NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	*Patient profiles and treatment patterns among ALK+ NSCLC patients treated with alectinib.*
Protocol number	*B7461031*
Protocol version identifier	*2.0*
Date	*31 August 2021*
Research question and objectives	This study aims to understand patient profiles, treatment patterns, and clinical outcomes among ALK+ NSCLC patients treated with alectinib, and post-alectinib treatment patterns and outcomes. **Phase 1 Landscape Objectives (structured data):** These analyses will be performed for all study-eligible patients who received alectinib during the study identification period. Results will be presented overall as well as for the subgroups of patients who received a subsequent therapy following alectinib: 1. Describe the demographic and clinical characteristics of ALK+ NSCLC patients who received alectinib overall, and stratified by subsequent treatment following alectinib. 2. Characterize post-alectinib treatment patterns and sequencing of other ALK inhibitors; categorizing type of treatments received after alectinib.

	3. Estimate duration of therapy with alectinib and duration of therapy for post-alectinib treatment. 4. Examine overall survival of patients post-alectinib stratified by subsequent treatment following alectinib. **Phase 2: Chart Review Objectives (unstructured data):** For Phase 2, structured data will be supplemented with a targeted chart review to confirm alectinib and other ALK inhibitor oral drug therapy information and collect additional unstructured data for a sample of front-line alectinib patients from the eligible study population. Results will be presented for all patients selected for chart review, as well as the subgroups of patients who received a subsequent therapy following alectinib: 5. Describe the demographic and clinical characteristics of ALK+ NSCLC patients who received alectinib overall, and stratified by subsequent treatment following alectinib. 6. Characterize post-alectinib treatment patterns and sequencing of other ALK inhibitors; categorizing type of treatments received after alectinib. 7. Estimate duration of therapy with alectinib and duration of therapy for post-alectinib treatment. 8. Examine reasons for treatment discontinuation of alectinib and post-alectinib treatment.

	9. Estimate progression-free survival (PFS) of patients post-alectinib stratified by subsequent treatment. 10. Examine overall survival of patients post-alectinib stratified by subsequent treatment. **Phase 3: Data Refresh (structured and unstructured data) and Exploratory Analysis (structured data)** Phases 1 and 2 study objectives will be updated with additional follow-up time through August 31, 2021. In addition, patients initiating lorlatinib following Food and Drug Administration (FDA) approval to end of study period will be identified in structured data and the following exploratory objectives will be examined: 11. Identify patients initiating lorlatinib and monitor lorlatinib uptake over time • Evaluate demographic and clinical characteristics of patients receiving lorlatinib • Characterize lorlatinib treatment sequencing utilization and patterns
Author	PPD , PhD PPD Phone: PPD Email: PPD PPD , PhD Ontada PPD

	PPD Phone: PPD Email: PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
ALK	anaplastic lymphoma kinase
ANOVA	analysis of variance
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CI	confidence interval
CNS	central nervous system
CRFs	case report forms
DCTs	data collection tools
DOT	duration of treatment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EHR	electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GEP	good epidemiological practice
GPP	guidelines for good pharmacoepidemiology Practices

Abbreviation	Definition
HIPAA	health insurance portability and accountability act
HITECH	health information technology for economic and clinical health
HR	hazard ratio
ICD	international classification of diseases
ICMJE	international committee of medical journal editors
IHC	Immunohistochemistry
iKM	iKnowMed
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
K-M	kaplan meier
LADMF	limited access death master file
MET	mesenchymal-to-epithelial transition
MRN	medical record number
NI	non-interventional
NIS	non-interventional study
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
OS	overall survival
PD-L1	programmed death-ligand 1

Abbreviation	Definition
PFS	progression free survival
QC	quality control
RECIST	response evaluation criteria in solid tumors
ROS1	ROS proto-oncogene 1
RT-PCDR	reverse transcriptase– polymerase chain reaction
SSDI	social security death index
SSN	social security number
US	United States
YRR	your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD, PhD	PPD Pfizer NI Study Lead	Pfizer	PPD
PPD, MA	PPD	Pfizer	PPD , USA PPD
PPD, PhD	PPD	Pfizer	PPD
PPD, MD	PPD	Pfizer	PPD PPD
PPD, PharmD	PPD	Pfizer	PPD
PPD, MD, MPH	Study Principal Clinical Investigator	PPD	PPD
PPD, PhD	Outcomes Researcher	Ontada	Office Affiliation: PPD
PPD, MPH	Biostatistician	Ontada	Office Affiliation: PPD

4. ABSTRACT

Title: Patient profiles and treatment patterns among anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients treated with alectinib.

Version and Date of Protocol: 2.0 31 August 2021

Main Author: PPD, PhD, Pfizer Inc; PPD, PhD, Ontada

Rationale and background:

Alectinib is a second-generation kinase inhibitor indicated for the treatment of patients with ALK+ metastatic NSCLC. Alectinib was first FDA approved in December 2015 for the treatment of ALK+ NSCLC in patients following treatment with the first generation ALK inhibitor crizotinib. In November of 2017, the FDA approved alectinib for use as first-line treatment for ALK+ metastatic NSCLC.

The approval was based on the Phase 3 ALEX trial of 303 first-line ALK+ NSCLC patients. Treatment with alectinib demonstrated a significantly reduced risk of progression or death by 47 percent (HR=0.53, 95 percent CI: 0.38, 0.73, p<0.0001) compared to crizotinib. Median PFS was 25.7 months (95 percent CI: 19.9, not estimable) for patients treated with alectinib compared with 10.4 months (95 percent CI: 7.7, 14.6) for patients who received crizotinib. Treatment with alectinib also reduced the risk of the brain or central nervous system (CNS) metastasis compared to crizotinib by 84 percent (HR=0.16, 95 percent CI: 0.10, 0.28, p<0.0001).[1]

With the availability of several therapeutic agents, current treatment patterns and outcomes with use of multiple ALK-inhibitor treatments in sequence are not well understood. For patients with ALK positive NSCLC, first-line therapy with alectinib is the preferred treatment option, however, sequence of therapy is not well-defined. This study aims to understand patient profiles, treatment patterns, and clinical outcomes among ALK+ NSCLC patients treated with alectinib, and post-alectinib treatment patterns and outcomes.

Research question and objectives

Describe patient profiles, treatment patterns, and clinical outcomes among real-world ALK+ NSCLC patients treated with alectinib, and post-alectinib treatment patterns and outcomes.

Specifically, we will answer the following objectives:

Phase 1: Landscape Objectives (structured data):

These analyses will be performed for all study-eligible patients who received alectinib (in any line of therapy) during the study identification period. Results will be presented overall as well as for the subgroups of patients who received a subsequent therapy following alectinib:

1. Describe the demographic and clinical characteristics of ALK+ NSCLC patients who received alectinib overall, and stratified by subsequent treatment following alectinib

2. Characterize post-alectinib treatment patterns and sequencing of other ALK inhibitors; categorizing type of treatments received after alectinib

3. Estimate duration of therapy with alectinib and duration of therapy for post-alectinib treatment

4. Examine overall survival of patients post-alectinib stratified by subsequent treatment following alectinib

Phase 2: Chart Review Objectives (unstructured data):

For Phase 2, structured data will be supplemented with a targeted chart review to confirm alectinib and other ALK inhibitor oral drug therapy information and collect additional unstructured data for a sample of front-line alectinib (i.e., first treatment administration of alectinib not preceded by any other product for NSCLC therapy) patients, from the eligible study population. Results will be presented for all patients selected for chart review, as well as the subgroups of patients who received a subsequent therapy following alectinib :

5. Describe the demographic and clinical characteristics of ALK+ NSCLC patients who received alectinib overall, and stratified by subsequent treatment following alectinib

6. Characterize post-alectinib treatment patterns and sequencing of other ALK inhibitors; categorizing type of treatments received after alectinib

7. Estimate duration of therapy with alectinib and duration of therapy for post-alectinib treatment

8. Examine reasons for treatment discontinuation of alectinib and post-alectinib treatment

9. Estimate progression-free survival (PFS) of patients post-alectinib stratified by subsequent treatment (as supported by the final sample size)

10. Examine overall survival of patients post-alectinib stratified by subsequent treatment (as supported by the final sample size)

Phase 3: Data Refresh (structured and unstructured data) and exploratory analysis (structured data)

For Phase 3, the structured and unstructured data study objectives (Phase 1 and Phase 2) will be updated with additional follow-up time through 31 August 2021.

In addition, patients initiating lorlatinib following FDA approval to end of study period will be identified in structured data and the following exploratory objectives will be examined:

11. Identify patients initiating lorlatinib and monitor lorlatinib uptake over time

    - Evaluate demographic and clinical characteristics of patients receiving lorlatinib
    - Characterize lorlatinib treatment sequencing utilization and patterns

Study design: This is a retrospective, observational, descriptive study to examine patient characteristics, treatment patterns, and outcomes of patients ALK+ NSCLC treated in The United States (US) Oncology Network and Non-Network practices utilizing the iKnowMed (iKM) electronic healthcare record (EHR).

Population: The study population will consist of patients with a diagnosis of NSCLC receiving alectinib within in The US Oncology Network and Non-Network practices .

Study Population

The study population for Phases 1 and 2 will be comprised of ALK+ NSCLC patients who have evidence of receiving alectinib during 01 June 2017 and 30 June 2019 with The US Oncology Network or Non-Network site. Study-eligible patients will be followed longitudinally until 31 December 2019, last patient record or date of death, whichever occurs first. The index date-1 will be the start date of alectinib treatment during the study identification period. Index date-2 will be the start date of the subsequent treatment following alectinib, among patients who receive a next treatment.

For Phase 3, the identification period for the study population will be extended to include ALK+ NSCLC patients who have evidence of receiving during 01 June 2017 and 31 August 2020 with The US Oncology Network or Non-Network site. Study-eligible patients will be followed longitudinally with additional follow-up until 31 August 2021, last patient record or date of death, whichever occurs first. The index date-1 will be the start date of alectinib treatment during the study identification period. Index date-2 will be the start date of the subsequent treatment following alectinib, among patients who receive a next treatment during the study identification period. For the lorlatinib exploratory analysis the identification period will be 02 November 2018 to 31 August 2020. Study-eligible patients will be followed longitudinally with additional follow-up until 31 August 2021, last patient record or date of death, whichever occurs first.

Variables: A complete list of study variables and their associated operational definition are presented in Table 1.

Data Sources: Structured data fields within the iKM EHR database will provide information needed to address most research questions. These data will be supplemented by additional unstructured data collected through chart review for a subset of the study population.

Study size
A preliminary feasibility assessment for Phases 1 and 2 identified 293 patients who were treated with alectinib after 01 November 2017, with approximately half treated in the front-line setting. Approximately 20-30% of these patients received a subsequent therapy after alectinib. It is estimated that approximately 300 patients will be included in the Phase 1 structured data analysis. Targeted chart review for Phase 2 is proposed to occur on 150 patients receiving alectinib to identify at least 100 patients who received alectinib as front-line.

For Phase 3 structured analysis, a preliminary feasibility assessment identified 521 patients who were treated with alectinib from 01 June 2017 through 31 December 2020. Chart review for Phase 3 will include patients who had ongoing treatment at the end of Phase 2 study period, and an additional 125 patients will be targeted to identify 100 new patient who received alectinib as front-line therapy. For Phase 3 exploratory analysis, a preliminary feasibility assessment identified 134 patients who were treated with lorlatinib from 01 November 2018 through 31 December 2020.

The final study population for analysis will be defined after identification and review of the patient population meeting the eligibility criteria in the iKM database. A specific power calculation will not be performed as this is a descriptive analysis.

Data analysis
Descriptive analyses will be conducted to evaluate demographic, clinical and treatment characteristics overall, as well as for each of the study cohorts. Time-to-event outcomes (OS, DOT, PFS) will be assessed using the Kaplan-Meier method with 95% CIs and summary tables. All analyses will be presented for each of the study cohorts and, as supported by the final sample size, stratified by front-line alectinib and non front-line alectinib treatment groups.

Milestones
Interim reports for Phase 1 are expected to be delivered May 2020, with the final study report expected October 2020.

The final report for Phase 3 is expected to be delivered in March 2022.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	31 August 2021	Sections 3, 4, 6, 7, 8, and 9	An amendment for Phase 3 includes a data refresh and updated analysis of Phases 1 and 2 with increased sample size and data through 31 August 2021. Responsible parties were updated.	Increased sample size and longer study period.

6. MILESTONES

Milestone	Planned date
Finalization of study protocol	February 2020
Submission to the Institutional Review Board (IRB)	February 2020
Start of structured data collection	December 2019
End of structured data collection	January 2020
Interim Report (analyses to meet the Phase 1 objectives)	May 2020
Start of chart review	May 2020
End of chart review	July 2020
Final Report (analyses to meet the Phase 2 objectives)	October 2020
Finalization of Phase 3 study protocol	September 2021
Phase 3 Submission to the Institutional Review Board (IRB)	September 2021
Structured data extraction for Phase 3	October 2021
Start of chart review for Phase 3	November 2021
End of chart review for Phase 3	January 2022
Analysis for Phase 3	February 2022
Final Report including updated analysis for Phase 3	March 2022

7. RATIONALE AND BACKGROUND

Lung cancer is the second most common cancer in the United States (US) with approximately 235,760 new lung cancer diagnoses estimated to occur in 2021 with 131,880 deaths during this time.[2] Worldwide, lung cancer is a predominant cause of cancer related mortality as the disease is usually diagnosed late. At the initial diagnosis, almost 70% of patients with lung cancer either have a locally advanced disease or have distant metastases. The median overall survival (OS) from diagnosis for patients with stage IV anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) is 6.8 years. [3]

Lung cancer is of mainly 2 types, small cell lung cancer and non-small cell lung cancer (NSCLC). These 2 subtypes are treated differently through different chemotherapy and radiotherapy regimens. NSCLC comprises around 85-90% of all lung cancers with 40% of these having adenocarcinoma histology. This type of lung cancer occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in non-smokers. It is more common in women than in men, and it is more likely to occur in younger people than other types of lung cancer. [4]

A genetic alteration of the anaplastic lymphoma kinase (ALK) gene is present in 3-5% of NSCLCs. Over the last decade, there has been an increase in the number of oral anticancer agents available for use as treatment. The availability of orally available cancer treatments has made it possible for patients to receive their treatments without having to travel long distances. [5]

Biomarker driven therapies have revolutionized the treatment of non-small cell lung cancer (NSCLC). The first FDA-approved ALK inhibitor for ALK+ (ALK+) metastatic NSCLC treatment in 2011, crizotinib, has shown significant improvement in progression-free survival (PFS) and tumor responses in patients with metastatic NSCLC who carry the ALK gene rearrangement. While crizotinib has demonstrated significant improvement in PFS in Phase 3 studies, a subset of patients may develop acquired resistance to the drug after approximately 12 months, most likely due to secondary mutations to the ALK gene. [6-15]

For patients who progress on crizotinib, second generation ALK-inhibitors have been developed. Additional ALK-inhibitors that have subsequently been approved include ceritinib (April 2014), alectinib (December 2015), and brigatinib (April 2017).

Alectinib is a second-generation kinase inhibitor indicated for the treatment of patients with ALK+ metastatic NSCLC. Alectinib was first FDA approved in December 2015 for the treatment of ALK+ NSCLC in patients following treatment with the first generation ALK inhibitor crizotinib. In November of 2017, the FDA approved alectinib for use as first-line treatment for ALK+ metastatic NSCLC.

The approval was based on the Phase 3 ALEX trial of 303 first-line ALK+ NSCLC patients. Treatment with alectinib demonstrated a significantly reduced risk of progression or death by 47 percent (HR=0.53, 95 percent CI: 0.38, 0.73, p<0.0001) compared to crizotinib. Median

PFS was 25.7 months (95 percent CI: 19.9, not estimable) for patients treated with alectinib compared with 10.4 months (95 percent CI: 7.7, 14.6) for patients who received crizotinib. Treatment with alectinib also reduced the risk of the brain or central nervous system (CNS) metastasis compared to crizotinib by 84 percent (HR=0.16, 95 percent CI: 0.10, 0.28, p<0.0001).[1]

Likewise, ceritinib (Zykadia®), has been tested in the frontline setting. In the ASCEND-4 Phase 3 trial, ceritinib was compared to a platinum/pemetrexed demonstrating a median progression free survival of 16.6 months as compared to only 8.1 months in the platinum/pemetrexed chemotherapy arm. Other comparisons of second and third generation ALK inhibitors to ceritinib are ongoing.[16]

More recently, in November 2018, the FDA granted accelerated approval to lorlatinib for patients with ALK+ metastatic NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy.[17] The accelerated FDA approval was converted to a full approval and the indication was expanded to include first-line treatment for patients with ALK+ metastatic NSCLC in March 2021. [18]

With the availability of several therapeutic agents, current treatment patterns and outcomes with use of multiple ALK-inhibitor treatments in sequence are not well understood. For patients with ALK positive NSCLC, first-line therapy with alectinib is the preferred treatment option, however, sequence of therapy is not well-defined. This study aims to understand patient profiles, treatment patterns, and clinical outcomes among ALK+ NSCLC patients treated with alectinib, and post-alectinib treatment patterns and outcomes.

8. RESEARCH QUESTION AND OBJECTIVES

The overall goal of this study is to understand the patient characteristics, treatment patterns, and clinical outcomes of ALK+ NSCLC patients treated with alectinib in US community oncology practices. To efficiently and effectively address research questions, we will leverage both the structured and unstructured data of the EHR and execute the study in 2 phases. Phase 1 will consider a population of ALK+ NSCLC patients who received alectinib during the study intake period. For Phase 2, a sample of patients who received alectinib as front-line therapy will be selected for chart review.

The study plan utilizes structured data and unstructured (chart review data). For the landscape objectives in Phase 1, study data will originate from structured fields of the EHR, which are controlled and mapped data elements, and will be available ahead of chart review data. For the second phase, specific study objectives will be assessed among a subset of patients selected for chart review using both structured and unstructured data. In this phase, data will also be derived from unstructured fields in the EHR, such as providers' free-text notes, which can only be captured through a chart review.

Phase 1: Landscape Objectives (structured data):

These analyses will be performed for all study-eligible patients who received alectinib (in any line of therapy) during the study identification period. Results will be presented overall as well as for the subgroups of patients who received a subsequent therapy following alectinib:

1. Describe the demographic and clinical characteristics of ALK+ NSCLC patients who received alectinib overall, and stratified by subsequent treatment following alectinib

2. Characterize post-alectinib treatment patterns and sequencing of other ALK inhibitors; categorizing type of treatments received after alectinib

3. Estimate duration of therapy with alectinib and duration of therapy for post-alectinib treatment

4. Examine overall survival of patients post-alectinib stratified by subsequent treatment following alectinib

Phase 2: Chart Review Objectives (unstructured data):

For Phase 2, structured data will be supplemented with a targeted chart review to confirm alectinib and other ALK inhibitor oral drug therapy information and collect additional unstructured data for a sample of front-line alectinib (i.e., first treatment administration of alectinib not preceded by any other product for NSCLC therapy) patients from the eligible study population. Results will be presented for all patients selected for chart review, as well as the subgroups of patients who received a subsequent therapy following alectinib:

5. Describe the demographic and clinical characteristics of ALK+ NSCLC patients who received alectinib overall, and stratified by subsequent treatment following alectinib

6. Characterize post-alectinib treatment patterns and sequencing of other ALK inhibitors; categorizing type of treatments received after alectinib

7. Estimate duration of therapy with alectinib and duration of therapy for post-alectinib treatment

8. Examine reasons for treatment discontinuation of alectinib and post-alectinib treatment

9. Estimate progression-free survival (PFS) of patients post-alectinib stratified by subsequent treatment (as supported by the final sample size)

10. Examine overall survival of patients post-alectinib stratified by subsequent treatment (as supported by the final sample size)

Phase 3: Data Refresh (structured and unstructured data) and Exploratory Analysis (structured data)

For Phase 3, the structured and unstructured data study objectives (Phase 1 and Phase 2) will be updated with additional follow-up time through 31 August 2021..

In addition, patients initiating lorlatinib following FDA approval to end of study period will be identified in structured data and the following exploratory objectives will be examined:

11. Identify patients initiating lorlatinib and monitor lorlatinib uptake over time

- Evaluate demographic and clinical characteristics of patients receiving lorlatinib
- Characterize lorlatinib treatment sequencing utilization and patterns

9. RESEARCH METHODS

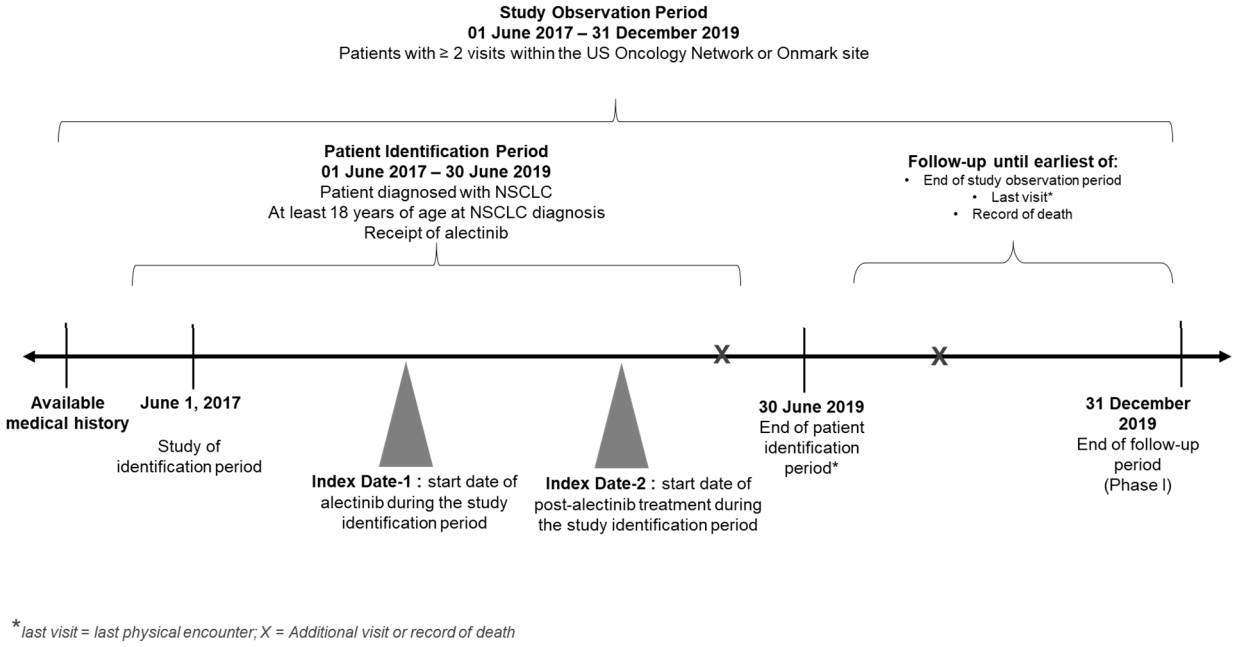
9.1. Study design Phases 1 and 2

This is a retrospective, observational, descriptive study to examine patient characteristics, treatment patterns, and outcomes of patients ALK+ NSCLC treated in The US Oncology Network and Non-Network practices utilizing the iKM EHR. During phases 1 and 2, patients who have evidence of receiving alectinib during 01 June 2017 and 30 June 2019 will be eligible for inclusion in the study.

Complete study eligibility criteria and cohort definitions are presented in Section 9.3. Study-eligible patients will be followed longitudinally until 31 December 2019, last patient record or date of death, whichever occurs first.

An overview of the study design for Phases 1 and 2 is presented below.

Figure 1. Phases 1 and 2 study design



*last visit = last physical encounter; X = Additional visit or record of death

Phase 1 objectives will be assessed among patients who meet study eligibility criteria as specified in Section 9.3.1 and stratified by subsequent treatment following alectinib.

Phase 2 objectives will be assessed in a sample of patients who received alectinib as front-line therapy and stratified by subsequent treatment following alectinib.

The number of cohort stratifications may depend on sample size of patients receiving subsequent therapy following alectinib[1] including chemotherapy (further stratified into platinum doublet and single agent), immunotherapy, and ALK inhibitors. Up to 5 cohorts will be considered:

Cohort A: Patients who received alectinib during the study period (overall population)

Cohort B (alectinib only cohort): Patients with ongoing alectinib treatment, or patients who discontinued alectinib, and patients who did not have a subsequent treatment[2]

Cohort C: patients who received alectinib followed by treatment X (top 3 most frequent)

Cohort D: patients who received alectinib followed by treatment Y (top 3 most frequent)

Cohort E: patients who received alectinib followed by treatment Z (top 3 most frequent)

[1] Final cohorts will be decided upon sample size. Patients receiving chemotherapy and immunotherapy after initiating alectinib will be included in the patient sample. Chemotherapy cohort may be further stratified into platinum doublet chemotherapy and single agent chemotherapy depending on sample size.

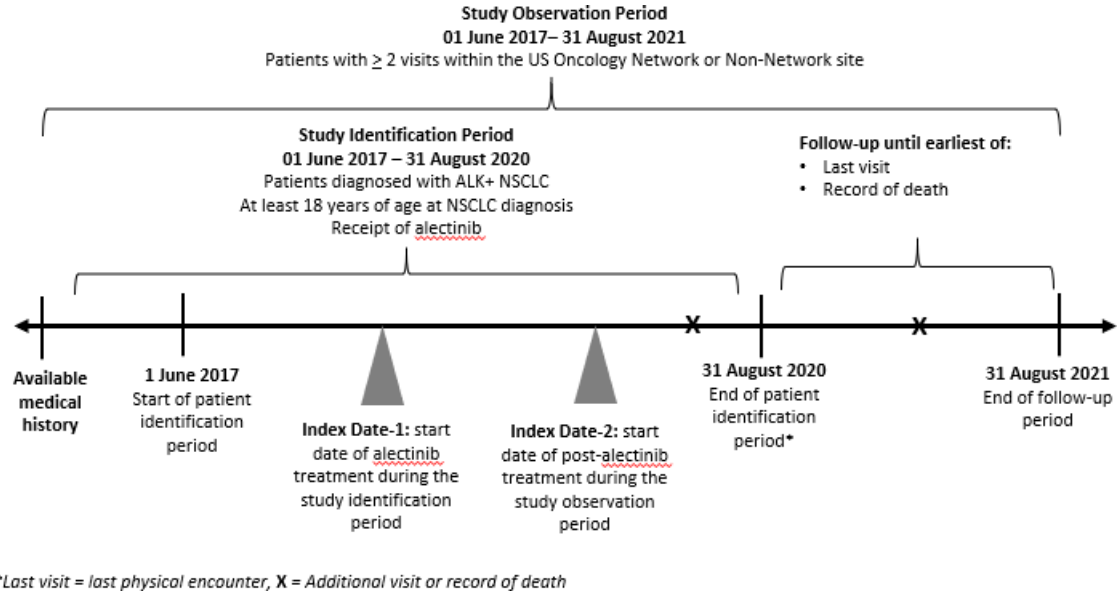
[2] Patients with ongoing alectinib treatment, patients who discontinued alectinib and patients who did not have a subsequent treatment may be analyzed as separate cohorts depending on sample size of patients

9.2. Study Design Phase 3 (study refresh and exploratory analysis)

During the Phase 3 data refresh, patients who have evidence of receiving alectinib during 01 June 2017 and 31 August 2020 will be eligible for inclusion in the study. Patients will be followed longitudinally until 31 August 2021, last patient record or date of death, whichever occurs first.

An overview of the study design for Phase 3 is presented in Figure 2.

Figure 2. Phase 3 data refresh study design



Last visit = last physical encounter, X = Additional visit or record of death

Phase 3 structured data objectives will be assessed among patients who meet study eligibility criteria as specified in 9.3.1 and stratified by subsequent treatment following alectinib.

Cohort A: All alectinib treated patients (overall population)

Cohort B (Alectinib only cohort): Alectinib treatment ongoing, or discontinued and no subsequent treatment[3]

Cohort C: Alectinib followed by treatment X (top 3 most frequent)

Cohort D: Alectinib followed by treatment Y (top 3 most frequent)

Cohort E: Alectinib followed by treatment Z (top 3 most frequent)

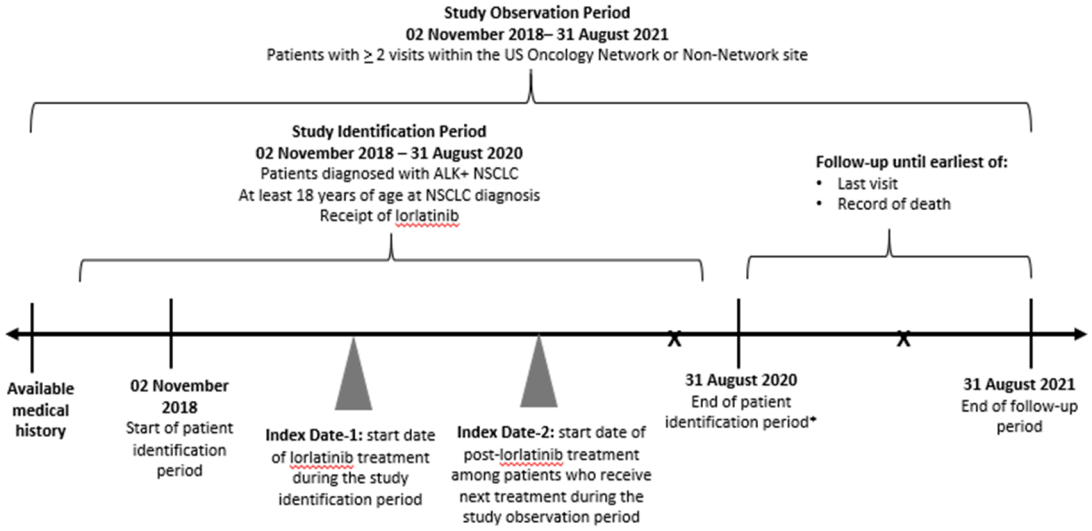
[3] Patients with ongoing alectibin treatment, patients who discontinued alectinib and patients who did not have a subsequent treatment may be analyzed as separate cohorts depending on sample size of patients

Two groups of patients are planned for chart review during Phase 3. The first group includes patients from Phase 2 chart review who had ongoing treatment at the end of the observation period (31 December 2019). These patients will undergo additional follow-up through 31 August 2021.

An additional sample of approximately 100 patients who meet the Phase 3 eligibility criteria and received alectinib as front-line therapy and received subsequent treatment among the following groups will also undergo chart review:

- Alectinib → lorlatinib
- Alectinib → crizotinib
- Alectinib → brigatinib
- Alectinib only
- Alectinib → chemotherapy (optional)

Figure 3. Phase 3 exploratory analysis study design



Last visit = last physical encounter,* **X *= Additional visit or record of death*

9.3. Setting

The study population will consist of patients with a diagnosis of NSCLC receiving alectinib within The US Oncology Network and Non-Network sites. The US Oncology Network includes approximately 1,400 affiliated physicians operating in over 480 sites of care across states and treats approximately 1.2 million US cancer patients annually. There are more than 2,650 active Non-Network supported oncology and non-oncology sites of care. [19]

Figure 1 and Figure 2 presents graphical depictions of the study time periods, which are as follows:

- Phase 1 and 2 study observation period: 01 June 2017 – 31 December 2019.
- Phase 1 and 2 study identification period: 01 June 2017 – 30 June 2019.
- Phase 3 study refresh observation period: 01 June 2017 – 31 August 2021.
- Phase 3 study refresh identification period: 01 June 2017 – 31 August 2020.
- Phase 3 exploratory analysis study observation period: 02 November 2018 – 31 August 2021.
- Phase 3 exploratory analysis study identification period: 02 November 2018 – 31 August 2020.
- Phase 1 and 2 index date-1: start date of alectinib treatment during the study identification period
- Phase 1 and 2 index date-2: start date of the subsequent treatment following alectinib, among patients who receive the next treatment during the study observation period
- Phase 3 study refresh index date-1: start date of alectinib treatment during the study identification period
- Phase 3 study refresh index date-2: start date of the subsequent treatment following alectinib, among patients who receive the next treatment during the study observation period
- Phase 3 exploratory analysis index date-1: start date of lorlatinib treatment during the study identification period
- Phase 3 exploratory analysis index date-2: start date of lorlatinib treatment among patients who receive next treatment during the study observation period
- Baseline: The baseline period or "at index" includes up to 30 days prior to and up to 30 days after index. If a patient has multiple baseline values for a particular demographic or clinical characteristic during this ± 30-day time frame, the one closest (in absolute value) prior to the index date will be used. If no values prior to index are available, then the one closest to the index date up to 30 days after will be used.
- Prior medical history: Patients' available history in the iKnowMed (iKM) EHR will vary based on the length of disease and the time within The US Oncology Network. Disease characteristics such as time of NSCLC diagnosis and date of metastatic

disease will take into account patients' available medical history. The prior medical history period will end the day prior to the index date-1.

- Follow-up: Patients will be followed through the end of the study observation period, date of last visit or date of death, whichever occurs first. For analysis, patients will have a potential of at least 6 months of follow-up duration; however, patients will have variable follow-up time periods, depending on their index dates and last contact dates.

9.3.1. Phase 1 and 2 (original study) and Phase 3 (refresh study) population

Inclusion criteria

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

1. Patients with a documented diagnosis of NSCLC.

2. Patients ≥ 18 years of age at initial recorded diagnosis of NSCLC.

3. Patients who received treatment with alectinib within The US Oncology Network or Non-Network sites during the study identification period.

4. During the study observation period, patients observed with at least 2 visits[4] after the index date-1.

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Receipt of treatment indicated for another primary cancer or diagnosis of another primary cancer (with the exception of non-melanotic skin cancer), within 5 years of index date-1 will be excluded.

2. Patients enrolled in clinical trials prior to receiving alectinib during the study ID period (index date-1), will be excluded.

[4] Visits are defined as physical encounters with the practice, detected by vital sign records. The second and third visits must be observed after the index date-1 to demonstrate continuity of care. There is no required time span between the additional visits and the index date-1.

9.3.2. Phase 3 exploratory analysis study population

Inclusion criteria

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

1. Patients with a documented diagnosis of NSCLC.
2. Patients ≥ 18 years of age at initial recorded diagnosis of NSCLC.
3. Patients who received treatment with lorlatinib within The US Oncology Network or Non-Network practices during the study identification period.
4. During the study observation period, patients observed with at least 2 visits[4] after the index date-1.

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Receipt of treatment indicated for another primary cancer or diagnosis of another primary cancer (with the exception of non-melanotic skin cancer), within 5 years of index date-1 will be excluded.
2. Patients enrolled in clinical trials prior to receiving lorlatinib during the study ID period (index date-1) will be excluded.

9.3.3. Cohort definitions and stratifications

Separate study cohorts will be considered in all phases of the project.

For Phase 1, results will be presented for all patients who meet study eligibility criteria listed in Section 9.3.1 and stratified by subsequent treatment following alectinib (as described in Section 9.1).

For Phase 2, a sample of patients who received alectinib as front-line therapy (i.e., first treatment administration of alectinib not preceded by any other product for NSCLC therapy) will be selected for chart review and results will be presented for all patients selected for chart review and stratified by subsequent treatment following alectinib.

For Phase 3, the stratifications for Phases 1 and 2 will be replicated for all patients who meet study eligibility criteria with the extended identification and observation period as outlined in 9.3. An additional sample of patients identified for chart review for Phase 3 will be stratified by the specified subsequent treatment groups specified in 9.3.1.

9.3.4. Chart review selection

9.3.4.1. Chart review for Phase 2

Among patients who meet the eligibility criteria defined by the inclusion/exclusion criteria listed in Section 9.3.1, a sample size of approximately 100 qualified front-line alectinib patient charts will be selected to undergo a targeted chart review. In the event the total number of eligible patients following structured data screening exceeds the planned number of charts for review, a random sample will be selected.

During the course of abstraction, patients' eligibility for the study will be verified and some of these patients may be found to be ineligible. A total of up to 150 charts are assumed to be reviewed to identify at least 100 patients who received alectinib as front-line.

9.3.4.2. Chart review for Phase 3 study refresh

Two groups of patients are planned for chart review during Phase 3. The first group includes patients from Phase 2 chart review who had ongoing treatment at the end of the observation period (31 December 2019). These patients will undergo additional follow-up through 31 August 2021.

An additional sample of approximately 100 patients who meet the Phase 3 eligibility criteria and received alectinib as front-line therapy and received subsequent treatment among the following groups will undergo chart review:

- Alectinib → lorlatinib
- Alectinib → crizotinib
- Alectinib → brigatinib
- Alectinib only
- Alectinib → chemotherapy (optional)

In the event the total number of eligible patients following structured data screening exceeds the planned number of charts for review, a random sample will be selected.

During the course of abstraction, patients' eligibility for the study will be verified and some of these patients may be found to be ineligible. A total of up to 125 charts are assumed to be reviewed to identify at least 100 patients who received post-alectinib treatment from the above listed priority groups.

9.4. Variables

Table 1. Study variables and operational definitions

Main Study

Index date-1= start date of alectinib treatment during the study identification period

Index date-2= start date of the subsequent treatment following alectinib, among patients who receive a next treatment during the study identification period

Exploratory Analysis

Index date-1= start date of lorlatinib treatment during the study identification period

Index date-2= start date of the subsequent treatment following lorlatinib, among patients who receive a next treatment during the study observation period

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Demographic and patient characteristics				
PatID	iKM structured data	Data linkage	Study observation period	Unique patient identifier that will be used to link clinical records. This information will not be disclosed to the study sponsor.
Medical record number (MRN)	iKM structured data	Data linkage	Study observation period	Unique patient identifier that will be used to link clinical records. This information will not be disclosed to the study sponsor.
Clinical trial participation	iKM structured data + chart review	Eligibility criteria	Follow-up	Patients enrolled in interventional clinical trials (patients in only observational studies will be retained, if applicable) in The US Oncology Network or Non-Network during the study observation period will be flagged.
Other cancer diagnosis	iKM structured data + chart review	Eligibility criteria	Prior medical history + study observation period	Patients will be confirmed as having no additional primary or secondary malignancies (with the exception of non-melanotic skin cancer) within the 5 years prior to and after the index date-1. Patients with a secondary diagnosis or receipt of treatment indicated for another primary cancer within 5 years prior to index date-1 will be excluded.
Additional visits	iKM structured data	Eligibility criteria	Follow-up	To capture a sample of patients with longitudinal records, patients will be required to have 2 records of either additional visits following the index date-1 visit and/or a record of death prior to the end of the study follow-up period. Visits are defined as physical encounters with the practice, detected by vital sign records. There will be no distinction made, for purposes of inclusion, between patients that have an

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
				additional US Oncology Network or Non-Network visit and those with a record of death. There is no minimum or maximum requirement on time from index date-1 to these qualifying events.
Gender	iKM structured data + chart review	Baseline characteristic	Prior medical history	Patients will be categorized as: Male Female
Date of birth	iKM structured data	Eligibility; Data linkage; Baseline characteristic	Prior medical history	Patient's date of birth as recorded in iKM. This information will not be disclosed to the study sponsor.
Age	iKM structured data (derived)	Eligibility; Baseline characteristic	Baseline	Patient's age (in years) at the date of diagnosis, which will be calculated as the integer of [(diagnosis date – date of birth + 1) / 365.25]. Patients aged less than 18 years at the initial recorded diagnosis of NSCLC will be excluded from the study.
Age groups	iKM structured data (derived)	Baseline characteristic	Baseline	Multiple age categories will be created based on the continuous age data: <65 years ≥65 years No information
Race	iKM structured data	Baseline characteristic	Prior medical history	Categorized as: Caucasian African American Asian Native American Other No information The specific categories outside of Caucasian and African American will be confirmed after reviewing sample sizes and the added value to the study with Ontada's Privacy and Compliance team.
Smoking history	iKM structured data	Baseline characteristic	Baseline	Categorized as: Never smoked Current smoker Former smoker No information
Healthcare setting and provider characteristics				
Practice location	iKM structured data (derived)	Baseline characteristic	Baseline	The US census region of The US Oncology Network clinic where the patient received care at the index visit: Midwest: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota,

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
				Missouri, Nebraska, North Dakota and South Dakota Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Pennsylvania, New Jersey and New York South: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma and Texas West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, California, Oregon and Washington State Missing clinic values will be captured in a "no information" category. Some of the regions may need to be collapsed if there are small sample sizes (e.g., South vs. non-South). This determination will be confirmed after reviewing sample sizes and the added value to the study with Ontada's Privacy and Compliance team.
Disease characteristics				
Initial NSCLC diagnosis	iKM structured data + chart review	Eligibility criteria, Baseline characteristic	Medical history prior to index	To assess NSCLC diagnoses that occurred prior to index date-1, patients' available medical history in iKM will be searched. The completeness of this history will vary based on the length of disease and the time within The US Oncology Network or Non-Network. Records may also be incomplete for patients with an initial NSCLC diagnosis that occurred outside of The US Oncology Network or Non-Network. Diagnosis of NSCLC will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care (International Classification of Diseases [ICD] codes will not be used). If no initial diagnosis date is documented, the first recorded diagnosis date in iKM will be used. This date will be used in calculations, not reported separately. Patients without a recorded diagnosis of NSCLC will be excluded from the study.
Stage at initial NSCLC diagnosis	iKM structured data	Baseline characteristic	Medical history prior to index	Categorized as: Early stage (IA, IB, IIA, IIIB) Limited/Regional (IIIA) Locally advanced (IIIB)

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
				Metastatic (IV) Unknown
Date of metastatic disease diagnosis	iKM structured data + chart review	Baseline characteristic	Medical history prior to index	Date of first recorded diagnosis of metastatic disease within the EHR. Patients will be qualified initially based on the date identified in the structured data; this will be confirmed during chart review among patients selected for chart review. Ultimately, the primary source will be the chart if available. All patients receiving ALK inhibitors are assumed to be metastatic at time of ALK inhibitor treatment. Structured data will confirm the patient as metastatic and as available, indicate the earliest associated date of any of these criteria: 1) Stage IV disease 2) TNM with M value of 1 3) Record of location of metastatic disease 4) Current or prior disease status containing reference to metastatic disease
Metastatic disease at diagnosis	iKM structured data + chart review	Categorized as: Baseline characteristic	At diagnosis	Categorized as: Yes No No information Note, "no information" can indicate that metastases were not documented in the chart, not necessarily that patients did not have metastases.
Distant metastatic site(s) at index date-1 (alectinib or lorlatinib start date)	iKM structured data + chart review	Baseline characteristic	Baseline	Baseline metastatic location(s) will be identified and categorized as: Bone (single) Bone (multiple) Brain CNS Liver (single) Liver (multiple) Lung (single) Lung (bilateral) Lung (pleural effusion) Lymph nodes (regional) Lymph nodes (distant) Ovary Other No information Note, "no information" can indicate that metastases were not documented in the chart, not necessarily that patients did not have metastases.

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Tumor histology	iKM structured data	Baseline characteristic	Baseline	Categorized as: Adenocarcinoma Squamous Large Not otherwise specified (NOS) Missing/unknown
ALK testing order source and date	iKM Chart Review	Baseline characteristic	Baseline	Categorized as: Lab report Order requisition Pathology report Progress note
ALK mutation status	iKM structured data + Chart Review	Baseline characteristic	Baseline	Categorized as: Not performed Positive fusion/rearrangement Negative Equivocal Indeterminate QNS Other Inconclusive Not documented If multiple test results are available, used last documented value
Biopsy type for ALK testing	Chart Review	Baseline characteristic	Baseline	Categorized as: Pleural Tissue Blood Other Not documented
Assay type for ALK testing	Chart Review	Baseline characteristic	Baseline	Categorized as: Fluorescence in situ hybridization (FISH) Immunohistochemistry (IHC) Next-generation sequencing (NGS) Reverse transcriptase– polymerase chain reaction (RT-PCDR) Other Not documented
Date of ALK mutation result	Chart Review	Baseline characteristic	Baseline	Date as captured in chart review
BRAF (v-raf murine sarcoma viral oncogene homolog B1) mutation status	iKM structured data	Baseline characteristic	Baseline	Categorized as: BRAF V600E (Mutated) Mutations Wild-type Unknown

Table 1. Study variables and operational definitions

<table>
<tr><th>Variable</th><th>Source(s)</th><th>Role(s) in study</th><th>Period of measurement</th><th>Operational definition</th></tr>
<tr><td>EGFR (epidermal growth factor receptor) mutation status</td><td>iKM structured data</td><td>Baseline characteristic</td><td>Baseline</td><td>Categorized as:
EGFR sensitizing mutation (+)
EGFR non-sensitizing mutation (+)
T790M (+)
EGFR mutation (-)
Equivocal
Not performed
Unknown</td></tr>
<tr><td>PD-L1 expression</td><td>iKM structured data</td><td>Baseline characteristic</td><td>Baseline</td><td>Categorized as:
>= 50% Expression
1-49% Expression
Negative
Unknown</td></tr>
<tr><td>ROS1</td><td>iKM structured data</td><td>Baseline characteristic</td><td>Baseline</td><td>Categorized as:
Positive,
Negative,
Unknown</td></tr>
<tr><td>MET (Mesenchymal-to-epithelial transition) exon 14 mutations</td><td>iKM structured data</td><td>Baseline characteristic</td><td>Baseline</td><td>Categorized as:
Positive,
Negative,
Unknown</td></tr>
<tr><td>Eastern Cooperative Oncology Group (ECOG) performance status</td><td>iKM structured data</td><td>Baseline characteristic</td><td>Baseline</td><td>The ECOG performance status score is a rating of a patient’s disease status, daily living activities and quality of life, with low scores indicating greater functioning than high scores:
0
1
2
≥3
No information
Karnofsky performance status is a similar measure and will be converted to ECOG using the methodology outlined below.[20]
<table>
<tr><th>Karnofsky Performance Status</th><th>ECOG Performance Status</th><th>ECOG Performance Status Description</th></tr>
<tr><td>100</td><td>0</td><td>Fully active</td></tr>
<tr><td>80, 90</td><td>1</td><td>Restricted in physically strenuous activity</td></tr>
<tr><td>60, 70</td><td>2</td><td>Ambulatory and capable of self-care</td></tr>
</table></td></tr>
</table>

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
				but unable to work **40, 50** 3 Capable only of limited self-care **10, 20, 30** 4 Completely disabled **0** 5 Dead
Treatment characteristics				
Date of alectinib or lorlatinib receipt during the patient identification period (i.e., index date-1)	iKM structured data + chart review	Eligibility criteria, Treatment characteristics	Study observation period	The date of alectinib or lorlatinib receipt during the study identification period. Patients who did not receive alectinib during the patient identification period for the main study and patient who did not receive lorlatinib for the exporatory analysis will be excluded from the study.
Prior chemotherapy or immunotherapy treatment	iKM structured data + chart review	Treatment pattern	Study observation period	Chemotherapy or immunotherapy received by patients for NSCLC treatment prior to the index treatment (adjuvant treatment will be excluded).
ALK inhibitor treatments	iKM structured data + chart review	Treatment pattern	Study observation period	Any ALK inhibitor treatment received by patients during the study identification period.
ALK inhibitor start date	iKM structured data + chart review	Treatment pattern	Study observation period	Date of initiation with ALK inhibitor during the study identification period.
ALK inhibitor stop date(s)	iKM structured data + chart review	Treatment pattern	Study observation period	Date of final treatment for each ALK inhibitor. It is possible that the patient's treatment stop date is not documented if the patient dies, is lost-to follow-up or is still on-therapy. The final treatment date, death date or end of study date will be used, whichever is earliest. If patient does not have a stop date and initiates a subsequent therapy, the start date of the subsequent therapy will be considered as stop date of initial therapy.
Subsequent treatments received post-alectinib or post-lorlatinib	iKM structured data + chart review	Treatment pattern	Study observation period	Immediate next treatment post-alectinib (or post-lorlatinib) and subsequent treatments received post-alectinib (or post-lorlatinib) treatment during the study period. *Lorlatinib treatment for the exploratory analysis will be sourced from structured data only

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Subsequent treatments (post alectinib or post-lorlatinib) start and end date(s)	iKM structured data + chart review	Treatment pattern	Study observation period	Date of initiation and end date of immediate next treatment post-alectinib (or post-lorlatinib) and subsequent treatments received post-alectinib (or post-lorlatinib) treatment during the study period. *Lorlatinib treatment for the exploratory analysis will be sourced from structured data only
Reason for ALK inhibitor (alectinib, and subsequent treatment) treatment discontinuation	Chart review	Treatment characteristics	Study observation period	Data for alectinib and subsequent treatment discontinuation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients discontinued treatment will be abstracted: Completion of therapy Provider-documented disease progression Death Insurance/cost-related Loss to follow-up Patient preference Toxicity Other No information Reviewers will specify other reasons; these will be reported if any represent >5% of patients.
ALK inhibitor treatment sequencing	iKM structured data + chart review	Treatment pattern	Study observation period	ALK inhibitor treatment paths (e.g. initiate crizotinib followed by ceritinib, initiate crizotinib followed by alectinib, etc.)
Front-line alectinib	iKM structured data + chart review	Treatment pattern	Study observation period	First treatment administration of alectinib not preceded by any other product for NSCLC therapy except up to 3 months of chemotherapy and immunotherapy preceding alectinib therapy initiation to classify patient as receiving 1L alectinib
Clinical outcomes				
Last US Oncology Network visit date	iKM structured data + chart review	Clinical outcomes	Study observation period	Each patient's most recent visit date, prior to or on close of study observation period, in the structured data will be recorded. A visit is defined as a physician encounter with the practice where either treatment is given, or vital signs are recorded. For patients with a death date, this last visit date should occur prior to the death date.

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
				This will not be reported separately; it will be used in calculating the patient's available follow-up time as a descriptive measure. Available follow-up time = Integer (latest of last visit date or death date – index date +1).7
Death date	iKM structured data + limited access death master file (LADMF) + chart review	Clinical outcomes	Study observation period	Date of death will be captured from the LADMF as well as iKM. If dates conflict between the 2 sources, the LADMF date will be prioritized. If severe data discordance is observed (i.e., death is reported to occur prior to the index date), then the iKM death date will be used.
Vital status	iKM structured data + LADMF + chart review (derived)	Clinical outcomes	Study observation period	Patients without a date of death in either the LADMF or iKM will be assumed to be alive at the end of the study. Those with a date of death in either LADMF or iKM will be flagged as deceased.
ALK inhibitor (alectinib and stratified by subsequent treatment) duration of therapy (DOT)	iKM structured data + chart review (derived)	Treatment characteristics	Study observation period	An intent to treat approach will be used. DOT will be defined as duration of time (in months) between alectinib initiation and discontinuation, or the last administration date of alectinib, or start date of a subsequent ALK inhibitor, or evidence of new non-ALK inhibitor treatment (as a proxy for evidence of discontinuation) will be used as a stop date. There may be some patients who do not have evidence of discontinuation or who do not move on to a subsequent therapy. Descriptive statistics (mean, median) and K-M methodology will be calculated from initiation of alectinib, until evidence of discontinuation for any reason, including but not limited to a treatment stop date, a last alectinib administration date, evidence of new ALK inhibitor treatment or non-ALK inhibitor treatment, death or check-in in a hospice. Patients who do not have evidence of discontinuing, starting new therapy, or whose last prescription date is <30 days from the end of

Table 1. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
				the study period, will be censored at last visit date or end of study period.
Overall survival (OS) (alectinib and stratified by subsequent treatment)	iKM structured data + LADMF + chart review (derived)	Clinical outcomes	Study observation period	OS will be defined as the interval (in months) between alectinib start date and the date of death (any cause) as documented in the LADMF and the iKM EHR database. OS will be reported for overall alectinib and stratified by subsequent treatment. Patients who did not die within the study observation period will be censored on the study end date or the last visit date available in the dataset, whichever occurred first. OS will be analyzed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients 3, 6, 12, 18, and 24 months.
Progression date after index date (physician-assessed)	Chart review	Clinical outcomes	Study observation period	Physician-assessed disease progression (and corresponding date of note) recorded from physician's progress notes in Chart Review.
Progression-free survival (alectinib, and subsequent treatment)	iKM structured data + LADMF + chart review (derived)	Clinical outcomes	Study observation period	The PFS will be measured from the initiation of alectinib to the date of progression or date of death due to any cause, censoring patients who are still alive at the end of the study observation period and did not progress at the last visit date. PFS will be reported for overall alectinib and stratified by subsequent treatment. The PFS will be estimated in weeks using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 3, 6, 12, 18, and 24 months.

9.5. Data sources

Table 1 presents the data elements that will be evaluated through this study and their associated source. Most study data will originate from the EHR system of The US Oncology Network and Non-Network, iKM. Independent community-based oncology practices that participate in the Non-Network Select Program have implemented the iKM EHR, although the clinics are distinct from The US Oncology Network. iKM captures outpatient practice encounter histories for patients under community-based care, including, but not limited to patient demographics such as age and gender; clinical information such as disease diagnosis, diagnosis stages, performance status information and laboratory testing results; and treatment information, such as dosages and treatment administration within The US Oncology Network.

Structured data fields within the iKM EHR database will provide information needed to address most research questions. These data will be supplemented by additional unstructured data collected through chart review for a subset of the study population (selection methodology described in Section 9.3.4). Electronic chart review data will be collected by means of a secure, web-based electronic case report form (eCRF) by healthcare professionals with oncology experience.

The study will only use data from US Oncology Network practices utilizing full EHR capacities of iKM. Data management and administrative processing is supported by Ontada's quality assurance procedures. Additionally, iKM has previously been used to evaluate patient profiles, treatment patterns and outcomes among metastatic NSCLC patients and the results have been consistent with other published studies.[21-23] Thus the study team does not plan to conduct any additional studies to validate the accuracy of demographic, clinical, treatment and outcome information in the iKM EHR database.

The Limited Access Death Master File (LADMF) of the Social Security Administration will be an additional source of vital status (death), in addition to death dates recorded in the EHR. Common patient identifiers (patient identification, name, and birth date) will be used to link patients from the iKM data warehouse and iKM chart review. The social security number (SSN) will be used to link patients from iKM and LADMF data sources. All patients within iKM are assigned a unique patient identifier by iKM version (e.g., some large practices have separate installations by location). When linking to the LADMF, patient SSN is used. Some practices do not collect SSN and some patients may not report it. In all cases, reported deaths captured in iKM will supplement the Social Security Administration data.

Data from all sources and any derived variables will be merged into one master dataset for analysis. Data will be handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH).

9.6. Study size

A preliminary feasibility assessment for Phases 1 and 2 identified 293 patients who were treated with alectinib after 01 November 2017, with approximately half treated in the front-line setting. Of the 293 patients receiving alectinib, 74% (n=217) patients had an ALK result. Approximately 20-30% of the 293 patients received a subsequent therapy after alectinib. It is estimated that approximately 300 patients will be included in the Phase 2 structured data analysis. Targeted chart review for Phase 2 is proposed to occur on 150 patients receiving alectinib to identify at least 100 patients who received alectinib as front-line. In the event the total number of eligible patients following structured data screening exceeds the planned number of charts for review, a random sample will be selected.

For Phase 3 structured analysis, a preliminary feasibility assessment identified 521 patients who were treated with alectinib from 01 June 1 2017 through 31 December 2020. Chart review for Phase 3 will include patients who had ongoing treatment at the end of Phase 2

study period, and an additional 125 patients will be targeted to identify 100 new patient who received alectinib as front-line therapy. For Phase 3 exploratory analysis, a preliminary feasibility assessment identified 134 patients who were treated with lorlatinib from 01 November 2018 through 31 December 31 2020.

The final study population for analysis will be defined after identification and review of the patient population meeting the eligibility criteria in the iKM database. A specific power calculation will not be performed as this is a descriptive analysis.

9.7. Data management

For Phases 1 and 2, the Ontada study team will collaborate with Ontada's Commercial Intelligence group to collect the structured iKM data that will be used for analysis. The Commercial Intelligence team will be provided with a Data Collections Variable List, which will detail the specific data elements that will need to be included in the study dataset. A Data Analyst will begin by generating high-level study sample counts that demonstrate attrition rates of the inclusion/exclusion criteria.

The study team will review the attrition count and the Data Analyst will proceed with collecting the remaining data elements on the Data Collections Variable List. The Data Analyst will perform an initial quality control check of the study dataset before providing the file to the study team's Biostatistician on a secure server. Once received by the Biostatistician, data validation will continue and will consist of, but is not limited to, quality control checks for appropriate values, logical sequences and quantity of missing values.

During Phase 3, the Ontada Biostatistician will collect the structured iKM data that will be used for analysis. The biostatistician will begin by generating high-level study sample counts that demonstrate attrition rates of the inclusion/exclusion criteria. The study team will review the attrition count and the Biostatistician will proceed with collecting the remaining data elements detailed in the study protocol. The Biostatistician will perform data validation activities that will consist of, but are not limited to, quality control checks for appropriate values, logical sequences, and quantity of missing values.

For Phases 2 and 3, the Biostatistician will generate a list of patients eligible for chart review and will apply a sampling technique to identify the specific patients that will undergo chart review. This list of patients will then be securely transmitted to the Chart Review Team Manager. The chart review team consists of experienced oncology healthcare providers.

The Ontada study team will lead a training session with chart abstractors to discuss study specific considerations. Reference materials will also be provided to abstractors at this time. If chart abstractors have questions during the abstraction process, these will first be raised to the Chart Review Team Manager. If needed, questions can be escalated to the Outcomes Researcher and Principal Investigator.

Chart review will be accomplished by use of a secure, web-based eCRF. The main purpose of the eCRF is to obtain data required by this non-interventional study protocol in a complete, accurate, legible and in a timely manner.

The unstructured data will be linked to structured data, which will be converted to structured form by a computer using automated/algorithmic methods, such as natural language processing. Analyses will be conducted using SAS® (SAS Institute Inc., Cary, NC, US) and/or R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) as appropriate.

9.7.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A completed CRF is required for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The Ontada study team shall ensure that the CRFs are securely stored and will be password protected to prevent access by unauthorized third parties.

The Ontada study team has ultimate responsibility for the collection and reporting of all data entered on the CRFs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRF serves as the source document. Any corrections to entries made in the CRFs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.7.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Ontada agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs[/DCTs] and hospital records), copies of all CRFs[/DCTs], safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by Ontada according to local regulations or as specified in the Ontada contract whichever is longer. Ontada must ensure that the records continue to be stored securely for so long as they are retained.

If Ontada becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Ontada and Pfizer have expressly agreed to a different period of retention

via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

Ontada must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.8. Data analysis

As the foreseen analyses are defined in enough detail in this protocol, no further statistical analysis plan will be developed.

9.8.1. Analysis sets

Phases 1 and 2

For analyses performed to meet the Phase 1 objectives, all patients who the meet the eligibility criteria defined in Section 9.3.1 will be considered. The study cohorts will be identified based on subsequent therapy following alectinib. For these analyses, datasets consisting of the structured data elements, plus the LADMF to confirm vitality status, required for the landscape analyses will be constructed.

The Phase 2 (chart review) analyses will be limited to a sample of 100 qualified front-line alectinib patient charts identified from Phase 1. The chart review analysis sets will be constructed from both structured and unstructured data, with the LADMF used to confirm vitality status.

Phase 3

For analyses performed to meet the Phase 3 unstructured objectives, all patients who the meet the eligibility criteria defined in Section 9.3.1 will be considered. The study cohorts will be identified based on subsequent therapy following alectinib. For these analyses, datasets consisting of the structured data elements, plus the LADMF to confirm vitality status, required for the landscape analyses will be constructed.

Phase 3 chart review analyses will include a subset of patients from Phase 2 chart review who had ongoing treatment at the end of the observation period and an additional sample of 100 qualified front-line alectinib patients from Phase 3. The chart review analysis sets will be constructed from both structured and unstructured data, with the LADMF used to confirm vitality status.

Some data elements will be captured with both structured and unstructured data. Since the chart review data are expected to provide a richer source of information, if data are available from both sources for a single patient, then chart review data will supersede what is available in the structured iKM data for the final analysis. To account for this, a final analysis data set will be constructed and used to update the landscape analyses once chart review data are available.

For Phase 3 exploratory analysis, all patients who meet the eligibility criteria defined in Section 9.3.2 will be considered. The study cohorts will be identified based on subsequent therapy following lorlatinib. For these analyses, datasets consisting of the structured data elements will be constructed.

9.8.2. Derived and transformed data

Some of the data elements needed for the study objectives will be derived from available data during the analysis phase of the study. Details about these calculations are provided along with the operational definition in Table 1. Prior to constructing these variables, the Ontada biostatistician will perform data validation activities. Data validation will continue and will consist of, but is not limited to, quality control checks for appropriate values, logical sequences, and quantity of missing values.

Missing data will be identified and reported in the results tables as percentages for all variables. If there is a large amount of missing or illogical data, a decision to include, exclude or impute that variable will be subsequently made based on the study sponsor's decision.

9.8.3. Statistical methods

Description of study enrollment

To be included in the study patients must meet each of the inclusion criteria and none of the exclusion criteria listed in Section 9.3.1. Counts of patients excluded for each criterion will be summarized.

Additionally, the counts of patients to be classified into the following subgroups will be presented[5]:

- Cohort A: All alectinib treated patients (overall population)
- Cohort B (Alectinib only cohort): Alectinib treatment ongoing, or discontinued and no subsequent treatment[6]
- Cohort C: Alectinib followed by treatment X (top 3 most frequent)
- Cohort D: Alectinib followed by treatment Y (top 3 most frequent)
- Cohort E: Alectinib followed by treatment Z (top 3 most frequent)

Description of patient demographic, clinical and treatment characteristics

Descriptive analyses will be conducted to evaluate the demographic, clinical and treatment characteristics overall, as well as for each of the study cohorts. Results will be reported in

[5] Final cohorts will be decided upon sample size. Patients receiving chemotherapy after initiating alectinib will be included in the patient sample

[6] Patients with ongoing alectibin treatment, patients who discontinued alectinib and patients who did not have a subsequent treatment may be analyzed as separate cohorts depending on sample size of patients

aggregate. Categorical variables (e.g., ECOG performance status) will be reported as frequency and percentage. Continuous variables such as age will be reported as mean, standard deviation, median and range (minimum-maximum). In the case of missing observations, the number and percentage of missing values will be reported.

For comparative analysis, i.e. comparing 2 or more treatment groups (e.g., ALK inhibitor sequences) or strata (front-line alectinib and non front-line alectinib), statistical significance will be reported with level of statistical significance based on p = 0.05 level as well as 95% confidence intervals.

Chi-square testing will be used to assess associations between categorical variables when patient counts for single cells within the results tables are greater or equal to 5. When distribution cannot be assumed to be Chi-square, then Fisher's exact test will be used. Depending on normality, Analysis of variance (ANOVA)/t-tests or Kruskall-Wallis tests will be used for continuous variables. An alpha level of 0.05 will be the primary criterion for statistical significance of this study.

All descriptive tables will be presented for each of the study cohorts defined above and, as supported by the final sample size, stratified by front-line alectinib and non front-line alectinib treatment groups.

For Phase 3 exploratory objectives, descriptive analyses will be conducted to evaluate the demographic, clinical and treatment characteristics among patients treated with lorlatinib. Results will be reported in aggregate. Categorical variables (e.g., ECOG performance status) will be reported as frequency and percentage. Continuous variables such as age will be reported as mean, standard deviation, median and range (minimum-maximum). In the case of missing observations, the number and percentage of missing values will be reported.

Clinical outcomes

ALK inhibitor DOT, OS, PFS will be assessed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 3, 6, 12, 18, and 24 months. Further details about these calculations are presented below and in Table 1.

Clinical outcome results will be presented by study cohort and stratified by front-line alectinib and non-front line alectinib (pending sample size).

Overall survival (OS) will be defined as the interval between start date of alectinib to the date of death as documented in the LADMF and/or iKM EHR database. Patients who did not die will be censored on the study end date or the last visit date available in the database, whichever occurred first. In order to handle censoring, the Kaplan-Meier method will be used to calculate median overall survival with 95% confidence intervals (in number of months). Additionally, 3, 6, 12, 18, and 24-month survival probabilities will be reported. OS will be estimated for the full study population and stratified by study cohort. Log-rank tests will be used to assess statistical differences.

Duration of Therapy (DOT) for ALK inhibitors: An intent to treat approach will be used. DOT will be defined as duration of time (in months) between alectinib treatment initiation and discontinuation, or the last administration date of alectinib, or start date of a subsequent ALK inhibitor, initiation of any subsequent non-ALK inhibitor treatment (as a proxy for evidence of discontinuation), death or check-in in a hospice will be used as a stop date.

There may be some patients who do not have evidence of discontinuation or who do not move on to a subsequent therapy.

Descriptive statistics (mean, median) and K-M methodology will be calculated from initiation of alectinib, until evidence of discontinuation for any reason, including but not limited to a treatment stop date, a last alectinib administration date, or evidence of new ALK inhibitor treatment or non-ALK inhibitor treatment. Patients who do not have evidence of discontinuing, starting new therapy, or whose last prescription date is <30 days from the end of the study period, will be censored at last visit date or end of study period.

$$DOT = \left(\frac{date\ of\ ALK\ treatment\ discontinuation - index\ date + 1}{30.4375}\right)$$

Progression-free survival: The PFS will be measured from the initiation of alectinib to the date of progression or date of death due to any cause, censoring patients who are still alive at the end of the study observation period and did not progress at the last visit date. Progression will be clinician-noted progression as noted per physician notes only, not by traditional Response Evaluation Criteria in Solid Tumors (RECIST) imaging, as this is impacted by frequency of imaging and may not be assessed the same across groups in daily clinical practice. Patients who did not progress or die will be censored on the study end date or the last visit date available in the database, whichever occurred first. The PFS will be estimated in months using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 3, 6, 12, 18, and 24 months. PFS will be estimated for the full study population and separately by study cohort. Log-rank tests will be used to explore statistical differences.

9.8.4. Sequence of analyses

Five separate data collection activities are planned for this study. First, structured data will be collected for all eligible patients and will be used to classify patients into the cohorts defined in Section 9.3. Chart review will then be undertaken in a sample of 100 front-line alectinib patients. As chart review data become available, analyses will be undertaken to meet the study objectives in Phase 2.

During Phase 3, all eligible patients for structured data and a sample of additional patients for chart review as defined by the cohorts specified in Section 9.3.1 will be identified. Structured data collection and chart review will occur simultaneously. Analyses to meet study objectives will occur after chart review is complete. No interim analysis is planned.

All eligible patients for the Phase 3 exploratory analysis as defined by the criteria in Section 9.3.2 will be identified and analyses to meet the exploratory objectives will occur after the main objectives are complete.

9.9. Quality control

For structured data, Ontada's Real World Research team conduct quality assurance checks on all analytics projects. The process includes both technical and clinical quality checks. Technical review of the dataset consists of identifying inappropriate values (e.g., out of range, illogical), logical sequences and quantity of missing values. Illogical and missing data will be reported to the study team, which may opt to exclude or impute these values. Clinical review of the data subsequently occurs to ensure aggregate data are aligned with expectations and prior publications.

The quality assurance process includes the following areas:

- Project scope and study rules
- Protocol development
- Data extraction and integrity
- Populated tables and study report development

As results of quality assurance and quality control, we confirm:

- The source of the data and/or results will be documented, and that results/data will be verified against the source
- The internal consistency of the medical research data presented
- The conclusions are objective, balanced and consistent with the study results
- The format and content of the document are aligned with the agreed upon template and standards

Quality control and validation of chart review (unstructured) data will occur in multiple phases. Prior to full chart review, a pilot will be conducted with at least 5% of the patient population, up to 25 patients. Charts will be reviewed by each reviewer on the team to ensure inter-rater reliability. Data Collection Manager/Team Lead will review pilot data for accuracy and consistency, including implausible dates (i.e., date of death prior to last date of treatment), non-standard treatments, results which are inconsistent with known clinical parameters or other clinical data which is inconsistent with known standards and outcomes. Chart review team will meet following pilot and before launch of full chart review to clarify ambiguous or conflicting data and address potential problems and questions. Pilot data will be presented to the research team for review and approval. If necessary, revisions to the tool and/or additional training will be implemented.

Once the pilot chart review is complete, the remaining chart reviews will proceed. During this phase of chart review, Data Collection Manager/Team Lead will perform random and detailed checks of the data by verifying original source data. The Data Collection Manager will also initiate queries, Quality Control (QC) of randomly selected charts and review of final data set before submission to researcher. Finally, the researcher and study's statistical lead will provide a final examination of the final dataset by looking for missing or illogical data before preparing it for analyses. This analysis will include a descriptive analysis of the provider characteristics, demographics, baseline clinical and disease characteristics, and characteristics of treatment patterns. Data points flagged as outliers will be reviewed by the Chart Review Team Lead.

Based on extensive experience with chart abstraction of real-world oncology data, the Ontada Life Sciences team has created chart abstraction guidelines to reflect best practices in data collection across a number of disease areas.[24] The intent of this document is to ensure accurate, objective and consistent data capture.

9.10. Limitations of the research methods

9.10.1. Internal validity of study design

Measurement error(s)/misclassification(s)
This observational and retrospective study uses iKM EHR data. The iKM database is not collected for research purposes but for clinical practice reasons. This may impede the standardization of the data collection methods and instruments and the reporting practices of the physician. As with all administrative databases, iKM data are subject to coding errors of omission and commission. Problems with inadequate or inaccurate codes in the databases may introduce some level of misclassification bias of certain diagnoses, events, or procedures of interest.in the study. Likewise, some variables of interest may not be as complete across the entire population. The iKM EHR contains information on patients only when they are seen by US Oncology Network physicians. Services and procedures provided outside of The US Oncology Network are not captured by the database, as well as drugs received by patients from pharmacies not affiliated with US Oncology Network practices.

A patient's treatment history prior to his/her first encounter at a US Oncology Network practice may be only available in physician progress notes and is not well captured in the iKM EHR. We cannot rule out the possibility that some patients coded as receiving being treatment naïve for advanced disease in iKM EHR actually had previous chemotherapy or other treatment for advanced disease in healthcare facilities outside The US Oncology Network.

Information bias
Due to the nature of the study design, there is potential for bias to be introduced into the calculations of clinical outcomes. Specifically, patients who received treatment during the patient identification period may be meaningfully different from other patients who received therapy prior or after the study identification period.

Confounding

The iKM system is used for clinical practice reasons, not solely for research purposes. As such, associations but not causality can be detected, thus bias may be introduced by confounding factors. For example, data may be collected with an intent-to-treat approach, meaning based on when treatment is assigned rather than received. In particular, it will not be possible to determine if oral therapies were dispensed or taken; therefore, we'll use an intent-to-treat approach for analysis, with the assumption that all prescribed oral therapies were taken. Likewise, patients who do and do not receive the treatment at one point in time may be fundamentally different than those who received treatment during the observation period. These confounding factors are most likely to affect the outcomes being considered for this estimation study.

9.10.2. External validity of study design

Not all community oncology practices are included in the iKM dataset. Furthermore, not all of The US Oncology Network utilize the full capabilities of the iKM EHR. The US Oncology Network encourages use of evidence-based treatment guidelines. Therefore, practices that participate in The US Oncology Network may be different from other community oncology practices in the patient population that is seen or the prescribing practices of the physicians.

9.10.3. Analysis limitations

As a retrospective observational study, data entry errors at the point of care cannot be detected or corrected during analysis.

9.10.4. Limitations due to missing data and/or incomplete data

Although data quality checks are conducted, it is possible that some variables of interest may not be as complete across the entire population.

9.11. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. Patient personal data will be stored at Ontada in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Ontada will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Ontada shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. Ontada will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

The Ontada study team will submit a request for exemption, waiver of informed consent and authorization to the IRB. This project involves the study of existing data and records; study information will be analyzed by the Ontada study team in such a manner that research participants will not be directly identified. Once exemption status and a waiver of informed consent are met, a waiver of authorization can be approved, allowing the retrospective study to occur.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., 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.

10.4. 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), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Structured Data Analysis

This study involves EHR 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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the eCRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.
All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.
Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible 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.

A phased approach to project execution will be undertaken, with interim results and reports provided at completion of the cohort analyses (see Section 9.8.4 for further description of the sequence of analyses). The completed study will be summarized in final reports that accurately and completely presents the study objectives, methods, results, limitations of the study and interpretation of the findings.

Publication

It is anticipated that the results of this analysis will be disseminated in the following publications:

- At least 1 conference abstract
- At least 1 manuscript

The Ontada study team will collaborate with the Sponsor to determine the appropriate conference(s) and journal(s) for submission, following assessment of the study findings.

Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors. All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed. Authors will adhere to the ICMJE guidelines, specifically, all authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; (3) approved the version to be published, and (4) agreed 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. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

13. REFERENCES

1. *Peters S, Ross CD, Shaw A, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. N Engl J Med 2017; 377:829-838.*
2. *Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA CANCER J CLIN 2019;69:7–34. .*
3. *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 Apr;14(4):691-700.*
4. *Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.*
5. *Camidge DR, Doebele RC. Treating ALK-positive lung cancer — early successes and future challenges. Nat Rev Clin Oncol 2012;9:268-77. .*
6. *Iragavarapu C, Mustafa M, Akinleye A, Furqan M, Mittal V, Cang S, et al. Novel ALK inhibitors in clinical use and development. J Hematol Oncol. 2015;8(1):17. doi: 10.1186/s13045-015-0122-8.*
7. *Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561-566. .*
8. *Garber K. ALK, lung cancer, and personalized therapy: portent of the future? J Natl Cancer Inst. 2010;102:672-675. .*
9. *Takeuchi K, Choi YL, Soda M, et al. Multiplex Reverse Transcription-PCR Screening for EML4-ALK Fusion Transcripts. Clin Cancer Res: 2008;14: 6618-24.*
10. *Palmer RH, Vernersson E, Grabbe C, et al. Anaplastic lymphoma kinase: signaling in development and disease. Biochem J. 2009;420:345-361. .*
11. *Mosse YP, Wood A, Maris JM. Inhibition of ALK signaling for cancer therapy. Clin Cancer Res. 2009;15:5609-14. .*
12. *Sasaki T, Rodig SJ, Chirieac LR, et al. The biology and treatment of EML4-ALK non-small cell lung cancer. Eur J Cancer. 2010;46:1773-80. .*
13. *Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res. 2008; 14:4275-83. .*
14. *Wong DW, Leung EL, So KK, et al. The EML4-ALK Fusion Gene Is involved in Various Histologic Types of Lung Cancers from Nonsmokers with Wild-type EGFR and KRAS. Cancer. 2009;115:1723–33.*
15. *Schein PS, Scheffler B. Barriers to efficient development of cancer therapies. Clin Cancer Res. 2006;12:3243-3248.*
16. *Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017 Mar 4;389(10072):917-929.*
17. *Solomon, BJ, Besse B, Bauer TM, et al: Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. Lancet Oncol 19:1654-1667, 2018.*

18. *FDA approves lorlatinib for metastatic ALK-positive NSCLC. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lorlatinib-metastatic-alk-positive-nsclc. Accessed 30 June 2021.*
19. *The US Oncology Network, 2018.*
20. *Ma C, Bandukwala S, Burman D, et al: Interconversion of three measures of performance status: an empirical analysis. Eur J Cancer 46:3175-83, 2010.*
21. *Reynolds C, Masters ET, Black-Shinn J, Boyd M, Mardekian J, Espirito JL, Chioda M. Real-World Use and Outcomes of ALK-Positive Crizotinib-Treated Metastatic NSCLC in US Community Oncology Practices: A Retrospective Observational Study. J. Clin. Med. 2018, 7, 129. .*
22. *Nadler E, Espirito JL, Pavilack M, Boyd M, Vergara-Silva A, Fernandes A. Treatment Patterns and Clinical Outcomes Among Metastatic Non-Small-Cell Lung Cancer Patients Treated in the Community Practice Setting.Clin Lung Cancer. 2018 Jul;19(4):360-370.*
23. *McKay C, Burke T, Cao X, Abernethy AP, Carbone DP. Treatment Patterns for Advanced Non-Small-cell Lung Cancer After Platinum-containing Therapy in U.S. Community Oncology Clinical Practice. Clin Lung Cancer. 2016 Sep;17(5):449-460.e7.*
24. *Robert N, Espirito J, Haydon W, et al: Development of Playbook for Chart Review in Real-World Data. Presented at the ISPOR, New Orleans, LA, May 21, 2019.*

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Annexes

Approval Signatures

Pfizer Signatures

[Pfizer Study Lead: PPD , PhD] Date (Day Month Year)

Ontada/US Oncology Network Signature(s)

[PI: PPD , MD, MPH] Date (Day Month Year)

[Ontada Outcomes Researcher: PPD , PhD] Date (Day Month Year)