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ORIGINAL ARTICLE

Use of ALK-tyrosine kinase inhibitors (ALK TKI) in clinical practice, overall survival, and treatment duration – a Swedish nationwide retrospective study

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ABSTRACT

Background: The real-world treatment and outcomes of patients with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer treated with ALK Tyrosine Kinase Inhibitor (TKI) drugs in Sweden is not well described.

Material and methods: A retrospective population-based cohort study was conducted using Swedish national registers. All patients with a filled prescription for an ALK TKI between January 2012 and October 2020 were included. The sequencing of ALK TKI and duration of treatment (DOT) were described, and overall survival (OS) was estimated using the Kaplan–Meier method. Patients were stratified based on treatment with frontline chemotherapy, presence of CNS metastases prior to the first ALK TKI, and generation of ALK TKI agent.

Results: Among the total of 579 patients, 549 (95%) underwent a therapy sequence in line with current clinical practice with 204 (37%) patients receiving frontline chemotherapy. Single-line ALK TKI was given to 366 patients (crizotinib: 211; alectinib: 146; ceritinib: 9), whereas 128 patients received two different ALK TKI (frontline crizotinib: 100, alectinib: 24, ceritinib: 4); 40 patients received three lines and 15 patients four ALK TKI lines or more. With frontline chemotherapy, the mean (standard deviation) DOT was 1.07 (1.25) years for the entire TKI therapy sequence compared to 1.23 (1.28) years with frontline ALK TKI. The median (95% confidence interval) OS was 1.83 (1.48–2.13) years for the entire cohort, 1.44 (0.89–1.98) years for patients given frontline chemotherapy, and 2.02 (1.60–2.58) years for patients given frontline ALK TKI.

Conclusion: This study provides a unique overview of the patient population treated with ALK TKI in Sweden and reveals the treatment patterns applied in real clinical practice. More research is needed when longer follow-up data are available for later-generation ALK TKI, to fully understand ALK TKI sequencing and its effect on patient survival in a real-world setting.

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KEYWORDS
NSCLC; ALK; overall survival; treatment duration

Background

One of the first oncogenic drivers discovered in lung adenocarcinoma is the genetic rearrangement in Anaplastic Lymphoma Kinase (*ALK*), which defines about 5% of non-small cell lung cancer (NSCLC) cases [1].

ALK-positive patients are typically younger than the average NSCLC patient, predominantly nonsmokers, and frequently women [2]. A particular feature of metastatic ALK-positive NSCLC is the high tendency of disease spread to the brain. Central nervous system (CNS)-metastases affect 24%–42% of patients with the risk increasing over time, reaching nearly 60% after 3 years [3]. The cumulative incidence of brain-spread is higher in ALK positive NSCLC, potentially markedly higher than in ROS1- and RET-rearranged NSCLC [4].

For over a decade, ALK Tyrosine Kinase Inhibitors (TKI) have shown remarkable benefits in the management of ALK-positive NSCLC compared to conventional chemotherapy [5–7]. First-generation ALK TKI crizotinib has been the standard of care (SoC) for several years until second-generation drugs, particularly alectinib, but also ceritinib and brigatinib, demonstrated superior efficacy over crizotinib, including notable CNS-penetration. Alectinib was established as the new SoC in the frontline setting whereas the highly potent CNS-penetrable and resistance-battling drug lorlatinib became the first third-generation agent to be approved.

According to international recommendations [8,9] and the latest available Swedish treatment guidelines [10], patients with ALK-positive NSCLC should first and foremost be offered treatment with ALK-inhibitors based on their superiority over standard platinum-based chemotherapy in untreated disease. Sequencing of TKI agents is an integral part of the treatment of ALK-positive NSCLC. Nearly, all patients who initially respond to ALK-inhibitors experience disease progression

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within 1–3 years of therapy due to the molecular evolution of their tumors rendering the targeting agent ineffective. The subsequent choice of drug will depend on which ALK TKI that had already been used and is dictated by individual drug approval/reimbursement status, therapy guidelines, and importantly the tumor molecular resistance mechanisms. This clinically based framework, alongside our growing understanding of molecular tumor biology, defines today several conventional sequencing approaches which array ALK TKI in the order that exerts the highest likelihood of patient benefit.

To our knowledge, this is the first population-wide real-world study investigating the use of ALK TKI in Swedish patients. It includes all patients in Sweden treated with ALK TKI between January 2012 and October 2020 and retrospectively observes treatment patterns, treatment duration, and overall survival (OS) for ALK-positive NSCLC patients.

Material and methods

Data sources

This study used patient-level data from the National Cancer Register, the National Patient Register, the Cause of Death Register, and the Prescribed Drug Register, which were linked using unique personal identifiers. All data were obtained from the Swedish National Board of Health and Welfare. The National Cancer Register provides specific information regarding primary tumors, such as clinical and morphological diagnosis. Information on diagnoses, hospitalizations, and outpatient specialist visits, as well as surgical and nonsurgical procedures, was obtained from The National Patient Register. The Prescribed Drug Register contains data on all prescriptions filled at pharmacies, including dispensation date and pack-size. The Cause of Death Register provides confirmed dates of death. Due to mandatory reporting and the coverage of the entire Swedish population, the national registers have a very high level of completeness.

Patient identification

All adult patients (age $\geq$18 years) were identified and included in the study population if they had at least one filled prescription of crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib (ATC codes: L01ED01, L01ED02, L01ED03, L01ED04, L01ED05) registered in the Prescribed Drug Register between 01 January 2012 and 31 October 2020. All dispensed prescriptions of ALK TKI before their respective European Medicines Agency (EMA) approval date (regardless of indication) were excluded. The index date for each patient was defined as the first identified prescription date of any of the above-mentioned therapies. Crizotinib was approved for reimbursement in Sweden in March 2014 (EMA October 2012), followed by ceritinib in December 2015 (EMA May 2015) and alectinib in November 2017 (EMA February 2017). Brigatinib was reimbursed in December 2018 (EMA November 2018) and lorlatinib in September 2019 (EMA May 2019).

Chemotherapy

Patients were stratified into those who have or have not received frontline chemotherapy in the 2 years prior to the first ALK TKI being initiated.

As only prescription drugs are included in the Prescribed Drug Register, chemotherapy cannot be identified with full certainty from the available data. Intravenous (IV) chemotherapies were defined based on procedure codes and recorded healthcare visits registered in the National Patient Register. The study definition of chemotherapy is that one or more procedure codes covering administration of IV chemotherapy treatment and/or ICD-10 codes for chemotherapy treatment are registered for the patient (see Table S1 in Supplementary material). Alternatively, chemotherapy treatment is also assumed when patients have had at least one outpatient visit to an oncology department within every 4-week period for $\geq$90 days without having received any ALK TKI treatment during this period. Chemotherapy was measured as a binary variable. Since treatment cycles and duration of treatment (DOT) is not captured, chemotherapy treatment was defined as 'one chemotherapy' if several chemotherapy courses were identified subsequently. Chemotherapy is assumed to have stopped when other treatments start, and potential chemotherapy administered later in the drug sequence or at the conclusion of therapy was not captured.

CNS metastases

Registered CNS-metastases were identified based on brain metastases diagnosis code according to the International Classification of Disease version 10 (ICD-10) in the National Patient Register and the Cancer Register (ICD-10 code C79.3). CNS-metastases identified up to 2 years prior to first ALK TKI served as subgroup identifier in OS analyses. In general, the registration of metastases in nationwide registers is incomplete and likely only a subgroup of patients with CNS metastases could be identified; results should be seen as exploratory.

Sequencing

The following prespecified sequences were of interest for this study:

- One ALK TKI
  - crizotinib
  - alectinib
  - ceritinib
- Two different ALK TKI
  - crizotinib + alectinib/ceritinib/brigatinib
  - alectinib + ceritinib/brigatinib/lorlatinib
  - ceritinib + alectinib/brigatinib/lorlatinib
- Three different ALK TKI
  - crizotinib + alectinib + ceritinib/brigatinib/lorlatinib
  - crizotinib + ceritinib + alectinib/brigatinib/lorlatinib
  - crizotinib + brigatinib + alectinib/lorlatinib

- alectinib + brigatinib + lorlatinib
- alectinib + lorlatinib + ceritinib/brigatinib
- ceritinib + alectinib + brigatinib/lorlatinib

- At least four different ALK TKI

Furthermore, some of the above sequences were summarized into cohort groups, based on drug generation:

- Group A: crizotinib + any second generation ALK TKI
- Group B: crizotinib + any second generation ALK TKI + any second generation ALK TKI
- Group C: crizotinib + any second generation ALK TKI + lorlatinib
- Group D: Any second generation ALK TKI + any second generation ALK TKI

Statistical analysis

Data management and statistical analysis was performed using R version 4.0. Results are presented for groups with five or more individuals only, to ensure that patients are not identifiable.

Patient characteristics

Patient characteristics were measured at treatment start (index), that is, the prescription fill date of the first ALK TKI. Patient comorbidity profile (Charlson-Quan Comorbidity Index) was assessed in the 5 years prior to index date. CNS metastases were identified over the whole study period.

ALK TKI sequencing

The number of patients per prespecified sequence of ALK-inhibitor drugs was reported. Patients were only attributed to one sequence. All patients not included in one of the specified sequences were excluded from further analyses but described in terms of administered treatments and their sequencing.

Treatment duration

The number of years with filled prescriptions during the follow-up period (treatment duration) was calculated using the prescription fill date, the number of packs and their size, and the recommended daily dose, according to the Swedish directory of approved medicines (Pharmaceutical Specialties in Sweden (FASS)) [11]. Medication stockpiling, that is, the accumulation of prescription medication for later use, was allowed. Patients were defined as persistent as long as they filled prescriptions of their ongoing treatment regardless of the time elapsed between prescriptions. Time on treatment calculations assumed that patients adhered to treatment during persistence, without any interruptions. Patients were defined as nonpersistent from the last day of supply or from the point of new treatment initiation.

Treatment duration was thus defined as the time between first filled prescription until nonpersistence and was reported as the mean length of treatment (years) for the entire sequence, and per individual ALK TKI. Results were stratified by sequences and by cohort groups.

Overall survival

Time-to-event analysis, the event being all-cause death, was used to estimate the probability of survival during the follow-up period, that is, from index date until death or end of study period. Results were measured as Kaplan-Meier estimates (survival function, 95% confidence interval (CI), and number of patients at risk). Results were stratified by frontline chemotherapy, presence of CNS metastases as well as sequences with one ALK TKI and cohort groups.

Results

Patient characteristics

Between 01 January 2012 and 31 October 2020, 579 NSCLC patients were treated with at least one ALK TKI in Sweden (Table 1). At least one prescription of crizotinib had been filled by 67% (389) of patients, alectinib by 48% (279), ceritinib by 19% (112), lorlatinib by 9% (55), and brigatinib by 8% (44) of patients. Ninety-five percent ($n = 549$) of all patients could be attributed to one of the pre-defined sequences (study population), the remaining 5% (30) are described below but are excluded from the analyses as sequencing deviates from current clinical practice with few patients per sequence. The median follow-up, from first ALK TKI until death or end of study period, for patients included in the study population, was 1.08 (SD: 1.43) years. Within the study population, frontline chemotherapy was identified for 37% (204) of patients.

In general, patient characteristics were similar across stratifications. Patients who received frontline chemotherapy had

Table 1. Patient characteristics.

	All patients ($N = 579$)	Study population[a] ($N = 549$)	No chemo before first ALK TKI, study population ($N = 345$)	Chemo before first ALK TKI, study population ($N = 204$)
Age at index, mean (SD)	62.92 (13.67)	63.13 (13.70)	63.08 (13.96)	63.24 (13.28)
Gender, % (*n*)				
Female	54.92% (318)	54.83% (301)	54.78% (189)	54.90% (112)
Male	45.08% (261)	45.17% (248)	45.22% (156)	45.10% (92)
Charlson Comorbidity Index score, mean (SD)	1.92 (0.83)	1.91 (0.82)	1.84 (0.84)	2.03 (0.78)
Registered CNS metastases before index date, % (*n*)	6.91% (40)	6.92% (38)	4.64% (16)	10.78% (22)
Registered CNS metastases after index date, % (*n*)	16.41% (95)	15.66% (86)	15.65% (54)	15.69% (32)

[a]Patients that could be attributed to one of the predefined sequences.
Abbreviations: SD, standard deviation.

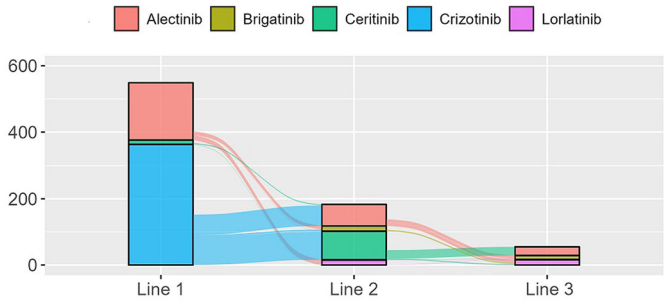

Figure 1. Sankey plot of ALK TKI sequencing up until three lines of treatment.

a slightly higher mean comorbidity index (2.03 vs. 1.84) and higher prevalence of registered CNS metastases before index date (11% vs. 5%) compared to those who were treated with ALK TKI in front line.

ALK TKI sequencing

Predefined sequences

Of the 549 included patients, 366 patients received only one ALK TKI (141 with frontline chemotherapy); 211 received only crizotinib (95 with frontline chemotherapy), 146 were treated with alectinib (41 with frontline chemotherapy), and 9 patients received ceritinib (5 with frontline chemotherapy). In total, 128 patients were treated with two different ALK TKIs of which 100 started on crizotinib (29 with frontline chemotherapy), 24 started on alectinib (10 with frontline chemotherapy), and 4 started on ceritinib (2 with frontline chemotherapy). Forty patients received three lines of ALK TKI (15 with frontline chemotherapy) whereas 15 patients received four or more ALK TKI lines (7 with frontline chemotherapy) see Figure 1 and Table S2 in Supplementary material.

Unconventional ALK TKI sequencing

The predefined sequences reflect expectations of successive treatment choices in clinical practice based on the mode-of-action properties of individual TKI and their molecular resistance profiles. Observed sequencing outside of these predefined patterns included the following:

- Rechallenge with the first or second ALK TKI (crizotinib, alectinib, ceritinib, or brigatinib) after a different ALK TKI had been used in second or third line ($n = 15$)
- Use of ALK TKI outside of indications approved during study period (n=11); including lorlatinib as first line or second line after crizotinib, and brigatinib used as first line ALK TKI
- Crizotinib in second line after any later generation ALK TKI (n=4)

Treatment duration

The mean duration per individual ALK TKI treatment varied but was below 1 year for most treatments in the cohort groups (Table 2). The duration of the total treatment sequence increased with the numbers of treatments included in the sequence. The total duration of the crizotinib + alectinib sequence ($n = 42$) was higher than other two-ALK-TKI sequences. With frontline chemotherapy, mean length of total ALK TKI treatment (entire sequence) was 1.07 years (SD: 1.28) compared to 1.23 years (SD: 1.28) if the therapy sequence began with an ALK TKI. Frontline chemotherapy generally decreased duration of ALK TKI treatment, see Table S4 in Supplementary material.

Overall survival

Overall median survival from first ALK TKI treatment was 1.83 years (95% CI: 1.48, 2.13), see Figure 2a. Among patients with at least 1 year of available data (i.e., inclusion before October 2019, 1 year prior to end of study period), 64% (284) were still alive at year one, and among patients with follow-up of at least 5 years, 16% (20) were still alive at year five (data not shown). Patients without first-line chemotherapy lived longer on average; median survival was 2.02 (95% CI: 1.60, 2.58) compared to 1.44 (95% CI: 0.89, 1.98) years for patients with frontline chemotherapy (Figure 2b). Median survival for patients with CNS metastases before treatment start was 0.61 (95% CI: 0.34, –[1]) compared to 1.94 (95% CI: 1.52, 2.26) for patients without registered CNS-diagnosis (Figure 2c).

Median survival among the patients treated with single line ALK TKI was 0.71 years (95% CI: 0.60, 0.89) for crizotinib, not reached for alectinib, and 0.59 years (95% CI: 0.40, –[1]) for ceritinib. Among patients receiving crizotinib as first-line therapy followed by one (Group A) or two (Group B) second generation ALK TKI, the median survival was 2.09 years (95% CI: 1.67, 2.78) and 3.14 years (95% CI: 2.51, –[1]), respectively. For cohort groups C and D median survival was not reached (Figure 3b).

Among patients treated with two ALK-TKI, median survival was longest, 4.34 years (95% CI: 3.35, –[1]), for those treated with crizotinib + alectinib, 1.27 years (95% CI: 1.14, 1.90) for crizotinib + ceritinib, 1.26 years (95% CI: 0.64, –[1]) for alectinib + brigatinib and not reached (95% CI: 1.09, –[1]) for alectinib + lorlatinib. Among patients treated with three ALK-TKI, median survival was 5.41 years (95% CI: 5.41, –[1]) for those treated with crizotinib + alectinib + lorlatinib, 3.10 years (95% CI: 2.41, –[1]) for crizotinib + ceritinib + alectinib and not reached for crizotinib + alectinib + brigatinib (Figure 3a).

Discussion

This retrospective study used data from nationwide Swedish administrative health registers and included all patients treated with an ALK TKI between January 2012 and October 2020. Data from 579 patients were analyzed identifying 549 patients who received conventional sequential ALK TKI therapy and were thus included in the study population.

The reported patient characteristics were in line with previously published data for this population [12]. However, the share of patients with CNS metastases at treatment start was

Table 2. Duration of ALK TKI treatment (presented for sequences/groups with ≥ 5 patients).

Definition	Number of patients, % (*n*) (*N* = 549)	Treatment length in years, mean (SD, median, min, and max)			
		Total sequence	ALK TKI 1	ALK TKI 2	ALK TKI 3
Crizotinib	38.43% (211)	0.62 (1.04, 0.24, 0.01, 6.74)	0.62 (1.04, 0.24, 0.01, 6.74)	–	–
Alectinib	26.59% (146)	0.88 (0.83, 0.49, 0.02, 2.87)	0.88 (0.83, 0.49, 0.02, 2.87)	–	–
Ceritinib	1.64% (9)	1.06 (1.20, 0.38, 0.08, 2.97)	1.06 (1.20, 0.38, 0.08, 2.97)	–	–
Crizotinib + alectinib	7.65% (42)	2.53 (1.33, 2.59, 0.31, 4.97)	1.10 (0.93, 0.84, 0.08, 4.40)	1.43 (1.09, 1.32, 0.02, 2.94)	–
Crizotinib + ceritinib	10.2% (56)	1.20 (0.90, 0.92, 0.14, 3.41)	0.68 (0.54, 0.57, 0.08, 2.43)	0.52 (0.71, 0.28, 0.01, 2.88)	–
Alectinib + brigatinib	1.82% (10)	1.10 (0.49, 1.04, 0.56, 2.03)	0.63 (0.47, 0.42, 0.15, 1.45)	0.47 (0.35, 0.35, 0.15, 1.08)	–
Alectinib + lorlatinib	2.37% (13)	1.04 (0.61, 0.85, 0.13, 1.99)	0.70 (0.63, 0.69, 0.08, 1.91)	0.34 (0.31, 0.25, 0.03, 1.05)	–
Crizotinib + alectinib + brigatinib	1.09% (6)	3.29 (1.49, 3.37, 1.23, 5.73)	1.35 (1.35, 0.87, 0.49, 4.08)	1.23 (0.83, 1.43, 0.15, 2.08)	0.71 (0.55, 0.65, 0.08, 1.50)
Crizotinib + alectinib + lorlatinib	1.46% (8)	3.12 (1.25, 2.87, 1.42, 4.78)	1.28 (1.15, 1.10, 0.08, 3.39)	1.38 (0.68, 1.33, 0.22, 2.47)	0.45 (0.35, 0.32, 0.08, 1.05)
Crizotinib + ceritinib + alectinib	3.1% (17)	2.72 (1.50, 2.45, 0.27, 5.80)	0.85 (0.51, 0.81, 0.15, 2.03)	1.09 (1.03, 0.79, 0.08, 3.52)	0.79 (0.94, 0.29, 0.01, 2.82)
Group A: crizotinib + any second generation ALK TKI	18.21% (100)	1.80 (1.30, 1.39, 0.14, 4.97)	0.88 (0.77, 0.66, 0.08, 4.40)	0.92 (0.99, 0.50, 0.01, 2.94)	–
Group B: crizotinib + any second generation ALK TKI + any second generation ALK TKI	4.37% (24)	2.83 (1.46, 2.60, 0.27, 5.80)	0.99 (0.79, 0.87, 0.15, 4.08)	1.10 (0.95, 0.92, 0.08, 3.52)	0.74 (0.83, 0.36, 0.01, 2.82)
Group C: crizotinib + any second generation ALK TKI + lorlatinib	2.55% (14)	2.67 (1.13, 2.34, 1.29, 4.78)	1.15 (0.92, 0.96, 0.08, 3.39)	1.13 (0.73, 1.22, 0.08, 2.47)	0.38 (0.36, 0.27, 0.08, 1.07)
Group D: any second generation ALK TKI + any second generation ALK TKI	1.64% (9)	1.36 (0.75, 1.05, 0.56, 2.91)	0.63 (0.48, 0.45, 0.15, 1.45)	0.73 (0.61, 0.58, 0.18, 2.11)	–

lower than expected. The identification of CNS metastases through diagnosis codes likely underestimated the number of patients with actual CNS-spread. This is probably due to not all CNS metastases being registered with a specific diagnosis code in the national registers, therefore rendering the CNS-spread lost to data crosslinking. The use of chemotherapy in front line was higher than expected (given the superiority of ALK TKI in this setting and the treatment guidelines). Considering that chemotherapy treatment was identified based on an algorithm, there is some uncertainty in the estimates. Nonetheless, 90% of chemotherapies were identified through recorded chemotherapy-specific procedures including ICD-10 codes in the Patient Register, which have a high degree of reliability. The share of patients receiving frontline chemotherapy decreased over time, indicating that the results herein may be driven by early patients and may have evolved toward targeted frontline strategy in more recent years.

We found that the majority (95%) of patients treated in Swedish clinical practice received their therapy in line with conventional, scientifically grounded, and/or regulatorily approved and reimbursed ALK TKI sequences. An Australian study by Itchins *et al.* [13] found that about half of the patients received at least two lines of ALK inhibitor therapy. In Sweden, the corresponding number was 33%, indicating that 67% of identified patients had only received one line of ALK TKI. This may be partly explained by the difference in median follow-up, which was twice as long compared to the present study. Davies *et al.* [14] studied treatment patterns for crizotinib and ceritinib patients in the US, showing predominant use of the two TKI from first- to third-line therapy. In general, a majority of the assessed ALK TKI sequences began with crizotinib followed by second generation ALK TKI [15–19]. In the present study crizotinib and alectinib were predominantly used from first- to third-line therapy, with crizotinib being first-line therapy for more than 60% of patients. Differences in sequencing of ALK TKI in comparison with previous findings likely depend on factors that change over time such as clinical evidence and access to treatment.

Overall, this study found that the median survival from initiation of first-line ALK TKI was 1.83 (95% CI: 1.48, 2.13) years, with a statistically significant longer OS among patients without frontline chemotherapy compared to those with chemotherapy. Jahanzeb *et al.* [19] reported a similar median OS from first-line ALK TKI of 2.14 (95% CI: 1.76, 2.62) years among the 581 patients treated in the UK. Contrarily, Britschgi *et al.* [18] found a median OS from diagnosis of stage IV disease to be 4.00 (95% CI: 2.7, 6.5) years among 121 patients with stage IV ALK-rearranged NSCLC in Switzerland and Italy, with no statistically significant difference in OS between patients stratified according to use of frontline chemotherapy. Further, in line with our findings, Ito *et al.* [17], found a longer OS in the alectinib-treated group compared to crizotinib-treated group in an analysis that included 46 Japanese patients. Not surprisingly, median OS for patients with registered CNS metastases was significantly shorter ($p = 0.0012$) than for patients without documented CNS spread, 0.61 (95% CI: 0.34, –[1]) and 1.94 (95% CI: 1.52,

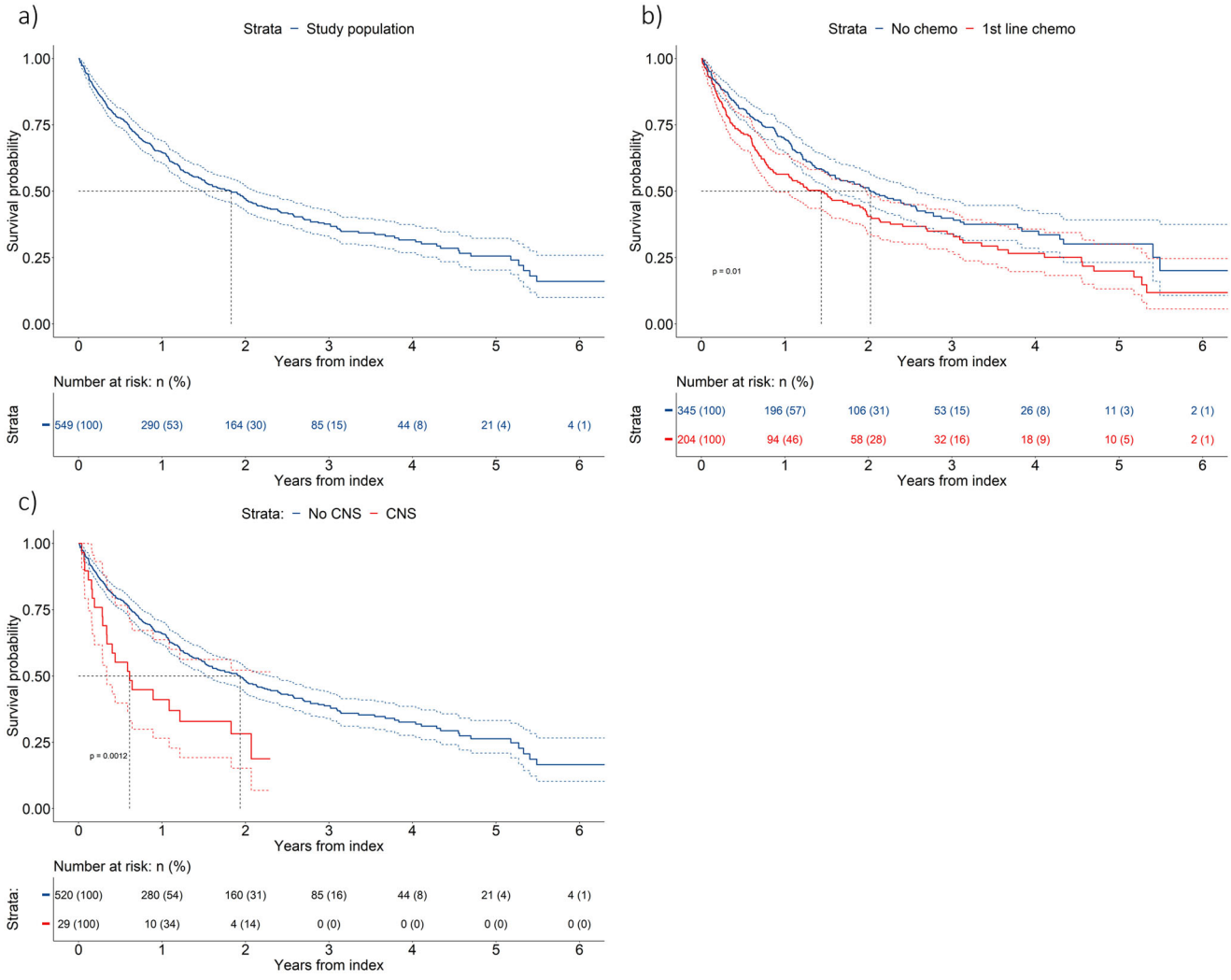

Figure 2. KM survival curves (95% CI) for (a) study population, (b) patients with and without chemotherapy, and (c) with and without CNS metastases.

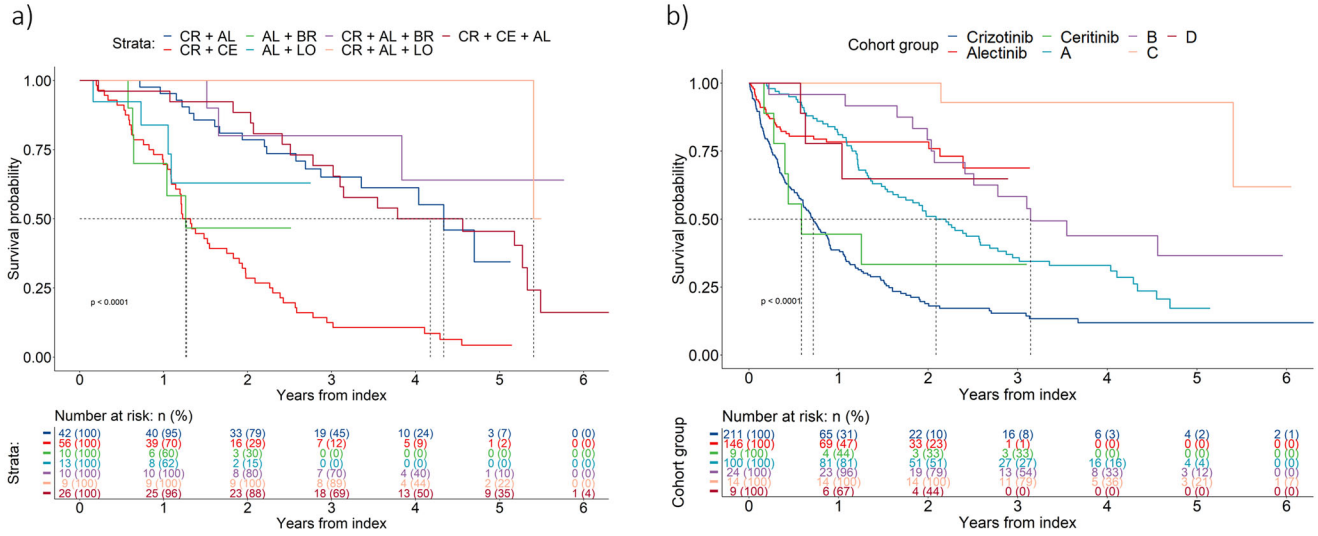

Figure 3. KM survival curves for (a) individual sequences and (b) cohort groups.

2.26), respectively. As described above, due to incomplete registration of CNS metastases in national registers, the non-CNS group likely contains some patients with CNS metastases. Thus, the true difference in survival between patients with and without CNS-spread is likely even more pronounced than what is suggested by data herein.

DOT was generally between 6 and 12 months per individual ALK TKI and was longer if no frontline chemotherapy was identified. Mean time on treatment was 0.62 (SD: 1.04) years among patients treated with crizotinib only, 0.88 (SD: 0.83) years among those treated with alectinib only, and 1.06 (SD: 1.2) years among those treated with ceritinib only (although based on solely nine patients). Similarly, Jahanzeb *et al.* [19] found a median time to treatment discontinuation for first line ALK TKI therapy of 0.57 (95% CI: 0.54, 0.69) years. Furthermore, they showed that frontline alectinib versus crizotinib significantly decreased the risk of treatment discontinuation.

Both treatment duration and OS estimates should be interpreted with caution since they are influenced by the relatively short follow-up, which is especially valid for later generation ALK TKI. This may partly explain why this study finds shorter OS and treatment duration as well as fewer patients with several lines of ALK TKI treatment, compared to other studies.

The register-based data employed in this analysis have certain limitations. Eligible patients were identified through filled pharmacy prescriptions, thus potentially missing patients who only receive treatment *via* clinics. Furthermore, it was assumed that patients prescribed ALK TKI are highly predominantly ALK-positive NSCLC patients; no information on the specific molecular subtype of lung cancer was available in the registers. Considering that ALK-inhibitors crizotinib as well as lorlatinib also exert clinically meaningful activity against *ROS1*-rearranged tumors, the inadvertent inclusion of ROS-1 positive patients in this study cannot be ruled out. However, considering the quite recent introduction of the routine molecular diagnostics and targeted ROS1-therapy in Swedish clinical practice, this would affect only the last years of the study period.

Moreover, given the lack of registration of drug treatments administered at hospitals, chemotherapy was identified based on algorithms and assumptions introducing uncertainty regarding the absolute capture of intravenously administered chemotherapy or its completely accurate patient attribution.

It is worth noting that drug treatments administered under compassionate use programs (CUP) are not registered as prescriptions and thus not captured in this study. Swedish CUP for lorlatinib was active from June 2017, that is, for more than 2 years prior to lorlatinib reimbursement.

Furthermore, stratification of patients into ALK TKI sequences based on treatment switches that occurred after the start of follow-up can potentially result in an immortal time bias if comparing sequences with more than one ALK TKI or a different number of ALK TKI. Another source for limitation is the fact that novel generation ALK TKI, especially the latest second- and third-generation agents, have been in use for a relatively short period of time leading to limited follow-up and potential underrepresentation of recent patient cases. Moreover, the use of chemotherapy in the early years of this study may not be representative of more recent clinical practice. A stratification of results over time was not feasible due to low patient numbers. Therefore, the data presented in this study should not be used to draw any formal conclusions regarding the comparative effectiveness of different treatment sequences.

Despite these limitations, this study provides a unique overview of all patients treated with ALK TKI therapies in Sweden and offers insight into the sequencing strategies used in clinical practice. The results show that most but not all patients are treated according to guidelines and that frontline chemotherapy had been used to a significant extent even with accessibility to ALK-targeted agents. Results on OS, interpreted with caution, are in line with reported real-world evidence and indicate a strong tendency that treatment with ALK TKI and sequencing of several TKI drugs leads to better outcomes. More research is needed to fully understand ALK TKI sequencing in clinical practice and its effect on patient survival, especially when longer follow-up data is available for later-generation drugs.

Note

1. Estimate could not be obtained.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the Swedish National Board of Health and Welfare. Restrictions apply to the availability of these data, which were used under license for this study.

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