Study Protocol

BI Study Number:	1200.227
BI Investigational Product	Non applicable
ANSM reference number:	2014-A00721-46
Title:	Evaluation of the impact of a nurse-led telephone follow-up on treatment compliance of patients treated from a locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation(s). The PARTAGE study
Clinical Phase:	Routine clinical practice study
Trial Clinical Monitor:	[redacted]
Principal Investigator :	[redacted]
Status:	*Protocol final*
Version and Date:	**Version: 1.2 Date: 19-May-2014**

PRINCIPAL INVESTIGATOR SIGNATURE

Study Title: Evaluation of the impact of a nurse-led telephone follow-up on treatment compliance of patients treated from a locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation(s). The PARTAGE study

Study Number: 1200.227

I herewith certify that I agree to adhere to the trial protocol and to all documents referenced in the trial protocol.

Name:_____ **Signature:**_____

Signed signature page is located in the electronic Clinical Trial Master File

Affiliation:

Date: _____

LOCAL SIGNATURES
(PRINCIPAL INVESTIGATOR OF SITE)

Study Title: Evaluation of the impact of a nurse-led telephone follow-up on treatment compliance of patients treated from a locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation(s). The PARTAGE study.

Trial Number: 1200.227

Protocol Version: 1.1 dated on 19-May-2014

I herewith certify that I agree to adhere to the protocol of the routine clinical practice trial and to all documents referenced in the trial protocol.

Principal Investigator (site):

Date Name

Full name

Organization/Department

Signed signature page is located in the electronic Clinical Trial Master File

PROTOCOL SYNOPSIS

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim		**Tabulated Study Protocol**	
Name of finished product: N/A			
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Protocol date: 19 May 2014	**Trial number:**	**ANSM reference number:**	**Revision date: N/A**

Title of study:	Evaluation of the impact of a nurse-led telephone follow-up on treatment compliance of patients treated from a locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation(s). The PARTAGE study
Principal Investigator:	[redacted]
Study site(s):	Approximately 75 centres in metropolitan France
Clinical phase:	Routine clinical practice study
Study rational:	The current management of patients with stage IIIb/IV non-small-cell lung cancer (NSCLC) uses targeted therapy as first, second and third-line therapy. These treatments belong to the group of oral cancer therapies, which are being increasingly developed and used in oncology. However, because patients become responsible for taking their treatment and managing the related toxicity, this practice raises the question of compliance. The literature shows that compliance rates range from less than 20 % to 100% during the treatment of cancer with oral therapies, with low compliance being mainly due to problems of cost, adverse reactions and dose schedule (e.g., relative to meals). To increase compliance during treatment with oral cancer therapies, several specific surveillance strategies have been implemented e.g. customised follow-up, education sessions for patients and caregivers (doctor, pharmacist, nurse), and telephone follow-up. In particular, the nurse-led telephone follow-up is recommended by the 'Plan Cancer 3' and is gradually being implemented in routine practice. In France, some institutions have established a nurse-led telephone follow-up with the patient, at least weekly for 4-8 weeks, and after discussion with the patient and, if possible, with his entourage. This follow-up should reassure patients, permit them to have their questions answered, help in the management of targeted therapy related adverse events (AEs) (e.g. by facilitating their reporting by the patient or their identification by the nurse) and may therefore improve patient treatment compliance or rectify certain situations of poor compliance. The objective of this study is to evaluate the impact of a personalised nurse-led telephone follow-up on treatment compliance of patients with stage IIIb/IV NSCLC with activated epidermal growth factor receptor (EGFR) mutation(s) who are treated with oral targeted therapy in routine clinical practice.
Objectives:	**Primary objective** • To evaluate, during routine clinical practice, the impact of nurse-led telephone follow-up on overall patient treatment compliance with oral targeted therapy (cumulated dose* during the 3-month follow-up). ** The cumulated dose (mg) of oral targeted therapy taken between 2 visits is the sum of the doses (mg) of the tablets taken by the patient. The cumulated dose (mg) of the oral targeted therapy taken during the 3-month follow-up is the sum of the doses (mg) cumulated taken*

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	between 2 visits during the 3 months follow-up. **Secondary objectives** To evaluate: • The impact of an additional nurse-led telephone follow-up on patient treatment compliance (Girerd questionnaire). • To evaluate, during routine clinical practice, the impact of nurse-led telephone follow-up on overall patient treatment non-compliance with oral targeted therapy, following decision of the medical team (cumulated dose not taken* during the 3-month follow-up). • To evaluate, during routine clinical practice, the impact of nurse-led telephone follow-up on overall patient treatment non-compliance with oral targeted therapy, following decision of the patient (cumulated dose not taken* during the 3-month follow-up). ** The cumulated dose (mg) of oral targeted therapy not taken between 2 visits is the sum of the doses (mg) of tablets not taken by the patient. The cumulated dose (mg) of oral targeted therapy not taken during the 3-month follow-up is the sum of the cumulated doses (mg) not taken between 2 visits during the 3-month follow-up.* • Overall patient satisfaction with the level of care provided (Visual Analogue Scale [VAS]). • Evolution of patient quality of life during the study (Functional Assessment of Cancer Therapy [FACT] Lung questionnaire). • Use of healthcare such as emergency department visits/admissions, number and duration of unplanned hospitalisations, number of unplanned visits during the 3-month follow-up (visits to the investigator, to any other specialist or to the general practitioner). • Overall satisfaction of the investigator (pneumologist/oncologist) and for the patients included in the group with a remote additional personalised nurse-led follow-up, the overall satisfaction of their pharmacist and general practitioner (VAS). • Safety (data collected according to the Common Terminology Criteria for Adverse Events [CTCAE] version 4.03). • Impact of the additional nurse-led follow-up on the frequency of calls to the general practitioners/specialists by the patient.
Methodology:	Routine clinical practice, randomised, multicentre study. Up to 450 specialised doctors will be contacted in order to recruit 130 participating medical team (investigators) in 75 centres. These centres should enrol around 400 patients in the study. In order to extrapolate the study results to the rest of the target population, the participating investigators will be selected by stratified random sampling of the PMSI 2011 file, which includes a list of all French hospitals providing healthcare for NSCLC patients. Stratification factors will be geographical breakdown and the size of the patient base.

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	The study will take place over a period of 27 months. The recruitment phase will last approximately 24 months and each patient will participate for approximately 3 months. At the inclusion visit (D0), the investigator will ask the patient whether he would like to participate in the study and will obtain his written consent. Refusal to participate including the reason if available will be collected in a register specific to this study (study register). The collected data will allow any selection bias to be identified. Patients agreeing to participate will be randomised (3:1 ratio) and included in one of the following 2 groups: • Group without 'remote additional personalised nurse-led follow-up': patients will receive the healthcare given routinely by their medical team (100 patients). • Group with 'remote additional personalised nurse-led follow-up': patients will receive telephone calls from a nurse in addition to the healthcare given routinely by their medical team (300 patients). All the patients will be seen according to normal practice by the study medical team. In this study, 3 data collection time points at monthly intervals are defined (D30, D60, D90); however, the frequency of visits should not be adjusted and the medical team should maintain his routine practice (example: if the investigator is used to see the patient on D15, the visit will still take place, but no information, except pharmacovigilance data, will be collected). As such, the data from the closest defined visit will be reported in the case report form (CRF) at each time-point. The telephone calls will be made by a nurse from a company specialised in patients support called Patientys. Patients in the group with 'remote additional personalised nurse-led follow-up' will be contacted 8 times during the study (at D1, D7, D14, D21, D28, D44, D59 and D89). The nurse will make sure that the treatment takes place in good conditions; she cannot intervene in the medical care of the patient, nor give answer to the questions relative to the disease or to the treatment of the patient. The medical team remains the privileged contact of the patient. During the first telephone call at D1, the nurse will confirm the enrolment of the patient in the study and will then inform the patient's general practitioner/pharmacist by letter or telephone call. During the following telephone calls, the nurse will perform an evaluation with the help of a questionnaire and will collect treatment related AEs. After each telephone call, the nurse will establish a report. These reports will be sent to the investigators on the same day of the nurse follow-up phone call. On arrival for the consultations (D0, D30, D60 et D90) with the investigator, the patient will be asked to complete questionnaires regarding treatment compliance, satisfaction and/or quality of life before the start of consultation, in the doctor's office or any other available private place.
No. of patients:	Around 400 patients.
Diagnosis:	Adult patients diagnosed with NSCLC locally advanced or metastatic, with activating mutation(s) of EGFR and who are EGFR-TKI naïve.

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Main criteria for inclusion:	• Male or female patient older than 18 years. • Adult patient diagnosed with stage IIIb/IV NSCLC locally advanced or metastatic, with activating mutation(s) of EGFR and who is EGFR-TKI naïve. • Patient for whom a decision of treatment with afatinib monotherapy has been taken in the frame of its marketing authorization. • Out-patient. • Patient having given written consent for participation in the study. • Patient who is able to participate in the investigator's opinion. • Patient affiliated with the French social security.
Test product(s):	NA
Comparator product(s):	NA
Study duration:	Approximately 27 months (September 2014-December 2016) • Recruitment: approximately 24 months. • Patient follow-up: approximately 3 months.
Criteria for efficacy*:*	**Primary criterion** • Cumulated dose of oral targeted therapy during the 3-month follow-up. *The cumulated dose (mg) of oral targeted therapy taken between 2 visits is the sum of the doses (mg) of the tablets taken by the patient. The cumulated dose (mg) of the oral targeted therapy taken during the 3-month follow-up is the sum of the doses (mg) cumulated taken between 2 visits during the 3-month follow-up.* **Secondary criteria** • Score (0–6) obtained with the Girerd questionnaire at D30, D60 and D90. • Cumulated dose of oral targeted therapy not taken (all categories) following decision of the medical team. • Cumulated dose of oral targeted therapy not taken due to dose reduction following decision of the medical team. • Cumulated dose of oral targeted therapy not taken due to temporary or definitive interruption following the medical team decision. • Cumulated dose of oral targeted therapy not taken (all categories) following patient decision. • Cumulated dose of oral targeted therapy not taken due to dose reduction following patient decision. • Cumulated dose of oral targeted therapy not taken due to temporary or definitive interruption following patient decision. *Cumulated dose (mg) of oral targeted therapy not taken between 2 visits is the sum of the doses (mg) of the tablets not taken by the patient. The cumulated dose (mg) of the oral targeted therapy not taken during the 3-month follow-up is the sum of the doses (mg) cumulated not taken between 2 visits during the 3-month follow-up. This dose can be calculated overall and by reason for not taking the prescribed dose:*

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	dose reduction, temporary or definitive discontinuation following decision of the medical team / patient decision. • VAS score (0–10) for overall patient satisfaction with the level of care (information, advice) at D90. • Absolute variation observed for the quality of life questionnaire FACT Lung score between D30 and D0, between D90 and D30 and between D90 and D0. • Number of emergency admissions (related to the treatment) during the 3-month follow-up. • Number and duration of unplanned hospitalizations (related to the treatment) during the 3-month follow-up. • Number of unplanned visits to the investigator during the 3-month follow-up. • Number of unplanned visits to a specialist, whatever is his specialty, other than the investigator during the 3-month follow-up. • Number of unplanned visits to the general practitioner during the 3-month follow-up. • VAS score (0–10) for overall investigator satisfaction with the level of patient care at D90. • VAS score (0–10) for overall general practitioner satisfaction with the level of patient care at D90 (only for the patients with 'remote additional personalised nurse-led follow-up) • VAS score (0–10) for overall pharmacist satisfaction with the level of patient care at D90 (only for the patients with 'remote additional personalised nurse-led follow-up). • Number of calls made by the patients to their general practitioner during the 3-month follow-up. • Number of calls made by the general practitioner to the patient during the 3-month follow-up. • Number of calls made by the patients to their medical team during the 3-month follow-up. • Number of calls made by the medical team to their patient during the 3-month follow-up. • Number of calls between the general practitioners and the medical team during the 3-month follow-up. • Number of AEs related to the oral biological therapy. • Number of AEs of grade ≥ 3 related to the oral biological therapy. • Number of serious adverse events (SAEs) related to the oral targeted therapy. • Number of AEs related to the oral targeted therapy which causes temporary or definitive discontinuation of the treatment or dose reduction.
Statistical methods:	**Analysis population** The primary analysis population will be the population of randomised patients who

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satisfy the essential inclusion and exclusion criteria, and for whom information is available for the major evaluation criteria (in particular the primary criterion).

Statistical methods

The statistical analysis will be performed using SAS (version 9.1 or a more recent version). All tests will be performed 2-sided with a cut-off of 5%.

Analysis of the primary criterion

The primary objective of the study is to evaluate overall treatment compliance after 3-months and to compare this compliance between the 2 study groups: the group with nurse-led follow-up and the group without nurse-led follow-up.

The cumulated dose (mg) of oral targeted therapy taken between 2 visits will be calculated as follows: sum of the doses (mg) of the tablets taken by the patient. The count of taken tablets by the patient between visit Vi-1 and visit Vi will be done by the medical team investigator during visit Vi based on the tablet boxes returned by the patient. The physician will indicate in the Case Report Form (CRF) for each dosage (20 mg, 30 mg, 40 mg and 50 mg [only in 2nd intent dose if the treatment is well tolerated and according to the recommendations of the patient leaflet]), the number of tablets taken by the patient. The cumulated dose between visit Vi-1 and visit Vi will then be calculated as follows:

$$[\text{Cumulated dose (mg)}]i = \sum_{\text{Dosages in 20, 30, 40, 50}} [\text{Dosage x Number of tablets(Dosage)}]$$

where Number of tablets is the number of tablets of 20mg, 30 mg, 40mg or 50mg taken.

The cumulated dose (mg) of oral targeted therapy taken during the 3-month follow-up will be the sum of the cumulated doses (mg) used between 2 visits during the 3-month follow-up. The total cumulated dose (mg) in 3 months will be calculated as follows:

$$\text{Cumulated dose (mg)} = \sum_{i} [\text{Cumulated Dose (mg)}]_i$$

As such, the cumulated dose (mg) of the oral targeted therapy over the 3-month follow-up will be described for each groups (number of observed values, mean, standard deviation, median, lower quartile, upper quartile, minimum, maximum, two-sided 95% confidence interval of the mean).

The mean cumulated dose will be compared between groups by Student test, or Wilcoxon rank sum test in case of non-normal data or non-homeogeneity of variance.

A complementary analysis using a Kaplan-Meier curve will also be performed on the principal criteria, to evaluate the time between start of treatment and the first dose modification or interruption of the targeted oral therapy.

The main analysis will also be completed by a descriptive analysis of the reasons for non-compliance. The numbers of the temporary and/or definitive stops due to the patient and/or to the investigator will be tabulated. Reasons will be listed.

Sample size

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In the absence of dose discontinuation or reduction, the cumulated dose of oral targeted therapy should be 3600 mg of afatinib, which corresponds to a daily dose of 40 mg for 90 days.

Clinical trials performed with afatinib before its marketing authorisation showed that over the first 3-month follow-up the mean dose of 3000 mg was taken (which corresponds to a dose intensity of 83%) (Boehringer Ingelheim First Interim Study Report 1200.32).

It was estimated that the mean dose observed in the group 'without remote additional personalised nurse-led follow-up' will be similar to the mean dose observed in the afatinib clinical trials and that adding an additional nurse-led follow-up will increase the mean dose by 6% (3180 mg, dose intensity of 88%).

As such, the number of patients to be included in the study has been calculated on the basis of a t-test for 2 unmatched samples with the following hypotheses:

- Mean cumulated dose of oral targeted therapy taken during the 3-month follow-up in the group without 'remote additional personalised nurse-led follow-up': 3000 mg (dose intensity of 83%).
- Mean cumulated dose of oral targeted therapy taken during the 3-month study in the group with 'remote additional personalised nurse-led follow-up': 3180 mg (dose intensity of 88%).
- Standard deviation of the cumulated dose of oral targeted therapy taken during the 3-month follow-up in both groups: 500.
- Type I error: $\alpha = 0.05$.
- Type II error: $\beta = 0.20$ (power = 80%).
- Ratio 'with remote additional personalised nurse-led follow-up' group/'without remote additional personalised nurse-led follow-up' group = 3.

Using these hypotheses, in order to show an increase in the cumulated dose with the addition of 3-month nurse-led follow-up, it is necessary to have 82 patients in the group 'without remote additional personalised nurse-led follow-up' and 246 patients in the group 'with remote additional personalised nurse-led follow-up '.

If it is considered that 20% of included patients will be non-evaluable for the primary criterion, it is necessary to include 99 patients in the group without 'remote additional personalised nurse-led follow-up' and 297 patients in the group with 'remote additional personalised nurse-led follow-up', i.e. 396 patients in total which can be rounded up to 400.

FLOW CHART

Table 1 Visit schedule and data collection

	D0	D1[a]	D7[a]	D14[a]	D21[a]	D28[a]	**D30 M1**	D45[a]	D59[a]	**D60 M2**	DJ89[a]	**D90[b] M3**
	MV Incl	NFPC 1	NFPC 2	NFPC 3	NFPC 4	NFPC 5	**MV1**	NFPC 6	NFPC 7	**MV2**	NFPC 8	**MV3**
Written consent	**X**											
Verification of eligibility	**X**											
Documentation of patient's acceptance or rejection of participation in the study file	**X**											
Demographic information [c]	**X**											
Physical exam [d]	**X**											
NSCLC characteristics [e]	**X**											
Past medical history, past treatments	**X**											
Concomitant diseases, concomitant medications	**X**						**X**			**X**		**X**
Randomisation	**X**											
Patient diary delivery	**X**											
Clinical evaluation by Patientys nurse		X	X	X	X	X		X	X		X	
Collection of AEs	**X**	X	X	X	X	X	**X**	X	X	**X**	X	**X**
Patient compliance (returned tablets and Girerd questionnaire)							**X**			**X**		**X**
Patient quality of life questionnaire	**X**						**X**					**X**
Patient global satisfaction questionnaires												**X**
Data collection on use of healthcare services							**X**			**X**		**X**
General practitioner and/or pharmacist global satisfaction questionnaires												**X**
Investigator global satisfaction questionnaires												**X**

[a] Only for patients 'With nurse-led follow-up' group
[b] Or end of study visit if the patient withdraws prematurely from the study
[c] Including age, gender, weight, height
[d] Complete physical exam at inclusion visit including: Vital signs (Heart & respiratory rate, blood pressure, temperature), and collection of the cutaneous, gastro-intestinal, respiratory, eye, cardiovascular and allergic symptoms
[e] Diagnosis date, disease stage, performance status (ECOG), biopsy date, type of mutation(s), method of mutation typing, previous treatments of NSCLC
f The drug accountability of taken and not taken tablets will be made by the medical team in the Case Report Form
D = day ; M = month ; MV = medical visit according to the routine practice of the centre, NFPC= nurse follow-up phone call, Incl.= inclusion, NSCLC = non-small-cell lung cancer ;
AE= adverse event.

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ABBREVIATIONS

AE	Adverse Event
AUC	Area under the Curve
CI	Confidence Interval
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CRF	Case Report Form
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Subteam
OPU	Operative Unit
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PV	Pharmacovigilance
q.d.	quaque die (once a day)
SAE	Serious Adverse Event
s.c.	subcutaneous
SmPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

1. INTRODUCTION

In recent years, changes have occurred in the management of oncology patients. This evolution is the result of increased chemotherapy in day hospitals which allows faster return home but with increase in the day hospital consultations, longer survival of patients, and development of new molecules and strategies of therapy. Implementing an individualized therapeutic strategy, during and after treatment, proves reassuring for the patient and improves overall care (APM news, Cancer Plan 2, measures 18 and 24). In this context, and with the introduction of nurse coordinators and follow-up visits conducted by specialized nurses, nurses have become key players in the management and support of oncology patients. These practices were developed around the world (Canada, England, and France) for different types of cancer (Allard 2008, Moore 2002, Cancer Plan 2, measures 18-24, Cancer Plan 2. Results of studies on individualized programs on patients during and after cancer). Similarly, a telephone follow-up conducted by specialized nurses to prepare chemotherapy sessions (Berhoune 2010) or to monitor patients after treatment was considered and evaluated in several countries such as Canada, the United Kingdom, Netherlands and Australia (Cox 2003, Barbu 2009, Kimman 2011, Beaver 2011, Beaver 2012, Harisson 2013). Studies involving telephone follow-up in the follow-up of oncology patients have demonstrated that such intervention was economically feasible and well accepted by the majority of patients (Lewis 2009). It can reassure patients and manage treatment related adverse events and recurrent symptoms (Cusack 2010). A recent study in France evaluated the impact of the implementation of a pilot program for remote follow-up involving a call centre specialised in follow-up of patients (Scotté 2013, Berhoune 2010). Nurses of this centre contacted patients 2 days before their chemotherapy to collect adverse events encountered during their treatment. These data combined with the results of routine blood tests have allowed confirming or adjusting chemotherapy regimens and improving the management of patients during the chemotherapy session. Compared to a control group retrospectively evaluated, this program has helped to optimize the utilization of healthcare services (reduction of hospital stays, increase in rates of bed occupancy and reduction in waste of chemotherapy preparations). In addition, the program has allowed adjusting and individualising the strategies of prevention of adverse events which may occur during chemotherapy and improving the overall management of side effects, resulting in better management of patients.

Telephone follow-up is part of the recommendations of the 'Cancer Plan 3' to develop the tools that facilitate patient information and treatment compliance. This comes in the context of both patient management and support. In France, some institutions have established a nurse-led telephone follow-up with the patient, at least weekly for 4-8 weeks, and after discussion with the patient and, if possible, with his entourage (Recommendations of Cancer Plan 3. Section 2.4.7). The use of this particular form of surveillance is not yet widespread and, to our knowledge, its impact on patient compliance to treatment and management of side effects has not yet been evaluated.

Non-small-cell lung cancer (NSCLC) accounts for approximately 80-85% of all cases of lung cancer (ESMO 2012). The therapeutic strategy varies depending on the stage and combines local treatments (surgery, radiotherapy) and systemic treatments (chemotherapy and targeted therapy). In patients with stage IIIb/IV (unresectable cancers), systemic therapies represent the mainstay of treatment including chemotherapy, vascular endothelial growth factor (VEGF) inhibitor, and

epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Treatment with an EGFR-TKI is the preferred option for patients with EGFR gene mutation (in France 9.4% of NSCLC, Barlési 2013). This treatment belongs to the group of oral anticancer therapies, which are being increasingly developed and used in oncology. Indeed, about 25% of anticancer molecules under development are oral therapies. In addition, when comparing equally effective therapies, patients generally prefer an oral anticancer treatment (Liu 1997). However, the use of oral home treatment brings changes to the doctor-patient relationship. Because patients become responsible for taking their treatment and managing the related toxicity, this practice raises the question of compliance. The literature shows that compliance rates range from less than 20% to 100% during the treatment of cancer with oral therapies (Ruddy, 2009; Geynisman 2013), with low compliance being mainly due to problems of cost, adverse events and dose schedule (e.g., relative to meals) (Ruddy, 2009; Geynisman 2013). To increase compliance during treatment with oral cancer therapies, several specific surveillance strategies have been implemented e.g. customized follow-up, education sessions for patients and caregivers (doctor, pharmacist, nurse), and telephone follow-up. This nurse-led follow-up should reassure patients, permit them to have their questions answered, help in the management of targeted therapy related_toxicity (e.g. by facilitating the adverse events reporting by the patient or their identification by the nurse) and may therefore increase patient treatment compliance or rectify certain situations of poor compliance.

The objective of this study is to evaluate the impact of personalised nurse-led follow-up phone call on treatment compliance of patients with stage IIIb/IV NSCLC with EGFR-activating mutation(s) being treated with oral targeted therapy in routine clinical practice.

2. RATIONALE AND OBJECTIVES

2.1 RATIONALE FOR PERFORMING THE STUDY

The current management of patients with stage IIIb/IV NSCLC uses targeted therapy (ESMO 2012) as first, second and third-line therapy. Targeted therapies are generally oral treatments which makes the patient responsible of the treatment intake. This approach affects patient compliance to treatment and management of AEs. In routine clinical practice, patients are regularly seen by their oncologists and a support program can be established following the recommendations of the Cancer Plan 3 (developing in the certification of healthcare institutions an approach to help patients with their care, improve communication and coordination between general practice and hospital, try new modalities of organisation in the management of patients treated with oral targeted therapy involving health professional in general practice and in hospital). A regular nurse-led telephone follow-up at the beginning of treatment may improve patient compliance. Therefore, the impact of the implementation of such a follow-up program on patient compliance to therapy will be evaluated in this real-life study.

2.2 OBJECTIVES

2.2.1 Primary objective

The primary objective of this study is to evaluate, during routine clinical practice, the impact of nurse-led telephone follow-up on overall patient treatment compliance with oral targeted therapy (cumulated dose* during the 3-month study).

** The cumulated dose (mg) of oral targeted therapy taken between 2 visits is the sum of the doses (mg) of the tablets taken by the patient. The cumulated dose (mg) of the oral targeted therapy taken during the 3-month follow-up is the sum of the doses (mg) cumulated taken between 2 visits during the 3 months follow-up.*

2.2.2 Secondary objectives

The secondary objectives are to evaluate:

- The impact of an additional nurse-led telephone follow-up on patient treatment compliance using Girerd questionnaire (Girerd 2001).
- To evaluate, during routine clinical practice, the impact of nurse-led telephone follow-up on overall patient treatment non-compliance with oral targeted therapy, following decision of the medical team (cumulated dose not taken* during the 3-month follow-up).
- To evaluate, during routine clinical practice, the impact of nurse-led telephone follow-up on overall patient treatment non-compliance with oral targeted therapy, following decision of the patient (cumulated dose not taken* during the 3-month follow-up).

* The cumulated dose (mg) of oral targeted therapy not taken between 2 visits is the sum of the doses (mg) of tablets not taken by the patient. The cumulated dose (mg) of oral targeted therapy not taken during the 3-month follow-up is the sum of the cumulated doses (mg) not taken between 2 visits during the 3-month follow-up.

- Overall patient satisfaction with the level of care provided (Visual Analogue Scale [VAS]).
- Evolution of patient quality of life during the study (Functional Assessment of Cancer Therapy [FACT] Lung questionnaire; Cella, 1995).
- Use of healthcare such as emergency department visits/admissions, number and duration of unplanned hospitalisations, number of unplanned visits during the 3-month follow-up (visits to the investigator, to any other specialist or to the general practitioner).
- Overall satisfaction of the investigator (pneumologist/oncologist) and for the patients included in the group with a remote additional personalised nurse-led follow-up, the overall satisfaction of their pharmacist and general practitioner (VAS).
- Safety (data collected according to the Common Terminology Criteria for Adverse Events [CTCAE] version 4.03).
- Impact of the additional nurse-led follow-up on the frequency of calls to the general practitioners/specialists by the patient.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL DESIGN AND PLAN

This is a randomized, multicentre, routine clinical practice study.

Selection of the participating investigators:
Up to 450 specialized doctors will be contacted in order to recruit 130 participating medical team (investigators) in 75 centres. These centres should include around 400 patients in the study (about 5 to 6 patients per centre).

In order to extrapolate the study results to the rest of the target population, the participating investigators will be selected by stratified random sampling of the PMSI 2011 file, which includes a list of all French hospitals providing healthcare for NSCLC patients. Stratification factors will be geographical breakdown and the size of the patient base.

Study design:
The study will take place over a period of 27 months. The recruitment phase will last approximately 24 months and each patient will participate for approximately 3 months.

At the inclusion visit (D0), the investigator will ask the patient whether he would like to participate in the study and will obtain his written consent. Refusal to participate including the reason if available will be collected in a register specific to this study (study register). The collected data will allow any selection bias to be identified.

Each patient agreeing to participate in the study will be randomised by receiving a randomisation number and assigned to its corresponding group. Randomisation will be done by envelopes (See Section 7.5). The investigators or medical team will send a randomisation fax to Patientys for each patient included in the study. Patientys will forward the anonymised data to the contract research organisation (CRO) in charge of the data monitoring.

The randomisation will follow a 3:1 ratio and the patients will be included in one of the following 2 groups:

- Group without ‘remote additional personalised nurse-led follow-up’: patients will receive the healthcare given routinely by their medical team (100 patients).

OR

- Group with ‘remote additional personalised nurse-led follow-up’: patients will receive telephone calls from a nurse in addition to the healthcare given routinely by their medical team (300 patients).

All the patients will be seen according to normal practice by the study medical team. In this study, 3 data collection time-points at monthly intervals are defined (D30, D60, D90); however the frequency of visits should not be adjusted and the medical team should maintain his routine practice (example: if the investigator is used to see the patient on D15, the visit will still take place, but no information, except pharmacovigilance data, will be collected). As

such, the data from the closest defined visit will be reported in the case report form (CRF) at each time point (see Figure 1).

During the inclusion consultation, the medical team will provide the patient with a patient diary with all the main information regarding its treatment and in which he should report some information (see Section 6.2).

The telephone calls will be made by a nurse from a company specialised in patients support called Patientys. Patients in the group with 'remote additional personalised nurse-led follow-up' will be contacted 8 times during the study (at D1, D7, D14, D21, D28, D44, D59 and D89, see Figure 1). The nurse will make sure that the treatment takes place in good conditions; she cannot intervene in the medical care of the patient, nor give answer to the questions relative to the disease or to the treatment of the patient. The medical team remains the privileged contact of the patient.

During the informed consent process, the patient may authorize a relative (i.e. a person he trusts and who can be among other, a family member, a friend or a housemate) to assist him during the nurse-led phone call. The first and last name of this person will be specified on the informed consent form.

During the first telephone call at D1, the nurse will confirm the enrolment of the patient in the study and will re-explain the calls schedule. Following this call, if the patient agrees to give the contact details of their physician and pharmacist, then the nurse will inform them, by letter or phone call, of the patient participation in the study.

During the following telephone calls, the nurse will perform a clinical evaluation by using a pre-established questionnaire and will collect treatment related AEs (see Section 6.2.3) as well as the pharmacovigilance (PV) information. After each telephone call, the nurse will establish a report.

The telephone call reports will be sent to the investigators on the same day of the nurse follow-up phone call.
The investigator will verify the severity of the AE and will determine the causal relationship with the oral targeted therapy.

- If case of serious adverse event (SAE), the investigator must complete and send immediately the serious adverse event (SAE) form (SAE form) to the CRO in charge of data monitoring (within 24h of the event). The causality will be determined by the investigator and recorded on SAE declaration form. In case of treatment exposure during pregnancy please refer to Section 5.3.2.2.
- In case of non-serious AE and/or of any other PV information, the investigator should complete and send the AEs page of the CRF to the CRO in charge of data monitoring within 7 days of the event. The causality will be determined by the investigator and recorded on the AEs page of the CRF.

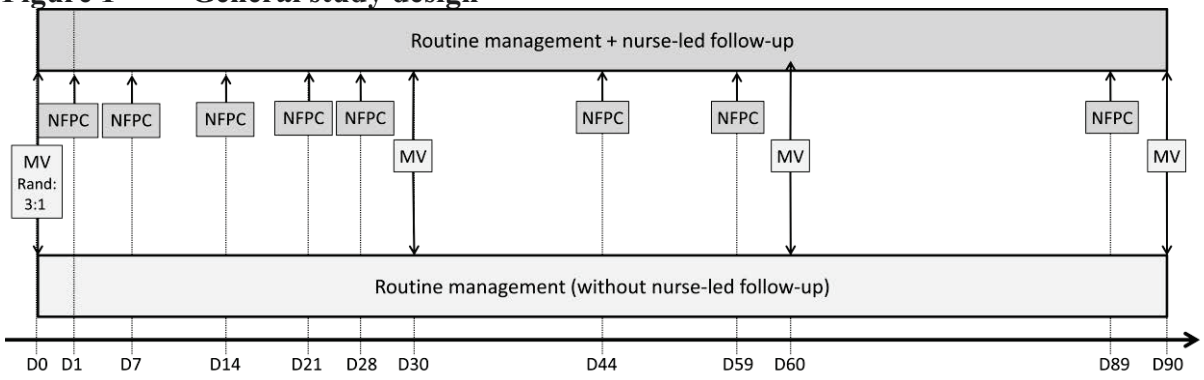
The nurse will also send, on the same day of follow-up phone call, all the information related to the SAEs, non-SAEs and any other PV information to the CRO in charge of data monitoring (copy of the AEs pages of the CRF sent to the investigators).

On arrival for the consultations with the investigator, the patient will be asked to complete questionnaires regarding treatment compliance, satisfaction and/or quality of life before the consultation, in the doctor's office or any other private place.

The CRO in charge of data monitoring will establish a hotline specifically for investigators and study personnel.

At Patientys centre, all incoming calls will be documented: during successful calls, an evaluation will be completed stating the date and time of the call. The failed calls will be documented in the study registry. No calls will be recorded.

Figure 1 General study design



At D1, the Patientys nurse will contact the general practitioner and the pharmacist of the patient in order to inform them of the patient's participation in the study.
MV : medical visit according to the routine practice of the centre (for example, if the investigator is used to seeing patients at D15, this consultation will still take place but no information, except pharmacovigilance data will, be collected); NFPC: nurse follow-up phone call ; rand : randomisation ; D = day

3.1.1 Administrative structure of the study

Gestionnaire de l'étude :
BOEHRINGER INGELHEIM France
14 rue Jean Antoine de Baïf
75013 Paris, France
Tel: +33 (0)1.44.34.67.25

Co-ordinating Investigator:
[redacted]
Tel : [redacted]

Patientys call-centre:
PATIENTYS – DIRECTMEDICA
31 rue des longs Prés
92100 Boulogne Billancourt, France

CRO in charge of study logistic and administrative management and data monitoring :
[redacted]

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The main objective of this study is to evaluate the impact of an additional nurse-led telephone follow-up during routine clinical practice of patients with stage IIIb/IV NSCLC. Based on recommendations of the Plan Cancer, nurse-led follow-up of patients becomes more and more common in order to ensure a better patient care. The implementation of nurse-led telephone follow-up in this study fits into this approach.

The current study is a routine clinical practice study and aims to evaluate the care provided to the patient and particularly the impact of the implementation of a nurse-led telephone follow-up in the patients' standard of care. In this routine clinical practice study, all the procedures and the products prescribed are part of the common practice. Only a particular method of follow-up is added for some patients. This method of monitoring has only negligible risks and constraints to patients enrolled in the study. The impact of the nurse-led telephone follow-up during healthcare given routinely will be assessed in terms of treatment compliance.

A control group that includes patients without additional nurse-led follow-up is needed to assess the benefit of the phone calls. To minimise the risk of patient's refusal to participate in the study and to collect sufficient data for patients with additional telephone follow-up, randomisation will be unbalanced. A ratio of 3:1 will be used for randomisation, giving each patient a probability of 0.75 to be included in the group with nurse-led follow-up' in addition to the healthcare given routinely by the specialised physician.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Main diagnosis for study entry

The study will be proposed to adult patients diagnosed with stage IIIb/IV NSCLC locally advanced or metastatic, with activating mutation(s) of EGFR and who are EGFR-TKI naïve.

3.3.2 Inclusion criteria

Patients will be eligible to enter the study if they meet all the following inclusion criteria:

- Male or female patient older than 18 years.
- Adult patient diagnosed with stage IIIb/IV NSCLC locally advanced or metastatic, with activating mutation(s) of EGFR and who is EGFR-TKI naïve.

- Patient for whom a decision of treatment with afatinib monotherapy has been taken in the frame of its marketing authorization.
- Out-patient.
- Patient having given written consent for participation in the study.
- Patient who is able to participate in the investigator's opinion.
- Patient affiliated with the French social security.

A copy of the written consent will be given to the patient, and the second copy will be filed in the study record.

3.3.3 Exclusion criteria

Patients meeting one of the following criteria will participating not be eligible

- Patients participating in an interventional clinical study.
- Patients for whom a participation in an interventional clinical study is foreseen within 3 months following the study inclusion.
- Patients participating in a therapeutic education program.

3.3.4 Removal of patients from therapy or assessments

Patients can decide to discontinue their participation in this study at any time.

Boehringer Ingelheim reserves the right to discontinue the overall study or in a particular centre for the following reasons:

- Inability to recruit the planned number of subjects across centres or in a particular centre.
- Evidence of information that could significantly affect the continuation of the study, or for other administrative reasons.
- Violation of Good Clinical Practice (GCP) or contract, by a study centre or an investigator, preventing the proper conduct of the study.

4. TREATMENTS

Not applicable.

5. EVALUATION CRITERIA

5.1 PRIMARY ENDPOINT

5.1.1 Primary endpoint

The primary endpoint of the study is the cumulated dose (mg) of oral targeted therapy during the 3-month follow-up.

5.1.2 Assessment methods

At each visit, patients should bring their oral targeted therapy packet delivered by their pharmacist (empty or started). Missing and remaining tablets will be counted by the medical team and reported in the CRF according to their dose.

The cumulated dose (mg) of the oral targeted therapy, taken between 2 visits, will be calculated as follows: sum of doses (mg) of the tablets used by the patient. Counting the tablets consumed by patients between consultations V_{i-1} and V_i will be done by the study team during consultation V_i from boxes of tablets returned by the patient. The doctor will report, in the CRF, and for each possible dosage (20 mg, 30 mg, 40 mg, 50 mg [only as second intention dose if the treatment is well-tolerated and as per product sheet recommendations]), the number of tablets used by the patient. The cumulated dose between consultations V_{i-1} and V_i will be calculated as follows:

$$[\text{Cumulated dose (mg)}]_i = \sum_{\text{Dosage} \in \{20,30,40\}} [\text{Dosage} \times Nbtab(Dosage)],$$

Where *Nbtab(Dosage)* is the number of consumed tablets of 20 mg, 30 mg 40 mg or 50 mg respectively.

The cumulated dose (mg) of oral targeted therapy over the 3-month study will be equal to the sum of the cumulated doses (mg) taken between the 2 visits, during the 3-month study. The total cumulated dose (mg) over 3 months will be calculated as follows:

$$\text{Cumulated dose (mg)} = \sum_i [\text{Cumulated dose (mg)}]_i$$

5.2 SECONDARY ENDPOINTS

5.2.1 Secondary endpoints

The following secondary endpoints will be evaluated in the study:

- Score (0–6) obtained with the Girerd questionnaire at D30, D60 and D90.
- Cumulated dose of oral targeted therapy not taken (all categories) following decision of the medical team.
- Cumulated dose of oral targeted therapy not taken due to dose reduction following decision of the medical team.

- Cumulated dose of oral targeted therapy not taken due to temporary or definitive interruption following the medical team decision.
- Cumulated dose of oral targeted therapy not taken (all categories) following patient decision.
- Cumulated dose of oral targeted therapy not taken due to dose reduction following patient decision.
- Cumulated dose of oral targeted therapy not taken due to temporary or definitive interruption following patient decision.
- VAS score (0–10) for overall patient satisfaction with the level of care (information, advice) at D90.
- Absolute variation observed for the quality of life questionnaire FACT Lung score between D30 and D0, between D90 and D30 and between D90 and D0.
- Number of emergency admissions (related to the treatment) during the 3-month follow-up.
- Number and duration of unplanned hospitalizations (related to the treatment) during the 3-month follow-up.
- Number of unplanned visits to the investigator during the 3-month follow-up.
- Number of unplanned visits to a specialist, whatever is his specialty, other than the investigator during the 3-month follow-up.
- Number of unplanned visits to the general practitioner during the 3-month follow-up.
- VAS score (0–10) for overall investigator satisfaction with the level of patient care at D90.
- VAS score (0–10) for overall general practitioner satisfaction with the level of patient care at D90 (only for the patients with ‘remote additional personalised nurse-led follow-up)
- VAS score (0–10) for overall pharmacist satisfaction with the level of patient care at D90 (only for the patients with ‘remote additional personalised nurse-led follow-up).
- Number of calls made by the patients to their general practitioner during the 3-month follow-up.
- Number of calls made by the general practitioner to the patient during the 3-month follow-up.
- Number of calls made by the patients to their medical team during the 3-month follow-up.
- Number of calls made by the medical team to their patient during the 3-month follow-up.
- Number of calls between the general practitioners and the medical teams during the 3-month follow-up.

5.2.2 Assessment methods

Girerd questionnaire is a questionnaire composed of 6 binary questions (yes/no) and is used to assess treatment compliance. The final score obtained is the number of questions to which the patient responded 'yes'. Thus, the score ranges from 0 to 6.

FACT Lung quality of life questionnaire is composed of 27 items of the FACT-G questionnaire, with the following 4 dimensions: physical well-being, social well-being,

emotional well-being, and functional well-being. It is composed of 9 questions specific to lung cancer. Each of the 36 questions is scored from 0 to 4 (cf. Section 7.3.3 for more details on the analysis of these questionnaires).

Cumulated dose (mg) of oral targeted therapy not taken between 2 visits is the sum of the doses (mg) of the tablets not taken by the patient. The cumulated dose (mg) of the oral targeted therapy not taken during the 3-month follow-up is the sum of the doses (mg) cumulated not taken between 2 visits during the 3-month follow-up. This dose can be calculated overall and by reason for not taking the prescribed dose: dose reduction, temporary or definitive discontinuation following decision of the medical team / patient decision.

VAS scores will be presented in the form of a horizontal ungraduated line of 10 cm, with the following extremities: left, 'completely unsatisfied' and right, 'very satisfied'. The number of points (0 to 10) obtained in VAS corresponds to the distance (cm) between the left extremity of the line and the mark placed on the line by the patient, investigator, general practitioner, or pharmacist to assess patient's level of satisfaction.

5.3 SAFETY DATA TOLERANCE

5.3.1 Safety endpoints

The current study will collect the AEs as follows:

- Number of adverse events (AE) related to the oral targeted therapy.
- Number of AE related to the oral targeted therapy of grade ≥ 3.
- Number of serious adverse events (SAE) related to the oral targeted therapy.
- Number of AE related to the oral targeted therapy and leading to a definitive or temporary discontinuation of the drug, or to a dose reduction.

5.3.2 Assessment of adverse events

The AEs will be collected by the medical team during patient consultation or by the nurse of the specialised call centre Patientys during the follow-up phone call.

The nurse will transmit to the investigator the telephone call report by e-mail or by FAX on the day of the follow-up phone call and will provide [redacted] with the AE page(s) of the CRF, if applicable. If needed the nurse may contact the medical team. The investigator will check, confirm, and comment the AEs reported by the nurse. [redacted] will add any relevant event. [redacted] will also complete the AEs page of the CRF sent by the nurse by adding the intensity and the causal relationship with the oral targeted therapy.

Each AE will be recorded in the CRF and send to the CRO in charge of the data monitoring. The modalities of transmission to the CRO in charge of data monitoring and to the sponsor of the study are described in Sections 3.1, 6.2.3 and 8.4.

5.3.2.1 Definition of adverse events

Adverse event
An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a person taking part in a clinical study. The event does not necessarily have to have a causal relationship with the study.

Serious adverse event
A SAE is defined as any AE which:

- Results in death.
- Is immediately life-threatening.
- Results in persistent or significant disability / incapacity.
- Requires or prolongs patient hospitalization.
- Is a congenital anomaly / birth defect.
- Or is considered as medically relevant for any other reasons.

Medical judgment is warranted to determine whether the event or adverse reaction is serious in other situations. Significant reactions or adverse events that are not immediately life-threatening or do not result in death or hospitalization, but may put the subject at risk or may require intervention to prevent the occurrence of one of the above criteria, must also be considered serious.

Intensity of adverse events
The intensity of adverse events should be classified and recorded according to the CTCAE criteria version 4.03 in the CRF.

Causal relationship of adverse events with the targeted oral therapy
Medical judgment should be used to determine the relationship with the oral targeted therapy while considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Worsening of the underlying disease or other pre-existing conditions
Worsening of the underlying disease or other pre-existing conditions and changes in vital signs, ECG, physical examination, and laboratory test results will be recorded as an AE in the CRF, if they are judged clinically relevant by the investigator.

Other pharmacovigilance information

- Non-conform use of the product i.e. any use outside the marketing authorisation (for instance: overdose, medical error, intentional misuse or abuse, administration outside the marketing authorisation, not in conformity with the marketing authorisation, administrated for a condition not cover by the marketing authorisation),
- Product's exposure during pregnancy or breast-feeding,
- Product's exposure during conception (father),
- Suspicion of contamination with an infectious agent,
- Suspicion of AE related to a professional exposure,
- Lack of efficacy or any increased in therapeutic effect or any unexpected benefit
- Any interaction with other product (drugs, food, tobacco, alcohol, radiation).

5.3.2.2 Adverse event and reporting

All SAEs, non-serious AEs and others PV information, occurring during the course of the study (i.e., from signing the informed consent onwards through D90) will be collected, documented and reported to the sponsor or the CRO in charge of the data monitoring by the investigator on the appropriate reporting forms (AE page of the CRF or SAE form).

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, causal relationship, and action taken with the targeted oral therapy. The investigator will determine the relationship of the oral targeted therapy to all AEs.

All personnel involved in the study (investigator, the Patientys call centre nurse, general practitioner, centre personnel…) must immediately report any SAE that they encounter to the CRO responsible of the data monitoring. The event must be notified within 24h, via telephone or FAX using the SAE reporting form to:

[redacted]
Follow-up of SAEs - PARTAGE
[redacted]
Fax: [redacted]
Back-up fax: [redacted]
E-mail: [redacted]

The notification of the SAEs must be immediate whether the oral targeted therapy was administered or not, whether there is a causal relationship or not, or whether the information is initial information or additional information.

All other non-serious AEs and PV information must be reported to the CRO in charge of the study management within 7 calendar days of knowledge The CRO must inform Boehringer Ingelheim within 7 calendar days of notification by the investigator.

Pregnancy
Any pregnancy occurring during the course of this study must be immediately reported following the same SAE reporting procedure using the pregnancy form. The pregnancy must be followed- up, its outcome documented, and the pregnancy form should be completed. In the absence of any AE, only the pregnancy monitoring is to be completed.

Health professional should comply with the applicable legislation regarding reporting obligations (Article R5121-161 of the French public health code).

5.3.3 Assessment of other safety parameters

Not applicable

5.4 APPROPRIATENESS OF MEASUREMENTS

All clinical evaluations made in this study are part of the routine monitoring of patients with NSCLC. The questionnaires used during patients follow-up are validated questionnaires, with the exception of the satisfaction questionnaires.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Table 2 Visit schedule and data collection

	D0	D1[a]	D7[a]	D14[a]	D21[a]	D28[a]	**D30 M1**	D45[a]	D59[a]	**D60 M2**	DJ89[a]	**D90[b] M3**
	MV Incl	NFPC 1	NFPC 2	NFPC 3	NFPC 4	NFPC 5	**MV1**	NFPC 6	NFPC 7	**MV2**	NFPC 8	**MV3**
Written consent	**X**											
Verification of eligibility	**X**											
Documentation of patient's acceptance or rejection of participation in the study file	**X**											
Demographic information [c]	**X**											
Physical exam [d]	**X**											
NSCLC characteristics [e]	**X**											
Past medical history, past treatments	**X**											
Concomitant diseases, concomitant medications	**X**						**X**			**X**		**X**
Randomisation	**X**											
Patient diary delivery	**X**											
Clinical evaluation by Patientys nurse		X	X	X	X	X		X	X		X	
Collection of AEs	**X**	X	X	X	X	X	**X**	X	X	**X**	X	**X**
Patient compliance (returned tablets and Girerd questionnaire)							**X**			**X**		**X**
Patient quality of life questionnaire	**X**						**X**					**X**
Patient global satisfaction questionnaires												**X**
Data collection on use of healthcare services							**X**			**X**		**X**
General practitioner and/or pharmacist global satisfaction questionnaires												**X**
Investigator global satisfaction questionnaires												**X**

[a] Only for patients 'With nurse-led follow-up' group
[b] Or end of study visit if the patient withdraws prematurely from the study
[c] Including age, gender, weight, height
[d] Complete physical exam at inclusion visit including: Vital signs (Heart & respiratory rate, blood pressure, temperature), and collection of the cutaneous, gastro-intestinal, respiratory, eye, cardiovascular and allergic symptoms
[e] Diagnosis date, disease stage, performance status (ECOG), biopsy date, type of mutation(s), method of mutation typing, previous treatments of NSCLC
f The drug accountability of taken and not taken tablets will be made by the medical team in the Case Report Form
D = day ; M = month ; MV = medical visit according to the routine practice of the centre, NFPC= nurse follow-up phone call, Incl.= inclusion, NSCLC = non-small-cell lung cancer ;
AE= adverse event.

6.2 DETAILS OF DATA COLLECTION AT EACH VISIT/ PHONE CALL

6.2.1 Inclusion (Incl. MV)

During the inclusion consultation, the medical team will ask the patient to participate in this study. Written consent will be obtained; however if the patient refuses to participate in the study, the refusal with the corresponding reason, if available, will be documented in the study registry. The patient accepting to participate in the study will be randomised to receive or not a remote additional nurse-led follow-up during the follow-up period (randomisation ratio of 3:1).

The registration form must be completed and forwarded to Patientys by e-mail or FAX.

If the patient agrees to participate in the study, the investigator will collect the following data:

- Demographic information (age, gender, weight, height).
- NSCLC characteristics (date of first diagnosis, disease stage, performance status from the Eastern Cooperative Oncology Group [ECOG], biopsy date, type of mutation(s) detected, test/method used to assess mutation and previous treatments).
- Medical history, concomitant diseases, previous and concomitant treatment.
- Results of the complete physical examination: vital signs (heart and respiratory rate,blood pressure, temperature), and presence of any of the following symptoms: coetaneous, gastrointestinal, respiratory, ocular, cardiovascular and allergic.

As with any initiation of oral targeted therapy treatment, the medical team will counsel the patient on the oral targeted therapy, treatment schedule and precautions (lifestyle changes) to be taken in order to prevent treatment related adverse events, in addition to giving the patient a diary to report information related to the utilisation of healthcare services (telephone calls with or visits to their general practitioner or specialist, with any specialty).

During this consultation, and as per routine practice, the medical team will set the schedule of upcoming consultations. In this study, 3 data collection time-points at monthly intervals are defined (D30, D60, and D90). The frequency of visits should not be adjusted and the medical team should maintain his routine practice (example: if the investigator is used to see the patient on D15, the visit will still take place, but no information, except pharmacovigilance data, will be collected). As such, the data from the closest defined visit will be reported in the CRF.

The patient will also be asked to complete quality of life questionnaire (FACT Lung).

6.2.2 Other visits (MV1, MV2, MV3)

At the 2nd and 3rd consultation visits (D30 and D60) during which data will be collected, the patient will be asked to:

- Complete the compliance questionnaire (Girerd).
- Complete the quality of life questionnaire (FACT Lung; only on D30).
- Bring their oral targeted therapy packets (empty or started) prescribed/consumed since the previous consultation visit.

- Bring their patient diary.

All the questionnaires will be completed before the start of consultations, in the doctor's office or any other available private place.

The medical team will record the number of tablets taken and not taken, and will report this information in the patient's CRF.

Adverse events and concomitant diseases and medications will be collected during these consultations. Data on the utilization of healthcare services (hospitalizations, emergency room visits, unscheduled consultation visits), including the number of visits and the number of calls to the general practitioner, will also be collected using the information reported by the patient in their patient diary.

During the last consultation visit (MV3 on D90), the patient will be asked to:

- Complete the compliance questionnaire (Girerd),
- Complete the quality of life questionnaire (FACT Lung),
- Complete the global satisfaction questionnaire,
- Bring their oral targeted therapy packets (empty or started) prescribed/consumed since the previous consultation visit,
- Bring their patient diary.

All the questionnaires will be completed before the start of consultations, in the doctor's office or any other available private place.

The medical team will record the number of tablets taken and not taken, and will report this information in the patient's CRF.

Adverse events and concomitant diseases and medications will be collected during these consultations. Data on the utilization of healthcare services will also be collected using the information reported by the patient in their patient diary.

Assessment of overall level of satisfaction of the general practitioner and the pharmacist will be collected via paper questionnaires that will be sent by Patientys along with a stamped return envelope to the address of the CRO responsible for the data monitoring of the study. The evaluation document of the overall level of satisfaction of the investigator of the medical team is given in the last page of the CRF and should ideally be completed at the last patient visit.

6.2.3 Remote additional nurse-led follow-up

This follow-up will be implemented only for patients in the 'with nurse-led follow-up' group. During each telephone call, the nurse will have to complete a pre-established questionnaire, an AE page, and a SAEs declaration form.

During the informed consent process, the patient may authorize a relative (i.e. a person he trusts and who can be among other, a family member, a friend or a housemate) to assist him

during the nurse-led phone call. The first and last name of this person will be specified on the informed consent form.

During the first telephone call (D1), nurses will confirm the registration of the patient. The name and contact details of the general practitioner and pharmacist of the patient will be collected in a study registry. These data will allow to inform the general practitioners and pharmacists of patients included in the 'with remote additional personalised nurse-led follow-up' group of the patient's participation in the study and to send them the global satisfaction questionnaire at the end of the study.

During subsequent telephone calls, the nurse will establish a 'clinical evaluation' using questions such as:

- "How are you feeling today?"
- "Did you take your medicine as your doctor has prescribed?"
- "Did you complete patient diary of the study?"

She will also collect AEs encountered during treatment intake. In particular, the following events will be collected:

- Gastrointestinal disorders (diarrhea, stomatitis, dyspepsia, cheilitis).
- Skin and subcutaneous tissue disorders (rash, acneiform dermatits, pruritus, dry skin, the palmar-plantar syndrome).
- Infections (paronychia, cystitis).
- Appetite or metabolic disorders (decreased appetite , dehydration, hypokalemia).
- Nervous system disorders (dysgeusia).
- Eye disorders (conjunctivitis, dry eye, keratitis, tearing, light sensitivity).
- Respiratory disorders (epistaxis, rhinorrhea, interstitial lung disease, pneumonia, respiratory distress, allergic alveolitis).
- Musculoskeletal disorders (muscular spasms).
- General disorders (fever).
- Investigations (weight loss).
- Others.

The nurse will transmit to the investigator the telephone call report by e-mail or by FAX on the day of the follow-up phone call and will provide him with the AE page(s) of the CRF, if applicable. If needed the nurse may contact the medical team. Each AE will be recorded in the CRF and send to the CRO in charge of the data monitoring. The investigator of the team will also complete the AEs page of the CRF sent by the nurse by adding the intensity and the causal relationship with the oral targeted therapy.

- If case of serious adverse event (SAE), the investigator must complete and send the serious adverse event (SAE) form (SAE form) to the CRO in charge of data monitoring within 24h of the event. The causality will be determined by the investigator and recorded on SAE declaration form.
- In case of non-serious AE, the investigator should complete and send the AEs page of the CRF to the CRO in charge of data monitoring within 7 days of the event. The causality will be determined by the investigator and recorded on the AEs page of the CRF.

The nurse will also send, on the same day of follow-up phone call, the information related to the SAEs and non-SAEs to the CRO in charge of data monitoring.

7. STATISTICAL METHODS AND DETERMINATION OF PATIENTS SAMPLE SIZE

7.1 STATISTICAL DESIGN

This is a routine clinical practice, randomised, open-label, multicentre, study.
Patients will be randomised in one of the following 2 groups:

- Group 'without remote additional personalised nurse-led follow-up': patients will receive the healthcare given routinely by the medical team (100 patients).

- Group with 'remote additional personalised nurse-led follow-up': patients will receive telephone calls from a nurse in addition to the healthcare given routinely by their medical team (300 patients).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The null and alternative hypotheses are as follows:

H_0 : no difference exists between the average doses of the first 3-month oral targeted therapy between 'with remote additional personalised nurse-led follow-up' and 'without remote additional personalised nurse-led follow-up' groups.

$$H_0: \text{average cumulated dose}_{\text{'With nurse-led follow-up'}} = \text{average cumulated dose}_{\text{'Without nurse-led follow-up'}}$$

H1 : a difference exists between the average doses of the first 3-month oral targeted therapy between 'With nurse-led follow-up' and 'Without nurse-led follow-up' groups.

$$H_1: \text{average cumulated dose}_{\text{'With nurse-led follow-up'}} \neq \text{average cumulated dose}_{\text{'Without nurse-led follow-up'}}$$

7.3 PLANNED ANALYSES

General considerations

The statistical analysis will be performed using SAS (version 9.1 or a more recent version). All tests will be performed 2-sided with a cut-off of 5%.

The primary analysis population will be the population of randomised patients who satisfy the essential inclusion and exclusion criteria, and for whom information is available for the major evaluation criteria (in particular the primary criterion). This population will be used for the analysis of the primary and secondary endpoints (except safety data).

The safety population, for which safety endpoints will be analysed, will include patients who had received at least one dose of the oral targeted therapy during the 3-month study.

Quantitative variables will be described, overall and by group, using number of observed values, mean, standard deviation, median, lower quartile, upper quartile, minimum, maximum, 2-sided 95% confidence interval of the mean. Comparison between the 2 groups will be done using Student test or Wilcoxon rank sum test in case of non-normal data or non-homogeneity of variance.

Qualitative variables will be described, overall and by group using number of observed values, percentage and two-sided 95% confidence interval of the percentage by category. Comparison between the 2 groups will be done using Student test or Fisher's exact test.

7.3.1 Demographic information and baseline characteristics

Demographic information and baseline characteristics will be described for all patients included in the study.

Past medical history and concomitant treatments will be described overall and per group.

The frequency of the previous medications will be calculated according to "patient" approach: the frequency will be calculated globally and by 'système organe classe' (SOC) and Preferred Term (PT) of the terminology used in the dictionary for regulatory activities (MedDRA).

The frequency of previous treatments will be presented in "patient" approach: the frequency of patients who received at least one concomitant medication and frequency of patients with at least one prior medication will be calculated. Frequencies will be calculated by term ATC (terminology WHO-DD). Each table will be sorted in a descending order of frequency of ATC terms.

7.3.2 Primary analyses

The primary objective of the study is to evaluate overall treatment compliance after 3-months follow-up and to compare this compliance between the 2 study groups: the group of patients with additional nurse-led follow-up and the group without nurse-led follow-up.

As such, the cumulated dose (mg) of the oral targeted therapy over the 3-month study will be described for each of the groups: number of observed values, mean, standard deviation, median, lower quartile, upper quartile, minimum, maximum, two-sided 95% confidence interval of the mean.

The mean cumulated dose will be compared between groups by Student test, or Wilcoxon rank sum test in case of non-normal data and/or non-homeogeneity of variance.

A complementary analysis using a Kaplan-Meier curve will also be performed on the principal criteria, to evaluate the time between start of treatment and the first dose modification or interruption of the oral Targeted therapy.

7.3.3 Secondary analyses

In addition to the primary analysis, a secondary analysis of Girerd questionnaire scores will be performed.

This questionnaire is composed of 6 binary questions (yes/no) and is used to assess treatment compliance. The final score obtained is the number of questions to which the patient responded 'yes'. Thus, the score ranges from 0 to 6.

A patient will be classified as:

- Good compliant: score = 0.
- Minor non-compliant: score = 1 or 2.
- Non-compliant: score > 2.

A sub-group descriptive analysis of patients per score category on D30, D60 and D90 will be presented: number of observed values, percentage, and 2-sided 95% confidence interval.

In addition, the percentage of patients with good compliance (score = 0) to the percentage of patients with minor non-compliance and / or non-compliance (score> 0) will be compared at each time point (D30, D60, D90), between the 2 groups of patients ('With nurse-led follow-up' and 'Without nurse-led follow-up'), using Chi-2 or Fisher-exact test.

The cumulated doses (mg) of the oral targeted therapy not taken during the 3-month follow-up by decision of the medical team (with details by type: dose reduction, temporary or definitive discontinuation) / by decision of the patient him/herself (with details by type: dose reduction, temporary or definitive discontinuation) will be described for each follow-up group, using number of observed values, mean, standard deviation, median, lower quartile, upper quartile, minimum, maximum, 2-sided 95% confidence interval of the mean.

Analysis of other secondary endpoints will simply be descriptive and inferential as described in the general statistical considerations, namely:

- Quantitative variables:
    - VAS score (0–10) for overall patient satisfaction with the level of self-care (information, counselling, advice...) at D90.
    - Absolute variation observed for the quality of life questionnaire FACT Lung score between D30 and D0, between D90 and D0, and between D30 and D90.
    - Duration of unplanned hospitalisations during the 3-month follow-up.
    - VAS score (0–10) for overall investigator satisfaction with the level of patient self-care at D90.
    - VAS score (0–10) for overall general practitioner satisfaction with the level of patient self-care at D90 (only for the patients with 'remote additional personalised nurse-led follow-up).

  - VAS score (0–10) for overall pharmacist satisfaction with the level of patient self-care at D90 (only for the patients with 'remote additional personalised nurse-led follow-up).

- Qualitative variables:
  - Number of emergency admissions during the 3-month follow-up.
  - Number of unplanned hospitalisations during the 3-month follow-up.
  - Number of unplanned visits to the investigator during the 3-month follow-up.
  - Number of unplanned visits to a specialist, whatever is his specialty, other than the investigator during the 3-month follow-up.
  - Number of unplanned visits to the general practitioner during the 3-month follow-up.
  - Number of calls made by the patients to their general practitioner during the 3-month follow-up.
  - Number of calls made by the general practitioner to their patient during the 3-month follow-up.
  - Number of calls made by the patients to their medical team during the 3-month follow-up.
  - Number of calls made by the medical team to their patient during the 3-month follow-up.
  - Number of calls between the general practitioners and the medical team during the 3-month follow-up.

Moreover, the impact of patient follow-up on the evolution of parameters measured repeatedly during the study will be studied using mixed model repeated measures, in which the patient will represent a random effect and the follow-up group will represent a fixed effect. A Follow-up*Visit interaction will demonstrate the existence of a different evolution of the parameters according to the type of follow-up. This analysis will only be performed for the criteria measured several times during the follow-up.

The identification of possible predictors of non-compliance will be conducted using a generalized mixed effect model (proc GLIMMIX in SAS) by including the patients and investigators characteristics and the group (with/without additional nurse-led follow-up) as explanatory variables (these characteristics will be detailed with more precision in the Statistical Analysis Plan [SAP]). A non-compliant patient will be defined as a patient with the ratio between the cumulated dose actually taken during the first 3 months of treatment and the cumulated dose taken during the first 3 months of treatment without interruption and dose reduction is strictly less than 80%. This modelling will be exploratory.

7.3.4 Safety analyses

Safety analyses will be performed on all patients who received at least one dose of oral targeted therapy during the 3-month follow-up. Only events considered related to oral targeted therapy will be considered in the statistical analysis.

For each study group, the number of patients with at least one of the following will be described:

- One AE related to the oral targeted therapy.

- One AE related to the oral targeted therapy of grade ≥ 3.
- One SAE related to the oral targeted therapy.
- One AE related to the oral targeted therapy leading to a definitive discontinuation of the drug.
- One AE related to the oral targeted therapy leading to a temporary discontinuation of the drug.
- One AE related to the oral targeted therapy leading to a dose reduction.

7.3.5 Interim analyses

No interim analysis is planned for this study.

7.4 HANDLING OF MISSING DATA

In general, no specific method of handling missing data is foreseen for this study. The analyses will be performed on all available data.

However, for the primary endpoint, a sensitivity analysis with missing data handling should be planned and detailed in the Statistical Analysis Plan (SAP) before database lock.

7.5 RANDOMISATION

Patients will be randomised in one of the 2 study groups following a ratio of 3:1 (3 patients in the with 'remote additional personalised nurse-led follow-up' group for each one patient in the without 'remote additional personalised nurse-led follow-up'), and according to a list of randomisation previously defined.

This list will be generated before the start of the study according to all the following criteria:

- Blocks of different size: 4 and 8.
- Parallel groups.
- Including 2 treatment groups.
- Following a 3:1 ratio.

It will be implemented using a validated computer tool which allows generating a sequence of pseudo-random numbers and selecting of a number called 'seed randomisation', not communicated to operational involved in the project, to ensure the non-reproducibility and non-predictability of the generation of randomisation list.

The allocation of a patient to one study group or the other ('with remote additional personalised nurse-led follow-up' versus 'without remote additional personalised nurse-led follow-up' will be done sequentially within each centre using randomisation envelope. To limit selection bias in the absence of central randomisation, the blocks of randomisation will be of varying size (4 or 8).

7.6 DETERMINATION OF SAMPLE SIZE

In the absence of dose discontinuation or reduction, the cumulated dose of oral targeted therapy should be 3600 mg of afatinib, which corresponds to a daily dose of 40 mg for 90 days.

Clinical trials performed with afatinib before its marketing authorisation showed that over the first 3-month follow-up the mean dose of 3000 mg was taken (which corresponds to a dose intensity of 83%) (Boehringer Ingelheim First Interim Study Report 1200.32).

It was estimated that the mean dose observed in the group 'without remote additional personalised nurse-led follow-up' will be similar to the mean dose observed in the afatinib clinical trials and that adding an additional nurse-led follow-up will increase the mean dose by 6% (3180 mg, dose intensity of 88%).

As such, the number of patients to be included in the study has been calculated on the basis of a t-test for 2 unmatched samples with the following hypotheses:

- Mean cumulated dose of oral targeted therapy taken during the 3-month follow-up in the group 'without remote additional personalised nurse-led follow-up': 3000 mg (dose intensity of 83%).
- Mean cumulated dose of oral targeted therapy taken during the 3-month study in the group 'with remote additional personalised nurse-led follow-up': 3180 mg (dose intensity of 88%).
- Standard deviation of the cumulated dose of oral targeted therapy taken during the 3-month follow-up in both groups: 500.
- Type I error: $\alpha = 0.05$.
- Type II error: $\beta = 0.20$ (power = 80%).
- Ratio 'with remote additional personalised nurse-led follow-up' group/'without remote additional personalised nurse-led follow-up' group = 3.

Using these hypotheses, in order to show an increase in the cumulated dose with the addition of 3-month nurse-led follow-up, it is necessary to have 82 patients in the group 'without remote additional personalised nurse-led follow-up' and 246 patients in the group 'with remote additional personalised nurse-led follow-up '.

If it is considered that 20% of included patients will be non-evaluable for the primary criterion, it is necessary to include 99 patients in the group 'without remote additional personalised nurse-led follow-up' and 297 patients in the group 'with remote additional personalised nurse-led follow-up', i.e. 396 patients in total which can be rounded up to 400.

8. INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

This study will be conducted according to the protocol, following the principles of Helsinki Declaration, GCPs requirements (transposition into French law of "ICH-GCP" [International Conference of Harmonization-Good Clinical Practice]) and the applicable legislation, and according to standard procedures of Boehringer Ingelheim. Routine medical care remains the responsibility of the general practitioner of the patient.

The medical team must immediately inform the sponsor or his representative of any emergency measures taken to protect patients from immediate danger, in addition to any violation of the protocol and GCPs.

Insurance:
This study is a clinical routine practice study and, in accordance with the law, is covered by the liability insurance of the participants in the study centres.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated once all documents are reviewed by ethics committee (Comité de Protection des Personnes [CPP] Ile de France II) and other relevant health institutions concerned with studies of routine practice in accordance with applicable French legislation (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la santé [CCTRIS] / Commission Nationale de l'Informatique et des Libertés [CNIL], Conseil National de l'Ordre National des Médecins [CNOM]). Any substantial change to the protocol will be implemented only after receiving the approval of the CPP. Non-substantial changes will be informed to the CPP.

Patients participating in a routine practice study should be informed of the purpose of the study, duration, number of participants and their right to refuse participation in the study. Patients will be verbally informed by the medical team and will receive a copy of the patient information consent form (Appendix 10.1) which they must sign. This written consent must be obtained prior to initiation of any procedure related to the study.

The data collected during this study will be processed by computer. Treatment may be carried out in France or abroad, and will be conducted in compliance with the French law n° 78-17 of 6 January 1978 relating to computers, files and freedoms, as amended by Law 2004-801 of August 6, 2004. All necessary measures to ensure data confidentiality will be taken in accordance with the applicable legislation. Patients will not be identified by name or date of birth on the case report form or any other study document submitted to the sponsor or his representative. Patients will receive a unique identification number upon their consent to participate in the study. Patients should be informed that their medical records may be reviewed by staff appointed by the sponsor or his representative or by inspectors from the related authorities.

8.2 QUALITY CONTROL

Investigators have the responsibility to collect and report data in the CRF. It shall ensure that data are fully and accurately reported and are consistent with the source data.

An audit or inspection of this study can be made by the sponsor or any of [redacted] representatives, or by relevant authorities to ensure that the study is being conducted according to GCP and applicable legislation.

8.3 RECORDS MANAGEMENT

8.3.1 Data management

All information required by the protocol will be recorded on paper CRFs which will be completed by the medical teams as well as on the self-administered questionnaires completed by patients.

The CRFs and questionnaires will be sent by the medical team to the CRO in charge of data monitoring by postal mail as soon as the patient has completed the study. The nurses in the call centre specialised in following-up patients will also send, weekly, a copy of the AEs page of to the CRO in charge of data monitoring.

A study-specific database will be created, tested and validated prior to data entry. Data entry will be performed by the team responsible for managing the duplicate data entry. A plan for data validation will be developed and will describe, in details, the controls run for each variable as well as the list of corrections that are obvious and authorized.

The integrity of the case report forms will be checked upon receipt and then will be used for data entry. The data will then be controlled by the team responsible for data management, by using the error messages from the validation programs. Obvious errors will be corrected. Other errors, omissions or inconsistencies, will be mentioned on query forms that will be sent to the investigator for correction (this measure concerns only the CRF of doctors and is not applicable to patient self-report questionnaires). After receiving the query forms completed by the investigator, corrections will be included in the database.

The database will be locked after a final quality control and finalisation of the SAP.

8.3.2 Source documents

CRF will be provided for each patient. Predefined questionnaires will be given to Patientys nurses to use for data collection during the telephone call. Patients should complete the self-administered questionnaires as specified in the protocol. All these documents are considered the source documents of the study.

Data on patient demographics and their medical history will be collected from the patient's medical record (See Section 6.2).

8.3.3 Access to source documents

The investigator or study centre will authorise audit visits and review of data by auditors or inspectors. CRFs and any other source documents, including study notes and copies of medical examination must be available upon request for review by the sponsor or auditors.

8.3.4 Storage of records

Investigators
Documents related to this study will be archived in accordance with GCP for a period of 15 years after the end of the study. Medical teams and the sponsor should archive documents related to the study in accordance with the applicable regulations.

Any change in the arrangements for archiving or any document destruction cannot be done without the consent of the sponsor. After the archival life, the sponsor will be consulted for the disposal terms and will have to agree in writing.

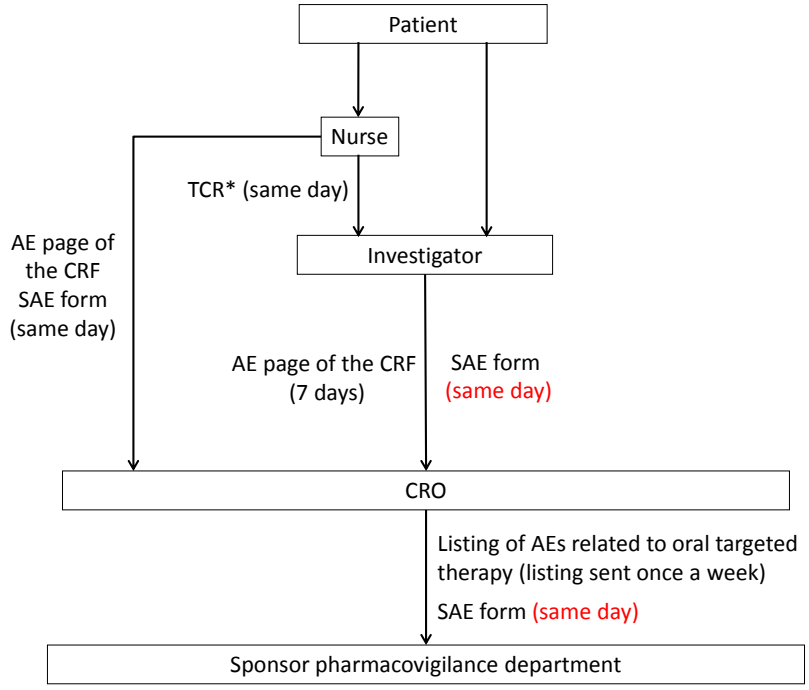
8.4 NOTIFICATION OF ADVERSE EVENTS AND OTHERS PHARMACOVIGILANCE INFORMATIONS

SAEs must be immediately reported to the CRO in charge of data monitoring (within 24h following the knowledge of the event) and forwarded by the CRO to the sponsor pharmacovigilance department on the same day. Non-serious AEs and any other PV information must be reported to the CRO in charge of the data monitoring within 7 days of knowledge and forwarded to the sponsor pharmacovigilance department within the next 7 days (Figure 2).

The Patientys call centre nurses will send information related to AE and other PV information to the investigator of the medical team via the telephone call report ([redacted] is responsible to assess the intensity and the causal relationship) on the day of the phone call.

- In case of SAE: the investigator must immediately send the completed SAE from to the CRO in charge of the data monitoring (within 24h of knowledge). The CRO must inform the sponsor's PV department and forward the SAE form on same day.
- In case of non-serious AE or of any other PV information: the investigator must complete and send the AEs page of the CRF to the CRO in charge of the data monitoring within 7 calendar days following the event. The CRO will establish a list of non-serious AEs related to the oral targeted therapy and will provide it to the sponsor weekly.

Figure 2 Procedure for reporting serious and non-serious adverse events



The telephone call report contains the AE page(s) of the CRF and the SAE form(s)
TCR = telephone call report, AE= adverse event, SAE = serious adverse event, CRF = case report form, CRO = contract research organization.

8.5 STATEMENT OF CONFIDENTIALITY

Individual medical information of each patient obtained as a result of this study are considered confidential and cannot be disclosed to a third party under any circumstances, except for cases mentioned below. Confidentiality will be ensured by the use of identification code.

Data generated as results of this study will be available upon request for review by investigators, representatives of the study sponsor, the scientific committee and the ethics committee (CPP).

8.6 COMPLETION OF STUDY

The sponsor or [redacted] representative will notify the CPP, in writing, of the termination of the study.

8.7 SCIENTIFIC COMMITTEE

No specific risks have been identified in the conduct of this routine clinical practice study where only the impact of additional nurse-led follow-up is evaluated. Thus, it can be considered that the risks to the patient participating in the study are negligible. Moreover, no treatment is administered blindly because treatments are administered as part of the routine practice of the medical team and no interim analysis will be performed. Therefore, it was decided not to establish an independent surveillance committee for this study.

A scientific committee was established for this study in order to participate in discussions on the study design, feasibility, implementation, monitoring, and analysis and interpretation of results.

Composition:

- [redacted]nstitut Bergonié, Bordeaux.
- [redacted] Centre Hospitalier, Mulhouse.
- [redacted] Institut Gustave Roussy, Paris.
- [redacted]; Centre René Gauducheau, Saint Herblain.
- [redacted] CHU Rennes.
- [redacted] Hôpital Européen Georges Pompidou, Paris.
- [redacted] Hôpitaux civils, Paris.
- [redacted] Hôpital Tenon, Paris.

8.8 RESULTS PUBLISHING

Any information obtained from this study will be treated as confidential until the analysis and final review by Boehringer Ingelheim and by members of the Scientific Committee are carried out. Any written or oral communication of the study results must receive the prior approval of Boehringer Ingelheim and the Scientific Committee.

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10. APPENDICES

10.1 INFORMED CONSENT FORM

10.2 GIRERD QUESTIONNAIRE

10.3 FACT-LUNG QUESTIONNAIRE

11. SUMMARY OF NON-INTERVENTIONAL STUDY PROTOCOL MODIFICATIONS

Not applicable.