NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Real-world study of non-small cell lung cancer treatment with ALK-tyrosine kinase inhibitors (ALK TKI) in Sweden: drug sequencing, treatment duration and overall survival – A retrospective study using Swedish register data
Protocol number	B7461035
Protocol version identifier	Version 1.2
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Active substance	L01XE16 Crizotinib L01XE44 Lorlatinib
Medicinal product	Xalkori (crizotinib) Lorviqua (lorlatinib)
Research question and objectives	The objectives are to analyse overall survival and duration of treatment in Swedish NSCLC patients. Primary objective: 1. Estimation of overall survival (OS) in ALK-inhibitor users. Secondary objective: 2. Estimation of duration of treatment (DOT) in ALK-inhibitor users.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ATC	The Anatomical Therapeutic Chemical Classification System
CDR	The Swedish Cause of Death Register
Chemo	Chemotherapy
CI	Confidence interval
CNS	Central nervous system
CUP	Compassionate use programme
CSF	Cerebrospinal fluid
DOT	Duration of treatment
EMA	European Medical Agency
FASS	Pharmaceutical specialities in Sweden
GPP	Guidelines for Good Pharmacoepidemiology Practices
ICD	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
ICMJE	International Committee of Medical Journal Editors
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ID	Identification
IEC	Independent ethics committee
IRB	Institutional review board
IV	Intravenous therapy
KM	Kaplan Meier
KVÅ koder	Procedure codes
NBHW	National Board of Health and Welfare
NCSP	NOMESCO Classification of Surgical Procedures
NI	Non-interventional
NOMESCO	The Nordic Medico-Statistical Committee
NPR	The Swedish National Patient Register
NSCLC	Non-small cell lung cancer
MPA	Medical Products Agency
OS	Overall survival
PIN	Personal identifiable number
PDR	The Swedish Prescribed Drug Register
ROS1	C-ros oncogene 1
SCLC	Small-cell lung cancer
CR	The Swedish Cancer Register
SD	Standard deviation
SoC	Standard of care
TKI	Tyrosine kinase inhibitor
TKR	Tyrosine kinase receptor
TLV	The Dental and Pharmaceutical Benefits Agency, Sweden

3. RESPONSIBLE PARTIES

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4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	23 November 2020
End of data collection	31 December 2020
Final study report	31 March 2021

6. RATIONALE AND BACKGROUND

Lung cancer is a malignant tumour characterized by uncontrolled cell growth in tissues of the lung. The disease is highly difficult to treat and is the most common cause of cancer-related death in Sweden, despite being only the sixth most common tumour type.[2] More than 4000 lung cancer cases are diagnosed in Sweden every year[3] with expected 5-year survival of 16.5%.[4] For patients with metastatic disease, the 5-year survival is even poorer amounting to only a few percent.[5]

Median age at lung cancer onset is 71 years, but the disease also affects younger.[2] Ninety one (91) patients under the age of 50 were diagnosed with lung cancer in 2017 in Sweden.[3] Over time, the composition of the group of newly diagnosed patients has gradually shifted from an overweighing majority of men diagnosed in the 1970's to a small majority of women in recent years,[1,3] likely reflecting changes in smoking habits over time. Even if cigarette smoking remains the most relevant contributing factor in the development of the disease, a distinct group of patients without significant smoking history also develops lung cancer due to an acquired genetic predisposition.[6]

The majority (~85%) of lung cancer cases falls into the category of Non-Small Cell Lung Cancer (NSCLC) whereas the Small Cell Lung Cancer (SCLC) represents the second largest subtype (~15%).[6] NSCLC is further categorized into three major histological subtypes according to the site and cell type of origin. Adenocarcinoma, which is most prevailing and often observed in non-smokers, represents approximately 40% of all lung cancers, whereas squamous cell carcinoma and large cell carcinoma account for 25-30% and 5-10% respectively.[6]

Advances in the understanding of molecular tumour biology have led to the deeper classification of lung adenocarcinomas through identification of several key genetic alterations as primary drivers of tumour growth. Somatic genetic rearrangements including genetic fusions can alter the structure and function of different Tyrosine Kinase Receptor (TKR) proteins resulting in uncontrolled stimulation of cell growth, proliferation and survival. Concurrently, the discovery of these alterations in NSCLC has opened a new realm of therapeutic possibilities via direct inhibition of the faulty receptor signalling by targeted Tyrosine Kinase Inhibitor (TKI) drugs.

One of the first oncogenic drivers recognized in lung adenocarcinoma is the genetic rearrangement in Anaplastic Lymphoma Kinase (ALK) which defines about 5% of NSCLC cases.[7] ALK-positive patients, the population pertinent to this study, are typically younger, non-smokers, and predominantly women.[8]

The treatment that cures most lung cancer patients is surgery. The intervention is however possible only in a fraction of patients with early disease, likely in combination with radiotherapy and/or chemotherapy.[2,9] As most lung cancer cases are discovered in a late stage, the available therapy options are limited to medical treatments; primarily immunotherapy and chemotherapy.[2,10] For oncogene-driven disease however, where

immunotherapy has shown largely ineffective, TKI drugs represent the principal therapeutic strategy followed by chemotherapy.[11] For almost a decade now, the ALK inhibitors have demonstrated significant benefits in the management of ALK-positive NSCLC and substantially exceeded the therapeutic outcomes of conventional approaches.[12-14] The possibility of ALK TKI sequencing, ie, successful management of acquired tumour resistance with next, more potent ALK-inhibitor drug, brings a major therapeutic advantage by providing long-term disease control alongside high quality of life.

According to the latest available Swedish national lung cancer therapy guidelines (2020),[11,15] and in concordance with international recommendations,[16,17] patients with ALK-positive NSCLC should primarily be offered treatment with an ALK-inhibitor. Nearly all of the patients who initially respond to ALK-inhibitors however progress within 1 to 2 years due to the molecular evolution of their tumors that renders the targeted agent ineffective. The subsequent choice of drug for combating this acquired resistance will depend on which ALK TKI has been used at the therapy onset and is dictated by drug approval/reimbursement status, therapy guidelines and tumour molecular resistance mechanisms.

The first ALK TKI which was approved in NSCLC and subsequently received reimbursement in Sweden was crizotinib. In addition, three second-generation products (ceritinib, alectinib and brigatinib) and one third-generation agent (lorlatinib) are now on the market. Regulatory status of individual ALK TKIs for treatment of ALK-positive NSCLC in Sweden is described and summarised in Table 1. The reimbursement status corresponds to the approved indication for all ALK TKIs with the exception of ceritinib which was evaluated by the Swedish reimbursement authority TLV in second-line treatment only. Therefore, for ceritinib the second approval date in Table 1. refers to the European Medical Agency (EMA) approval date, the timepoint at which ceritinib implicitly gained reimbursement.

Crizotinib, the first ALK TKI developed, has been the standard of care (SoC) for years and it still plays a minor role as first-line therapy for selected Swedish patients. Second-generation inhibitors however, particularly alectinib, have recently demonstrated superior efficacy over crizotinib, especially in the central nervous system (CNS), thereby becoming the new SoC in frontline setting.

With regard to first-line therapy, the Swedish guidelines recommend alectinib as a first-hand choice and recognize both crizotinib and ceritinib as alternatives. Regarding the second-line treatment, Swedish guidelines deem that patients previously treated with crizotinib should be offered second generation agents alectinib, ceritinib or brigatinib. For all patients treated with second-generation agents (alectinib, ceritinib or brigatinib) regardless of the line of therapy, the Swedish guidelines recommend lorlatinib. Due to their minor efficacy in ALK-positive NSCLC, immunotherapies (eg, nivolumab, pembrolizumab and atezolizumab) are not preferred by Swedish treatment guidelines and are spared for conclusion of therapy.

An important aspect which should be mentioned alongside the Swedish lung cancer therapy guidelines is the national healthcare regulation which allows for use of drugs outside their approved indication in the event of high unmet patient need and at the discretion of the treating physician.

In addition, a lorlatinib Compassionate Use Program for ALK+/ C-ros oncogene 1 (ROS1) + NSCLC has been active in Sweden from 26 June 2017 until the drug's EMA-approval. According to the agreement with the Swedish MPA, patients who were active in the Compassionate use programme (CUP) at the time of lorlatinib approval could continue in the program until the reimbursement decision was made by the The Dental and Pharmaceutical Benefits Agency in Sweden (TLV) in September 2019. At the time of the reimbursement decision, the few patients who were still under ongoing lorlatinib therapy were switched to commercial product. This switch to commercial lorlatinib may therefore manifest in the Prescribed Drug Register in a form of lorlatinib prescription after a period of drug therapy gap. In all CUP-patients, lorlatinib was given at the point of failure of all other appropriate available treatment options.

Table 1. Regulatory Status of ALK Inhibitors in Sweden

ALK inhibitor	Date of EMA approval[18-22]	Date of reimbursement	Description of reimbursement
Crizotinib	23 October 2012	March 2014	Treatment of adults with previously treated ALK+ advanced NSCLC
		June 2016	First-line treatment of adults with ALK+ advanced NSCLC
Ceritinib	06 May 2015	December 2015	Treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib
		June 2017	First-line treatment of adults with ALK+ advanced NSCLC
Alectinib	16 February 2017	November 2017	Treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib
		April 2018	First-line treatment of adult patients with ALK+ advanced NSCLC
Brigatinib	22 November 2018	December 2018	Treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib
		July 2020	First-line treatment of adult patients with ALK+ advanced NSCLC
Lorlatinib	06 May 2019	September 2019	Treatment of adult patients with ALK+ advanced NSCLC whose disease has progressed after: - alectinib or ceritinib as the first ALK TKI therapy; or - crizotinib and at least one other ALK TKI

Sources: [3,23,29].

Several real-world evidence studies have reported on treatment patterns and clinical outcomes in patients receiving ALK inhibitors. A majority of the studies assessed the TKI sequences began with crizotinib followed by second generation ALK TKIs and chemotherapy, confirming the benefits of successive ALK TKI treatment.[30-32] Davies et al.[33] recently studied treatment patterns for crizotinib and ceritinib patients in the US, showing predominant use of the two TKIs from first- to third-line therapy. In an Australian study by Itchins et al.,[34] about half of the patients received at least two lines of ALK inhibitor therapy. This retrospective observational study aims to inform on sequencing of ALK-inhibitors, the settings in which ALK-inhibitors are initiated (eg clinical and demographic characteristics of patients), treatment duration and overall survival (OS) for Swedish lung cancer patients.

7. RESEARCH QUESTION AND OBJECTIVES

This study is, to our knowledge, the first real-world study of sequencing of ALK-inhibitors and overall survival in Swedish NSCLC patients. The primary objective is to analyse overall survival in Swedish NSCLC patients.

Primary objective:

- Estimation of overall survival (OS) in ALK-inhibitor users.

Secondary objective:

- Estimation of duration of treatment (DOT) in ALK-inhibitor users.

8. RESEARCH METHODS

8.1. Study Design

To address the research objectives, a national retrospective cohort analysis will be conducted aiming to study duration of treatment and overall survival in Swedish ALK-positive NSCLC patients. The observational study design, which uses and crosslinks several registries, will allow the inclusion of a large and broad patient population and analysis of multiple real-world outcomes.

The objectives of the study are:

Primary:

1. Estimation of overall survival (OS) in ALK-inhibitor users.

Secondary:

1. Estimation of duration of treatment (DOT) in ALK-inhibitor users.

Based on the study objectives, the study outcomes are:

- Primary: Median survival using Kaplan-Meier estimates, and proportion of patients alive after 5 and 6 years.

- Secondary: DOT (days) for ALK-inhibitor users.

8.2. Setting

The study population will be inclusive of all adults (age ≥18 years) with at least one filled prescription of crizotinib, ceritinib, alectinib, brigatinib or lorlatinib (Anatomical Therapeutic Chemical Classification System-codes (ATC) listed in Table 2) registered in the Swedish Prescribed Drug Register between 01 January 2012 and 31 December 2020 or last available data. The first identified prescription date of any of the above-mentioned therapies will correspond to the patient's index date. The study population will be representative of Swedish ALK-inhibitor users.

Table 2. ALK-inhibitors

Substance	Product name	ATC-code
Alectinib	Alecensa	L01XE36
Brigatinib	Alunbrig	L01XE43
Ceritinib	Zykadia	L01XE28
Crizotinib	Xalkori	L01XE16
Lorlatinib	Lorviqua	L01XE44

De-identified individual-level data will be collected from administrative registers in Sweden; the National Patient Register (NPR), the Prescribed Drug Register (PDR), the Cause of Death Register (CDR) and the Swedish Cancer Register (CR). The study will encompass complete data on all inpatient and specialist outpatient hospital care, dispensed prescriptions, and mortality for the study period, for all patients included in the study population. The study will take advantage of the rich content of the Swedish population-based registries with universal coverage and detailed patient-level data.

The study period is defined as 01 January 2007 to 31 December 2020 or last available data date. The study period is longer than the inclusion period to allow for a look-back period for the included patients.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. One or more (≥1) filled prescription/s of one or several of the following ALK inhibitors (ATC-codes in Table 2):
2. Crizotinib.
3. Ceritinib.
4. Alectinib.
5. Brigatinib.
6. Lorlatinib.
7. Age ≥18 years at index date.

8.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

8.2.3. Study Definitions

8.2.3.1. Overall Study Period

The overall study period is defined as the period during which patients are studied and data are used to characterize them. The study period spans from 01 January 2007 to 31 December 2020 or last available data.

8.2.3.2. Identification Period

Patients will be identified for possible inclusion in the study populations based on recorded prescriptions of ALK-inhibitors (Table 2) in the prescription register between 01 January 2012 to 31 December 2020 or last available data.

8.2.3.3. Index Date

The index date will be defined as the date of the first dispensed prescription (initiation date) of an ALK-inhibitor (ATC-codes in Table 2). The index points will be identified from 01 January 2012 to 31 December 2020 or last available data.

All dispensed prescriptions of ALK-inhibitors before their respective EMA approval dates (regardless of indication) will be excluded from the data analyses. EMA approval dates are specified in Table 1.

8.2.3.4. Baseline Period

The baseline period will be defined as the period five years prior to index date. This period will be used for the assessment of baseline demographics and comorbidities.

8.2.3.5. Follow-up Period

All patients will be followed until the end of the overall study period. Patients who die will still be included in the analyses, however, with their status at death carried forward. The follow-up period will be used to analyse drug sequencing and to assess the overall survival.

8.2.3.6. Number of Days on ALK-inhibitor Treatment

The number of days on each ALK inhibitor (treatment duration) for each patient will be reported. The number of days with available medication during the follow-up period will be calculated using the date when a prescription was filled, the number of packs and their size and the recommended daily dose according to the Pharmaceutical Specialties in Sweden (FASS) (see Table 3). In this calculation, we will consider medication stockpiling, which is the accumulation of prescription medications for later use. A patient that dispenses a prescription while he/she is still expected to have parts of the previous prescription of the same drug left, is assumed to start using the new prescription when the previous is expected to end. For study definition of persistence and treatment initiation, see Sections 8.2.3.8 and 8.2.3.9.

Table 3. FASS Recommended Daily Dose

Substance	FASS recommended daily dose	ATC-code
Alectinib	1200 mg	L01XE36
Brigatinib	First 7 days: 90 mg After 7 days: 180 mg	L01XE43
Ceritinib	Before June 1st, 2018: 750 mg From June 1st, 2018: 450 mg	L01XE28
Crizotinib	500 mg	L01XE16
Lorlatinib	100 mg	L01XE44

Source: [35]

8.2.3.7. Permissible Gap

The "permissible gap" is defined as the maximum time period allowed from the end of the previous prescription's supply until the next prescription. This study will investigate different permissible gaps, such as 4 weeks (28 days) and 8 weeks (56 days) as well as "no permissible gap enforced", ie, assuming patients are on treatment until they fill the next prescription or begin the next line of treatment. The number of patients identified per sequence using the above approaches will be reported. The primary analysis will utilize the alternative "no permissible gap enforced". As sensitivity analyses, one or two alternative permissible gaps may be utilized.

8.2.3.8. Persistence

Patients will be defined as persistent as long as they fill prescriptions of the current treatment, at least within the defined permissible gap. Time on treatment calculations will assume uninterrupted treatment during persistence. Patients will be defined as non-persistent from the last day of supply if the permissible gap is exceeded or if a new treatment is initiated. If patients switch drugs the stopping date of the old treatment will be defined as the date of the first dispensed prescription of the new treatment, even if this date lies within the permissible gap for the previous treatment.

8.2.3.9. Treatment Initiation of Pharmaceuticals

Treatment initiation will be defined as the first filled prescription of that drug (codes specified in Table 2). The start of the new treatment will be defined as the date of the first dispensed prescription of the new treatment, even if this date lies within the permissible gap for the previous drug.

All dispensed prescriptions of ALK-inhibitors before their respective EMA approval dates (regardless of indication) will be excluded from the data analyses. EMA approval dates are specified in Table 1.

8.2.3.10. Chemotherapy

In this study, we will stratify patients into those who have received first-line chemotherapy and those who have not, prior to the first ALK-inhibitor being initiated. This stratification is included since chemotherapy may decrease the effect of the ALK-inhibitor treatment. The time period of interest is up to two years prior to the index date.

Since only prescription drugs are found in the Swedish Prescribed Drug Register (and not hospital-only drugs), Intravenous therapy (IV) therapies are difficult to identify among the study data. We will therefore use procedure codes and recorded healthcare visits to inform the assumption that patients received first-line chemotherapy. Chemotherapy administered later in the drug sequence including amid ALK TKIs and at the conclusion of the therapy will not be captured.

The study definition of chemotherapy is at least one of the following:

- Procedure codes listed in Table 9.
- The patient has at least one outpatient healthcare visit at a oncology department/clinic recorded in the Swedish National Patient Register every 4 weeks for ≥3 months (90 days), but has not received other treatments (Table 2) during this period.

Chemotherapy is assumed to stop when other treatments start. If several treatment courses are found after each other, this will be defined as "one chemotherapy".

8.2.3.11. CNS Metastases

A particular feature of metastatic ALK-positive NSCLC is the high tendency of disease spread to the brain. CNS-metastases affect from 24 to 42% of patients with the risk increasing over time, reaching nearly 60% at 3 years.[36] It remains controversial however, whether this increased risk is an expression of the natural ALK-rearranged disease course independent of the therapy received, or if it relates to low Cerebrospinal fluid-penetrance (CSF-penetrance) of chemotherapy and early generation ALK TKIs.

We will identify CNS-metastases over the whole study period and report the number of patients that received a diagnosis before and after initiation of first ALK TKI, respectively. For analysis of the primary objective, concerned with OS, CNS-metastases identified up to two years prior to first ALK TKI will serve as sub-group identifier.

The study definition of CNS-metastases is at least one of the following:

- Brain metastases diagnosis code in the Swedish National Patient Register (International Statistical Classification of Diseases and Related Health Problems code - tenth revision [ICD-10] C79.3).
- Brain metastases diagnosis code in the Swedish Cancer Register (ICD-10 code C79.3).

8.2.3.12. Sequencing of ALK Inhibitors

The sequencing of ALK-inhibitor drugs in Sweden between 01 January 2012 and 31 December 2020 will be described in terms of number of patients per sequence. Patients will only be counted once.

Sequences relevant for this study are summarized in Table 4. In total, results will be reported for 52 cohorts, where 26 cohorts have received chemotherapy as first-line treatment (cohorts 2, 4, 6 and 8) and 26 cohorts have not (cohorts 1, 3, 5 and 7). Patients in cohorts 1 and 2 have received one line of ALK-inhibitor, patients in cohorts 3 and 4 have received two, patients in cohorts 5 and 6 have received three and patients in cohorts 7 and 8 have received at least four ALK inhibitors.

Table 4. ALK Sequencing Cohorts

1 ALK treatment line: Cohort A (ALK) and Cohort B (Chemo + ALK)	**Cohort number**
Crizotinib	1.1, 2.1
Alectinib	1.2, 2.2
Ceritinib	1.3, 2.3
2 ALK treatment lines: Cohort C (ALK + ALK) and Cohort D (Chemo + ALK + ALK)	
Crizotinib + Alectinib/Brigatinib/Ceritinib	3.1, 3.2, 3.3, 4.1, 4.2, 4.3
Alectinib + Brigatinib/Ceritinib/Lorlatinib	3.4, 3.5, 3.6,4.4, 4.5, 4.6
Ceritinib + Alectinib/Brigatinib/Lorlatinib	3.7, 3.8, 3.9, 4.7, 4.8, 4.9
3 ALK treatment lines: Cohort E (ALK + ALK + ALK) and Cohort F (Chemo + ALK + ALK + ALK)	
Crizotinib + Alectinib + Ceritinib/Lorlatinib/Brigatinib	5.1, 5.2, 5.3, 6.1, 6.2, 6.3
Crizotinib + Ceritinib + Alectinib/Lorlatinib/Brigatinib	5.4, 5.5, 5.6, 6.4, 6.5, 6.6
Crizotinib + Brigatinib + Alectinib/Lorlatinib	5.7, 5.8, 6.7, 6.8
Alectinib + Brigatinib + Lorlatinib	5.9, 6.9
Alectinib + Lorlatinib+ Brigatinib/Ceritinib	5.10, 5.11, 6.10, 6.11
Ceritinib + Alectinib + Lorlatinib/Brigatinib	5.12, 5.13, 6.12, 6.13
≥4 ALK treatment lines: Cohort 7 (≥ALK*4) and Cohort 8 (Chemo + ≥ALK*4)	
At least 4 different ALK inhibitors	7.1, 8.1

Abbreviations: ALK=anaplastic lymphoma kinase, Chemo=chemotherapy.

Furthermore, results will also be reported for 7 cohort groups, created based on drug generation. The first two cohort groups are created based on a sequence of crizotinib followed by one second generation drug:

- **Group A1:** chemo + crizotinib + any 2nd generation ALK TKI (Cohorts 4.1, 4.2 and 4.3 in Table 4).
- **Group A2:** crizotinib + any 2nd generation ALK TKI (Cohorts 3.1, 3.2, and 3.3 in Table 4).

The second two groups are created based on a sequence of crizotinib followed by two second generation drugs:

- **Group B1:** chemo + crizotinib + any 2nd generation ALK TKI + any 2nd generation ALK TKI (Cohorts 6.1, 6.3, 6.4, 6.5 and 6.7 in Table 4).
- **Group B2:** crizotinib + any 2nd generation ALK TKI + any 2nd generation ALK TKI (Cohorts: 5.1, 5.3, 5.4, 5.6 and 5.7 in Table 4).

The third two groups are created based on a sequence of crizotinib followed by one second generation drug, followed by lorlatinib:

- **Group C1:** chemo + crizotinib + any 2nd generation ALK TKI + lorlatinib (Cohorts: 6.2, 6.5 and 6.8 in Table 4).
- **Group C2:** crizotinib + any 2nd generation ALK TKI + lorlatinib (Cohorts: 5.2, 5.5 and 5.8 in Table 4).

Finally, one group is created based on a sequence of two consecutive second generation drugs:

- **Group D1:** Any 2nd generation ALK TKI + any 2nd generation ALK TKI (Cohorts: 3.4, 3.5, 3.7 and 3.8).

8.3. Variables

Below is an overview of the variables needed for the outcomes and study variables of the proposed analyses. The operational definition describes variables to be processed.

Variable	Role	Data source(s)	Operational definition
Index date	Baseline characteristics	PDR	Date of first filled prescription of any of the ALK inhibitors in Table 2.
Age	Baseline characteristic	PDR	Age will be defined as age at index date (continuous; years).
Sex	Baseline characteristic	PDR	Male or female gender. (dichotomous [0=female, 1=male]).
Place of residence	Baseline characteristic	PDR	County council at index date (categorical), see Table 11.
Comorbidity profile	Baseline characteristic	NPR, CR	Charlson-Quan comorbidity index (ICD-10 codes: Table 10) primary and secondary diagnosis measured in the baseline period of five years in specialist outpatient care and inpatient care (continuous; score).
CNS metastases prior to index date	Baseline characteristic, sub-group identifier	NPR, CR	Defined as patients with CNS metastasis diagnosis up to 2 years prior to dispensed prescription of first ALK-inhibitor, details in Section 8.2.3.11. Dichotomous; yes/no.
Index drug	Exposure	PDR	First filled prescription of ALK inhibitor (ATC codes in Table 2).
Received chemotherapy before index date (ie, first-line chemo)	Sub-group identifier	NPR, PDR	Patient has received chemotherapy in the 2-year time period before first ALK TKI, ie, index date (dichotomous; yes/no). Details in Section 8.2.3.10.
Number of ALK-inhibitor users	Outcome	PDR	All unique patients with at least one dispensed prescription of any ALK-inhibitor (ATC codes in Table 2).
Number of users per sequence	Sub-group identifier	PDR	All unique patients per identified ALK treatment sequence. Relevant sequences are described in Section 8.2.3.12.
Duration of treatment	Outcome	PDR	Number of days on treatment calculated based on FASS recommended dose for filled prescriptions of ALK-inhibitors (ATC codes in Table 2) taking permissible gap

Variable	Role	Data source(s)	Operational definition
			and stockpiling into account. Details in Sections 8.2.3.6, 8.2.3.7 and 8.2.3.9.
Overall survival	Outcome	CDR, PDR	Time from index date to date of death (number of days) where death is defined as all-cause death; stratification per treatment sequence. If no date of death is recorded, data is censored at latest available date in data.

8.4. Data Sources

The Swedish administrative registries offer high quality data for research with nation-wide coverage and close to complete data for most available variables. Patient-level data from each register are available for research purposes and individual patients can be linked between all datasets via the personal identifier given to all citizens. The administrative registers to be used in this study are summarized in Table 5.

Table 5. Overview of Data Sources

Type of register	Name	Data holder	Start of data collection	Variables
Patient registers	Swedish National Patient Register (NPR)	NBHW	1987/2001	Diagnosis codes (ICD-9/10), dates and types of visit
Prescription registers	Swedish Prescribed Drug Register (PDR)	NBHW	2005	Dispatch dates, type of medication, strengths and dosage info (incomplete)
Information on mortality	Swedish Causes of Death Register (CDR)	NBHW	1961	Date and cause of death (ICD-10)
Cancer register	Swedish Cancer Register (CR)	NBHW	1958	Tumour size, tumour spread, localisation of tumour, morphological diagnosis of the tumour (ICD-O/3)

NBHW=National Board of Health and Welfare.

8.4.1. The Swedish National Patient Register

The Swedish National Patient Register, held by the National Board of Health and Welfare (NBHW), contains patient data, geographical data, administrative data and medical data for both inpatient and outpatient specialist care. The register contains main and secondary diagnosis codes (ICD-10) for each admission and outpatient specialist visit as well as procedure codes. The outpatient register includes physician visits only. Surgical procedures are recorded based on The Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP). The patient register has nationwide coverage and long follow-up with several decades of available data (first data year: 1987).

Diagnoses from the National Patient Register will be used to assess comorbidities and CNS metastases. In addition, recorded visits and hospitalizations will be used to analyse previous cancer treatments.

8.4.2. The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register, also held by NBHW, contains information on all filled prescriptions (ie, dispensed at a pharmacy, excluding prescriptions that are never collected by the patient). Data on prescribed drugs can be captured using ATC codes, prescription date, dispensing date, dose, pack size, healthcare professional issuing the prescription, as well as sex, age and residency of the patients. The Prescribed Drug Register has nationwide coverage and long follow-up (first data year: 2005). Data from the Prescribed Drug Register will be used to identify the study population and to evaluate sequencing of ALK-inhibitors.

8.4.3. The Swedish Cause of Death Register

The Swedish Cause of Death Register contains main and contributing causes of death presented as diagnosis codes (ICD-10). The register covers all deaths of Swedish residents, whether the person in questions was a Swedish citizen or not and irrespective of whether the death occurred in Sweden or not. The Cause of Death Register has nationwide coverage and long follow-up with several decades of available data (first data year: 1961). Date and cause of death will be obtained from the Cause of Death Register. This information will be used to study mortality of patients.

8.4.4. The Swedish Cancer Register

The Swedish Cancer Register contains information on site of tumour, clinical and morphological diagnosis, and tumour development stage at diagnosis among other. There is some underreporting to the Swedish Cancer Register, the extent of which varies with the cancer site and the age of the patient. The Cancer Register has nationwide coverage and long follow-up with several decades of available data (first data year: 1958). The register is updated annually. Only primary tumours are registered in the register. Recurrence as well as metastases of previously known and reported primary tumours are not included. Metastases are only recorded in cases where the primary tumour is unknown. If the primary tumour is clarified at a later stage, the registration shall be updated regarding location code and

potentially also morphology. Data from the Cancer Register will be used to identify metastatic disease.

8.5. Study Size

Sample size calculations are not applicable since there are no a priori hypotheses specified. However, using publicly available data for the number of patients receiving crizotinib, ceritinib, alectinib, brigatinib or lorlatinib shows that ~300 men and women had filled at least one prescription in 2018 (Table 6). Including 2019 and 2020 in the data extraction will likely allow for >500 patients to be extracted for analysis.

Table 6. Number of ALK Inhibitor Patients by Year

Year	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib	Total
2012	1	0	0	0	0	1
2013	5	0	0	0	0	5
2014	53	0	0	0	0	53
2015	112	9	0	0	0	121
2016	129	58	0	0	2	189
2017	123	56	32	0	2	213
2018	104	41	143	3	1	292

Source: National Board of Health and Welfare.[37]

Note: Patients can be double counted between years.

8.5.1. Data Management

In broad terms, the data management for this study will be initiated by the creation of a broad study population including patients with at least one filled prescription of ALK-inhibitors identified by the national prescription register. A study key including the selected cases personal identifiable number (PIN) and a randomly created study identification (ID) will be created by the register holder, the NBHW. The NBHW compiles a completely pseudonymized analytical dataset comprising all observations and variables required from the different registers for the planned analyses. The compiled datasets are shared with Quantify Research where all PINs will be exchanged with the study ID. No direct identifiable personal information will therefore be shared with Quantify Research. The analytic dataset will be person-level.

The central statistical software programs used to evaluate the data will be STATA and/or R.

All data management will be performed by Quantify Research. A data validity quality check is always undertaken before data management is started to verify that all variables are complete and to create logs for corrupt or ambiguous data entries.

8.6. Data Analysis

An overview of the planned analyses by research questions are presented in Sections 8.6.1 and 8.6.2. In general, the study is descriptive and does not involve hypothesis testing. Any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The study population will be stratified in two main groups with respect to first-line chemotherapy: patients who are chemotherapy-naïve prior to first fill of ALK-inhibitor and patients who are not. The study definition for chemotherapy is described in Section 8.2.3.10.

Patient characteristics of ALK-inhibitor users will be described per treatment sequence (number, mean, standard deviation (SD), median, proportions). Patient characteristics include age, sex, region, comorbidities and CNS metastases. Patients will only be counted once and patient characteristics will be measured at, or for 5 years lookback from, index date (date of first ALK-inhibitor prescription). Correlative trends may be investigated using a correlation matrix and statistical testing. If any correlative trends are identified, these may be further investigated through the use of simple regression models.

8.6.1. Primary Objective – Overall Survival of ALK-inhibitor Users

The primary objective is to estimate overall survival (OS) per ALK-inhibitor.

Time-to-event analysis, where the event is all-cause death, will be used to estimate the probability of surviving. Results will be presented using Kaplan-Meier curves. All patients included in the study are eligible for this analysis. In this survival analysis, patients will also be stratified into those with CNS-metastases and those without CNS-metastases in the two-year period prior to index date (Table 7).

Table 7. Primary Objective – Summary of Data Analysis

Objective	**Describe the overall survival of ALK inhibitor users**
Design	Cohort
Analysis type	Survival analysis
Outcomes	Overall survival
Measures	Kaplan-Meier estimates (survival function, 95% confidence interval (CI), risk table, median survival) Proportion of patients alive after 5 and 6 years from index

Objective	Describe the overall survival of ALK inhibitor users
Strata	Cohort group (see Section 8.2.3.12) Chemotherapy: First line chemotherapy No first-line chemotherapy CNS-metastases: CNS-metastases prior to index No CNS-metastases prior to index
Index date	Date of first prescription (Table 2)
Analysis period	01 January 2012 – 31 December 2020
Reporting interval	Per month from index date (Kaplan Meier [KM] analysis)

8.6.2. Secondary Objective – Duration of Treatment of ALK-inhibitor Users

The secondary objective is to estimate the duration of treatment (DOT) per ALK-inhibitor. Treatment duration will be estimated for the sequences as described in Section 8.2.3.12. In each sequence both the total treatment duration for that sequence and treatment duration per ALK-inhibitor within the sequence will be reported.

Table 8. Secondary Objective – Summary of Data Analysis

Objective	Describe the treatment duration of ALK inhibitor users
Design	Cohort
Analysis type	Descriptive
Outcomes	Treatment duration per ALK-inhibitor and sequence
Measures	Number (mean, standard deviation (SD), min, max, median)
Strata	Cohort group (see Section 8.2.3.12) Chemotherapy: First line chemotherapy No first-line chemotherapy

Objective	Describe the treatment duration of ALK inhibitor users
Index date	Date of first prescription (Table 2)
Analysis period	01 January 2012 – 31 December 2020
Reporting interval	Multi-year periods

8.7. Quality Control

The national and compulsory health registers included in the present study are governed by the national authority in charge of public health and welfare. Reporting of information to the registers is compulsory by all healthcare providers and pharmacies, thus this guarantees high completeness rates and nationwide coverage. Rigorous validation work is constantly ongoing in order to ensure that data are complete, comprehensive and of the highest quality possible. Data will be examined for completeness and missing data are anticipated to be minimal based on previous research and the compulsory nature of the data collection.

A team of researchers at Quantify Research will conduct tasks such as data management, analyses, and report writing. The team will be led by a research leader with experience from similar projects.

The steps involved in data management and analysis will be recorded in carefully maintained scripts and logs. This will simplify data updates and ensure reproducibility of results, from raw data to the end result.

Data analyses are quality controlled according to an in-house protocol that includes a code review. The data cleaning and analysis steps performed in the statistical software will be reviewed by another programmer. Any errors or omissions found during this review will be communicated back to the original analyst and updated accordingly. All quality checks will be documented.

8.8. Limitations of the Research Methods

8.8.1. Internal Validity of Study Design

The study on patients treated with ALK-inhibitors is dependent on a successful identification strategy and definition of the patients. The current protocol allows a generous study population of users, requiring minimum one filled ALK-inhibitor prescription to be included in the study. Using another identification strategy when defining patients may lead to a different patient population.

In addition, the results from this study are reliant on study definitions which to some extent are based on assumptions eg, for persistence and treatment initiation and/or algorithms (chemotherapy, CNS-metastases, ALK-positive NSCLC). Using other assumptions and algorithms for these study definitions may lead to different study results.

Another possible limitation of this study is the potential underrepresentation of cases using newer generation drugs due to the relatively short period of time under which some of the products have been available on the Swedish market. For certain research questions therefore the low number of total cases could preclude meaningful analysis due to the risk of producing results unrepresentative of the entire patient population treated with ALK-inhibitors in Sweden.

Finally, the switch of lorlatinib CUP patients to commercial product post-reimbursement decision in Sweden may create a minor additional uncertainty by introducing a variable therapy "gap" imminently before the lorlatinib-prescriptions for these patients appear in the Prescribed Drug Register. In general, the plausible compassionate drug use remains a general confounding factor with regards to OS-analyses as it is not possible to capture nor evaluate compassionate use of any ALK TKIs or other agents among patients included in this study.

8.8.2. Missing or Incomplete Information

This study will to a large extent rely on register-based data which are known to have a high degree of completeness. The reporting of many variables in the national health care registers used in this study is mandatory and there is therefore almost complete coverage of the information related to healthcare visits and prescriptions.

If information regarding dates, diagnosis codes or treatment information is absent, these records would be excluded from analysis since imputation of these types of variables would be difficult to implement and justify. In the unlikely event that a patient's health care visit or prescription would not have been captured at all by the registers, this instance of missing data would not be possible to identify.

8.8.2.1. Measurement Errors and Misclassifications

Diagnoses of outcomes and comorbidities will be identified using diagnosis and procedure codes, which are subject to potential miscoding. Since the study includes already collected data, there is no risk of observer bias in this study.

8.8.2.2. Information Bias

Given that outcomes will be defined using national and population-based health register data, there will be an inherent risk of information bias resulting from classification error.

One limitation of the study is that the presumed treatment date will be based on the date of filling the prescription at the pharmacy, which is not necessarily the date of treatment administration. There is also a risk that the dispensation of the respective drug does not equal actual consumption. This will always be the case in observational studies of self-administered treatments since the actual patient behaviour cannot be observed.

8.8.2.3. Selection Bias

The main analyses in this study will be conducted using the Prescribed Drug Register, the Patient Register and the Cause of Death Register. Given that these national registers have complete coverage, selection bias does not pose a threat of lung cancer patients treated in specialist care, given correct identification of the patients. The severity of the disease and clinical practice in Sweden makes it improbable that some patients are managed in primary care.

Inclusion criteria for ALK-positive NSCLC patients will be based on prescription data. Only prescriptions filled at pharmacies can be captured in prescription registers, as they do not include data on hospital drugs. This is however not likely to introduce a selection bias, given that most ALK-inhibitor treatments for patients with NSCLC are given outside the hospital setting.

8.8.3. External Validity of Study Results

The findings of this study will be based on Swedish data and will as such not necessarily be directly transferable to other countries or regions.

8.9. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be a prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

Ethical approval will be obtained from the Swedish Ethical Review Authority.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves secondary data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be summarized in a study report. It is further planned to submit at least one publication based on the results of this study to an international peer-reviewed journal.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

11.1. Publication Policy

Authorship of any publications resulting from this study will be based on the *"Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals"* by the International Committee of Medical Journal Editors (ICMJE):[38]

- Authorship credit should be based on (1) substantial contributions to conception or design, or acquisition analysis or interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4. When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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13. LIST OF TABLES

14. LIST OF FIGURES

None.

15. ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

16. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

17. ANNEX 3. ADDITIONAL INFORMATION

17.1. Diagnosis and Procedure Codes

Table 9. Chemotherapy – Procedure Codes (KVÅ-codes)

Procedure codes	Description (Swedish)
DT016	Läkemedelstillförsel, intravenös
DT107	Cytostatikatillförsel med annat specificerat administrationssätt
DT108	Cytostatikatillförsel UNS
DT112	Cytostatikatillförsel, intratekal
DT116	Cytostatikatillförsel, intravenös
DT135	Cytostatikatillförsel, intraperitoneal
DV046	Läkemedelsbehandling, utdelning av dosett eller enstaka dos
Z082	Kontrollundersökning efter kemoterapi för malign tumör
Z092	Kontrollundersökning efter kemoterapi för andra tillstånd
Z292	Annan förebyggande kemoterapi
Z511	Kemoterapeutisk behandling för tumör
Z512	Annan kemoterapi
Z542	Konvalescens efter kemoterapi
Z926	Kemoterapi för tumörsjukdom i den egna sjukhistorien

Table 10. Charlson Comorbidity Score

Disease	ICD-10 Code	Score
Myocardial Infarction	I21; I22; I23	1
Congestive Heart Failure	I50; I11.0; I13.0; I13.2	1
Peripheral Vascular Disease	I70; I71; I72; I73; I74; I77	1
Cerebrovascular Disease	I60-I69; G45; G46	1
Dementia	F00-F03; F05.1; G30	1

Disease	ICD-10 Code	Score
Chronic Pulmonary Disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
Connective Tissue Disease	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86	1
Ulcer Disease	K22.1; K25-K28	1
Mild Liver Disease	B18; K70.0; K70.3; K70.9; K71; K73; K74; K76.0	1
Diabetes Mellitus		1
Insulin dependent	E10.0; E10.1; E10.9	
Non-Insulin dependent	E11.0; E11.1; E11.9	
Hemiplegia or paraplegia	G81; G82	2
Moderate-Severe Renal Disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
Diabetes Mellitus with End Organ Damage		2
Insulin dependent	E10.2-E10.8	
Non-Insulin dependent	E11.2-E11.8	
Any Tumour	C00-C75	2
Leukaemia	C91-C95	2
Lymphoma	C81-C85; C88; C90; C96	2
Moderate-Severe Liver Disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
Metastatic Solid Tumour	C76-C80	6
AIDS	B21-B24	6

17.2. Additional Codes

Table 11. County Council Codes

County name	County code
Stockholm County	01
Uppsala County	03
Södermanland County	04
Östergötland County	05
Jönköping County	06
Kronoberg County	07
Kalmar County	08
Gotland County	09
Blekinge County	10
Skåne County	12
Halland County	13
Västra Götaland County	14
Värmland County	17
Örebro County	18
Västmanland County	19
Dalarna County	20
Gävleborg County	21
Västernorrland County	22
Jämtland County	23
Västerbotten County	24
Norrbotten County	25