understanding of resistance mechanisms.

Methods

Study design and study population

A retrospective cohort study of NSCLC patients was identified in electronic health records (EHRs) at the Karolinska University Hospital in Stockholm. All patients

diagnosed with *ALK*-rearranged NSCLC between January 2009 and December 2021 were reviewed. To minimize selection bias, we used uniform inclusion and exclusion criteria. Only patients with unresectable stage III, stage IV, or recurrence from earlier stages were included in the study. Patients treated with at least one line of ALK-TKI were included and subdivided into either receiving crizotinib or 2nd generation ALK-TKI in the first line in the subsequent analyses.

The *ALK*-positivity of the tumors was assessed by either fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC). If enough tumor specimens were at hand, *EML4-ALK* fusion variants were also determined by reverse transcription polymerase chain reaction (RT-PCR). Patients diagnosed after 2015 were analyzed by NGS. Resistance mechanisms were evaluated in patients who underwent a re-biopsy of resistant tumor tissue by using NGS.

ALK treatment scenario in Sweden

During the study period, five different ALK-TKIs were approved by the European Medical Agency (EMA) and reimbursed in Sweden: crizotinib (after progression on chemotherapy and as first-line treatment), ceritinib (after progression on crizotinib or as first-line treatment), alectinib (after crizotinib treatment and first-line treatment), brigatinib (as first-line treatment or after crizotinib), and lorlatinib (as second-line treatment after progression on 2nd generation ALK-TKIs, after the study period also approved in first-line).

Data collection

The study was approved by the external Ethical Review Authority (Dnr 2022-00323-01) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (18). Individual consent for this retrospective analysis was waived. The data were collected using patients' EHRs and pseudo-anonymized with identification codes. The following variables were retrospectively collected: demographic data, e.g., age and gender; tumor stage according to the eighth edition of the tumor-node-metastasis (TNM) classification, date of diagnosis of advanced disease; metastatic sites; oncological treatment including start and stop dates; histopathology; smoking status at diagnosis; thromboembolic events; physicians' evaluations of Eastern Cooperative Oncology Group (ECOG) performance status (PS); and date of death or last follow-up.

Detection of ALK status, fusion variants, and ALK secondary mutations

A molecular testing algorithm was established and tested for the most reported *EML4-ALK* fusion variants. All the tests were performed on formalin-fixed paraffin-embedded (FFPE) material (4 µm thick). Tumor cell content was confirmed to be >20 % and around 500 cells per section at minimum was evaluated. All samples were deparaffinized before RNA extraction and further analysis. The test algorithm included in this report consisted of four techniques, FISH, IHC (19), NGS (20), and semi-quantitative RT-PCR (21), according to the standard protocol for clinical routine testing.

Statistical analysis

Categorical data were presented as percentages and continuous data was described by medians. The Chi-squared test was used to analyze categorical/ordinal variables and the Mann-Whitney test for continuous variables to determine the significance of clinicopathological differences between patients receiving either crizotinib or a 2nd generation ALK-TKI as initial treatment.

OS was defined as from the date of advanced lung cancer diagnosis until the date of last follow-up (April 22, 2022) or the date of death from any cause. In a subsequent step, OS was also evaluated from the start of the initial ALK-TKI until the date of the last follow-up or death. PFS, from the date of starting ALK-TKI until the date of progression, death, or last follow-up. Both OS and PFS were estimated using the time-to-event approach, described in Kaplan-Meier curves, and differences were analyzed by log-rank tests. In the next step, univariable Cox regression models were performed and statistically significant prognostic factors were further included in a multivariable Cox regression model to assess potential variables that were associated with poor prognosis and to control for confounders. Results from the models were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Swimmer's plots were used to summarize sequential therapy on those patients who underwent a re-biopsy after progression on ALK-TKI with the duration of treatment and occurrence of *ALK* secondary mutations.

All statistical tests were two-sided and a P value of <0.05

was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27, except for the Swimmer plot that was created using the swim plot package in R version 4.2.0.

Results

Patient and tumor characteristics

We identified a total cohort of 160 patients with metastatic *ALK*-positive NSCLC treated at Karolinska University Hospital between January 2009 and December 2021. Only patients treated with at least one line of ALK-TKI were included in the final analysis, 10 patients were excluded (five patients without any systemic treatment and five patients treated with only chemotherapy). The patient characteristics and demographics are described in *Table 1*.

The median age in our cohort was 61 (range, 23–89) years and 89 (59.3%) were females. The majority of the patients had adenocarcinoma histology (95.3%), were never smokers (57.3%), and had a good ECOG PS of 0–1 (94.0%). Ten patients had chronic lung disease, either chronic obstructive pulmonary disease (COPD) or asthma, as comorbidity.

Most of the patients (44.0%) had multiple metastases at baseline (M1c). Thirty patients presented with brain metastases at diagnosis (20.0%) and 41 patients (27.3%) developed brain metastases while on treatment. Radiotherapy to the brain, stereotactic radiosurgery (SRS) (17.3%), or whole-brain radiotherapy (WBRT) (6.7%), was given in 36 patients (24.0%).

Most patients received ALK-TKI as first-line treatment (64.0%), mostly alectinib (40.0%) and crizotinib (18.7%). Fifty-four patients (36.0%) received a TKI as a subsequent line after progression on chemotherapy. All patients were treated with a median of one line of ALK-TKI (range, 1–6).

The most common fusion variants detected in the cohort were variant 1 (24.7%) and variant 3a/b (19.3%). Programmed cell death-ligand 1 (PD-L1) status was checked in 76 patients and 42 (28.0%) had positive results with a staining threshold of 1%. Re-biopsies were performed in 18 cases during progression on ALK-TKI and secondary *ALK* mutations were found in eight patients. Fifty-seven patients developed thromboembolism throughout their disease and 76 patients were still alive on the day of analysis.

Clinical outcome analyses of ALK-TKI treatments

The median follow-up time from initiation of an initial ALK-TKI is presented in *Table 1*. The median PFS and median OS were significantly longer for 2nd generation ALK-TKI compared to crizotinib (*Figure 1*). The median PFS for 2nd generation ALK-TKI was 52.0 months (95% CI: 37.3–66.7) but not reached (NR) for the median OS.

The median PFS and median OS for crizotinib were 8.0 months (95% CI: 5.2–10.8) and 35.0 months (95% CI: 26.6–43.4), respectively. Median OS in the crizotinib group who were treated with 2nd generation ALK-TKI upon progression was 50.0 months compared to those who were not (14.0 months, P<0.001). For the full cohort, 60% were treated with a 2nd generation ALK-TKI upon progression on either another 2nd generation ALK-TKI or crizotinib with a median OS of 57.0 *vs*. 16.0 months (P<0.001) (Table S1).

Of the 150 patients, 134 were available for response evaluation. Overall response rate (ORR) was significantly higher in patients receiving 2nd generation ALK-TKI compared to crizotinib, 91% (95% CI: 82–97%) *vs*. 69% (95% CI: 56–79%).

Median OS for the whole cohort was 49.0 months (95% CI: 30.5–67.5), but was higher in the group who received ALK-TKI as first-line treatment at 65.0 months (95% CI: 22.7–107.3) compared to those who were treated with chemotherapy before ALK-TKI with 44.0 months (95% CI: 22.8–65.2); this was not statistically significant between the groups (log-rank P=0.76) (Table S1). Patients treated with at least three ALK inhibitors had significantly longer median OS compared to those treated with one or two (79.0 *vs*. 43.0 months, log-rank P=0.008; HR =0.46, 95% CI: 0.25–0.83) (Figure S1 and Table S2).

Univariate and multivariable analyses of OS and PFS for initial ALK-TKI

We studied the impact of clinical and molecular factors on PFS and OS on initial ALK-TKI. Both univariate and multivariable analyses are shown in *Table 2*.

Univariate analysis of OS showed that age ≥70 years, males, PS as ordinal variable, smokers, thromboembolism, crizotinib treatment, and chronic lung disease were significant factors. Furthermore, multivariable analysis of OS showed that poor prognostic factors were males (HR =1.64; 95% CI: 1.10–2.70; P=0.050), thromboembolism (HR =2.09; 95% CI: 1.27–3.46; P=0.004), patients who started crizotinib in the first line (HR =2.17; 95% CI: 1.21–3.89; P=0.009), and patients with COPD or asthma (HR =3.71; 95% CI: 1.59–8.70; P=0.003).

Univariate analysis of PFS showed that patients with

Table 1 Clinical and demographic characteristics of patients with advanced ALK-positive non-small cell lung cancer treated at Karolinska University Hospital between January 2009 and December 2021

Variables	Total cohort (n=150)	Initial ALK-TKI		P value†
		Crizotinib (n=74)	2nd generation ALK-TKI (n=76)	
Age (years)	61 [23–89]	61.5 [30–85]	60.5 [23–89]	0.63
Age category (years)				0.07
≤70	118 (78.7)	63 (85.1)	55 (72.4)	
>70	32 (21.3)	11 (14.9)	21 (27.6)	
Sex				0.72
Male	61 (40.7)	29 (39.2)	32 (42.1)	
Female	89 (59.3)	45 (60.8)	44 (57.9)	
Histology				0.54
Adenocarcinoma	143 (95.3)	71 (95.9)	72 (94.7)	
Squamous carcinoma	5 (3.3)	2 (2.7)	3 (3.9)	
Undifferentiated carcinoma	1 (0.7)	0 (0.0)	1 (1.3)	
Adenosquamous carcinoma	1 (0.7)	1 (1.4)	0 (0.0)	
ECOG PS				0.32
0–1	141 (94.0)	71 (95.9)	70 (92.1)	
≥2	9 (6.0)	3 (4.1)	6 (7.9)	
Smoking history				0.09
Never smoker	86 (57.3)	43 (58.1)	43 (56.6)	
Ex-smoker	49 (32.7)	20 (27.0)	29 (38.2)	
Smoker	15 (10.0)	11 (14.9)	4 (5.3)	
Chronic lung disease				0.44
COPD/asthma	10 (6.7)	6 (8.1)	4 (5.3)	
No	140 (93.3)	68 (91.9)	72 (94.7)	
M stage				0.10
M0 (advanced)	7 (4.7)	4 (5.4)	3 (3.9)	
M1a	35 (23.3)	21 (28.4)	14 (18.4)	
M1b	42 (28.0)	24 (32.4)	18 (23.7)	
M1c	66 (44.0)	25 (33.8)	41 (53.9)	
Brain metastasis				<0.001*
Primary	30 (20.0)	6 (8.1)	24 (31.6)	
Secondary	41 (27.3)	37 (50.0)	4 (5.3)	
No	79 (52.7)	31 (41.9)	48 (63.1)	
Skeletal metastasis				0.10
Primary	59 (39.3)	29 (39.2)	30 (39.5)	
Secondary	13 (8.7)	10 (13.5)	3 (3.9)	
No	78 (52.0)	35 (47.3)	43 (56.5)	
Liver metastasis				0.27
Primary	35 (23.3)	18 (24.3)	17 (22.4)	
Secondary	20 (13.3)	13 (17.6)	7 (9.2)	
No	95 (63.3)	43 (58.1)	52 (68.4)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total cohort (n=150)	Initial ALK-TKI		P value†
		Crizotinib (n=74)	2nd generation ALK-TKI (n=76)	
Adrenal metastasis				0.34
Primary	18 (12.0)	7 (9.5)	11 (14.5)	
Secondary	8 (5.3)	5 (6.8)	3 (3.9)	
No	124 (82.7)	62 (83.4)	62 (81.6)	
First-line ALK-TKI				
Crizotinib	28 (18.7)	28 (37.8)	0 (0.0)	
Ceritinib	7 (4.7)	0 (0.0)	7 (9.2)	
Alectinib	60 (40.0)	0 (0.0)	60 (78.9)	
Brigatinib	1 (0.7)	0 (0.0)	1 (1.3)	
Chemotherapy cycles before ALK-TKI				<0.001*
0	96 (64.0)	28 (37.8)	68 (89.5)	
1	39 (26.0)	35 (47.3)	4 (5.3)	
2–6	15 (10.0)	11 (14.9)	4 (5.3)	
Total number of ALK-TKIs				0.003*
One or two ALK inhibitors	125 (83.3)	54 (73.0)	71 (93.4)	
≥ Three ALK inhibitors	25 (16.7)	20 (27.0)	5 (6.6)	
Brain radiotherapy				0.003*
SRS	26 (17.3)	14 (18.9)	12 (15.8)	
WBRT	10 (6.7)	10 (13.5)	0 (0.0)	
None	114 (76.0)	50 (69.4)	64 (84.2)	
EML4-ALK fusion type				0.03*
Variant 1	37 (24.7)	19 (25.7)	18 (23.7)	
Variant 2	7 (4.7)	5 (6.8)	2 (2.6)	
Variant 3a/b	29 (19.3)	19 (25.7)	10 (13.2)	
Other variants	18 (12.0)	11 (14.9)	7 (9.2)	
Non-EML4	1 (0.7)	0 (0.0)	1 (1.3)	
Missing	58 (38.7)	20 (27.0)	38 (50.0)	
PD-L1 status				<0.001*
Positive (≥1%)	42 (28.0)	11 (14.0)	31 (40.8)	
Negative (<1%)	34 (22.7)	3 (4.1)	31 (40.8)	
Not determined	74 (49.3)	60 (81.1)	14 (18.4)	
Thromboembolism				0.002*
Yes	57 (38.0)	43 (58.1)	14 (18.4)	
No	93 (62.0)	31 (41.9)	62 (81.6)	
Deceased				<0.001*
Yes	76 (50.7)	60 (81.1)	16 (21.1)	
No	74 (49.3)	14 (18.9)	60 (78.9)	
Follow-up from diagnosis (months)	54.0 (40.9–67.1)	117.0 (86.5–147.5)	28.0 (20.9–35.1)	
Follow-up from ALK-TKI (months)	45.0 (41.4–48.6)	87.0 (69.0–105.0)	26.0 (20.3–31.7)	

Results are presented as median [range], n (%), or median (95% CI). †, P value for the statistical difference between patients receiving crizotinib and 2nd generation ALK-TKI; *, clinical variables that are statistically significant between the groups. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status; COPD, chronic obstructive pulmonary disease; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy; EML4, echinoderm microtubule-associated protein-like 4; PD-L1, programmed cell death-ligand 1; CI, confidence interval.

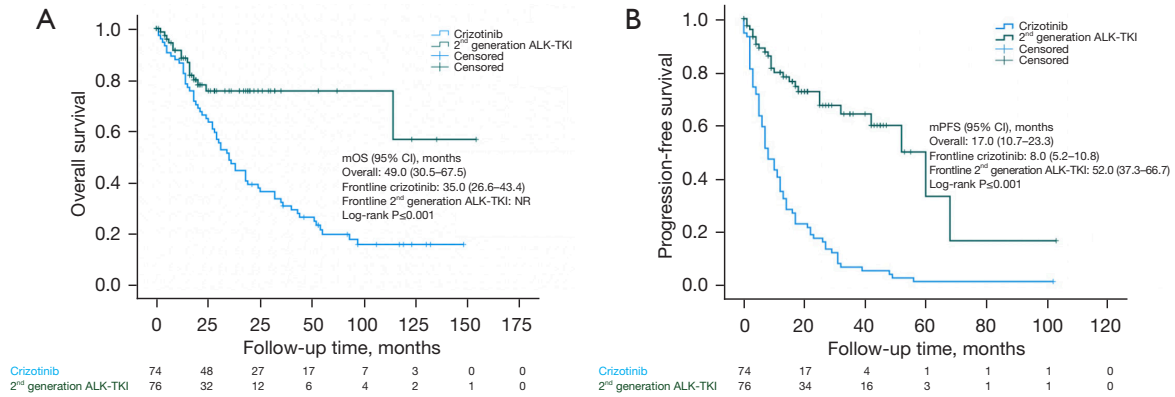

Figure 1 Kaplan-Meier curves of all patients. OS (A) and PFS (B) were significantly different between ALK-positive NSCLC patients receiving crizotinib and a 2nd generation ALK-TKI. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; mOS, median overall survival; CI, confidence interval; NR, not reached; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer.

baseline brain metastases or PD-L1 negative tumors had better PFS than those without brain metastases and PD-L1 positive tumors, respectively. Patients smoking, crizotinib treatment, or with prior chemotherapy had worse PFS. Patients receiving crizotinib as initial ALK-TKI was the only significant prognostic factor in the multivariable analysis (HR =5.41; 95% CI: 2.95–9.94; P<0.001).

Treatment patterns, metastatic sites, and discontinuation reasons after progression on initial ALK-TKI

We analyzed the different sequences of ALK-TKIs in the crizotinib and 2nd generation ALK-TKI groups (Table S3). The majority of the patients in the cohort were treated with one ALK inhibitor (57%, n=85) and the most common ALK inhibitor was alectinib (37%, n=56). Forty patients (27%) received two ALK-TKIs and 25 patients (17%) were treated with 3–6 lines of ALK-inhibitors. Patients treated with more than one ALK inhibitor had predominantly crizotinib-initiated sequences (32%, n=48) followed by alectinib-initiated sequences (9%, n=13) and ceritinib-initiated sequences (3%, n=4). There was only one patient who started with brigatinib. Forty-nine patients (67%) received a 2nd generation ALK-TKI after progression on crizotinib (Figure S2).

We next analyzed treatment status after the start of initial ALK-TKI, discontinuation reasons, and sites of progressive disease for the total cohort, 2nd generation ALK-TKI, and crizotinib (*Figure 2*). Most of the patients in the 2nd generation group had still ongoing therapy (66%, n=50), while only one patient was still on crizotinib at the time of analysis. The most common discontinuation reason was progressive disease in both groups. Brain metastasis after progression on initial ALK-TKI was the most common metastatic spread and was more common in the crizotinib group (40%, n=20 *vs.* 29%, n=5). The second most common metastatic spread was to multiple organs, 36% for crizotinib and 24% for 2nd generation ALK-TKI. The proportion of progression with skeletal metastasis was higher in patients receiving a 2nd generation ALK-TKI (24%, n=4 *vs.* 6%, n=3). Adverse events were more common in the crizotinib group (10%, n=7 *vs.* 1%, n=1) and death was the discontinuation reason in 16 patients in the crizotinib group (22%) and eight patients in the 2nd generation group (11%).

Impact of secondary ALK mutations and EML4-fusion variants

Eighteen patients underwent a re-biopsy after progression on an ALK inhibitor and eight patients were found to have secondary *ALK* mutations while the rest were without resistance mutations (*Figure 3*). All patients were treated with a subsequent line of ALK-TKI except for one patient (ID 15) who had oligoprogression and continued with the same TKI with the addition of stereotactic body radiotherapy (SBRT).

Patients with secondary *ALK* mutations experienced worse median PFS during the next treatment line of ALK inhibitors compared to those without existing resistance mutations (7.0 *vs.* 1.0 months, log-rank P=0.01). We also observed a longer

Table 2 Univariate and multivariable Cox proportional hazards regression analysis of covariables associated with OS and PFS

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
OS				
Age (≥70 years)	1.79 (1.03–3.12)	0.04*	1.45 (0.75–2.80)	0.27
Sex (male)	1.74 (1.09–2.77)	0.02*	1.64 (1.10–2.70)	0.050*
PS†	1.47 (1.06–2.02)	0.02*	1.43 (0.98–2.08)	0.07
Tumor stage M1c (yes)	1.33 (0.84–2.11)	0.22	–	–
Primary brain metastasis (yes)	0.74 (0.40–1.37)	0.33	–	–
Smokers (yes)	2.41 (1.30–4.49)	0.005*	1.24 (0.63–2.42)	0.53
TE (yes)	2.80 (1.77–4.44)	<0.001*	2.09 (1.27–3.46)	0.004*
Prior chemotherapy (yes)	1.10 (0.68–1.71)	0.76	–	–
Initial ALK-TKI (crizotinib)	2.64 (1.51–4.61)	<0.001*	2.17 (1.21–3.89)	0.009*
Chronic lung disease (yes)	5.13 (2.27–11.59)	<0.001*	3.71 (1.59–8.70)	0.003*
Variant 3a/b (yes)	1.03 (0.60–1.75)	0.92	–	–
PD-L1 negative (yes)	0.68 (0.32–1.43)	0.31	–	–
PFS				
Age (≥70 years)	1.24 (0.76–2.04)	0.40	–	–
Sex (male)	1.26 (0.84–1.88)	0.27	–	–
PS†	1.17 (0.91–1.50)	0.23	–	–
Tumor stage M1c (yes)	0.95 (0.63–1.42)	0.78	–	–
Primary brain metastasis (yes)	0.57 (0.33–0.99)	0.046*	1.14 (0.61–2.14)	0.68
Smokers (yes)	1.90 (1.05–3.41)	0.03*	1.01 (0.53–1.93)	0.98
No. previous lines of CT†	1.17 (0.97–1.40)	0.10	–	–
Prior chemotherapy (yes)	1.76 (1.18–2.62)	0.006*	0.66 (0.41–1.08)	0.10
Initial ALK-TKI (crizotinib)	4.60 (2.91–7.27)	<0.001*	5.41 (2.95–9.94)	<0.001*
Chronic lung disease (yes)	3.07 (1.40–6.73)	0.005*	1.92 (0.81–4.53)	0.14
Variant 3a/b (yes)	1.37 (0.86–2.19)	0.19	–	–
PD-L1 negative (yes)	0.35 (0.18–0.67)	0.002*	0.72 (0.35–1.51)	0.39

†, PS as ordinal variable and No. previous lines of CT as a continuous variable; *, clinical variables that are statistically significant between the groups. OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PS, performance status; TE, thromboembolism; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; PD-L1, programmed cell death-ligand 1; No., number; CT, chemotherapy.

median post-biopsy survival in those without *ALK* mutations, but the result was not statistically significant (11.0 *vs.* 5.0 months, log-rank P=0.17) (Figure S3).

We analyzed 91 patients with known *EML4-ALK* fusion variants (V1 found in 37 patients, V2 in seven patients, V3a/b in 29 patients, and 18 patients had the other *EML4*-fusion variants 4–7). We did not find any statistically significant difference between the *EML4*-fusion variants regarding OS and PFS on initial ALK-TKI (Figure S4). Patients with variant 2 had longer mPFS compared to *EML4*-non V2 (27.0

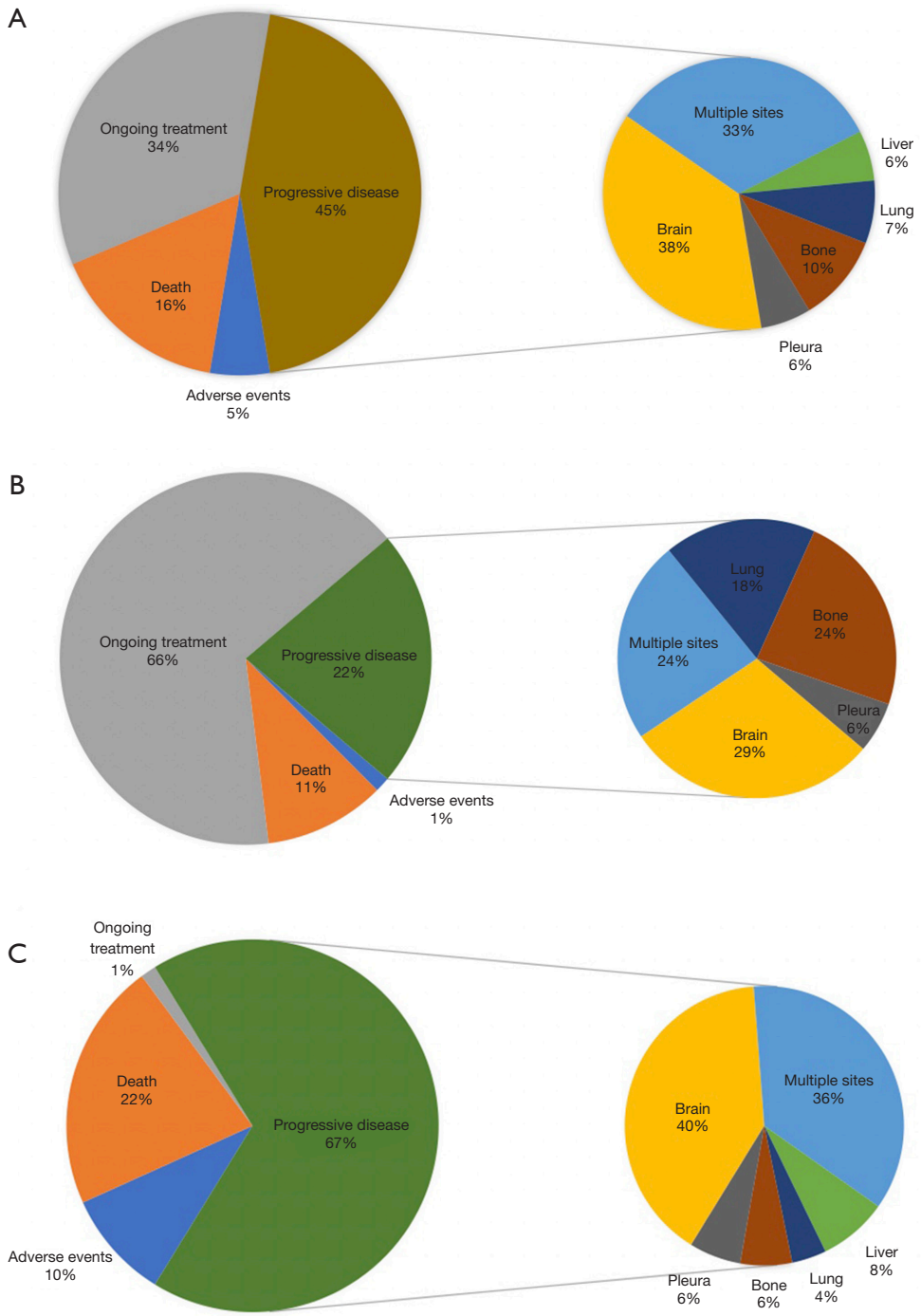

Figure 2 ALK-TKI status, discontinuation reasons, and sites of progressive disease: (A) total cohort, (B) 2nd generation ALK-TKI, and (C) crizotinib. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

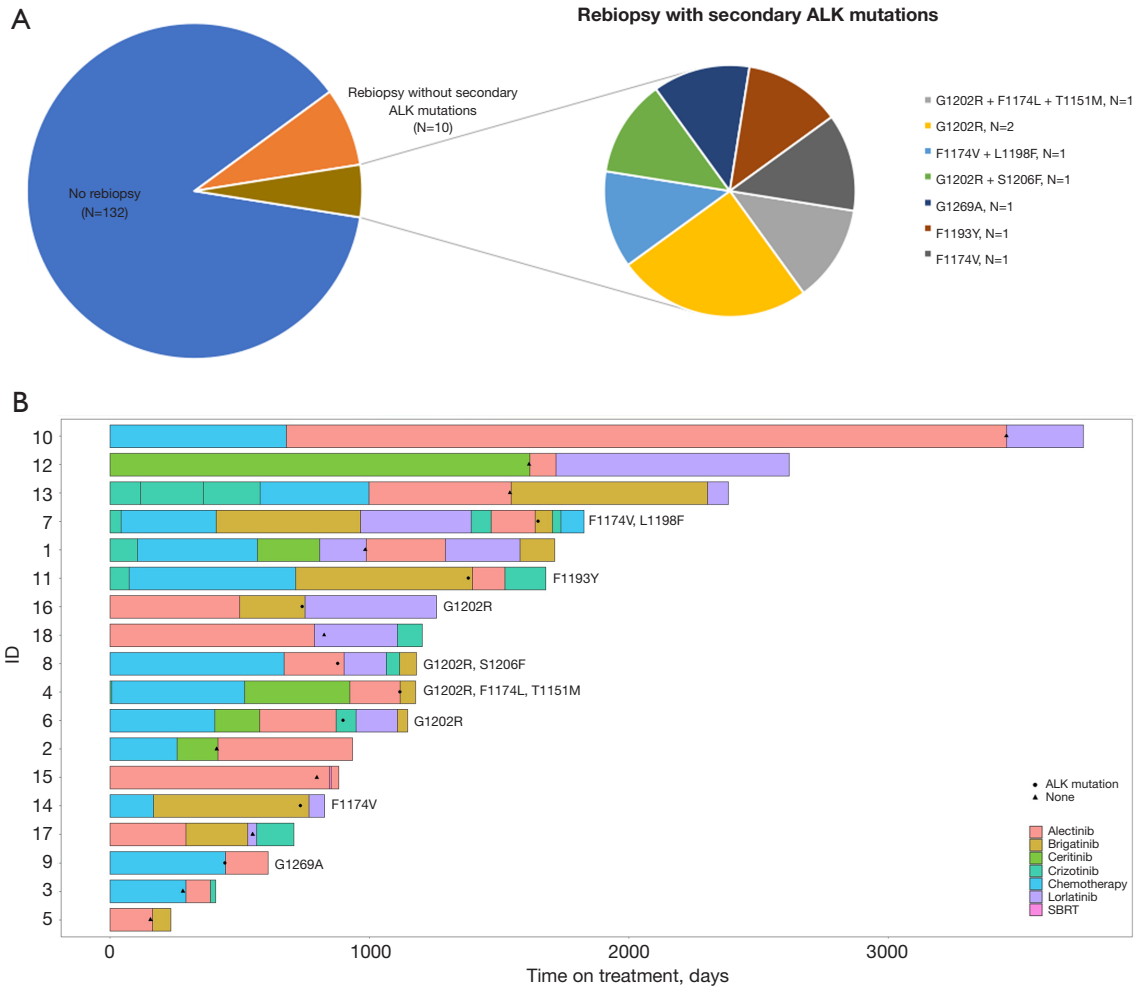

Figure 3 The results of rebiopsy after ALK-TKI progression. (A) The occurrence of secondary *ALK* mutations after progression on ALK-TKI treatment. (B) Individual swimmer plots for patients who underwent re-biopsy after progression on ALK-TKI, a black circle indicates secondary *ALK* mutation and a black triangle if no mutation was found. Patient ID 15 had oligoprogression during treatment with alectinib and received stereotactic body radiation therapy without change of TKI treatment. ALK, anaplastic lymphoma kinase; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor.

vs. 12.0 months, P=0.63; HR =0.80; 95% CI: 0.32–2.00).

Lorlatinib therapy and clinical outcomes

In a separate analysis, we included 23 patients who received lorlatinib (*Table 3*). Fifteen patients received ALK-TKI as first-line treatment without any previous chemotherapy. The majority of the patients had brain metastases (n=19, 83%). The median previous lines of ALK-TKI before lorlatinib were two. Eleven patients received lorlatinib after progression on a 2nd generation ALK-TKI and 12 patients after progression on both crizotinib and a 2nd generation ALK-TKI (Figure S2). The median follow-up time from diagnosis was 93.0 months (95% CI: 72.9–113.1). ORR was 57% and disease control rate (DCR) was 65%. Median PFS was 9.0 months (95% CI: 0.77–17.2), median post-lorlatinib survival was 13.0 months (95% CI: 0.0–29.7) and median OS was 79.0 months (95% CI: 26.6–131.4). Median PFS was higher in patients who received a 2nd generation ALK-TKI before lorlatinib compared to those who received crizotinib and a 2nd generation ALK-inhibitor (9.0 *vs.* 5.0 months, log-rank P=0.69) (Figure S5).

Table 3 Descriptive patient characteristics of advanced ALK-positive NSCLC patients receiving lorlatinib therapy and clinical outcome measures

Variables	Results (n=23)
Age (years)	67.0 [30–84]
Sex	
Male	7 (30.4)
Female	16 (69.6)
Histology	
Adenocarcinoma	22 (95.7)
Adenosquamous carcinoma	1 (4.3)
ECOG PS	
0–1	15 (65.2)
≥2	8 (34.8)
Smoking history	
Never smoker	11 (47.8)
Ex-smoker	11 (47.8)
Smoker	1 (4.3)
Brain metastasis	
Yes	19 (82.6)
No	4 (17.4)
First-line treatment	
TKI	15 (65.2)
Chemotherapy	8 (34.8)
Previous lines of ALK-TKI	2.0 [1–3]
Prior ALK-inhibitors	
Crizotinib + 2nd generation ALK-TKI	12 (52.2)
2nd generation ALK-TKI	11 (47.8)
Objective response rate	13 (56.5)
DCR	15 (65.2)
Complete response	2 (8.7)
Partial response	11 (47.8)
Stable disease	2 (8.7)
Progressive disease	5 (21.7)
Not evaluable	3 (13.0)
Censored	12 (52.2)
Follow-up (months)	93.0 (72.9–113.1)
PFS (months)	9.0 (0.77–17.2)
Post-lorlatinib survival (months)	13.0 (0.0–29.7)
OS (months)†	79.0 (26.6–131.4)

Results are presented as median [range], n (%), or median (95% CI). †, median OS from advanced or metastatic NSCLC diagnosis. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TKI, tyrosine kinase inhibitor; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Discussion

This study investigates the real-world clinical experience and outcomes of ALK-TKI-treated metastatic ALK-positive NSCLC in a Swedish cohort from 2009 to 2021, including the impact of sequenced therapy, fusion variants, and resistance mutations.

We present detailed real-world data from one of the largest described single-center cohorts with advanced *ALK*-positive NSCLC. The strength of this study includes a long median follow-up time of 54.0 months from advanced lung cancer diagnosis and 45.0 months from the start of initial ALK-TKI treatment. The 10-month gap is attributed to the inclusion of patients diagnosed before the approval of ALK-TKI as first-line treatment in Sweden. These patients initially received chemotherapy before transitioning to ALK-TKI therapy upon its subsequent approval. The long timespan, in this study, also allows for a more balanced cohort with a mixture of both advantageous and disadvantageous cases with the sequential use of multiple generations of ALK-TKIs. The majority of the patients in the total cohort received ALK-TKI as first-line treatment and the most common ALK-TKI used was alectinib. This results in a modern representative cohort with up-to-date real-world treatment patterns in the present era with targeted therapy reflecting high generalizability and external validity.

Despite similar therapeutic indications and treatment guidelines, global differences are described in real-world cohorts (RWCs) with advanced ALK-positive NSCLC who receive ALK-TKI treatment. A recently published study showed an overview of ALK-TKI treatment patterns in Sweden but was conducted from the prescribed drug register (22). Since there is a lack of real-world clinical data based on detailed information from EHRs from Sweden,

we chose to conduct this study for patients with advanced ALK-positive NSCLC at the time of their first exposure to either crizotinib or a 2nd generation ALK-TKI treatment.

The patients in the study aligned with previously published cohorts and consisted of predominantly younger female never smokers with adenocarcinoma histology, good PS, and high risk of brain metastases (23-27). However, in Sweden, routine computed tomography (CT)/magnetic resonance imaging (MRI) of the brain at the time of diagnosis for ALK-positive NSCLC patients (diagnosed before 2015) was not performed if the patients were asymptomatic. This practice is reflected in our data, where only 20% of patients had brain metastases at diagnosis. This lower percentage is likely due to the absence of routine brain imaging in asymptomatic patients rather than a true lower incidence of brain metastases. The higher incidence of 31.6% observed in the 2nd generation ALK-TKI cohort aligns more closely with other reported ALK-positive cohorts, as routine brain imaging at diagnosis was implemented for all ALK-positive NSCLC patients.

The prolonged median OS and PFS observed in this study underscore the significant efforts made in the discovery and availability of ALK-TKIs for these patients with metastatic NSCLC. Our survival results, with a median OS of 65.0 months, are higher than those reported in other RWCs where median OS ranges from 24.8 to 30.9 months across the USA, China, France, and India (28-31). Median OS, in line with our study, was seen in two other RWCs in Italy and Canada (23,32), and an impressive median OS of 81.0 months was reported in one study with 110 advanced ALK-positive NSCLC patients by Pacheco *et al.* (17).

In our study, median OS was higher in those patients who received ALK-TKI as first-line treatment compared to those treated with previous chemotherapy but was not statistically significant. Consistent with other studies, we found a superior median OS in the 2nd generation ALK-TKI group compared to crizotinib but median survival data was NR in the first group. The median OS was influenced by access to a 2nd generation ALK-TKI post-failure. We also observed a prolonged survival in those who received at least three lines of ALK-TKIs compared to one or two lines. This was also reported by Pacheco *et al.* where patients receiving a next-generation ALK-TKI after progression on crizotinib had a median OS of 86.0 months instead of 52.0 months for those who did not. One possible explanation for the higher median OS found in their study is that they had a higher proportion of patients who were further treated with a 2nd generation ALK-TKI drug (78%). Still, their results were not statistically significant (P=0.09) (17). Another study by Waterhouse *et al.* also showed an increase in OS with the increasing number of ALK-TKIs used, suggesting that multiple ALK-TKIs were achievable in those who lived long enough to be able to receive several lines of treatment and supports the use of sequential ALK therapies (33). Further analysis to investigate the best optimal sequencing was difficult to perform in our study because of the small subgroups and additional studies will be required for a better understanding of the best strategy for therapy sequencing. A reason for this heterogeneity in treatment options is that the choice of subsequent next-line ALK-TKI is often not guided by molecular factors upon treatment failure.

We found superior PFS of initial treatment with 2nd generation ALK-TKI compared to crizotinib, 52.0 *vs.* 8.0 months, where alectinib was the most frequently used drug. This extended PFS compared to crizotinib was higher in the present study than that observed in the ALEX clinical trial (34.8 *vs.* 10.9 months) (11) and the observed median PFS of crizotinib was lower than in the PROFILE 1014 study (10.9 months) (6).

Our study demonstrated a higher aggregated ORR of 79% compared to the phase 3 trial of Peters *et al.* (ORR, 60%) comparing first-line alectinib and crizotinib (11). The ORR (91%) of the 2nd generation ALK-TKI group aligns with the ORR (92%) of alectinib in the J-ALEX study (11). Discrepancies between real-world response evaluations and Response Evaluation Criteria in Solid Tumors (RECIST)-based assessments in clinical trials may explain these variations.

We analyzed prognostic factors in the whole cohort and found that male gender, thromboembolism, chronic lung disease at diagnosis, and crizotinib as initial ALK-TKI treatment were associated with negative effects on survival outcomes. The latter group included patients who received it as a first-line therapy and those who received it after progressing on chemotherapy. We did not separate these two groups in our analysis. However, our univariate analysis indicated that receiving prior chemotherapy before transitioning to ALK-TKI did not significantly affect OS. This suggests that the poor prognostic impact of crizotinib is consistent regardless of its sequence relative to chemotherapy. One possible explanation could be the pattern of progression. The most common reason for discontinuing the initial ALK-TKI treatment was progressive disease, mostly due to progression in the brain. CNS-progression was higher post-crizotinib than post-

2nd generation ALK-TKI. This emphasizes the necessity of brain-penetrating ALK-TKIs as the first-line therapy.

During treatment with either a 2nd generation ALK-TKI or crizotinib, the only prognostic factor for PFS was the ALK-TKI used as the initial treatment. Brain metastasis at baseline, current smokers, previous chemotherapy, PD-L1 negative tumors, and chronic lung disease were all significant prognostic factors in the univariate analysis but did not hold in the multivariable Cox regression model. Our results need validation in a larger cohort.

A recent study by Li *et al.* found that *ALK* fusion variant 3a/b, concomitant mutations, and high PD-L1 expression were associated with poor clinical response to 2nd generation ALK-TKI (34). Positive PD-L1 expression was also correlated with poor response in crizotinib-treated patients reported by Yang *et al.* (35) and that there is an association between high PD-L1 expression and poor prognosis in *ALK*-rearranged NSCLC patients (36). These studies suggest that high PD-L1 expression is associated with fusion variant 3a/b and concomitant mutations leading to resistance to ALK-TKIs, but underlying mechanisms need to be further investigated. Regarding CNS involvement in our study, the observed better PFS in the univariate analysis is likely attributable to confounding factors, for example most patients with brain metastases at diagnosis received treatment with a 2nd generation ALK-TKI, and thus the result did not hold in the multivariable analysis.

We did not find any significant association in terms of OS or PFS between different fusion variants. ALK-fusion variant was not reported in 38.7% of the patients, either because it was not tested for using PCR/NGS or that fusion variant was detected but not specified in the pathological report. This lack of data is primarily because advanced diagnostic techniques, such as RNA-NGS, were not widely available or implemented during the earlier years of the study period. Conflicting data have been reported regarding the predictive roles of *ALK* fusion variants, where some studies report that variant non-3a/b is associated with longer PFS on crizotinib compared to other variants. In contrast, others show that there is no difference (37,38). These conflicting results could be explained by smaller cohorts, variations across different geographic areas, and heterogeneity in terms of ALK-TKI-treated patients.

We identified secondary *ALK* mutations, predominantly emerging after progression on 2nd generation ALK-TKIs. This finding aligns with resistance mutations previously reported in the literature (39). We found superior median PFS on subsequent ALK-TKI in those who lacked secondary *ALK* mutations compared to those with resistance mutations, but no statistically significant effect in post-biopsy survival. This is in contrast to what was found by Zou *et al.* with longer PFS on subsequent ALK-TKI in those patients who had secondary *ALK* mutations after treatment with alectinib compared to those who had not (40). One explanation could be the heterogeneity in our group with re-biopsies after progression on different ALK-TKIs and the use of ineffective "off-target" drugs in subsequent lines since the sensitivity of ALK-TKIs is different for each secondary mutation in the *ALK* kinase domain. The majority of our patients with secondary *ALK* mutations were also treated with several ALK-TKIs before the re-biopsy was performed and poorer PFS has been described the more prior ALK-TKIs that have been administered (41). The rebiopsies were crucial in guiding subsequent treatment choices. Lorlatinib was specifically utilized when the G1202R mutation was detected, as this mutation is known to confer resistance that lorlatinib can effectively overcome. However, in the case of patient ID 4, lorlatinib was not accessible at the time of progression on alectinib.

We also analyzed the patients who received lorlatinib in our cohort and where real-world data is scarce. Most of the patients had brain metastases before initiation of lorlatinib, ORR and median PFS were consistent with previously described data from RWCs with baseline brain metastases of 70–84%, ORR 33–67%, and median PFS 6.2–9.7 months (42-46). These findings suggest that the real-world efficacy of lorlatinib is comparable with results found in clinical trials (15). The observed decreasing percentage of patients receiving lorlatinib after progression on initial ALK-TKI can be primarily attributed to the fact that many patients in the crizotinib group did not live long enough to receive lorlatinib after progressing on both crizotinib and second-generation ALK-TKIs. Additionally, lorlatinib was not available at the time of progression for some patients. However, prior treatment to lorlatinib did not affect PFS even if there was a trend towards superior PFS in those patients who only received 2nd generation ALK-TKIs.

A limitation of this study is its single-center retrospective nature with missing data in some parameters, such as *EML4-ALK* fusion type and PD-L1 expression. Another limitation of the study is the immature survival data in the 2nd generation ALK-TKI group. Radiological progression in the real world is also not as frequently measured as in prospective clinical trials which might affect PFS. Even if the data were obtained retrospectively, we attempted

to ensure the validity of the patients' characteristics and clinical outcome assessments.

Conclusions

This study of patients with advanced ALK-positive NSCLC showed prolonged survival with a median OS exceeding 5 years. Access to ALK-TKIs with good penetration to the CNS, effective against multiple resistance mutations, and with good long-term tolerability are necessary to achieve prolonged survival. Re-biopsies during treatment are important to enhance our understanding of resistance mechanisms and the tumor dynamics that develop during ALK-TKI therapy and to increase the individualized management of this disease within the era of precision medicine.

Acknowledgments

Funding: This project was supported by the grant from the Swedish Cancer Society [Nos. CAN2023/2919 (S.E.) and CAN2021/1469 (R.L.)], the Stockholm Cancer Society [Nos. 221212 (R.L.) and 221383 (K.V.)], the King Gustaf V Jubilee Fund [No. 204053 (S.E.)], the Stockholm County Council [contract Nos. FoUI-966345 (R.L. and K.V.), 909121 and 750032 (R.L. and K.V.), and 987911 (S.E.)], the Sjöberg Foundation [No. 2022-2024 (S.E.)], the Erling Persson Family Foundation (K.V. and R.L.), and the Swedish Foundation for Strategic Research [No. SIP21-0106 (R.L.)].

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-396/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-396/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-396/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-396/coif). G.T. reports honoraria from MSD, Roche AB for lectures and reports paid participation at ELCC 2023 from Roche AB. K.V. is supported for salary and other project related costs by the indicated private funding bodies or region grants Stockholm Cancer Society (contract No. 221383), Stockholm County Council (contract Nos. 909121, 750032, and FoUI-966345), and Erling Persson Family Foundation. R.L. reports grant from the Swedish Cancer Society (No. CAN2021/1469), the Stockholm Cancer Society (No. 221212), the Stockholm County Council (contract Nos. FoUI-966345, 909121, and 750032), the Erling Persson Family Foundation, and the Swedish Foundation for Strategic Research (No. SIP21-0106). S.E. reports grants from the Swedish Cancer Society (grant No. CAN2023/2919), the King Gustaf V Jubilee Fund (grant No. 204053), the Sjöberg Foundation (No. 2022-2024), and the Stockholm County Council (No. 987911). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the external Ethical Review Authority (Dnr 2022-00323-01) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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Cite this article as: Kamali C, Tsakonas G, Hydbring P, Jatta K, Berglund A, Viktorsson K, Lewensohn R, De Petris L, Ekman S. Treatment of metastatic ALK-positive non-small cell lung cancer: real-world outcomes in a single center study. Transl Lung Cancer Res 2024;13(11):2918-2933. doi: 10.21037/tlcr-24-396

