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Treatment Patterns and Outcomes in a Cohort of Finnish NSCLC Patients with *ALK* Rearrangement Reflect Rapid Evolution in Treatment Practices

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Abstract: *Background*: In Finland approximately 2,500 people are diagnosed with lung cancer annually. A small proportion of non-small cell lung cancer (NSCLC) patients (3–7%) have tumorigenic rearrangement of the anaplastic lymphoma kinase (*ALK*) gene (*ALK*-positive). *ALK* tyrosine kinase inhibitors (TKI) are the standard of care for these patients, showing superior efficacy compared to traditional chemotherapy (CT). Due to the rapid development of novel next-generation *ALK* TKIs, treatment practices have undergone substantial changes. In Finnish real-life clinical practice the choice of treatment is largely determined by the reimbursement status of available drugs. We set out to assess the prevailing treatment practices and outcomes for NSCLC patients harbouring *ALK* rearrangement. *Materials and methods*: This was a retrospective, non-interventional, two-centre study. Adult NSCLC patients from the Hospital District of Southwest Finland and *ALK*-positive NSCLC patients from the Hospital District of Helsinki and Uusimaa diagnosed between 2013–2017 were included. Patients were followed until death or until the end of study period (May 2018). Data were extracted retrospectively from electronic health records from University Hospital data lakes. *Results*: A total of 1,260 patients were included, of which 60 were *ALK*-positive. *ALK* TKI regimens were mainly received in second and later lines of treatment. Median time-to-next treatment (TTNT) during *ALK* TKI treatment was 11.0 months (95% CI; 5.0–35.0) and during CT treatment 7.0 months (5.0–11.0) when assessed irrespective of treatment line (p=0.08). Patients who received at least one *ALK* TKI treatment regimen during the follow-up had median overall survival (OS) of 33.6 months (16.9–NR) from diagnosis vs. 11.5 months (4.6–NR) in patients who were treated with CT regimens only (p=0.054). *Conclusions*: *ALK*-positive patients benefit from treatment with *ALK* targeting agents in real-world clinical practice.

Keywords: *ALK* Rearrangement, Non-small Cell Lung Cancer, Chemotherapy, *ALK* Tyrosine Kinase Inhibitor, Crizotinib, Data Lake

1. Introduction

Lung cancer is the most common malignancy and the leading cause of cancer deaths worldwide [1]. The majority, 80–85%, of all lung cancers are non-small cell lung carcinomas (NSCLC), which are commonly diagnosed at an advanced stage. A small proportion (3–7%) of NSCLC patients harbor a tumorigenic rearrangement of the anaplastic lymphoma kinase (*ALK*) gene [2]. Rearrangement in the *ALK* gene results in the oncogenic activation of *ALK* membrane receptor tyrosine kinase in the lung tissue [3, 4]. NSCLC patients with *ALK* rearrangements are typically younger, never or light smokers, and have adenocarcinoma histology [5, 6].

Since the first identification of *ALK* rearrangement in NSCLC patients in 2007, there has been rapid progress in the development of targeted therapies for *ALK*-positive NSCLC [7, 8]. *ALK* rearrangements confer sensitivity to *ALK* tyrosine kinase inhibitors (*ALK* TKIs). The first-in-class *ALK* TKI approved for *ALK*-positive advanced/metastatic NSCLC was crizotinib, which shows improved clinical outcomes in *ALK*-positive NSCLC compared to standard chemotherapy, in both second- and first-line settings, and is better tolerated [9–11]. The new era of treatment begun in 2017 when the second-generation *ALK* TKI alectinib showed improved progression-free (PFS) and overall survival (OS) as first-line therapy compared to first-generation compound crizotinib in a head-to-head comparison [12, 13]. In recent years, also other second-generation compounds, namely ceritinib and brigatinib, have demonstrated improved efficacy in the first- and second-line settings [14–17]. Compared to crizotinib, the second-generation TKIs are more selective, cover more *ALK* resistance mutations, and show better central nervous system (CNS) penetration [8, 18]. The latest advancement in the treatment of *ALK*-positive NSCLC occurred when the third-generation TKI lorlatinib was approved for the treatment of *ALK*-positive patients after progression on a second-generation *ALK* inhibitor or on crizotinib and a subsequent *ALK* TKI [19, 20].

In Finland, approximately 2,500 patients are diagnosed with lung cancer annually. In general, Finnish lung cancer treatment practices follow the guidelines set by the European Society for Medical Oncology (ESMO). According to the current ESMO treatment algorithm for stage IV lung carcinoma harboring *ALK* rearrangement, the recommended first-line treatment options are alectinib, brigatinib, crizotinib, or ceritinib, with alectinib and brigatinib having the highest grade of recommendation (A, strongly recommended). After disease progression with the first-line crizotinib treatment, alectinib, ceritinib, or brigatinib are recommended. If progression occurs after at least one *ALK* TKI other than crizotinib, lorlatinib is recommended [21]. In practice, the reimbursement status of different compounds imposes certain restrictions for the selection of treatment of *ALK*-positive NSCLC in Finland. Until 2018, the only *ALK* TKI with reimbursement status in Finland was crizotinib, which was reimbursable as a second- line treatment. This is reflected by the fact that Finnish Current Care Guidelines advise using a frontline pemetrexed-based treatment if a combination treatment of one platinum compound together with a cytotoxic agent (vinorelbine, gemcitabine, pemetrexed, or a taxane) is chosen [22]. After 2018, several novel *ALK* TKIs have become available and been granted reimbursement status in Finland. As of July 2021, two second-generation compounds, brigatinib and alectinib, have been available with full reimbursement in all approved indications. This recent development has rapidly changed the treatment practices of *ALK*-positive NSCLC during the past few years.

Data on the real-world treatment patterns of *ALK*-positive NSCLC patients in routine clinical practice in Finland is scarce. Due to a low incidence of *ALK*-positive NSCLC, and a relatively small number of patients in clinical trials, data collected from the actual clinical setting is particularly important to provide a benchmark for the evolving therapeutic field. The objective of this real-world study was to characterize clinical practices for *ALK*-positive NSCLC in Finland between 2013–2018 before the next-generation *ALK* TKIs (ceritinib, alectinib, brigatinib, and lorlatinib) were confirmed as reimbursable. We retrospectively assessed patient characteristics, therapy lines, and outcomes, for *ALK*-positive NSCLC patients in two Finnish University Hospitals.

2. Materials and Methods

2.1. Study Population and Data Collection

This was a retrospective, two-centre study designed to assess patient characteristics, therapy lines, and treatment outcomes of *ALK*-positive NSCLC patients. All adult (≥ 18 years of age) patients diagnosed with NSCLC (ICD-10: C34.xx) at the Hospital District of Southwest Finland (population base 470,000) between the years of 2013–2017, were included in the study. In addition, all *ALK*-positive NSCLC patients diagnosed at the Hospital District of Helsinki and Uusimaa (population base 1.6 million) between the years of 2013–2017, were included. Each patient was followed-up from the time of diagnosis until death or 31st of May 2018 (which ever occurred first). Patients were identified as *ALK*-positive based on the result of *ALK* immunohistochemical (IHC) staining or fluorescence *in situ* hybridization (FISH). Data were collected retrospectively from electronic health records and other hospital databases via the data lakes of Auria Clinical Informatics and HUS Data Administration. Extracted data was supplemented with data manually collected by the clinician or study nurse regarding *ALK*-positive patients to achieve better coverage of essential variables. *ALK*-positive patients were initially identified by the data administration using text mining from pathology statements, which include *ALK* screening results. Pathology statements were further reviewed by the study

group member, and *ALK* status was ultimately confirmed by the clinician.

The following information on demographics and clinical characteristics were collected at baseline for all patients included in the study: age, sex, C34-diagnosis, TNM stage (AJCC 7th edition), Eastern Cooperative Oncology Group (ECOG) performance status, and smoking status. In addition, data on *ALK*-positive patients' anti-cancer medication use (administration of in-hospital medication and prescriptions), radiation therapy, and surgical procedures was collected.

2.2. Outcome Measures

2.2.1. Treatment Lines

Data on administration of in-hospital medication and anti-cancer drug prescriptions was used to determine treatment lines (treatment regimen and the length of the treatment line). Treatment line was defined by the pharmacological agent or combination of agents administered. If only a single agent of the total regimen was discontinued or changed to another compound of the same chemical subgroup (ATC, 4th level) in a multi-drug regimen, this was not considered a new line of treatment. If the regimen was interrupted and restarted again without any other intervening regimen, it was counted as a single treatment line from the start date until the final end date. For further analyses, the treatment regimens were subcategorized to *ALK* tyrosine kinase inhibitor (*ALK* TKI) regimens, chemotherapy regimens (CT) and other regimens (other agents than *ALK* TKI or CT).

2.2.2. Time-to-Next-Treatment (TTNT)

TTNT was defined as the length of time from the date of initiation of one treatment regimen to the date when next treatment regimen was initiated. TTNT was studied in *ALK* TKI and CT subcategories. Other treatment regimens were not included in the TTNT analyses.

2.2.3. Overall Survival (OS)

Overall survival time was defined as the length of time from primary diagnosis of NSCLC until the date of death. For the OS analyses the *ALK*-positive patients were divided into two subgroups based on the treatment received. The '*ALK* TKI' subgroup included all patients who had received one or more lines of *ALK* TKI treatment during the study follow-up irrespective of other lines received prior to or after *ALK* TKI treatment (patients were allowed to have also received CT treatment or other systemic anti-cancer treatments). The 'Only CT' subgroup consisted of patients who received only chemotherapy during the study follow-up period (no *ALK* TKI (s) nor other anti-cancer agents).

2.3. Statistical Analyses

Descriptive analyses were conducted to assess demographic characteristics and treatment pattern. Distributions of continuous variables were expressed as mean with standard deviation (SD), and categorical variables as number and percentage of proportions. Baseline demographic characteristics were compared between patients who received *ALK* TKI treatment (*ALK* TKI subgroup) and who received only chemotherapy (only CT subgroup), using a Chi-square test or Fisher's exact test for categorical variables. Normally distributed continuous variables were tested by unpaired t-test or one-way analysis of variance test, and non-normally distributed variables by Kruskal Wallis test (Mann-Whitney U-test for two groups). Kaplan-Meier survival analysis and log-rank test were used to compare the difference in TTNT and OS time. Crude hazard ratio (HR) with 95% confidence intervals (CI) was calculated using Cox regression analysis. All statistical analysis and plots were produced using R (v.3.5.3, http://www.r-project.org). The R package called "survival" was utilized to perform the survival analysis [23, 24].

2.4. Ethical Considerations

The study was performed in accordance with the declaration of Helsinki and in compliance with applicable national laws. The study was approved by the Hospital District of Southwest Finland (T159/2018) and the Hospital District of Helsinki and Uusimaa (HUS/46/2018). The study was based on existing data and no interventions were performed. The pseudonymized research data was analyzed in the secure data analysis platform of HUS Data Administration to maximize the privacy of the study subjects.

3. Results

3.1. Patient Characteristics

A total of 1,260 patients were included in the study, of which 60 had *ALK* rearrangement (*ALK*-positive) based on the *ALK* IHC or FISH results. 76.7% (46/60) of *ALK*-positive patients were positive for *ALK* rearrangement using IHC staining and 45.0% (27/60) had a recorded positive FISH result. This indicates that the testing practices are variable and some patients (14/60; 23.3%) were not initially screened using the IHC staining method.

Baseline information was extracted for *ALK*-positive and *ALK*-negative (n=1,200, no *ALK* rearrangement recorded) patients (Table 1). At diagnosis, the mean age (standard deviation) of *ALK*-positive patients was 63.4 (13.8) years and 70.1 (9.9) years for *ALK*-negative patients. Besides being slightly younger, the majority of *ALK*-positive patients were female (60.0%; 36/60) and all had adenocarcinoma histology (100%; 60/60). In the *ALK*-negative group, 34.8% (417/1,200) were female and 34.1% (409/1,200) had adenocarcinoma histology. A total of 18.1% (217/1,200) of patients in the *ALK*-negative group had squamous cell histology and 39.1% (469/1,200) had unspecified histology based on the ICD-10-level data search. The most prevalent TNM stage in the *ALK*-positive group was IV (40.0%; 24/60) and the majority of patients had ECOG status 0 or 1 (80.0%; 48/60). In the *ALK*-negative group, TNM staging was unknown for 53.7% (644/1,200) of the patients, and stage IV was recorded for 18.4% (221/1,200). The most prevalent ECOG status in the *ALK*-negative group was 0–1 (45.8%;

550/1,200) but the number of patients with missing information was greater (27.5% vs. 6.7% in the *ALK*-positive group). The proportion of patients with no smoking history (never smokers) was ten times higher in the *ALK*-positive group than in the *ALK*-negative group (45.0% vs. 4.3%). The majority of the patients in the *ALK*-negative group were current smokers (61.8%; 741/1,200), whereas the corresponding number in the *ALK*-positive group was 23.3% (14/60).

Table 1. *Baseline characteristics in ALK-positive and ALK-negative patients.*

	***ALK*$^+$**		***ALK*$^-$**	
	(n=60)		**(n=1,200)**	
	n	Mean (SD)	n	Mean (SD)
Age (y)	60	63.4 (13.8)	1200	70.1 (9.9)
Alive at the end of FU	31	51.7%	324	27.0%
Gender	n	%	n	%
Male	24	40.0	784	65.2
Female	36	60.0	417	34.8
Histology	n	%	n	%
Adenocarcinoma	60	100.0	409	34.1
Squamous cell carcinoma	-	-	217	18.1
Unspecified	-	-	469	39.1
Other	-	-	105	8.7
TNM	n	%	n	%
I	11	18.3	134	11.2
II	4	6.7	62	5.1
III	15	25.0	139	11.6
IV	24	40.0	221	18.4
Unknown	6	10.0	644	53.7
ECOG	n	%	n	%
0–1	48	80.0	550	45.8
>1	8	13.3	320	26.7
Unknown	4	6.7	330	27.5
Smoking status	n	%	n	%
Current smoker	14	23.3	741	61.8
Former smoker	17	28.4	233	19.4
Never smoker	27	45.0	52	4.3
Unknown	2	3.3	174	14.5

y, years; FU, follow-up; SD, standard deviation; TNM, tumor-node-metastasis (AJCC, 8th edition); ECOG, Eastern Cooperative Oncology Group performance status; *ALK*, anaplastic lymphoma kinase rearrangement (present +; absent –).

3.2. Treatment Characterization

A total of 44 (73.3%) of the 60 *ALK*-positive patients received pharmacological anti-cancer treatment (Figure 1, Table 2). The majority of these patients (90.9%, 40/44) received CT regimens as a first-line treatment. Only four patients (9.1%) received *ALK* TKIs, namely crizotinib, in first-line treatment. Platinum-pemetrexed regimens were the most common chemotherapy agents administered in the first-line (Figure 1). In the second line, 3/25 (12.0%) patients received CT regimens and 21/25 (84.0%) received *ALK* TKI treatment. Nearly all patients treated with *ALK* TKI in the second-line received crizotinib (one patient received ceritinib) (Figure 1). Altogether, 7 patients were treated beyond the second-line (3L+), and they received altogether 9 individual treatment lines. The majority of the treatment lines in the 3L+ group were *ALK* TKI treatments (55.6%; 5/9) (crizotinib, ceritinib, alectinib, or lorlatinib) (Figure 1). In total, 78 treatment lines were recorded for the 44 patients receiving pharmacological anti-cancer treatment (Figure 1). Except in rare cases, the presence of *ALK* rearrangements in NSCLC tumors tends to occur independently of epidermal growth factor receptor (EGFR) or Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations [25]. Interestingly, our study cohort includes one patient with confirmed *ALK* rearrangement who was treated with EGFR inhibitors, gefitinib, and osimertinib, suggesting the concurrent presence of EGFR mutation.

We performed Kaplan-Meier analyses to calculate the median TTNT for CT vs. *ALK* TKI treatment regimens at different treatment lines (treatment lines 3 and 4 were grouped (3L+)) and all lines combined. Only *ALK* TKI and CT regimens were included in the analysis. Based on the Kaplan-Meier estimates, the median TTNT (95% CI) for CT irrespective of treatment line was 7.0 months (5.0–11.0) and for *ALK* TKI 11.0 months (5.0–35.0) (p=0.08) (Table 2, Figure 2a). Hazard ratios derived from Cox regression model were 1.93 (0.58–6.42), 1.79 (0.50–6.45), and 1.59 (0.93–2.71) for 1L, 2L, and in all lines combined, respectively. Statistical comparisons were not feasible in the 3L+ setting due to small sample size.

Besides pharmacological treatments, 40.0% (24/60) of all *ALK*-positive patients received radiation therapy for NSCLC. 22/24 (91.7%) of these patients received palliative radiation either targeted to primary tumor or metastases. Only two patients (8.3%; 2/24) received radiation therapy with curative intention. Altogether, 11 *ALK*-positive patients (18.3%)

underwent surgery for NSCLC. A total of 16 *ALK*-positive patients (26.7%) did not receive any pharmacological anti-cancer treatment during the study period. Out of these 16 patients 7 underwent surgery and 6 patients died within 6 months after the diagnosis (having a mean age of 74.8 years at diagnosis).

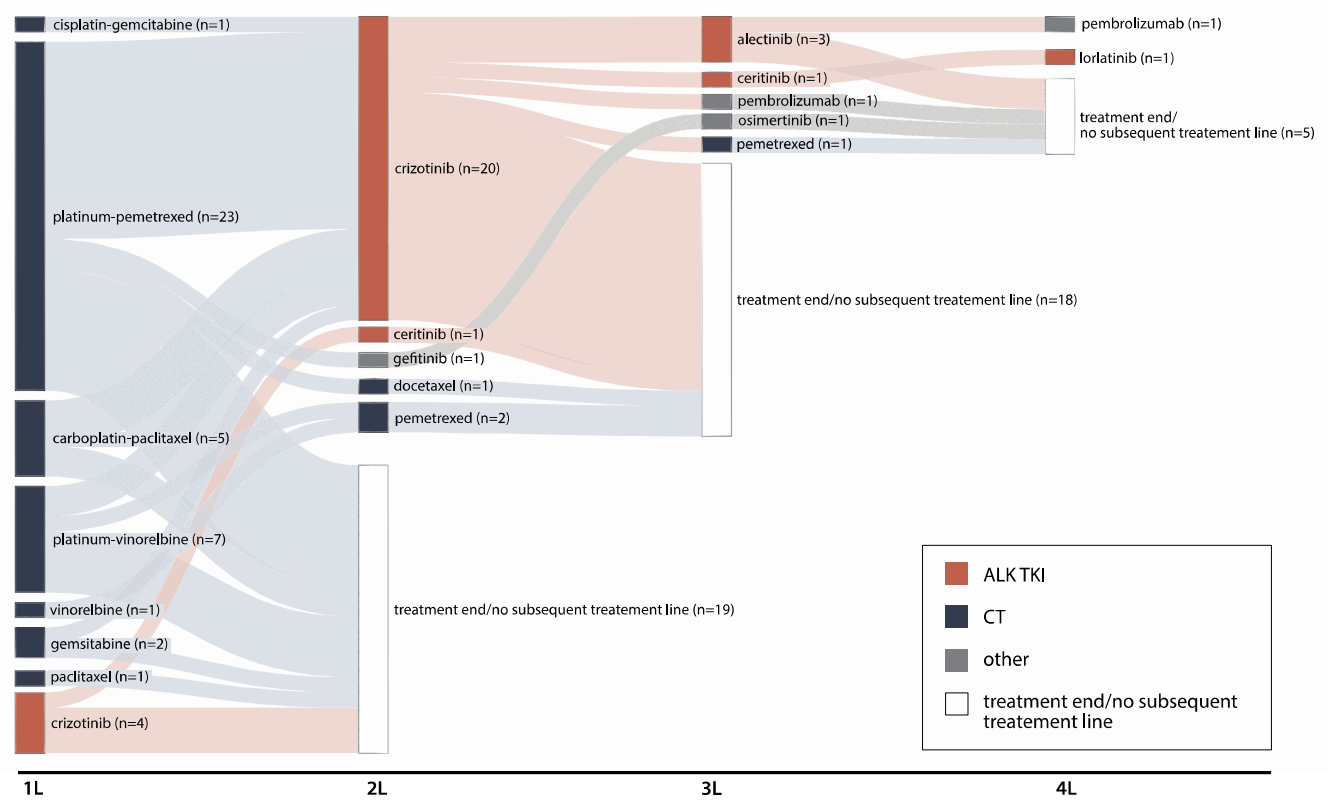
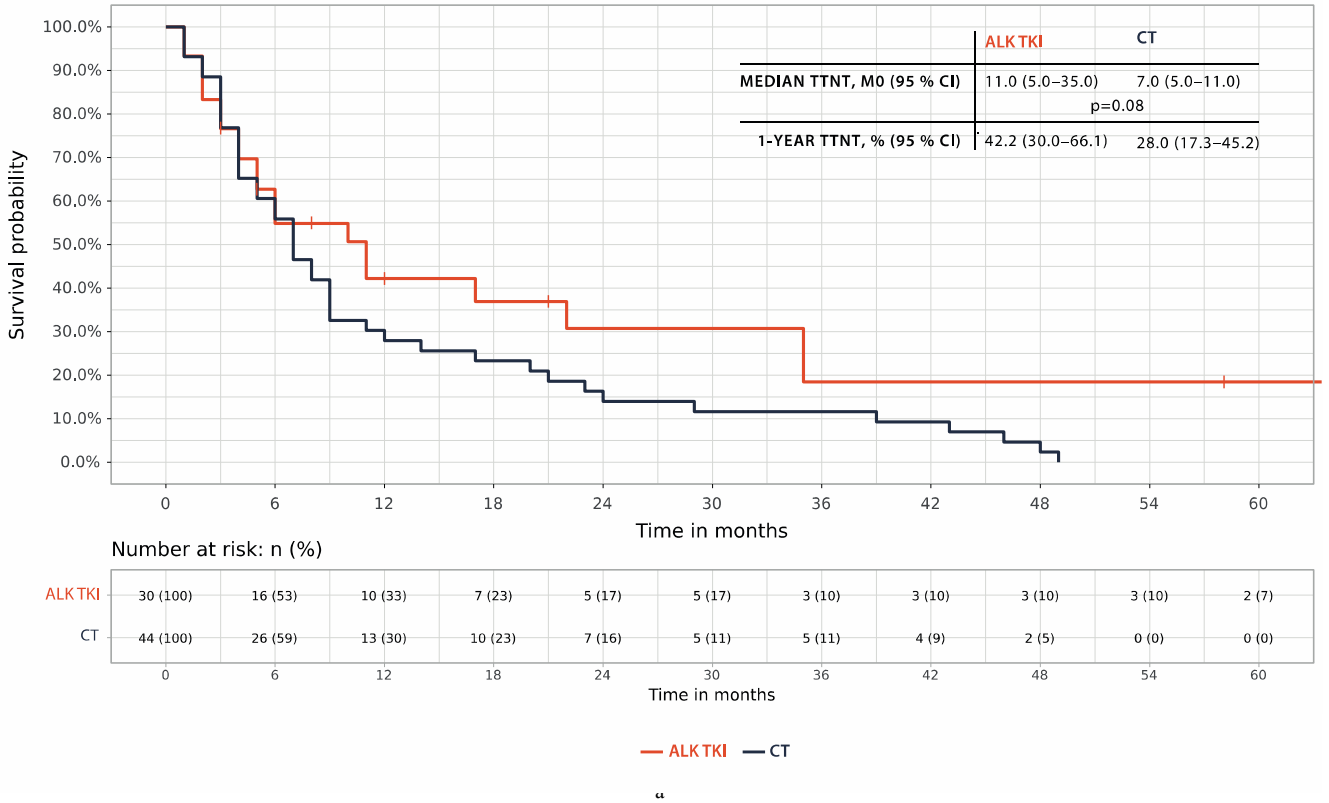


Figure 1. *Treatment patterns of ALK-positive patients across lines of therapy visualized as a Sankey diagram. Dark blue color represents CT regimens, red ALK TKI regimens, and grey other treatment regimens.*



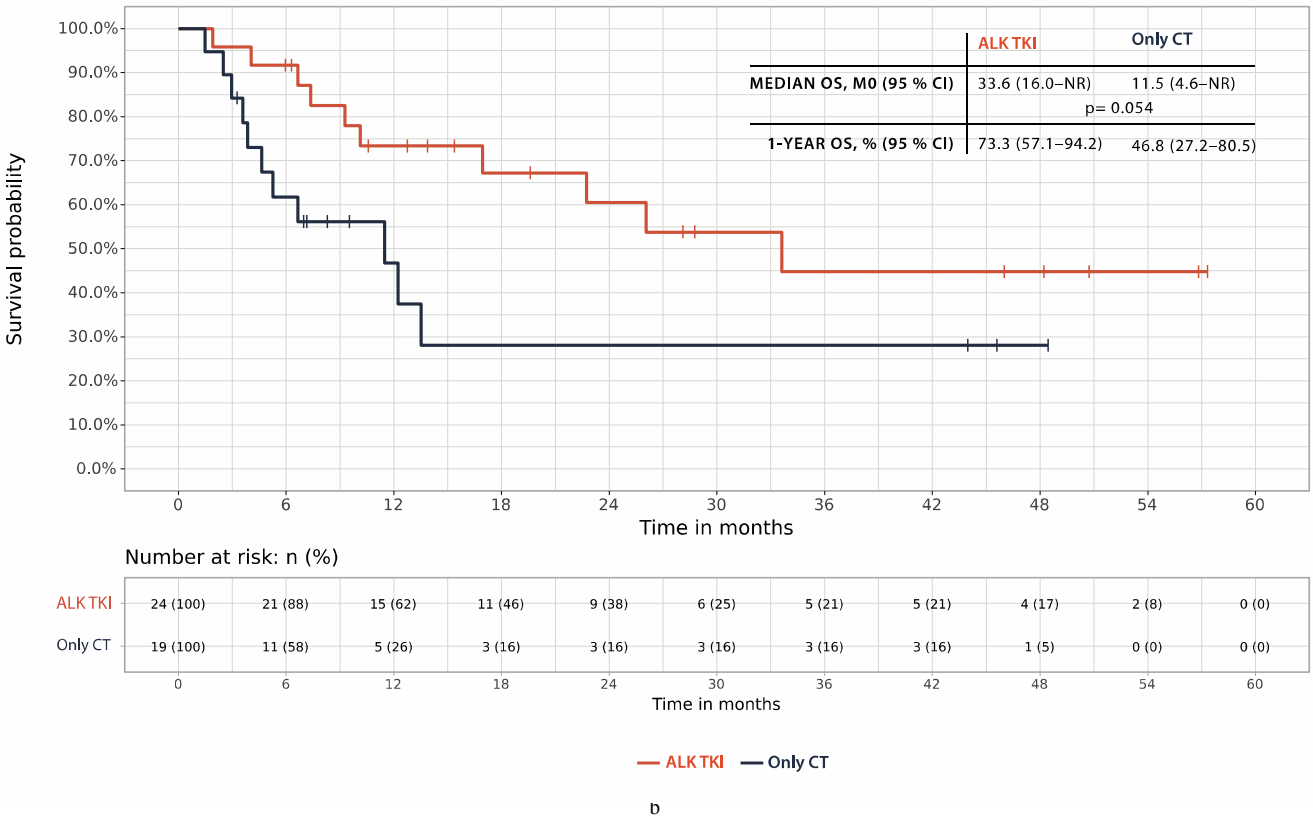


Figure 2. *TTNT and OS. a Time-to-next-treatment (TTNT) based on treatment regimen (ALK TKI or CT) and b Overall survival (OS) from diagnosis in ALK TKI and only CT subgroups analyzed by Kaplan-Meier method.*

Table 2. *CT and ALK TKI treatment regimens and TTNT per treatment line and all lines combine.*

	1L		**2L**		**3L+ [1]**		**ALL**	
	(n=44)		**(n=24)**		**(n=6)**		**(n=74)**	
Treatment regimen[2]	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
CT	40	90.9	3	12.5	1	16.7	44	59.5
ALK TKI	4	9.1	21	87.5	5	83.3	30	40.5
TTNT	*median*	*95% CI*	*median*	*95% CI*	*median*	*95% CI*	*median*	*95% CI*
CT	7.0	4.0–9.0	9.0	3.0–NR	21.0	NR	7.0	5.0–11.0
ALK TKI	12.5	1.0–NR	11.0	6.0–NR	4.0	2.0–NR	11.0	5.0–35.0
	p=0.20		p=0.40		*not feasible*		p=0.08	

[1]Including third and later treatment lines. [2]Other treatments (gefitinib, osimertinib and pembrolizumab) excluded. CI, confidence interval; NR, not reached; L, treatment line; CT, chemotherapy; *ALK* TKI, *ALK* tyrosine kinase inhibitor; TTNT, time-to-next treatment.

3.3. Overall Survival

As the number of patients receiving only *ALK* TKI treatment during the follow-up period was very low (n=4) we assessed the OS of *ALK*-positive patients in the *ALK* TKI subgroup (receiving >1 regimen of *ALK* TKI, n=24) vs. only CT subgroup (receiving only CT regimens, n=19). The Kaplan-Meier method was used to estimate the median OS from diagnosis. The median OS (95% CI) in the *ALK* TKI subgroup was 33.6 months (16.0NR) and in the only CT subgroup 11.5 months (4.6–NR) (log-rank p=0.054). The hazard ratio derived from a Cox regression model showed a trend approaching significance (HR=2.30 (0.96–5.48, p=0.061) (Figure 2b).

In addition, we compared the patient characteristics between the subgroups (*ALK* TKI vs. only CT) (Table 3). The compared characteristics were mean age at diagnosis, gender, TNM, ECOG, and smoking status. The only characteristic reaching statistical significance was smoking status (p=0.044). The most prevalent smoking status in the *ALK* TKI subgroup was “never smoker” (66.7% vs. 27.8% in the only CT subgroup) as in the only CT subgroup it was “former smoker” (38.9% vs. 16.7% in the *ALK* TKI subgroup). In addition, the TNM stage difference between the subgroups was borderline significant (p=0.05). This indicates that the two subgroups had highly similar baseline characteristics and the statistical trend favoring the *ALK* TKI subgroup for superior OS was likely due to the treatment received.

Table 3. *Comparison of baseline characteristics among ALK-positive patients treated with ALK TKI or only CT.*[1]

	***ALK* TKI (n=24)**		**Only CT (n=19)**		***p-value***
	Mean	***SD***	***Mean***	***SD***	
Age (y)	62.2	13.1	63.7	13.2	0.633
Gender	*n*	*%*	*n*	*%*	0.864
Male	7	29.2	6	31.6	
Female	17	70.8	13	68.4	
TNM	*n*	*%*	*n*	*%*	0.050
I	1	4.3	1	6.2	
II	0	0	3	18.8	
III	6	26.1	7	43.8	
IV	16	69.6	5	31.2	
ECOG	*n*	*%*	*n*	*%*	0.113
0–1	21	91.3	12	70.6	
>1	2	8.7	5	29.4	
Smoking status	*n*	*%*	*n*	*%*	0.044
Current smoker	4	16.7	6	33.3	
Former smoker	4	16.7	7	38.9	
Never smoker	16	66.7	5	27.8	

[1]Patients having missing information excluded from the analysis per missing category (TNM: *ALK* TKI [1], only CT [3]; ECOG: *ALK* TKI [1], CT [2]; smoking status: CT [1]).

y, years; SD, standard deviation; TNM, tumor-node-metastasis (AJCC, 8th edition); ECOG, Eastern Cooperative Oncology Group performance status; *ALK* TKI (subgroup) patients received one or more lines of *ALK* TKI treatment; Only CT (subgroup), patients received only CT.

4. Discussion

Finland possesses a long history of management and usage of nationwide registers (e.g., prescriptions, hospital and primary care, medical births, and causes of death) in real-world evidence research. The field of oncology is heading towards increasingly personalized medication and treatment options that are designed for a subset of patients, e.g., patients harboring a specific genomic alteration. As a result, the need to extract more complex clinical variables from electronic health records to perform register-based research has also increased. Such information is usually recorded as a narrative text rather than in the prespecified structural fields of electronic health records. This makes extraction of the relevant data more challenging, as has been discussed in a recent Finnish retrospective study on adenocarcinoma patients using a similar data source [26]. The data lakes of the Finnish University Hospitals are the repositories in which data from electronic health records of specialty care are gathered.

We performed this retrospective RWE study by combining data from two different data lakes. To our knowledge, this is the first research project in Finland that utilizes data extracted from two separate University Hospital data lakes as the main data source. As the number of *ALK*-positive patients in the cohort was low, it allowed us to perform manual quality checks and complement the algorithm-based data extraction with manually extracted data when it was necessary. At the same time, it showed that even if the automated data extraction is a powerful tool for register studies it still has limitations (e.g., the amount of missing data) and, on many occasions, needs a human-in-the-loop approach to supplement data with sufficient quality.

Our study design differed from the majority of the retrospective studies addressing the treatment patterns of *ALK*-positive NSCLC as we included all *ALK*-positive patients irrespective of disease stage or treatment received. The aim was to describe the treatment landscape of the entire *ALK*-positive NSCLC population as a whole using two University Hospital data lakes as a primary data source. *ALK*-positive NSCLC patients represent unique clinicopathological features when compared to the general NSCLC population; younger age at diagnosis, history of never or light smoking, and adenocarcinoma histology of the tumor [6]. Our study population of *ALK*-positive patients meets these characteristics in terms of smoking history and tumor histology, but the patients were clearly older (mean age 63.4 years) compared to earlier reports. It is important to also notice that in our study the patients who did not harbor *ALK* rearrangement were relatively older (mean age 70.1) than reported in observational settings earlier [6].

There is a relatively short time period over which *ALK* TKI treatment has been widely available for the treatment of *ALK*-positive NSCLC in Finland, since the first *ALK* TKI crizotinib only became reimbursable as a second-line treatment in mid-2014. Thus, the study period (2013–2018) reflects the transition time when the treatment practices started to shift towards the wider usage of targeted agents. It is evident, that the treatment armamentarium for *ALK*-positive patients has significantly expanded after the time period of this study, during the last four years. From the initial cohort of 60 *ALK*-positive patients, 44 received first-line pharmacological treatment for NSCLC, and over 90% of those 44 received chemotherapy regimens. This reflects well the treatment recommendations and the reimbursement status of the *ALK* targeted compounds prevailing at the time with most of the patients receiving treatment with a platinum compound in combination with pemetrexed as first-line treatment [22, 27]. Altogether 84.0% (21/25) of the patients receiving second-line treatment were treated with an *ALK* TKI and of these *ALK* TKI treated patients

all except one received crizotinib. In third or later lines, next-generation *ALK* TKIs (alectinib, ceritinib, and lorlatinib) were also received (altogether four patients, one received ceritinib and lorlatinib). This is in line with the fact that the only *ALK* TKI with reimbursement status at the time was crizotinib, which was reimbursable only as a second-line treatment. Due to the relatively high costs of targeted treatments, the reimbursement status largely determines the use of these compounds in Finland. Thus, patients receiving next-generation *ALK* TKIs during the study period are most probably patients in early access programs.

In a phase III clinical trial on patients who had received one prior platinum-based regimen, crizotinib showed median progression-free survival (PFS) of 7.7 months vs. 3.0 months in patients receiving standard chemotherapy (either pemetrexed or docetaxel) (HR 0.49; 95% CI 0.37–0.64, p<0.001) [10]. In treatment-naive patients receiving crizotinib, the median PFS was 10.9 months vs. 7.0 months in patients receiving platinum-based chemotherapy (HR 0.45; 0.35–0.60, p<0.001) [11]. Real-world data sources have historically provided limited access to information about the occurrence of disease progression. As a result, PFS, a standard effectiveness outcome measure in oncology, has been calculated using proxies such TTNT. In this study, we assessed TTNT for CT and *ALK* TKI regimens per line of treatment and all lines combined. Due to the low number of patients, we did not assess the TTNT by individual treatment regimen. In the analysis combining all treatment lines (1L, 2L, and 3L+), median TTNT was longer during *ALK* TKI treatment compared to CT treatment (11.0 months vs. 7.0 months), but the result didn't reach statistical significance (p=0.08). An extensive systematic literature review assessing the outcomes of patients treated with *ALK* inhibitors both in clinical trials and in observational studies, especially when *ALK* inhibitor was followed by another *ALK* inhibitor, was recently conducted [28]. In the observational studies, median PFS of *ALK* inhibitor-naive patients (with or without prior chemotherapy) ranged from 7 months to 17.7 months (measured from diagnosis of advanced NSCLC) according to the review [28]. In our cohort, median TTNT during first- and second-line *ALK* TKI regimens (representing *ALK*-naive patients, except one patient who received ceritinib in the second-line after crizotinib) was 12.5 months and 11.0 months, respectively.

Median OS has been consistently reported to be around 50 months from the time of diagnosis of metastatic disease in several observational studies of *ALK* inhibitors used in sequence [29–31]. In addition, there are currently several examples of median OS being reported as "not reached" in studies of the full sequence of an *ALK* inhibitor after an initial *ALK* inhibitor [28]. This is not surprising given that only relatively recently have multiple *ALK* inhibitors become available. It is worth noticing that the study design, population, and method of reporting the results may vary substantially between different observational studies, which means that comparison between these studies needs to be treated with caution. A Canadian retrospective study reported a median OS of 31.6 months (from NSCLC diagnosis) in a patient cohort of 49 patients in whom crizotinib treatment had failed [29]. This cohort included patients who received crizotinib in the first-line (39.0%), second-line (23.0%), or third-line or beyond (33.0%). Treatment patterns prior to crizotinib were not reported but post-crizotinib treatment lines included different CT regimens and ceritinib. Thus, the Canadian cohort had similar OS results as were observed in this study (33.6 months in the *ALK* TKI subgroup). In an exploratory analysis, patients who received crizotinib followed by ceritinib had a median OS of 51.0 months compared to 18.1 months in patients who did not receive ceritinib after crizotinib treatment. This indicates that sequential use of *ALK* inhibitors is likely to be clinically beneficial to patients [29]. A very low number of patients receiving second-generation *ALK* inhibitors in our study (n=5) did not allow further characterization of outcomes in a setting of second-generation *ALK* inhibitor following crizotinib treatment.

After the next-generation inhibitors emerged as a treatment option in the first-line setting the paradigm of selecting between the 'historical' sequential treatment approach (first-generation TKI followed by next-generation compound) and strategy with upfront use of second-generation inhibitors has risen [32]. As the efficacy data reported in clinical trials are from the initiation of the second-generation *ALK* inhibitors only, it does not provide information on the impact of the full sequence of *ALK* inhibitors on patient survival. The lack of comparative survival outcomes between the two different treatment strategies has hampered the elucidation of the most beneficial strategy for patients in the long term. The sum of PFS values from studies with different *ALK* TKI compounds used in different treatment lines has provided a crude estimate of the theoretical benefit between several inhibitor sequences. Even if the approach is not supported statistically, it suggests that earlier use of second-generation compounds is associated with major improvements in PFS, control of intracranial disease, and tolerability [32, 33]. Since no prospectively designed studies have evaluated this question to date, retrospective studies are currently very valuable in providing such information. Still, a growing need exists for further research, especially head-to-head comparative trials, to directly compare *ALK* inhibitor sequences and to understand the outcomes of second-generation-led sequences.

5. Conclusions

The results of this two-center retrospective study suggest that *ALK*-positive patients benefit from treatment with *ALK*-targeted agents, even if the patient population in clinical practice is much more heterogeneous compared to clinical trials and patients have traditional chemotherapy administered prior to initiation of *ALK* TKIs. The introduction of next-generation *ALK* TKIs to clinical practice has rapidly expanded the treatment armamentarium for *ALK*-positive NSCLC, enabling sequential treatment with several targeted *ALK* agents providing improved treatment outcomes. Still, the optimal sequencing of different *ALK* agents awaits further investigations.

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Conflicts of Interest

The authors declare that they have no competing interests.

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