




Lung cancer patients with anaplastic lymphoma kinase rearrangement lose affiliation with labor market at diagnosis

Jon Lykkegaard Andersen¹, Jakob Sidenius Johansen^{1,12}, Edyta Maria Urbanska² , Peter Meldgaard³, Peter Hjorth-Hansen⁴, Charlotte Kristiansen⁵, Miroslaw Stelmach⁶, Eric Santoni-Rugiu⁷ , Maiken Parm Uihøi³, Betina Højgaard^{8,13}, Morten Sall Jensen^{9,14}, Anders Bondo Dydensborg^{*,10}, Christina Dünweber¹⁰ & Karin Holmskov Hansen¹¹ 

¹Department of Oncology, Herlev & Gentofte University Hospital, DK-2730, Herlev, Denmark

²Department of Oncology, Rigshospitalet, Copenhagen University Hospital, DK-2100, Copenhagen, Denmark

³Department of Oncology, Aarhus University Hospital, DK-8000, Aarhus, Denmark

⁴Department of Oncology, Aalborg University Hospital, DK-9000, Aalborg, Denmark

⁵Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, DK-7100, Vejle, Denmark

⁶Department of Oncology, Næstved Hospital, DK-4700, Næstved, Denmark

⁷Department of Pathology, Rigshospitalet, Copenhagen University Hospital, DK-2100, Copenhagen, Denmark

⁸VIVE, Copenhagen, Denmark (The Danish Center for Social Science Research), DK-1052, Copenhagen, Denmark

⁹VIVE, Aarhus, Denmark (The Danish Center for Social Science Research), DK-8230, Åbyhøj, Denmark

¹⁰Takeda Pharma A/S, Delta Park 45, DK-2665, Vallensbæk Strand, Denmark

¹¹Department of Oncology, Odense University Hospital, DK-5000, Odense, Denmark

¹²Present address: Employment with Dept. of Oncology, Herlev & Gentofte University hospital, DK-2730, Herlev, Denmark, Denmark ended during the writing of the article

¹³Present address: Steno Diabetes Center, DK-2730, Herlev, Denmark

¹⁴Present address: Novo Nordisk, Søborg, DK-2860, Denmark

*Author for correspondence: anders-bondo.dydensborg@takeda.com

Aim: The main purpose of the present study was to investigate the labor market affiliation of *ALK*+ NSCLC patients in long-term treatment as well as overall survival and incidence/prevalence. **Materials & methods:** Nationwide retrospective study of all patients with *ALK*+ NSCLC in Denmark diagnosed between 2012 and 2018. **Results:** During the study period *ALK*+ NSCLC patients had a median overall survival of 44.0 months and a 7.8-fold increase in disease prevalence. Six months prior to diagnosis, 81% of *ALK*+ NSCLC patients ≤ 60 years of age were employed. At the end of the 18-month follow-up period, 36% were employed. **Conclusion:** *ALK*+ NSCLC patients have prolonged survival following diagnosis, but a large fraction of patients lose affiliation with the labor market.

Plain language summary: The purpose of this study was to examine the employment status and survival of patients with *ALK*+ NSCLC who are undergoing long-term treatment. The researchers conducted a study analyzing data from all such patients diagnosed between 2012 and 2018 in Denmark. The results showed that *ALK*+ NSCLC patients had a median overall survival of 44.0 months and that the number of patients increased almost eightfold during the study period. Prior to diagnosis, 81% of *ALK*+ NSCLC patients who were 60 years of age or younger were employed. However, at the end of the 18-month follow-up period, only 36% of these patients were still employed. In conclusion, *ALK*+ NSCLC patients tend to have prolonged survival after diagnosis. However, a considerable proportion of these patients lose their affiliation with the labor market, indicating the impact of the disease on employment status.

Tweetable abstract: *ALK*+ NSCLC patients have prolonged survival following diagnosis, but a large fraction of patients lose affiliation with the labor market following diagnosis. #alkpositive #lscm.

First draft submitted: 13 October 2023; Accepted for publication: 21 February 2024; Published online: 11 March 2023

Keywords: *ALK*+ • labor market affiliation • nationwide • non-small-cell lung cancer • prevalence • retrospective • return to work

Globally, lung cancer has a historic 5-year overall survival (OS) rate of 10–20% [1]; in Denmark 5-year survival is currently slightly less than 20% [2]. However, lung cancer survival is currently improving rapidly due to the advent

of drugs that either target distinct molecular alterations driving tumorigenesis or activates the immune system to fight cancer [3]. Indeed, targeted inhibition of PD-L1, mutant *EGFR*, *ALK* fusions, VEGF expression and *ROSI* fusions are all associated with continuously better survival due to continued approval of new generation of drugs within each class [4]. Additional future gains of survival of lung cancer patients are predicted based on current developments of medicines aimed at targets currently treated by conventional chemotherapy [4]. Further to the improved survival caused by targeted therapy, targeted agents are associated with less treatment burden and side effects as compared with non-targeted chemotherapy [5]. Lung oncologist and their patients are thus in an era with marked improvement in treatment characterized by significant increases in survival and diminished treatment burden for selected patients [3–5].

Returning to work after a cancer diagnosis is important to patients and society, as it provides patients with financial means to live independent lives, a sense of normality, confidence, and self-satisfaction while providing society with taxable income and drivers of economic growth [6,7]. Clinical factors (age, organ of origin, stage of disease) and socio-economic factors (income, gender, physical vs non-physical labor) have been demonstrated to affect cancer patient's affiliation to the labor market and ability/willingness to return to work [6,8,9]. Factors predicting for losing affiliation with labor market are old age at diagnosis and chemotherapy-based treatments [6,9]. Among lung cancer patients specifically, clinical factors associated with successful return to work have been found to be young age at diagnosis and lower fatigue scores [10].

With a median age at diagnosis of 71 years [2,11], lung cancer patients are relatively old and therapy often include chemotherapy and radiotherapy [12,13]. It is therefore not surprising that a lung cancer diagnosis carries independent risk for losing workplace affiliation as compared with other cancer types [14,15]. On the other hand, lung cancer patients with targetable driver alterations are frequently of younger age [16–19] and are treated with targeted agents instead of chemotherapy. Importantly, treatment with targeted agents provides both significantly longer survival and less therapy-related toxicity [5,18,20].

Chromosomal rearrangement of the *ALK* gene, creating constitutively active fusion proteins expressed in lung epithelium leads to *ALK*+ non-small-cell lung cancer (NSCLC) [21]. *ALK*+ NSCLC is not associated with smoking and the patient population is therefore younger and comprise fewer smokers or former smokers than lung cancer patients in general [22]. Importantly, none of the different classes of targeted therapies currently approved for treatment of lung cancer, has led to bigger survival gains than the drugs that target *ALK*. Indeed, patients with advanced stage (stage IV) *ALK*+ NSCLC have been reported to reach median survival times of 80 months when treated sequentially with medicines targeting *ALK* [23]. Additionally, the quality of life of patients treated with *ALK*-TKIs is better as compared with those receiving chemotherapy, reflecting a lessened toxicity burden [24]. Finally, all *ALK*-TKIs are administered as tablets in the outpatient setting minimizing treatment burden for the patients.

Given the dramatically improved survival, younger age at diagnosis and lessened toxicity/treatment burden we hypothesized that patients with *ALK*+ NSCLC are inclined to remain in active employment following their diagnosis. The purpose of our study was therefore to describe the labor market affiliation of *ALK*+ NSCLC patients as a distinct subpopulation of lung cancer patients that can serve as a proxy for lung cancer patients with targetable driver alterations in general.

Methods

Danish registries

All Danish citizens have a 10-digit personal social security number given at birth or immigration. The personal social security number is a unique personal identifier recorded in all public registries, thus allowing linkage between national registries, and ensuring 100% coverage. Accordingly, it was possible to describe the total mortality and the sociodemographic variables of the *ALK*+ cohort and the control group using distinct national registries.

ALK-cohort & the control group

An *ALK*-cohort (patients with *ALK*+ NSCLC) and a control group were included in this national, non-interventional registry- and medical chart review study.

The *ALK*-cohort consisted of every patient with *ALK*+ NSCLC diagnosed in Denmark between 1 January 2012 and 31 December 2018. The *ALK*-cohort was identified using the National Pathology Registry (Patobank). The inclusion criteria for the *ALK*-cohort were thus a diagnosis of *ALK*+ NSCLC (as adenocarcinoma, adenosquamous carcinoma or non-small-cell carcinoma not otherwise specified/NOS) registered in the National Pathology Registry.

Exclusion criteria was absence of such a diagnosis. Clinical data for the identified patients were obtained by retrospective review of medical charts from the seven treating departments of Oncology in Denmark. Data from the medical charts were extracted, anonymized, and compiled using REDCap[®] (Vanderbilt University, TN, USA) [25]. The data were subsequently handled in Microsoft Excel 16. Data on survival are updated and equal to timepoint for entering the data into REDCap[®] (July throughout September 2020).

Information regarding age, gender, education, labor market affiliation and marital status of the *ALK+* NSCLC patients in the *ALK-* cohort was derived from the Danish National Pathology Registry and the national registries: The Danish National Patient Registry, The Danish Civil Registration System, The Danish Cancer Registry, DREAM and Statistics Denmark.

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

The control group was derived from national registries, and based on the year of diagnosis (i.e., the requisition date of the Danish National Pathology Registry [26]), each patient with *ALK+* NSCLC was matched (ratio 1:10) by age, gender, education, level of education, marital status and region of residence with ten controls who were otherwise randomly selected. Psmatch2 [27] was used to perform the matching. As *ALK+* NSCLC is not caused by, or significantly associated with smoking [22] the control group was not matched for smoking. The individuals in the control group had no diagnosis of *ALK+* NSCLC during the period considered. Information on the following sociodemographic variables: age, gender, region of residence, marital status and education level was obtained from the Danish Civil Registration System as well as from the Education Registry. Information about Social Transfer Payments were obtained from the DREAM database and used to follow-up on labor market affiliation consequences of the *ALK+* Cohort and the control group. The DREAM database contains all social transfer payments for all citizens in Denmark [28].

Ethical considerations

The study was approved by the Danish Patient Safety Authority (#3-3013-3274/1 and #3-3013-3161/1) 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.

In accordance with Danish regulations, the exact number is not shown for results with fewer than five patients. The results fewer than 5 are shown as <5.

Study variables

Labor market affiliation was classified into the following four categories: in employment (full- or part-time), subsidized (unemployment benefits, unemployment educational benefits and sick leave benefits) retirees (retirement and early retirement benefits) and died or left the country.

Incidence & prevalence

The annual incidence of *ALK+* NSCLC (as absolute number and per million people) and 1-, 3- and 5-year prevalence were estimated from 2012 to 2018. The 1-year prevalence was defined as the number of patients living with *ALK+* NSCLC on the 31 December of the current year and diagnosed within the year and correspondingly within the last three years for the 3-year prevalence, and within the last 5 years for the 5-year prevalence.

Survival analysis

Kaplan–Meier methodology was used to describe the survival of the patient cohort and to assess median OS. The index date for the OS-analysis was set to the date of lung cancer diagnosis regardless of *ALK*-diagnosis. Follow-up was until end of study period. Patients who were alive, or had left the country, at last follow-up date were censored.

Labor market affiliation consequences

In the study period the retirement age in Denmark qualifying for full publicly paid retirement was 66. However, other more restricted options for publicly assisted withdrawal from the labor market exists with the most easily accessible starting at age 60 years. To minimize potential confounding related to such early age-driven retirement, only individuals in the *ALK*-cohort and the control group younger than 60 years of age ($n = 75$ and $n = 748$, respectively) were included in the labor market affiliation analyses. Included patients were not censored if they turned 60 years old during follow-up. The difference in labor market affiliation status (in employment, subsidized,

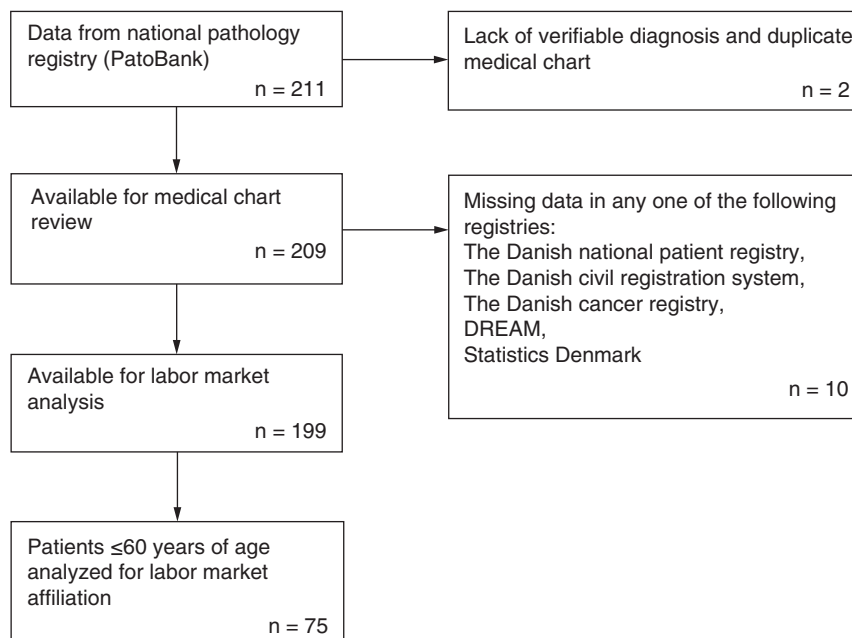


Figure 1. CONSORT diagram for *ALK+* NSCLC patients included in the study.

retired and died or left the country) between individuals in the *ALK*-cohort and the control group were analyzed at: 6 months before diagnosis, at time of diagnosis, and 6, 12 and 18 months after diagnosis.

Missing data

In case data were missing, the patient's data was omitted from the individual analysis. No attempts at imputation/fill in were performed.

Results

All 211 patients diagnosed with *ALK+* NSCLC between 1 January 2012 and 31 December 2018, were identified using the National Pathology Registry, Figure 1. One patient was excluded since the original diagnosis of *ALK+* NSCLC could not be verified, and one patient was excluded since the corresponding medical chart appeared twice in the data. Thus, the *ALK+* cohort available for Medical Chart Reviews consisted of a total of 209 patients with *ALK+* NSCLC, Figure 1. Using the unique 10-digit Social Security number as cross-reference, information regarding age, gender, education, labor market affiliation and marital status of the identified patients was obtained from The Danish National Patient Registry, The Danish Civil Registration System, The Danish Cancer Registry, DREAM and Statistics Denmark. For ten identified patients at least one of these pieces of information was missing; of the remaining 199 patients only, patients aged ≤ 60 years ($n = 75$) were analyzed for Labor Market affiliation, Figure 1.

Patient characteristics

Baseline characteristics of the *ALK+* NSCLC patients are summarized in Table 1. *ALK+* NSCLC patients were found to have a slight enrichment for women with a male:female ratio at 44%:56%, Table 1. The median age was 64.6 years, while the mean age was 61.6 years with a standard deviation of 14.2 years, Table 1. The majority (70%) of the patients were diagnosed with incurable stage IIIb–IVb disease (Table 1), treated with life prolonging intentions, while 28% were diagnosed with stage I–IIIa disease (Table 1), treated with curative intentions. Disease stage information at diagnosis was missing from 2% of the patients (Table 1). For extended baseline characteristics of the *ALK*-cohort, please refer to [17]. Supplementary Table 1 summarizes sociodemographic parameters for the patient and control group (Supplementary Table 1).

Table 1. Baseline characteristics of the ALK-cohort.

Characteristics	n = 209, n (%)
Gender:	
– Male	91 (43.5)
– Female	118 (56.5)
Age (years):	
– Mean (standard deviation)	61.6 (14.2)
– Median	64.6
Cancer stage at time of diagnosis:	
– I–IIIA	58 (28)
– IIIB–IVB	146 (70)
– Unknown/missing	5 (2)

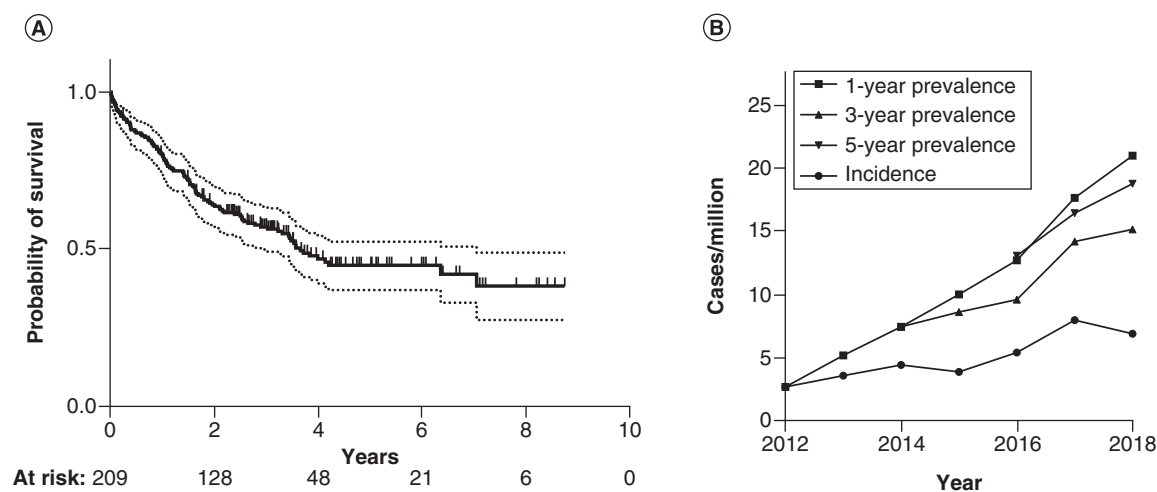


Figure 2. Overall survival and incidence and prevalence of ALK+ NSCLC in Denmark. (A) Overall survival of the ALK+ NSCLC patient group. Dotted lines represent 95% CIs. **(B)** Incidence and prevalence of ALK+ NSCLC patients in Denmark from 2012 to 2018. Square represents: 1-year prevalence. Triangles pointing up and down represents 3- and 5-year prevalence, respectively. Closed circles represent annual incidence. All values are cases/million Danes.

Clinical features, OS, treatment intentions & incidence/prevalence

During the study period, 5 and 50% of the individuals in the control group and ALK-cohort group died, respectively. To confirm that our ALK cohort did indeed have a different clinical course than lung cancer patients without targetable driver alterations, we performed an OS analysis for the ALK cohort. With a median follow-up of 32.0 months the median OS of the ALK-cohort patients was 44.0 months (Figure 2A). During the study period the yearly incidence of detected ALK+ NSCLC patients increased threefold from 15 patients/year to 46 patients/year (Figure 2B). Correspondingly, the prevalence increased almost eightfold from 2.7/million to 21.0/million during the same period (Figure 2B). This may at least in part reflect the fact that during the study period there was a gradual significant increase in testing for ALK rearrangements (“ALK positivity”) from being performed at single institutions to becoming standard of care at all Danish cancer centers.

A median OS of 44.0 months compares very favorable to the median OS of Danish lung cancer patients in general. Indeed, in general, Danish lung cancer patients had a median OS of less than 12 months in the years from 2012 to 2018, exemplified for 2015 in [11]. To exclude the possibility that this difference in OS was driven by large differences in stages of disease at diagnosis, we compared the disease stages at diagnosis for our ALK-cohort to the Danish lung cancer patients in general in 2015: 28% ALK+ NSCLC and 36% general lung cancer patients were diagnosed with stage I–IIIA disease (typically treated with curative intentions) [11]; 70 and 56% were diagnosed with stage IIIB–IVB disease, respectively and 2 and 8% had unknown disease stage [11].

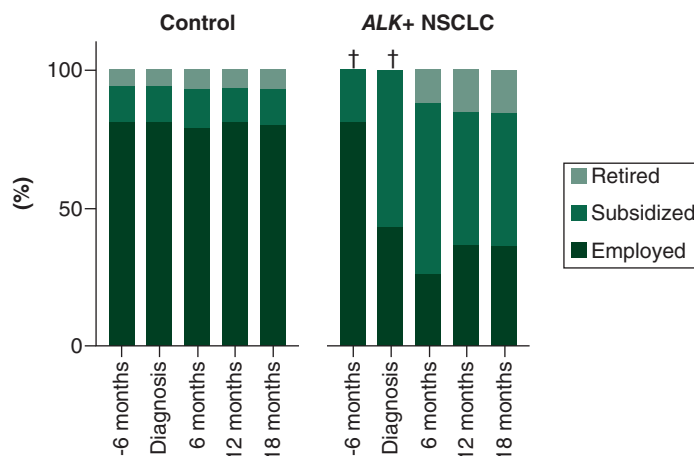


Figure 3. Labor market affiliation of working age (≤ 60 years of age) control group and ALK+ NSCLC survivors 6 months before diagnosis, at diagnosis, 6, 12 and 18 months following diagnosis. Labor market affiliation is classified into three categories: 1) employed (full- or part-time; black bar), 2) subsidized (receiving unemployment benefits, unemployment educational benefits and sick leave benefits; light gray bar), and 3) retirees (receiving retirement and early retirement benefits; dark grey bars).
 †Data on retirement were not shown for these data points as fewer than five individuals were retired among the ALK+ NSCLC patients.

Table 2. Overview of labor market affiliations (employed, subsidized, or retired) for ALK+ NSCLC patients and control survivors ≤ 60 years of age.

Labor market affiliation of survivors	-6 months		At diagnosis		6 months		12 months		18 months	
	n	%	n	%	n	%	n	%	n	%
ALK+ NSCLC (n = 75)										
In employment	61	81%	32	43%	18	26%	24	36%	21	36%
Subsidized	14	19%	43	57%	43	62%	32	48%	28	48%
Retired	<5	<5	<5	<5	8	12%	10	15%	9	15%
Control group (n = 748)										
In employment	606	81%	605	81%	591	79%	603	81%	586	80%
Subsidized	95	13%	95	13%	102	14%	88	12%	95	13%
Retired	47	6%	48	6%	55	7%	50	7%	51	7%

Subjects were censored from the labor market affiliation analysis if they died or left the country. Note that absolute values less than 5 are not reported due to Danish data protection laws.

Labor market affiliation for ALK+ NSCLC survivors

We performed our analysis of labor market affiliation among ALK+ NSCLC survivors in the subset of ALK+ NSCLC patients aged ≤ 60 years (n = 75) of age to minimize confounding impacts of advanced age and death from lung cancer on the affiliation to the labor market (in Denmark publicly funded retirement payments started at age 66 during the study period). In the control group the labor market affiliation was stable throughout the study period (Figure 3). On the other hand, a significant drop in labor market affiliation was observed in the experimental group, starting already at diagnosis, where the affiliation had dropped from 81% six months prior to diagnosis to 43% at diagnosis (Figure 3). During the follow-up period of 18 months, we observed a further drop to 26%, 36% and 36%, at 6, 12, and 18 months following diagnosis, respectively. Table 2 provides a detailed overview of the data in Figure 3. An analysis not taking survivorship status into account for labor market affiliation was performed and is presented in Table 3.

Discussion

Using nationwide registries linked through individual patient identifiers with 100% coverage, we report here that the median onset of ALK+ NSCLC in a nationwide cohort from Denmark is 64 years of age. This is older than findings from other studies where the median age of onset of ALK+ NSCLC was reported to be between 52 and 63 years [16,23,29–31]. However, a median age at diagnosis of 64 years of age remain younger than the median age of diagnosis of lung cancer in general, at 71 years [2,11]. Our finding of a median OS of 44.0 months compares well to other recent studies which found a median OS for ALK+ NSCLC patients ranging from 22 months to 48.5 months [16,29–31], while data from a single academic center in the US stands out with a median OS of 81 months [23]. In this context of median survival times well above 40 months, our finding of a median OS of 44.0 months further supports the consensus that ALK+ NSCLC patients live longer than lung cancer patients in

Table 3. Overview of labor market affiliations (employed, subsidized, retired, or dead/left the country) for *ALK+* NSCLC patients and control subjects ≤ 60 years of age.

Labor market affiliation and survivorship of study populations	-6 months		At diagnosis		6 months		12 months		18 months	
	n	%	n	%	n	%	n	%	n	%
<i>ALK+</i> NSCLC (n = 75)										
In employment	61	81%	32	43%	18	24%	24	32%	21	28%
Subsidized	14	19%	43	57%	43	57%	32	43%	28	37%
Retired	<5	<5	<5	<5	8	11%	10	13%	9	12%
Died or left the country	0	0	0	0	6	8%	9	12%	17	23%
Control group (n = 748)										
In employment	606	81%	605	81%	591	79%	603	81%	586	78%
Subsidized	95	13%	95	13%	102	14%	88	12%	95	13%
Retired	47	6%	48	6%	55	7%	50	7%	51	7%
Died or left the country	0	0	0	0	<5	<5	7	1%	16	2%

Subjects were not censored from the labor market affiliation analysis if they died or left the country. Note that absolute values less than 5 are not reported due to Danish data protection laws.

general [18,32]. Given the comparatively young age (61 vs 71 years) and prolonged survival/treatment period, it is thus reasonable to characterize *ALK+* NSCLC patients as a distinct group of lung cancer patients from a clinical outcome perspective.

We found an increase in the prevalence of *ALK+* NSCLC patients during the study period. This was likely driven by the increase in testing and incidence during the study.

Most of the research into labor market affiliation/return to work of cancer patients is focused on breast cancer patients [8]. In contrast, comparatively little is known of the labor market affiliation of lung cancer patients and the rate by which survivors of lung cancer return to work following diagnosis. However, one recent qualitative review of 23 studies found that lung cancer survivors are 2–three-times more unlikely to be employed as compared with control groups [7]. Unfortunately, the heterogenous nature of the studies, including control groups used, precluded a quantitative analysis of the return to work-rate of lung cancer survivors [7]. On the other hand, registry studies in patient populations originating in societies characterized by free healthcare and social security programs much like Denmark, have found return to work rates for lung cancer patients in general to be between 33 and 45% [10,33,34]. Among these, Rashid *et al.* [10] found that 33% of working age (<65 years of age) German lung cancer survivors were affiliated with the labor market about one year following diagnosis, with the mean time to return to work being 13 months [10]. Yang *et al.* [34] found a slightly higher labor market affiliation rate at 41% after 2 years in a Taiwanese population somewhat enriched for stage I–II patients (69% as compared with <28% in our study), while a Dutch study found a return to work rate of 45% after 2 years [33]. Our finding that 36% of *ALK+* NSCLC patients are employed 18 months following diagnosis, thus tracks well with findings of return to work rates for lung cancer patients in general.

During the conduct of our study, two studies containing data on labor market affiliation of lung cancer patients treated with targeted agents were published. One study reported that 25% of a small cohort (N = 20) of patients with metastatic lung cancer treated with PD-L1 inhibitors and tyrosine kinase inhibitors from a single institution in Australia were employed following lung cancer diagnosis (median time 27 months) [35]. The other, larger study used an online survey specific for patients with *ALK+* NSCLC in the US and found a labor market affiliation of 40% among 104 patients 25.6 months (median) after diagnosis [36]. 25% of the patients surveyed in this study matched our definition of working age (<60 years of age), and the majority (77%) of the patients had metastatic or regionally spread disease [36]. The patient population thus resembles the patient population of our study quite well as does the findings related to labor market affiliation (40 and 36% in the US study and our study, respectively). While the two studies arrive at near identical findings, our study relies on data from national, interlinked registries and thus does not have an inherent methodological inclusion-bias of an online survey, which relies on patients being willing and capable of participating.

Our finding of a labor market affiliation for working age (<60 years of age) *ALK+* NSCLC patients of 36% 18 months following diagnosis thus compares very well with previous findings both among lung cancer patients in general [10,33,34], among lung cancer patients treated with targeted agents at large [35], and among patients with

ALK+ NSCLC specifically [36]. Our results thus suggest that *ALK+* NSCLC patients when assessed according to labor market affiliation currently do not comprise a distinct subgroup of lung cancer patients, despite their superior survival and lessened toxicity burden. As returning to work following a cancer diagnosis is associated with a higher degree of self-satisfaction, financial means, sense of normality and confidence, this finding is disappointing. Our finding also suggests that the overall well-being of this patient population could be strengthened by efforts to retain affiliation to the labor market. In this context, it is important to note, that Rashid *et al.* found that lung cancer patients who used social and legal counseling services had a higher likelihood of returning to work [10].

Our study's strength is usage of national registries with 100% coverage, which allows us to eliminate recruitment bias associated with surveys, for instance. On the other hand, the use of registries precluded more granular understanding of the impact of an *ALK+* NSCLC diagnosis on employment. For instance, it would have been beneficial to be able to differentiate between full- and part-time employment. In addition, our study did not compare *ALK+* NSCLC patients to NSCLC patients at large, making any conclusions regarding differences in employment indirect and based on comparisons to published literature. We chose to use aged-matched controls without NSCLC as controls rather than NSCLC patients, as the large differences in treatment, treatment burden, comorbidities and age of NSCLC and *ALK+* NSCLC patients would require matching based on clinical parameters not available in national registries, and it allows a direct quantification of the consequence of an *ALK+* NSCLC diagnosis on labor market affiliation. Danish society is egalitarian with many options for societal and monetary support in case of illness. Our findings may therefore not be representative of societies characterized by different options for societal and monetary support. Finally, our study used *ALK+* NSCLC patients as a proxy for lung cancer patients with extended survival. Our conclusions could have been extended with more assurance if we had included all lung cancer survivors instead of using a single patient group with a favorable prognosis as a proxy for long-term survivors.

Conclusion

In conclusion, using *ALK+* NSCLC patients as a proxy for NSCLC patients with targetable driver alterations, we did not find evidence to support our hypothesis, that NSCLC patients with targetable driver alterations retain their affiliation to the labor market in larger proportions than what has been published for NSCLC patients in general. Considering the increasing prevalence of *ALK+* NSCLC patients, the long-term survival of *ALK+* NSCLC patients [23,29,30], the demonstrated positive effects of retaining an affiliation with the labor market [6,7] and that lung cancer patients who use legal or social service counseling at diagnosis have a higher likelihood of returning to work as compared with lung cancer patients who do not [10], a concerted effort to provide legal and social counseling should be implemented. Such counseling could be offered either by clinicians or patient advocacy groups in collaboration with relevant social service sectors.

Summary points

- Returning to work after a cancer diagnosis is important for patients' financial stability and well-being, as well as for society's economic growth.
- Returning to work after a lung cancer diagnosis is associated with young age and lessened treatment burden.
- Patients with *ALK+* NSCLC have improved survival, are often younger, and experience less treatment burden compared with chemotherapy-treated patients. We therefore hypothesized that such patients would be more likely to return to work following their diagnosis.
- Using nationwide data of all *ALK+* NSCLC patients diagnosed in Denmark between 2012 and 2018 we found:
 - An almost eightfold increase in prevalence of *ALK+* NSCLC patients in the study period, possibly due to the gradual implementation of sensitive *ALK* testing in the different Danish lung cancer centers.
 - That *ALK+* NSCLC patients live longer than NSCLC patients with-out targetable alterations.
 - That *ALK+* NSCLC patients did not return to work following their diagnoses in greater numbers than what has historically been published for lung cancer patients in general.
- We recommend that *ALK+* NSCLC patients receive social and legal counseling to aid in maintaining an affiliation to the labor market following diagnosis.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/lmt-2023-0013

Author contributions

All authors contributed to the study conception and design. Data collection was performed by JS Johansen, P Hjort-Hansen, M Parm Ulhøj, P Meldgaard, E Maria Urbanska, K Holmskov Hansen, C Kristiansen, B Højgaard and M Sall Jensen. Data analyses were performed by B Højgaard, M Sall Jensen and A Bondo Dydensborg. The first draft of the manuscript was written by A Bondo Dydensborg, and all authors reviewed the manuscript critically. All authors read and approved the final manuscript.

Financial disclosure

The study was funded and initiated by Takeda Pharma A/S, a subsidiary of Takeda Pharmaceuticals Inc. Authors A Bondo Dydensborg and C Dünweber are employees of Takeda Pharma A/S. P Meldgaard has received research funding from Roche, Takeda and Astra Zeneca, as well as consultancy fees from Amgen, Astra Zeneca, Roche, Sanofi, Pfizer and Takeda. E Maria Urbanska has received honorarium and consultancy fees from Roche, Amgen, Astra Zeneca, Novartis, Takeda and Pfizer. E Santoni-Rugiu has received consultancy/lecture honorarium from Amgen, Bayer, Roche, Sanofi, Takeda Astra Zeneca, Bristol Myers Squibb, Roche, Takeda, conference participation support from Takeda, and research grants from Roche and Sanofi. M Parm Ulhøj has received consultancy / lecture honorarium from Takeda, Pfizer, Amgen and Sanofi as well as conference participation support from Sanofi and MSD. JL Andersen has received honoraria for lectures, advisory boards, and congress expenses from Abbvie, Amgen, Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharp and Dohme (MSD), Novartis, Pfizer, Pierre Fabre, Roche, Sanofi and Takeda. M Stelmach has received honoraria for lectures and advisory board from Takeda. All other authors report no other conflicts of interest in this work. Authors B Højgaard and M Sall Jensen were employees of the Danish Center for Social Science Research (VIVE) and were contracted by Takeda Pharma to extract data from the National Registries and perform analysis in this matter. B Højgaard's and M Sall Jensen's employment with VIVE ended during the writing of the article, B Højgaard is now employed at Steno Diabetes Center, Copenhagen, Denmark and M Sall Jensen is now employed at Novo Nordisk, Søborg, Denmark. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Ethical conduct of research

The study was approved by the Danish Patient Safety Authority (#3-3013-3274/1 and #3-3013-3161/1) and registered at the Danish Data Protection Agency. There are no Danish legislation requirements to obtain approval from ethics review committees nor obtaining 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.

Previous presentation

Presented at: World Conference on Lung Cancer (WCLC), 2021, Vienna [#795].

DOI:10.1016/j.jtho.2021.08.311.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Sung H, Ferlay J, Siegel RL *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* 2021;71(3):209–249.
2. Rasmussen TR, Jakobsen E, Rasmussen C *et al.* *Dansk Lunge Cancer Register Årsrapport 2021*. Aarhus, Denmark: Regionernes Kliniske Kvalitetsudviklingsprogram; 2021.
3. Howlader N, Forjaz G, Mooradian MJ *et al.* The effect of advances in lung-cancer treatment on population mortality. *N. Engl. J. Med.* 2020;383(7):640–649.
4. Rebuzzi SE, Zullo L, Rossi G *et al.* Novel emerging molecular targets in non-small-cell lung cancer. *Int. J. Mol. Sci.* 2021;22(5):2625.

5. Ricciardi S, Tomao S, de Marinis F. Toxicity of targeted therapy in non-small-cell lung cancer management. *Clinical Lung Cancer* 2009;10(1):28–35.
6. de Boer AG, Torp S, Popa A *et al.* Long-term work retention after treatment for cancer: a systematic review and meta-analysis. *J. Cancer Surviv.* 2020;14(2):135–150.
7. Vayr F, Savall F, Bigay-Game L *et al.* Lung cancer survivors and employment: a systematic review. *Lung Cancer* 2019;131:31–39.
8. Butow P, Laidsaar-Powell R, Konings S *et al.* Return to work after a cancer diagnosis: a meta-review of reviews and a meta-synthesis of recent qualitative studies. *J. Cancer Surviv.* 2020;14(2):114–134.
9. Paltrinieri S, Fugazzaro S, Bertozzi L *et al.* Return to work in European cancer survivors: a systematic review. *Support. Care Cancer* 2018;26(9):2983–2994.
10. Rashid H, Eichler M, Hechtner M *et al.* Returning to work in lung cancer survivors—a multi-center cross-sectional study in Germany. *Support. Care Cancer* 2021;29(7):3753–3765.
- **This paper found that factors associated with return-to-work of lung cancer patients included young age and being recipient of legal and social counseling.**
11. Rasmussen TR, Jakobsen E, Rasmussen C *et al.* *Dansk Lunge Cancer Register Årsrapport 2015*. Hedeager, DK-8200, Aarhus, Denmark: Regionernes Kliniske Kvalitetsudviklingsprogram; Regionshuset Aarhus; 2021 2016.
12. Planchard D, Popat S, Kerr K *et al.* Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2018;29(Suppl. 4):iv192–iv237.
13. Postmus PE, Kerr KM, Oudkerk M *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2017;28(Suppl. 4):iv1–iv21.
14. Lindbohm ML, Kuosma E, Taskila T *et al.* Cancer as the cause of changes in work situation (a NOCWO study). *Psychooncology* 2011;20(8):805–812.
15. Paraponaris A, Teysier LS, Ventelou B. Job tenure and self-reported workplace discrimination for cancer survivors 2 years after diagnosis: does employment legislation matter? *Health Policy* 2010;98(2–3):144–155.
16. Lauppe R, Nilsson FOL, Fues Wahl H *et al.* Use of ALK-tyrosine kinase inhibitors (ALK TKI) in clinical practice, overall survival, and treatment duration - a Swedish nationwide retrospective study. *Acta Oncol.* 2022; 61(11):1–8.
17. Hansen KH, Johansen JS, Urbanska EM *et al.* Clinical outcomes of ALK+ non-small-cell lung cancer in Denmark. *Acta Oncol.* 2023;62(12):1775–1783.
- **Describes the clinical course of the ALK+ NSCLC cohort of the present study.**
18. Sakamoto T, Matsubara T, Takahama T *et al.* Biomarker testing in patients with unresectable advanced or recurrent non-small-cell lung cancer. *JAMA Netw Open.* 2023;6(12):e2347700.
- **Describes that lung cancer patients with targetable mutations who are treated with targeted therapies lives significantly longer than patients treated with conventional therapies, regardless of presence of targetable mutations.**
19. Schmid S, Cheng S, Chotai S *et al.* Real-world treatment sequencing, toxicities, health utilities, and survival outcomes in patients with advanced ALK-rearranged non-small-cell lung cancer. *Clin. Lung Cancer* 2023;24(1):40–50.
20. Marinelli D, Siringo M, Metro G *et al.* Non-small-cell lung cancer: how to manage ALK-, ROS1- and NTRK-rearranged disease. *Drugs Context* 2022;11:2022-3-1.
21. Soda M, Choi YL, Enomoto M *et al.* Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448(7153):561–566.
- **Describes chromosomal rearrangements leading to ALK-fusion proteins expressed in non-small-cell lung cancer for the first time.**
22. Skov BG, Clementsen P, Larsen KR *et al.* The prevalence of ALK rearrangement in pulmonary adenocarcinomas in an unselected Caucasian population from a defined catchment area: impact of smoking. *Histopathology* 2017;70(6):889–895.
23. Pacheco JM, Gao D, Smith D *et al.* Natural history and factors associated with overall survival in stage IV ALK-rearranged non-small-cell lung cancer. *J. Thorac. Oncol.* 2019;14(4):691–700.
24. Solomon BJ, Mok T, Kim D-W *et al.* First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* 2014;371(23):2167–2177.
25. Harris PA, Taylor R, Minor BL *et al.* The REDCap consortium: building an international community of software platform partners. *J. Biomed. Inform.* 2019;95:103208.
26. Erichsen R, Lash TL, Hamilton-Dutoit SJ *et al.* Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin. Epidemiol.* 2010;2:51–56.
27. Leuven E, Sianesi B. PSMATCH2: stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. [Statistical Software Components]. <http://EconPapers.repec.org/RePEc:boc:bocodes:432001> 2003.
28. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scandin. J. Public Health* 2007;35(5):497–502.

29. Britschgi C, Addeo A, Rechsteiner M *et al.* Real-world treatment patterns and survival outcome in advanced anaplastic lymphoma kinase (ALK) rearranged non-small-cell lung cancer patients. *Front. Oncol.* 2020;10:1299.
 30. Gibson AJW, Box A, Dean ML *et al.* Retrospective real-world outcomes for patients with ALK-rearranged lung cancer receiving ALK receptor tyrosine kinase inhibitors. *JTO Clin. Res. Rep.* 2021;2(4):100157.
 31. Eide IJZ, Nilssen Y, Stensland EM *et al.* Real-world data on EGFR and ALK testing and TKI usage in Norway-A nation-wide population study. *Cancers (Basel)* 2023;15(5):1505.
 32. Pacheco JM, Camidge DR. Is long-term survival possible for patients with stage IV ALK+ non-small-cell lung cancer? *Exp. Rev. Respir. Med.* 2019;13(5):399–401.
 33. Roelen CA, Koopmans PC, Groothoff JW *et al.* Sickness absence and full return to work after cancer: 2-year follow-up of register data for different cancer sites. *Psychooncology* 2011;20(9):1001–1006.
 34. Yang ZY, Lai CH, Ho CL *et al.* Epidemiological study of return to work and mortality in lung cancer survivors. *Int. J. Environ. Res. Public Health* 2021;19(1):309.
 35. Lai-Kwon J, Heynemann S, Flore J *et al.* Living with and beyond metastatic non-small-cell lung cancer: the survivorship experience for people treated with immunotherapy or targeted therapy. *J. Cancer Surviv.* 2021;15(3):392–397.
 36. Lin HM, Pan X, Biller A *et al.* Humanistic burden of living with anaplastic lymphoma kinase-positive non-small-cell lung cancer: findings from the ALKConnect patient insight network and research platform. *Lung Cancer Manag.* 2020;10(1):Lmt42.
- **Using an online survey, this paper found that 40% of American ALK+ NSCLC patients were employed following diagnosis.**