Non-Interventional Study Protocol

A8081060

Characteristics of adult patients treated with crizotinib for advanced non-small-cell lung cancer (NSCLC) with ALK gene rearrangement or ROS1 gene rearrangement in general hospitals.

Statistical Analysis Plan (SAP)

Version: 2

Author: PPD (EURAXI PHARMA)

Date: 18-Jun-2020

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Effective Date	Change Type (New, Revise, Admin)	Summary of Revisions
1	31-Jan-2020	New	
2	18-Jun-2020	Revise	To modify the definition of the FAS. To add the analysis of ORR, DCR and TEAEs

2. INTRODUCTION

Lung cancer is a major public health issue due to its frequency and its poor prognosis.

In France, according to the latest INCa data, LC represented 12% of all new cases of cancer and was the leading cause of cancer-related deaths in 2015; the 5-year survival rate in 2008 did not exceed 17%.

Most cases of LC are NSCLC, most often adenocarcinomas, diagnosed at an advanced stage.

As such, in 2010, 86% of cases of LC followed-up in the study KBP 2010-CPHG were NSCLC and 67.8% was diagnosed at stage IIIB or IV.

The study KBP-2010-CPHG also confirmed the major epidemiological change observed in recent years, namely the decreasing proportion of squamous carcinomas among these cases of NSCLC in favour of adenocarcinomas: adenocarcinomas represented almost half of the cases of NSCLC.

The molecular breakdown of NSCLC is most advanced for NSCLC and particularly adenocarcinomas.

At the present time, molecular alterations such as EGFR mutations and ALK and ROS1 rearrangements are predictive markers of the efficacy of targeted therapeutics on the market and/or under development.

Moreover, ESMO recommends systematic ALK and ROS1 gene rearrangement testing, which should be conducted systematically for all non-squamous, locally advanced or metastatic bronchial cancers. The gold standard method according to ESMO remains FISH; IHC should be used for patient screening. A recent expert consensus on ROS1 testing recommends testing for ROS1 at the same time as ALK or EGFR.

ALK gene rearrangement is detected in approximately 3 to 5% cases of NSCLC. Patients with ALK+ NSCLC would appear to belong to a younger and more frequently non-smoker or light-smoker population (< 10 pack-years) than that with ALK-negative NSCLC. In the vast majority of cases, ALK gene rearrangements are involved in adenocarcinomas (between 85% and 100%), particularly those having a so-called "signet ring" morphology. For patients with ROS1+ NSCLC, a similar profile to that observed in patients with ALK+ NSCLC is found.

Crizotinib is the first medicinal product targeting ALK and ROS1 gene rearrangements, and having an MA in NSCLC. It is the gold standard first-line treatment for adult patients with advanced ALK- or ROS1-positive NSCLC and in the treatment of adult patients having received at least one prior treatment for advanced ALK- or ROS1-positive NSCLC.

In this context, Pfizer proposes to conduct a prospective, observational epidemiological study, on adult patients with advanced ALK+ or ROS1+ NSCLC treated with crizotinib regardless of the line of treatment.

The purpose of this study is to enhance knowledge on the use of crizotinib under real-life conditions by compiling data on the characteristics of the tumour and patients treated with crizotinib, on the prescription and discontinuation conditions of crizotinib and on the compliance, efficacy and tolerance of this treatment.

The study shall be conducted in partnership with the College des Pneumologue des hopitaux géneraux – CPHG (French General Hospital Pulmonary Medicine Specialist Association)

The choice of CPHG as a partner is based on its experience in long-term observational studies on LC patients, which guarantees quality in terms of data collection.

It is also based on the fact that CPHG includes almost all pulmonary medicine specialists in pulmonary medicine departments in French non-university hospitals, making it possible to envisage national coverage and an exceptional number of participating centres for this study.

The main studies conducted on LC by CPHG are:

- *the study KBP-2000-CPHG from 2000 to 2005 (137 investigation centres and 5,667 new cases of LC diagnosed between 1 January and 31 December 2000), in which the primary objective was 5-year survival*

- *the study KBP-2010-CPHG from 2010 to 2015 (104 investigation centres and 7,051 new cases of LC diagnosed between 1 January and 31 December 2010), in which the primary objective was 5-year survival*

- *the study ESCAP-2011-CPHG from 2010 to 2012 (53 investigation centres and 3,943 new cases of LC diagnosed between 1 January and 31 December 2010), in which the primary objective was therapeutic strategy follow-up over the 2 years post-diagnosis.*

In these 3 studies in particular, the investigation centres were distributed throughout French territory and in the 2 studies KBP-2000-CPHG and KBP-2010-CPHG, 20% or more than 20% of all patients with a new case of LC in 2000 or in 2010 in France were included.

2.1. Study Design

ALK-2016-CPHG is an observational, descriptive, longitudinal, national multicentre study with prospective and partially retrospective data collection from a cohort of patients treated with crizotinib for ALK+ or ROS1+ NSCLC.

From 1 January 2017 until 31 December 2018 (i.e. for 24 months), each physician shall include sequentially all volunteer patients followed up in the department for locally advanced (stage IIIB not suitable for radiotherapy) or metastatic (stage IV) ALK+ NSCLC initiating (or having initiated in the previous 3 months) treatment with crizotinib, regardless of the line of treatment.

And From Novembre 2017 until 31 Décember 2018 each physician shall include sequentially all volunteer patients followed up in the department for locally advanced (stage IIIB not suitable for radiotherapy) or metastatic (stage IV) ALK+ ROS1+ NSCLC initiating (or having initiated in the previous 3 months) treatment with crizotinib, regardless of the line of treatment.

Follow-up shall commence from the date on which the patient signs his/her consent form and shall end on the date of the final visit of the final patient, i.e. theoretically from January 2017 to June 2020. The maximum follow-up period for each patient shall be 18 months.

The study envisages data collection during not more than 7 visits (1 inclusion visit + not more than 5 follow-up visits + 1 end-of-follow-up visit).

Visits	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Month (± 1)		**M3**	**M6**	**M9**	**M12**	**M15**	**M18**
Date of visit	X	X	X	X	X	X	X
Date of signing of consent	X						
Verification of inclusion/non-inclusion criteria	X						
Patient characteristic							
Date of birth	X						
Gender	X						
Height	X						
Weight	X	X	X	X	X	X	X
BMI	X						
Smoking status	X	X	X	X	X	X	X
Performance status (ECOG)	X	X	X	X	X	X	X
Tumour characteristics							
Date of biopsy resulting in diagnosis	X						
Histological type	X						
Tumour location	X						
Presence of metastasis/metastases and if yes, location	X	X	X	X	X	X	X
Stage (TNM, 8th edition)	X						
ALK/ROS1 gene rearrangement							
Date of dispatch of specimen to platform	X						
Date of receipt of ALK or ROS1-positive result	X						
Interval between dispatch and receipt of result	X						
Source of specimen	X						
Diagnostic method	X						
Analytical platform	X						
Technique used (FISH, IHC, RT-PCR, NGS, other)	X						
Other biomarkers							
Yes/No	X						
If yes, date of receipt of result	X						

Visits	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Month (± 1)		**M3**	**M6**	**M9**	**M12**	**M15**	**M18**
Prior therapeutic strategy for advanced NSCLC							
Yes/No	X						
Start date of first strategy	X						
Treatment type	X						
Doses/number of cycles/Start date/End date	X						
Cycle end date	X						
Crizotinib							
Initiation date	X						
Dosage	X	X	X	X	X	X	X
Prescribed preventative treatments	X	X	X	X	X	X	X
Date of discontinuation and reason for discontinuation		X	X	X	X	X	X
Treatment response evaluation							
Clinical response (physician)		X	X	X	X	X	X
Tumour response on imaging according to participating physician		X	X	X	X	X	X
Progression: date, site of progression, biopsy (yes/no)		X	X	X	X	X	X
Post-progression							
• Continuation of crizotinib		X	X	X	X	X	X
• Initiation of new therapeutics		X	X	X	X	X	X
Crizotinib treatment plan							
Change of dose/Temporary discontinuation/Definitive discontinuation		X	X	X	X	X	X
In case of definitive discontinuation, initiation of new therapy (Chemotherapy/next-generation ALK/Temporary Authorisation for Use/Inclusion in clinical trial)		X	X	X	X	X	X
Additional information							
Prescribed preventative treatment		X	X	X	X	X	X
Local treatment		X	X	X	X	X	X

Visits	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Month (± 1)		**M3**	**M6**	**M9**	**M12**	**M15**	**M18**
Patient questionnaires							
Therapeutic compliance (Morisky)		X	X	X	X	X	X
Quality of life (QLQ-LC13)	X	X	X	X	X	X	X
Serious or non-serious adverse events (see section 9)	Throughout the study						

The total duration of the study shall be 42 months.

2.1.1. Study population

Inclusion criteria

- *Age ≥18 years.*
- *Locally advanced or metastatic NSCLC with ALK gene rearrangement or ROS1 gene rearrangement.*
- *Patient having initiated in the previous 3 months or patient initiating crizotinib treatment regardless of the line of treatment.*
- *Patient followed up by a physician in a hospital pulmonary medicine department.*
- *Subject of reproductive age, using an effective method of contraception.*
- *Patient informed verbally and in writing on the study and having consented to his/her personal data being collected within the scope of the study.*

Non-inclusion criteria

- *Patient included within the scope of an interventional therapeutic trial.*
- *Patient not presenting with ALK gene rearrangement or ROS1 gene rearrangement.*
- *Patient not available for follow-up throughout the duration of the study.*
- *Patient deemed to be incapable of responding to the study questions for linguistic, cognitive or organisational reasons.*

Study size

The number of participating centres should be close to 70 to be able to enrol at least between 70 and 100 patients with ALK+ or ROS1+ (include at least 15 patient ROS1) consenting to take part in the study.

Including at least 70 to 100 patients should make it possible to obtain representativeness for each line of treatment and meet the primary objective of the study which is to describe the characteristics of patients treated with crizotinib (regardless of line of treatment and according to line of treatment).

2.1.2. Data source

A case report form shall be used to record data. Within the scope of this protocol, the term case report form (CRF) refers to the collection of medical data in electronic or hard copy format. The data shall be collected using 2 methods:

- *By the physicians in an electronic case report form (e-CRF);*
- *By the patient on hard copy self-administered questionnaires.*

2.1.3. Treatment/cohort labels

NA.

2.2. Study Objectives

Primary objective

- *Describe the characteristics of patients treated with crizotinib (regardless of line of treatment and according to line of treatment).* Characteristics of patients and tumour, prior therapeutic strategy for advanced NSCLC will be given on overall population and according to the line of treatment.

Secondary objectives

- *Describe the conditions for conducting ALK gene and ROS1 gene rearrangement testing (source of specimen, technique used and time frames).* Diagnosis method, origin of the specimen, technique used and number of patients ALK+ and ROS1+ will be given *on overall population and according to the line of treatment*.
- *Evaluate the impact of the anti-cancer treatment in terms of:*
    - *clinical response (evaluation by physician).* Number and percentage of patients with disease improvement, disease stabilisation or disease degradation according to the physician will be described on overall population and by line of treatment.

- *tumour response on imaging according to the physician*. Number and percentage of patients with total response, partial response, stable disease or disease progression on imaging according to the physician will be described on overall population and by line of treatment.

- *survival, PFS, OS and 12 and 18-month survival probabilities.* PFS and OS will be estimated using Kaplan-Meier method and survival curves will be done. OS and PFS median times will be provided with 95% confidence interval (CI).

- *Tolerance.* Vital signs, incidence and characteristics of all AE(s) and SAE(s) will be given on overall population and according to the line of treatment.

- *Quality of life (self-administered questionnaire QLQ – LC13)*. EORTC LC13 symptom scales scores (ranging from 0 to 100) will be described on overall population and according to the line of treatment.

- *Compliance (Morisky self-administered questionnaire)*. Morisky score (ranging from 0 to 4) will be described on overall population and according to the line of treatment.

- *Describe crizotinib prescription and discontinuation conditions (scheduled end of treatment, intolerance/toxicity, progression, other)*. Crizotinib initiation, dose modification, temporary interruption, definitively discontinuation and reasons of these treatment modifications will be described on overall population and according to the line of treatment.

- *Describe the treatment plan after progression (local treatments, systemic treatment, crizotinib maintenance) and the impact of this treatment*. Number and percentage of patients who continue crizotinib or init new therapy after progression will be given on overall population and according to the line of treatment. The new therapy will be also described.

These objectives are used to determine the conditions of prescription and use of crizotinib in clinical practice and ensure proper usage of the medicinal product as well as the evaluation of the impact of the treatment on the population under study.

3. INTERIM ANALYSES

An interim analysis will be conducted after 12 months of follow-up in February 2020. This analysis will be performed to describe all inclusion data like characteristics of patients and tumour, ALK/ROS1 gene rearrangement testing, prior therapeutic strategy for advanced NSCLC, prescription of Crizotinib (initiation line, dosage), and quality of life. Clinical data, prescription of Crizotinib (dosage, modification, discontinuation), treatment response evaluation and patients questionnaires until M12 will be described,

PFS and OS will be analysed. All adverse events and severe adverse events will be also described.

The monthly inclusion rate will be provided.

4. HYPOTHESES AND DECISION RULES

NA.

4.1. Statistical Hypotheses

NA.

4.2. Statistical decision rules

NA

5. POPULATIONS

5.1. FULL ANALYSIS SET (FAS)

This population is defined as all eligible patients who received at least one dose of Crizotinib.

5.2. Safety POPULATION

All enrolled patients who received at least one dose of Crizotinib will be included in the Safety population.

5.3. Subgroups

All data will be described on the total population and according to the lines of treatment:

1st Line : L1

2nd Line : L2

3rd Line : L3

> 3rd Line : Other,

and according to the presence of biomarkers ALK+ or ROS1.

6. ENDPOINTS AND BASELINE VARIABLES

6.1. PRIMARY Endpoint

Characteristics of patients treated with crizotinib (See § 6.5 Baseline Variables).

6.2. SECONDARY ENDPOINTS

- Conditions for conducting ALK or ROS1 gene rearrangement testing:
  - Diagnostic method: Histology/Cytology;
  - Origin of the specimen: Primitive tumour / Thoracic lymph node / Extrathoracic lymph node / Brain / Liver / Bone / Adrenal glands / Other; if other, specify;
  - Analysis platform;
  - Technique used: IHC / FISH / RT-PCR / NGS / Other and associations of techniques; if other, specify;
  - ALK: Positive ALK rearrangement (Yes/No), period between sending and receipt of the result (days) (will be derived, see § Appendix 1);
  - ROS1: Positive ROS1 rearrangement (Yes/No), period between sending and receipt of the result (days) (will be derived, see § Appendix 1);
  - Other biomarkers (Yes/No).
- Clinical response evaluated by physician: Improvement / Stabilisation / Degradation.
- Tumour response on imaging according to the physician: Total response / Partial response / Disease stable / Progression:
  - If progression, time since diagnosis (months) (will be derived, see § Appendix 1), site of progression: Primary tumour / Metastasis(es) that already exists / New metastases;
  - If metastasis(es) that already exists, localization.
  - If new metastases, localization : Contralateral lung / Extrathoracic lymph node / Brain / Liver / Bone / Adrenal glands / Other:
    - If other, specify;
    - If brain metastases, treatment duration until progression with brain metastases (weeks) (will be derived, see § Appendix 1);

- Biopsy on progression (Yes/No), if yes, results;
- Objective Response Rate (ORR) is defined as the percent of patients with complete response (CR) or partial response (PR) according to RECIST 1.1 as determined by the independent radiology review, relative to the FAS.

  Patients will be considered non responders until proven otherwise. Thus, patients who:

  - Do not have CR or PR while on study; or
  - Do not have a baseline or post-baseline tumor evaluation; or
  - Do not have an adequate baseline tumor evaluation; or
  - Receive anti-tumor treatment other than the study medication prior to reaching a CR or PR; or
  - Die, progress, or drop out for any reason prior to reaching a CR or PR, will be counted as non-responders in the assessment of ORR.
- Disease Control Rate (DCR) at 12 and 18 months is defined as the percent of patients with CR, PR or stable disease (SD) at 12 and at 18 months according to the physician.

EORTC LC13 symptom scales scores (Coughing / Haemoptysis / Dyspnoea / Sore mouth / Dysphagia / Peripheral neuropathy / Alopecia / Pain in chest / Pain in arm or choulder / Pain in other parts) (these scores will be derived, see § Appendix 1).

Progression-free survival (PFS) is defined as the time between the treatment start (date of the first Crizotimib intake) and the date of the first disease progression or the all-cause death (in months). Patients who have not progressed or still alive at the end of the ALK2016 study or at the date of cut-off will be censored at the last disesase evaluation date.

Event	Decision	Date of event or censor taken into account in the analysis
Progressive disease	Not censored	Date of disease progression
All-cause death without previous progressive disease	Not censored	Death date
Patient lost to follow up without progressive disease nor death reported	Censored	Last disease evaluation date (i.e. date of last follow-up visit)
End of study (without progressive disease nor death)	Censored	Last disease evaluation date (i.e. date of last follow-up visit)

Overall survival (OS) is defined as the time between the treatment start date (date of the first Crizotinib intake) and the all-cause death. Patients still alive at the end of the the ALK2016 study or at the date of cut-off or lost to follow-up will be censored at the last date they are known to be alive.

Event	Decision	Date of event or censor taken into account in the analysis
All-cause death	Not censored	Date of death
Patient lost to follow up (no death)	Censored	Last date they were known to be alive (i.e. max (date of last contact, date of loss to follow up))
End of study (no death)	Censored	Last date they were known to be alive (i.e. date of last contact)

6.3. Safety Endpoints

- Vital signs: Body weight (kg), number and percentage of patients who lost weight (See § Appendix 1) and weight loss (%) for these patients, Smoking status for active smoker, ECOG (Yes/No); if yes, ECOG score.

- Incidence and characteristics of AE(s), TEAE (s), SAE(s), Non-SAE(s), STEAE(s), and Non-STEAE(s) according to the NCI-CTCAE version 4.0 scale.

- Crizotinib prescription and discontinuation conditions:
  - Time since diagnosis of NSCLC to Crizotinib initiation (months) will be derived (See § Appendix 1).
  - Initiation: Dosage (250mg 2 times/day / 200mg 2 times/day / 250mg/day) and line of initiation (for patients ALK+ and patients ROS1+).
  - Dose modification (Yes/No): if yes, dose increase / dose reduction (will be derived, see § Appendix 1), new dose (250mg 2 times/day / 200mg 2 times/day / 250mg/day / Other), reason (Intolerance / AE resolved / Lack of efficacy / Other), modification date - time since Crizotinib initiation to modification (days) will be derived (See Appendix 1).
  - Temporary interruption (Yes/No): if yes, duration (days) / in progress, reason for the interruption (Intolerance / Drug interaction / Local treatment), temporary interruption date - time since Crizotinib initiation to temporary interruption (days) will be derived (See § Appendix 1).
  - Definitive discontinuation (Yes/No): if yes, reason for discontinuation (Progression / Intolerance/toxicity / Patient's choice / Lost to follow-up / Death / Other (if other, specify)), definitive discontinuation date - treatment duration (days), treatment exposure (days) will be derived (See § Appendix 1), initiation of new therapeutics (Yes/No).
    - if yes, new treatment: Chemotherapy / 2nd generation ALK inhibitor / Temporary authorization for use / Immunotherapy / Inclusion in a clinical study / Palliative care.
  - Local treatments (Yes/No): if yes, Brain irradiation (Yes/No), Radiotherapies (Yes/No), Other, specify.
    - If brain irradiation: number of brain irradiation, start date / end date – duration of brain irradiation (days), time since temporary interruption to brain irradiation start (days), time since brain irradiation stop to Crizotinib restart (days) (See § Appendix 1).
    - If radiotherapies: number of radiotherapies, start date / end date – duration of radiotherapy (days), time since temporary interruption to radiotherapy start (days), time since radiotherapy stop to Crizotinib restart (days) (See § Appendix 1).

The treatment plan after progression:

- Continuation of Crizotinib (Yes/No), date of progression - treatment duration until progression date (weeks) and treatment duration since the progression date (weeks) will be derived (See § Appendix 1).

- Initiation of new therapeutics (Yes/No): if yes, new treatment (Chemotherapy / 2nd generation ALK inhibitor / Temporary authorization for use / Immunotherapy / Inclusion in a clinical study / Palliative care).

6.4. Other endpoints

Compliance (Morisky self-administered questionnaire) (this score will be derived, see § Appendix 1).

6.5. Baseline variables

Patient characteristics

- Date of birth – Age (years) will be derived (See Appendix 1).

- Gender: Male/Female.

- Body weight (kg).

- BMI (kg/m²) will be derived (See Appendix 1).

- Smoking status: Non-smoker / Ex-smoker / Current smoker:

  - If ex-smoker: quantity (Pack years), start year / stop year - Duration of smoking (years), duration of quitting smoke (years) will be derived (See § Appendix 1).

  - If current smoker: quantity (Pack years), start year / stop year - Duration of smoking (years) will be derived (See § Appendix 1).

- ECOG (Yes/No); if yes, ECOG score (0-1, ≥ 2).

Tumour characteristics

- Date of the biopsy that enables making the diagnosis - Time since diagnosis (months) will be derived (See Appendix 1).

- Histological type of tumour: Adenocarcinoma / Epidermoid / Large cell / Other; if Other, specify.

- Tumour stage (TNM, 8th edition): IIIB/IV.

- Tumour location: Upper right lobe / Lower right lobe / Middle right lobe / Upper left lobe / Lower left lobe.

- Presence of metastases (Yes/No); if yes, number of metastatic sites (1 / 2 / ≥ 3) will be derived (See Appendix 1), location (Contralateral lung / Extrathoracic lymph node / Brain / Liver / Bone / Adrenal glands / Pleural effusion / Other); if Other, specify.

Prior advanced NSCLC treatments

- Prior treatment strategies : Start date of the first strategy – Time since the first strategy start (months) to Crizotinib initiation will be derived (See Appendix 1).

- Chemotherapy 1L (Yes/No), number of cycles, start date of the first cycle / end date of the last cycle – duration of chemotherapy 1L (months) will be derived (See § Appendix 1).

- Chemotherapy 2L (Yes/No), number of cycles, start date of the first cycle / end date of the last cycle – duration of chemotherapy 2L (months) will be derived (See § Appendix 1).

- Chemotherapy 3L (Yes/No), number of cycles, start date of the first cycle / end date of the last cycle – duration of chemotherapy 3L (months) will be derived (See § Appendix 1).

- Brain irradiation (Yes/No); if yes, number of brain irradiation, start date / end date – duration of brain irradiation (days) will be derived (See § Appendix 1).

- Radiotherapies (Yes/No); if yes, number of radiotherapies, start date / end date – duration of radiotherapy (days) will be derived (See § Appendix 1).

- Tyrosine Kinase inhibitor (Yes/No); if yes, treatment name and reason to stop (Progression / Safety), start date / end date – duration of treatment by tyrosine kinase inhibitor (days) will be derived (See § Appendix 1).

6.6. Covariates

NA.

7. HANDLING OF MISSING VALUES

Missing data shall not be replaced.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analyses for Quantitative Data

Quantitative variables will be summarized in summary tables indicating, for each treatment group and for the overall population, the number of non missing observations (n), the number of missing values, the mean and standard deviation, the median and the interquartile range, the minimum and maximum.

8.1.2. Analyses for Qualitative Data

Qualitative variables will be summarized in summary tables indicating, for each treatment group and for the overall population, the number of non missing observations (n), frequency and percentage of each modality. The number of missing values will also be reported but they will not be counted for the percentage calculation.

8.2. Statistical Analyses

8.2.1. Primary Endpoint

The primary analysis will be performed on the FAS overall, according to the line of treatment and according to the presence of biomarkers ALK and ROS1.

Descriptive statistics will be used to summarize baseline characteristics.

To describe previous advanced NSCLC treatments, systemic treatments (chemotherapy and TKI) and local treatments (brain irradiation, radiotherapy, surgery) will be presented separately.

8.2.2. Secondary Endpoints

The secondary analyses will be performed on FAS overall, according to the line of treatment and according to the presence of biomarkers ALK and ROS1.

Descriptive statistics will be used to summarize:

- Number of patients having initiated crizotinib before inclusion and after inclusion;
- Conditions for conducting ALK or ROS1 gene rearrangement testing at baseline, period between sending and receipt of the result will be provided by platform for ALK, ROS1 and both testings;
- Clinical response evaluated by physician;
- Tumour response on imaging according to the physician, ORR and DCR;
- EORTC LC13 symptom scales scores.

PFS and OS will be estimated using Kaplan-Meier method and survival curves will be plotted. OS and PFS median times will be provided with 95% confidence interval (CI).

8.2.3. Safety Analyses

Safety analyses will be performed on the Safety population overall, according to the line of treatment and according to the presence of biomarkers ALK and ROS1.

Summary tables will be provided for vital signs.

Adverse events will be graded by the investigator according to the NCI CTCAE version 4.0. If an AE occurs more than 28 days after the last crizotinib administration, it will not be analysed.

The number and percentage of patients experiencing an adverse event (any AE and, serious AE and non-serious AE) and the number of adverse events will be tabulated by system organ class, preferred term according to the MedDRA coding system initially, and the severity will be added subsequently for the following subsets of events:

- Any adverse event regardless of relationship;
- Drug-related adverse events.

The same analyses will be performed on patients experiencing a serious adverse event, a treatment emergent adverse event, a serious treatment emergent adverse event.

Note: Severe AEs will be defined as those with NCI-CTC grade 3, 4 or 5 or unknown NCI-CTC grade with severity = "Severe". An AE that starts after the first dose is treatment-emergent.

Characteristics of adverse events (seriousness, grade/severity, relationship to study drug and outcome) will be presented using summary statistics by line of treatment, by presence of biomarkers ALK and ROS1 for all events.

A data listing will detail all adverse events for all patients (description, time to onset, duration, seriousness, grade or severity, relationship to study drug and outcome).

Crizotinib prescription and discontinuation conditions and the treatment plan after progression will be summarized.

8.2.4. Analyses of other endpoints

The compliance analysis will be performed on the Safety population overall, according to the line of treatment and according to the presence of biomarkers ALK and ROS1.

Descriptive statistics will be used to summarize the compliance.

8.2.5. Summary of Analyses

Endpoint	Analysis	Statistical Method	Timepoint	Population
Characteristics of patients treated with crizotinib	Descriptive analysis		Baseline	FAS Overall By line of treatment By presence of biomarkers ALK and ROS1
Conditions for conducting ALK or ROS1 gene rearrangement testing	Descriptive analysis		Baseline	FAS Overall By line of treatment By presence of biomarkers ALK and ROS1
Clinical response evaluated by physician	Descriptive analysis		M3, M6, M9, M12, M15 and M18	FAS Overall By line of treatment By presence of biomarkers ALK and ROS1
Tumour response on imaging according to the physician	Descriptive analysis		M3, M6, M9, M12, M15 and M18	FAS Overall By line of treatment By presence of biomarkers ALK and ROS1
EORTC LC13 symptom scales scores	Descriptive analysis		Baseline, M3, M6, M9, M12, M15 and M18	FAS Overall By line of treatment By presence of biomarkers ALK and ROS1
PFS and OS	Survival analysis	Kaplan-Meier	NA	FAS Overall By line of treatment By presence of biomarkers ALK and ROS1
Vital signs & ECOG (0-1 & ≥ 2)	Descriptive analysis		Baseline, M3, M6, M9, M12, M15 and M18	Safety population Overall By line of treatment By presence of biomarkers ALK and ROS1
AE, SAE, Non-SAE, TEAE & STEAE	Descriptive analysis			Safety population Overall By line of treatment By presence of biomarkers ALK and ROS1
Crizotinib prescription & discontinuation conditions	Descriptive analysis		Baseline (only for Crizotinib initiation), M3, M6, M9, M12, M15 and M18	Safety population Overall By line of treatment By presence of biomarkers ALK and ROS1
Treatment plan after progression	Descriptive analysis		M3, M6, M9, M12, M15 and	Safety population

Endpoint	Analysis	Statistical Method	Timepoint	Population
			M18	Overall By line of treatment By presence of biomarkers ALK and ROS1
Compliance	Descriptive analysis		M3, M6, M9, M12, M15 and M18	Safety population Overall By line of treatment By presence of biomarkers ALK and ROS1

9. TEMPLATES FOR SUMMARY TABLES

14.1. STUDY POPULATION

14.1.1. DISPOSITION OF PATIENTS

Table 14.1.1.1. Patients enrollment

Patients enrollment	
Number of enrolled patients	XXX
Inclusion date of first patient	XX/XX/XXXX
Inclusion date of last patient	XX/XX/XXXX
Duration of inclusions (months)	XX.XX
Number of active physicians	XX
Mean of included patients by physicians	XX.XX
Best recruiter	N°XXXX (XX patients)

Table 14.1.1.2. Number of inclusions by month

	Total (N=XXX)
January 2017	XX (XX.X%)
February 2017	XX (XX.X%)
March 2017	XX (XX.X%)
[…]	XX (XX.X%)

14.1.2. ANALYSIS POPULATIONS

Table 14.1.2.1. Number and percentage of patients in each analysis population

		L1 (N=XXX)	L2 (N=XXX)	L3 (N=XXX)	Other (N=XXX)	Total (N=XXX)
Enrolled	Yes					XX
Total population	No					XX
	Yes	XX	XX	XX	XX	XX
Safety population	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.1.2.2. Reason for non inclusion in Total population

Variables		Total (N=XXX)
Total population	No	XX (XX.X%)
	Yes	XX (XX.X%)
Reason for non inclusion in Total population	XXXX	XX (XX.X%)
	YYY	XX (XX.X%)
	ZZZZ	XX (XX.X%)

Table 14.1.2.3. Number of patients by visit - Total population

Variables		Total (N=XXX)
Visit	Inclusion	XX (XX.X%)
	M3	XX (XX.X%)
	M6	XX (XX.X%)
	M9	XX (XX.X%)
	M12	XX (XX.X%)
	M15	XX (XX.X%)
	M18 – End of study - Patient receiving treatment	XX (XX.X%)
	M18 – End of study - Patient who discontinued Crizotinib	XX (XX.X%)

Table 14.1.2.4. Prematurely withdrawn and reasons – Total population

Variables		L1 (N=XXX)	L2 (N=XXX)	L3 (N=XXX)	Other (N=XXX)	Total (N=XXX)
Prematurely withdrawn	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason of prematurely withdrawn	XXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	YYY	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	ZZZZ	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

14.1.3. BASELINE DESCRIPTION

Table 14.1.3.1. Patients characteristics – Total population

		L1 (N=XXX)	L2 (N=XXX)	L3 (N=XXX)	Other (N=XXX)	Total (N=XXX)
Gender	Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Age	N	XX	XX	XX	XX	XX
	Mean (+/- SD)	XX.XX (+/-XX.XX)	XX.XX (+/-XX.XX)	XX.XX (+/-XX.XX)	XX.XX (+/-XX.XX)	XX.XX (+/-XX.XX)
	Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	Q1 ; Q3	XX.XX ; XX.XX	XX.XX ; XX.XX	XX.XX ; XX.XX	XX.XX ; XX.XX	XX.XX ; XX.XX
	Min ; Max	(XX.XX; XX.XX)	(XX.XX; XX.XX)	(XX.XX; XX.XX)	(XX.XX; XX.XX)	(XX.XX; XX.XX)
	Missing data	X	X	X	X	X

[…]

10. REFERENCES

1. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

11. APPENDICES

11.1. APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition and use of visit windows in reporting

NA.

A1.2 Definition of Derived Data

Age (years) = Integer((Inclusion visit date – birth date) / 365.25),

Note: the day of the birth date will be replaced by the 1st of the month for calculation

BMI (kg/m²) = weight (kg) / (height (cm) / 100)² (rounded to 1 decimal),

Note: BMI will be also described in categories according to the WHO classification:

- Underweight: BMI < 18.5 kg/m²
- Normal weight: 18.5 kg/m² ≤ BMI ≤ 24.9 kg/m²
- Pre-obesity: 25 kg/m² ≤ BMI ≤ 29.9 kg/m²
- Obesity class I: 30 kg/m² ≤ BMI ≤ 34.9 kg/m²

- Obesity class II: 35 kg/m² ≤ BMI ≤ 39.9 kg/m²
- Obesity class III: BMI ≥ 40 kg/m²

For ex-smokers, duration of smoking (years) = (Year of smoking stop – Start year),

For current smokers, duration of smoking (years) = (Year of Inclusion visit date – Start year),

Duration of quitting smoke (years) = (Year of Inclusion visit date – Year of smoking stop),

Time since diagnosis of NSCLC (months) = (Inclusion visit date – Date of the biopsy that enabled making the diagnosis) / (365.35/12) (rounded to 1 decimal),

Note: If the day of the diagnosis is missing, it will be replaced by the 15th of the month for calculation

Time since diagnosis of NSCLC to Crizotinib initiation (months) = (Crizotinib initiation date – Date of the biopsy that enabled making the diagnosis) / (365.35/12) (rounded to 1 decimal),

Note: If the day of the diagnosis or the day of the start date is missing, it will be replaced by the 15th of the month for calculation

Number of metastatic sites = Contralateral lung = 1 + Extrathoracic lymph node = 1 + Brain = 1 + Liver = 1 + Bone = 1 + Adrenal glands = 1 + Other = 1,

Note: Number of metastaic sites will be derived using the SAS function SUM

Time since the first strategy start to Crizotinib initiation (months) = (Crizotinib initiation date – Start date of the first strategy) / (365.35/12) (rounded to 1 decimal),

Note: If the day of the start date is missing, it will be replaced by the 15th of the month for calculation

Duration of chemotherapy (months) = ((End date of the last cycle – Start date of the first cycle) + 1) / (365.25/12)) (rounded to 1 decimal),

Note: For calculation of durations, if the day of the date is missing, it will be replaced by the 15th of the month. If the month of the date is missing, the duration will be considered as missing.

Duration of brain irradiation (days) = (End date – Start date) + 1,

Duration of radiotherapy (days) = (End date – Start date) + 1,

Duration of treatment by tyrosine kinase inhibitor (months) = ((End date – Start date) + 1) / (365.25/12)) (rounded to 1 decimal),

For positive ALK, period between sending and receipt of the result (days) = (Date positive ALK result received - Date sent to the platform),

For positive ROS1, period between sending and receipt of the result (days) = (Date positive ROS1 result received - Date sent to the platform),

Time since diagnosis to progression (months) = (Progression date – Date of the biopsy that enabled making the diagnosis) / (365.35/12) (rounded to 1 decimal),

Note: If the day of the diagnosis is missing, it will be replaced by the 15th of the month for calculation. If the day of the progression is missing, it will be replaced by the 1st of the month for calculation

EORTC LC13 symptom scales scores [1]:

Scoring the QLQ-LC13

	Scale	Number of items *(n)*	Item range*	QLQ-LC13 items numbers *(I_1, I_2,…,I_n)*
Symptom scales / items				
Coughing	LCCO	1	3	31
Haemoptysis	LCHA	1	3	32
Dyspnoea [a]	LCDY	3[a]	3	33-35
Dyspnoea when resting [a]	*LCDYR*	*1*	*3*	*33*
Dyspnoea when walking [a]	*LCDYW*	1	3	34
Dyspnoea when stairs [a]	*LCDYS*	1	3	35
Sore mouth	LCSM	1	3	36
Dysphagia	LCDS	1	3	37
Peripheral neuropathy	LCPN	1	3	38
Alopecia	LCHR	1	3	39
Pain in chest	LCPC	1	3	40
Pain in arm or shoulder	LCPA	1	3	41
Pain in other parts	LCPO	1	3	42

* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 4, giving range = 3.

[a] The dyspnoea scale should only be calculated if all three items have been answered. Some respondents ignore question 35 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 35 is missing then items 33 and 34 should be used as single-item measures.

Principle for scoring

1) Raw score

For the multi-item scale, calculate the average of the corresponding items.

$$Raw\ Score = RS = \{(I1 + I2 + \ldots + In) / n\}$$

For each single-item measure, the score of the concerning item corresponds to the raw score.

There are no reverse scoring items.

2) Linear Transformation

To obtain the Score S, standardize the raw score to a 0 – 100 range using the following transformation:

$$S=\{(RS-1) / range\}\times 100$$

For directions on Missing Data or for more detailed information on the Interpretation of Scores, we redirect to the EORTC QLQ-C30 Scoring Manual (2001).

Remark

The scoring of item 43 is optional.

Interpretation: A high score for item 43 represents a high level of pain relief.

Scoring information for scoring item 43

	Number of items	Item range	Item
Pain relief after medication*	1	3	43

* Item 43 might not be applicable and must only be scored if the answer to the question "Have you taken any pain medicine" is "Yes".

Dose increase: if last dose of Crizotinib at M12 is higher than dose at baseline then dose increased between baseline and M12.

Dose reduction: if last dose of Crizotinib at M12 is lower than dose at baseline then dose reduced between baseline and M12.

Time since Crizotinib initiation to modification (days) = (First modification date – Initiation date of Crizotinib) + 1,

Note: If the day of the modification date is missing, it will be replaced by the 15th of the month for calculation

Time since Crizotinib initiation to temporary interruption (days) = (First interruption date – Initiation date of Crizotinib) + 1,

Treatment duration (days) = (last treatment intake date – first treatment intake date) + 1,

Treatment exposure (days) = Treatment duration - ∑ of number of days of interruption,

Time since temporary interruption to brain irradiation start (days) = Brain irradiation start date – Temporary interruption date,

Time since brain irradiation end to Crizotinib restart (days) = Interruption Duration - Duration of brain irradiation - Time since temporary interruption to brain irradiation start,

Time since temporary interruption to radiotherapy start (days) = Radiotherapy start date – Temporary interruption date,

Time since radiotherapy end to Crizotinib restart (days) = Interruption Duration - Duration of radiotherapy - Time since temporary interruption to radiotherapy start,

Treatment duration until progression date (weeks) = ((First treatment intake date – Date of progression) + 1) / 7 (rounded to 1 decimal),

Note: If the day of the progression is missing, it will be replaced by the 1st of the month for calculation

Treatment duration since the progression date (weeks) = ((Last treatment intake date or cutoff date – Date of progression) + 1) / 7 (rounded to 1 decimal),

Note: If the day of the progression is missing, it will be replaced by the 1st of the month for calculation

Treatment duration until progression with brain metastases (weeks) = ((Date of progression - First treatment intake date) + 1) / 7 (rounded to 1 decimal),

Note: If the day of the progression is missing, it will be replaced by the 1st of the month for calculation

Compliance will be evaluated using Morisky score:

The generic questionnaire for rating therapeutic compliance contains 4 complementary questions in which the scale is 0 for "YES" (indicating poor compliance) and 1 for "NO" (indicating good compliance) scored in the same manner.

The items are summed to give a range of scores from 0 to 4. A score of 4 indicates a high compliance, a score of 2-3 indicates a medium compliance and a score of 0-1 indicates a low compliance.

Time to onset of AE (days) = AE start date – first treatment intake,

Note: If the day or the month of the AE start date is missing, the time to onset will be considered as missing.

Duration of AE (days) = (AE resolution date – AE start date) + 1.

For survival analyses, times will be calculated and expressed in months as follows:

Time to death (months) = (Date of death – Crizotinib start date + 1) / (365.25/12) (rounded to 1 decimal),

Note : If the day of start date is missing, it will be replaced by the 15th of the month for calculation. If the day of the death is missing, it will be replaced by the 1st of the month for calculation

Weight loss:

If patient's weight at baseline is greater than patient's weight at the last observation then the patient will be considered as a patient who lost weight.

11.2. APPENDIX 2: additional STATISTICAL METHODOLOGY DETAILS

NA.