Statistical Analysis Plan

PROTOCOL NUMBER :1200-0322

PROTOCOL 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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	2022/12/07	[redacted]	Not Applicable – First version

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1. 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
[redacted]	
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
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

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the analysis and presentation. It describes the data to be summarized and analyzed, including specifications of the statistical analyses to be performed.

This SAP is based on protocol version 1.0, dated 2020/09/04 and case report forms (CRFs) ver.6.0, dated 2021/03/08.

All planned analyses identified in this SAP will be performed by [redacted] Real-World Evidence Solutions (RWES) Biostatistics following Database Lock.

3. STUDY OBJECTIVES AND OUTCOMES

The primary objective is to confirm Time on Treatment (TOT) related to afatinib treatment as the first-line therapy (TOT1) in patients with EGFR mutation-positive NSCLC. 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.

3.1 Primary Outcome

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, which occurs first.

3.2 Secondary Outcomes

- TOT from the start of afatinib until end of subsequent therapies in the second-line setting or death by any cause, whichever occurs first
- TOT from start of the second-line treatment until end of the second-line treatment or death by any case (TOT2), whichever occurs first
- OS and survival rate at 18 and 36 months
- Time to initial dose reduction of afatinib
- Proportion of patients with dose modifications of afatinib

3.3 Safety Outcome

NA.

4. STUDY DESIGN

4.1 General Description

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. 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 will be performed one year after completion of first round data extraction.

4.2 Schedule of Events

The schedule of events can be found in Section 6 of the protocol.

Milestone	Planned Date
Start of data extraction	Q1 2021
End of data extraction	Q3 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	Q4 2022

4.3 Changes to Analysis from Protocol

The following changes were made in this SAP.

- Additional subgroups will be explored in the subgroup analysis. Refer to Section 8.3 for the subgroups to be analyzed.
- All the analyses other than patient disposition and subgroup analysis by initial dose of afatinib will be repeated for patients who initiated afatinib 40mg as first-line setting.

5. PLANNED ANALYSES

5.1 Interim Analysis

The following data will be analyzed in the interim analysis.

- Patient disposition (participating facilities, reasons for exclusion, etc.)
- Demographics
- Disease characteristics (stage / pathology, type of EGFR gene mutation, etc.)
- Treatment for NSCLC (first-line treatment regimen, second-line treatment regimen, treatment period, reason for treatment discontinuation)
- Outcomes described in Sections 3.1 and 3.2 other than OS and survival rate

5.2 Final Analysis

The following data will be analyzed in the final analysis.

- OS and survival rate described in Section 3.2.

6. ANALYSIS SETS

6.1 All Subjects Enrolled [ENR] Set

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study. This will be used for the analysis of patient disposition.

6.2 Analysis Set

The analysis set will contain all enrolled subjects who fulfil all the inclusion criteria and do not present with any of the exclusion criteria. This will be used for all analyses other than patient disposition.

All the analyses other than patient disposition and subgroup analysis by initial dose of afatinib will be repeated for patients who initiated afatinib 40mg as first-line setting.

7. GENERAL CONSIDERATIONS

7.1 Censoring rule

Censoring rule for time-to-event outcomes is described below.

・ ToT1: If patients did not discontinue first-line treatment with afatinib and did not die at the data extraction, they will be censored on the date they are last verified to have been on first-line treatment with afatinib.

・ ToT: If patients did not discontinue second-line treatment and did not die at the data extraction, they will be censored on the date they are last verified to have been on second-line treatment. If patients were on first-line treatment and did not move to second-line treatment at the data extraction, ToT is same as ToT1 for these patients.

・ ToT2: If patients did not discontinue second-line treatment and did not die at the data extraction, they will be censored on the date they are last verified to have been on second-line treatment.

・ OS: If patients did not die at the data extraction, they will be censored on the date they are last verified to be alive.

・ Time to initial dose reduction of afatinib: If patients did not reduce initial dose of afatinib at the data extraction, they will be censored on the date they are last verified to have been on the initial dose of afatinib or increased dose of afatinib.

7.2 Software Version

All analyses will be performed using SAS® Software version 9.4 (32bit) or higher.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Tests and Confidence Intervals

A two-sided 95% confidence interval (CI) will be considered as a default (alpha= 5%). Statistical tests will not be performed.

8.2 Missing data

Missing data will not be imputed for the analysis of demographic and disease characteristics described in Section 5.1. Missing data imputation for time-to-event outcomes such as TOT and OS is described in Section 7.1.

8.3 Examination of Subgroups

The subgroup categories described below may be modified, depending upon the numbers of patients observed in each subgroup. Some subgroup analyses might not be performed for categories with few patients.

Subgroups:

- Patient and disease characteristics
  - Age at the initiation of first-line treatment (>=75 years, <75 years) [Outcomes analysed: TOT1, TOT]
  - EGFR mutation status at the first diagnosis of NSCLC

        - common, uncommon [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]
        - each mutation type (Del19, G719X, S768I, L858R, L861Q, Exon 20 insertion, Other) [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]
        - T790M, Exon 20 insertion, Uncommon mutation other than T790M and Exon 20 insertion [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]
    - ECOG PS at the initiation of first-line treatment (0/1, >=2) [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]
    - Brain metastases at the initiation of first-line treatment (Yes, No) [Outcomes analysed: TOT1, TOT, OS, Time to initial dose reduction of afatinib]
- EGFR mutation status at the initiation of second-line treatment
    - common, uncommon [Outcomes analysed: TOT, TOT2]
    - each mutation type (Del19, G719X, S768I, L858R, L861Q, Ins 20, Other) [Outcomes analysed: TOT, TOT2]
    - T790M, Exon 20 insertion, Uncommon mutation other than T790M and Exon 20 insertion [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, TOT2, TOT, OS]

9. OUTPUT PRESENTATIONS

- Continuous variables

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

- Categorical variables

Categorical variables will be presented as absolute and relative frequency.

- Dates & Times

Depending on data available, dates and times will take the form yyyy/mm/dd

- Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

subject ID, record ID

10. DISPOSITION AND WITHDRAWALS

Patients disposition in Section 5.1 will be presented for All Subjects Enrolled Set.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The descriptive statistics are planned for the following demographic and disease characteristics.

- Age (years) - calculated relative to the day of the first dose of Afatinib as first-line treatment
- Sex
- ECOG PS at the initiation of first-line treatment
- Race
- Height (cm) at the initiation of first-line treatment
- Weight (kg) at the initiation of first-line treatment
- Body mass index (BMI) (kg/m^2) at the initiation of first-line treatment
- Smoking status at the initiation of first-line treatment
- Smoking history (years) at the initiation of first-line treatment
- Smoking history (number/day) at the initiation of first-line treatment
- Period from the day of first diagnosis of NSCLC to the day of the first dose of Afatinib as first-line treatment (month)

- Tumor histology at the initiation of first-line treatment
- Type of EGFR mutation at the first diagnosis of NSCLC
- Stage of disease at the initiation of first-line treatment
- Presence of any metastases at the initiation of first-line treatment
- Sites of any metastases at the initiation of first-line treatment
- Treatment with EGFR-TKI before first-line treatment with Afatinib
- Type of EGFR-TKI before first-line treatment with Afatinib
- Period from the end date of EGFR-TKI treatment to the day of the first dose of Afatinib as first-line treatment (year)

11.1 Derivations

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

12. STUDY MEDICATION EXPOSURE

The descriptive statistics are planned for the data on the treatment for NSCLC.

12.1 Derivations

Duration of exposure to afatinib as first-line treatment (days) = Cumulative of (Stop date – Start date +1, where daily dose $\neq$ 0)

Total dose of afatinib therapy (mg) = Cumulative of daily dose $\times$ (Stop date – Start date +1).

Duration of off-treatment period for afatinib therapy (days) = Cumulative of (Stop date – Start date +1, where daily dose = 0).

13. IF AFATINIB THERAPY IS ONGOING AND 'STOP DATE' IS BLANK, THEN 'LAST CONFIRMATION DATE' IS USED AS 'STOP DATE'. OUTCOMES

13.1 Primary outcome

The derivation of primary outcome is described in Section 7.1.

Primary outcome 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).

13.2 Secondary outcomes

The derivation of time-to event outcomes (TOT, TOT2, OS and time to initial dose reduction of afatinib) is described in Section 7.1.

These time-to-event outcomes 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). For OS, survival rate at 18 and 36 months and its two-sided 95% CI will also be displayed.

14. SAFETY OUTCOMES

NA

15. REFERENCES

NA

Study Title: 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

Study Number: 1200-0322

Protocol Version: 1.0

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
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Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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