NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Descriptive observational study ALK-2016-CPHG. **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.**
Protocol Number	**A8081060**
Protocol version ID	**Version 4.0**
Date of latest version of protocol	**19 July 2018**
Active substance	**crizotinib**
Medicinal product	**XALKORI®**

Research topic and objectives	Primary objective - Describe the characteristics of patients treated with crizotinib (regardless of line of treatment and according to 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). - Evaluate the impact of the anti-cancer treatment in terms of: • clinical response (evaluation by physician) • tumour response on imaging according to the physician • survival (progression-free survival (PFS), overall survival (OS) and 12 and 18-month survival probabilities) - Adverse events - Quality of life (QoL) (self-administered questionnaire QLQ-LC13) - Compliance (Morisky self-administered questionnaire) - Describe crizotinib prescription and discontinuation conditions (scheduled end of treatment, intolerance/toxicity, progression, other). - Describe the treatment plan after progression (local treatments, systemic treatment, crizotinib maintenance) and the impact of this treatment.
Author	PPD

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ALK	Anaplastic lymphoma kinase
MA	Marketing authorisation
LC	Lung cancer
NSCLC	Non-small cell lung cancer
CH	Hospital
CNIL	French Data Protection Commission
CNOM	French national medical association
CPHG	French general hospital pulmonary medicine specialist association
CPP	Committee for the protection of persons
CT	Chemotherapy
Dr	Doctor
e-CRF	Electronic-case report form
AE	Adverse event
SAE	Serious adverse event
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
FISH	Fluorescence in situ hybridisation
HR	Hazard ratio
95% CI	95% confidence interval
IHC	Immunohistochemistry
INCa	French national cancer institute
M	Month
NGS	Next-Generation Sequencing
WHO	World Health Organization
ORR	Overall response rate
PS	Performance status
QoL	Quality of life
QLQ-LC 13	Quality of life Questionnaire for Lung Cancer 13 items.
SPC	Summary of Product Characteristics
RECIST	Response evaluation criteria in solid tumours
ROS1	Proto-oncogene 1, receptor tyrosine kinase
RT	Radiotherapy
qRT-PCR	quantitative Reverse transcriptase polymerase chain reaction
OS	Overall survival
PFS	Progression-free survival
TNM	Tumour, Node, Metastasis
V	Visit

1. RESPONSIBILITIES

Scientific Committee experts

Surname	Title	Establishment	Address
PPD	Dr	PPD	PPD France.
PPD	Dr	PPD	PPD France
PPD	Dr	PPD	PPD France
PPD	Dr	PPD	PPD France

Scientific Committee coordinator

Surname	Title	Establishment	Address
PPD	Dr	PPD	PPD France

2. SUMMARY

Title of study	**Descriptive observational study ALK-2016-CPHG.** 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.
Sponsor	Pfizer
Coordinator	**Dr.** PPD PPD France
Scientific Committee	**Coordinator** - Dr. PPD **Members:** - Dr. PPD - Dr. PPD - Dr. PPD - Dr. PPD
Participating centres and physicians	- France (Metropolitan France and overseas departments and regions and overseas authorities [DROM-COM]) - Hospital pulmonary medicine departments - All physicians practising in a hospital pulmonary medicine department - Approximately 50-70 centres are expected for the study.
Rationale	**Lung cancer is a major public health issue due to its frequency and its poor prognosis.** In France, with approximately 40,000 new cases estimated in 2012, lung cancer (LC) represents 11% of all new cancer cases. It is the 4th most common form of cancer and the leading cause of cancer-related deaths. In 2012, the number of LC-related deaths was estimated at approximately 30,000, and in 2008, the 5-year survival rate observed in France was approximately 15% [1]. **Most cases of LC are non-small-cell cancers (NSCLC), most often adenocarcinomas, diagnosed at an advanced stage.** As such, in 2010, 86% of the 7,051 LC cases receiving care in the 104 general hospitals included in the study KBP-2010-CPHG were cases of NSCLC [2]. According to the same study, 67.8% of these cancers were diagnosed at stage IIIB or IV according to the TNM classification (7th edition) [15]. Furthermore, a major epidemiological change has been observed in recent years: the proportion of squamous carcinomas among these cases of NSCLC has decreased in favour of adenocarcinomas. As such, in 2010, in the study KBP-2010-CPHG [2], adenocarcinomas represented 46% of cases of NSCLC. **The molecular breakdown of LC is most advanced for NSCLC and particularly adenocarcinomas.** Molecular alterations such as mutations of *epidermal growth factor receptor* (EGFR) and ALK (*anaplastic lymphoma*

kinase) and ROS1 (*proto-oncogene 1, receptor tyrosine kinase)* gene rearrangement are at the present time predictive markers of the efficacy of targeted therapeutics on the market and/or under development.
At the present time in France, testing for ALK and ROS1 gene rearrangements is performed in 28 hospital molecular biology platforms funded by the French national cancer institute (INCa) and the French Healthcare Directorate (DGOS).
According to the latest data from INCa, the number of ALK gene rearrangement tests is rising steadily. Testing was performed on 4,543 patients with NSCLC in 2011, 18,861 in 2013, 21,183 in 2014 and 22,667 in 2015. **The mean ALK gene rearrangement rate in cases of NSCLC is 2.84%. As regards ROS1 gene rearrangement, 14,268 samples were tested in 2015, with the incidence of ROS1 gene rearrangement being 1.3% [3].**
The patient population with ALK+ or ROS1+ NSCLC would appear to be younger and have a lighter smoking profile (more non-smokers and smokers with less than 10 pack-years) than the ALK- or ROS1-negative patient population and their tumour would appear to be more frequently an adenocarcinoma [4].
The *European Society for Medical Oncology* (ESMO) recommends, moreover, systematic ALK gene rearrangement testing for all locally advanced or metastatic non-squamous bronchial cancers and also suggests testing the tumours of non-smoker or light smoker patients with a squamous tumour [5]. A recent expert consensus on ROS1 testing recommends testing for ROS1 at the same time as ALK or EGFR [24].
The therapeutic management of NSCLC differs according to the type (squamous or adenocarcinomas) and the cancer stage (I, IIA, IIB, IIIA, IIIB, or IV). In the early stages, the gold standard treatment is surgery. At advanced stages, cancer management is based on a systemic medical treatment. Many criteria are involved in the therapeutic decision including tumour histology, patient performance status and patient comorbidities. However, the presence of a genomic mutation is decisive in directing the therapeutic strategy in cases of advanced NSCLC.

Crizotinib (XALKORI®) is a small selective inhibitory molecule of the ALK and ROS1 tyrosine kinase activity receptor (RTK) as well as their oncogenic variants.
RTK inhibition of crizotinib blocks a cellular signalling pathway required for the growth and survival of tumour cells.

Crizotinib has demonstrated its efficacy in patients with ALK+ NSCLC, as a first-line treatment or second-line treatment particularly in advanced forms, where its activity is greater than that of conventional chemotherapy [6, 7].
It has proven to be superior than chemotherapy on the median progression-free survival (PFS, primary criterion) and on the overall response rate. As a first-line and second-line treatment, respectively, the median PFS was 10.9 months versus 7.0 months and 7.7 months versus 3.0 months (absolute difference of 3.9 months and 4.7 months in favour of the crizotinib group; *hazard ratio* [HR] = 0.45 and 0.49; 95% confidence interval [95% CI]: [0.37 - 0.60] and [0.37 - 0.64]; p <

	0.0001). The *overall response rate* (ORR) was 74% versus 45% as a first-line treatment and 65% versus 20% as a second-line treatment. Moreover, crizotinib has also demonstrated its efficacy in patients suffering from ROS1+ LSCLC (median PFS: 19.2 months, ORR: 72%). [8] Crizotinib is the first medicinal product targeting ALK and ROS1 rearrangements having a marketing authorisation (MA) in NSCLC. It is currently the gold standard treatment in the first-line and second-line treatment of adult advanced ALK-positive NSCLC patients and in the treatment of adult ROS1 NSCLC patients [9] In this context, Pfizer proposes to conduct a prospective (partially retrospective) observational 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 will be conducted in partnership with the French general hospital pulmonary medicine specialist association (CPHG) due to this association's experience in this type of study [2, 10] and because CPHG includes almost all non-university hospital pulmonary medicine specialists. This will help ensure the quality of the data compiled and envisage national coverage and an exceptional number of participating centres for this study.
Study objectives	**Primary objective** - Describe the characteristics of patients treated with crizotinib (regardless of line of treatment and according to line of treatment). **Secondary objectives** - Describe the conditions for conducting ALK gene and ROS1 gene rearrangement testing (source of specimen, technique used and time frame). - Evaluate the impact of the anti-cancer treatment in terms of: • clinical response (evaluation by physician) • tumour response on imaging according to the investigating physician • survival (progression-free survival (PFS), overall survival (OS) and 12 and 18-month survival probabilities) - Adverse events - Quality of life (self-administered questionnaire QLQ-LC13) - Compliance (Morisky self-administered questionnaire).

	- Describe crizotinib prescription and discontinuation conditions (scheduled end of treatment, intolerance/toxicity, progression, other) - Describe the treatment plan after progression (local treatments, systemic treatment, crizotinib maintenance) and the impact of this treatment.
Population concerned	**Inclusion criteria** - Age ≥ 18 years - Locally advanced or metastatic NSCLC - Patient presenting 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 type and methodology	**Observational, descriptive, longitudinal, national, multicentre study**, with prospective (partially retrospective) data collection from a cohort of patients treated with crizotinib for locally advanced or metastatic ALK+ or ROS1+ NSCLC in general hospitals. **Enrolment of participating physicians** From November 2016, all physicians known to practise in a hospital pulmonary medicine department shall be invited to take part in the study by email. Physicians accepting to take part shall return the "participating physician" form attached to the invitation email to the study administration centre by 31 December 2017. **Patient enrolment** 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+ or ROS1+ NSCLC treated with crizotinib. **Data collection** Each participating physician shall complete an anonymised electronic questionnaire (e-CRF) for each patient included. He/she shall undertake to collect the data in the questionnaire exhaustively. The follow-up period for each patient shall be 18 months.

Data collected	**Data collected at <u>inclusion visit</u>** • Date of visit • Date of signing of consent • Patient characteristics: date of birth, gender, smoking status, height, weight, BMI, ECOG performance status as per the World Health Organization (WHO) • <u>Tumour characteristics</u>: date of biopsy resulting in diagnosis, histological type, location of tumour, presence and location of metastases, TNM stage (8^{th} edition) • <u>ALK/ROS1 gene rearrangement:</u> diagnostic method, date of dispatch of specimen to platform, date of receipt of result, interval between dispatch and receipt, source of specimen, test platform, techniques used. • <u>Other biomarkers</u> (yes/no), date of receipt of result • <u>At time of inclusion:</u> prior therapeutic strategy for advanced/metastatic NSCLC treatment (start date and end date, dose) • <u>Crizotinib:</u> start date, line of treatment (1^{st}, 2^{nd} line or 3^{rd} line or other), dosage • Ongoing/prescribed preventative treatments at inclusion visit. • Quality of life (self-administered questionnaire QLQ-LC 13) • Adverse events if crizotinib had been started prior to the inclusion visit (retrospective collection) **Data collected at <u>each follow-up visit</u> (M3, M6, M9, M12, M15)** • Date of visit • Patient characteristics: smoking status, weight, performance status • Evaluation of efficacy of treatment (clinical and radiological) • Progression (date and site) • Crizotinib treatment plan (modification, temporary or definitive discontinuation) • Supplementary information (preventative treatments, tolerance, Morisky self-administered questionnaire (compliance), QLQ-LC13 self-administered questionnaire (quality of life) **Data collected at End-of-follow-up visit (M18):** • <u>In the case of continuation of crizotinib treatment until the end of the study:</u> The data collected in cases in which crizotinib treatment is continued shall be the same as those collected at the follow-up visits. • <u>In the case of discontinuation of crizotinib prior to the end of the study.</u> <u>Note</u>: If crizotinib is discontinued, the patient shall only be seen again at M18. No further data apart from adverse events shall be collected from the discontinuation of crizotinib until the end-of-follow-up visit.

	At the end-of-follow-up visit (M18), the following data shall be collected: • Date of visit • Patient characteristics: smoking status, weight, Performance Status, post-crizotinib management characteristics • Tolerance (see section 9) **End-of-study visit**: • Date of visit • Scheduled end-of-study visit (yes/no) • If no, reason for withdrawal from study
Study duration and schedule	- Duration of inclusion period: 24 months - Follow-up period for each patient: 18 months - Total duration of study: 42 months (from 1st visit of 1st patient to final visit of final patient)
Analysis method **Data analysis**	No statistical hypothesis shall be tested for the primary objective or for the secondary objectives. A descriptive analysis of all of the evaluation criteria shall be conducted on the total population and according to the lines of treatment. Adverse events shall be presented according to their frequency according to their type, their relationship with the treatment, their severity and their duration. The data collected shall be described: - Mean, standard deviation (SD), median and quartile for quantitative variables - Population size and percentage for qualitative variables. The 12- and 18-month survival and progression-free survival rates shall be calculated using the Kaplan-Meier method and presented with their 95% confidence interval (95% CI) Supplementary analyses may be conducted at the request of the scientific committee. A new statistical analysis plan shall then be prepared by the CRO and validated by Pfizer.
Number of Patients	As the statistical analysis is descriptive, the sample size calculation is not based on a statistical hypothesis test. The number of patients with ALK+ and ROS1+ NSCLC treated with crizotinib treated in total and by line of treatment should however be sufficient to enable a descriptive analysis of the data. In 2015, according to INCa data, ALK rearrangement testing was conducted on 22,667 patients, namely a 61% increase in activity since 2012. According to the same data, the expected rearrangement rate for ALK+ NSCLC patients is 2.84%. In parallel, ROS1 rearrangement testing was conducted on 14,268 patients in 2015. The rearrangement rate observed was 1.3% [3]. Based on CPHG experience, each hospital following up patients with NSCLC should therefore observe one patient with ALK+ NSCLC and one patient with ROS1+ NSCLC for every 100 patients. For this reason, between 50 and 70 hospitals should be enlisted to take part in

	this study. Therefore, they should make it possible to include at least 50 to 70 patients with advanced NSCLC. Due to the enrolment capacity, the inclusion of at least 15 ROS1-positive patients is expected. In addition and due to the number of open centres, the inclusion of consenting ALK+ and ROS+ patients over the 24-month enrolment period should make it possible to reach the target of 50 to 70 patients. 50 to 70 patients should enable representativeness for each line of treatment.
Regulatory procedures	- Healthcare Research Data Processing Advisory Board (CCTIRS) - French Data Protection Commission (CNIL) - Observational research protocol review committee (CEPRO) - French national medical association (CNOM)

3. AMENDMENT

Amendment	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	29 March 2017	Substantial	5.2.2. ROS 1 gene rearrangement 5.3.2. ROS 1+ NSCLC treatment 5.3.1.1. First-Line Treatment 5.3.1.2. Second-Line Treatment 7.3.1.3. ALK gene and ROS 1 gene rearrangement Appendix 1 Patient information letter and consent form Appendix 2 Physician CRF Appendix 3 Morisky questionnaire	-Inclusion of patients presenting with ROS1 rearrangement in inclusion criteria -Update of dates of granting of regulatory approvals from the authorities and of dates of key stages. -Update of results of studies 1007 and 1014 to understand the latest published data.	Following the granting on 30 August 2016 of the MA extension of crizotinib for patients suffering from NSCLC presenting with ROS1+ rearrangement, for all lines and in order to better characterise the set of patients currently treated with crizotinib.

			Appendix 5 Summary of Product Characteristics		
2	17 MAY 2018	Substantial	4. Key stages 5.1.2.2 Stages 7.1. Study design 7.5. Study size 7.10.3. Archival 8.1. Patient information letter 8.2. Patient consent form 8.4.1. French public health regulation act "2004-806 of 9 August 2004" 8.4.3. Data Protection: French National Data Protection Commission "CNIL" 11. References Appendix: 1 Patient information letter and consent form	- Extension of inclusion period (6 months) - Increase of population size from 50-70 to 70-100 - Update of data collection start and end dates - Update of TNM classification (TNM 8th) - Update of reference - Update of key stage dates. - Revision to comply with the European Union (EU) General Data Protection Regulation (GDPR)	Reach the minimum inclusion target of 15 ROS1-positive patients to be able to conduct a descriptive analysis. Following the entry into force in January 2017 and use in routine practice of the new version of the TNM classification. Following the introduction of ceritinib 1L onto the market, Publication of Overall survival data from study 1014

4. KEY STAGES

The key stages are presented below.

Key stage	Scheduled date
Physician enrolment – feasibility study	November 2016 – December 2017
Start of data collection:	

- 1st patient included - Final patient included	January 2017 December 2018
End of data collection: - 1st patient included - Final patient included	 June 2018 June 2020
Study progress report	December 2018 (inclusion report)
Intermediate report	March 2019 (inclusion report, characteristics of patients and tumour at time of inclusion)
Final study report	August 2020

5. STATEMENT AND CONTEXT

This non-interventional study relates to the follow-up of the treatment plan of patients with ALK+ or ROS1+ NSCLC treated with crizotinib and is conducted voluntarily by Pfizer.

5.1. Lung cancer

5.1.1. Incidence and mortality

Lung cancer features strongly in France in terms of the number of new cases diagnosed each year and the number of deaths.

With almost 40,000 estimated new cases in 2012, LC ranks second for cancers in men after prostate cancer, third for cancers in women after breast cancer and colorectal cancer, and ranks fourth for all genders combined [1].

Since 1980, the incidence of lung cancer in France is practically 50 cases per 100,000 person-years in 1980 and 51.7 cases in 2012, i.e. a 0.1% annual rate increase between 1980 and 2012.

In women, the incidence of lung cancer has been rising strongly since the 1980s due to the increase in female smoking. The standardised incidence rate increased in women in France from 3.5 in 1980 to 18.6 in 2012, i.e. a 5% increase in 30 years [1].

In France, in 2012, the number of lung cancer-related deaths for all genders combined was estimated at approximately 30,000. Lung cancer was by far the leading cause of cancer-related deaths in men (approximately 21,400 deaths, or almost 25% of all male cancer-related deaths) and the 3rd cause of cancer-related deaths in women (approximately 8,600 deaths, or almost 14% of all cancer-related deaths) [1]

Lung cancer (LC) is one of the cancers with the poorest prognosis; ranking 5th after pancreatic, pleural, liver and oesophageal cancers in Europe. The 5-year survival rate for LC diagnosed between 1989 and 2004 was 14% [1].

According to US data, the 5-year survival rate of patients diagnosed between 2006-2012 is estimated at 59.2% for the localised stage versus 4.9% for the metastatic stage [11]. According to the studies KBP-2000-CPHG and KBP-2010-CPHG [10, 12], the 1-year survival rate in 2000 in patients with LC diagnosed and followed up in a non-university hospital pulmonary medicine department was approximately 38%. Only 10.4% of these patients were still alive at 5 years. Ten years later, the 1-year survival rate had improved, however; it was approximately 44%. [12]

5.1.2. Classification and staging

Positive diagnosis of lung cancer is based on the anatomopathological test results [13]. This test will also help specify the histological type of the tumour and guide the treatment [14].

5.1.2.1. Histological types

The histological types most commonly encountered according to the World Health Organization (WHO) histological lung cancer classification [15] are:

- Squamous carcinomas
- Small-cell carcinomas
- Adenocarcinomas
- Large-cell carcinomas.

In practice, these different histological types are grouped into 2 categories:

- Non-small cell lung cancers (NSCLC)
- Small cell lung cancers (SCLC).

Patient management will be dependent on these 2 categories. As such, at limited stages, for NSCLC, if the patient's condition permits it, surgery is the gold standard treatment, whereas for SCLC, treatment is based on concomitant radio-chemotherapy followed by preventative brain radiation. For both types of cancers, the gold standard treatment of advanced stages in the absence of biomarkers is based on chemotherapy, in some cases associated, for NSCLC, with radiotherapy.

In France, the majority of cases of lung cancer are NSCLC [16].

The results of studies KBP-2000-CPHG and KBP-2010-CPHG demonstrate that, of the 5,667 and 7,051 new cases of LC diagnosed between 1 January and 31 December 2000 and 2010, respectively, 83.4% and 86.5%, respectively, were cases of NSCLC [10, 12].
While the SCLC/NSCLC ratio has been relatively stable for 10 years, the proportion of adenocarcinomas among cases of NSCLC has, on the other hand, increased significantly in

10 years (+50.7%). The percentage of adenocarcinomas among cases of NSCLC has risen from 34.9% to 52.6% (p<0.0001), making adenocarcinoma the most frequently encountered histological type in France [12].

The increase in the risk of adenocarcinoma observed between 2000 and 2010 was independent of the patient's gender, age and smoking status [12]. In addition, it was more pronounced in men than in women (+54.6% in 10 years versus +22.3%).
In men, 48.7% of cases of NSCLC in 2010 versus 31.5% in 2000 were adenocarcinomas and in women, 64.6% of cases of NSCLC in 2010 versus 52.8% in 2000. However, the percentage of adenocarcinomas among cases of NSCLC remained consistently higher in women, non-smokers and young subjects than in other patients (Tab.1).

Tab.1 Percentage of patients by histological NSCLC type in 2010 according to their gender, age and smoking status - Results of study KBP-2010-CPHG (N = 6,083)

		Squamous carcinoma	Adenocarcinoma	Large-cell carcinoma	Other (including composite cancers)
Gender	**Male**	34.9	48.7	12.2	4.1
	Female	16.7	64.6	12.9	5.8
Age	**≤ 50 years**	14.8	64.9	13.5	6.9
	51 to 70 years	29.5	54.5	11.9	4.0
	> 70 years	36.0	46.4	12.8	4.7
Smoking	**Non-smokers**	8.8	72.5	11.4	7.4
	Ex-smokers	36.4	47.2	11.6	4.7
	Smokers	30.7	52.3	13.4	3.7

5.1.2.2. Stages

Since January 2017, the LC staging system used is the TNM classification, 8th edition [17]. This version accounts for the size and location of the primary tumour, the number and sites of regional lymph nodes containing cancerous cells and the spread of cancer, or metastases, to another part of the body. The results of this classification make it possible to define different stages. Management will be dependent on the stage of the cancer [18].

In France, NSCLC is generally diagnosed at the metastatic stage (stage IV).
According to studies, lung cancer would appear to be diagnosed at the metastatic stage (stage IV) in 40% to 50% of cases and at the locally advanced stage (stage III) in 20% of cases [19]. In the study KBP-2010-CPHG, 9.5% of patients had stage IIIB NSCLC and 58.3% of patients stage IV NSCLC (TNM 7th edition) at the time of diagnosis [12].

5.2. Molecular classification and targeted therapies in lung cancer

Molecular classification in lung cancer is only relevant for cases of NSCLC at a metastatic development or advanced stage as it determines their treatment.

Indeed, 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.
The molecular breakdown of NSCLC is more advanced for adenocarcinomas than for other histological types.
EGFR mutations (activating and/or T790M resistance), KRAS, BRAF, HER2 mutations, as well as ALK and ROS1 gene rearrangements are among the emerging biomarkers for which testing is recommended by the *European Society for Medical Oncology* (ESMO) [5] and which should be conducted systematically for all non-squamous, locally advanced or metastatic bronchial cancers

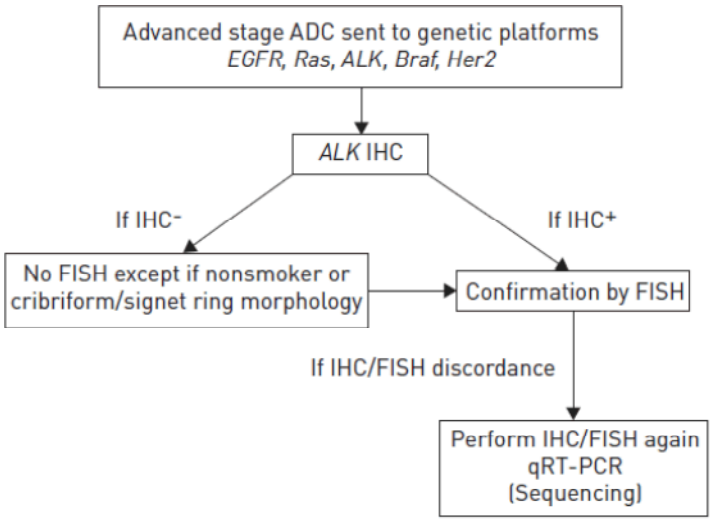
This testing is performed in molecular biological platforms accredited by the French national cancer institute (INCa). These platforms have been set up by INCa and the French Healthcare Directorate (DGOS) since 2006. At the present time, there are 28 platforms. In 2012, the programme for the prospective detection of emerging biomarkers set up by INCa made it possible to conduct 58,400 tests in lung cancer for 20,750 patients [19].

EGFR mutations, detected in 10% of cases of NSCLC are more frequent than ALK gene rearrangement (3 to 5% of NSCLC) or ROS1 gene rearrangement (1 to 2% of cases of NSCLC) [19, 20]. EGFR mutations are detected more frequently in adenocarcinomas, in non-smokers, women and subjects of Asian origin. 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 [4]. For patients with ROS1+ NSCLC, a similar profile to that observed in patients with ALK+ NSCLC is found [21]

5.2.1. ALK gene rearrangement

This rearrangement is due to an inversion on chromosome 2 with fusion of the ALK kinase domain with a partner gene (the most frequent being EML4). This rearrangement induces constitutive activation of ALK kinase which becomes highly oncogenic.
Numerous diagnostic methods can be used to detect ALK gene rearrangement: immunohistochemistry (IHC), RT-PCR (reverse transcription and gene amplification by means of polymerase chain reaction) and FISH (fluorescence *in situ* hybridisation). FISH is the gold standard technique. Recent publications demonstrate the benefit of using IHC as a screening tool and FISH for detecting and confirming ALK gene rearrangement [4, 22, 23].

Figure 1 Testing algorithm proposed by Lantuejoul et al. [23]



The result is positive if more than 15% of the tumour cells exhibit rearrangement.
In 2015, according to INCa data, ALK rearrangement testing was conducted on 22,667 patients, namely a 61% increase in activity since 2012. According to the same data, the ALK gene rearrangement rate was 2.84% [3].

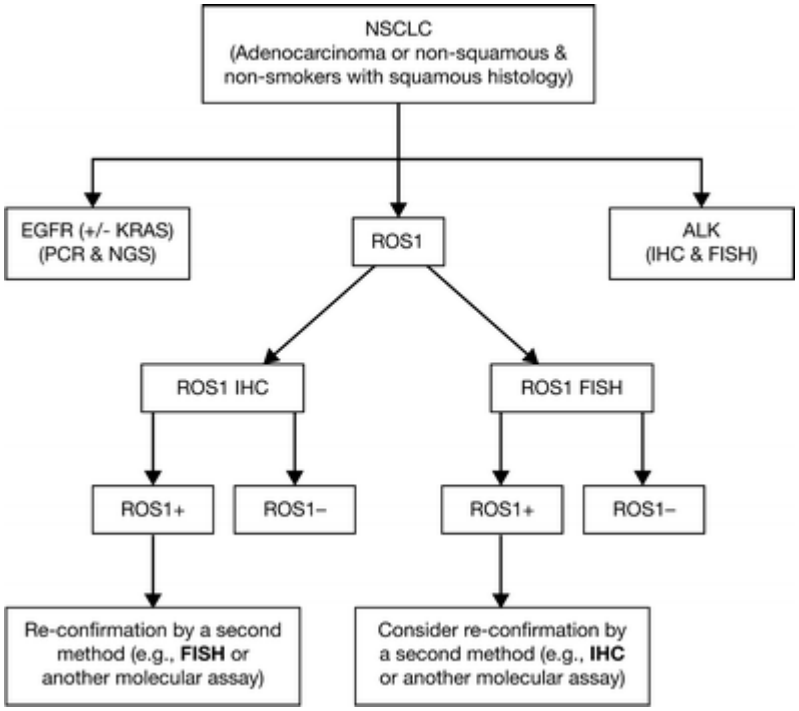
In the study ESCAP-2011-CPHG, reviewing routine lung cancer care practices in France in 2010, it is reported that ALK gene rearrangement testing was only performed on 38 patients out of 3943 patients included in 53 NSCLC centres ([29])

The existence of ALK gene rearrangement is generally mutually exclusive of other known oncogenes in NSCLC, such as EGFR and KRAS mutations.

5.2.2. ROS1 gene rearrangement

This rearrangement is due to an inversion on chromosome 6 with fusion of the ROS1 gene with a partner gene (the most frequent being CD74). This fusion induces constitutive activation of ROS1 kinase which becomes highly oncogenic. Numerous diagnostic methods can be used to detect ROS1 rearrangement: next-generation sequencing (NGS), RT-PCR techniques, immunohistochemistry (IHC) or FISH. FISH is the gold standard technique. Recent publications demonstrate the benefit of using IHC as a screening tool and FISH for detecting and confirming ROS1 gene rearrangement.
This rearrangement appears to be mutually exclusive of other known oncogenes in NSCLC. [23]

Figure 2 Testing algorithm proposed by Bubendorf et al. [24]



5.2.3. Role in therapeutic strategy

The therapeutic management of NSCLC differs according to the stage of the cancer. In the early stages, the gold standard treatment is surgery. However, a large proportion of patients are diagnosed at an advanced stage of the disease [25]. For this patient population, cancer management is based on a systemic medical treatment. Numerous criteria are involved in the therapeutic decision: tumour histology, patient performance status and comorbidities. However, the presence of a genomic mutation will be decisive in directing the therapeutic strategy.

For advanced or metastatic NSCLC, in the absence of EGFR mutation or ALK or ROS1 rearrangement, as a first-line treatment, the gold standard is based on bitherapy combining a third-generation molecule (gemcitabine, docetaxel, paclitaxel, vinorelbine or pemetrexed) with a platinum salt (cisplatin or carboplatin).
In the case of predominantly non-squamous tumours, bevacizumab may also be added to the "platinum salt-based doublet" combination. The second-line treatments available are: pemetrexed, docetaxel, or erlotinib as well as nivolumab (immunotherapy). All of these treatments have no specific action on ALK or ROS1 rearrangements [25].

Crizotinib is the first medicinal product targeting ALK and ROS1 rearrangements.

5.3. Crizotinib

Crizotinib (XALKORI®) is a small selective inhibitory molecule of the ALK and ROS1 tyrosine kinase activity receptors (RTK) as well as their oncogenic variants.
RTK inhibition of crizotinib blocks a cellular signalling pathway required for the growth and survival of tumour cells.
XALKORI® is indicated as a first-line treatment for adult patients with advanced ALK-positive or ROS1-positive NSCLC and in the treatment of adult patients having received at least one prior treatment for advanced ALK-positive NSCLC [9].
Crizotinib treatment should be initiated and monitored by a physician experienced in the use of anti-cancer medicinal products [9].
ALK/ROS1 status testing using a specific, validated technique is required to select patients to be treated with crizotinib. The ALK+ or ROS1 NSCLC diagnosis should be confirmed prior to initiating crizotinib treatment. The screening should be performed by a laboratory with proven expertise in the use of these specific technologies [9].

5.3.1. ALK+ NSCLC treatment

5.3.1.1. First-line treatment

In the Profile 1014 study [6], evaluating patients with ALK+ NSCLC treated with crizotinib as a first-line treatment versus chemotherapy, the median progression-free survival (PFS) was 10.9 months versus 7 months (p<0.001). The probability of survival at 1 year was 84% for crizotinib versus 79%.

Tab.2 presents the therapeutic response in the intention-to-treat population.

Tab.2 Therapeutic response (intention-to-treat population) – Results of Profile 1014 study [6]

		Crizotinib (N=172)	Chemotherapy (N=171)
Response type N (%)	Full	3 (2)	2 (1)
	Partial	125 (73)	75 (44)
	Stable disease	29 (17)	63 (37)
	Progressive disease	8 (5)	21 (12)
	Not suitable for evaluation	7 (4)	10 (6)
Overall response rate % (95% CI)		74 (67-81)	45 (37-53)

Response time (months)	**Median (95% CI)**	1.4 (0.6-9.5)	2.8 (1.2-8.5)
Response duration (months)	**Median (95% CI)**	11.3 (8.1-13.8)	5.3 (4.1-5.8)

Tab. 3: **Response in terms of overall survival and progression-free survival (intention-to-treat population) – Results of Profile 1014 study (30)**

Response criterion	**Crizotinib (N = 172)**	**Chemotherapy (N = 171)**
Progression-free survival (as per IRR)		
Median PFS in months (95% CI)	10.9 (8.3 – 13.9)	7.0 (6.8 – 8.2)
HR (95% CI)	0.45 (0.35-0.60)	
p-value	< 0.0001	
Overall survival (OS) - After 46-month follow-up period in each arm		
Median OS in months (95% CI)	NR (45.8 - NR)	47.5 (32,2 - NR)
HR (95% CI)	0.76 (0.5'_-1.05 »)	
p-value	0.0978	

In this study, the most commonly observed adverse events for crizotinib were as follows: vision disorders (71% versus 9% in the chemotherapy group), diarrhoea (61% versus 13%), swelling (49% versus 12%), vomiting (46% versus 36%). Under chemotherapy, the most commonly observed adverse events were fatigue (38% versus 29%), neutropoenia (30% versus 20%)

5.3.1.2. Second-line treatment

The European Commission approved the conditional MA on 23 October 2012. This approval is based on a phase 3 study evaluating the use of crizotinib versus gold-standard chemotherapy (pemetrexed 500 mg/m² or docetaxel 75 mg/m²) in monotherapy for the treatment of advanced-stage ALK+ NSCLC with or without brain metastases.

Tab.3 presents the results in terms of progression-free survival (PFS), overall survival (OS) and tumour response.

Tab.4 Efficacy results (full analysis set population) – Results of Profile 1007 study [7].

Response criterion	Crizotinib (N = 173)	Chemotherapy (N = 174)
Progression-free survival (as per IRR)		
Number of patients reporting an event, n (%)	100 (58)	127 (73)
Median PFS in months (95% CI)	7.7 (6.0-8.8)	3.0 (2.6-4.3)
HR (95% CI)[a]	0.49 (0.37-0.64)	
p-value	< 0.0001	
Overall survival (OS)[b]		
Number of deaths, n (%)	49 (28%)	47 (27%)
Median OS in months (95% CI)	20.3 (18.1-NR)	22.8 (18.6-NR)
HR (95% CI)	1.02 (0.68-1.544)	
p-value	0.54	
Tumour response (as per IRR)		
Overall response rate, % (95% CI)	65 (58 -72)	20 (14 - 26)
p-value	< 0.0001	
Response duration[c]		
Median[d], months (95% CI)	7.4 (6.1-9.7)	5.6 (3.4-8.3)

HR: *Hazard ratio;* 95% CI: 95% confidence interval; NR: not reached; IRR: independent radiologic review
a The median PFS was 4.2 months (95% CI: 2.8-5.7) with pemetrexed (HR=0.59; p = 0.0004 versus crizotinib) and 2.6 months (95% CI: 1.6-4.0) with docetaxcel (HR= 0.30; p < 0.0001 versus crizotinib).
b Based on the intermediate OS analysis conducted after observing 40% of the total number of events required for the final analysis.
c Based on the Kaplan-Meier method
d The ORR was 29% (95% CI: 21%-39%) with pemetrexed (p<0.0001 versus crizotinib) and 7% (95% CI: 2%-16%) with docetaxel (p<0.0001 versus crizotinib)

Furthermore, crizotinib had a beneficial effect with respect to chemotherapy on symptoms, significantly extending the time to deterioration (median interval of 5.6 months versus 1.4 months) of chest pain, dyspnoea or coughing symptoms reported by patients. The tolerance profile observed was as expected and acceptable. The most commonly observed AEs under crizotinib were vision disorders and diarrhoea (60% each) and nausea (55%).

5.3.2. ROS1+ NSCLC treatment

The use of crizotinib as monotherapy in the treatment of advanced ROS1-positive NSCLC was evaluated in a single-arm, international, multicentre study: the Profile 1001 study [8]
In this study, the overall response rate was 72% with median progression-free survival of 19.2 months.

Tab.4 presents the results obtained in this study.

Tab.5 Results of Profile 1001 study [8]

		Crizotinib (N=50)
Response type N (%)	**Full**	3 (6%)
	Partial	33 (66%)
	Stable disease	9 (18%)
	Progressive disease	3 (6%)
Overall response rate % (95% CI)		72 (58-84)
Response duration (months)	**Median (95% CI)**	17.6 months (14.5-NR)
Progression-free survival	**Median (95% CI)**	19.2 months (14.4-NR)
Overall survival at 12 months % (95% CI)		85 (72-93)

The tolerance profile observed is similar to that observed in the previous studies. The most commonly observed adverse events were as follows: vision disorders (82%), diarrhoea (44%), nausea (40%), swelling (40%). 94% of these events were grade 1 or 2. Of the grade 3 events, the most common were hypophosphataemia (10%), neutropoenia (10%) and alanine aminotransferase elevation (4%).

Moreover, in the retrospective study, EUROS1 [26], conducted on 32 patients treated with crizotinib and suffering from ROS1+ NSCLC, the overall response rate was 80% and the median progression-free survival was 9.1 months versus 57.7% and 7.2 months with pemetrexed (received before or after crizotinib). The disease control was 86.7% with crizotinib.

5.4. Study rationale

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% [1].

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 [12].
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 [12].

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 [4, 23]. 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 [4]. For patients with ROS1+ NSCLC, a similar profile to that observed in patients with ALK+ NSCLC is found [21]

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 [9].
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 French General Hospital Pulmonary Medicine Specialist Association (CPHG).
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 [10]
- 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 [2, 12]
- 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 [unpublished data].

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.

6. RESEARCH OBJECTIVES

6.1. Primary objective

- Describe the characteristics of patients treated with crizotinib (regardless of line of treatment and according to line of treatment).

6.2. Secondary objectives

- Describe the conditions for conducting ALK gene and ROS1 gene rearrangement testing (source of specimen, technique used and time frames).
- Evaluate the impact of the anti-cancer treatment in terms of:
    - clinical response (evaluation by physician)
    - tumour response on imaging according to the physician

- survival, PFS, OS and 12 and 18-month survival probabilities

- Tolerance
- Quality of life (self-administered questionnaire QLQ – LC13).
- Compliance (Morisky self-administered questionnaire)
- Describe crizotinib prescription and discontinuation conditions (scheduled end of treatment, intolerance/toxicity, progression, other)
- Describe the treatment plan after progression (local treatments, systemic treatment, crizotinib maintenance) and the impact of this treatment.

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.

7. RESEARCH METHODS

7.1. 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.

This study does not affect patients' medical care: no supplementary examinations shall be conducted for the study and no treatments shall be administered specifically for this study. Furthermore, the study visits, though regular, are in keeping with the usual frequency of follow-up and treatment evaluation for these patients.

ALK-2016-CPHG includes 2 main phases:

- **Cohort enrolment period and data collection at time of inclusion**

The 1st visit of the 1st patient should take place from January 2017 and the 1st visit of the final patient should be completed in December 2018.

The duration of the inclusion period shall be 24 months.

- **Follow-up period and data collection during follow-up**

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).

7.1.1. Cohort enrolment and data collection at time of inclusion

From November 2016, all physicians known to practise in a hospital pulmonary medicine department shall be invited to take part in the study by email. Physicians accepting to take part shall return the "participating physician" form attached to the invitation email to the study administration centre by 31 December 2017.

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+ or ROS1+ NSCLC initiating (or having initiated in the previous 3 months) treatment with crizotinib, regardless of the line of treatment.

For all patients included, the participating physicians shall complete the page corresponding to the Inclusion visit (Vi).

From the 1st inclusion and until the end-of-inclusion date (December 2018), the participating physicians undertake to conduct exhaustive data collection on all cases of ALK+ or ROS1+ treated with crizotinib.

Cohort enrolment shall take 24 months (January 2017 to December 2018).

7.1.2. Patient follow-up

During the 18-month follow-up period or until the patient's death or early withdrawal from the study for another reason, the physicians undertake to conduct regular exhaustive follow-up data collection for each patient included.

The total follow-up period for a patient shall be not more than **18 months**.

The total duration of the study shall be **42 months**.

Data shall be collected on an e-CRF available on a specific site for the study. The e-CRF shall be completed, at each visit, by the participating physicians and the clinical research associates working with them.

7.2. Context

7.2.1. 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

7.2.2. 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

7.2.3. Study withdrawal

The reasons for study withdrawal should be indicated on a page of the e-CRF provided for this purpose.

The date of the end-of-study visit shall be recorded.

Study withdrawals before the scheduled end of follow-up shall be classified according to the following categories:

- Lost to follow-up (if yes, specify the measures taken to contact the patient)
- Failure to comply with study procedures (if yes, specify the cause: for example, repeated absence from follow-up visits)
- Study withdrawal requested by the patient (if yes, specify the reason cited by the patient)
- Study withdrawal due to adverse event (if, yes, specify type)
- Serious adverse event (if yes, specify type)
- Death (cause and date)
- Other reason (if yes, specify)

7.3. Variables

The e-CRF is the tool for collecting data used to meet the study objectives.
The data shall be collected from inclusion and until the scheduled or unscheduled study withdrawal.

Tab.2 Data collection schedule

Visits	**V 0**	**V 1**	**V2**	**V3**	**V4**	**V5**	**V6**
Month (± 1)		**M 3**	**M 6**	**M 9**	**M 12**	**M 15**	**M1 18**
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						
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						
- Initiation line	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 o Continuation of crizotinib o Initiation of new therapeutics		 X X	 X X	 X X	 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
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						

M: month; V: visit

7.3.1. Data at time of inclusion

The data to be collected at the inclusion visit are as follows:

Any patient included and initiating crizotinib within 4 months shall be deemed to be a minor deviation, despite the 3-month interval initially envisaged in the inclusion criteria.

7.3.1.1. The patient

- Date of birth (month and year, age calculation)
- Gender (male/female)
- Height (cm)
- Weight (kg)
- BMI (kg/m²)
- Smoking habit:
    - Smoking status: non-smoker, ex-smoker, active smoker

NB. An ex-smoker patient is defined as a patient who has not smoked in at least 1 year

  - Consumption for active smoker and ex-smoker:
    - active smoker: year of start of smoking habit
    - ex-smoker: year of start and year of end of smoking habit
    - smoker or ex-smoker: tobacco consumption in pack-years

NB. The number of pack-years is calculated by multiplying the number of packs consumed per day and the number of years that the subject has smoked this quantity of packs

- Performance status (WHO *performance status*: PS0 to PS4)

7.3.1.2. NSCLC

- Date of biopsy resulting in NSCLC diagnosis
- Histological type of NSCLC (anatomopathological classification: adenocarcinoma, squamous, large-cell, or other to be specified)
- Presence and location of metastases (contralateral lung, extrathoracic lymph node, brain, liver, bones, adrenals, or other to be specified).
- Location of primary tumour (right/left upper lobe or right/left lower lobe, right middle lobe).
- Tumour stage at time of diagnosis (TNM, 8th edition: IIIB or IV).

7.3.1.3. ALK/ROS1 gene rearrangement

- ALK/ROS1 gene rearrangement testing
  - Date of dispatch to platform
  - Diagnostic method (histological/cytological)
  - Source of specimen (primary tumour, thoracic lymph node, extrathoracic lymph node, brain, liver, bones, adrenals, or other to be specified)
  - Analytical platform
  - Technique used (FISH, IHC, RT-PCR, NGS, other)
  - Date of receipt of result
  - Interval in days between dispatch and receipt

7.3.1.4. Other biomarkers

- Testing for other biomarkers:
  - yes/no
  - If yes, date of receipt of result

7.3.1.5. Prior therapeutic strategy for advanced NSCLC

- Start date of first strategy
- Treatment type (chemotherapy, radiotherapy (other sites), brain radiation, TKI),
- Cycle start date and end date
- Doses (in Gy if RT) or number of cycles (if CT)

7.3.1.6. Crizotinib

- Initiation date

- Initiation line (1st line; 2nd line; 3rd line or other)
- Dosage at initiation

7.3.1.7. Additional information:

- Preventative treatments of crizotinib treatment side-effects.
- Tolerance: retrospective pharmacovigilance data collection is only performed for patients having initiated crizotinib prior to inclusion (See section 9)

7.3.1.8. Patient questionnaires

- Quality of life: QLQ-LC13 self-administered questionnaire

7.3.2. Data at tumour evaluation visits (M3, M6, M9, M12, M15),

The date of the visit shall be recorded. A 1-month window before or after the initially scheduled follow-up visit is allowed.

7.3.2.1. The patient

- Weight (kg)
- Smoking status (if active smoker): quit (yes/no)
- Performance status (PS0 to PS4)

7.3.2.2. Treatment response evaluation

- Clinical response (opinion of participating physician: improvement, stabilisation, deterioration)
- Tumour response on imaging (full response, partial response, stable disease, progression)
- In case of progression: date, site of progression (on primary tumour, pre-existing metastasis and/or new metastases)
- In case of progression: continuation of crizotinib (yes/no)
- Biopsy on progression: yes/no

7.3.2.3. Crizotinib treatment plan (changes in prescription or repeat)

- Change of dose (yes/no). If the answer is yes, record the date of the change, the new dose prescribed and the reason for the change (intolerance/AE/drug interaction/lack of efficacy, other).

- Temporary discontinuation of crizotinib (yes/no). If the answer is yes, record the date and duration of the discontinuation (or if the discontinuation is ongoing) and reason (intolerance, proven toxicity, adverse event, local treatment).
- Definitive discontinuation of treatment (yes/no): If the answer is yes, the date of discontinuation and reason (progression, intolerance/toxicity, patient choice, lost to follow-up or other to be specified).
- Initiation of new therapy in the event of discontinuation of crizotinib treatment: chemotherapy, new-generation ALK, temporary authorisation for use, immunotherapy, inclusion in clinical trial, palliative care.

7.3.2.4. Additional information

- Preventative treatments prescribed since previous visit
- Local treatment: brain radiotherapy, radiotherapy (other site), other: initiation date, discontinuation date, dose (in Gy)
- Tolerance (see section 9)

7.3.2.5. Patient questionnaires

- Crizotinib treatment compliance rated using Morisky self-administered questionnaire
- Quality of life rated using QLQ-LC13 self-administered questionnaire

7.3.3. Data collected at end-of-follow-up visit (M18)

7.3.3.1. In the case of continuation of crizotinib treatment until the end of the study:

In the case of continuation of crizotinib until the end of the study, the data collected during the end-of-follow-up visit shall be same as those collected during the follow-up visits.

7.3.3.2. In the case of discontinuation of crizotinib prior to the end of the study.

Note: If crizotinib is discontinued during the follow-up period, the patient shall only be seen again at M18.
No further data apart from adverse events shall be collected from the time of discontinuation of crizotinib until the end-of-study visit.

The data collected at the end-of-study visit are:

- Date of visit
- Patient characteristics: smoking status, weight, ECOG performance status
- Post-crizotinib management characteristics
    - CT, next-generation ALKi, clinical study, immunotherapy, temperature authorisation for use, palliative care
    - Name of treatment/initiation and discontinuation date/ongoing treatment

7.3.4. Data collection throughout the study

- Serious or non-serious adverse events deemed to be linked with crizotinib or not by the participating physician.

Adverse event data shall be collected by means of patient interview and examination.

The adverse event reporting date shall be recorded.

For each adverse event reported, the participating physician shall record:

- The date of onset and end date
- The nature of the adverse effect
- The severity (grade 1 or minor, not interfering with the patient's normal activity; grade 2 or moderate, interfering slightly with the patient's normal activity; grade 3 or severe, modifying the patient's normal activity considerably)
- The actions taken due to the event (medication, medical advice, medical advice and medication, hospitalisation, other)
- The effects (see section 10.4.2, definition of SAE).

The participating physician shall also assess the relationship between the event and the product (possible, probable, definite relationship or unrelated).

7.4. Data sources

All adult patients with locally advanced (stage IIIB not suitable for radiotherapy) or metastatic (stage IV) NSCLC with ALK rearrangement or ROS1 gene rearrangement and treated with crizotinib, attending the pulmonary medicine department of one of the hospitals participating in the study, shall be informed verbally and in writing of the study, its objectives and its duration.

Patients volunteering to take part in the study shall give their prior written consent to be included in the study and for the participating physician to complete at least one of the items of the e-CRF.

The physician shall note this consent in the patient's source file (hospital medical record) in accordance with best practices.

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

The questionnaires collected at the different measurement stages are:

- At patient inclusion: inclusion questionnaire completed by the physician; the quality of life questionnaire completed by the patients
- During patient follow-up: follow-up questionnaire completed by the physician; compliance and quality of life questionnaire completed by the patients
- During end-of-follow-up visit: end-of-follow-up questionnaire completed by the physician according to patient status (ongoing crizotinib treatment or not); compliance and/or quality of life questionnaire completed by the patients
- In the event of early withdrawal from study: study withdrawal questionnaire completed by the physician for patients lost to follow-up, in the event of withdrawal of consent or other reason.

7.4.1. Patient data

The social and medical data collected shall be obtained from the patients' medical records at the follow-up visits taking place as normal in the centres as part of the patient's routine care, at an estimated frequency of every 3 months within the scope of the radiological evaluation of the treatment response. The physician shall complete the questionnaire corresponding to the current visit (inclusion – follow-up – end-of-follow-up – study withdrawal).

Patients shall also be required to complete self-administered questionnaires to rate treatment compliance (Morisky self-administered questionnaire) and rate quality of life (QLQ-LC13 self-administered questionnaire) in hard copy format, completed on-site and submitted to the physicians at the end of the corresponding visit.

7.4.1.1. Inclusion visit

Included patients shall be the subject of indirectly nominative medical data collection (patient questionnaires completed by the physician via the e-CRF).

7.4.1.2. Follow-up visit (M3 to M15)

At each follow-up visit, conducted as part of normal care, at an estimated frequency of every 3 months in accordance with care guidelines, the physicians shall complete, via the e-CRF, a follow-up visit for all patients.

7.4.1.3. End-of-follow-up visit (M18)

During the end-of-follow-up visit taking place as part of normal care, the physicians shall complete the data via the e-CRF according to patient status (ongoing crizotinib treatment or not).

7.4.1.4. Study withdrawal questionnaire

A study withdrawal visit shall be completed by the participating physician, for any patient discontinuing the study before the 18 months of follow-up required by the protocol (patient lost to follow-up, deceased, having withdrawn their consent or other).

7.4.1.5. Treatment compliance rating

Treatment compliance shall be evaluated directly with the patients using the Morisky validated standardised questionnaire. 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.

This completed questionnaire shall be submitted by the patient to the participating physician at the end of the visit. Any adverse event identified by the participating physician via these questionnaires, if the patient has answered YES to question 4, should be recorded in the study database and be reported to the Pfizer Pharmacovigilance department according to pharmacovigilance obligations (see section 9)

7.4.1.6. Quality of life rating

Patients' quality of life is dependent on the treatments received and complications encountered. It shall be rated at the inclusion visit, at the follow-up visits and at the end-of-study visit for patients treated with crizotinib by completing the French-language validated standardised questionnaire, QLQ-LC13.

The QLQ-LC13 questionnaire is a questionnaire specifically developed for lung cancer (13 items).

This generic questionnaire for rating quality of life contains 12 questions in which the scale ranges from 1 for "not at all", to 4 for "very much" and a 13th question with 2 options, "yes" or "no", if the patient answers "yes", a supplementary question is used to qualify the degree of agreement (from 1 to 4).

This completed questionnaire shall be submitted by the patient to the participating physician at the end of the visit. Any adverse event identified by the participating physician via this questionnaire should be recorded in the study database and be reported in the e-CRF and shall be reported to the Pfizer Pharmacovigilance department according to pharmacovigilance obligations (see section 9)

7.4.1.7. Non-inclusion register

Patients who are eligible but not included should be entered in a non-inclusion register, collecting at least the following parameters:

- Demographic characteristics (year of birth, gender)
- Reason for non-inclusion**.**

7.5. Study size

The number of participating centres should be close to 70 to be able to enrol at least between 50 and 70 patients with ALK+ or ROS1+ consenting to take part in the study.

Including at least 50 to 70 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).

In 2015, according to INCa data [22], ALK gene rearrangement testing was conducted on 22,667 patients, namely a 61% increase in activity since 2012. According to the same data, the expected rearrangement rate for ALK + patients is 2.84%. In parallel, ROS1 rearrangement testing was conducted on 14,268 patients in 2015. The rearrangement rate observed was 1.3%

Based on CPHG experience, each hospital following up patients with NSCLC should therefore observe one patient with ALK+ NSCLC and one ROS1 patient, for every 100 patients
For this reason, between 50 and 70 hospitals should be enlisted to take part in this study. Therefore, they should make it possible to include at least between 50 and 70 patients with advanced NSCLC.

Due to the enrolment capacity, the inclusion of at least 15 ROS1 + patients is expected.
Due to the mean number of patients followed up annually in hospitals (roughly 70 on average in 2010 according to the study KBP-2010-CPHG), 24 months shall therefore be required for the follow-up of at least 1 patient with ALK+ NSCLC and/or the follow-up of one ROS1+ patient in each participating hospital (between 50 and 70 participating centres).

The consecutive inclusion of patients meeting the eligibility criteria until the end of the inclusion period estimated at 24 months shall ensure the representativeness of the study participants.

7.6. Data management

These data shall be in electronic format for data collected from the physicians during the visits, and in hard copy format for data collected from the patients. All data management operations shall be performed in accordance with Pfizer requirements and with the Standard Operating Procedures of the CRO responsible for data management. The database and a data management manual, used to define and describe all biometrics activities, shall be developed by the CRO and validated by Pfizer.

The participating physician is responsible for recording and reporting all collected data. He/she ensures that they are legible, accurate and complete. He/she must make the source data available at the appropriate time.

The CRF must be signed by the participating physician, validating and checking a box acknowledging his/her obligations. This signature guarantees the authenticity of the data collected. Any corrections made to the e-CRF or source documents must be dated, signed and justified and must not overwrite the initially entered data.

In most cases, the source documents are the individual's file kept at the hospital or at the physician's practice. In these cases, the data recorded in the e-CRF must match those listed in these files.
In some cases, the CRF or part thereof may also serve as a source document.
Electronic data collection and statistical analyses shall be carried out by a contract research organisation (CRO) supervised by Pfizer.

7.6.1. Case report form (CRF)

As used in this protocol, the term CRF (Case Report Form) should be understood as referring to a data record in hard copy or electronic format, or both, depending on the data collection method used in this study.

A CRF is required and must be filled in for each patient included in the study. The duly completed original CRFs are the sole property of Pfizer and must not be made available to any third party in any form, with the exception of authorised Pfizer representatives, or the appropriate regulatory authorities, without Pfizer's written consent. The participating physician must ensure that CRFs are stored securely on the study site in encrypted electronic and/or hard copy format and that they will be password-protected or secured in a locked room to prevent access by unauthorised third parties.

The participating physician has the ultimate accountability for collecting and reporting all clinical, tolerance and biological data entered in CRFs and any other data collection format

(source documents) and for ensuring that they are accurate, authentic, original, attributable, complete, consistent, legible and available (if required).

CRFs must be signed by the participating physician or by an authorised member of staff to guarantee the authenticity of the data entered in the CRF. Any corrections made to the data entered in the CRF or source documents must be dated, initialled and justified (if required) and must not conceal the original data entry.

In most cases, the source documents consist of files held by the hospital or the physician. In these cases, the data collected in the CRF must match these files.

In some cases, the CRF may also serve as a source document. In this case, a document, available on-site and on Pfizer premises, should clearly indicate the data to be recorded in the CRF, for which the CRF will serve as the source document.

7.6.2. Data storage

In order to enable assessments and/or inspections/audits by the regulatory authorities or Pfizer, the investigator accepts to keep files, including the identity of all participating patients (sufficient details to link for example CRFs and hospital files with the files), all signed original informed consent forms, copies of all CRFs, pharmacovigilance report forms, source documents, detailed treatment distribution records and sufficient documentation of relevant correspondence (for example, letters, minutes of meetings and telephone call reports). The files must be stored by the participating physician in accordance with local regulations or as specified by the agreement drafted for the study, whichever period is longer.

The participating physician must ensure that the files continue to be stored securely throughout their storage period.
Should the participating physician no longer be able, for whatever reason, to continue keeping the study files for the required period (e.g.: retirement, move), the participating physician should notify Pfizer accordingly. The study files must be transferred to an appointed individual upon acceptance by Pfizer, such as another participating physician, another institution, or an independent third party appointed by Pfizer.

The participating physician's files must be kept for a period of a minimum period of 15 years after the end (final visit of final patient) or discontinuation of the study, or for longer if required by local regulations**.** The participating physician must obtain Pfizer's written permission before disclosing any record, even if the storage requirements have been met.

7.6.3. CRF circuit

The data collected from the participating physician upon inclusion and during the patient follow-up visits shall be directly entered into the study e-CRF by the participating physician or clinical research associate.

Adverse events shall be collected via the e-CRF, by the physicians, during normal follow-up consultations, for all patients in the study. Where applicable, requests for additional information by the Pfizer pharmacovigilance department shall be sent to the person who declared the event (participating physician). The declarations (initial and follow-up declarations) shall be compiled by centre number and patient number.

Patient questionnaires for rating compliance and patient questionnaires for rating quality of life shall be sent to Pfizer, who shall forward them to the CRO responsible for the input thereof.

7.6.4. Data input

Once the database has been validated by Pfizer, the hard copy questionnaires shall be entered in duplicate using the CRO's software. The latter shall be available for viewing by the physician and the clinical research associate in read-only format on the e-CRF. Periodic input progress reports shall be printed by the CRO and sent to Pfizer.

7.6.5. Database construction

An annotated questionnaire shall be prepared by the CRO in charge of data management. This document shall list the names of the tables and variables. For each variable, the document shall give its type, length and format if applicable. The annotated questionnaire shall be submitted to Pfizer for validation.

The CRO shall then create a database using its own software. The structure of the database shall be documented and checked on printouts, comparing the attributes of the database variables to the specifications listed on the annotated questionnaire.

Before actual data entry, the database structure and input screens shall be tested and validated in accordance with the CRO and Pfizer Standard Operating Procedures. For this purpose, a number of fictitious questionnaires shall be filled in and entered. Validation shall be performed by printing out the data and comparing them to the data on the questionnaires. A validation report shall be drafted and submitted to Pfizer. The final database structure shall be submitted to Pfizer for validation before the actual data can be entered.

An audit file shall be created to save any changes made to the database. The original datum, the modified datum, the modification date and time, along with the person who made the change and the reason for the change shall be recorded in the audit file. Audit file function shall be tested by altering fictitious data. A report shall be drafted and submitted to Pfizer.

7.6.6. Data control

A list of consistency checks used to detect any inconsistencies or aberrant answers in the questionnaires shall be printed by the CRO and validated by Pfizer. These checks shall be

programmed using the CRO's software, then tested on fictitious data. These fictitious data, along with test-related documents, shall be kept in the study binder by the CRO and made available for review by Pfizer.

After input, the checks shall be performed continuously: a query specific to each inconsistency shall be generated electronically by the data control system. In order to limit the number of queries submitted to the participating physicians, a guide to obvious corrections may be prepared by the CRO and validated by Pfizer.

The CRO shall provide the data control documents on simple request by Pfizer. Periodic control progress reports shall be printed by the CRO and sent to Pfizer.

7.6.7. Data access

The databases and the servers on which they are stored shall be located in locked premises. Only personnel specifically assigned to the study shall have access to the databases**.**

7.6.8. Database freeze

The database shall only be frozen once the CRO has finished input, data control and possible coding. The database shall be frozen in accordance with Pfizer's CT-24 procedure. After validation by Pfizer, the database shall be frozen by the CRO and made ready for statistical analysis.

7.6.9. Data management report

A data management report shall be produced by the CRO and transmitted to Pfizer after freezing the database.

7.7. Data analysis

The statistical analyses shall be conducted by a CRO under Pfizer's responsibility.

The detailed methodology of the statistical analyses of the data collection within the scope of this study shall be documented in a statistical analysis plan (SAP), which shall be dated, recorded and administered by Pfizer. The SAP may modify the plans described in the protocol; any major changes to the definitions of the primary evaluation criterion or their analyses shall be reflected in an amendment to the protocol**.**

7.7.1. Statistical Method

During this observational study, no statistical hypothesis shall be tested for the primary objective or for the secondary objectives.

A descriptive analysis of all of the evaluation criteria shall be conducted on the total population and according to the lines of treatment.

Adverse events shall be presented according to their frequency according to their type, their relationship with the treatment, their severity and their duration.

The data collected shall be described**:**

- Mean, standard deviation (SD), median, quartiles for quantitative variables
- Population size and percentage for qualitative variables.

Survival is defined as the interval between the date of histological or cytological diagnosis of the primary LC and the date of death.

Progression-free survival is defined as the interval between the treatment initiation date and radiological progression.

The 12- and 18-month survival and progression-free survival rates shall be calculated using the Kaplan-Meier method and presented with their 95% confidence interval (95% CI).

Supplementary analyses may be conducted at the request of the scientific committee. A new statistical analysis plan shall then be prepared by the CRO and validated by Pfizer.

The study population shall include all patients with a questionnaire returned on time. Missing data shall not be replaced.

7.7.2. Representativeness of participating centres

The sample of centres shall be described retrospectively. At that time, it shall be checked that the centres are distributed throughout French territory.

It shall then be checked that the sample of participating physicians is representative of oncologists/pulmonary medicine specialists in France in terms of centre size and type, in order to guarantee external study validity.

7.8. Quality control

7.8.1. Participating centre set-up

The eligible physicians shall be invited to take part in the study. This participation shall be embodied through the signing of the financial agreement. Upon validation of this agreement, an on-site or telephone set-up visit shall be organised by the ALK-2016-CPHG project team to present the study and all relevant documents to the participating physician and to appointed members of his/her staff, if applicable.

7.8.2. Participating centre logistics and monitoring

Throughout the study, the participating physicians shall be contacted to ensure comprehension and compliance of the protocol and electronic questionnaire. All contacts shall be documented.

An inspection visit shall take place on-site for 5 to 10 centres selected at random. A quality control report shall be drafted and presented to the scientific committee for review and advice on any corrective actions to be undertaken. On the decision of the scientific committee, a further on-site quality control campaign may be conducted.

Key indicators of satisfactory progress of the study (number of active centres, number of patients included, number of follow-ups conducted, etc.) shall be generated from the study database. This database shall be used to issue study progress reports used to manage centre reminders.

7.8.3. Data quality and accuracy

The participating physician shall be responsible for collecting and reporting all clinical, safety and laboratory data entered in the e-CRF and/or other data collection formats (source documents) and should ensure that they are accurate, authentic, attributable to the patient, complete, consistent, legible, up-to-date and available if required.

In order to enable inspections and/or audits by the regulatory authorities or Pfizer, the participating physician accepts to keep registers, including the identity of all participating patients (sufficient details to link files (e.g. e-CRF and hospital medical files). The participating physician shall keep all the original informed consent forms, the copies of adverse event reports, the source documents and medical results leading to therapeutic decisions.

7.9. Limitations of research methods

This protocol has been constructed so as to meet the objectives defined for this observational study optimally. However, it involves some limitations which must be discussed and should be taken into account when setting up the study and processing the results.

7.10. Other aspects

7.10.1. Physician and patient enrolment

Participating physician enrolment is conducted on a voluntary basis. This choice shall help ensure national distribution of inclusions and data homogeneity.

The list of potential participating centres consists of the hospital pulmonary medicine departments in which at least one pulmonary medicine specialist is a member of CPHG.

All physicians practising in the pulmonary medicine departments of these hospitals shall be invited to take part in the study via an email from the study sponsor, Pfizer. A feasibility questionnaire to be completed by the physicians accepting to take part in the study, a summary of the protocol, a blank sample copy of the questionnaire shall be attached to this email and letter.

The physicians accepting to take part in the study shall return the completed participation form to the study administration centre by the end of August 2016.

The participating physician enrolment period initially envisaged in the protocol is 18 months from November 2016 to December 2017. However, all physicians contacting Pfizer to take part in the study shall be included in the list of investigators. All patients seen by the participating physicians and meeting the inclusion criteria and not presenting non-inclusion criteria shall receive a suggestion to take part in the study. The study shall be presented to them verbally and by means of an informed consent form.

Only informed patients who have given their written consent to take part in the study shall be included. The participating physicians shall record the patient's participation in this observational study in his/her file.

The patient enrolment period is 24 months.

So as to obtain exhaustive data on the population of interest, patients meeting the inclusion criteria and not presenting non-inclusion criteria but not wishing to take part in the study shall be reported in the non-inclusion register.

7.10.2. Data collection

After the signature of the contract and the set-up visit, the physicians participating in the study shall receive the link with their access codes to the e-CRF.

These codes are personal, each person participating in the centre shall receive their own ID and code.

The participating physicians shall complete the questionnaire for each patient included at regular (generally quarterly) scheduled consultations when these consultations coincide with the study visits. An interval of one month before and after the theoretical date shall be tolerated for the follow-up visits to be entered in the e-CRF.

Should the patient withdraw from the study during the follow-up period, the physician shall complete the end-of-study questionnaire and shall give the reason for the study withdrawal (Section 7.2.3).

Should a patient fail to attend one of the study visits, the physician shall do his/her utmost to contact the patient in order to collect the minimum data required to complete the end-of-study form of the questionnaire.

All the questions must be completed by the participating physicians.

The participating physicians undertake to collect exhaustive data for each patient.

7.10.3. Archival

The participating physicians shall keep the questionnaires for up to 15 years after the final visit of the final patient (theoretically June 2020)

The study administration centre shall keep any documentation linked with the study (including questionnaires received by fax and responses of the participating physicians) for up to 15 years after the final visit of the final patient (June 2020).

All documents shall then be returned to the study sponsor**.**

8. PATIENT PROTECTION

8.1. Patient information letter

All parties shall comply with the legislation in force, particularly laws relating to the implementation of organisation and technical measures aimed at protecting patients' personal data. These measures shall include the omission of patients' names or other data that may be used to identify them directly in all reports, publications and any other disclosures, with the exception of requirements stipulated by the legislation in force.

Personal data shall be stored at the study centre in encrypted electronic or hard copy format and shall be password-protected or secured in a locked room so as to ensure access solely by authorised study personnel. The study centre shall implement suitable technical and organisational measures to ensure that personal data can be retrieved in the event of an incident. In the event of a potential personal data breach, the study centre shall be accountable for determining whether this breach actually occurred and, if so, making the legally required reports.

With a view to protecting the rights and freedoms of individuals as regards personal data processing, where the study data are compiled for the purposes of transfer to Pfizer and to other authorised parties, the patients' names shall be removed and replaced by a unique specific numerical code, based on a numbering system defined by Pfizer. All other data that may be used to identify patients to be transferred to Pfizer or to other authorised parties shall be identified with this unique code specific to each patient. The investigator's centre shall keep a confidential list of patients having taken part in the study, with the link between the numerical codes of each patient and the actual identity of each individual. In the event of data transfer, Pfizer shall retain high confidentiality and personal data protection standards in respect of patients, pursuant to the study agreement and the data protection legislation in force.

All parties shall comply with all applicable legislation, including legislation relating to the implementation of organisation and technical measures aimed at protecting patients' personal data. Such measures shall include the omission of patients' names and other directly identifiable data in reports, publications or other disclosures, unless required by the applicable legislation.

Personal data shall be stored at the study centre in encrypted electronic or hard copy format and shall be password-protected or secured in a locked room so as to ensure access solely by authorised study personnel. The study centre shall implement suitable technical and organisational measures to ensure that personal data can be retrieved in the event of a disaster. In the event of a potential personal data breach, the study centre shall be accountable for determining whether a personal data breach actually occurred and, if so, submitting the legally required reports in respect of the breach.
So as to protect the rights and freedoms of individuals as regards personal data processing, where the study data are compiled for the purposes of transfer to Pfizer and to other authorised parties, the patients' names shall be deleted and replaced by a unique specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or to other authorised parties shall be identified with this unique, patient-specific, code. The investigator's centre shall keep a confidential list of patients who have taken part in the study, linking each patient's numerical code to his/her actual identity. In the event of data transfer, Pfizer shall uphold high confidentiality and personal data protection standards in respect of patients, as per the Study Contract and applicable confidentiality legislation.

8.2. Patient consent form

Informed consent forms and all materials intended for patient enrolment must comply with local regulatory and legislative requirements, particularly the data protection legislation in force.

The informed consent forms used during the informed consent process and all materials used for patient enrolment must be reviewed and approved by Pfizer, approved by the committee for the protection of persons (CPP)/independent ethics committee (IEC) prior to use, and must be available for inspection.

The investigator must ensure that all patients in the study [or their legal representative or their parent(s)/legal guardian in the case of a minor] are fully informed of the nature and aims of the study, the communication of the data associated with the study and any risks associated with their participation, particularly the risks associated with the processing of the patients' personal data. The investigator must also ensure that all patients in the study, or their legal representative, are fully informed of their rights to access and rectify their personal data, and to withdraw their consent to the processing of their personal data.

Where consent is obtained from the patient's legal representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient is capable of giving such assent, as per the terms determined by the CPP/IEC. Should the investigator deem a patient's decision-making capacity to be too limited for him/her to be consulted notably,

then, if authorised by the CPP/IEC and pursuant to local regulatory and legislative requirements, an exemption from patient assent may be granted, stating in the source documentation the reason for which it was not possible to obtain assent. In the event of the patient not giving his/her own consent, the source documents must state why the patient has not given consent (e.g. minor, adult with impaired decision-making capacity), how the investigator determined that the person signing the consent form was the patient's legal representative, the relationship between the signatory of the consent form and the patient participating in the study (e.g. parent, spouse), and whether the patient's assent was obtained or an exemption was granted. If verbal assent is obtained, it must be documented in the source documents.

The investigator, or a person appointed by the investigator, shall obtain the written informed consent of the patients or the patient's legal representative, and the patient's assent if applicable, prior to any study-specific activity being carried out. The investigator shall retain the original of each patient's informed consent form.

8.3. Early withdrawal of patient

Patients may withdraw early from the study at any time at their request, or they may be excluded at any time at the participating physician's or sponsor's discretion due to safety, behavioural concerns or administrative problems. In any case, all necessary measures should be taken to document the patient's progression, if possible. The participating physician must make enquiries about the reason for the early withdrawal and patient follow-up in relation to any unresolved adverse events.

Should the patient withdraw from the study early, also withdrawing his/her consent to the disclosure of future information, no further evaluations should be conducted and no additional data should be collected. The sponsor may keep and continue to use any data collected prior to said withdrawal of informed consent.

8.4. Regulatory aspects

8.4.1. French public health regulation act "2004-806 of 9 August 2004"

This study is an observational study in no way affecting the normal medical care of the subjects included in the study, involving no physical or psychological harm and not requiring specific follow-up visits for the subjects enrolled in the study. All procedures are performed and products used in the usual manner, without any additional or unusual diagnostic or monitoring procedure.

Under these conditions, this study does not fall within the scope of programme act No. 2006-450 of 18 April 2006 for research or of act No. 2004-806 of 9 August 2004 article 88 chapter II article L1121-1 and the project is therefore not required to be submitted to the French

Medicinal Product and Healthcare Product Safety Agency (ANSM), or to a Committee for the Protection of Persons (CPP). However, the protocol shall be submitted to a CPP in order to validate the non-interventional nature of the study.

Order No. 2016-800 dated 16 June 2016 on research involving humans states in article 8 that regularly declared or authorised research on the date of entry into force of the application decree (application decree of the so-called Jardé Act No. 2016-1537 dated 16 November 2016) is to continue for five years pursuant to the initially applicable legislation.

At the end of this 5-year period, they will be subject to a further review by a Committee for the Protection of Persons and, if applicable, by the French National Medicinal Product and Healthcare Product Safety Agency as per the terms of French public health regulations.

8.4.2. French national medical association

The participating physicians and the scientific committee experts shall receive remuneration for their participation in this study. The study protocol and the financial agreements shall be submitted to the French national medical association, section H (article L4113-6 of French Public Health Regulations and articles R4113-104 and R4113-105).

Each participating physician and scientific expert should forward a copy of his/her contract to the association's departmental committee (articles L4113-9, L4113-10 and L4163-10 of French Public Health Regulations).

8.4.3. Data Protection: French National Data Protection Commission "CNIL"

In accordance with act 78-17 of 6 January 1978 on data protection, amended by act 2004-801 of 6 August 2004 on the protection of individuals with regard to the processing of personal data, this protocol shall, where applicable, be submitted to the Healthcare research data processing advisory board (CCTIRS) for approval. However, as the Healthcare Research Data Processing Advisory Board (CCTIRS) was abolished on 5 May 2017, the date of the decree creating the Expert Committee for Health Research, Studies and Evaluations (CEREES) pursuant to the French healthcare system modernisation act No. 2016-41 dated 26 January 2016, and the application decree of the so-called Jardé Act No. 2016-1537 dated 16 November 2016, it is no longer within the jurisdiction of the departments of the ministry of research to review amendments made to research projects.

Given that the study ALK-2016-CPHG falls within the scope of MR003, Pfizer's compliance commitment allows us to commence without the review by the French national data protection commission "CNIL".

8.5. Observational research protocol review committee (CEPRO)

The sponsor should submit the study protocol, amendments to the protocol, as well as the informed consent forms and other relevant documents to the CEPRO for review. (For example: advertisements for enrolment)

The CEPRO shall rule on whether the study is indeed observational or not and the favourable pronouncement obtained is equivalent to the review by an independent institution (institutional review board) when submitting an article for publication.

8.6. Ethical conduct of the study

The study shall be conducted in compliance with legal and judicial obligations, as well as the objective, scientific value and rigour and in keeping with the generally accepted research practices described in the Good Pharmaco-epidemiological Practice (GPP) guidelines published by the *International Society for Pharmacoepidemiology* (ISPE), the Good Epidemiological Practice (GEP) guidelines published by the *International Epidemiological Association* (IEA), the Good Practices for Outcomes Research published by the *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR), the International Ethical Guidelines for Epidemiological Studies published by the *Council for International Organizations of Medical Sciences* (CIOMS), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) of the European Medicines Agency (EMA), the FDA guidance for methodological standards in pharmacoepidemiology and guidance for industry: Good Pharmacovigilance and Pharmcoepidemiological Assessment Practices (*Good Pharmacovigilance and Pharmacoepidemiologic Assessment*), *Food and Drug Administration* (FDA) guidance for industry and FDA personnel: Best practices for conducting and reporting pharmacoepidemiological safety studies using electronic healthcare data sets, guidance for industry: Patient reported outcome measures: Use in medical product development to support labelling claims and/or equivalent.

9. ADVERSE EVENT MANAGEMENT AND REPORTING

9.1. Pharmacovigilance obligations

The table below summarises the requirements for recording adverse events in the electronic case report form and for declaring adverse events via the Non-interventional study adverse event report form (NIS AEM Report Form) to the Pfizer pharmacovigilance department. These requirements are defined for three types of events:

(1) serious adverse events (SAE)
(2) non-serious adverse events (AE) (if applicable) and

(3) situations involving exposure to a medicinal product, including exposure during pregnancy or breastfeeding, medication errors, overdosage, misuse, extravasation, or occupational exposure. These events are defined in the section "Definition of an adverse event".

	Recorded in the study electronic CRF	**Declared by the NIS AEM Report Form to the Pfizer Pharmacovigilance department within 24 h of being made aware of the event**
SAE	All	All
Non-serious AE	All	**Potential risks (applicable XALKORI RMP)** These risks are identified important risks. Important potential risks are: • -Toxicity for reproduction • -Photosensitivity • -Malignant melanoma **Missing important information (applicable XALKORI RMP)** • Pregnancy and Breastfeeding • Risk in paediatric patients • Risk in patients suffering from severe liver failure • Medicinal product interactions with strong inhibitors of CYP3A4, strong inducers of CYP3A4, substrates of CYP3A4 with restricted therapeutic indexes and P-glycoprotein substrates • - Risks in patients having long-term treatment

	Recorded in the study electronic CRF	**Declared by the NIS AEM Report Form to the Pfizer Pharmacovigilance department within 24 h of being made aware of the event**
Situations involving exposure to a study medicine, including exposure during pregnancy or breastfeeding, medication errors, overdosage, misuse, extravasation, lack of efficacy, or occupational exposure	All (independently of the presence of an associated AE), **except for occupational exposure**	All (independently of the presence of an associated AE)

For each AE, the participating physician must identify and gather sufficient information both to determine the outcome of the adverse event and to ascertain whether it meets the criteria for classification as an SAE (see the "serious adverse events" section below).

Adverse events must be reported to Pfizer within 24 hours of the participating physician being made aware of them, whether the participating physician considers that the event is linked to the study medicine or not**.**

In particular, if the serious adverse event is fatal or life-threatening, Pfizer must be immediately notified, whatever the information available concerning the adverse event. This time frame also applies to any new (follow-up) information concerning previously notified adverse events. In rare situations where the participating physician is not immediately informed of the occurrence of an adverse event, the participating physician must declare the event within 24 hours of being made aware and must specify the moment at which he/she was first made aware of this adverse event.

For adverse events considered to be serious or identified in the right-hand column of the above table, that must be declared to Pfizer within 24 hours of being made aware, the participating physician must seek and provide Pfizer with all additional information within this 24-hour time frame. Moreover, Pfizer may ask a participating physician to urgently obtain specific additional follow-up information. This information may be more detailed than that entered into the study case report form. In general terms, this information shall include a sufficiently detailed description of the adverse event to enable a complete medical evaluation of the case, along with the independent determination of a possible causality. All relevant information concerning the event, such as concomitant treatments or diseases, must

be provided. In the event of the patient's death, a summary of the available autopsy results must be sent as soon as possible to Pfizer, or to its accredited representative.

9.2. Notification period

For each patient, the adverse event notification period starts from the moment that the patient receives his/her first dose of study medicine, or from the date on which the patient provides his/her informed consent, if he/she has already been exposed to the study medicine, and ends at the end of the study observation period, i.e. at least at the end of a period of 28 calendar days after the last administration of the study medicine; a declaration must be sent to the Pfizer Pharmacovigilance department, or to its accredited representative, for all types of adverse events listed in the table above and occurring during this period. If the patient receives the study medicine on the last day of the observation period, the notification period is extended by a further 28 calendar days after the end of the observation period.

In cases where the patient gives his/her consent but is not included in the study (e.g.: the patient changes his/her mind concerning his/her participation; screening test failure), the notification period ends on the date of the decision not to include the patient.

If the participating physician is made aware of a serious adverse event occurring at any time after the end of the observation period that he/she considers may be linked to the study medicine, this serious adverse event must also be declared to the Pfizer Pharmacovigilance department.

9.3. Evaluation of causality

The participating physician must assess and report the causal relationship. For all adverse events, sufficient information must be obtained by the participating physician to determine the causality of each adverse event. The participating physician must monitor those AEs considered to be related to a study medicine until the resolution or stabilisation of the event and/or its sequelae, at a level deemed acceptable by the participating physician, and Pfizer must agree with this evaluation.

The evaluation of causality by the participating physician is the determination of the fact that there is a reasonable possibility that a study medicine caused or contributed to the adverse event. If the final determination of causality is "unknown" and if the participating physician is unable to determine whether the study medicine caused the event, then the event must be reported within 24 hours.

If the participating physician is unable to determine the aetiology of the event, but has determined that the study medicine is not the cause of the event, this fact must be clearly stated in the case report form and on the non-interventional study adverse event report form.

9.4. Definition of an adverse event

9.4.1. Adverse events

An adverse event is an adverse manifestation occurring in a patient to whom a medicinal product has been administered. The event does not need to present a causal relationship with the treatment or use. Some examples of adverse events include, though this list is in no way restrictive:

a. Abnormal test results (see below for circumstances under which an abnormal test result constitutes an AE);
b. Clinically significant symptoms and signs;
c. Alteration of clinical examination results;
d. Hypersensitivity; lack of efficacy; drug abuse;
e. Drug dependence.

Moreover, for medicines, they may include signs or symptoms resulting from:

a. Overdosage;
b. Withdrawal;
c. Misuse;
d. Off-MA (Marketing Authorisation) use;
e. Drug interactions;
f. Extravasation;
g. Exposure during pregnancy;
h. Exposure during breastfeeding;
i. Medication error;
j. Occupational exposure.

Abnormal test results

The criteria used to determine whether an abnormal result for an objective test should be reported as an adverse event are as follows:

- The test result is associated with symptoms and/or
- The test result requires additional diagnostic investigations, or a medical/surgical procedure and/or
- The test result leads to a dosage change or withdrawal from the study, to the administration of a significant additional concomitant treatment, to another treatment and/or

- The test result is considered as an adverse event by the participating physician or sponsor.

Simply repeating an abnormal test, failing any of the above-mentioned conditions, does not constitute an adverse event. An abnormal test result arising from an error does not need to be reported as an adverse event**.**

9.4.2. Serious adverse events

A serious adverse event is defined as an adverse manifestation in a patient receiving a medicinal product or nutritional product, at any dose, or using a medical device, and:

- Causing the patient's death;
- Creating a life-threatening situation;
- Requiring the patient's hospitalisation or extension of hospitalisation (see below for circumstances under which this does not constitute an adverse event);
- Causing permanent or major invalidity or disability (significant impairment in the ability to perform tasks of everyday life);
- Leads to a congenital anomaly or malformation.

The progression of the malignant disease during the study (including signs and symptoms of progression) must not be reported as a serious adverse event, except if the outcome is death during the study, or during the adverse event notification period. Hospitalisation due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignant disease causes the patient's death during the adverse event notification period, then the event leading to death must be recorded as an adverse event, and as a grade 5 serious adverse event.

An event shall be defined as a medically significant event based on a medical and scientific judgement. A medically significant event may not be immediately life-threatening and/or lead to death or hospitalisation. If, however, it is established that the event could represent a danger to the patient and/or require a procedure to avoid any of the aforementioned outcomes, the medically significant event must be reported as serious.

For example, this category of medically significant events includes allergic bronchospasm requiring intensive care at the A&E department or at home, blood crasis disorders, convulsions not leading to hospitalisation, or the development of drug dependence or drug abuse.

Moreover, any suspected transmission of an infectious agent, whether pathogenic or not, by a Pfizer product, is considered to be a serious adverse event. Suspicion of this event may be induced by clinical symptoms or examination results indicating infection in a patient

exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered to be synonymous.

These cases are considered to be unexpected and must be managed as serious cases by the Pfizer Pharmacovigilance department. These cases may also where applicable be reported as product defects.

Hospitalisation

Hospitalisation is defined as any initial admission (even for periods of less than 24 hours) to a healthcare establishment, or any extension of admission.

Admission also includes transfer, within the hospital, to an intensive care unit (e.g.: from the psychiatric unit to a medical unit, from the medical unit to a coronary care unit, or from the neurology unit to a tuberculosis treatment unit).

An A&E consultation does not necessarily constitute a hospitalisation; an event leading to an A&E consultation, however, must be considered as medically significant.

Hospitalisation in the absence of adverse event does not constitute an adverse event in and of itself and requires no declaration. For example, the following reasons for hospitalisation, without AE, do not need to be declared:

- Social admission (e.g.: the patient has nowhere to sleep)
- Administrative admission (e.g.: for an annual examination)
- Optional admission not associated with a triggering AE (e.g.: for a scheduled plastic surgery procedure)
- Hospitalisation for observation, with no associated AE
- Admission for the treatment of a re-existing ailment unrelated to the development of a new AE, or to aggravation of the pre-existing ailment (e.g.: for an examination following on from persistent biological anomalies pre-dating the treatment)
- Admission scheduled by the protocol during the clinical study (e.g.: for a procedure required by the study protocol).

9.5. Situations requiring declaration to the Pfizer Pharmacovigilance department within 24 hours.

Situations involving exposure during pregnancy or breastfeeding, medication error, overdosage, misuse, extravasation, lack of efficacy or occupational exposure, are described below.

Exposure during pregnancy (or exposure *in utero*)

Exposure during pregnancy occurs if:

1. A woman becomes pregnant or is found to be pregnant while receiving or exposed to a study medicine (e.g.: environmental exposure), or the woman becomes pregnant or is found to be pregnant after having discontinued and/or having been exposed to a study medicine (maternal exposure);
   An example of environmental exposure would be a case involving direct contact with a Pfizer product by a pregnant woman (e.g.: a nurse reports that she is pregnant and has been exposed to chemotherapeutic agents).
2. A man has been exposed, in the context of a treatment or of environmental exposure, to a study medicine before or during the conception period and/or he was exposed during his partner's pregnancy (paternal exposure).

As a general rule, cases of prospective and retrospective exposure during pregnancy, whatever the source, should be declared according to the serious adverse events declaration procedure, whether an associated adverse event is observed or not.

If a female patient enrolled in the study, or the partner of a male patient in the study becomes pregnant or is found to be pregnant during the patient's treatment with the study medicine, the participating physician must declare this information to Pfizer, whether an adverse event is observed or not, by filling the non-interventional study adverse event report form, along with the supplemental "Exposure during pregnancy" form.

Moreover, the information concerning the environmental exposure to the study medicine by a pregnant woman (e.g.: a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or by accidental spillage) must be declared to Pfizer, whether an adverse event is observed or not, by filling the non-interventional study adverse event report form, along with the supplemental "Exposure during pregnancy" form.

The information submitted must include the expected date of birth (see below for information concerning the date of birth).

A follow-up must be implemented to obtain general information concerning the pregnancy.

Moreover, a follow-up must be implemented to obtain information concerning the outcome of the pregnancy for all cases giving rise to a notification of exposure during pregnancy whose outcome is unknown.

A pregnancy must be monitored to its term, or to its termination (e.g.: elective abortion) and Pfizer must be informed of the outcome.

This information shall be provided as a follow-up to initial exposure during pregnancy report. In the case of a birth, the neonate's structural integrity can be ascertained at birth.

In the event of termination of pregnancy, the reason must be specified and, if possible, the structural integrity of the foetus should be evaluated by visual inspection (unless the results of the tests conducted before the procedure suggested a congenital abnormality and that these results were declared).

If the outcome of the pregnancy meets the criteria for an SAE (e.g.: ectopic pregnancy, spontaneous abortion, foetal death *in utero*, neonatal death, or congenital anomaly [for a living baby, an aborted foetus, foetal death *in utero*, or neonatal death]), the SAE declaration procedures must be observed.

Additional information concerning the outcomes of pregnancies declared as SAEs are as follows:

- Spontaneous abortion, including miscarriage and foetal retention;
- Neonatal deaths occurring within one month of birth must be declared as SAEs, regardless of the cause of death. Moreover, the death of an infant under the age of 1 month must be declared as an SAE when the participating physician considers that the infant's death is connected, or potentially connected, to exposure to the study medicine.

Additional information concerning exposure during pregnancy may be requested. Follow-ups of outcomes after birth shall be dealt with on a case-by-case basis (e.g.: follow-up of premature babies to identify any developmental retardation).

In the case of paternal exposure, a form for communicating information for pregnant partners shall be issued to the study participant for his partner. The issuing of this document to the study participant for transmission to his partner must be documented.

Exposure during breastfeeding

Exposure situations during breastfeeding must be reported, irrespective of whether an associated AE is observed.

Exposure during breastfeeding does not need to be notified when a Pfizer product specifically indicated for use in breastfeeding women (e.g.: vitamins) is administered in accordance with the MA.

However, if the infant presents with an AE associated with the administration of such a medicinal product, the AE must be declared along with the exposure during breastfeeding.

Medication error

The term medication error refers to any unintentional error in the prescription, dispensing or administration of a medicinal product, that could cause or result in inappropriate use of a medicinal product or in harm to the patient, while under the supervision of the healthcare professional, the patient or the consumer. These events may be linked to professional practice, products, procedures and systems, in particular: prescription; transmission of an order; product information, packaging and nomenclature; composition; delivery; distribution; administration; product training; surveillance and use.

Medication errors include**:**

a. Near misses, whether directly involving a patient or not (e.g.: inadvertent/erroneous administration, which is the accidental use of a non-indicated product, or prescription by a healthcare professional or patient/consumer);
b. Confusion concerning the product name (e.g.: trade name, brand name).

The participating physician must declare the following medication errors to Pfizer, irrespective of whether an associated AE/SAE is observed:

a. Medication errors involving patient exposure to the product, irrespective of whether the medication error is accompanied by an adverse event or not.
b. Medication errors not directly involving a patient (e.g.: potential medication errors or near misses). When a medication error does not involve patient exposure to the product, the following minimum criteria constitute a case of medication error:
    - Identifiable notifier;
    - Suspicious product;
    - Medication error.

Overdosage, Misuse, Extravasation

Cases of overdosage, misuse and extravasation associated with the use of a Pfizer product must be declared to Pfizer by the participating physician, irrespective of whether or not an associated AE/SAE is observed.

Lack of efficacy

Cases of lack of efficacy of a Pfizer product must be declared to Pfizer by the participating physician, irrespective of whether or not an associated AE/SAE is observed, whatever the indication of the Pfizer product.

Occupational exposure

Cases of occupational exposure to a Pfizer product must be declared to Pfizer by the participating physician, irrespective of whether or not an associated AE/SAE is observed.

9.6. Single reference safety document

The reference document to be used during this study is the current version of the Summary of Product Characteristics (SPC) of crizotinib in France.

This single reference safety document must be used by the participating physician for prescription information and guidelines.

10. STUDY RESULT COMMUNICATION PLANS

Pfizer and the scientific committee undertake to forward the study results to all physicians participating in the study.

The list of participating physicians shall be systematically associated with all publications.

At least one communication and one publication are envisaged at the end of the study

10.1. Confidentiality

Appropriate care must be taken when collecting all data concerning the study participants, to ensure the confidentiality of these data, in accordance with the applicable data protection acts and regulations (French act 78-17 of 6 January 1978, amended by act 2004-801 of 6 August 2004).

The patients' identities shall remain strictly confidential in all presentations of study results, meetings or publications, and all data shall be anonymised.

10.2. Data property

Pfizer shall remain the owner of all case report forms, data analyses and reports resulting from this study.

10.3. Communication and publication

Any information obtained from this study shall be considered as confidential, until the analysis and final review, by Pfizer and the members of the scientific committee, have been completed.

The study results may be printed or presented by the members of the scientific committee after revision and agreement by Pfizer, and in such a manner that any confidential or industrial property data are not revealed. Prior to publication or presentation, a copy of the final text must be sent by the members of the scientific committee to Pfizer for comments. Such comments shall be intended to check the scientific content of the proposed publications and/or presentations and to ensure that the data and materials relating to Pfizer's products and activities are fairly, accurately and reasonably presented.

10.4. Communication of problems

In the event of a ban or restriction imposed (for example, suspension of the study) by a competent authority in any region worldwide, or if the participating physician is made aware of new information that could influence the evaluation of the benefits or risks of a Pfizer product, Pfizer must be informed immediately.

Moreover, the participating physician shall notify Pfizer immediately of any urgent safety measures taken by the participating physician to protect the study participants against any immediate danger and of any serious breaches of this non-interventional study protocol of which the participating physician has been made aware.

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31. LIST OF TABLES

12. LIST OF FIGURES

APPENDIX 1. PATIENT INFORMATION LETTER AND CONSENT FORM

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

Dear Patient,

Thank for taking the time to consider taking part in this study. This consent form may help you in making your decision by explaining **the procedure for this non-interventional study**, also referred to as an observational study.

Your participation in this study is **completely voluntary (it is your choice)**. Take the time needed to make your decision. You may also choose to take part in the study now, and then change your mind at any time.

We encourage you **to discuss your participation in this study with your family, the caregiving team, your doctor or any other healthcare professional or the study team,** in order to determine whether taking part in this study would be suitable for you. The study team will respond to the questions that you may have in relation to the study. This team includes the study physician, the nursing staff and any other person working with the study physician.

If you choose to take part in this study, **you should sign and initial this consent form** before starting the study so that those in charge of the study are made aware of your decision.

You will receive a signed copy of this consent form to be kept in your personal records. Please keep this consent form as proof of your consent.

We appreciate you considering taking part in this study.

Sincerely,

_____

Study Physician

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

Table of Contents

This table of contents describes the different sections of this consent form. Please read all of the sections of this consent form before deciding whether or not to take part in this study.

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

Supplementary personal data document

1. Key information on the study and contact details

The study team will respond to the questions, concerns or complaints that you may have before, during and after completing the study. This team includes the study physician, the nursing staff and any other person working with the study physician.

If you have any general queries on your rights as a participant in the study or require information or suggestions, or if you wish to speak to someone who is not directly involved in the study, you can contact **the contact persons** mentioned below.

Name of study:
Sponsor consent form version number (Study/Country/Centre): / /
Study registration number [Institution]:
Sponsor study number:
Name of study Sponsor:
Name of primary investigator (Study physician):
Centre contact details:
Contact person:
Address:
Telephone number (Business hours):
Telephone number (Outside business hours):

2. Brief summary of this study

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

It has been suggested that you take part in a study conducted by Pfizer (the "Sponsor"). The study physician / institution receives remuneration from the Sponsor for taking part in the study.

This consent form is intended for participants who may or may not be capable of giving consent to take part. If you are a legally authorised representative / a legally acceptable representative, bear in mind that "you" refers to the study participant.

You are invited to take part in this research study because you have advanced non-small cell lung cancer (NSCLC) with ALK gene rearrangement or ROS1 gene rearrangement, treated with crizotinib. This study will provide us with more information on the use of crizotinib under real-life conditions of use. This study is referred to as "non-interventional" as it merely collects information. Your physician will provide your care in the same way as if you were not taking part in the study.

You will be taking part in this study for a period of 18 months.

This study will consist of recording information on your medical treatment and your health each time you attend your physician during the study.

This study does not involve any change in your current treatment and is being conducted for research purposes only. This study is being conducted to gain a better understanding of [name of drug under study] or your [disease / condition]. There is no direct benefit for you if you take part, but the information obtained from the study could help others in the future.

Taking part in this study is completely voluntary (it is your choice). There will be no penalty or modification of your medical care should you decide not to take part. You may choose to take part in the study now, and then change your mind later, at any time, without losing the benefits or medical care to which you are entitled. We encourage you to discuss your participation in the study with your family, the caregiving team, your doctor or the study team, to determine whether it would be suitable for you. The study team will respond to the questions that you may have in relation to the study.

You will receive a signed copy of this consent form to be kept in your personal records. Keep it for future reference.

3. What is the purpose of this study?

Dear Patient,

You are invited to take part in this study conducted on patients with advanced non-small cell lung cancer (NSCLC) with ALK gene rearrangement or ROS1 gene rearrangement and treated with crizotinib.

We need more information on the use of crizotinib under real-life conditions of use. For this reason, Pfizer is conducting this descriptive, non-interventional study, which in no way affects your care, to collect additional information on the efficacy and tolerance of crizotinib, which has been prescribed for you by your physician.

Compliance and patient quality of life will also be assessed.

Your attending physician will be notified of your participation in the study, unless you request otherwise.

4. How long will I be taking part in this study?

You will be taking part in this study for a maximum period of **18 months.**

In the course of this study, you will attend 7 visits included in the normal care plan of your disease. There are no additional visits associated with this study.

5. How many subjects will be taking part in this study?

Between **50 and 70 French hospitals** will take part in this study. This will enable the inclusion of at least 50 to 70 patients presenting with advanced NSCLC (non-small cell lung cancer) with ALK gene rearrangement or ROS1 rearrangement having accepted to take part in this study over the 24-month enrolment period.

6. What will happen during the study?

The study envisages collecting data during 7 visits (at most): 1 inclusion visit, 5 follow-up visits (at most) at 3, 6, 9, 12 and 15 months and one end-of-study visit at 18 months.

After the consent form has been signed, the following data will be collected and entered in an electronic questionnaire directly by your physician or by a duly authorised clinical research associate bound to confidentiality:

Inclusion visit:

- Sociodemographic characteristics* (e.g. gender, age)
- Morphological characteristics* (e.g. weight)
- Risk factors (e.g. smoking habit)
- History of your disease* (e.g. date of diagnosis, histological cancer type, ALK/ROS1 gene rearrangement)
- ALK/ROS1 rearrangement testing method.
- State of health and progression of this state of health as perceived by the physician (e.g. performance status or radiological criteria) or by you (quality of life questionnaire, reported adverse events)
- Treatment of your disease (e.g. prescribed crizotinib dose, prescribed side treatments of side-effects)

** Data collected at inclusion visit only.*

Tumour assessment follow-up visit taking place approximately every 3 months according to normal disease management:

Within the scope of the normal management of your disease, you will see your physician approximately every 3 months for 15 months (i.e. 5 follow-up visits at most) and an end-of-study visit at M18. Your physician will assess the progression of your disease, any changes to your crizotinib treatment and/or ongoing treatments and will collect your self-administered questionnaires for rating treatment compliance and quality of life.

The self-administered questionnaires should be returned to your physician at the end of the visit. This will enable your physician to confirm that no adverse event not discussed during the visit has been omitted.

Your physician will also ask you whether any adverse events have occurred since your last visit.

7. What are the potential risks and disadvantages associated with my participation in this study?

Crizotinib may have some side-effects, as described in the product information leaflet. Any adverse events that you may encounter should be reported to your physician. Should you experience serious adverse events, such as unscheduled hospitalisation, for example, notify your physician immediately or as soon as possible.

As this is a non-interventional study and you are receiving this crizotinib treatment as part of your normal care, an adverse event following crizotinib treatment will not be considered to be attributable to the study.

In the event of pregnancy (your own or that of your partner), notify the study physician immediately, and also your attending physician or that of your partner. It is important that the latter knows that you or your partner is undergoing crizotinib treatment during the pregnancy. The study physician will ask you whether you/your partner or the attending gynaecologist is prepared to provide information on its progress and outcome. If you/your partner agree, this information will be forwarded to Pfizer for tolerance follow-up.

8. What are the potential benefits of my participation in this study?

This study is merely being conducted for research purposes. You will not obtain any direct benefit from taking part in the study. The information obtained from the study may however be useful for other patients in the future.

9. Which other options do I have if I do not join this study?

This study is merely being conducted for research purposes. It is understood that you may decide not to take part and continue to follow your treatment and your normal care.

10. What happens if I experience harm during this study?

This study merely collects information, therefore, if it unlikely that you will experience harm associated with this study. You will receive crizotinib treatment as part of your routine medical care. Any adverse reaction that you may experience while taking part in this study will not be considered to be study-related harm.

11. What happens if I join this study and I change my mind?

If you accept to take part in this study and you change your mind for any reason, you are free to withdraw your participation at any time. Your decision will not affect your routine medical care or the benefits to which you are entitled. Notify your physician if you are considering withdrawing or if you decide to withdraw your participation.

Occasionally, your physician or the Sponsor may decide to withdraw you from the study if:

- The study is discontinued by the Sponsor, the ethics committee (Committee for the Protection of Persons, a group of people who review the study to protect your rights), or by a government or regulatory body.

- [Include any other reasons for which a participant may be withdrawn from the study.]

The study team will provide you with a supplementary personal data document, which is an integral part of this consent form. It describes what happens to your personal data and how these data may be used if you withdraw from the study.

12. What will I have to pay if I take part in this study?

Your participation in this study does not involve any additional financial burden for you. Indeed, the assessments related to this study are part of your normal care.

13. Will I receive remuneration for my participation in this study?

You will receive no payment for taking part in this study.

The Sponsor may use the information/data resulting from the study to develop products or processes from which it may generate profit. It is not envisaged to remunerate you or provide you with products developed on the basis of this study. All products or processes developed using the information/data from the study will remain the property of the Sponsor.

14. What will happen to my personal data?

The study team will provide you with a supplementary personal data document, which is part of this consent form. The supplementary personal data document describes:

- Which personal data may be collected directly from you during the study?
- How your personal data will be used and by whom (including by the centre participating in the study, the Sponsor, and other third parties outside the centre participating in the study);
- How your biological specimens and images will be processed (if they are collected);
- How your personal data may be used for other research projects;
- How your personal data will be protected during transfer;
- Your data protection rights, and which persons or authorities you can contact about your rights or for any other concern or complaint; and
- What happens to your personal data if you decide to stop taking part in the study

15. Where can I obtain further information on this study or the results of the study?

The results of the study will be presented at scientific conferences and published in scientific journals. After the end of the study, if you so wish, you will be notified of the results of the study.

A description of this study will be available at http://www.ClinicalTrials.gov. This website will not include any information liable to identify you. At the very most, the site will include a summary of the results. You may run searches on this website at any time. Several years may pass before the results of this study are available on this site.

The ClinicalTrials.gov website is in English only. Should you require assistance in understanding the content of the website, please ask your physician.

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

16. Signatures

Consent to take part and to personal data processing	Patient's initial
1. I hereby confirm that I have read (or, if I cannot read, a member of the study team has read to me) and understood this consent form for the study described above and that I have had the opportunity to ask questions. I have had sufficient time to read this consent form. I have also had the opportunity to ask questions on the details of the study and to decide whether to take part or not.	
2. I have read and understood the supplementary personal data document. I understand that participation in the study will require processing (including collection, use, transfer, storage, analysis and report generation) of my personal data, as explained in the supplementary personal data protection document. I understand and consent to the processing of my personal data within and outside my country of residence for healthcare, medical research and/or regulatory purposes. .	
3. I understand that my participation is voluntary and that I am free to stop taking part in this study or to withdraw my consent to the processing of my personal data at any time. I do not need to justify my reasons and my routine medical care and my legal rights will not be affected. However, even if I withdraw my consent to the processing of my data, my personal data collected until that point may be retained in order to comply with legislation and regulations and to maintain the cohesion of the study.	
4. I consent to the study team accessing my medical history, including the information contained in my medical records and my test results and any medical treatment received during the study and, if required, I authorise them to contact my doctor or any other healthcare professional providing me with care, in order to access this type of information.	
5. I understand that the Sponsor and/or other parties working with the Sponsor, ethics committees (Committees for the Protection of Persons (CPP)) and regulatory authorities may need to access the personal data	

collected on-site or collected by the study team, for the study or any other research. I consent to them accessing my personal data.	
6. By signing this consent form, I am in no way relinquishing my legal rights. I have been informed that I will receive a signed and dated copy of this document.	
7. I consent to take part in the study described in this document.	

_____

Name of study participant in block letters

_____	_____	_____
Signature of study participant	Date of signature§	Time **(if required)***

_____

Name of legal representative in block letters

and relationship

_____	_____	_____
Signature of legal representative	Date of signature§	Time **(if required)***

PERSON COLLECTING CONSENT

_____

Name in block letters of person conducting discussion in relation to consent

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

_____	_____	_____
Signature of person conducting discussion in relation to consent [†]	Date of signature	Time **(if required)***

[§]Participant/participant's legal representative must date their signature in person.

* The time is only required if the information was provided and consent was given on the same day, or if consent is given and all the study-specific activities are to be carried out on the same day.

[†]The participating physician, or a duly qualified and trained person, appointed by the participating physician to conduct the informed consent procedure, must sign and date the consent form during the meeting at which the patient signs the consent form.

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL STUDY

SUPPLEMENTARY PERSONAL DATA DOCUMENT

This supplementary personal data document describes how we will collect, use and share your personal data. It also specifies your rights in terms of personal data.

A. Which personal data may be collected about you during this study?

The study team and those assisting them in the provision of your care associated with the study will collect or furnish data pertaining to you, some of which are sensitive. These data may include:

- **Data identifying you directly** such as your name, your address, your telephone number and your date of birth (month and year).
- **Sensitive personal data** such as your medical history, the data resulting from this study (including test results and study procedures), demographic data (for example, your age and your gender) and other sensitive data required for this study such as diagnoses and treatments.
- **Data from tests and analysis of biological specimens** (such as blood or urine) **and images** (such as X-rays, CT scans and medical imaging). This may also include genetic data.

B. Who will use my personal data, how will they be used and where will they be stored?

Any personal data pertaining to you, collected during this study, will be stored by the study team in your participating centre. The study team is obliged keep your personal data confidential.

Your personal data may be accessed by:

- Your study physician and the other members of the study team;
- The Sponsor and its representatives (including affiliated companies)
- Individuals or organisations providing services or working with the Sponsor;
- Any organisation obtaining all or part of the Sponsor's business or rights on the product under study;
- Governmental or regulatory authorities (including those from other countries); and

- The Institutional Evaluation Committee (IEC) or the Independent Ethics Committee(s) (Committee for the Protection of Persons (CPP)) supervising this study.

The individuals and groups listed above will use your personal data to conduct this study and to comply with legal or regulatory requirements, in particular:

- to determine whether you are eligible for this study;
- to verify that the study is conducted properly and that the study data are accurate;
- to respond to questions from CPPs, IECs or governmental bodies or regulatory authorities;
- to contact you during and after the study (if required);
- to monitor your health, including the use of publicly accessible sources, in the event of the study team not being able to contact you using the information available in your file;
- to protect your vital interests or the interests of your pregnant partner (e.g. in a critical medical scenario, requiring the provision of information to a hospital emergency department where you are being treated); and
- to respond to your data protection requests (if applicable).

Your study centre will store your personal data for the period required to fulfil the aims described in the consent form, which, depending on the circumstances, may be up to 15 years after the end of the study.

If you provide a third party's personal data (e.g. an emergency contact or information of family medical history), you should inform them that you have provided this information. We will only use these personal data pursuant to this and to the applicable legislation.

C. What happens to my personal information sent outside the study centre?

Before the study team transfers your personal data outside the study centre, the centre will replace your name by a unique code and will delete data identifying you directly. We refer to such data as "**Encoded data**". The centre will keep the link between the code and your personal and confidential data, and the Sponsor will not have access to this link. The Sponsor's employees and representatives are obliged to protect your encoded data and will not attempt to re-identify you.

Your encoded data will be used by:

- The Sponsor and its representatives (including affiliated companies);
- Individuals and/or organisations providing services or working with the Sponsor;
- Any organisation obtaining all or part of the Sponsor's business or rights on the product under study;
- Other researchers;
- The CPP or IEC that approved this study;
- governmental or regulatory authorities; and

The parties above may use your personal data for the following purposes:

- **Conducting the study**, including:
  - Studying your response to crizotinib;
  - Understanding the study and the findings of the study and learning more about advanced non-small cell lung cancer (NSCLC) with ALK gene rearrangement or ROS1 gene rearrangement; and
  - Assessing the safety and efficacy of Crizotinib.

- **Complying with legal and regulatory requirements such as:**
  - Ensuring that the study is conducted in compliance with good clinical and epidemiological practice;
  - Making the required disclosures to CPPs, IECs or to governmental or regulatory authorities;
  - Requesting the authorisation from government or regulatory authorities to market crizotinib (these governmental or regulatory authorities may disclose your encoded data to other researchers for the purpose of future scientific research); and
  - Sharing the study data with other researchers not affiliated with the Sponsor or with the study team (including by publishing on the Internet or via other media, but the information that could identify you directly will not be made available to other researchers).
- **Publishing summaries of the findings of the study** in medical journals, on the Internet or for training meetings of other researchers. You will not be identified directly in any publication or study report. However, some medical journal representatives may need to access your encoded data to verify the findings of the study and ensure that the research complies with the quality standards of the medical

journal. Furthermore, medical journals may request that genetic information and other information stemming from the study not identifying you directly be made available to other researchers for other research projects.
- **Improving the quality, design and safety** of this study and of other studies.

The Sponsor will store your Encoded data for the period required to fulfil the aims described in the consent form, which may be up to 15 years after the end of the study.

D. How are my biological specimens and my images processed?

If biological specimens or images of you are taken during the study, these specimens and images will be processed in the same way as your encoded data. All specimens will be processed in line with legal requirements. From time to time, your study centre may be unable to delete data that may identify you from your images before sending them to the Sponsors and to its representatives.

E. Can my personal data be used for other research projects?

Your encoded data may be used to bring about progress in scientific research and public health in other projects conducted in the future. At the present time, we do not know the specific details of these future research projects.

These other research projects may be conducted (1) in combination with data **from other sources**, (2) for the purposes of **supplementary scientific research** beyond the aims of this study, and (3) subject to **specific protection measures**.

- **(1) Other sources**: The Encoded data may be combined with data from other sources outside the scope of the research project. These sources may include: encoded electronic health records, healthcare cost and payment and complaint data and databases, product and disease registers, data collected by your telephone, tablet or other devices and mobile applications, social media, pharmaceutical data, biobanks or patient engagement programmes.
- **(2) Supplementary scientific research**: Your Encoded data may be used to understand how to manufacture new medicinal products, devices, diagnostic products, tools and/or other therapies treating diseases and to enhance future research. They may also be used to assess the value, cost-effectiveness ratio and price, and to optimise access to medicinal products.

- **(3) Specific protection measures** will be used to protect your encoded data, such as:
  - Restricting access to Encoded data to specific persons who will be obliged to keep this information confidential and who will be prohibited from attempting to re-identify your encoded data.
  - Using security measures to prevent data alteration, loss and unauthorised access.
  - Anonymising data by deleting and/or replacing information from your Encoded data and/or by deleting the link to your Encoded data.
  - Reviewing data protection systems to identify and reduce privacy risks, if applicable, associated with each supplementary scientific research aim.
  - Where required by the applicable legislation, ensuring that the scientific research has been approved by the CPPs, IECs or other similar research review groups.

F. How will my personal data be protected when they are transferred from the participating centre to the Sponsor?

Your personal data will be processed in accordance with the applicable data protection legislation. The Sponsor and the participating centre are the processing managers of your personal information. The participating centre will be the processing manager of your personal data and the Sponsor will be the processing manager of your Encoded data.

Some parties using your personal data, including your Encoded data, may be based in countries other than your country, including the United States. Data protection legislation may be different in these countries. The European Commission is of the view that some of these countries offer an adequate level of data protection (the full list of these countries is available on this site: http://ec.europa.eu/justice/data-protection/international-transfers/adequacy/index_fr.htm).

The Sponsors and those working with the Sponsor will take measures to keep your personal data confidential. Should your data be transferred by the Sponsor from the European Union (EU), the European Economic Area (EEA) and/or Switzerland to other countries which do not meet personal data protection requirements in the view of the European authorities, the Sponsor has set up transfer agreements to protect your personal data. Please contact the study team to obtain a copy of these data transfer agreements.

G. What are my rights in terms of data protection? Who can I contact about these rights or for any concern or complaint?

If you would like to exercise any of the rights described below, or if you have concerns about the manner in which your personal data are processed, it is preferable to contact the participating centre and not the Sponsor. As a general rule, the Sponsor will not know who you are (by your name) because the Sponsor, usually, only holds your Encoded data, which would not include your name or any other information which could be used to identify you easily. To contact the participating centre, the study physician or the participating centre's data protection officer, please refer to **the contact details** in Section 1 of the consent form.

- You have the right to access your personal data held by the study team. To ensure cohesion of the study, you will not be able to revise some of the data until the study has come to an end.
- You have the right to amend or update your personal data.
- You have the right to restrict the collection and use of your personal data under certain circumstances (e.g. if the data are inaccurate).
- You have the right to receive your personal data in a structured common electronic format (e.g. in a readable electronic text file) for your own requirements or to give to others, as per the applicable data protection legislation. You may not have the right to obtain your personal data that have been used for the purposes of public interest (e.g. to report cases of disease to the authorities responsible for public health) or in exercising the official authority granted to the Sponsor or to the participating centre (e.g. responding to requests for information from public authorities or monitoring medicinal product safety).
- You have the right to request the deletion of your personal data if you are no longer taking part in the study and you are withdrawing your consent to the use of your personal data as described in this document. However, there are limitations to the possibility of accepting a request to delete your personal data. Some or all of your personal data may be retained and used if the deletion seriously compromises the study (e.g. if the deletion affects the consistency of the findings of the study) or if your personal data are required to comply with legal requirements.
- You have the right to set out instructions in relation to the outcome of your personal data after your death
- You have the right to submit a complaint to a data protection authority (http://ec.europa.eu/justice/data-protection/article-29/structure/data-protection-authorities/index_en.htm).

H. What happens if I do not wish to continue the study?

As mentioned in the consent form, you are free to stop taking part in this study at any time by notifying the study team.

If you are no longer taking part in the study and you have not notified the study team, they may contact you and check whether you wish to continue taking part in the study. If the participating centre is unable to contact you, the Sponsor may consult publicly accessible registers pertaining to your health to monitor the long-term safety of the medicinal product under study. This will only be carried out if authorised by law.

If you stop taking part in the study without withdrawing your consent, your personal data will continue to be used as per this document and the applicable legislation. No further data or specimens pertaining to you will be collected by the study team, unless you have agreed to provide them.

If you decide to withdraw your consent:

- You will no longer be able to take part in the study.
- No further information or specimens pertaining to you will be collected by the study team;
- The study team must systematically report any adverse event that you may have experienced during your participation in the study to the Sponsor;
- Your personal data, including Encoded data, collected up to the time of your withdrawal from the study will be stored and used by the Sponsor to ensure the cohesion of the study, to determine the effects on the safety of crizotinib, to meet legal or regulatory requirements, and/or for any other purpose permitted by the applicable data protection and privacy legislation;
- Your personal data (including Encoded data) will not be used for other scientific research. However, if your personal information has been anonymised, so that you cannot be identified personally, this information may continue to be used for other scientific research (as described in section E of this document), as permitted by the applicable legislation; and
- Biological specimens that have been taken but not tested will no longer be used, unless permitted or required by the applicable legislation. You also have the right to request that all your remaining specimens collected within the scope of the study be disposed of. You may exercise this right by notifying the study team of your wish to

have your specimens disposed of. The team will then send your encoded request to the Sponsor. In some countries, local legislation or regulations may require that your specimens be disposed of or anonymised if you withdraw from the study, whether you make a specific request or not. However, we cannot guarantee the disposal of specimens as it may not be possible to retrace the specimen back to you, it may have been used in full or have been transferred to a third party. In this case, it will not be possible to erase and dispose of your biological specimens and any related data.