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Clinical outcomes of *ALK*+ non-small cell lung cancer in Denmark

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ABSTRACT

Background: Real-world clinical outcomes of anaplastic lymphoma kinase positive (*ALK*+) non-small cell lung cancer (NSCLC) patients vary. This study aimed to investigate the treatment and clinical outcomes of all *ALK*+ NSCLC patients in Denmark in the period 2011–2018, regardless of disease stage.

Materials and Methods: A national pathology database with complete coverage was used to identify *ALK*+ NSCLC patients diagnosed between 2011 and 2018. Clinical data were obtained through retrospective chart reviews. Overall survival (OS) and duration of treatment (DOT) were analyzed using Kaplan-Meier methodologies.

Results: A total of 209 *ALK*+ NSCLC patients were included. The cohort had a slight overrepresentation of female patients (56.5%) with a mean age of 61.6 years. Most patients were adenocarcinoma cases (97%) and presented with an ECOG performance status of 0–1 (79%). Stage IIIb–IVb patients comprised 70% of the cohort. The use of ALK-tyrosine kinase inhibitors (TKIs) as first-line treatment increased over time, with the 1st generation ALK-TKI crizotinib being the predominant treatment in the 1st line. In 1st line treatment, 2nd generation ALK-TKIs had a median DOT more than twice the median DOT of crizotinib (25.1 and 9.1 months, respectively). The median OS for the entire cohort was 44.0 months. Patients with stage I–IIIA disease had a median OS that had not been reached, while those with stage IIIb–IVb disease had a median OS of 31.8 months. Patients with stage IIIb–IVb disease receiving an ALK-TKI as 1st line treatment had a median OS of 42.5 months with immature follow-up. Brain metastases at diagnosis or choice of 1st line treatment did not statistically significantly impact OS.

Conclusion: This study gives insights into the treatment and outcome of *ALK*+ NSCLC patients in Denmark and provides a real-world confirmation of the superior disease control provided by 2nd generation ALK-TKIs as compared to the 1st generation ALK-TKI crizotinib.

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nationwide; ALK+non-small cell lung cancer; retrospective; prevalence; clinical outcome; treatment use and duration

Background

Genomic rearrangements of anaplastic lymphoma kinase (*ALK*) driving tumorigenesis have been identified in 3-5% of patients with non-small cell lung cancer (NSCLC) [1–3], and several targeted therapies have entered clinical practice for the treatment of patients with stage IIIb–IVb disease. The first-generation ALK-tyrosine kinase inhibitor (ALK-TKI) crizotinib was approved in 2011 and was rapidly followed by four later-generation ALK-TKIs approved between 2014 and 2018 [4]. This rapid availability of increasingly efficacious therapeutic interventions has greatly improved the prognosis of advanced *ALK*+ NSCLC to the extent that long-term overall survival (OS) is possible [5]. Indeed, more than 80 months of median OS have been reported for selected advanced-stage patients receiving several lines of ALK-TKI-based treatments [6–8].

However, not all patients with *ALK*+ NSCLC have access to treatment with several lines of ALK-TKIs and the OS of unselected patient cohorts is reported somewhat shorter at 24.7–48.5 months depending on treatment availability [9–12]. The real-world clinical outcome measured as OS thus varies considerably and appears to be associated with the availability of continued treatment options targeting ALK [5].

Given the above mentioned heterogeneity in study design (selected patients vs. unselected), treatments (privileged settings vs. underprivileged settings), and outcomes reported in the literature, we wished to investigate the treatment and clinical outcome for all *ALK*+ lung cancer patients when

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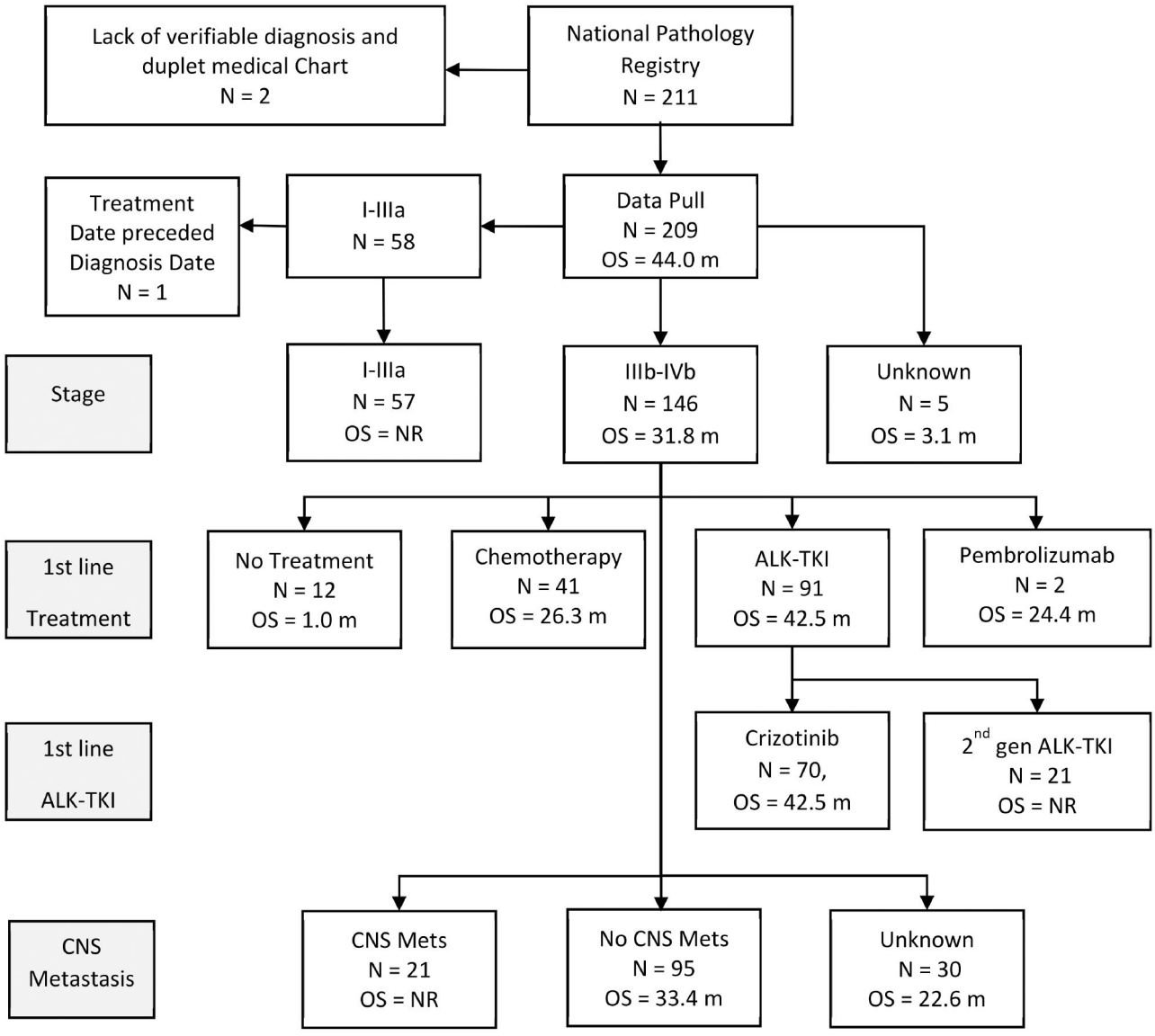

Figure 1. Patient flow for OS analysis based on stage of disease, 1st line treatment choice, and presence or absence of Central Nervous System (CNS)-metastases among stage IIIb–IVb patients. NR: not reached; OS: overall survival; m: months.

receiving treatment in an egalitarian healthcare system with few restrictions on the availability of treatments. We, therefore, analyzed the clinical outcome and treatment patterns for all Danish *ALK*+ NSCLC patients diagnosed between 2011 and 2018. We did so by using a national pathology database with 100% coverage for the identification of patients followed by chart reviews of the patients.

Methods

Patients and data sources

The inclusion criterion for the *ALK*-Cohort was a diagnosis of *ALK*+ NSCLC (adenocarcinoma, adenosquamous carcinoma, or non-small cell carcinoma) registered in the Danish National Pathology Registry between 2011 and the end of 2018. The exclusion criterion was the absence of such a diagnosis. Clinical data for the identified patients was obtained by a retrospective review of medical charts from all seven treating Department of Oncology in Denmark. Linkage between the Pathology Registry and medical charts was done using unique personal identifiers issued to all Danish citizens or other users of the health care system. All pathology tests in Denmark are required to be uploaded to the Danish National Pathology Registry, which subsequently provides local hospitals with pathology reports. The registry thus has a 100% coverage rate; a total of 211 patients were identified; and 209 were available for medical chart reviews, Figure 1.

Date of last follow-up for clinical data was September 2020.

Variables

Overall Survival was defined as the time from diagnosis of NSCLC to death. Patients still alive at the end of the follow-up, were censored from the analysis at the date of the last follow-up. Duration of treatment (DOT) was calculated as the time elapsed from the first date of medicine delivery at the

treating department, to the last day of active treatment as recorded by the treating physician; 'drug holidays' were not considered as an end to treatment. Patients still undergoing treatment at the end of follow-up, were censored at the date of last follow-up.

Missing data

Information on the disease stage was missing for five patients. No attempts at imputation/fill-in were performed for these patients; they were analyzed for OS as a separate group, Figure 1, but were not analyzed for treatment. The treatment date for one patient was entered as the preceding date of diagnosis. This patient was omitted from further analysis, Figure 1. No patients were lost to follow-up.

Data collection and analysis

Patient-level data from the medical charts were extracted, anonymized, and compiled using REDCap® (Vanderbilt University, Nashville, TN, USA). The data were subsequently handled and analyzed in Microsoft Excel 16. Duration of treatment and OS analysis were performed in Graph Pad Prism 9.4.1 (GraphPad Software, CA, USA). Overall survival analyses were performed using Kaplan-Meier methodologies using Log-rank (Mantel-Cox) testing for significance and hazard ratio (HR). Test for differences in distribution was performed using Chi^2-methodology.

Results

Clinical characteristics of patients in the study

Figure 1 summarizes the number of individuals in the study according to eligibility for analysis and stage of disease. Table 1 summarizes the clinical characteristics of the cohort at the time of diagnosis. Briefly, the mean age was 61.6 years of age (min: 22.9, max: 97.8, SD: 14.2), and the median age was 64.4. Ten percent of the patients had confirmed brain metastases at the time of diagnosis. Of the 21 patients found to have brain metastases at diagnosis, eight were diagnosed in 2018 (Supplementary Table 1). Most patients were diagnosed at an advanced stage (IIIb–IVb, 70%); 2% had an unknown stage of disease at diagnosis.

Diagnostic methods, ALK-fusion partners, and diagnostic delay

The molecular methods used for the diagnosis of *ALK*-translocation and *ALK*-fusion partners identified for 28 patients tested with NGS are summarized in Table 1. Correlation between *ALK*-fusion partner and response for these patients has been described elsewhere [13]. The delay between diagnosis of NSCLC and *ALK*+ diagnosis decreased throughout the period. Thus, the median time to *ALK*+ diagnosis following NSCLC diagnosis was 29 days in the period 2011–2013, while it was 0 days in the periods 2014–2016 and 2017–2018 (Supplementary Figure 1A). The number of diagnosed patients per year steadily increased from <5 in 2011 (not shown) to 40+ in 2018 (Supplementary Figure 1B).

Table 1. Clinical and test characteristics of the *ALK* + NSCLC patients included in the study.

Gender, $N = 209$	*n* (%)
Male	91 (43.5)
Female	118 (56.5)
Age, $N = 209$	Years (SD, range)
Mean (SD, range)	61.6 (14.2, 22–98)
Median	64.6
Smoking, $N = 209$	*n* (%)
Current	23 (11)
Former	79 (38)
Never	104 (50)
Unknown/missing	3 (1)
Median pack years current and former smokers (SD)	20 (18.15)
Tumor biology, $N = 209$	*n* (%)
Adenocarcinoma	204 (97.5)
Squamous cell carcinoma	2 (1)
Adenosquamous cell carcinoma	2 (1)
Unknown/missing	1 (0.5)
ECOG-performance status, $N = 209$	*n* (%)
0	97 (46)
1	68 (33)
2	26 (13)
3	7 (3)
4	2 (1)
Unknown/missing	9 (4)
Brain metastases (at time of diagnosis), $N = 209$	*n* (%)
No/unknown/missing	188 (90)
Yes	21 (10)
Cancer stage at time of diagnosis, $N = 209$	*n* (%)
Ia	19 (9)
Ib	8 (4)
IIa	6 (3)
IIb	5 (2)
IIIa	20 (10)
IIIb	15 (7)
IVa	71 (34)
IVb	60 (29)
Unknown/missing, *n* (%)	5 (2)
Diagnostic Methods (IHC, FISH, NGS), $N = 209$	*n* (%)
One test	67 (32)
IHC	53 (25)
FISH	10 (5)
NGS	4 (2)
Two tests	111 (54)
IHC + FISH	111 (53)
FISH + NGS	0 (0)
IHC + NGS	2 (1)
Three tests	25 (12)
IHC + FISH + NGS	25 (12)
Unknown/missing	4 (2)
Identified *ALK*-fusion variants, $N = 28$[a]	*n* (%)
*EML4-ALK*v1	9 (32)
*EML4-ALK*v2	5 (18)
*EML4-ALK*v3	4 (14)
Others	2 (7)
KIF5B(17)-*ALK*(20)	1 (3.5)
TEMP3(6)-*ALK*(20)	1 (3.5)
No fusion partner detected by RNA-NGS[b]	8 (28%)

[a]Identified by RNA-NGS. [b]Tested positive for *ALK*-translocation by IHC-FISH

Treatments and use of ALK-TKIs for patients with stage I–IIIa disease

Patients with stage I–IIIa disease were treated with curative intent according to ESMO or Danish guideline specifications applicable to the specific disease stage. Thus, most of the patients underwent surgery (41/57, 72%), either alone (27/57,

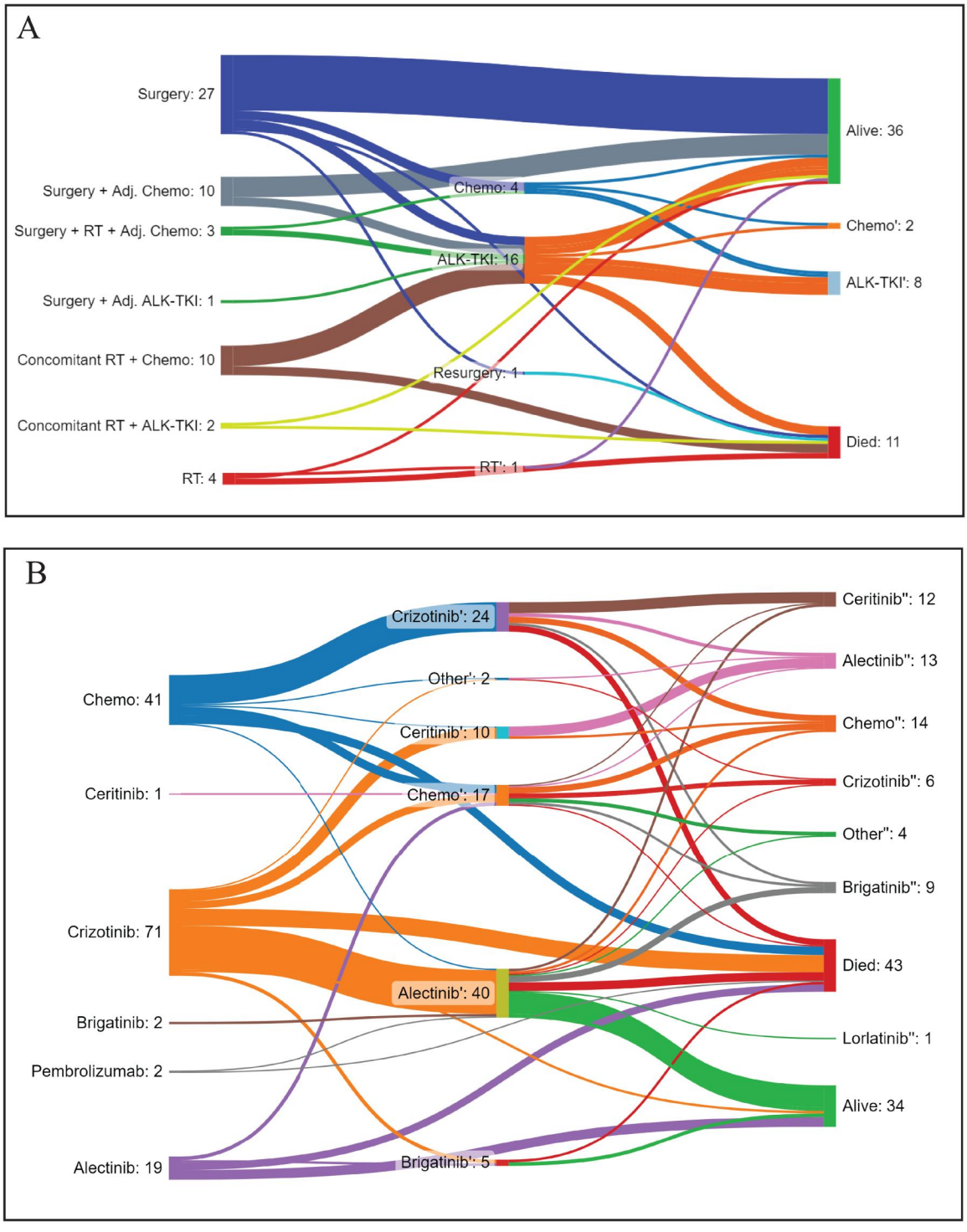

Figure 2. Treatment pattern of *ALK*+ NSLCL patients. A: stage Ia–IIIa patients. B: stage IIIb–IVb patients. Other: treatment with lorlatinib (1), erlotinib (2), dabrafenib (1), and nivolumab (1).

47%) or in combination with adjuvant chemotherapy (10/57, 18%), radiotherapy (3/57, 5%%), or ALK-TKI (1/57, 2%), Figure 2A. Twenty-three percent (10/57) received concomitant chemo- and radiotherapy. Thirty-three percent (19/57) of the patients received ALK-TKIs as part of their treatment following the progression of initially curatively intended treatment; 11% (6/57) of the patients received two lines of ALK-TKIs and 28% (16/57) died during the study period. Supplementary Table 2 and Figure 2 summarize and detail the treatment of stage I–IIIa patients.

Treatments and lines of treatment for patients with advanced disease

Almost all patients (134/136) with advanced disease (stage IIIb–IVb) received chemotherapy (mostly platin + vinorelbine), or ALK-TKIs as first-line treatment; only two patients received pembrolizumab as first-line treatment, Figure 2B. Reflecting the period we investigated, most of the patients received crizotinib as 1st line treatment followed by 2nd generation ALK-TKIs and in rare instances chemotherapy. Similarly, most of the

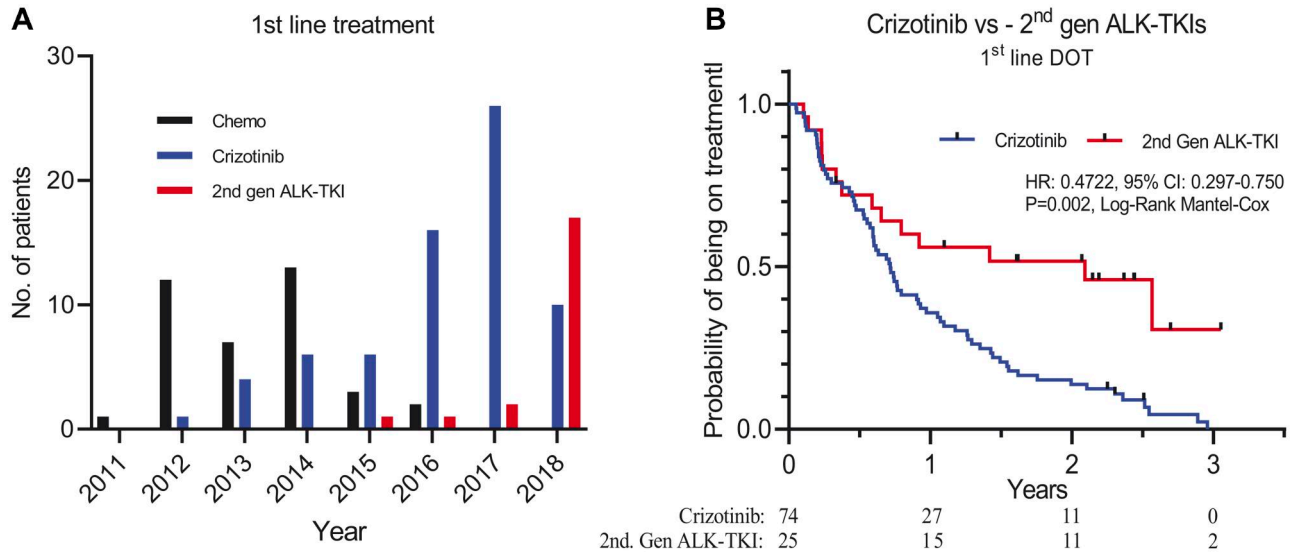

Figure 3. A: treatment choice in 1st line of *ALK*+ NSCLC patients. *Black bars*: chemotherapy. *Blue bars*: 1st generation ALK-TKI crizotinib. *Red bars*: 2nd generation ALK-TKIs (alectinib, ceritinib, or brigatinib). B: duration of treatment of 1st generation ALK-TKI crizotinib (*blue*) vs. 2nd generation ALK-TKIs (alectinib, ceritinib, or brigatinib) (*red*) in 1st line treatment of *ALK*+ NSCLC patients.

Table 2. Fraction of advanced stage patients receiving 1st, 2nd, and 3rd line treatment.

	Stage IIIb–IVb treated with chemotherapy or ALK-TKIs in 1st line	Stage IIIb–IVb treated with ALK-TKIs in 1st line
1st line treatment, *n* (%)	136 (100)	95 (100)
2nd line treatment, *n* (%)		
New treatment	98 (72)	64 (67)
No PD since 1st line	10 (7)	10 (11)
Dead before 2nd line	28 (21)	21 (22)
3rd line treatment, *n* (%)		
New treatment	59 (43)	31 (33)
No PD since 1st or 2nd line	34 (25)	33 (35)
Dead before 3rd line	43 (32)	31 (33)

Left column summarizes all patients treated with either chemotherapy or ALK-TKIs in 1st line; right column summarizes patients treated with ALK-TKIs in 1st line. New treatment: number of patients receiving a new treatment since the previous line of therapy. No PD since 1st line: number of patients who had not progressed from 1st line therapy at end of study follow-up. No PD since 1st or 2nd line: amount out patients who had not progressed from 1st or 2nd line therapy at end of study follow-up. Dead before 2nd line: number of patients who received 1st line therapy but died prior to receiving 2nd line therapy. Dead before 3rd line: number of patients who received 1st and 2nd line therapy but died prior to receiving 3rd line therapy.

patients receiving chemotherapy as 1st line treatment received crizotinib as 2nd line treatment. This trend of treatments being reflective of the availability of treatment options is also seen in 3rd line treatment, where later iterations of ALK-TKIs are well represented (e.g., use of ceritinib post-chemo-crizotinib and use of brigatinib post-crizotinib–alectinib). Similarly, chemotherapy and ALK-TKIs dominated 2nd and 3rd line treatments with only four patients receiving alternative treatments in the 3rd line (two erlotinib, one dabrafenib, and one nivolumab). One patient received lorlatinib in the 3rd line following treatment with crizotinib–alectinib, Figure 2B.

Supplementary Table 3 and Figure 3 detail the different treatment paths experienced by stage IIIb–IVb patients. Of these, a total of six patients did not receive an ALK-TKI as part of the first three lines of treatment (disregarding seven patients who died following 1st line of treatment with chemotherapy (Supplementary Table 3). Across years and treatment lines ALK-TKIs were thus offered to 95% (123/129) of the patients whose guidelines recommend ALK-TKIs.

Uptake of crizotinib as 1st line treatment was rapid and preceded EMA approval for this indication in November 2015: thirty-three percent of the stage IIIb–IVb patients diagnosed from January 2012 to December 2015 were treated with crizotinib as 1st line treatment, Figure 3A. Contrary to this, the uptake of 2nd generation ALK-TKIs as 1st line treatment largely followed national guidelines from the Danish payers. Thus, 79% of the 2nd generation ALK-TKIs used as 1st line treatment outside of clinical trials were prescribed following approval of alectinib by the Danish payers in May 2018, Figure 3A.

Number of treatment lines and treatment duration with ALK-TKIs for patients with ALK+ NSCLC irrespective of disease stage

Supplementary Tables 4 and 5 summarize the treatment duration of ALK-TKIs across treatment lines and according to the use of chemotherapy in 1st line for all *ALK*+ NSCLC patients. We found that 16/99 (16.2%) patients received three lines of therapy solely based on ALK-TKIs, and that the use of chemotherapy in 1st line treatment did not substantially affect the DOT of subsequent ALK-TKIs, Supplementary Table 4. Among stage IIIb–IVb patients, 43% received three lines of therapy, while 33% of the stage IIIb–IVb patients treated with ALK-TKIs in the 1st line received three lines of therapy,

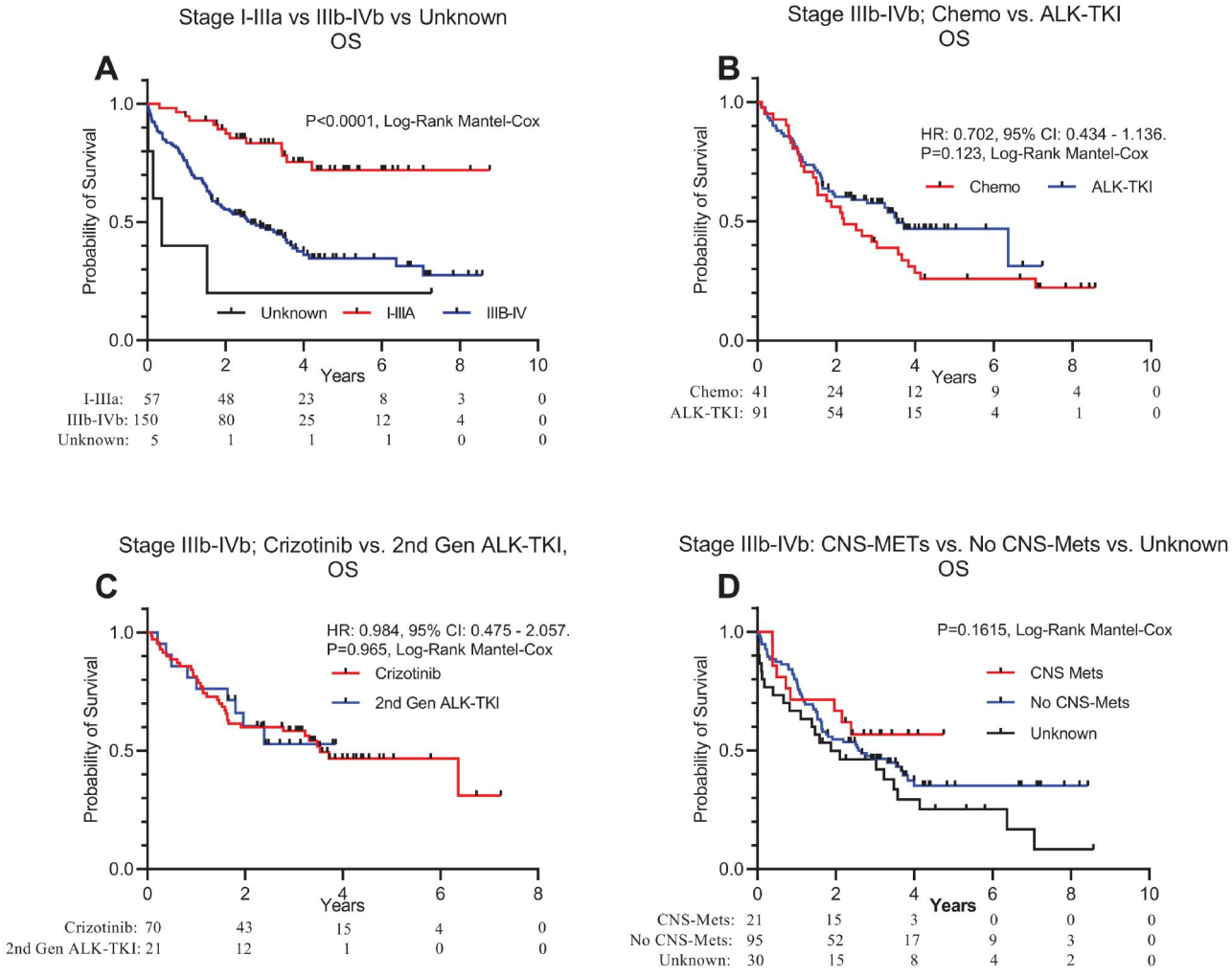

Figure 4. Overall survival analysis of selected patient populations. A: patients with either unknown stage disease (*black*), stage I–IIIa disease (*red*) or stage IIIb–IVb disease (*blue*). B: advanced stage patients receiving either ALK-TKIs (*blue*) or chemotherapy (*red*) in 1st line. C: advanced stage patients receiving either crizotinib (*red*) or 2nd generation ALK-TKIs (*blue*) as 1st line treatment. D: patients with advanced stage disease with CNS-metastasis (*red*), without CNS-metastasis (*blue*) or with unknown CNS involvement (*black*). in all analyses a *black vertical bar* denotes censoring of one subject. Numbers below graph denotes patients at risk for event at a given time.

Table 2. However, only 32% and 33% of these patients died from their disease before reaching three lines of treatment, respectively, Table 2. The remaining patients had either not progressed from 1st and 2nd line treatment or were in active-line treatment, Table 2.

With a median follow-up (FU) of 8.5 and 17.0 months, respectively, the median treatment durations in 1st line treatment with crizotinib and 2nd generation ALK-TKIs were 9.1 and 25.1 months, respectively (HR: 0.4722, 95% CI: 0.297–0.750, $p = 0.002$), Figure 3B.

Discontinuation rates due to toxicity in treatment line 1–3 of stage IIIb–IVb patients were statistically similar ($p = 0.082$) between chemotherapy, crizotinib, and 2nd generation ALK-TKIs, at 10.8, 10.9, and 3.5%, respectively (Supplementary Table 6).

Survival outcome

Several survival analyses of distinct subgroups of patients were performed. Figure 1 summarizes the flow of patients through the various OS analysis.

With a median follow-up of 32.0 months, the OS in the entire *ALK*+ cohort was 44.0 months (Figure 1). Among patients diagnosed with stage I–IIIA disease, the median OS had not been reached (FU: 42.5 months), while the median OS for patients diagnosed with stage IIIb–IVb disease was 31.8 months (FU: 28.0 months) (hazard ratio (HR) 0.275, 95% confidence interval (CI): 0.183–0.415, $p < 0.0001$), Figure 4A. Information about the stage of disease was not registered for five patients'; the median OS in this group was 3.1 months (Figure 1). Among 146 patients diagnosed with stage IIIb–IVb disease, 12 patients did not receive any treatment (Figure 1) and had a median OS of 1 month. The remaining 134 advanced-stage patients who received treatment had a median OS of 39.8 months and a 2-year OS rate of 59% (not shown). Among these patients, two received pembrolizumab as first-line treatment (Figure 1). Of the remaining 132 patients, 91 received an ALK-TKI as 1 L treatment with a median OS of 42.5 months (median follow-up: 29.2 months) and 41 received chemotherapy as 1st line treatment with a median OS of 26.3 months (median follow-up: 26.3 months) (HR: 0.703, 95% CI: 0.434–1.136, $p = 0.123$),

Figure 4B. Among those who received an ALK-TKI as first line treatment, 70 received crizotinib, while the remaining 21 patients received a 2nd-generation ALK-TKI (alectinib, ceritinib, or brigatinib). The median OS for these patient groups was 42.5 months (median follow-up 34.9 months) and not reached (NR), respectively (median follow-up 27.0 months) (HR 0.984, 95% CI: 0.475–2.040, $p = 0.925$), Figure 4C. Stage IIIb–IVb patients with brain metastases at diagnosis did not obtain a statistically different median OS as compared to patients with no brain metastases or unknown brain metastases at the time of diagnosis, NR (median follow-up: 29.0 months), 31.8 months (median follow-up: 28.7 months), and 22.6 months (median follow-up 21.2 months), respectively ($p = 0.162$), Figure 4D.

Discussion

Current real-world evidence on the prognosis and care of *ALK*+ NSCLC patients is based on a variety of data sources, such as registry studies or medical chart extraction, carried out at single centers in particular patient cohorts or in national cohorts in wealthy or underdeveloped nations [6–12,14,15]. Accordingly, reported OS outcomes for *ALK*+ NSCLC patients vary considerably from 24 to >80 months [6–12,14,15]. Our study is, to our knowledge, the first study to combine national registry data with complete coverage with medical chart reviews to identify and describe a completely unselected cohort of *ALK*+ NSCLC patients of all stages for clinical features, treatment, and outcome.

At 64 years of age (median), our cohort was somewhat older as compared to other reported cohorts, with median ages ranging from 50 to 63 [6–12,14–16]. In accordance with previous reports, half of the patients were nonsmokers and were diagnosed with advanced adenocarcinomas [7,14]. The median pack years was 20 with an SD of 18, suggesting a wide range of smoking consumption. Ten percent of the patients had confirmed brain metastases at the time of diagnosis; however, patients were not routinely scanned for brain metastases at diagnosis in the early part of the study period, so this number is likely underestimated. The year-over-year increase in patients diagnosed with brain metastases as brain scans at diagnosis became standard supports this view. The delay between diagnosis of NSCLC and *ALK*+ NSCLC we observed at the beginning of the period disappeared as all treating departments implemented guidelines stipulating up-front reflex testing in the years 2013–2016, resulting in a year-over-year increase in patients diagnosed with ALK+ NSCLC. This increase in diagnoses in the latter period of this study underscores the positive effects of up-front reflex testing as compared to testing based on clinical suspicion or indication as done in the early time period.

The median DOT of 2nd generation ALK-TKIs in the 1st line was 25.1 months, more than double the DOT of crizotinib at 9.1 months. Taking DOT as a proxy for progression-free survival, this is in accordance with data from randomized clinical trials [17–20] and is thus a real-world confirmation, in an unselected patient cohort, of the better disease control provided by 2nd generation ALK-TKIs as compared to crizotinib.

Our cohort contained all patients diagnosed with *ALK*+ NSCLC, irrespective of stage. We found that treatment followed stages of the disease, with stage I-IIIa patients mostly receiving curatively intended treatments as well as ALK-TKIs following relapses. Correspondingly, low-stage patients had a significantly longer OS than patients with advanced disease. For the advanced-stage patients receiving ALK-TKIs as first-line treatment, the median follow-up was shorter than the median OS. We therefore expect the median OS to be longer when this cohort matures. Nonetheless, an immature median OS of 42.5 months for unselected patients with advanced disease receiving ALK-TKIs as first treatment is consistent with data from unselected cohorts from Canada and Switzerland/Italy, where such patients obtained a median OS of 48.5 months [9] and 35.8 months [6], respectively. The survival is not as long as what has been reported from selected cohorts at single centers, where survival times of 81 months and 56 months have been reported [8,15]. It is unclear if the longer survival reported from these studies is due to early access to 2nd generation ALK-TKIs, other parameters reflected by the selected nature of the cohorts, or the relative immaturity of our cohort. However, several studies have found that treatment with multiple lines of ALK-TKIs can lead to long-term survival of 80+ months [7,8,14] suggesting that the availability of several ALK-TKIs for continued targeted treatment at progression can be a factor in reaching long-term survival. As five ALK-TKIs are currently reimbursed in Denmark and roughly two-thirds of all patients were positioned to receive three or more lines of therapy, our cohort may thus be well positioned to reach a longer median OS as it matures.

CNS-metastasis at diagnosis of advanced disease is typically considered an adverse clinical parameter, and real-world studies have demonstrated numerically and statistically different survival outcomes for patients with CNS-metastases at diagnosis as compared to patients without CNS-metastases [6,10]. However, we and others [8] did not find a statistical, or numeric, difference in survival outcome for patients with detected CNS-metastases at diagnosis, suggesting that survival outcomes can be similar for *ALK*+ NSCLC patients with and without CNS-metastases at diagnoses.

The 2-year OS rate for treated patients with advanced disease (59%) presented herein is aligned with a recent Norwegian study showing a 2-year OS rate of slightly more than 60% for patients with stage IV disease treated with ALK-TKIs [16]. On the other hand, the OS appears longer than what was recently reported from Sweden [10]. Thus, the median OS reported by a Swedish study was 24.2 months for patients who received ALK-TKIs as first-line treatment [10], while our cohort obtained a median OS of 42.5 months. Similarly, the Swedish study found a reduction in median OS from 23.3 months for patients without CNS metastases to 7.3 months for patients with CNS metastases [10], while we found no difference in median OS for patients with and without brain metastases at diagnosis (NR and 31.8 months), suggesting a clinically significant better outcome for

ALK+ NSCLC patients in Denmark than in Sweden. Given that Sweden and Denmark have very strong historical and societal ties, resulting in very similar healthcare systems with free universal coverage, this difference was surprising. The reason for this putative discrepancy in OS is unclear, but it is noteworthy that the duration of treatment (DOT) of ALK-TKIs in the Swedish study [10] was consistently found to be shorter than in this study (Supplementary Tables 4 and 5). For instance, 1st line DOT of 2nd generation ALK-TKIs was 4.9 and 10.7 months in Sweden [10] vs. 25.1 months in our study. Similarly, to this seemingly large difference in DOT for 2nd generation ALK-TKIs in 1st line, we found that more patients received 3rd line ALK-TKI therapy than what was reported in the Swedish paper (33 vs. 7.3%) [10]. Combined, this suggests that the patients in our cohort were treated longer and in more lines than patients in Sweden. Whether this reflects differences in availability (reimbursement) of ALK-TKIs in the clinic, differences in clinical features of the patient populations, differences in the management of toxicities, or differences in study design (e.g., length of follow-up) is unclear.

Real-world studies have reported conflicting results regarding the optimal use of chemotherapy in the treatment of *ALK*+ NSCLC [6,10–12]. We did not find a statistically significant difference in the OS of advanced patients treated with either chemotherapy or ALK-TKIs in the 1st line but observed a trend toward longer survival for patients treated with ALK-TKIs in the 1st line. Considering that the ALK-TKIs cohort was quite immature, it is possible this trend in longer OS will reach statistical significance as the cohort matures.

Crizotinib was widely used as 1st line treatment prior to EMA approval (November 2015), suggesting a willingness to treat patients with novel treatments if available, irrespective of labeling, in the early part of the study period. Contrary to this, use of 2nd generation ALK-TKIs as 1st line treatment was very rarely done outside of clinical trials prior to EMA approval of 1st line indication and recommendation by the Danish national payer guidelines issued in May 2018. This shift in clinical decision-making suggests a strong adherence by Danish oncologists to the treatment guidelines issued by the Danish payers and underscores how successful national treatment guidelines can be in ensuring equal treatment for all patients.

Our study is based on the identification of patients with *ALK*+ NSCLC in a nationwide database with complete coverage followed by medical chart reviews of the individual patients diagnosed between 2011 and 2018. Thus, our study captures and describes *all* patients diagnosed with *ALK*+ NSCLC in Denmark in the study period irrespective of treatment site or stage of disease. The primary and secondary clinical measures, median OS and DOT, are robust and relevant clinical outcomes that do not rely on integration of secondary data from other sources. We therefore consider our study to be very robust and clinically relevant. On the other hand, two factors suggest caution in the interpretation and generalization of the data. Firstly, despite a relatively long median follow-up of 32.0 months, the median OS was still longer than the median follow-up for several sub-groups of patients (e.g., patients receiving ALK-TKIs as 1st line treatment) suggesting that the median OS for such groups were not reached at time of data collection. The reported median OS for these groups is therefore possibly underestimated and should be interpreted with this caveat in mind. Secondly, the Danish healthcare system is generally egalitarian and publicly funded with very few monetary restrictions on the clinical care of *ALK*+ NSCLC patients. The data may therefore not be representative of outcome and treatment patterns in other healthcare systems characterized by different availability of resources.

Author contributions

All authors contributed to the study's conception and design. Data collection was performed by Jakob Sidenius Johansen, Peter Hjorth-Hansen, Maiken Parm Ulhøi, Edyta Maria Urbanska, Karin Holmskov Hansen, and Charlotte Kristiansen. Data analysis were performed by Anders Bondo Dydensborg. The first draft of the manuscript was written by Anders Bondo Dydensborg, and all authors reviewed the manuscript critically. All authors read and approved the final manuscript

Ethics approval

The study was approved by the Danish Patient Safety Authority (#3-3013-3274/1) and registered at the Danish Data Protection Agency. There are no Danish legislation requirements to obtain informed consent from the patients to use the data in this study, as the patients were not contacted at any point during this study, the study did not affect the treatment of the patients, and only pseudonymized data were used.

Disclosure statement

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Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

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