Non-Interventional Study Protocol
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Prospective observational study to IDEntify patients with advanced/metastatic NSCLC and ALK and ROS1 translocation and to establish their therapeutic management (IDEALK&ROS)

Statistical Analysis Plan
(SAP)

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CONTENTS

1 AMENDMENTS TO PREVIOUS VERSIONS

This is a second version, which will only analyse the patients included in the ROS1 sub-study.

2 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical analyses that will be performed to generate the final report for the IDEALK&ROS study. This includes a brief summary of the main study characteristics and the aim of the SAP, which refers to the statistical analysis plan for this study.

Lung cancer is a disease with a significant social and public health impact, which for decades has been one of the most common types of cancer worldwide. In 2008, there were an estimated 1.61 million new cases, accounting for 12.7% of all new cancers worldwide. Its large incidence also has an impact on mortality rates, and with 1.38 million deaths it is one of the leading causes of death from cancer[1]. In 2012, approximately 160,000 people were expected to die of lung cancer in the United States[2] and 262,000 in the European Union[3].

The World Health Organisation (WHO) divides lung cancer into two main categories based on their biology, therapy and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer. Non-small cell lung cancer accounts for more than 85% of all cancer cases and includes 2 important types: (1) non-squamous carcinoma (including adenocarcinoma, large cell carcinoma, other cell types); and (2) squamous cell carcinoma (epidermoid). Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer recorded in the USA and is also the most common cell type among non-smokers[4].

In recent years, the improved understanding of the biology of NSCLC has led to the identification of molecular events that are crucial for the malignant transformation and survival of cancer cells, and the identification of 'molecular subgroups' of NSCLC patients who may be candidates for 'targeted therapy'. These aberrant molecular events are critical oncogenic drivers and therefore represent potential therapeutic targets[5]. As a result, new targeted treatment options have been developed and continue to evolve. Erlotinib and gefitinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), have been approved for the treatment of NSCLC[6]. EGFR TKIs in particular represent a new paradigm in the treatment of NSCLC. EGFR mutations are found in 10-12% of Caucasian patients and 30-40% of Asian patients with NSCLC, and are associated with a higher response to EGFR TKIs[6]. Multiple randomised clinical trials have shown that patients harbouring EGFR-activating mutations benefit more from EGFR TKIs than standard chemotherapy in terms of ORR, progression-free survival (PFS), toxicity profile and quality of life[6]. The success of EGFR TKIs highlights the

importance of identifying specific molecular drivers of NSCLC so that the targeted agents can be properly directed at specific patient populations.

The discovery of anaplastic lymphoma kinase (ALK) gene rearrangement in NSCLC in 2007[7] represents another major milestone in the era of targeted molecular therapy in NSCLC. ALK was first identified as a fusion protein produced by chromosomal translocation in the majority of anaplastic large cell lymphomas (ALCL). When fused to other proteins, ALK becomes constitutively active, causing an increase in the kinase catalytic function, signal transduction activity and oncogenic function. The expression of EML4-ALK, a new fusion protein between ALK and the echinoderm microtubule-associated protein-like 4 (EML4) gene, has been shown in transgenic mice to induce tumour formation, suggesting the therapeutic potential of inhibiting the EML4-ALK fusion protein in NSCLC[7]. The frequency of EML4-ALK rearrangement in NSCLC patients is relatively low, being found in about 2-8% of analysed tumours[8,9,7]. However, although the incidence of this type of tumour in Spain is not known with any accuracy due to a lack of pertinent studies, the available scientific literature (especially with a North American population) suggests that NSCLC patients with ALK rearrangement are similar to those with EGFR mutations (i.e. adenocarcinoma, non-smokers or light smokers and young people)[10].

Moreover, it is important to have a detailed description of the clinical features of patients with NSCLC who have ALK translocation and its incidence, since no data are available for the Spanish population.

Crizotinib, an oral inhibitor of the ALK, ROS and MET tyrosine kinases, has been developed for patients with advanced/metastatic NSCLC with ALK rearrangements who have progressed after first-line treatment. Crizotinib was associated with clinically significant response rates of 60% and 48%, respectively, in two single-arm trials in 136 and 119 patients, respectively, with locally advanced or metastatic ALK-positive NSCLC who had been previously treated with standard chemotherapy (75% with two or more regimens)[11]. The responses were fast, with the majority patients achieving an objective and lasting response in the first 8 weeks of treatment, with a median duration of response (DOR) of 48.1 and 47.3 weeks, respectively, in each of the studies[12].

The use of crizotinib monotherapy in the treatment of ALK-positive advanced NSCLC was studied in a phase III, randomised, open-label, multicentre, multinational study (Study 1), in which a second-line treatment with crizotinib was compared to a second-line treatment with standard chemotherapy.

Crizotinib significantly increased PFS compared to chemotherapy, as assessed by an independent radiologic review (IRR), with a median PFS of 7.7 months in the crizotinib arm versus 3.0 months in the chemotherapy arm (HR 0.49; 95% CI 0.37-0.64). The improvement in PFS obtained with crizotinib was homogeneous across the patient subgroups, taking their baseline characteristics into account, and crizotinib also significantly improved the ORR assessed by IRR compared with chemotherapy.

The median DOR was 32.1 weeks (95% CI: 26.4; 42.3) in the crizotinib arm and 24.4 weeks (95% CI: 15.0; 36.0) in the chemotherapy arm. Data on overall survival (OS) were not final at the time of the PFS analysis.

For the evaluation of quality of life, a total of 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm had answered the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and LC-13 questionnaires at the baseline visit and at least one subsequent visit. Crizotinib led to an improvement in symptoms by significantly increasing the time to the worsening (median of 5.6 months versus 1.4 months) of chest pain, dyspnoea or cough reported by the patient, compared to chemotherapy (HR 0.54; 95% CI: 0.40; 0.71; logarithmic p adjusted by the Hochberg method <0.0001).

The speed with which crizotinib progressed from first being developed to approval has had a major impact on second-line treatment for patients with ALK+ NSCLC. However, this very fact means that the experience with and knowledge about its use is limited, with very little data to date on its use in routine clinical practice[13].

Crizotinib efficacy data for first-line treatment were presented in the PROFILE 1014 study, a comparative study of crizotinib versus cisplatin or carboplatin plus pemetrexed. Crizotinib obtained a median PFS of 10.9 months versus 7.0 months of chemotherapy, with an HR of 0.45 (95% CI 0.35 -0.60) and p <0.01. These data were later confirmed with the publication of the overall survival data from the same study, where the median OS for crizotinib had not been reached (NR) compared to 47.5 months of chemotherapy with an HR of 0.76 (95% CI 0.548 - 1.053) and p = 0.0978. The high OS achieved by chemotherapy reflects the high crossover allowed in the study (84%) and is the reason why statistical significance was not reached[14].

Another milestone of scientific importance is the discovery of the V-Ros Avian UR2 Sarcoma Virus Oncogene Homolog 1 (ROS1). The incidence of ROS1 disease in non-small cell lung cancer (NSCLC) patients is approximately 1-2% according to the different published series[15]. Given that approximately 29,000 patients were expected to have lung cancer in Spain in 2019 according to the Spanish Society of Medical Oncology[16], the incidence of the ROS1 disease would be around 500 patients per year. The real incidence of this condition in Spain is unknown.

Since its initial description as a biomarker for lung cancer in 2007, ROS1 disease began to gain diagnostic and therapeutic importance thanks to the 2016 EMA approval of crizotinib based on the results of an expansion cohort of the phase I PROFILE 1001 study evaluating 53 patients, which showed a median progression-free survival (PFS) of 19.2 months. The final overall survival (OS) results of the PROFILE 1001 study in the ROS1 cohort have recently been published, showing a median OS of 51.4 months[17]. These results further support the efficacy of crizotinib in this condition.

Currently, the diagnosis of ROS1 disease is indicated in all patients with a previous diagnosis of non-small cell lung cancer and in those where the phenotypic characteristics of a young patient, light/non-smoker and with adenocarcinoma histology suggest it. The ROS1 disease testing figures in Spain are unknown. According to an exploratory registry study of NSCLC cases collected since 2016, the ROS1 disease testing rate is around 20%[18]. It can be diagnosed using the immunohistochemical (IHC) technique that must then be confirmed with fluorescent in situ hybridisation (FISH). Another method currently being developed is next-generation sequencing, a cost-effective method in the diagnosis not only of this type of biomarker, but of many others at the same time and with a minimum amount of sample containing deoxyribonucleic acid (DNA) [19].

There are currently no data in Spain on the efficacy and safety of crizotinib in the ROS1 population; for these reasons, it is important and necessary to provide data on ROS1 disease and the benefit to these patients of a targeted therapy such as crizotinib, currently accepted as the only standard of treatment for these patients.

2.1 STUDY DESIGN

This is a multicentre, observational post-authorisation study with retrospective and/or prospective follow-up for the ALK population and a retrospective multicentre study for the ROS1 population. Both studies are non-interventional, and aim to describe the routine clinical practice or the standard clinical practice guidelines for both patient populations.

The study will be carried out on patients with advanced/metastatic non-small cell lung cancer (NSCLC).

- ROS1 Treatment Sub-study: Patients with advanced/metastatic NSCLC with confirmed ROS1-positive translocation and who have been treated with crizotinib. Within this population, data on the treatment of patients who have received crizotinib according to routine clinical practice will be collected.

It is estimated that 50 patients will be included in this sub-study, all ROS1+ with advanced/metastatic NSCLC who have received treatment with crizotinib as per routine clinical practice (patients who started treatment with crizotinib on or after 8 February 2017, the market launch date of crizotinib in Spain for the ROS1 indication, will be included retrospectively, until the opening of the site).

The study is expected to be conducted at approximately 50 sites across Spain in order to include the planned number of study patients. This sample number is equivalent to the inclusion of at least 1 ROS1+ patient per site, considering the low incidence of the disease of 1-2% of all patients with non-small cell lung cancer.

For the ROS1 treatment sub-study, a patient will be considered assessable if they have confirmed ROS1 translocation and provided they have received at least one dose of crizotinib.

2.1.1 Study population

Inclusion criteria

In general, all patients must meet all the inclusion criteria below to be eligible for inclusion in the study:

1. Diagnosis of advanced/metastatic non-small cell lung cancer
2. Patients over 18 years of age

For the ALK incidence sub-study, in addition:

1. Patients who are going to undergo molecular testing in order to establish ALK translocation will be included

For the ALK treatment sub-study, patients must meet the following additional criteria:

1. Confirmation of NSCLC with ALK-positive translocation
2. Be eligible to receive treatment with crizotinib according to routine clinical practice
3. Patients should have a predetermined minimum amount of data recorded in their medical records.

Where patients are included prospectively, evidence of an informed consent form personally signed and dated stating that the patient (or their legal representative) has been informed of all relevant aspects of the study.

For the ROS1 treatment sub-study:

1. Confirmation of NSCLC with ROS1-positive translocation
2. Have been eligible to receive treatment with crizotinib according to routine clinical practice since the market launch of the ROS1 indication in Spain on 8 February 2017 until the opening of the site.
3. Patients should have a predetermined minimum amount of data recorded in their medical records.

Exclusion Criteria

Any patient who does not meet any of the inclusion criteria defined in the previous section, according to the sub-study in which they are to be included.

2.2 STUDY OBJECTIVES

The objective of this sub-study is to determine the actual incidence of ALK translocations in patients with advanced/metastatic NSCLC in Spain and to describe the clinical characteristics of these patients (Incidence Sub-study) and the efficacy and safety of crizotinib in routine clinical practice in ALK (ALK Treatment Sub-study) and ROS1 (ROS1 Treatment Sub-study) patients. Henceforth, we will focus on the ROS1 treatment sub-study.

ROS1 Treatment Sub-study:

Primary Objective: To study the efficacy of treatment with crizotinib in patients with advanced/metastatic NSCLC with ROS1 translocation in terms of progression-free survival (PFS).

Secondary objectives:

- To describe the clinical characteristics of these patients.
- To evaluate the efficacy of treatment with crizotinib in these patients in terms of ORR, DOR and DOT.
- To evaluate the survival of these patients in terms of OS.
- To study the safety profile of the drug, especially for potentially serious adverse events (prolonged QTc interval, bradycardia, skin photosensitivity, vision disorders, oedema, elevated liver enzymes and neutropenia).

3 HYPOTHESIS AND DISCUSSION ROLE

3.1 STATISTICAL HYPOTHESES

As this is a descriptive and exploratory study, the sample size is not based on any statistical assumption.

The population has been estimated on the basis of the known data on advanced/metastatic ALK+ and ROS1+ NSCLC, and with the objective of performing the recruitment for ALK over a period of three years, as described in the study schedule, and also to collect data retrospectively, until the opening of the site, on patients who have started treatment with crizotinib as of 8 February 2017, the start date for the marketing of crizotinib in Spain for the ROS1 indication).

3.2 STATISTICAL DECISION RULES

For the statistical analyses, the programme SAS 9.3 (SAS Institute Inc., Cari, NC, USA) will be used. The level of statistical significance is set at 0.05

4 ANALYSIS POPULATIONS

4.1 FULL ANALYSIS SET

For the ROS1 treatment sub-study, a patient will be considered assessable if they have confirmed ROS1 translocation and provided they have received at least one dose of crizotinib.
All inclusion and no exclusion criteria are met

4.2 SAFETY ANALYSIS

The safety analysis will be performed for the same population as for the full analysis.
The safety analysis will only be carried out in the ALK + y ROS1 + treatment sub-study, which will take into account all the patients with advanced/metastatic NSCLC with ALK/ROS1 + who meet all the study screening criteria and have received at least one dose of treatment with crizotinib.

4.3 OTHER ANALYSES

N/A

4.4 SUBGROUPS

The main efficacy variables, ORR, DOR, OS and PFS will be studied according to:

- Treatment line in which crizotinib was received.
  - 1st line of treatment
  - 2nd line of treatment
  - 3rd line of treatment

As well as the sub-groups established depending on whether crizotinib is received as first line or later:

- 1st line of treatment
- 2nd line of treatment or later

- Presence of brain metastases
  - Yes
  - No
- Baseline ECOG
  - 0
  - 1
  - 2
  - >2
- Initial stage of NSCLC diagnosis
  - I
  - II
  - III
  - IV
- Histology in the diagnosis of advanced/metastatic NSCLC
  - Adenocarcinoma
  - Epidermoid
  - Large cells
  - NOS
  - Other
- Gender
  - Male
  - Female
- Smoking status
  - Yes
  - No

Conversely, certain characteristics of patients with ALK+/ROS1+ will be studied according to whether or not the patient is regarded as a responder to crizotinib, it being understood that a patient who does not respond to crizotinib is one with DP in the first response evaluation, and a responder is a patient who responds to treatment at any time (CR+PR). Patients who experienced clinical benefit from the treatment (SD+PC+CC) at any time have also been analysed. The characteristics to be evaluated would be:

- The patient's data: age, gender, smoking habit, baseline ECOG
- Sample data: sample type, origin of histology sample
- Diagnostic data: advanced stage, histological type
- Presence/absence of brain metastases

5 OBJECTIVES AND VARIABLES

A full description of these patients will be compiled to determine the clinical profile of ALK/ROS1 positive patients, and the treatments administered will be described retrospectively and/or prospectively.

By analysing the collected variables, the following aspects will be assessed:

Primary endpoints to analyse:

- Patient characteristics: age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) Quality of Life score, previous relevant medical history.

- Tumour characteristics: origin and type of sample, histological subtype (adenocarcinoma, squamous, etc.), stage, molecular alterations, location of metastases.

- Treatment-related: different lines of treatment, adverse effects, treatment response, survival.

5.1 EFFICACY/EFFECTIVENESS OBJECTIVES

- Progression-free survival (PFS): defined as the period between the first day of treatment and the first day that progressive disease (PD) is observed according to RECIST criteria (Version 1.1), or *death*. Patients who have not had an event at the time of the analysis of the study data will be censored at the date of the last available follow-up.
- Objective Response Rate (ORR): defined as the proportion of subjects who achieve complete remission (CR) or partial response (PR) as the best response attained. Additionally, the patients with stable disease (SD) will be evaluated. The subjects will be evaluated in accordance with RECIST criteria (Version 1.1).
- Duration of response (DOR): in patients with PR or CR, it will be defined as the interval from the date the best response is documented to the first date that progressive disease is observed.
- Overall survival (OS): defined as the period from the first day of treatment until death or censored up to the last date on which it was known that the subject was alive.

5.2 SAFETY OBJECTIVES

The safety of crizotinib will be evaluated describing the incidence of all adverse effects and their severity.

5.3 OTHER OBJECTIVES:

N/A

5.4 COVARIATES

All the covariates have been gathered on the electronic CRF designed for this study as specified in the study protocol.

6 MANAGEMENT OF MISSING VALUES

No replacement criterion for lost values will be used, except for dates, as appropriate.

- If the year is unknown, the date will not be imputed and will it be treated as a missing value.
- If the day and month are unknown, it will be imputed as July 1.
- If the day is unknown, the value of 15 will be assigned.

7 METHODOLOGY AND STATISTICAL ANALYSIS

7.1 STATISTICAL METHODS

The characteristics of patients with advanced/metastatic NSCLC enrolled in the study, with positive ALK/ROS1, will be studied using absolute and relative frequencies for qualitative variables and the main measures of centrality and dispersion (median, minimum, maximum and interquartile range (IQR)) for quantitative variables.

Also, with the aim of evaluating the efficacy and safety of treatment with crizotinib in patients with advanced/metastatic and ALK/ROS1-positive NSCLC, the Kaplan Meier estimator for the survival function will be used to study patients' PFS, DOR and OS. The ORR will be studied by presenting absolute and relative frequencies. This analysis will be performed using Kaplan Meier survival curves.

Comparisons performed with qualitative variables will use Pearson's Chi-Square test (Fisher's exact test for 2x2 tables, where applicable); in the case of quantitative variables, Student's t-test or ANOVA will be used, depending on the number of categories or their

non-parametric equivalents (the Mann-Whitney U test or the Kruskal-Wallis test) in the event of not following a normal distribution.

The log-rank test will be used to compare the survival functions.

The incidence rate of specific adverse effects will be described in the total population included in the treatment sub-study.

The assumptions of normality and homoscedasticity of the variables for the use of parametric tests will be studied. Estimations will be made with a 95% confidence level, using SAS 9.3 software (SAS Institute Inc., Cari, NC, USA).

7.2 STATISTICAL ANALYSIS

The statistical analysis described below will be performed on the total sample of patients with diagnosed advanced/metastatic NSCLC, with a positive result in the determination of ALK/ROS1 and who have been or will be treated with crizotinib.

7.2.1 Descriptive analysis

Demographic data:

The median, minimum, maximum and interquartile range (IQR) values will be given for the following variables:

- Age of the patients at the start of treatment.
- No. of packets/year, in patients who are smokers
- Time since stopping smoking, in ex-smokers

The frequency distribution of patients will be presented according to:

- Gender
  - Male
  - Female

- Smoking habit
  - Non-smoker
  - Smoker
  - Former smoker

- Baseline ECOG:
  - 0
  - 1
  - 2
  - 3
  - 4
  - Not available

Sample data:

The frequency distribution of patients will be presented according to:

- Sample type
  - Biopsy
  - Cell block
  - Cytology

- Sample Origin
  - Primary tumour
  - Metastasis

- Histology
  - Adenocarcinoma
  - Squamous
  - Large cell
  - NOS
  - Other (specify)
- eGFR:
  - Not performed
  - Negative
  - Positive
  - Not assessable
- ALK
  - Not performed
  - Negative
  - Positive
  - Not assessable
- ROS1 performed by:
  - FISH
  - IHQ
  - CRP
  - Other (specify)

- Presence of other molecular abnormalities
  - No
  - Yes (specify)

Relevant pre-existing conditions:

The number of relevant previous pathologies presented by the patients will be described qualitatively and quantitatively, considering those appearing in the eCRF.

- Presence of cardiovascular diseases
  - No
  - Yes (specify)

- Presence of neoplastic diseases
  - No
  - Yes (specify)

- Presence of gastrointestinal disorders
  - No
  - Yes (specify)

- Presence of pulmonary diseases
  - No
  - Yes (specify)

- Presence of surgery
  - No
  - Yes (specify)

- Presence of other relevant diseases
  - No
  - Yes (specify)

Disease diagnosis data:

The median, minimum, maximum and interquartile range (IQR) values will be given for the following variables:

- Time from the diagnosis of lung cancer until the start of treatment with crizotinib
- Time from the diagnosis of advanced/metastatic NSCLC until the start of treatment with crizotinib
- Time between both diagnoses

The frequency distribution of patients will be presented according to:

- Initial stage of lung cancer:
  - I
  - II
  - Unknown
- Surgery subsequent to initial diagnosis
  - Yes
  - No
- Radiotherapy subsequent to initial diagnosis
  - Yes
  - No
- Chemotherapy subsequent to initial diagnosis
  - Yes (specify drugs)
  - No
- Stage in advanced/metastatic diagnosis
  - IIIA
  - IIIB
  - IV
  - Unknown
- Site of metastases
  - Nodes
  - Lung
  - Bone
  - Brain
  - Liver
  - Other location (specify)
- Histological type (advanced/metastatic NSCLC)
  - Adenocarcinoma
  - Squamous
  - Large cells
  - NOS
  - Other (specify)

Previous treatment:

The number and percentage of patients who received treatment prior to crizotinib as well as the number of prior treatments (1 or 2) will be given.

For each of the previous lines, the following will be given:

- Drug, providing the frequency distribution of the patients for each one.

- Time on treatment, calculated as the difference between the treatment start date and end date. It will be studied by means of the main measures of centrality and dispersion.
- Concomitant radiotherapy, the absolute and relative frequency distributions of the patients on the basis of whether or not they received concomitant radiotherapy will be given.
- Best response rate achieved, presenting the frequency distribution of the patients based on the best response achieved with said treatment.
    - CR
    - PR
    - SD
    - DP
    - Not assessable
    - Unknown

- Maintenance treatment, the absolute and relative frequency of patients who received maintenance treatment will be presented. For the sub-population of patients who received maintenance treatment, the following will be determined:
    - Drug used, by means of the number and percentage of patients for each response.
    - Time on maintenance treatment, calculated as the difference between the maintenance start and end date. This will be studied by means of the main measures of centrality and dispersion.
    - Best response achieved, giving the distribution of patient frequencies according to the best response obtained in maintenance:
        - □ CR
        - □ PR
        - □ SD
        - □ DP
        - □ Not assessable
        - □ Unknown

Subsequent to the previous second line of treatment, it was asked whether maintenance treatment had been received. In this regard, the number and percentage of patients who received it will be given. For those patients who did receive it, the drug will be described.

Moreover, it will be specified whether patients received other treatments before starting treatment with crizotinib.

- Radiotherapy
- Surgery
- Other

Treatment with crizotinib

- **Starting** dose, frequencies of patients on the basis of the following will be provided:
  - 250 mg/12 h
  - 200 mg/12 h
  - 250 mg/24 h
  - Other dose
- **Baseline ECOG**, providing the frequency distributions of patients on the basis of initial ECOG at the start of treatment with crizotinib:
  - 0
  - 1
  - 2
  - 3
  - 4
  - Not available
- **Time from the end of the previous treatment until the start of treatment with crizotinib** calculated as the difference between the end of the final previous treatment received and the start date of treatment with crizotinib This will be studied by means of the main measures of centrality and dispersion.
- **Time from diagnosis of the metastatic disease until the start of treatment with crizotinib**, calculated as the difference between the date of diagnosis of advanced/metastatic NSCLC and the start date of treatment with crizotinib. This will be studied by means of the main measures of centrality and dispersion.
- **Best response achieved**, giving the distribution of patient frequencies according to the best response obtained during the treatment:
  - CR
  - PR
  - SD
  - DP
  - Not assessable
  - Unknown
- **Time to the best response**, calculated as the difference between the start date of treatment with crizotinib and the date on which the best response is achieved. This will be studied by means of the main measures of centrality and dispersion.
- In the case of brain metastases, the distribution of patients on the basis of **the response of brain metastases** will be given:
  - CR
  - PR
  - SD
  - DP

The number and percentage of patients who have **completed the treatment** with crizotinib will be given. If the affirmative case, these must be described:

- Reason for terminating the treatment, giving the frequency distribution of the patients according to the reason for terminating the treatment:
  - Adverse event
  - Progression
  - Other reason
- Time on treatment with crizotinib, calculated as the difference between the start date and end date of treatment with crizotinib. This will be studied by means of the main measures of centrality and dispersion.
- ECOG on finishing treatment with crizotinib, giving the frequency distribution of the patients.
  - 0
  - 1
  - 2
  - 3
  - 4
  - Not available

Lastly, the number and percentage of patients who **progress to treatment** with Criztonib will be given, indicating the ECOG at the time of progression and the reason for progression on the basis of:

- Progression of existing lesions
- Emergence of new lesions
- Emergence of brain metastases
- Symptomatic deterioration

For patients who progressed, the number of patients who received **treatment with crizotinib post-progression according to RECIST will be indicated**

- Time on treatment, calculated as the difference between the treatment start date and end date of treatment with crizotinib. This will be studied by means of the main measures of centrality and dispersion.
- Best response achieved, giving the distribution of patient frequencies according to the best response obtained:
  - CR
  - PR
  - SD
  - DP
  - Not assessable
  - Unknown

- Time to the best response, calculated as the difference between the start date of treatment with crizotinib and the date on which the best response is achieved. This will be studied by means of the main measures of centrality and dispersion.
- In the case of brain metastases, the distribution of patients on the basis of the response of brain metastases will be given:
  - CR
  - PR
  - SD
  - DP
  - Not assessable
- Reason for terminating the treatment, giving the frequency distribution of the patients according to the reason for terminating the treatment:
  - Toxicity
  - Progression
  - Other reason

It will be stated whether the patient has received other **non-systemic treatments** during treatment with crizotinib, providing the frequency distribution on the basis of the following:

- Radiotherapy
- Surgery

In the case of radiotherapy, the time undergoing treatment with radiotherapy will be given, calculated as the difference between the start and end dates of radiotherapy.

In the case of surgery, the time elapsed since the start of treatment with crizotinib until surgery was performed will be indicated.

Modification and/or interruption of dose

- Dose reductions, the absolute and relative frequency of patients who required a dose reduction at some point during treatment with crizotinib will be calculated. The frequency distribution of the patients will be presented for this sub-population according to the number of dose reductions required. For the total number of dose reductions, depending on the order in which they order took place, the frequency distributions will be presented based on:
  - Reason for dose reduction
    - Toxicity
    - Other (specify)

- New dose administered
  - 200 mg/12 h
  - 250 mg/12 h
  - 250 mg/24 h
  - Other dose (specify)
- As well as the mean time elapsed from the start of treatment until reduction, using the principal measures of centrality and dispersion to do so.

– Dose interruptions, the absolute and relative frequency of patients who have required an interruption of the dose at some point during treatment will be calculated. The frequency distribution of the patients will be presented for this sub-population according to the number of interruptions required. For the total number of interruptions as well as on the basis of it being the first, second, etc., the frequency distributions thereof will be presented on the basis of the following:
  - Reason for interruption
    - Toxicity
    - Other (specify)
  - New dose administered after the interruption
    - 200 mg/12 h
    - 250 mg/12 h
    - 250 mg/24 h
    - Other dose (specify)
  - And the time from the start of treatment with crizotinib until the first interruption, as well as the time with the interrupted treatment, calculated as the difference between the date of the interruption of treatment and the date on which it was restarted, using the principal measures of centrality and dispersion to do so.

7.2.2 Efficacy analysis

First, the patient follow-up time will be provided, defined as the time from the start of treatment until the final follow-up available or death. This will be studied in terms of centrality and dispersion.

On the basis of the primary objective:

Primary Objective: To study the efficacy of treatment with crizotinib in patients with advanced/metastatic NSCLC with ROS1 translocation in terms of progression-free survival (PFS).

- **Progression-Free Survival (SLP)**, progression-free survival will be studied by means of the Kaplan Meier survival analysis, calculated as the time elapsed from the start date of treatment with crizotinib through to the date of progression/death, if the event takes place, or otherwise it will be censored on the date of the last follow-up of the patient

On the basis of the secondary objectives:

- To evaluate the efficacy of treatment with crizotinib in these patients in terms of ORR, DOR.
- To evaluate the survival of these patients in terms of OS.

- **ORR**, the absolute and relative frequency of patients who have reached the target objective response rate will be given (CR+PR).

- **DOR,** for the sub-population of patients who reached the ORR, the time from the date of the response to the date of progression will be calculated, in terms of measures of centrality and dispersion.

We are going to introduce another term, which we will call **clinical benefit**, defined as patients who obtain CR+PR+SD.

- **Overall Survival (OS)**, overall patient survival will be studied by means of the Kaplan Meier survival analysis, calculated as the time elapsed from the start date of treatment with crizotinib until the date of death, if the event takes place, or else it will be censored to the date of the last follow-up in the case of living patients.

  In case of death the frequency distribution will be presented depending on the reason for the patient's death:
  - Due to the disease
  - Due to treatment-related toxicity
  - Other reason (specify)

For each of the groups described in Section 4.4 of this analysis plan, the efficacy objectives of the study will be studied: PFS, ORR, DOR and OS.

7.2.3 Safety analysis

A further secondary objective of the study is:

- To study the safety profile of the drug, especially for potentially serious adverse events (prolonged QTc interval, bradycardia, skin photosensitivity, vision disorders, oedema, elevated liver enzymes and neutropenia).

Toxicity to crizotinib: the absolute and relative frequencies of patients who have presented some type of toxicity (Grade 1-2 toxicity and 3-4 or 5 toxicity) to the following will be given:

- Asthenia
- Visual disorders
- Diarrhoea
- Nausea
- Vomiting
- Elevated AST
- Elevated ALT
- Elevated bilirubin
- Oedema
- Bradycardia
- QTc interval prolongation
- Anaemia
- Leukopenia
- Neutropenia
- Neuropathy
- Dysgeusia
- Renal cysts
- Pneumonitis
- Constipation
- Photosensitivity
- Other toxicity

The absolute and relative frequencies of patients who presented some type of serious event will be given.

7.2.4 Other study analyses

The number and percentage of patients who have received treatment post crizotinib will be given.

The number of post-crizotinib treatments received per patient will be presented qualitatively and quantitatively.

In the sub-population of patients who received post crizotinib treatment, the frequency distribution of patients will be determined on the basis of the treatment received, depending on whether it was the first, second or third treatment received after crizotinib.

For each of the treatments after crizotinib, the following will be studied

- **Best response rate achieved**, presenting the frequency distribution of the patients based on the best response achieved with said treatment
    - CR
    - PR
    - SD
    - DP
    - Not assessable
    - Unknown

- **Time on treatment**, calculated as the difference between the treatment start date and end date. This will be studied by means of the median, range, and interquartile range values.

- **Reason for terminating treatment**, the frequency distribution of the patients will be given according to the reason leading them to terminate the treatment:
    - Disease progression
    - Toxicity
    - Maximum number of complete cycles
    - Other reason

- **Other palliative treatments,** the absolute and relative frequency of patients who received any of the following palliative treatments will be given:
    - Radiotherapy
    - Surgery
    - Other

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