NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Retrospective, Multicenter, Observational Study to Evaluate Clinical Real World Outcomes of Lorlatinib After Alectinib in ALK-Positive NSCLC Japanese Patients
Protocol number	B7461038
Protocol version identifier	Version 2
Date	15Apr 2021
Active substance	Lorlatinib
Medicinal product	Lorlatinib (LORBRENA®)
Research question and objectives	To evaluate the clinical real world outcomes of lorlatinib in 2ndsecond /later line setting as ALK TKI-TKI sequence treatment after failure of alectinib as a first-line treatment in Japanese ALK+ NSCLC patients
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
ALK	anaplastic lymphoma kinase
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	clinical study agreement
DCF	Data Clarification Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
IEC	independent ethics committee
IQR	interquartile range
IRB	institutional review board
MHLW	Ministry of Health, Labour and Welfare
NIS	non-interventional study
NR	not reached
NSCLC	non-small cell lung cancer
PD	progressive disease
PFS	progression-free survival
Ph1 / Ph2 / Ph3	Phase1 / Phase2 / Phase3
PR	partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SAP	statistical analysis plan
SD	stable disease
TKI	tyrosine kinase inhibitor
TNM	Tumor, Node and Metastasis
TTF	time-to-treatment failure
UMIN-CTR	University Hospital Medical Information Network - Clinical Trials Registry

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

List of Principal Investigators in this study will be prepared as *Annex1*.

4. ABSTRACT

Not applicable

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Start of data collection	*02 Aug 2021*
End of data collection	*31 Oct 2021*
Analytical dataset lock	*30 Nov 2021*
Completion of Analysis	*31 Dec 2021*

7. RATIONALE AND BACKGROUND

Based on the results of J-ALEX/ALEX studies [1), 2)], alectinib granted the highest recommendation in the Japanese Lung Cancer Treatment Guideline (2020) [3)], and is broadly prescribed in the actual clinical setting in the first line setting and optimal subsequent therapy is one of the clinical question for the anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) treatment strategy.

In the 2020 clinical practice guideline for lung cancer in Japan, lorlatinib is recommended as a subsequent therapy option for select patients with ALK-positive (ALK+) NSCLC whose disease has progressed after any ALK-TKIs treatment (Recommendation level 2). Alectinib, brigatinib and ceritinib is also recommended as a subsequent therapy option for the patients with ALK+ NSCLC whose disease has progressed after ALK-TKI treatment (Alectinib : Recommendation level 1, Brigatinib: Recommendation level 2, Ceritinib: Recommendation level 2).

The third-generation ALK-TKI, lorlatinib was approved (September 2018) in the second/later line setting in Japan. It has good central nervous system (CNS) penetration and inhibits a broad range of ALK resistance mutations that develop after treatment with first (crizotinib)- and second-generation ALK inhibitors (alectinib, ceritinib). Lorlatinib in Exp 2-3A of Ph2 trial (patients treated with previous crizotinib only or patients treated with previous crizotinib and chemotherapy) showed the median progression-free survival (PFS) (not reached (NR) months [95% confidence interval (CI) 12.5–NR]). Lorlatinib in Exp 3B of Ph2 trial (patients treated with one second-generation ALK-TKI) showed the median PFS (5.5 months [95% CI 2.7–9.0]) [4)].

Brigatinib in ALTA trial (patients with ALK+ NSCLC previously given crizotinib) showed the median PFS (12.9 months [95% CI 11.1–NR]) [5)] and J-ALTA trial (patients with ALK+ NSCLC previously given alectinib ± crizotinib) demonstrated clinical benefit in the median PFS (7.3 months [95% CI 3.7–9.3]) [6)].

Ceritinib in ASCEND-5 trial (patients with ALK+ NSCLC previously given chemotherapy and crizotinib) showed a significant improvement in median PFS compared with chemotherapy (5.4 months [95% CI 4.1–6.9] for ceritinib vs 1.6 months [95% CI 1.4–2.8] for chemotherapy; hazard ratio 0.49 [95% CI 0.36–0.67]; p<0·0001) [7)]. Ceritinib in ASCEND-9 trial (patients with ALK+ NSCLC previously given alectinib) also demonstrated clinical benefit (median PFS: 3.7 months) [8)] .

Although there is various evidence for the treatment sequence of ALK-TKI followed by another ALK-TKI in clinical trials as above mention, chemotherapy as subsequent treatment after failure of alectinib is widely accepted in Japan without robust evidence from clinical trials.

There is a paucity of information on the real-world utilization of lorlatinib and clinical

outcomes among patients with ALK+ NSCLC for ALK TKI-TKI sequence treatment including lorlatinib as the second /later line in Japan, although the results of lorlatinib, brigatinib and ceritinib after alectinib in the clinical trial were as described above with the same level of recommendation in the guideline in ALK+ NSCLC. Based on favorable efficacy data on lorlatinib from clinical trials, this study is designed to collect the information on utilization of lorlatinib in an ALK+ NSCLC patients in a real-world clinical setting in Japan. In addition, this study will also describe characteristics and clinical outcomes of these patients. Findings from the study will help in addressing the knowledge gaps of lorlatinib.

8. RESEARCH QUESTION AND OBJECTIVES

To evaluate the clinical real world outcomes of lorlatinib in second /later line setting as ALK TKI-TKI sequence treatment after failure of alectinib as a first-line treatment in Japanese ALK+ NSCLC patients.

8.1. Primary objective

The primary objective is to describe the demographic characteristics of patients with ALK+ NSCLC patients treated with lorlatinib as the second/later-line therapy in a real-world clinical setting, describe clinical usage and observed effectiveness of lorlatinib.

8.2. Secondary objectives

The secondary objectives are as follows:

- To describe treatments received including alectinib as a first-line treatment prior to lorlatinib
- To describe treatment pattern after lorlatinib as a second/later-line treatment

9. RESEARCH METHODS

9.1. Study design

This study is a post-approval, company-sponsored, observational study. This study is a multicenter, non-interventional, retrospective, chart review of patients with ALK+ NSCLC patients treated using lorlatinib as the second/later line therapy in Japan after failure of alectinib treatment as the first line therapy from 20 November 2018.
All decisions regarding clinical management and treatment of the participating patients were made by an investigator as part of standard care in real-world clinical setting and were not contingent upon the patient's participation in the study. Data will be collected if available per study site. Patients in this study are those who started treatment with lorlatinib from 1 May 2019 to 31 December, 2020 in clinical practice..

Observation period : From start date of alectinib to 15 Oct 2021

9.1.1. Primary endpoint

- Description of patient characteristics at baseline (at the timing of alectinib initiation date) and at lorlatinib initiation date
  - Age
  - Sex
  - Body mass index (BMI)
  - Eastern Cooperative Oncology Group Performance Status (ECOG PS)
  - NSCLC histopathological subtype
  - Number and site of metastases
  - Complications/medical history (related to history of treatment for ALK+ NSCLC)
  - Smoking history
  - ALK test result (ALK testing method, date of test result/diagnosis and test result)
  - # of treatment regimens administered to the target disease prior to the start of lorlatinib treatment
  - Time-to-treatment failure (TTF) for lorlatinib as the second line and the 3rd/later line (see Section 9.3.2. for definition)

9.1.2. Secondary endpoint

- Reason for discontinuation of each treatment line therapy
- Objective response of lorlatinib as the second line and the 3rd/later line
- TTF of alectinib and subsequent therapy except for lorlatinib
- Objective response of alectinib
- Combined TTF; combined TTF will be defined as the sum of alectinib and subsequent therapy including TTF of lorlatinib

9.1.3. Definition of endpoint

9.1.3.1. TTF and Objective response

TTF is defined as the following:

Endpoint	Start date	Event (whichever occurs earlier)	Censored
TTF	Date of first treatment	Date of any-cause treatment discontinuation including disease progression, treatment toxicity, and death.	Date of last treatment or end of observation period

Objective response is defined as the following:

Complete or partial response as the best adjudication result (complete response [CR] > partial response [PR] > stable disease [SD] > progressive disease [PD], unknown) in a method complies with RECIST version. 1.1 tumor assessment as closely as possible in clinical practice by investigator's judgment.

9.1.4. Study flow

The study flow is shown below (Figure 1 and Figure 2)

9.1.4.1. Patients who are alive and visit the study site upon enrollment in this study

1. Investigators will check whether the patient meets the eligibility criteria. Patients will then be included in this study.
2. Investigators will explain the study and obtain written informed consent from patients.
3. Data of these patients will be collected at each study site.

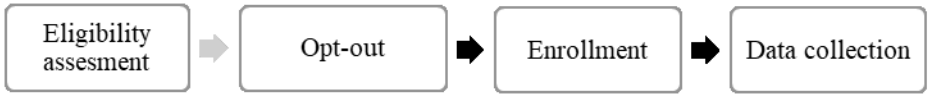
Figure1Study flow for patients who are alive and visit the study site

9.1.4.2. firstPatients who have died

1. Investigators will check whether the patient meets the eligibility criteria, and patients will then be included in this study.
2. The details of the study will be disclosed to the patient's legal representative must be guaranteed the opportunity to refuse participation or continuation in the study.

   Information about this study must be easy for the patient's legal representative to find: posted on a website or displayed in a location where patient's legal representative can check it.
3. The data of these patients will be collected at each study site.

   Figure 2 Study flow for patients who have died



9.2. Setting

9.2.1. Inclusion criteria

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

1. Histologically or cytologically confirmed NSCLC, with any TNM stage.
2. Confirmed ALK gene rearrangement by any validated test.
3. Confirmed the treatment with alectinib in the first line setting as systemic therapy in the medical record.
4. Confirmed the start treatment with lorlatinib as the second/later-line therapy from 1st May 2019 to 31st December 2020.
5. Availability of clinical information from medical record.
6. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

(1) Written consent is not required for patients who were transferred to a hospital, and registration with verbal consent is acceptable.(2) Opt-out enrollment is allowed for patients who have already died.

9.2.2. Exclusion criteria

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

1. Participating on any clinical trials of which final results has not yet been reported during the study period.

9.3. Variables

9.3.1. Patient characteristics at baseline

All included cases will be treated with lorlatinib (exposure). Variables for patient characteristics, treatment and outcomes are presented in Table 1

Variables planned at the baseline will be collected at the time of obtaining the informed consent as much as possible.

Table 1 Key variables of interest and data collection timepoints.

Role	Variable	Timepoint			
		Baseline	**Initiation of lorlatinib**	**Subsequent follow-up visits**	**End of observation period**
Patient characteristics	• Age	X			
	• Sex	X			
	• Weight	X	(X) [c]		
	• Height	X	(X) [c]		
	• Smoking status (Current smoker, Former smoker, Never smoker)	X			
	• Brinkman index	X			
	• ECOG PS (Grades 0 to 5) [a]	X	X	X	
	• Date of initial NSCLC diagnosis	X			
	• Date of advanced NSCLC (TNM stage IIIb-IV) diagnosis	X			
	• NSCLC histopathological subtype	X			
	• Clinical NSCLC staging (based on Tumor, Node and Metastasis, TNM) [b]	X	X		
	• Presence and location of metastasis (including central nervous system, CNS) at initial diagnosis and lorlatinib initiation	X	X	X	
	• Complications/medical history (related to history of treatment for ALK+ NSCLC)	X			
	• Date of ALK testing	X		X	
	• Method of ALK testing	X		X	
	• Alectinib initiation date	X			
	• Alectinib discontinuation date		X		
	• Presence and location of metastasis (including central nervous system, CNS) during Alectinib treatment		X		
	• Presence of treatment for some metastasis (including		X		

Role	Variable	Timepoint			
		Baseline	Initiation of lorlatinib	Subsequent follow-up visits	End of observation period
	CNS) during Alectinib treatment, and type of treatment(i.e. Radiation Therapy)				
	• Reason for alectinib discontinuation		X		
	• second-line treatment start/ end date and drug name, reason for the discontinuation, if lorlatinib is 3rd line treatment		X		
Treatment	• Line for lorlatinib		X		
	• Lorlatinib initiation date		X		
	• Dose of lorlatinib		X	X [d]	
	• Lorlatinib discontinuation date			X	
	• Reason for lorlatinib discontinuation			X	
	• Third-line or later treatment start and end dates, if lorlatinib is second or later line treatment.			X	
	• Reason for Third-line or later discontinuation, if lorlatinib is second or later line treatment.			X	
Outcomes	• TTF for lorlatinib				X
	• TTF for alectinib				X
	• If anticancer drug other than lorlatinib is used as 2nd line: TTF of anti-cancer treatment				X
	• If anticancer drugs are used after 2nd line lorlatinib: TTF of anti-cancer treatment				X
	• Tumor response to lorlatinib based on the RECIST			X	
	• Tumor response to alectinib and second/3rd line treatment based on the RECIST				(X) [c]

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; CNS, central nervous system; NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; TNM, Tumor Node Metastasis; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time-to-treatment failure.

[a] See Annex 3A for more information.
[b] See Annex 3B and C for more information.
[c] Not mandatory, but if available.
[d]at the date of discontinuation

9.3.2. Time to treatment (TTF)

Definitions of TTF is defined in Section 9.1.3.The following lorlatinib treatment data will be collected: initial date of administration, actual dosage at the date of discontinuation, the date and the reason for discontinuation.

9.3.3. Objective Response

Definitions of objective response are defined in Section 9.1.3. The following data will be collected: tumor response, and date of tumor response assessment.

Best objective response will be assessed based on reported overall responses at different evaluation time points from each initiation of treatment therapy until discontinuation.

9.3.4. 3rd-line/later line regimen after lorlatinib or pretreatment regimen before lorlatinib treatment

The following 3rd/later-line regimen data will be collected, if lorlatinib treatment is the second line setting: medication, initial date of administration, and reason for discontinuation.

The following second-line regimen data will be collected, if lorlatinib treatment is 3rd/later-line setting: medication, initial date of administration, and reason for discontinuation.

9.3.5. Combined TTF

Definitions of Combined TTF is the sum of alectinib and subsequent therapy including TTF of lorlatinib and other treatment.

9.4. Data sources

As this is a retrospective study, all data will be collected from medical records at the participating study site.

9.5. Study size

This study is descriptive study which aims to describe the demographic characteristics of patients who were treated with lorlatinib in the second/later line treatment for ALK+ NSCLC patients, rather than testing any pre-defined hypothesis. Therefore, calculation of sample size and statistical power are not relevant.

The expected number of patients will be approximately 50 patients treated with loratinib in total (# of patients for the second line lorlatinib treatment will be approximately 30). However, the number should be considered flexible.

9.6. Data management

Investigators will fill out relevant CRFs based on source documents (e.g., patients' medical charts) by EDC. After the completion of the CRFs, the investigator will promptly submit them.

When receiving a query from the sponsor on the completed CRF (i.e., Data Clarification Form [DCF]), investigators will reconfirm the information on source documents, fill out the DCF as required, and submit the DCF.

9.6.1. 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 CRF is required and should be completed 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 investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent, copies of all CRFs, 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 the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless 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.

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

9.6.3. Record disposal

Study records must be disposed of appropriately according to each site regulation.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Analysis Methods

Characteristics, treatment patterns and outcomes of ALK+ NSCLC patients treated with lorlatinib will be described in SAP .

Continuous variables will be summarized using n, means, standard deviations, medians, IQRs, minimums and maximums. Categorical variables will be summarized using frequencies (counts) and percentages. For the time-to-event endpoints, e.g. TTF, the Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median TTF with 2-sided 95% CIs using Brookmeyer and Crowley method. Censoring rule is shown in Section 9.1.3.1. These endpoint will also be displayed graphically.

Exploratory analyses using Cox proportional hazards model may be performed to examine the association between time-to-event outcomes and independent variables such as baseline patient, disease characteristics (e.g. age, sex, line of lorlatinib therapy, ECOG performance status, CNS metastasis, etc), and the reason for discontinuation of lorlatinib.

9.8. Quality control

The sponsor will train investigators and study site staff with an onsite training visit or web-training on the protocol, CRFs, and any applicable study processes. Any new information

relevant to the performance of this study will be forwarded to the investigator and study site staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of data, data integrity, and consistency. CRFs for all included patients will be made available to the remote data monitor for review. The study sites will be queried and managed to request resolution to any issues that may arise during the course of the study.

9.9. Limitations of the research methods

- Because this study is retrospective in nature, only existing data reported in patient records will be available. Variables that are often missing may affect estimation accuracy.
- High-volume centers will be preferentially selected in this study, so site selection and outcome reporting bias may be included. For this reason, the study results may not reflect all Japanese clinical outcomes.
- Evaluation of disease response may differ at each site, and measurement errors may be included in the estimated value.

9.10. Other aspects

9.10.1. Report to the chief executive of the study site

Each study site's investigator shall report the following to the chief executive of the study site in writing:

1） points to be revised in the protocol;
2） progression of the study
3） termination, discontinuation, and interruption of the study.

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.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site 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, the study site 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, patient names will be removed and will be replaced by a single, specific, numerical

code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site 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

10.2.1. Subjects who are alive and visit the study site

The investigator explains participation to patients using the reviewed and approved patient information sheet. An informed consent form is then used to obtain written consent from fully informed patients. The investigator explains that participation in the research is completely voluntary and that subjects are free to withdraw their consent at any time, even after providing consent form. In addition, the attending physician have to take necessary measures to ensure that subjects' rights to self-determination and treatment choice are not limited and that they would not be penalized for refusing or withdrawing consent from participation in the study. The informed consent form will then be revised after institutional review board (IRB)/independent ethics committee grants approval, and written consent will be obtained from each subject.

・Information to be provided to subjects

1) Title of the study and the fact that approval of the chief executive of the study site has been given concerning its implementation.
2) Names of the study site and the principal investigator (including names of the collaborative study site(s) and principal investigators of such collaborative study site(s), when the study is conducted collaboratively with other study site(s));
3) Objectives and significance of the study;
4) Method and time period of the study (including purpose of utilization of specimens or information acquired from the subject);
5) Reasons why asked to be enrolled in the study;
6) Burdens to be caused on the subjects and predictable risks and benefits;
7) The fact that subjects, etc. may withdraw their consent at any time even after they have given consent with regard to the study being commenced or continued (when it can be difficult to take measures that follow the withdrawal made by the study subject, etc., a statement to that effect and the reason for the difficulty).
8) The fact that the refusal or withdrawal of consent by a study subject, etc., with regard to the study is to be commenced or continued does not cause any disadvantage to such subject, etc.
9) Means to make information on the study public;

10) The fact that subjects, etc. can request and obtain or read the study protocol and documents concerning method of the study, to the extent it does not interfere the protection of personal information, etc. of other subjects, etc. or the originality of the study, as well as the procedure to obtain or read such protocols and documents;
11) Handling of personal information, etc. (including process of anonymization, when anonymization is conducted);
12) Means for storage and disposal of specimens and information;
13) Status of study-related conflicts of interest of the study site, such as study fund resources as well as study-related conflicts of interest of each investigator, such as his/her individual income.
14) Response to consultation, etc. made by subjects, etc. and other individuals concerned.
15) When the study involves any financial expenditure on or remuneration for the subject, etc., a statement to that effect and details of such;
16) When the study involves any invasiveness, whether compensation will be offered for study-related injury and details of such compensation.
17) With respect to specimens and information acquired from the subject, when any of those may be utilized or provided to other study site(s) for future study that is not identified at the time of obtaining consent from the study subject, etc., a statement to that effect and the contents of utilization assumed at the time of obtaining consent; or
18) When the study involves any invasiveness (not including minor invasiveness) and intervention, the fact that the monitor(s), the auditor(s), and the ethical review committee will be granted direct access to the specimens and information acquired from the subjects to the extent necessary, without violating the confidentiality of the subjects.

10.2.2. Subjects who are alive and had been transferred to another hospital

It is not always necessary to obtain written informed consent when existing information is provided to another hospital, but the individual providing existing information must obtain oral informed consent.

10.2.3. Subjects who have died

Because the study is retrospective, informed consent could not be obtained from subjects who had died or had failed to visit the study site. Instead of informed consent, the investigator must provide the legal representatives of the subjects an opportunity to refuse participation in the study. The following information must be made public:

1) purpose for which the information will be used;
2) item of collected information;

3) person responsible for information management;
4) organization that will be provided information;
5) how to manage refusal—if the subject refuses participation in the study, their data cannot be used.

10.3. Patient withdrawal

10.3.1. Subjects who are alive and visit the study site, or subjects who are alive and had been transferred to another hospital

During the course of this study, the subject can withdraw his/her consent at any time. In any circumstance, every effort should be made to document patient outcomes, if possible. If the patient withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before withdrawal of consent.

10.3.2. Subjects who have been died

When the legal representatives of subjects refuse to participate in the study during the study period, all of their data must be excluded from the analysis dataset. If the results of this study are disclosed on paper or conference at the time of refusal, the subject's data cannot be excluded.

10.4. 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.

10.5. 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 the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labor and Welfare (MHLW).

10.6. Predictable risks and benefits

10.6.1. Risk

The subjects' data will be collected retrospectively in this study, so there is no added risk to any individual subject.

10.6.2. Benefits

For individual subjects, there is no particular benefit because the study had a retrospective study design.

10.7. Conflicts of interest

This study will be performed with funding from Pfizer Inc. The investigators will review any conflicts of interests that may affect the planning of this study or the interpretation of results by the IRB/IEC or the Conflicts of Interest Committee, according to the regulations of the study site. When the results of the study are published, accurate information will be disclosed by self-reporting in compliance with the guidelines of the academic society or journal used for publishing the results of the study.

10.8. Registration and publication of study

Prior to implementation, this study and a summary were registered in the public database of UMIN-CTR and clinicaltrials.gov. Registered content will be properly updated without delay.

10.9. Secondary use of specimens and information obtained from subjects

The data obtained from this study may be used in other studies with different purposes. Such use will only be possible if another protocol is developed and approved by the IRB/IEC.

10.10. Responding to consultations from subjects and other related parties

The principal investigator will set up a helpline for handling consultations about this study from subjects and other related parties. Information about each site helpline is included in the informed consent form and document related to opt-out.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 <data collection tool (e.g., chart abstraction form)> nd 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:

"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)".

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 investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

The results of this study are not part of any regulatory submission. The results of this study will be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System upon final study completion.

13. REFERENCES

1) Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer（J-ALEX）: an open-label, randomised phase 3 trial. Lancet. 2017; 390（10089）: 29-39.

2) Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017; 377（9）: 829-38.

3) https://www.haigan.gr.jp/guideline/2020/1/2/200102070100.html#cq59

4) 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. 2018; 19（12）: 1654-67.

5) Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase Ⅱ trial. J Clin Oncol. 2017; 35（22）: 2490-8.

6) Nishio M, Yoshida T, Kumagai T, et al. Brigatinib in Japanese Patients With ALK-Positive NSCLC Previously Treated With Alectinib and Other Tyrosine Kinase Inhibitors: Outcomes of the Phase 2 J-ALTA Trial. JTO. 2020 Nov 25; S1556-0864(20)31026-1.

7) Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib（ASCEND-5）: a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017; 18（7）: 874-86.

8) Hida T, Seto T, Horinouchi H, et al. Phase II study of ceritinib in alectinib-pretreated patients with anaplastic lymphoma kinase-rearranged metastatic non-small-cell lung cancer in Japan: ASCEND-9. Cancer Sci. 2018; 109（9）: 2863-72.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Annex 3A. Description of the Eastern Cooperative Oncology Group (ECOG) Performance Status.

Grade	Description
Grade 0	Fully active, able to carry on all pre-disease performance without restriction.
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
Grade 3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
Grade 4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
Grade 5	Dead

Reference: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

Annex 3B. Definitions for Tumor, Node and Metastasis (TNM) descriptors.

Grade	T (primary tumor)
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)
T1	Tumor ≤3cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways
T1a	Tumor ≤1cm
T1b	Tumor >1 but ≤2cm
T1c	Tumor >2 but ≤3cm
T2	Tumor >3 but ≤5cm or tumor involving: visceral pleura, main bronchus (not carina), atelectasis to hilum
T2a	Tumor >3 but ≤4cm
T2b	Tumor >4 but ≤5cm

T3	Tumor >5 but ≤7cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor >7cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe
	N (regional lymph nodes)
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
	M (distant metastasis)
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases (1 or >1 organ)

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.

Annex 3C. Lung cancer stage grouping based on Tumor, Node and Metastasis (TNM) grades.

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.

Document Approval Record

Document Name:	B7461038_Protocol_ver_2(E)
Document Title:	B7461038_Protocol_ver_2(E)

Signed By:	Date(GMT)	Signing Capacity
PPD	13-Apr-2021 12:23:20	Manager Approval
PPD	15-Apr-2021 00:32:34	Final Approval