Non-Interventional Study Protocol
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Lorlatinib in Patients with Advanced Non-Small Cell Lung Cancer Who Progress on First- and Second-Generation Tyrosine Kinase Inhibitor: A Real-world Evidence among Taiwanese Population, Non-Interventional Study

Statistical Analysis Plan
(SAP)

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

It is the first draft version of Statistical Analysis Plan (SAP).

2 INTRODUCTION

Non-small cell lung cancer (NSCLC; 80–85% of all lung cancers) remains the most common cause of cancer-related mortality globally, most often diagnosed in advanced stages. Targeted drugs are currently the most often used therapies for advanced NSCLC patients that harbor molecular alterations, including the echinoderm microtubule-associated protein like 4 (EML4)-anaplastic lymphoma kinase (ALK) translocation [1]. For ALK-positive NSCLC patients, crizotinib, ceritinib, alectinib, and brigatinib, are the first- and second-generation tyrosine kinase inhibitors (TKIs). Although the benefit of them has been demonstrated in series of pivotal clinical trials, most patients who initially derive the benefit latterly develop resistance due to secondary mutations [1, 2].

Lorlatinib, a selective, brain-penetrant and new generation TKI, is reversible, potent adenosine triphosphate (ATP)-competitive small molecule inhibitor of ALK and Receptor Tyrosine Kinase C-Ros Oncogene I (ROS-1) and is also a potent ALK-TKI that is
effectively against all known resistant mutants, including certain mutations that are the most difficult to inhibit such as the ALK G1202R mutation. The potential of lorlatinib to improve progression-free survival (PFS) of the treatment-naïve advanced ALK-positive NSCLC patients and patients who had progressed on crizotinib and second-generation ALK-TKIs has demonstrated by clinical trials [3, 4]. The broad coverage and the mechanism of lorlatinib against all known single point mutations that mediate resistance to first- and second-generation ALK-TKIs is also elucidated by trials and studies [1, 5].

Currently, there are limited data describing the use of lorlatinib and its outcomes in real-world practice settings outside the highly controlled environs of clinical trials. The objective of this study is therefore to evaluate real-world systemic treatment patterns, clinical outcome, therapeutic effect, safety profile of Lorlatinib in advanced NSCLC patients, and also factors associated with clinical outcome in those Lorlatinib treated patients.

2.1 STUDY DESIGN

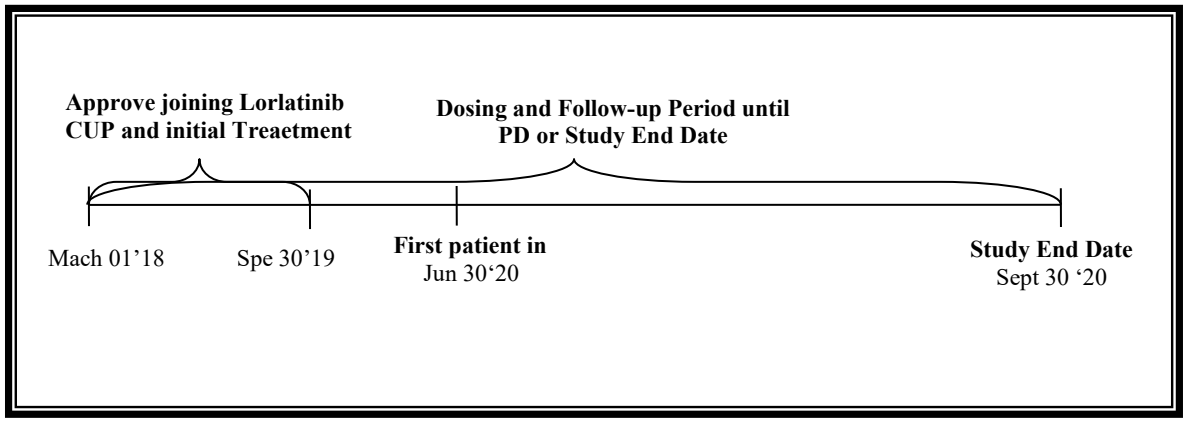
This is a retro- and prospective, multi-center, observational study with patients who are treated by Lorlatinib for advanced NSCLC after failure of chemotherapy, first- or second- generation TKI. Approximately 90 patients from Lorlatinib compassionate use program (CUP), who 1) approved joining Lorlatinib CUP on / before 31 Jul 2019; 2) initiate Lorlatinib treatment before 30 Sep 2019, are expected to be enrolled in the study in Taiwan. Prior to study entry, each eligible patient shall provide his/her written informed consent, except retrospective patients who died before this study approved by Institutional Review Board (IRB).

All enrolled subjects will be followed until study completion on 30 Sep 2020 to make sure all subjects are followed at least 1 year from first dose of Lorlatinib. The data to be captured from this group of patients includes advanced NSCLC diagnosis, gene mutation status, tumor assessment, Lorlatinib Adverse Drug Reaction (ADR) and prescription records during usage of Lorlatinib.

The list below is the information, prior the first dose of Lorlatinib, to be captured as disease history.

1. Prescription and diagnose record of NSCLC from initial NSCLC diagnose
2. Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infection status
3. NSCLC related gene examination result,
4. Best tumor response in four categories, including complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD), for all pre-Lorlatinib NSCLC treatment

Figure 1 Flow Diagram.



The site staff will collect patient data from medical record according to the schedule below.

Procedure/ Assessment	**Baseline visit (V1)**	**Follow-up Data Collection**
Day	D1	Every 12 to 14 weeks until 30 Sep 2020
Informed consent	X*	
Inclusion/Exclusion Criteria	X	
Demographic data	X	
HBV/HCV Infection Status		
NSCLC Related Genetic Examination Result		
NSCLC specific medical/ treatment history	X	
Primary diagnose at Lorlatinib prescription	X	
Tumor assessment record	X	X
Lorlatinib related ADR	X	→
Drug and non-drug treatment from fist dose Lorlatinib to study completion	X	→

* Informed consent process will be waived for subjects who died before the study approved by IRB.

Study population

Advanced NSCLC patients enrolled from Lorlatinib CUP after failure of chemotherapy, 1st and 2nd generation TKI.

According to current Lorlatinib CUP in Taiwan, the estimated recruiting number is 90. All eligible subjects who signed and agree to the informed consent or not available to provide the informed consent will constitute the cohort to be analyzed for this observational study.

Data source

The entire study will be undertaken among patients who in 6 participated study sites, including subjects approved from Lorlatinib Compassionate Use Program (CUP) and should be entered into this observational study at the physician's discretion.

In 31 May 2020, the study can start to collect full records for CUP patients. The data will be collected through medical record review including the followings:

- Subject demographic characteristics
- HBV and HCV infection status
- Prescription and diagnose record for NSCLC
- NSCLC related gene examination result
- Prescription and diagnose record for Lorlatinib related ADR
- Tumor Assessment for NSCLC from initial diagnose.

Treatment/cohort labels

The the treatment pattern will be analyzed into following **subpopulations**:

1) Group A: Lorlatinib treatment after one prior ALK TKI different from crizotinib in ALK gene mutation subject;
2) Group B: Lorlatinib treatment after two prior ALK TKI in ALK gene mutation subject;
3) Group C: Lorlatinib treatment after at more than two prior ALK TKI in ALK gene mutation subject;
4) Group D: Lorlatinib treatment in ROS-1 gene mutation subject with any pretreatment.

2.2 STUDY OBJECTIVES

2.2.1 Primary Objective

To evaluate real-world systemic treatment patterns among advanced non-small cell lung cancer (NSCLC) patients treated with Lorlatinib who were progressed on chemotherapy, first- and second-generation TKI among Taiwanese population.

2.2.2 Secondary Objective

To summarize the therapeutic effect and safety profile of Lorlatinib-treated patients with advanced NSCLC.

CCI [redacted]

[redacted]

3 HYPOTHESES AND DECISION RULES

Not applicable.

3.1 STATISTICAL HYPOTHESES

The primary objective of this study is to investigate the different treatment pattern among NSCLC patients treated with Lorlatinib who were progressed on previous chemotherapy or TKI therapy. The treatment pattern can be approximately divided into four subgroups in SAP section 2.1.

In terms of showing available clinical efficacy results between four subgroups, the treatment pattern for CUP patients can provide a supportive evidence to show clinical benefit when subjects switched from previous therapy to Lorlatinib. However, under limited sample size, no formal statistical hypothese will be claimed. All statistical testing is only for investigation.

3.2 STATISTICAL DECISION RULES

The alpha level will be 0.05, 2-sided. No adjustments for multiple comparisons will be made.

4 ANALYSIS SETS/POPULATIONS

In this study, three analysis set will be utilized for statistical analysis.

4.1 ENROLLED ANALYSIS SET

The enrolled analysis set refers to the subjects who sign informed consent form and who can be waived from the inform consenting process.

4.2 SAFETY ANALYSIS SET

The safety analysis set refers to the subjects who received at least one dose of Lorlatinib.

4.3 EVALUABLE RESPONSE ANALYSIS SET

The evaluable response analysis set refers to the treated subjects who have tumor baseline values and at least one post-baseline tumor assessment and received at least one month Lorlatinib treatment.

4.4 SUBGROUPS

Since the study patients have been divided into four subpopulations based on treatment pattern, therefore only few patients are included in each subpopulation. If any subgroup is interested, suggesting to check if sufficient sample size under each subgroup then can analyze clinical efficacy for each subgroup, if appropriate.

5 ENDPOINTS AND COVARIATES

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

The efficacy includes objective response rate (ORR), overall Survival (OS), PFS, 1-year OS rate, Time to Treatment Failure (TTF) for all NSCLC treatment and TTF of Lorlatinib based on investigator's final assessment.

All study patients treatment by Lorlatinib are followed up every 12 to 14 weeks (3 to 3.5 month) until 30 Sep 2020. During each follow-up, patients' tumor results will be collected by each visit.

5.2 SAFETY ENDPOINTS

The clinical nature, incidence, duration, and severity of Lorlatinib related adverse drug reaction; outcome and possible causality will be recorded.

CCI [redacted]

[redacted]

5.4 COVARIATES

CCI [redacted]

[redacted]

Please evaluate if the actual sample size within each level under each covariate is enough to add the specific covariate into primary analysis model. This selection is also justified by expert judgement. If any grouping rule has been applied to dichotomize continuous variables, please ensure each group under covariate has similar same size.

		CCI [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

6 HANDLING OF MISSING VALUES

There will be no imputation of incomplete or missing data. Covariates will have a 'unknown' category for patients with missing data, and will be included in the analyses.

In summaries of categorical variables which have missing values for multiple patients, percentages may be reported both relative to the total number of subjects and relative to the number of subjects with non-missing data.

As the data are from a real-world study, investigators only record what clinical management has provided or is available in the patient notes. Incomplete or unknown data should not be considered as low quality, but simply reflect real-world data collection.

As study data will be analyzed on an ongoing basis, some patient records may have incomplete data entry at the time of a data cut. Missing information should be set to unknown rather than exclude the patient.

For any unknown date of collected data, the 1st of the month will be recorded in database and Jan will be recorded in database for unknown month.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Descriptive statistics will be used to summarize the proportion of gene mutations in all patients, demographics, smoking history, clinical characteristics, treatments pattern, as well as response rate and duration of response under different treatment pattern.

7.1.1 Analyses for Continuous Data

The continuous data will be summarized using descriptive statistics (e.g. n, mean, standard deviation [SD], median, minimum, maximum for continuous variables).

If any possible confounding factors (such as baseline variables) should be adjusted to investigator how these factors effect binary outcomes, multiple regression model is suggested to use.

7.1.2 Analyses for Categorical Data

The analysis of correlation in categorical data will be performed by chi-square tests.

7.1.3 Analyses for Binary endpoints

The number and corresponding percentages by groups (such as categorical result of gene mutation and response results) will be listed when analyzing binary endpoints, and exact Clopper Pearson methods of calculating confidence intervals for binomial proportions will be presented.

If any possible confounding factors (such as baseline variables) should be adjusted as covariates to investigator how these factors effect binary outcomes, Logistic Regression Model is suggested to be used to check how multiple variables effect the binary endpoint, such as objective response rate.

7.1.4 Analyses for Time to Event data

The time to event endpoints (duration of response, progression-free survival, or overall survival) will be assessed by the Kaplan-Meier method and analyzed by the log rank test. Time to event curves between the four subpopulations will be compared with a log-rank test along with the corresponding hazard ratio. The 1-year OS rate will be estimated along with the corresponding 95% CI.

Possible covariates should be taken into consideration into the multivariate model. Multivariate analyses will be carried out by fitting multiple Cox's proportional hazard models to predict patient's hazard rates of treatment response.

All data analysis will be executed using statistical software SPSS version 17 or later.

7.2 STATISTICAL ANALYSES

7.2.1 Demographic data and baseline characteristics

Demographic data and baseline characteristics will be analyzed by Safety Analysis Set.

For the subject demographic data, baseline characteristics will be summarized and tabulated.

The tables and lists will include the following subject demographic data:

- Age: describe statistics (number, mean, standard deviation, median, minimum and maximum of the subjects without missing);
- Gender: male, female;

The tables and lists will include the following subject baseline characteristics:

- Smoking History: non-smoking, current smoking, previous smoking;
- Gene Examination: results of ALK, ROS-1, EGFR and PD-L1;
- Hepatitis B/C Virus Infection;
- ECOG result.
- Disease classification by AJCC 8th
- Metastases at Initiation of Lorlatinib
- Mutation status at initiation of Lorlatinib

7.2.2 Medical History

The clinical nature, incidence, duration, and severity of Lorlatinib related adverse drug reaction; outcome and possible causality will be recorded.

The medical history before first dose of Lorlatinib will be collected by following item.

- Hyperlipidemia;
- Hyperglycemia;
- Skin Rash;
- Mental Disorder;
- Edema;
- Body Wight Gain;
- Amylase Escalation;
- Other

The medical history is graded by CTCAE 4.03 and recorded with status of “Unstable”, “Stable” or “Resolved”. Therefore, the number and percentage of patients with any category of medical history, with different grade and status will be presented.

7.2.3 Safety Analyses

The clinical nature, incidence, duration, and severity of Lorlatinib related adverse drug reaction; outcome and possible causality were recorded.

An overview table of Lorlatinib adverse drug reaction(ADR) will be summarize the number and percentage on subject level of the following categories:

- The grading of the ADR (according to CTCAE v4.03)
- The mean and SD of the ADR duration
- Subjects with any ADR with outcome, including "Recovered," "Recovered with Sequelae," "Recovering," "Not Recovered," and "Unknown."

All adverse drug reaction summaries should provide the number of subjects reporting at least one adverse event and the total number of events reported.

For the summarization of number of subjects, a subject is counted only once for each system organ class and preferred term even if he/she reported one or more events.

In addition to above summary, patients experience any adverse drug reaction related to Lorlatinib before first dose of Lorlatinib during study will be summaried in the same manner as medical history.

7.2.4 Analyses of ORR in intracranial, extracranial of Lorlatinib

The study period which is defined from first dose of Lorlatinib until 30 Sep 2020 or death which comes first. Therefore, the best overall response is defined as the optimal response of overall response during Lorlatinib treating period and is determined by the order of complete response (CR), partial response (PR), stable disease (SD), progressed disease (PD) and not evaluable (NE) according to investigator's clinical discretion.

By using best overall response, the objective response rate (ORR) is defined as the proportion of patients in whom complete response (CR) or partial response (PR) is observed. Disease control rate (DCR) is defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD).

ORR and DCR will be presented for the Evaluable Response Analysis Set. If possible, the tumor response by each post-baseline visit should be presented as well.

For ORR and DCR, the objective response rate will be reported along with 95% exact confidence interval (Clopper Pearson).

Covariates to be considered including in the multivariate model such as variables identified in SAP section 5.4. The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing preliminary results. Multivariate analyses will be carried out and variables include subpopulation, and adjusted by possible covariates (may include first-line ALK TKI prescribed, sex, pathology, stage) and the potential interactions of any two factors when fitting Logistic Regression Model.

7.2.5 Analyses of PFS

PFS refers to the duration from the first study treatment of Lorlatinib to the first documentation of disease progression or death. The PFS will be presented for the Evaluable Response Analysis Set.

Primary PFS censoring is defined as follows:

Situation	Date of Censoring
No adequate baseline disease status	Date of last screening assessment, if

assessment	collected
No documented progression or death before data cutoff	Date of last adequate disease status assessment
Documented progression or death following a long gap between adequate disease status assessments (eg, 2 or more consecutive missed scheduled disease status assessments)	Date of last adequate disease status assessment before the gap
New anticancer treatment or procedure started before documented progression	Date of last adequate disease status assessment

Above censoring rule can be discussed with Investigator to get a full information to determine applicable censoring time. If one patient satisfied multiple censoring rule, the latest censor date will be applied and analysed in Kaplan-Meier method.

Number of subjects with events, types of events (progression or death before progression), number of subjects censored, number of subjects for each reason of censoring, estimates and 95% confidence intervals for the 25th percentile, median, and 75th percentile for PFS will be presented by four subpopulations. A Cox's proportional hazard models (1-sided) will be used to compare PFS of subpopulations A, B, C and D (SAP section 2.1) at final analyses with the overall 1-sided significance level controlled at 0.025. Under global null hypothesis (β=0, βoverall Hazard Ratio), the p-value of overall likelihood ratio will be provided for subpopulation difference.

PFS will be plotted for each subpopulation using the Kaplan-Meier method. The plot will include the number of subjects at risk for each subpopulation group over time.

Covariates to be considered including in the multivariate model such as variables identified in SAP section 5.4. The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing preliminary results. Multivariate analyses will be carried out and variables include first-line ALK TKI prescribed, sex, pathology, stage, and the potential interactions of any two factors used by fitting multiple Cox's proportional hazard models to predict patient's hazard rates of treatment response.

7.2.6 Analyses of OS

OS will be evaluated at the end of study. The OS will be presented for the Enrolled Analysis Set.

Subjects without documentation of death at the time of the data cutoff for analysis will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier. OS refers to the time from the first diagnose of NSCLC to the death at any reason.

The medium and quartile survival computed from Kaplan-Meier method by subpopulation group will be presented. Additionally, the OS rate and its 95% confidence interval (CI) estimate at Month 6 and 12 of Kaplan-Meier estimators will be reported as well.

OS will be plotted for each subpopulation using the Kaplan-Meier method. The plot will include the number of subjects at risk for each subpopulation group over time.

The same Cox's proportional hazard models (1-sided) utilized in PFS analysis will be applied to OS result.

Covariates to be considered including in the multivariate model such as variables identified in SAP section 5.4. The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing preliminary results. Multivariate analyses will be carried out and variables include first-line ALK TKI prescribed, sex, pathology, stage, and the potential interactions of any two factors used by fitting multiple Cox's proportional hazard models to predict patient's hazard rates of treatment response.

7.2.7 Analyses of Treatment Failure (TTF)

Time to TTF of each treatment and TTF of Lorlatinib are to be analysed as another time-to-event data. The TTF will be presented for the Evaluable Response Analysis Set.

TTF of Lorlatinib will be summarized from first dose of Lorlatinib to treatment failure in CUP study (defined as any discontinuation, including cancer progression, adverse events, or death). The censored date is defined as last tumor assessment results of non-PD (CR/PR/SD) before end of this study.

The same Cox's proportional hazard models (1-sided) utilized in PFS/OS analysis will be applied to TTF results.

Covariates to be considered including in the multivariate model such as variables identified in SAP section 5.4. The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing preliminary results. Multivariate analyses will be carried out and variables include first-line ALK TKI prescribed, sex, pathology, stage, and the potential interactions of any two factors used by fitting multiple Cox's proportional hazard models to predict patient's hazard rates of treatment response.

7.2.8 Interim Analysis

No interim analysis will be performed in this study.

8 LIST OF TABLES AND TABLE SHELLS

The main table and figure shells planned for this study is listed in Appendix.

9 REFERENCES

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2. Casaluce, F., et al., Resistance to Crizotinib in Advanced Non-Small Cell Lung Cancer (NSCLC) with ALK Rearrangement: Mechanisms, Treatment Strategies and New Targeted Therapies. Curr Clin Pharmacol, 2016. 11(2): p. 77-87.
3. Akamine, T., et al., Spotlight on lorlatinib and its potential in the treatment of NSCLC: the evidence to date. Onco Targets Ther, 2018. 11: p. 5093-5101.
4. Solomon, B.J., 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): p. 1654-1667.
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exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem, 2014. 57(11): p. 4720-44.

10 APPENDICES

10.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition and use of visit windows in reporting

The timepoint for data collected on subsequent visits after baseline are suggested in accordance with following windows, if appropriate. Since patients return sites for assessment may not be consistent for each visit, the is a suggested visit window. Please adjust it based on real data, then implement into statistical programming and document in CSR if necessary.

Visit Label	Visit Window	Definition for Window
Day 1	Baseline	= An assessment with the same date as recorded on the Day 1 CRF prior to Lorlatinib
Week 12 (3 months)	Week 12 + 2 weeks	= An assessment where 'Date of assessment' – 'Date Day 1' + 1 = [1 through 99]
Week 24 (6 months)	Week 24 + 2 weeks	= An assessment where 'Date of assessment' – 'Date Day 1' + 1 = [100 through 183]
Week 36 (9 months)	Week 36 + 2 weeks	= An assessment where 'Date of assessment' – 'Date Day 1' + 1 = [184 through 267]
Week 48 (12 months)	Week 48 + 2 weeks	= An assessment where 'Date of assessment' – 'Date Day 1' + 1 = [268 through data cut off date]

10.2 APPENDIX 1: TABLE AND FIGURE SHELL

The following Table and Figure shells are just and example for programming, the details outputs should be adjusted based on real data received.

11 TABLE 1 DEMOGRAPHIC CHARACTERISTICS

Characteristic	Patients number, n (%)
Age at Initiation of Lorlatinib	
Mean (SD)	
Median (range)	
Gender	
Male	
Female	
Hepatitis B/C Virus Infection	
HBV Infection	
HCV Infection	
Unknown	
Smoking History	
Never	
Current smokers	
Former smokers	
ECOG Performance Status	
0	
1	
2	
Unknown	
Disease Classification at Initiation of Loratinib	
Stage IIIB	
Stage IIIC	
Stage IVA	
Stage IVB	
Metastases at Initiation of Lorlatinib	
Brain	
Leptomeningeal	
Bone	
Liver	

Lung	
Pleural/pericardial effusion	
Adrenal Gland	
Others	
Mutation status	
ALK	
ROS-1	
EGFR	
PD-L1	

Table 2.1 Gene Mutation Status for Lorlatinib Prescription

Genetic Exam Method	**Patients number, N (%)**
ALK	n
Positive	
Negative	
Not Interpretable	
ROS-1	n
Positive	
Negative	
Not Interpretable	
EGFR	n
Positive	
Negative	
Not Interpretable	
PD-L1	n
Positive	
Negative	

Table 2.2 Gene Exam Method at Lorlatinib Prescription

Genetic Exam Method	Patients number, n (%)
ALK	
IHC – Conventional	
IHC – Ventana	
FISH	
NGS	
ROS-1	
FISH	
IHC	
NGS	
EGFR	
RT-PCR	
NGS	
PD-L1	
IHC – 22C3 TPSTC% (Mean, SD)	
IHC – 28-8 TPSTC% (Mean, SD)	
IHC – SP263 TPSTC% (Mean, SD)	
IHC – SP142 TC% (Mean, SD) IC% (Mean, SD)	

Table 2.3 Gene Exam – Mutation Status Change pre- and post- Lorlatinib

Genetic Exam Method	Patients number, n (%)
ALK	position/type/fusion type of mutation will be re-checked if any mutation status changed.
Positive to Negative	
Negative to Positive	
ROS-1	position/type/fusion type of mutation will be re-checked if any mutation status changed.
Positive to Negative	

Negative to Positive	
EGFR	position/type/fusion type of mutation will be re-checked if any mutation status changed.
Positive to Negative	
Negative to Positive	
PD-L1	
Positive to Negative	
Negative to Positive	

Table 3 Medical History

Diagnose	**Patients number, n (%)**			
	Grade 1	Grade 2	Grade 3	Grade 4
Hyperlipidemia				
Hyperglycemia				
Skin Rash				
Mental Disorder				
Edema				
Body Weight Gain				
Amylase Escalation				

Table 4.1 Treatment pattern – First-line Therapy

Therapeutics	**Patients number, n (%)**
Chemotherapy	
Pemetrexed	
Cisplatin	
Paclitaxel	
Vinorelbine	
TKI	
1st gen – Crizotinib	
2nd gen – Certinib	
2nd gen – Brigatinib	
2nd gen – Alectinib	

Table 4.2 Treatment Pattern of NSCLC

Therapeutics	Patients number, n (%)		
	All	Brain Metastasis (+)	Brain Metastasis (-)
2nd generation/ Lorlatinib			
Ceritinib / Lorlatinib			
Alectinib / Lorlatinib			
Brigatinib / Lorlatinib			
Two ALK TKI/ Lorlatinib			
Crizotinib / Ceritinib / Lorlatinib			
Crizotinib / Alectinib / Lorlatinib			
Crizotinib / Brigatinib / Lorlatinib			
More than two ALK TKI/ Lorlatinib			
(The treatment series will be listed by actual data)			
Lorlatinib in ROS-1 (+) subject			
(Analyze by actual treatment patent)			
Non-Drug Treatment			
Surgery			
Radiation			
Specify location of radiation			

Table 4.3 Concomitant Medication with Lorlatinib

Therapeutics	Patients number, n (%)
Indication Categories	
Primary Diagnose	
Adverse Drug Reaction Related to Lorlatinib	
Underline Disease Related Condition	
Reason for Lorlatinib Discontinuation	
Disease Progression	
Toxicity/ADR (Specify ADR)	
Treatment Completed	
Death	

Unknown	
Others	
Non-Drug Treatment	
Surgery	
Radiation	
Specify location of radiation	

Table 4.3 Subsequent Treatment

Therapeutics	**Patients number, n (%)**
Indication Categories	
Primary Diagnose	
Adverse Drug Reaction Related to Lorlatinib	
Underline Disease Related Condition	
Reason for Discontinuation	
Disease Progression	
Toxicity/ADR (Specify ADR)	
Treatment Completed	
Death	
Unknown	
Others	
Non-Drug Treatment	
Surgery	
Radiation	
Specify location of radiation	

Table 5.1 Treatment effectiveness – All evaluable subjects

Endpoint	Patients number, n (%)		
	Overall Response	**Intracranial Disease Assessment**	**Extracranial Disease Assessment**
Best Response During Lorlatinib Treatment			
Complete			
Partial			
Stable Disease			
Progression			
Death			
Could not be evaluated			
Disease Control Rate During Lorlatinib Treatment			
Overall Survival Rate for NSCLC			
Patient alive at 6 months			
Patient alive at 12 months			
Patient alive at 18 months			
1-year Overall Survival Rate on Lorlatinib			

Table 5.2 Treatment effectiveness –Brain Metastasis

Endpoint	Patients number, n (%)		
	Overall Response	**Intracranial Disease Assessment**	**Extracranial Disease Assessment**
Best Response During Lorlatinib Treatment			
Complete			
Partial			
Stable Disease			
Progression			
Death			
Could not be evaluated			
Disease Control Rate During Lorlatinib Treatment			
Overall Survival Rate for NSCLC			
Patient alive at 6 months			
Patient alive at 12 months			
Patient alive at 18 months			
1-year Overall Survival Rate on Lorlatinib			

Table 5.3 Treatment effectiveness – Non-Brain Metastasis

Endpoint	Patients number, n (%)		
	Overall Response	Intracranial Disease Assessment	Extracranial Disease Assessment
Best Response During Lorlatinib Treatment			
Complete			
Partial			
Stable Disease			
Progression			
Death			
Could not be evaluated			
Disease Control Rate During Lorlatinib Treatment			
Overall Survival Rate for Lorlatinib			
Patient alive at 6 months			
Patient alive at 12 months			
Patient alive at 18 months			
1-year Overall Survival Rate on Lorlatinib			

Table 6 All grade adverse drug reaction

Adverse Drug Reaction	Grade, Patient Number n(%)				
	1	2	3	4	5
hyperlipidemia					
hyperglycemia					
rash					
mental disorder					
edema					
Body weight gain					
Amylase level escalation					
pancreatitis					

Figure 1 Patient Entry Flow

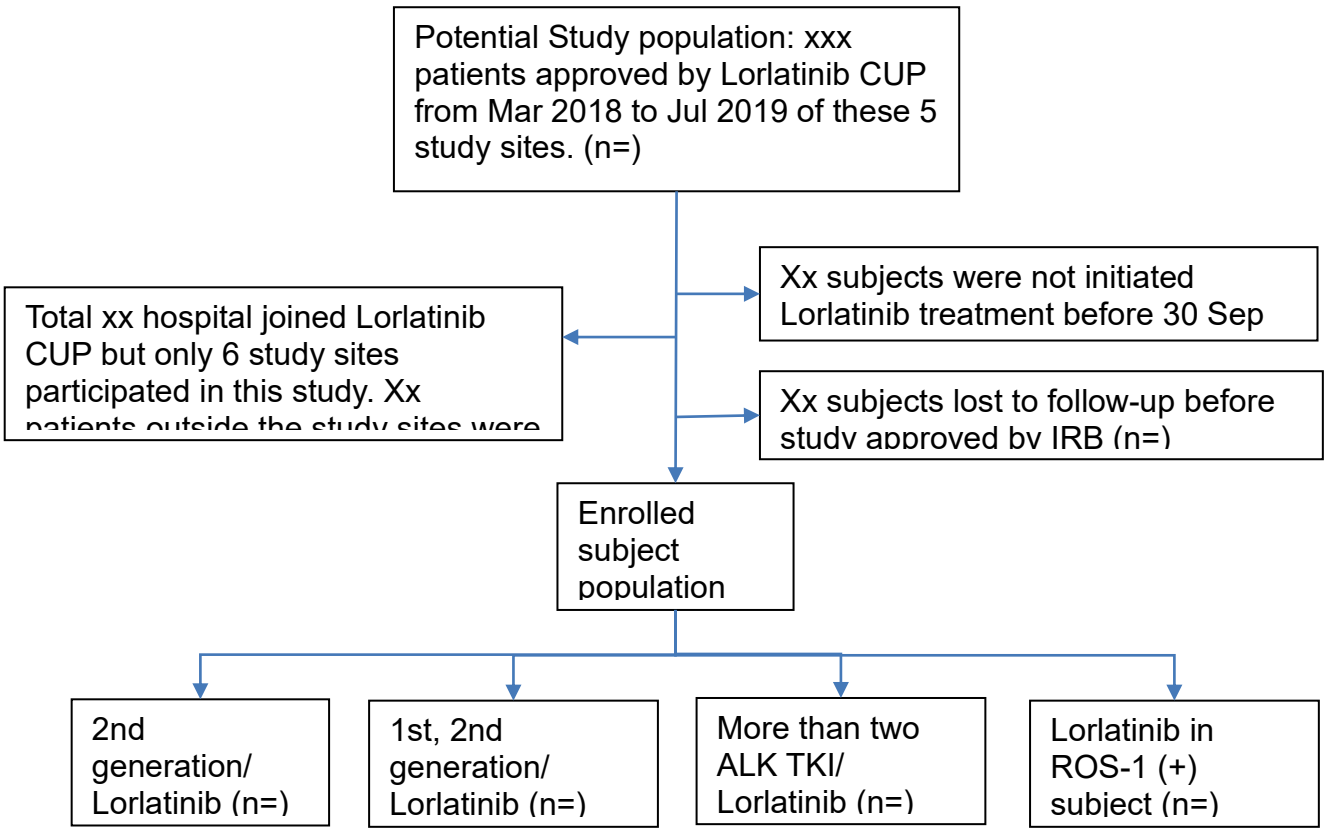

Figure 2. PFS for Lorlatinib among 4 different treatment group

1) Group A: Lorlatinib treatment after one prior ALK TKI different from crizotinib in ALK gene mutation subject;
2) Group B: Lorlatinib treatment after two prior ALK TKI in ALK gene mutation subject;
3) Group C: Lorlatinib treatment after at more than two prior ALK TKI in ALK gene mutation subject;

4) Group D: Lorlatinib treatment in ROS-1 gene mutation subject with any pretreatment.

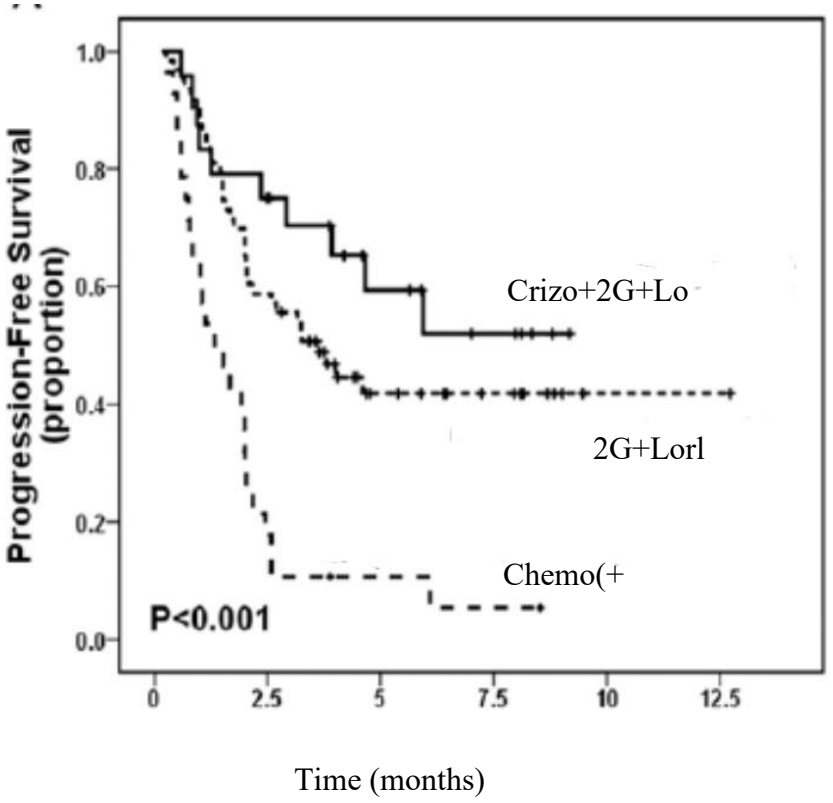

Figure 3 PFS for patient with brain metastases among 4 different treatment group (Kaplan-Meier)

Figure 4 PFS for patient with brain meta/ non-brain meta group (Kaplan-Meier)

Figure 5 Time to Treatment Failure for all NSCLC treatment among 4 different treatment group (Kaplan-Meier)

Figure 6 Time to Treatment Failure for Lorlatinib treatment (Kaplan-Meier)