Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document number:	N/A
BI study number:	1200-0322
BI investigational product(s):	Giotrif® (afatinib)
Title:	J-REGISTER: Japanese REal-world data for treatment of afatinib (GIotrif®) in first-line setting and Subsequent Therapies for patients with advanced EGFR mutation-positive lung adenocarcinoma
Lay title:	Non-interventional study for real-world data of afatinib treatment in first-line setting and of subsequent therapies for patients with advanced EGFR mutation-positive lung adenocarcinoma
Protocol version identifier:	2.0
Date of last version of protocol:	Not applicable
PASS:	No
EU PAS register number:	N/A
Active substance:	Afatinib (ATC code: L01XE13)
Medicinal product:	Giotrif®: 50mg, 40mg, 30mg, 20mg tablet
Product reference:	Giotrif®: 20mg: Japan/22600AMX00017000 30mg: Japan/22600AMX00018000 40mg: Japan/22600AMX00019000 50mg: Japan/22600AMX00020000
Procedure number:	N/A
Joint PASS:	No
Research question and objectives:	Determination of time on treatment (TOT) related to afatinib treatment as first-line therapy in patients with EGFR mutation-positive NSCLC.
Country(-ies) of study:	Japan

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Marketing authorisation holder(s):	[redacted]
Date:	4 September 2020

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
CI	Confidence Interval
CRO	Contract Research Organisation
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EGFR-TKI	Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor
eTMF	Electronic Trial Master File
HR	Hazard Ratio
ICF	Informed Consent Form
IRB	Institutional Review Board
ISF	Investigator Site File
LL3	LUX-Lung 3 study
NBI	Nippon Boehringer Ingelheim
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PS	Performance Status
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

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SOP	Standard Operating Procedures
TMF	Trial Master File
TOT	Time on Treatment
TOT1	First-line TOT
TTF	Time-to-Treatment Failure
TTP	Time to Progression
UMIN	University hospital Medical Information Network

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3. RESPONSIBLE PARTIES

3.1 SPONSOR

The study is sponsored by Nippon Boehringer Ingelheim (NBI).

[redacted]

Tel.: [redacted]

NBI has appointed a Clinical Trial Leader, responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the study team in the preparation, conduct, and reporting of the study, ordering the materials as needed for the study, ensuring appropriate training and information of the internal study team and external contract research organisation (CRO, see Section 3.3) team members (e.g. CRO project managers and/or CRO Clinical research associates), and investigators of participating countries.

The organisation of the study will be done by a CRO with which the responsibilities and tasks will have been agreed and a signed contract filed before initiation of the study.

Data management and statistical evaluation will be performed by a CRO which is appointed by NBI.

Tasks and functions assigned in order to organise, manage, and evaluate the study will be defined according to CRO's and Boehringer Ingelheim (BI)'s SOPs. A list of responsible persons and relevant local information (as protocol reference, if applicable) are in the Investigator Site File (ISF) and the Study Master File (Trial Master File, [TMF]).

3.2 SPONSOR'S MEDICAL EXPERT

[redacted]

Tel.: [redacted]

The medical expert advises NBI on any medical problems arising in the study.

3.3 CONTRACT RESEARCH ORGANISATION

[redacted]

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[redacted]
Tel.: [redacted]

[redacted] has been delegated all the activities related to study operation by NBI and is responsible for considering and taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

Main tasks
Study site selection
Preparing and providing study related documents and materials
Supporting the preparation of submission documents to Ethics Committee (EC)
Medical writing
Data centre
Statistical analysis
Monitoring
Pharmacovigilance

3.4 INVESTIGATORS AND STUDY SITE PERSONNEL

The list of principal investigators at each site is separately prepared and provided as needed basis.

The investigators and study site personnel will perform the study in accordance with this protocol, "Ethical Guidelines for Medical and Health Research Involving Human Subjects", and applicable local regulations in Japan.

It is the main responsibility of investigators and study site personnel to:

- Obtain written informed consent from patients prior to including in the study.
- Fill in the electronic case report form (eCRF) and to record all data pertinent to the study. She/he will ensure that the information reported in the eCRF is precise and accurate.
- Maintain an ISF containing all relevant study related documentation according to local regulations and CRO SOPs.

3.5 STATISTICAL ANALYSIS

[redacted]
Tel.: [redacted]

The responsible person for the statistical analysis has the responsibility of reviewing the Statistical Analysis Plan (SAP) and the results of statistical analysis.

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[redacted]

Tel.: [redacted]

The responsible person prepares the draft SAP and statistical analysis.

3.6 DATA MANAGEMENT

[redacted]

Tel.: [redacted]

The responsible person for data management has the responsibility of preparing the data management plan and is responsible for the operation of data management.

3.7 PHARMACOVIGILANCE

[redacted]

Tel.: [redacted]

[redacted]

Tel.: [redacted]

The responsible person for pharmacovigilance has the responsibility of safety reporting.

3.8 QUALITY ASSURANCE

The responsible person for quality assurance prepares the audit plan and conducts an audit.

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4. ABSTRACT

Name of company:		Nippon Boehringer Ingelheim Co., Ltd.	
Name of finished medicinal product:		Giotrif®	
Name of active ingredient:		Afatinib (ATC code: L01XE13) Antineoplastic agents Tyrosine kinase inhibitors	
Protocol date: 4 Sep 2020	**Study number:** 1200-0322	**Version/Revision:** 1.0	**Version/Revision date:** -
Title of study:	J-REGISTER: Japanese REal-world data for treatment of afatinib (GIotrif®) in first-line setting and Subsequent Therapies for patients with advanced epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma		
Rationale and background:	Afatinib was commercialised on 7 May 2014 in Japan for treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have activating epidermal growth factor receptor (EGFR) mutations, and the approval of afatinib was based on the results observed in the pivotal trial LUX-Lung 3 study (LL3). There is a dearth of information regarding afatinib treatment in first-line setting, such as proportion of acquired resistance of T790M mutation, treatment status of subsequent therapy for patients having acquired resistance other than T790M mutation, and existence of consistent time on treatment (TOT) with afatinib followed by osimertinib for Japanese patients comparing to Asian patients in GioTag study which was conducted as an international non-interventional study (NIS). Although retrospective analyses of Japanese patients enrolled in LL3 or other related studies showed consistent results between the studies, the available sample size is very limited to be conclusive for the consistency. Therefore, the better sequence of treatment in use of EGFR tyrosine kinase inhibitor (TKI) is still unclear for patients with harbouring EGFR mutation. Based on the background, a NIS was planned to observe TOT related to afatinib treatment in the first-line setting with TOT of subsequent therapies in patients with EGFR mutation-positive NSCLC.		
Research question and objectives:	The primary objective is to confirm TOT related to afatinib treatment as first-line therapy (TOT1) in patients with EGFR mutation-positive NSCLC. The TOT of subsequent second-line therapy (TOT2) would be extracted in secondary objectives. The observation in the real-world setting of the time from the start of the first-line afatinib until the end of subsequent treatment in this study will provide insights on the sequence of treatment for patients. The Japanese healthcare system will enable this study to evaluate multiple treatment options after afatinib treatment.		

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	- This study was designed as a non-interventional, multi-centre study from existing data of patients who were treated with afatinib in the first-line setting in each study site after the launch of Giotrif® on 7 May 2014 on a regular basis; their information will be chosen. In first round of data extraction, the data will be extracted retrospectively once patients are enrolled into this study. A second round of data extraction for additional follow-up for information of survival will be performed one year after completion of first round data extraction.
Study design:	Non-interventional, multi-centre study from existing data of patients treated with afatinib as the first-line treatment
Population:	The patients who were treated with afatinib in the first-line setting in each study site after the launch of Giotrif® on 7 May 2014 on a regular basis; their information will be chosen. Inclusion criteria All patients will be consecutively included from each study site, if all the following criteria are present: 1. Patients with EGFR mutation-positive advanced NSCLC 2. Patients who were/are treated with afatinib in the first-line setting at least 20 months* prior to data entry 3. Patients 20 years of age or older at the time of consent 4. Patients who provided consent to participate in this study (for cases of death or lost to follow-up, instructions from the Ethics Committee [EC] / Institutional Review Board [IRB] at each site should be followed) *Inclusion will be restricted to patients with treatment initiation with afatinib at least 20 months prior to enrolment to avoid early censoring. Exclusion criteria Patient will not be included if any of the following criteria are present: 1. Any contraindication to afatinib as specified in the label of Giotrif® 2. Patients treated with afatinib within an interventional trial 3. Patients with active brain metastases at start of afatinib treatment* * Patients with non-active brain metastases (asymptomatic state) are eligible.

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Variables:	Patient and disease characteristics: - The status of informed consent and its date - Patient birthday - Gender - Smoking status at the start of afatinib treatment - Body weight and height at the start of afatinib treatment - Eastern Cooperative Oncology Group (ECOG) performance status (PS) (if available) at the start of afatinib treatment - Stage (IIIb, IIIc or IV) at the start of afatinib treatment - Previous treatment status to NSCLC and its setting (e.g. adjuvant [eligible except for afatinib treatment] or first-line setting [ineligible]) - Type of EGFR mutations at initial diagnosis of NSCLC Treatment pathways (details of treatments received): - Dates of start and end of afatinib treatment - Starting dose of afatinib - Modified dose of afatinib and dates of start and end for each modification - The progression status of brain metastasis in several lines - Type of EGFR mutations at the start of subsequent treatment in the second-line setting - Drug name of the subsequent treatment in the second-line setting - Dates of start and end of subsequent treatment in the second-line setting - Modified dose of subsequent treatment in the second-line setting and dates of start and end for each modification - Date of death - Reason for discontinuation of treatment in several lines (progressive disease [PD], adverse event [AE], or other[s]) - Last date of confirmed survival or death at second round data extraction Follow-up data will be extracted for the same patients, who were enrolled at patient recruitment period, one year after completion of first round (second round) during the study period. Outcomes: Primary outcome will be assessed as: - The time from the start of afatinib (Giotrif®) as first-line treatment until the end of afatinib treatment or death date by any cause (TOT1) Secondary outcomes will be assessed as:

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	- TOT from the start of afatinib until end of subsequent therapies in the second-line setting or death date by any cause - TOT from start of the second-line treatment until end of the second-line treatment or death by any cause (TOT2) Overall survival (OS) and survival rate at 18 and 36 months - Time to initial dose reduction of afatinib - Proportion of patients with dose modifications of afatinib
Safety criteria:	Drug exposure during pregnancy, adverse drug reactions (ADRs) with causality to Giotrif® (serious or non-serious) and all fatal AEs will be reported to pharmacovigilance on the NIS AE Form/Pregnancy Monitoring Form - excluding deaths to PD of the underlying malignancy (see Section 11.2). Safety data will be reviewed and analysed as part of routine global pharmacovigilance procedures. All AEs and ADRs collected per study protocol will be included and summarised in the final study report.
Data sources:	Data will be extracted from patients' existing data and recorded in electronic case report forms (eCRFs).
Study size:	It is planned to enrol approximately 1000 patients across 50 sites.
Data analysis:	TOT with afatinib (TOT1) will be analysed using Kaplan-Meier method, and the median along with two-sided 95% confidence interval (CI) will be displayed (using the Greenwood's formula for estimation of standard errors). In the analyses of TOT1, missing or incomplete data will be managed by standard survival analysis techniques. Patients who are still on treatment or who are not known to have discontinued treatment will be censored on the date they are last verified to have been on treatment. Continuous variables will be presented as mean, median, minimum, maximum, Q1, Q3e, and standard deviation. Categorical variables will be presented as absolute and relative frequency.
Milestones:	Start of data extraction in Q1 2021 End of data extraction in Q4 2022 Final report of study results expected in Q2 2023

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5. AMENDMENTS AND UPDATES

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6. MILESTONES

Milestone	Planned Date
Start of data extraction	Q1 2021
End of data extraction	Q4 2022
Registration in University hospital Medical Information Network (UMIN)	Register number not yet assigned as the study is not yet registered. The study will be registered shortly before the start of data extraction.
Final report of study results	Q2 2023

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7. RATIONALE AND BACKGROUND

Afatinib was commercialised on 7 May 2014 in Japan for treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have activating epidermal growth factor receptor (EGFR) mutations [1], and the approval of afatinib was based on the results observed in the pivotal trial LUX-Lung 3 study (LL3).

In LL3, a total of 1269 patients were screened, and 345 patients were randomly assigned to treatment (afatinib or chemotherapy in the first-line setting). Median progression free survival (PFS) was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR]: 0.58, 95% confidence interval [CI]: 0.43 to 0.78, p=0.001) [2]. The Japanese group showed an extension of PFS compared to the LL3 overall. Median PFS was 13.8 months for afatinib and 6.9 months for chemotherapy (HR: 0.38, 95% CI: 0.20 to 0.70, p=0.0014). The Japanese group in the afatinib arm showed 14.0 months in time on treatment (TOT) and an extension of median overall survival (OS) compared to the LL3 overall. In the meantime, the adverse event (AE) grade tended to be higher in Japanese group. The most common treatment-related AEs (all-grade) with afatinib in the Japanese population were diarrhoea (100.0%), rash/acne (100.0%), nail effects (92.6%), and stomatitis (90.7%). Although grade 3 diarrhoea and rash/acne occurred in Japanese patients receiving afatinib, these AEs did not lead to discontinuation. Compared with the overall LL3 population, Japanese patients were more likely to have an AE leading to dose reduction (57.2% vs 75.9%, respectively) [3].

In the real-world data from RealGiDo study, there were no new safety signals and there were fewer grade ≥3 adverse drug reactions (ADR)s (28.4% versus 48.9%) and serious adverse events (SAEs) (5.2% versus 14.0%) than in afatinib arm of LL3. The median time-to-treatment failure (TTF) and median time to progression (TTP) in the first-line setting were 18.7 and 20.8 months, respectively, and were not impacted by reduced starting dose or dose modification [4]. Based on the outcomes from LL3 and RealGiDo, it is assumed that afatinib treatment duration under general practice in Japan may have been extended by improving experience of treatment management in comparison with LL3 where the treatment setting was the same as the general practice.

Although EGFR Tyrosine Kinase Inhibitors (TKI) provides significant clinical benefit in patients with EGFR-mutant NSCLC, approximately 50–70% of the patients acquire T790M resistance mutation [5, 6, 7, 8, 9]. Based on a result of a real-world molecular testing in the patients with Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) treatment failure in Japan, the EGFR T790M secondary mutation was detected in 25.8% of the patients. The detection rate of T790M was limited [10].

Osimertinib was commercialised on 25 May 2016 in Japan as a third generation EGFR-TKI and a standard of care for patients whose tumour developed the acquired T790M resistance mutations during previous EGFR-TKI treatments. The reason for approval condition was replaced to the result from AURA3 study after the results were available. The result of this study shows 10.1 months of median PFS with the osimertinib (HR: 0.30, 95% CI: 0.23 to 0.41, p<0.001) after the first-line EGFR-TKI (gefitinib: 59%, erlotinib: 34% and afatinib: 7%) in comparison with the chemotherapy (4.4 months) [11].

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The real-world data from GioTag study suggested the sequential treatment of afatinib followed by osimertinib was one of the effective treatment options. Overall median TOT was about 27.6 months (with 14.3 months of median TOT with osimertinib) in all patients with T790M mutation. Furthermore, a median TOT of 46.7 months in the Asian group tended to be prolonged (19.6 months of median TOT with osimertinib) [12].

In FLAURA study, osimertinib has shown the extension of the median PFS as 18.9 months (HR: 0.46, 95% CI: 0.37 to 0.57, p<0.001) in patients with previously untreated, EGFR mutation-positive advanced NSCLC in comparison with first-generation EGFR-TKI (gefitinib: 66%, erlotinib: 34%) [13].

Although osimertinib was approved as the first-line setting based on the results of FLAURA study, osimertinib is only option for patients with acquired T790M mutation after treatment with EGFR-TKI. The significant difference on OS data between osimertinib and first-generation EGFR-TKI as standard of care were reported for intention to treat population [14]. However, the difference of OS was notably small for Asian population (HR: 1.00, 95% CI: 0.75 to 1.31). Also, afatinib was not included in FLAURA, difference on OS benefit is still unclear between osimertinib and afatinib in Asian patients.

Afatinib and osimertinib have demonstrated significant extension of median PFS versus first-generation EGFR-TKI, however these is no direct comparison as first-line setting between two compounds.

Based on the retrospective analysis of Japanese patients enrolled in LL3, of the Japanese patients who were assigned to afatinib and had discontinued afatinib (47 patients), 18 patients (38%) received platinum-based combination chemotherapy, eight patients (17%) received first-generation EGFR-TKI, and two patients (4%) received single agent chemotherapy in second-line setting [15]. The median TOT with first-generation EGFR-TKI was similar and range of TOT was broader in comparison with platinum-based chemotherapy in second-line setting (median [range]: 4.1 [0.7–15.7] versus 4.0 [0.4–41.0]).

A retrospective analysis of 1660 Japanese patients with EGFR mutation-positive NSCLC reported a median OS of 30.8 months, with EGFR-TKIs representing major components of the treatment regimens used in the real-world setting. It was common for Japanese patients in this cohort to switch between EGFR-TKIs and to receive multiple courses of EGFR-TKI therapy, suggesting that switching and re-challenge are common practice in Japan and might further extend the survival of patients with EGFR mutation-positive NSCLC [16]. There is no inconsistency between the results of Japanese subgroup in LL3 and Japanese retrospective analysis mentioned above, however the available sample size from Japanese subgroup in LL3 is very limited to be conclusive for the consistency. Also, osimertinib was given to only one Japanese patient in second-line setting in LL3 [15]. Therefore, the better sequence of treatment in use of EGFR-TKI is still unclear for patients with harbouring EGFR mutation.

In addition, there is a dearth of information regarding afatinib treatment in first-line setting, such as proportion of acquired resistance of T790M mutation, treatment status of subsequent therapy for patients having acquired resistance other than T790M mutation, and existence of

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consistent TOT with afatinib followed by osimertinib for Japanese patients comparing to Asian patients in GioTag study which was conducted as an international non-interventional study (NIS).

Even in patients without T790M mutation, Japan has an effective and easily accessible healthcare system and reimbursement policies. Therefore, Japanese patients can receive the opportunity for more treatment options.

Based on the background, NIS was planned to observe TOT related to afatinib treatment in first-line setting with TOT of subsequent therapies in patients with EGFR mutation-positive NSCLC. The observation in this real-world setting of the time from the start of the first-line afatinib until the end of subsequent treatment in this study will provide insights on the sequence of treatment for patients. The Japanese healthcare system will enable this study to evaluate multiple treatment options after afatinib treatment.

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8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to confirm TOT related to afatinib treatment as the first-line therapy (TOT1) in patients with EGFR mutation-positive NSCLC. The TOT of subsequent second-line therapy (TOT2) would be extracted in secondary objectives. The observation in the real-world setting of the time from the start of the first-line afatinib until the end of subsequent treatment in this study will provide insights on the sequence of treatment for patients. The Japanese healthcare system will enable this study to evaluate multiple treatment options after afatinib treatment.

This study was designed as a non-interventional, multi-centre study from existing data of patients who were treated with afatinib in the first-line setting in each study site after the launch of Giotrif® on 7 May 2014 on a regular basis; their information will be chosen. In first round of data extraction, the data will be extracted retrospectively once patients are enrolled into this study. A second round of data extraction for additional follow-up for information of survival will be performed one year after completion of first round data extraction.

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9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, multi-centre study from existing data of patients treated with afatinib as the first-line treatment.

In total, about 1000 eligible patients in 50 sites are planned to be enrolled to this study.

The study will involve secondary use of data. Since the extracted data will also include genetic data, the appropriate strategies to ensure data protection (such as strong authentication) will be implemented in the electronic case report forms (eCRF) employed for data extraction.

9.2 SETTING

It is planned that around 50 study sites in Japan will be participating in this NIS and about 1000 eligible patients will be enrolled to the study consecutively per each site. Every patient who fulfils inclusion and exclusion criteria and agree to participate in the study will be selected until the required sample size is achieved. Deceased patients should be enrolled whenever possible. Instructions from the Ethics Committee (EC) / the Institutional Review Board (IRB) at each site should be followed. Investigators who fails to enrol at least one patient in the first 8 weeks of the study may be excluded from further participation. If enrolment is delayed additional sites may be recruited.

Recruiting of patients for this study is competitive, i.e., recruitment will stop at all sites when it is determined that a sufficient number of patients have been enrolled. A maximum of 50 patients (5% of all patients) will be limited for enrolment per site to avoid differential study site influence on study results. Investigators will be notified when the appropriate number of patients has been enrolled and recruitment is complete and will not be allowed to recruit additional patients for this study.

9.2.1 Selection of study population

Patient selection:

The patients who were treated with afatinib in the first-line setting in each study site after the launch of Giotrif® on 7 May 2014 on a regular basis; their information will be chosen.

Inclusion criteria

All patients will be consecutively included from each study site, if all the following criteria are present:

1. Patients with EGFR mutation-positive advanced NSCLC
2. Patients who were/are treated with afatinib in the first-line setting at least 20 months* prior to data entry

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3. Patients 20 years of age or older at the time of consent
4. Patients who provided consent to participate in this study (for cases of death or lost to follow-up, instructions from the EC / IRB at each site should be followed)

* Inclusion will be restricted to patients with treatment initiation with afatinib at least 20 months prior to enrolment to avoid early censoring.

Exclusion criteria

Patient will not be included if any of the following criteria are present:

1. Any contraindication to afatinib as specified in the label of Giotrif®
2. Patients treated with afatinib within an interventional trial
3. Patients with active brain metastases at start of afatinib treatment*

* Patients with non-active brain metastases (asymptomatic state) are eligible.

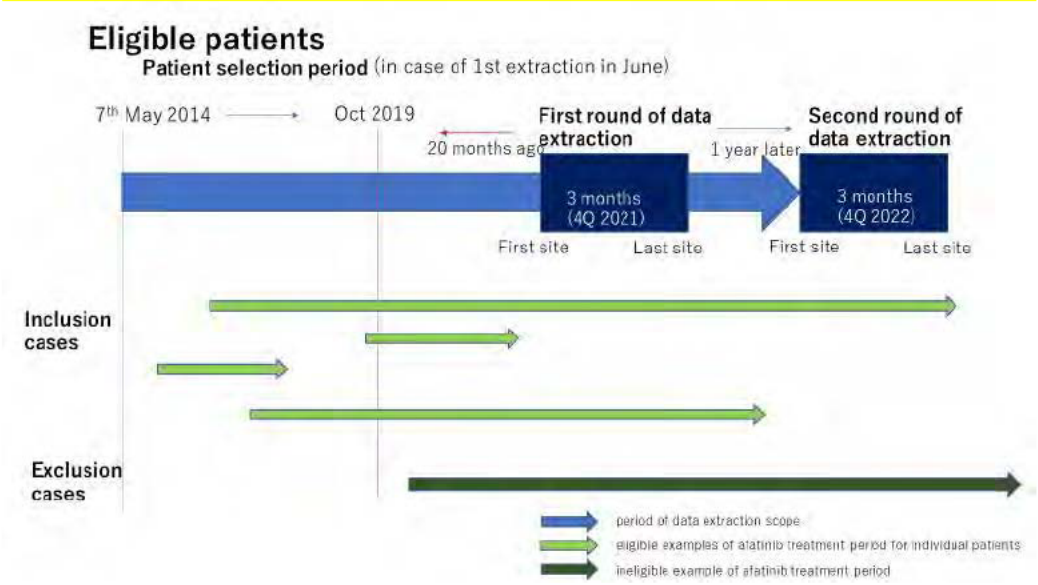


Figure Overview of the eligible patients

Deceased patients fulfilling the eligibility criteria should be enrolled whenever possible.

In LL3 [1] and RealGiDo [4], the median PFS of afatinib were 13.6 and 18.7 months respectively. The median OS was 46.9 months in Japanese patients in LL3 [3]. The TOT was 27.6 months in overall population and 46.7 months in the Asian sub-group in GioTag [12]. Based on these study outcomes, longer than 18 months and 50 months of follow-up time would be considered for Japanese patients to ensure accuracy of median TOT and median OS respectively. In this study, over 50 months of median follow-up time is expected for eligible patients by treatment initiation of afatinib since authorization of using commercially in May 2014 to 20 months before study enrolment, and by addition second round of data extraction.

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Patients treated with afatinib (Giotrif®) in interventional trials are excluded to ensure the non-interventional setting of this study. All patients fulfilling inclusion and exclusion criteria from a study site will be enrolled to avoid bias. A log of all patients included in the study will be maintained in the Investigator Site File (ISF) at the study site.

9.3 VARIABLES

The following data will be extracted retrospectively from existing data for patients who received afatinib (Giotrif®) as first-line treatment during the period from launch of afatinib (Giotrif®) to at least 20 months prior to the time point of enrolment of patients (first round), and follow-up for information of survival will be extracted for the same patients one year after completion of first round during the study period (second round). These data will be recorded in the eCRF by investigators (or designees):

Patient and disease characteristics:

- The status of informed consent and its date
- Patient birthday
- Gender
- Smoking status at the start of afatinib treatment
- Body weight and height at the start of afatinib treatment
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (if available) at the start of afatinib treatment
- Stage (IIIb, IIIc or IV) at the start of afatinib treatment
- Previous treatment status to NSCLC and its setting (e.g. adjuvant [eligible except for afatinib treatment] or first-line setting [ineligible])
- Type of EGFR mutations at initial diagnosis of NSCLC

Treatment pathways (details of treatments received):

- Dates of start and end of afatinib treatment
- Starting dose of afatinib
- Modified dose of afatinib and dates of start and end for each modification
- The progression status of brain metastasis in several lines
- Type of EGFR mutations at the start of subsequent treatment in the second-line setting
- Drug name of the subsequent treatment in the second-line setting
- Dates of start and end of subsequent treatment in the second-line setting
- Modified dose of subsequent treatment in the second-line setting and dates of start and end for each modification
- Date of death
- Reason for discontinuation of treatment in several lines (progressive disease (PD), AE, or other[s])
- Last date of confirmed survival or death at second round data extraction

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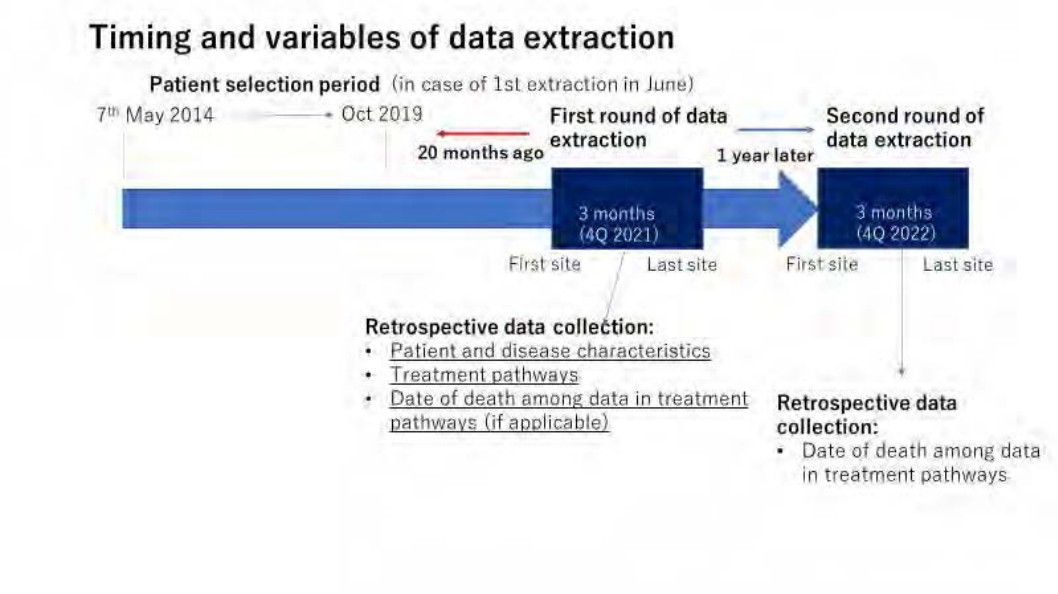


Figure Timing and variables of data extraction

9.3.1 Exposures

Afatinib (Giotrif®):
Patients were treated with afatinib (Giotrif®) 50, 40, 30, or 20 mg tablet once daily as indicated in the approved labels of afatinib (Giotrif®).

The Summary of Product Characteristics on afatinib is contained in the ISF.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome of this study is TOT with afatinib in TOT1. This will be assessed as the time from the start of afatinib (Giotrif®) as first-line treatment until the end of afatinib treatment or death date by any cause.

9.3.2.2 Secondary outcomes

- TOT from the start of afatinib until end of subsequent therapies in the second-line setting or death by any cause

- TOT from start of the second-line treatment until end of the second-line treatment or death by any case (TOT2), OS and survival rate at 18 and 36 months

- Time to initial dose reduction of afatinib
- Proportion of patients with dose modifications of afatinib

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9.3.3 Covariates

NA.

9.4 DATA SOURCES

Data will be extracted from patients' existing data and recorded in eCRFs.

9.4.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data extracted. Source documents are filed at the study site.
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 existing data or transfer records, and current existing data must be available.

For eCRFs, all data must be derived from source documents.

9.4.2 Records

Case report forms for individual patients will be provided by Nippon Boehringer Ingelheim (NBI) or appointed the contract research organisation (CRO) via Electronic Data Capture (EDC) system.

9.4.3 Direct access to source data and documents

The investigator / study site will permit study related monitoring, audits, EC / IRB 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 NBI's clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The clinical research associate / on site monitor and auditor may review all eCRFs and written informed consents (if applicable). The accuracy of the data will be verified by reviewing the documents described in Section 9.4.1.S_9_4_1

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9.4.4 Storage of records

Study site (s):
The study site(s) must retain the source documents and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the study (whatever is longer).

NBI:
NBI must retain the essential documents according to BI's SOPs.

It is the responsibility of NBI to inform the investigator / study site as to when these documents no longer need to be retained. After the retention period will pass over, the data will be disposed appropriately under protection of the privacy.

9.5 STUDY SIZE

It is assumed that the median time on treatment with afatinib (TOT1) is 13.1 months according to the result of Japanese data in LL3 [17].

Based on the assumption that TOT1 follows an exponential distribution with a median of 13.1 months and 5% of censoring probability, the table below shows the required sample size to keep the expected 95% CI within the specified width.

Table 9.5.1

95% confidence interval width (months)	2	3	4	5
Sample size	698	313	178	116

nQuery Version 8.5.0.0

In order to get the estimate of median TOT1 in overall study population with sufficient precision, at least 698 patients will be needed.

Considering the other objectives of this study to estimate the median TOT1 in subgroups of mutation and the feasibility of patient recruitment, 1000 patients will be enrolled to increase the precision of the estimate within each subgroup as much as possible.

9.6 DATA MANAGEMENT

Data will be extracted in EDC system prepared by NBI or appointed CRO. The details of data management procedures to ensure the quality of the data will be described in the Statistical Analysis Plan (SAP) available in electronic Trial Master File.

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9.7 DATA ANALYSIS

TOT1 will be analysed using Kaplan-Meier method, and the median along with two-sided 95% CI will be displayed (using the Greenwood's formula for estimation of standard errors).

In the analyses of TOT1, missing or incomplete data will be managed by standard survival analysis techniques. Patients who are still on treatment or who are not known to have discontinued treatment will be censored on the date they are last verified to have been on treatment.

Continuous variables will be presented as mean, median, minimum, maximum, Q1, Q3, and standard deviation.

Categorical variables will be presented as absolute and relative frequency.

The secondary outcomes will be analysed similarly to the primary outcome.

The subgroup analysis is also planned. The subgroup categories described below will likely need to be modified, depending upon the numbers of patients observed in each potential subgroup. Some analyses might be limited to listings of data, or not performed, for categories with few patients.

Subgroups:

- Patient and disease characteristics at the start of afatinib treatment [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]
  - baseline EGFR mutation status (common/uncommon and each mutation type; Del19, G719X, S768I, L858R, L861Q, Ins 20, Other)
  - ECOG PS (0/1, >=2)
  - brain metastases (Yes, No)
- Type of EGFR mutation status at the initiation of second-line treatment (T790M + / − / unknown [not confirmed]) [Outcomes analysed: TOT, TOT2]
- Type of treatment class for subsequent treatment in second-line setting [Outcomes analysed: TOT, TOT2]
- Initial dose of afatinib (Patients starting afatinib 40 mg will be analysed) [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]

9.7.1 Safety analysis

All AEs and ADRs collected per study protocol will be included and summarised in the interim safety analysis and in the final study report.

9.8 QUALITY CONTROL

All entries in the eCRF will be stored in a database. The structure of the database is based on

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the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF 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 eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. 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 investigator or study site personnel.

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

For the further quality assurance of the documented patient observations, the CRO will perform a sample size-based source data verification on about 10% of included patients.

In accordance with the monitoring instruction, which will be separately prepared, persons in charge of monitoring should confirm that the study has been conducted in compliance with "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and the protocol. When source data verification is conducted, after confirmation of various procedure manuals specified in the study, data in the source documents and entry in the EDC system should be cross-checked to confirm the integrity, accuracy and consistency of extracted data. After the completion of monitoring activities, monitoring reports should be prepared. In addition, persons in charge of monitoring should not leak information which he/she can obtain in the course of his/her work without any justifiable cause even after he/she is no longer engaged in the relevant work.

Patient replacement may be considered if there are major quality issues identified from the extracted data. The decision of whether or not to enforce a patient replacement will be made by NBI / study team after evaluations. Data of the replaced patients will not be included in the final data analysis.

A quality assurance audit / inspection of this study may be conducted by NBI or NBI's designees or by ECs / IRBs or by regulatory authorities. The quality assurance auditor will have access to all existing data, the investigator's study related files and correspondence, and the informed consent documentation of this study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Potential limitations of the study design:

1. Site selection:
The study results may be limited by the participation in the study of only those sites, that prescribe Giotrif® on a regular basis to ensure sufficient patient recruitment.

2. Patient population:

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Patients treated by investigators with less experience might experience more side effects during their treatment with Giotrif®.

3. Retrospective data collection:
The limitation may be due to data availability. Since no additional data will be extracted for the study purpose except from source data on existing data, the data which are not available in the existing data of patients will be considered as missing data.
External validity is provided by the broad inclusion criteria but limits to patients treated within the label, start dose of afatinib and at the selected, experienced sites.

9.10 EXTERNAL AND INTERNAL VALIDITIES

External validity
All patients will be consecutively included from each study site, if they meet all criteria for the patient selection. Subgroup analysis for patients who received 40 mg of afatinib initial dose will be performed to be compared with overall population in this study as real-world setting and LL3 as clinical trial setting.

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

The accuracy of data for external/internal validities, this will be ensured through the source data verification.

9.11 OTHER ASPECTS

9.11.1 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.

Medical information of subjects will be shared only with the parties directly involved in the study. All data will be coded before sharing. Subjects' personal information will not be used in any documents. Only investigators and their teams, or several persons in charge in the organisation working with NBI of the study will be able to access the coded data and the information by which name of each subject can be identified. The third parties involved in the study and the parties of NBI shall comply with up-to-date standards for privacy. Once all information by which each subject can be identified is deleted from extracted data, the data will be determined as anonymised and considered as non-personal data.

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Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with “Ethical Guidelines for Medical and Health Research Involving Human Subjects”, “Act on the Protection of Personal Information” and related notifications which are applicable to the protection of personal information for subjects.

The parties involved in this study should give due consideration for the protection of personal information and privacy of subjects, and the information extracted for this study will be anonymised. However, a specific individual can be identified if a correspondence table is checked. The table will be stored by a personal information manager at the study sites under strict security.

The data of each subject and other information related to the study might be shared after anonymising for scientific and medical studies, such as sharing with researchers, disclosure of study information, sharing of the results with subjects participating the study, and disclosure of the results through publication. All information by which subjects can be identified will be deleted prior to data disclosure to protect privacy of subjects.

For the purpose of checking the quality of the study, NBI and a person who is entrusted by NBI with a task to support implementation of the study (e.g. monitor) may review the information which is not anonymised, such as existing data. Even in such cases, these parties are obliged to maintain confidentiality of subjects’ data and the personal information will be protected. Personal information which can be obtained only through the conduct of this study must not be leaked without any valid reason. The same will be applicable even after the parties involved in the present study have left their posts.

Data extracted as a result of the study need to be available for inspection on request by the participating investigators, NBI’s representatives, by the EC / IRB and the regulatory authorities.

9.11.2 Patient completion

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

9.11.3 Completion/termination of study

The end of the study will occur when the end of data extraction of the last patient’s data. No further data will be extracted afterwards.

When the study is completed, the principal investigator should inform the head of the study site of the completion in writing, and the head of the study site should promptly inform the EC and NBI, of the completion in writing.

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

1. Failure to meet expected enrolment goals overall or at any particular study site.
2. Violation of the Study Protocol, "Ethical Guidelines for Medical and Health Research Involving Human Subjects" or the contract by a study site, disturbing the appropriate conduct of the study.

When interruption or termination of the study is decided upon, NBI and the CRO will document the reasons and the method to be used to inform enrolled subjects and study sites as soon as possible.

9.12 SUBJECTS

Please refer to Section 9.2.1 for Selection of study population.

9.13 BIAS

Methodological efforts have been taken to minimise selection bias: these efforts including only consecutive patients meeting each of the inclusion criteria and none of the exclusion criteria.

The study is not including the impact of the patients who died during first-line treatment, introducing immortal time bias. Based on clinical trials LUX-Lung 3 and LUX-Lung 6, from the 6% of the patients who have died during afatinib (Giotrif®) treatment, this NIS analysis is excluding results of 3% of the patients (who started the first-line treatment but did not reach the second-line treatment), which is not expected to be a significant impact on the study results.

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10. PROTECTION OF HUMAN SUBJECTS

10.1 DATA PROTECTION AND STUDY RECORDS

The study will be carried out in compliance with the protocol, the principles laid down in "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and relevant CRO's and BI's SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating investigator of the patient.

The investigator should inform NBI 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 and "Ethical Guidelines for Medical and Health Research Involving Human Subjects".

10.2 STUDY APPROVAL

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective EC / IRB before enrolment of subjects. The same applies for the implementation of changes introduced by amendments. Principal investigators are responsible for submitting and obtaining initial and continuing review of this study by their EC / IRB via the heads of study sites.

10.3 PATIENT INFORMATION, AND INFORMED CONSENT

Before enrolment, investigators or study site personnel should provide patients with information sheet approved by EC / IRB and describe following details, which should include in the information sheet.

1. Name of the study and the fact that permission for the conduct of the study has been obtained from the head of the study site
2. Names of the study site and the principal investigator
3. Objective and significance of the study
4. Method and period of the study
5. Reason why the patient has been selected as a subject
6. Costs to be paid by subjects and expected risks/benefits
7. The fact that subjects can withdraw their consent anytime even after they give consent to participate in or continue the study
8. The fact that subjects do not receive any disadvantages by refusing or withdrawing their consent to participate in or continue the study
9. Methods for the publication of information related to the study

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10. The fact that the subject can obtain or access the study protocol or documents related to methods of the study when they demand it in a manner which does not interfere with the protection of personal information of other subjects or securement of the originality of this study, as well as methods for obtaining or accessing such materials
11. Handling of personal information (including method of anonymisation)
12. Methods for storing and discarding samples/information
13. Status of conflict of interest (source of funding, possible conflict of interest, and relationships of investigators or other personnel with associated organisation)
14. Response to inquiries from subjects and related parties
15. Any financial burden for the subject (explanation of medical expense needs under general practice conditions)
16. If there is any possibility that samples/information obtained from subjects will be used for future research which cannot be identified at the time when informed consent is obtained from subjects, etc. or provided to other research study sites, the fact that such provision of samples/information may occur and details of such provision which can be assumed at the time of informed consent
17. Information about disclosure of personal information
18. The fact that subjects will not be paid for providing samples/information
19. The patient must be informed that his / her existing data may be examined by authorised monitors (e.g. CRO monitors) or Clinical Quality Assurance auditors appointed by NBI, by appropriate EC / IRB members, and by inspectors from regulatory authorities

The investigator or study site personnel, under the principal investigator's responsibility, should fully inform the participating patient on all aspects of the study including the information sheet. Patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the study, the Informed Consent Form (ICF) should be signed, name filled in and personally dated by the patient and/or their legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated ICF will be provided to the patient.

EC / IRB may grant a waiver of consent for deceased patients. In order to avoid bias by exclusion of subjects that cannot give informed consent for any reason like death, missing contact information etc., exempt from a written informed consent should be asked for such situations. Instructions from EC / IRB at each site should be followed.

If the consent is obtained from legally acceptable representative(s), the relationship between the patient and the legally acceptable representative should be documented on the ICF and be filed appropriately. Legally acceptable representative(s) should preferentially be parents, guardians of minor, relatives except for minors, or legal representatives.

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10.4 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF STUDY RELATED INJURY

Data will be extracted from patients treated within the conditions of the approved marketing authorisation of afatinib in this study, and all treatments are administered under the patients' medical insurance policy, therefore, participation in this study will not cause any study related injuries, and participants in the study will pay their medical expenses.

In the event of health injury associated with marketed product in routine medical practice, NBI is not responsible for compensation.

10.5 PREDICTABLE BENEFIT AND RISK

Data will be extracted from patients in routine medical practice, therefore there are no changes in the therapeutic strategy for the subjects. There is no particular benefit or risk for subjects participating in this study.

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

An 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 (including an abnormal laboratory 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 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 fulfils at least one of the following criteria:
- results in death,
- is life-threatening,
- requires in-patient hospitalisation, or
- requires 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 a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might 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 dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

An AE which possibly leads to disability will be reported as an SAE.

Adverse event of special interest (AESI)

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The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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 studied BI drug. For this reason, the following AE collection and reporting requirements have been defined.

Drug exposure during pregnancy, ADRs with causality to Giotrif® (serious or non-serious) and all fatal AEs will be reported to pharmacovigilance on the NIS AE Form/Pregnancy Monitoring Form - excluding deaths to PD of the underlying malignancy. Safety data will be reviewed and analysed as part routine global pharmacovigilance procedures.

All AEs and ADRs collected per study protocol will be included and summarised in the final study report.

The following must be reported on the NIS AE Form and/or Pregnancy Monitoring Form for Studies in case such AE/drug exposure during pregnancy information is identified in the course of the review of the individual records.

Type of Report	Timeline
All **Serious Adverse Drug Reactions** (SADRs) 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
AE which possibly leads to disability in patients exposed to afatinib (Giotrif®)	immediately within 24 hours
All **non-serious ADRs** associated with afatinib (Giotrif®)	7 calendar days
Drug exposure during **pregnancy**	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events.

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The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Exemption
*Death due to disease progression of the underlying malignancy is a study outcome 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 Giotrif® and the progression of the underlying malignancy, the event must be reported as an SAE on the NIS AE Form and eCRF.

Causal relationship of AEs

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 judgement 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 aetiologies** 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 the dose-response (i.e. greater effect size if the dose is increased, smaller effect size if 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 five half-lives).

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Of note, this criterion may not be applicable 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 AEs

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing an inability to work or to perform usual activities

Pregnancy

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken afatinib (Giotrif®) the investigator must report any drug exposure during pregnancy, which occurred in a female subject to NBI by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.
The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and Part B).

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise, the NIS AE Form is to be completed and forwarded as well within the respective timelines.

Reporting of related AEs associated with any other BI drug

The investigator is encouraged to report all AEs related to any BI drug other than Giotrif® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

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

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY INFORMAITON / RESULTS

12.1 REGISTRY

The study plan and summary of this study will be recorded and published at the database "University hospital Medical Information Network (UMIN) Centre (https://www.umin.ac.jp/)".

12.2 PUBLICATION

The rights of the investigator and of NBI about the publication of the results of this study are described in the investigator contract. As a rule, no study results should be published prior to the finalisation of the Study Report.

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

12.3 RESEARCH FUNDING

This study will be conducted as an industry-sponsored observational study with research funding provided by the study sponsor, NBI. NBI will take the ultimate responsibility for this study and delegate the operation of this study to the CRO. NBI will be involved in the protocol development, the CRO selection and advisement, reviewing and approving SAP, interpretation of study results, and confirmation of data management plan, however, will not be directly involved in the data management, source document verification at study sites, and statistical analysis.

12.4 CONFLICT OF INTEREST

NBI appropriately oversees the study conduct to ensure neutrality and equity in the management of any conflict of interest in accordance with local regulations, which may affect the interpretation of the results.

Investigators and study site personnel ensure that their conflict of interest will be confirmed by their local ECs or Conflict of Interest Committees in accordance with each site's regulations, which may affect to the study plan and/or an interpretation of the study results. The status of that conflict of interest will be documented in the ICF, and consent should be obtained from patients after explanation is provided. When the study results are disclosed, the conflict of interest should be documented in detail in accordance with publication policies or guidelines of the appropriate academic society and its journal.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

1. Informed Consent Form
2. Statistical Analysis Plan

The stand-alone documents listed above will be archived in the electronic Study Master File (Trial Master File).

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ANNEX 2. ADDITIONAL INFORMATION

ANNEX 2.1 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