Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c38958167-01
BI Study Number:	1200-0318
BI Investigational Product (s):	Giotrif® (afatinib)
Title:	Real-world study on afatinib as first-line treatment in patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC)
Brief lay title	The study observes afatinib as first-line treatment in patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer
Protocol version identifier:	3.0
Date of last version of protocol:	26 Aug 2019 (v2.0) 03 July 2019 (v1.0)
PASS:	No
EU PAS register number:	TBD
Active substance:	Afatinib Antineoplastic agents, tyrosine kinase inhibitors ATC code: L01XE13
Medicinal product:	Giotrif®, 30 mg and 40 mg tablets
Product reference:	30 mg: EU/1/13/879/004, EU/1/13/879/005, EU/1/13/879/006 40 mg: EU/1/13/879/007, EU/1/13/879/008, EU/1/13/879/009
Procedure number:	N/A
Joint PASS:	No
Research question and objectives:	Primary objective: To assess the time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment or death date by any cause.

	Secondary objective: To assess objective response rate, overall survival and safety of afatinib first-line therapy in advanced NSCLC patients with EGFR mutation. Exploratory Objective： To collect data on acquired resistance mechanism (T790M mutation, etc) to afatinib first-line therapy.
Country（-ies） of study:	China
Author:	[redacted]
Study Team Members:	[redacted]: Clinical Trial Leader [redacted] [redacted]: Biostatistician [redacted]: Data management [redacted]: Epidemiologist [redacted] PV Physician [redacted]: Publication [redacted]
Marketing authorisation holder:	[redacted]
In case of PASS, add: **MAH contact person:**	N/A
In case of PASS, add: **EU-QPPV:**	N/A
In case of PASS, add: **Signature of EU-QPPV:**	N/A
Date:	8 Mar 2022

1. TABLE OF CONTENTS

[redacted]

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event(s)
AESI	Adverse Event of Special interest
ASD	Absolute Standardised Differences
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use Programmes
DCR	Disease Control Rate
EAP	Expanded Access Programme
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
MAH	Marketing Authorisation Holder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
NCI	National Cancer Institute
NGS	Next generation sequencing
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PD	Progressive Disease
PFS	Progression-Free Survival

PR	Partial Response
PS	Performance score
PT	Preferred Term
RDC	Remote Data Capture
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Stable Disease
SEAP	Statistical and Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SOP	Standard Operating Procedures
SqCC	Squamous Cell Carcinoma
T790M	Thr790Met
TKI	Tyrosine Kinase Inhibitor
TMF	Trial Master File
TOT	Time on treatment
TTF	Time-to-Treatment Failure
US	United States
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

This study is sponsored by Boehringer Ingelheim (BI).

BI appointed a clinical trial leader (CTL) who is responsible for coordinating the activities required in this study. CTL will manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs). In addition, CTL will instruct the study team to conduct related procedures in this study, including preparing, conducting and reporting, ordering the materials as needed for the study. CTL will ensure that appropriate training and information are delivered to internal clinical trial manager (CTM), clinical research associates (CRAs) or external contract research organisation (CRO) members (CRO Project Managers and/or CRO CRAs), and investigators of participating sites.

The study will be done by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. Data management and statistical evaluation will be performed by a CRO, which is appointed by the sponsor.

Tasks and functions assigned to organise, manage and evaluate the study will be defined according to BI SOPs. A list of responsible persons and relevant local information (as reference in protocol if applicable) are in the investigator site file (ISF) and the trial master file (TMF) document.

A coordinating investigator and a co-coordinating investigator will be nominated to coordinate principal investigators at different sites participating in this multicentre study. Tasks and responsibilities for the coordinating investigator will be defined in a contract filed before the initiation of the study.

Relevant documentation on the participating (principal) investigators and other important participants (e.g., their curricula vitae) will be filed in the ISF. An ISF containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Giotrif®			
Name of active ingredient: Afatinib			
Protocol date: 03 July 2019	**Study number:** 1200-0318	**Version/Revision:** 3.0	**Version/Revision date:** 26 Aug 2019 8 Mar 2022
Title of study:	Real-world study on afatinib as first-line treatment in Chinese patients with EGFR mutation-positive advanced non-small-cell lung cancer		
Rationale and background:	Afatinib, an irreversible ErbB family blocker, is approved in epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) naïve patients. Afatinib showed a median progression-free survival (PFS) of approximately 11.0 months in previous clinical trials in China (LUX-Lung 3, LUX-Lung 6) as first-line treatment in patients with EGFR mutation positive non-small cell lung cancer (NSCLC) (P13-07382, P14-00758). In addition, afatinib showed a significant better median PFS and time-to-treatment failure (TTF) versus geftinib in LUX-Lung 7 (P16-04350). In LUX-Lung 3 and LUX-Lung 6 trials, patients with Exon 19 deletion had more than 12 months [LUX-Lung 3 OS with Del19 patients: 33.3m vs 21.1m, HR0.54(0.36-0.79), LUX-Lung 6 OS with Del19 patients: 31.4m vs 18.4m, HR0.64(0.44-0.94) OS benefit versus platinum-base chemotherapy (P15-00344). In addition, in LUX-Lung trials, afatinib demonstrated clinical benefit in patients with baseline brain metastases and with the uncommon mutations G719X,L861Q, and S768I (P16-01306,P15-05932). However, resistance developed in most of patients, and the most common mechanism of resistance to 1st or 2nd generation EGFR TKIs (>50%) was the emergence of a second-site EGFR-mutation, thr790met (T790M) (R15-6101, P09-09950). There are limited real world data with afatinib first-line therapy in EGFR mutated, advanced NSCLC Chinese patients who are treatment naive. Therefore, this study aims to assess the effectiveness and safety of afatinib first-line treatment in EGRF mutated, advanced NSCLC Chinese patients in routine clinical practice.		
Research question and objectives:	The primary objective of this study is to assess the time on treatment of afatinib as first-line therapy in advanced NSCLC patients with EGFR mutation. Time on treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment or death date by any cause. The secondary objectives of this study are to assess objective response		

Name of company: Boehringer Ingelheim **Name of finished medicinal product:** Giotrif® **Name of active ingredient:** Afatinib	
	rate, overall survival and safety of afatinib first-line therapy in advanced NSCLC patients with EGFR mutation. The exploratory objective is to collect data on acquired resistance mechanism (T790M mutation, etc) to afatinib first-line therapy.
Study design:	Non-interventional, prospective, multicentre study based on real-world data of Chinese EGFR-mutated NSCLC patients treated with afatinib as first-line treatment .
Population:	It is planned that approximately 10 study centres in China will participate in this non-interventional study (NIS), and 76 eligible patients will be enrolled. Every patient who fulfils eligibility criteria and agrees to participate in the study will be enrolled in the study. Recruitment of patients for this study is competitive. Inclusion criteria: • Patients who are diagnosed with locally advanced or metastatic NSCLC with EGFR sensitive mutation • Patients who will initiate afatinib as first-line treatment for EGFR mutation-positive NSCLC • Male or female patients age ≥18 years • Written informed consent per local regulatory requirement Exclusion criteria: • Patients who have received previous systemic therapy (previous adjuvant or neo-adjuvant therapies are permitted) • Patients with symptomatic brain metastases (patients with brain metastases, who were previously treated, are eligible provided they have asymptomatic brain metastasis for at least 4 weeks on stable doses of medication) at the start of afatinib treatment • Patients with concurrent participation in an interventional Oncology clinical trial during the first-line treatment phase or within the last 30 days prior to the first-line treatment phase. If patients join another interventional study during the period of second-line treatment or later-line treatment, this patient should not be excluded from this study.
Variables:	<u>Primary outcomes</u> Time on treatment of afatinib (ToT) as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on treatment is defined from the start of afatinib treatment until the end of the afatinib treatment or death date by any cause. Patients that are lost to follow up or

Name of company: Boehringer Ingelheim		
Name of finished medicinal product: Giotrif®		
Name of active ingredient: Afatinib		

	withdraw before the end of study will be censored at the time of last known contact. Secondary outcomes Overall survival (OS) from the start of afatinib until the date of death, loss to follow up (including patient withdrawal) or end of study period Objective response rate (ORR), [objective response is defined as best overall response of complete response (CR), partial response (PR)] according to RECIST 1.1 with afatinib first-line therapy Adverse events (AEs), serious adverse events (SAEs), afatinib-related AEs (ADRs) as indicated by incidence, seriousness and intensity graded according to United States (US) national cancer institute's (NCI) common terminology criteria for AEs version 5.0 (CTCAE Version 5.0) Further outcome Resistance mechanisms (Type and proportion:T790M,etc) after afatinib first-line treatment.
Data sources:	Data for this study will be obtained via the following sources: - Patient medical information: The investigator or authorized medical staff will record clinical and treatment data from patients' medical records into an electronic case report form (eCRF) at baseline and at every visit up to end of the follow up period (refer to Section 9.4)
Study size:	76 patients
Study duration:	The duration of data collection for an individual patient will be a maximum of approximately 33 months, It is anticipated that all data collection for this study started from May 2020(first patient enrolled) and will continue until December 2023 (two years after the last patient was enrolled)
Data analysis:	Time on treatment (TOT) will be analysed using Kaplan-Meier method, and the median Time on Treatment (TOT) along with two-sided 90% confidence interval (CI) will be calculated. Overall survival (OS) will be analysed similarly. Objective response rate (ORR) and acquired resistance mutation type, and AEs will be summarised descriptively by frequency and proportions.
Milestones: IRB/IEC Approval: May 2020 First Patient In: May 2020	

Name of company: Boehringer Ingelheim		
Name of finished medicinal product: Giotrif®		
Name of active ingredient: Afatinib		
Last Patient In: Dec 2021 Interim Analysis: Dec 2022 Last Patient Out: Dec 2023 Database Locked: Mar 2024 Final NIS Report: Jun 2024		

4.1 FLOW CHART

Table 1. Patient Flow Chart

Procedure	Baseline	Treatment (first-line)	Treatment (second-line)	Further subsequent treatment(s) up to death	End of study (Until Dec 2023 or death)
Observation period	Before initiation of afatinib	Initiation of afatinib first-line treatment: Followed by regular visits according to institution standards	Start second-line treatment (first visit ≤1 months followed by regular visits according to institution standards)	Start further subsequent treatment(s) followed by regular visits according to institution standards	
Informed consent[a]	X				
Demographics (age, gender, height, etc.)	X				
Body weight	X	X			
Presence of brain metastases	X	X			
Afatinib dose		X			
ECOG Performance Status	X	X			
Baseline characteristics • Type of EGFR mutation at start of afatinib therapy • Genetic testing information[b] • Disease stage • Comorbidities	X[a]				

• Medical history					
Laboratory testing information [c]	X	X			
Eligibility (I/E criteria)	X				
Administration/Concomitant therapies	X	X	X		
Tumour assessment according to local institutional standards[d]	X	X	X		
Patient vital status	X	X	X	X	X
Regular follow-up		X	X		
Genetic testing[b]			X[f]		
Adverse events (AEs)	X	X	X[e]	X[e]	X[e]

[a]: Written informed consent must be obtained before any screening/baseline data collection are performed.

[b]: Genetic testing report (including PCR, NGS, etc.) will be collected if available

[c]: Detailed Laboratory tests are included in section 9.3.3. The estimated GFR (glomerular filtration rate) using modification of diet in renal disease (MDRD) formula, eGFR = 186 x SCr (mg/dL)$^{-1.154}$ x Age$^{-0.203}$ x (0.742 if female) (R02-2529).

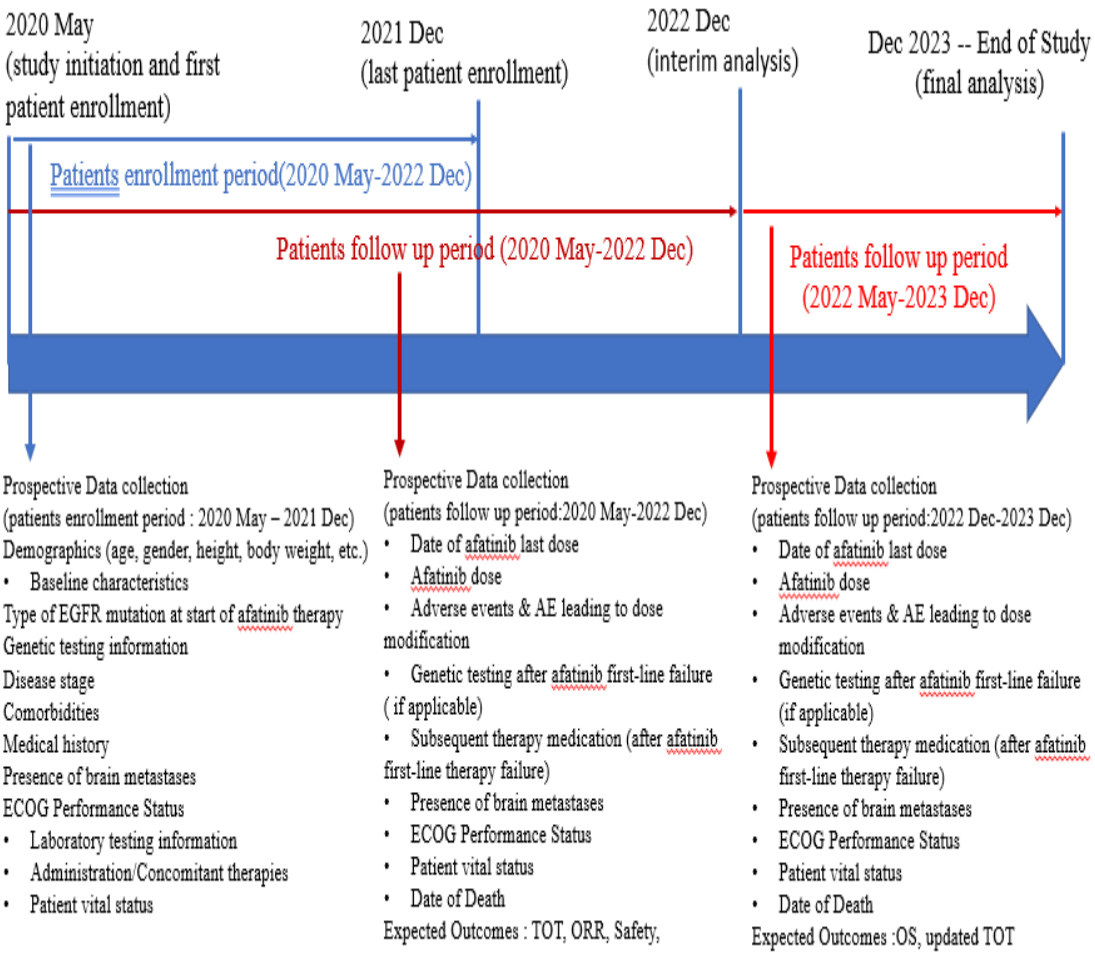
[d]: Tumour assessment will only be applied while patients with anti-tumour therapy (first-line and second-line or later lines). If the treatment finish, the assessment will end.

[e:] All AEs have to be collected and documented on the eCRF from the day of signing informed consent up to 30 days after the last dose of afatinib administration. In addition, all ADRs associated with afatinib and AEs with fatal outcome must be collected and documented on the eCRF after the end of residual effect period (30 days after the last dose of afatinib administration) up to the end of study. Progression of underlying malignancy is exempted from reporting as adverse event on the eCRF AE page and on the NIS AE form, when considered not related to afatinib, requirements for reporting on NIS AE form are included in section 11.2.

f: Genetic testing is needed according to clinical practice prior to subsequent treatment.

Below Firure 1 is the study flow chart:

Figure 1:Study Flow Chart



5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1.0	*03 Jul 2019*	*NA*	*NA*	*NA*
2.0	*26 Aug 2019*	Refer to Protocol Version 2.0	Refer to Protocol version 2.0	Refer to Protocol Version 2.0
3.0	8 Mar 2022	4	Abstract updating per protocol 3.0	Abstract updating per protocol 3.0
		6	Milestone updating per updated study timeline	Milestone updating per updated study timeline
		7	Adding related information of study rationale and background： 1. Afatnib clinical benefit in uncommon EGFR mutation and brain metastases. 2. Limited real world data with afatinib first-line treatment in EGFR-mutated, advanced non-small cell lung cancer Chinese patients.	Study rationale and background changing
		8	Primary objective and secondary objective were updated to : 1. The primary objective of this study is to assess the time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment 2. The secondary objective is to assess objective response rate , overall survival and safety of	Research question and objectives updating per study rationale

			afatinib first-line therapy in advanced NSCLC patients with EGFR mutation. To collect data on acquired resistance mechanism (T790M mutation, etc) to afatinib first-line therapy.	
		9	Related sessions in research methods were updated to: 1. Study design: This NIS will be conducted at 10 study sties in China and the patients treated with first-line afatinib will be followed up until death, lost to follow-up, withdraw from the study, or end of the study for other reasons, whichever comes first and no later than 2023. 2. Study Setting: 76 patients treated with afatinib first line treatment, will be enrolled into this prospective NIS across multiple centres in China. 3. Study Variables - Outcomes: Primary outcome is time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on Treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment. Patients that are lost to follow up or withdraw before the end of study will be censored at the time of last known contact. Secondary outcomes are overall survival, Objective response rate, Resistance mechanisms and safety. 4. Study size: Seventy-six patients will be included in this study. 5. Data analysis: We conducted time on treatment (TOT) of afatinib first-line therapy and overall survival (OS) for the main analysis. Moreover , ORR,	Research methods updating per updated study objectives

			resistance mechanism and AEs will be for further analysis. If data allows, it would also be of interest to look at the overall survival in patients who had different subsequent treatments after afatinib.	
		11	Updating Adverse events reporting with Pregnancy	Updating Adverse events reporting with Pregnancy

6. MILESTONES

Milestone	Planned Date
IRB/IEC Approval	May 2020
First Patient In	May 2020
Last Patient In	Dec 2021
Interim Analysis	Dec 2022
Last Patient Out	Dec 2023
Database Locked	Mar 2024
Final NIS Report	Jun 2024

7. RATIONALE AND BACKGROUND

Lung cancer is the leading cause of cancer-associated mortality worldwide. In 2018, World Health Organisation (WHO) reported approximately 2.1 million new lung cancer cases annually and 1.8 million deaths which represents 18.4% of the total cancer deaths worldwide (R18-3308). In China, lung cancer is also considered as a leading cause of death among males. A total of 0.73 million new lung cancer cases and 0.61 million deaths (R18-1649). For NSCLC, it accounts for approximately 85% of all primary lung cancers where most patients were presented with advanced and unresectable disease at the time of diagnosis (R18-3355, R08-2617).

Current available therapeutic strategy varies depending on the disease stages with some combining local treatments (surgery and/or radiotherapy) and systemic treatments (chemotherapy and/or targeted therapy). Systemic therapies are the mainstay treatment for patients with stage IIIb/IV (unresectable cancers) (P11-07424). These may include chemotherapy, vascular endothelial growth factor (VEGF) inhibitor, immunotherapy and target therapy. Treatment with EGFR-TKI is the preferred option for patients with EGFR gene mutation as metastatic EGFR-mutant lung cancers are sensitive to EGFR TKIs (P18-01881).

Acquired resistance to EGFR-targeted TKIs therapy is inevitable due to tumour evolution. Kohsaka and team reported in 2018 that EGFR mutation-positive NSCLC is highly heterogeneous at the cellular level, facilitating clonal expansion of resistant tumours via multiple molecular mechanisms (P18-10855). To date, the 6 approved EGFR-TKIs can be classified into three different generations - 1st generation (erlotinib, gefitinib and icotinib), 2nd generation (afatinib and dacomitinib) and 3rd generation (osimertinib) (R18-0130, P19-03609).

Efficacy and safety of TKIs of different generation are widely investigated in WJTOG3405, NEJ002, ARCHER 1050, EURTAC, OPTIMAL, NEJ026, LUX-Lung 3, LUX-Lung 6, LUX-Lung 7, AURA3 and FLAURA(P19-00432). The range of PFS reported with the longest being 18.9 months was indicated in patients who were with EGFR-mutated advanced NSCLC and treated with osimertinib as the first-line (FLAURA) comparing to standard of care (10.2 months) (either received gefitinib or erlotinib) in EGFR mutant NSCLC treatment naïve patients (R18-0130). To date, osimertinib it is the only commercially approved 3rd generation EGFR TKI for the treatment of patients with EGFR thr790met (T790M) positive tumour in China (P19-00432).

The first marketing authorisation of afatinib was granted on 12 Jul 2013 in the US (trade name Gilotrif®) as first-line treatment for patients with metastatic NSCLC and whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (P13-10659) and the indication was updated in 2018 in US for the First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have non-resistant EGFR mutations as detected by an FDA-approved test. In the European Union (EU), afatinib was approved on 25 Sep 2013 (trade name Giotrif®) as monotherapy for the treatment of EGFR TKI-naïve patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s). Furthermore, in US and EMA, afatinib is also approved in for squamous cell carcinoma (SqCC) of the lung progressing after

platinum-based chemotherapy. In China, afatinib (trade name Giotrif®) was approved on 21 Feb 2017 for patients with NSCLC with activating EGFR mutation that previously were not treated with EGFR TKI and for squamous cell carcinoma (SqCC) of the lung progressing after platinum-based chemotherapy.

Afatinib showed a median PFS of approximately 11 months in treatment-naïve patients with EGFR common and uncommon mutations in LUX-Lung 3 (P13-07382), LUX-Lung 6 (P14-00758) and LUX-Lung 7 (P16-04350). Furthermore, when comparing with gefitinib, it reduced the risk of PFS (HR=0.73 [95% CI 0·57–0·95],) in LUX-Lung 7. In addition, in LUX-Lung trials, afatinib demonstrated clinical benefit in patients with baseline brain metastases and with the uncommon mutations G719X,L861Q, and S768I (P16-01306,P15-05932). Nevertheless, most patients (approximately >50%) developed resistance to either 1st or 2nd generation EGFR TKIs due to the emergence of a second-site EGFR-mutation, the T790M (R15-6101, P09-09950).

There are limited real world data with afatinib first-line therapy in EGFR-mutated, advanced non-small cell lung cancer Chinese patients who are treatment naive. Therefore, this study aims to assess the effectiveness and safety of afatinib first-line treatment in EGFR mutated, advanced non-small cell lung cancer Chinese patients in routine clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

Data from real-world setting will provide information on afatinib first-line treatment in Chinese patients diagnosed with advanced EGFR mutation-positive NSCLC.

Primary objective:

- The primary objective of this study is to assess the time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment or death date by any cause. Patients that are lost to follow up or withdraw before the end of study will be censored at the time of last known contact..

Secondary objective:

- To assess objective response rate , overall survival and safety of afatinib first-line therapy in advanced NSCLC patients with EGFR mutation.

Exploratory objective:

To collect data on acquired resistance mechanism (T790M mutation, etc) to afatinib first-line therapy.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a NIS to be conducted at approximately 10 sites in China where real world data are from EGFR mutation positive NSCLC patients who will initiate afatinib as first-line treatment and receiving subsequent therapy. All the study sites will need to have afatinib used in regular clinical practice. Participating investigators will screen patients for eligibility, obtain informed consent, and enrol patients who meet the eligibility criteria. Investigators or trained site personnel will then complete the eCRF to capture information on demographic, medical history, and treatment information at the time of enrolment.

This study will only include patients who are newly diagnosed and who will receive afatinib as first-line treatment, regardless if they will receive 3rd generation or other treatment subsequently. Data will be collected for the patients who receiving afatinib first-line therapy and subsequent therapy. Data of patients' resistance mechanism after afatinib treatment will also be collected.

Day 0 is the date that the patient sign the informed consent . Day 1 is the first dose of afatinib. We collected the date of initial and metastatic diagnosis. Day 1 is the first dose of afatinib therapy (index date). The patients will be followed up by regular visits according to institution standards after start of afatinib until death, lost to follow-up, withdraw from the study, or end of the study for other reasons, whichever comes first and no later than Dec 2023. Please refer to Section 4.1 for the visit plan and major information collected during each visit.

This study is descriptive only and there are no comparisons between groups. To assess the presence of this bias (discussed in Section 9.9), data from 1200.0066 study [where patients were diagnosed with locally advanced or metastatic NSCLC harbouring EGFR mutation(s)] may be used to verify if this study contains potential channelling bias.

9.2 SETTING

76 patients, who are diagnosed with locally advanced or metastatic NSCLC (with activating EGFR mutation) and will be treated with afatinib as fist line treatment, are be enrolled into this prospective NIS across multiple centres in China.

Eligibility will be assessed prior to enrolment during a scheduled visit. Patients who fulfil eligibility criteria as well as agree to participate in the study by signing an informed consent (required by local regulation and legal requirement) will be included into the study.

Participation of patients in this study is not intended to change the routine treatment that patients receive as determined by their clinicians; all treatment decisions, type and timing of disease monitoring are at the discretion of the treating physician. Patients will be followed by regular visits according to institution standards after the treatment is initiated. Study sites

Site selection criteria in China:

- Sites prescribe afatinib on a regular clinic basis to patients with EGFR mutation-positive NSCLC
- Capability of conducting an NIS, including qualification, experience, availability and research resource of investigators
- A genetic test [(next-generation sequencing (NGS) or polymerase chain reaction, (PCR)] is applicable for patients diagnosed with NSCLC

After completing the sites feasibility for this study, 10 study sites participated in this prospective observational study.

Table 2. Study Sites

No	City	Site
1	Beijing	[redacted]
2	Chengdu	
3	Zhengzhou	
4	Hangzhou	
5	Haikou	
6	Zhongshan	
7	Guangzhou	
8	Guangzhou	
9	Shenyang	
10	Shenzhen	

9.2.1 Study population

Eligible patients will be enrolled in this study and will receive afatinib (first-line) and subsequent treatment (second-line) of either 3rd generation EGFR TKI or other treatments.

Patients who are administrated with afatinib as first-line treatment started from May 2020 (first patient enrolled) and will be followed up until death, lost to follow-up, withdraw from

the study, or end of the study for other reasons, whichever comes first and no later than Dec 2023.

9.2.2 Study duration

It is anticipated that all data collection for this study started from May 2020 (first patient enrolled) and will continue until Dec 2023 or the event of OS . The maximum duration of data collection for an individual patient will be a maximum of 33 months. this period may be truncated due to treatment switching, patient withdrawal from the study, or death or end of study for any other reason.

9.2.3 Eligibility

Patients must meet all of the following inclusion criteria and not meet any of the exclusion criteria to be eligible for the study:

- **Inclusion criteria:**
  - Patients who are diagnosed with locally advanced or metastatic NSCLC with EGFR sensitive mutation positive
  - Patients who will initiate afatinib as first-line treatment for EGFR mutation-positive NSCLC
  - Male and female patients with age ≥18 years
  - Written informed consent per local regulatory requirement
- **Exclusion criteria:**
  - Patients who have received previous systemic therapy (previous adjuvant or neo-adjuvant therapies are permitted)
  - Patients with symptomatic brain metastases (patients with brain metastases, who were previously treated, are eligible provided they have asymptomatic brain metastasis for at least 4 weeks on stable doses of medication) at the start of afatinib treatment
  - Patients with concurrent participation in an interventional oncology clinical trial during the first-line treatment phase or within the last 30 days prior to the first-line treatment phase. If patients join another interventional study during the period of second-line treatment or later-line treatment, this patient should not be excluded from this study

All patients who fulfil eligibility criteria and provide written informed consent will be enrolled

Patients' record in the study will be maintained in the ISF at the investigational sites.

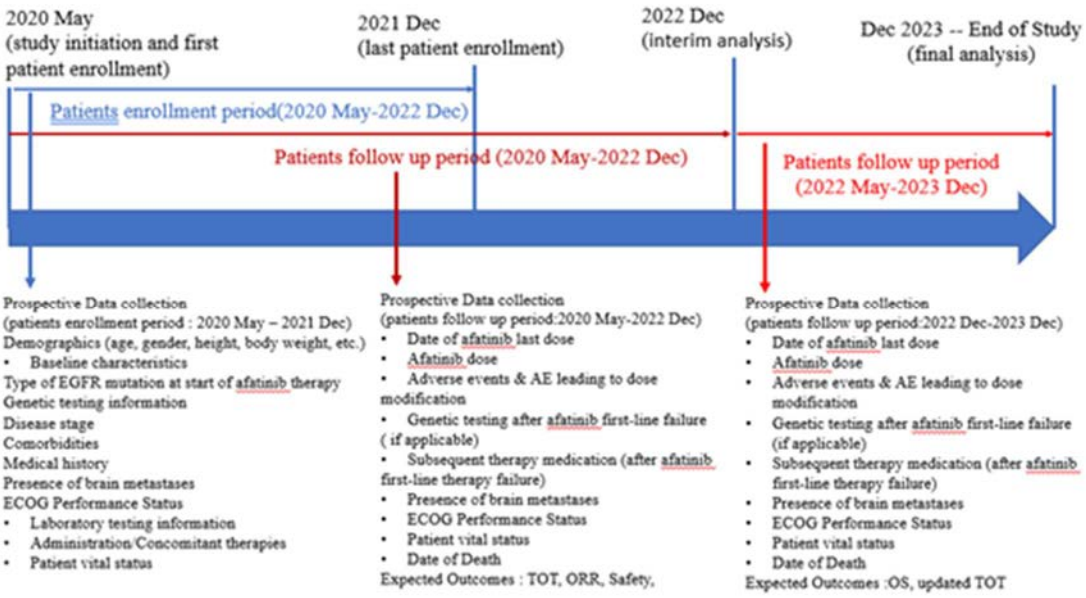
9.2.4 Study visits

This NIS does not impose a therapy protocol, diagnostic/therapeutic procedure, but a regular clinical visit schedule. Patients will be enrolled in the study during a regularly scheduled clinic visit prior to initiating their treatment (Day 0). Day 1 is defined as the day that the patient initiates afatinib (index date). Patients will be followed by regular visits according to institution standards since enrolment. After progression on first-line treatment with afatinib, based on the clinical practice, patients may have an appropriate genetic examination (such as NGS or PCR) in order to identify the best treatment option based on the testing result.

Lab testing and additional procedures would be based on physician's judgement and clinical practice.

Below Figure 1 list the study flow chart and visits

Figure 1: Study Flow Chart



9.2.5 Study discontinuation

BI reserves the right to discontinue the study or at a particular study site at any time for the following reasons:

- Failure to meet expected enrolment goals overall or at a particular study site
- Emergence of any efficacy/safety information that could significantly affect the continuation of the study, or any other administrative reasons

- Violation of regulations, the study protocol, or the contract by a study site, disturbing the appropriate conduct of the study

The investigator/the study site will be reimbursed for reasonable expenses incurred in the event of study termination (except in the event of the third reason).

9.3 VARIABLES

This is a prospective , observational study. Clinical data will being collected and enters data directly into the eCRF during or after the patient visit per study protocol. The study protocol does not mandate treatments, each participating site provides and documents patient care and outcomes according to usual care, physician discretion and local practice standards. Thus, study variables may not be available for all patients at all data collection time points per routine medical care. All the data will be continuously and directly into the eCRF during or after the patient visit in the whole study period.

The study variables to be collected include:

- Date of diagnosis
- Demographics: age at the start of afatinib treatment, gender, smoking status
- Laboratory test: hematology, biochemistry and urine examinations. List below table 2:

Table 3. Laboratory test

Category	Parameters
Hematology	Hemoglobin, platelet count, white blood cell (WBC), absolute neutrophil count (ANC)
Chemistry	<u>Electrolytes:</u> Sodium and potassium <u>Liver function tests:</u> Alkaline phosphatase, aspartate amino transferase (AST/SGOT), alanine amino transferase (ALT/SGPT), γ-glutamyltransferase (GGT), total bilirubin <u>Renal function parameters:</u> Blood urea/Blood Urea Nitrogen (BUN), creatinine <u>Other:</u> Glucose, albumin, phosphorus, lactate dehydrogenase (LDH), total protein,
Urinalysis	pH, protein, glucose, blood/erythrocytes, leucocytes, nitrite; in case of clinically significant finding further evaluation should be performed and results documented. Dipstick testing is sufficient.

- Stage of disease at the start of afatinib treatment
- Tumour histology

- Type of EGFR mutations at the start of afatinib and subsequent treatment, specifically the type of acquired resistance mutation
- Sites of metastases at start of afatinib treatment
- Body weight and height at the start of afatinib treatment
- Eastern cooperative oncology group (ECOG) performance score (PS) (if available) at start of afatinib treatment
- Date of start and end of afatinib treatment
- Starting dose of afatinib
- Afatinib dose modification(s) and date(s) (if applicable)
- ECOG PS (if available) at start of subsequent treatment
- Sites of metastases at the start of subsequent treatment
- Reason for discontinuation of afatinib treatment (e.g., progressive disease (PD), AE)
- If subsequent treatment was provided within an expanded access programme (EAP)/compassionate use programmes (CUP) or prescribed as clinical practice
- Comorbidities (hepatitis B, gastritis, liver cirrhosis, etc.)
- Concomitant medications including (PPIetc.)
- AEs (leading to dose modification)
- Date & Cause of death

9.3.1 Exposures

Afatinib:

Patients will be treated with afatinib 30 mg or 40 mg tablet once daily as indicated in the approved labels of afatinib.

3rd generation EGFR TKI or other subsequent treatment:

Patients may be treated with 3rd generation EGFR TKI or other subsequent treatment as indicated in the approved labels.

The Summaries of Product Characteristics on Giotrif® is contained in the ISF in the "Summary of Product Characteristics" (SmPC) section.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on Treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment. Patients that are lost to follow up or withdraw before the end of study will be censored at the time of last known contact.

9.3.2.2 Secondary outcomes

- Overall Survival(OS) from the start of afatinib until the end of study, date of death, patient withdrawal or loss to follow-up
- ORR [OR is defined as best overall response of CR and PR] according to RECIST 1.1 by investigator review with afatinib in first-line treatment
- AEs, SAEs, afatinib-related AEs (ADRs) as indicated by incidence seriousness and intensity graded according to United States (US) national cancer institute's (NCI) (CTCAE Version 5.0)

[redacted]

9.3.3 Covariates

As mentioned previously, the data from study 1200-0066 will be used to assess presence of potential channelling bias and to put the results into perspective. Therefore, the baseline characteristics of patients in 1200-0066 trial will be described. The covariates to be collected in the both studies (if applicable) are listed as following.

- Baseline demographic: age, gender, height, weight, body mass index, , smoking status (former, current, never)
- Clinical characteristics including medical history, surgery history, lab testing information (haematology, biochemistry and urine examinations), disease stage, tumour histological classification, EGFR mutation at start of afatinib therapy, ECOG PS score, brain metastases, afatinib starting dose
- Current/Concomitant medications

9.4 DATA SOURCES

Data for this study will be obtained via the following sources:

- Patient medical information: The investigator or authorised medical staff will record clinical and treatment data from patients' medical records/laboratory tests/physical examination into an eCRF at baseline and at every visit up to the end of the follow-up period.

There are no protocol-mandated tests, procedures, or clinic visits for this study. All the data will be continuously and directly into the eCRF during or after the patient visit in the whole study period.

9.5 STUDY SIZE

Seventy-six patients will be included in this study.

Based on LUX-Lung trials, we assume the median time on treatment (TOT) on afatinib to be 12 months in this study. Assuming that the time on treatment (TOT) follows an exponential distribution, it is expected to have 35 events till 2 years after last patient in, given total sample size equal to 76, considering a 30% drop out rate.

9.6 DATA MANAGEMENT

9.6.1 Electronic data capture system

Data will be gathered in the electronic data capture (EDC) system prepared by the sponsor or appointed CRO. The details of data management procedures to ensure the quality of the data will be described in the statistical and epidemiological analysis plan (SEAP) available in eTMF.

9.6.2 Data entry

All the data will be continuously and directly into the eCRF during or after the patient visit in the whole study period. All reported data from the enrolled investigator's site will be entered via a secured web-based EDC study database. All site personnel will be fully trained in using the EDC system, including eCRF completion guidelines. Site personnel will be provided with secure usernames and passwords in order to enter study data into the EDC system. All participating sites will only have access to view and enter the data for their patients. A data manager will perform concurrent review during the course of the data collection period. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available. For eCRFs all data must be derived from source documents. Data queries generated from the database will be created on an ongoing basis, queries will be based on the data management system logic deck and database validation for adequacy and consistency. The site management team will follow-up to request the completion of such queries.

9.6.3 Statistical software

All analyses will be performed using statistical analysis software (SAS) for Microsoft Windows operating system statistical software ([redacted]) version 9.3 or higher, using validated implementations of each application or SAS custom programming.

9.7 DATA ANALYSIS

For the purpose of this study, analyses will generally be descriptive in nature and will be conducted using SAS statistical software (version 9.3 or higher). Descriptive data regarding patient demographic and clinical characteristics will be calculated. For categorical measures, data will include the frequency (number of cases (n)) and percentage (%) of total study

patients observed in each category (N). All variables will be summarised descriptively through tabular displays of mean, median, ranges and standard deviations of continuous variables and frequency distributions of categorical variables. When necessary, continuous variables also will be categorised into intervals, with the distribution of patients (n, N, %) for each interval provided.

AEs will be graded in accordance with CTCAE Version 5.0. The safety analyses include frequency and intensity of AEs, SAEs and ADRs by System Organ Class (SOC)/Preferred Term (PT) using a current medical dictionary for regulatory activities (MedDRA) dictionary. In addition, AEs resulting in the discontinuation of treatment will be studied.

To assess the presence of channelling bias, we will use the data from study 1200-0066 to assess potential channelling and to put the results into perspective. The baseline characteristics of patients in this study and in study 1200-0066 separately. Patient characteristics will be compared between the two groups using absolute standardised differences (ASD), where an ASD of at least 10% will be considered a meaningful difference.

9.7.1 Main analysis

All patients treated with afatinib will be included in the analysis of the primary outcome, Time on Treatment (TOT) on afatinib. Time on Treatment (TOT) will be evaluated by Kaplan-Meier analysis. Median Time on Treatment (TOT) and two-side 90% CI, and the quartiles will be calculated from the Kaplan-Meier curve. Patients who are lost to follow up without providing the end date of treatment with afatinib will be censored at the time of last known contact.

Overall survival (OS) will be evaluated by Kaplan-Meier analysis. Median overall survival (OS) and two-side 90% CI, and the quartiles will be calculated from the Kaplan-Meier curve. Patients who are lost to follow up (including patient withdrawal) without providing the end date of treatment will be censored at the time of last known contact. Patients who reach the end of study period without providing the end date of treatment will be censored at the end of study.

[redacted]

9.7.3 Safety Analysis

All adverse events and adverse drug reactions collected per study protocol will be included and summarised in the interim safety analysis and in the final study report.

9.8 QUALITY CONTROL

This NIS will be conducted according to Guidelines for Good Pharmacoepidemiology SPractice (GPP) and Good Pharmacovigilance Practice (GVP), and also will be conducted following the standards of International Council for Harmonisation/Good Clinical Practice (ICH/GCP) (7) in accordance with local regulations, particularly regarding ethics, protection of patient's privacy, and processing of data. All necessary related data and documents will be made available for inspection.

All entries in the eCRFs will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRFs. To improve and ensure data quality, data checks will be performed automatically in the eCRFs directly on electronic entry at the study site.

Plausible value ranges for numerical data entries, and logical data and list entries will be filed in the eCRFs. The tests for consistency and completeness based on this will be performed during entry in the eCRFs. The validity of the recorded data will, therefore, be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.

If corrections are necessary after the data are saved, these will be documented in an audit trail.

For further quality assurance of the documented patient observations, a sample-size based source data verification will be performed on about 30% of patients included (not including the additional data collected for follow-up analyses). In addition, a risk-based monitoring will be taken for critical data and documents of all patients, and 100% of these critical data and documents will be verified.

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by independent ethics committees (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Prospective data collection brings its own challenges. Even with a careful controlled design, there may be various sources of bias that can completely distort the results. In this study, potential limitations of the study design can be listed as:

9.9.1 Lost to follow-up

All patients will be followed up until the event of OS. If a patient misses more than 1 clinic care visit, the site will attempt to communicate with the patient and document the patient's reason for not returning. Sites will be requested to contact patients at various times of the day and evening and on different days of the week. If the patient cannot be contacted after the due diligence process, the treating physician will attempt to contact the patient's designated secondary contacts, including the patient's general practitioner and next-of-kin or out-of-household contacts to obtain information on the patient's whereabouts and vital status. If the patient's care has been transferred to another healthcare professional, the treating physician at the enrolling site will be responsible for obtaining the required follow-up information from the new treating physician. Patients who do not return for at least 2 scheduled visits, and for whom no information is available will be considered lost to follow-up and will be censored at time of last visit or last known contact with the healthcare provider.. Follow-up information collecting could be accepted by phone call if the information is available and complete.

9.9.2 Channelling bias

Channelling bias can occur due to preferential prescribing in relation to different risks for the events of interest. For example, if aftinib therapy would be prescribed more often compared with other treatments to high risky Chinese patients with EGFR mutation positive NSCLC (e.g., patients in this study are more severe than other Chinese EGFR mutation positive NSCLC patients or with more comorbidities at baseline). Thus, more incidences of outcome events were expected in the group with afatinib therapy (e.g., the incidence rates of AEs/ADRs will be affected). Furthermore , all patients who fulfil eligibility criteria and provide written informed consent will be enrolled. as patients with severe disease or other disabilities (eg those who are likely to have poorer outcomes) may be excluded from the study. This study is descriptive only and there are no comparisons between groups.To assess the presence of the bias, we plan to use the data from study 1200-0066 to put the results into perspective to compare baseline demographic and clinical characteristics of the NSCLC patients. Through this, we can verify that safety or efficacy difference is due to patient baseline characteristics or the sequential therapy.

9.9.3 Study Sample Size

76 patients were enrolled in this study, this is a small sample size which may impact the assessment of study outcomes. A sample size of 76 patients is expected to ensure an 80% chance to observe the width of the 90% CI of median TOT of afatinib smaller than or equal to 11 months.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Patient completion

The collection of the data of patients will continue until the end of data collection or withdrawal of consent (if applicable) which occurs first.

9.10.3 Completion of study

The end of the study will occur when the data is collected from the last patient's data. No further data will be collected afterwards.

9.10.4 Study records

eCRFs for individual patients will be provided by the sponsor via remote data capture.

9.10.4.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRFs that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

9.10.4.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IEC review, and regulatory inspection, providing direct access to all related source data/documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results, must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g.,NMPA). The CRA/CTM and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.4.1.

9.10.5 Protocol deviations

NA

9.10.6 Compensation available to the patient in the event of study related injury

NA

9.11 BIAS

Methodological efforts have been taken to minimise channelling bias and attrition bias: these efforts including using the data from study 1200-0066 to assess potential channelling and to put the results into perspective, which will help address this issue. Details of bias can be referred to Section 9.9.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for GCP (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), guidelines for GPP, and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective IEC and competent authority (CA) according to national and international regulations. The same applies to the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her study-related data will be used by BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors (CTM/CRA) or quality medicine auditors appointed by BI, by appropriate IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage, and processing of patient data by principle 6 and 12 of the WHO GCP handbook.

Data generated as a result of the study need to be available for inspection on request by the participating investigators, the sponsor's representatives, by the IEC and the regulatory authorities.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal test finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from the use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.

Serious adverse event

SAE is defined as any AE which
- results in death
- is life-threatening
- requires in-patient hospitalisation, or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction

Adverse Event of Special Interest (AESI)

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The study design is of non-interventional nature, and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the afatinib. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF from signing the informed consent onwards until the end of the study:

- From signing the informed consent onwards until 30 days after the last dose of afatinib administration:
    - *All AEs (serious and non-serious)
- From the end of the residual effect period (30 days after the last dose of afatinib administration) onwards until the individual patient's end of study:
    - All ADRs (serious and non-serious) associated with afatinib
    - *All AEs with fatal outcome

*Exemption regarding progression of underlying malignancy:
"Progressive Disease (PD) of the malignancy" is the study endpoint and will be recorded on the appropriate page of the eCRF.

During the whole study, progression of the malignancy under study (including signs and symptoms of progression) should not be reported as adverse event unless the progression is considered related to afatinib.

When there is evidence suggesting a causal relationship between afatinib and the progression of the underlying malignancy, the event must be reported as an AE on the eCRF and on the NIS AE Form.
All AEs that are to be collectedincluding those persisting after study completion, must be followed up until they are resolved, have been sufficiently characterised, or no further information can be obtained.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g., pre-existing or concomitant diseases, or co-medications)
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g., Stevens-Johnson syndrome)
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if the dose is diminished)

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives). Of note, this criterion may not apply to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of AEs should be classified and recorded according to the CTCAE criteria in the eCRF.

Pregnancy:

In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male

trial participant becomes pregnant. This requires a written consent of the pregnant partner. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or AESI, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or AESI associated with the pregnancy a NIS AE form must be completed in addition.

Expedited reporting of AEs and drug exposure during pregnancy

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provide o BI unique entry point:

Table 4: Expedited reporting of AEs and drug exposure during pregnancy

Type of Report	Timeline
All **serious ADRs** associated with ~~afatinib~~ Giotrif®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to afatinib Giotrif® *Exemption applies	immediately within 24 hours
All **non-serious ADRs** associated with afatinib Giotrif®	7 calendar days
Drug exposure during pregnancy	7 calendar days

**Exemption*
Death due to disease progression of the underlying malignancy is a study endpoint and the natural course of the disease. As such it is exempted from reporting as an SAE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the eCRF only and will not be reported on the NIS AE Form. However, when there is evidence suggesting a causal relationship between afatinib and the progression of the underlying malignancy, the event must be reported as an SAE on the NIS AE Form and on the eCRF.

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions, the investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax and/or email the NIS AE form.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate eCRF pages and the NIS AE form (if applicable).

11.3 REPORTING TO HEALTH AUTHORITIES

AE reporting to regulatory agencies will be done by the Marketing Authorisation Holder（MAH）according to local and international regulatory requirements.

Exemptions are described in section 11.2, if applicable.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and the sponsor with regard to the publication of the results of this study are described in the investigator contract.

The publication for study design is planned for Dec 2019, the interim analysis for the primary outcome and some secondary outcomes is planned for Dec 2022, and the publication kick-off for primary outcome is planned for Jun 2023 after the interim analysis report is completed. The final publication will be written after the final NIS report is completed in Dec 2024.

BI intends to use data from this study to prepare peer-reviewed publications and other scientific communications such as abstracts, posters, and podiums presentations.

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13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

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c14668275-03 Protocol for non-interventional studies: GioTag: Real-world data study on sequential therapy with Gi(l)otrif®/afatinib as first-line treatment followed by osimertinib in patients with EGFR mutation positive advanced non-small cell lung cancer

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	*NA*	*3-Sep-2019*	*Informed consent form*
2	*NA*	*26-Dec-2019*	*Statistical and epidemiological analysis plan*

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

ANNES 3.1 ECOG PERFORMANCE STATUS

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

ANNES 3.2 PROPOSED TNM STAGE GROUPINGS

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c	N2	M0
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a-c	N3	M0
	T2a-b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

ANNES 3.3 RECIST GUIDELINE, VERSION 1.1

Refer to the Revised RECIST guideline (version 1.1) which was published in by Eisenhauer EA,et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) Eur J Cancer; 2009; 45; 228-247.(R09-0262)

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA			
Global PVWG Chair	X		
GPV SC			
Global CTIS representative			
Local Medical Director /Market Access	X (if local study)		X
Local Head MAcc / HEOR Director			
Global TA Head Epi*			
Global TA Head Clinical Development / Medical Affairs / Market Access*			
Global TA Head PV RM*			
RWE CoE (for NISnd only)	X	X	X
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM			
Local Head MA/Clinical Development			

** After review by Global TM for function*

Study Title: Real-world study afatinib as first-line treatment in patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC)**Study Number: 1200.0318**

Protocol Version: V3. 0

I here with certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Position: _____	Name/Date: _____	Signature**:** _____
Position: _____	Name/Date: _____	Signature**:** _____
Position: _____	Name/Date: _____	Signature**:** _____
Position: _____	Name/Date: _____	Signature**:** _____
Position: _____	Name/Date: _____	Signature**:** _____
Position: _____	Name/Date: _____	Signature**:** _____
Position: _____	Name/Date: _____	Signature**:** _____