Boehringer Ingelheim International GmbH

Protocol c14668275-02

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

Statistical Analysis Plan

Project Number: 234137

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BI	Boehringer Ingelheim
CRA	Clinical Research Associate
CRF	Case Report Form
CUP	Compassionate Use Program
EAP	Early Access Program
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
PD	Progressive Disease
PFS	Progression-Free Survival
PS	Performance Score
RDC	Remote Data Capture
RWD	Real-World Data
SAP	Statistical Analysis Plan
SD	Standard Deviation
TLF	Tables, Listings and Figures
TKI	Tyrosine Kinase Inhibitors
US	United States of America

1 INTRODUCTION

Metastatic epidermal growth factor receptor (EGFR)-mutant lung cancers are sensitive to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib and afatinib (P14-03814).

Afatinib is an irreversible ErbB family blocker and the first marketing approval of afatinib was granted on 12 Jul 2013 in the United States of America (US) – trade name Gilotrif® – for the indication of first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an Food and Drug Administration (FDA) - approved test. It was approved in the European Union (EU) on 25 Sep 2013 (trade name Giotrif®) as monotherapy indicated for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s). In total, marketing authorisation for Gi(l)otrif® has been granted in 70 other countries world-wide as of today (c01802941-10).

On the clinical trials LUX-Lung 3 (P13-07382), LUX-Lung 6 (P14-00758) and LUX-Lung 7 (P16-04350), afatinib (Gi(l)otrif®) showed a median progression-free survival (PFS) of 11.1, 11.1 and 13.6 months, respectively, for patients with EGFR common mutations (Del19 and L858R) treatment-naïve. Time to treatment failure in LUX-Lung 7 was 13.7 months. Eventually, resistance develops for most patients and the most common mechanism of resistance to EGFR TKIs (>50%) is the emergence of a second-site EGFR-mutation, the T790M (R15-6101, P09-09950).
Explorative analysis of LUX-Lung 7 showed a median overall survival of not being reached for patients who started with afatinib (Gi(l)otrif®) and received subsequently osimertinib or olmutinib (follow-up period of 42.6 months) indicating a long-time benefit from this sequence (P16-13901).

Osimertinib, a third generation EGFR TKI, was approved for patients whose tumours have developed the EGFR T790M mutation by several countries. The first marketing approval of osimertinib was granted on 13 Nov 2015 in the US (R16-5838). The EU and Japan also gave a similar approval on 03 Feb 2016 and 29 Mar 2016 separately (P16-15191, P16-15190).

In addition, osimertinib has been studied in the first-line treatment in an expansion cohort from AURA trial, whose reported result looked promising (median PFS for the 80 mg cohort had not yet been reached but for the 160 mg cohort was shown to be 19.3 months) (R16-5840). Confirmation of these results in a phase III randomized trial is still needed to define the role of osimertinib in the treatment of patients with EGFR mutation-positive. FLAURA is comparing osimertinib to either gefitinib or erlotinib in EGFR mutant NSCLC treatment naïve patients and results are expected to be presented during 2017 (R16-5841).

Whether osimertinib will extend PFS versus available therapies if used as front-line therapies remains unknown. Investigating in this real-world data (RWD) study the time from start of first-line afatinib (Gi(l)otrif®) until the end of second-line osimertinib in this study provides insights on treatment sequence that can inform on the most beneficial treatment sequence for the patients.

The data analysed on this study will be collected from medical records of patients treated with afatinib (Gi(l)otrif®) as the first-line treatment followed by osimertinib in case the T790M resistance mutation was developed.

This statistical analysis plan (SAP) provides the description of the variables to be collected and the methodology on which the analysis will be based.

This SAP is based upon the following study documents:

- Study Protocol, Version 2.0 (September 11, 2017)
- Case Report Form (CRF), Version 3.0 (February 06, 2018)

2 STUDY OBJECTIVES

Primary objective:
To determine the time on treatment of afatinib (Gi(l)otrif®) as first-line therapy in patients with EGFR mutation-positive NSCLC followed by osimertinib in case the T790M resistance mutation was developed in real-world setting. Time on treatment is defined from the start of the first-line treatment until the end of the second-line treatment or death date by any cause.

Secondary objective:
To collect data on acquired resistance mechanism to osimertinib.

3 STUDY DESIGN

This is a non-interventional, multi-country, multi-centre cohort study based on existing data from medical records of patients with EGFR mutation-positive advanced NSCLC treated with afatinib (Gi(l)otrif®) as the first-line treatment followed by osimertinib in case the T790M resistance mutation was developed.

In total, at least 190 eligible patients are planned to be enrolled to this study.

Key study outcome:
The time on treatment with afatinib (Gi(l)otrif®) followed by osimertinib.

It is planned that around 65 study centres in 11 countries will be participating in this non-interventional study (NIS) and at least 190 consecutive eligible patients will be enrolled to the study. Every patient who fulfils inclusion and exclusion criteria and agree to participate in the study (if a written informed consent is required for this NIS by local regulation and legal requirement) will be selected until the required sample size is achieved. Deceased patients should be enrolled whenever possible.

Recruiting of patients for this study is competitive, i.e., recruitment will stop at all centres when it is determined that a sufficient number of patients have been enrolled.

3.1 Identification of Analysis Population

3.1.1 Site selection

Sites in countries meeting the criteria below:

- Sites in countries with afatinib (Gi(l)otrif®) launch dates prior to 01 Jan 2015 and known to prescribe afatinib (Gi(l)otrif®) on a regular basis;
- Osimertinib used in patients with EGFR T790M mutation-positive NSCLC within an early access program/ compassionate use program (EAP/CUP) or regular clinical practice; osimertinib provided via a clinical trial is not permitted.

3.1.2 Inclusion criteria

1. Patients with EGFR mutation-positive advanced NSCLC
2. The tumour harbours common EGFR mutations (Del19, L858R) at start of first-line treatment
3. Patients who initiated second-line osimertinib treatment for acquired T790M mutation at least 10 months prior to data entry, AND who were treated with afatinib (Gi(l)otrif®) in the first-line
4. Patients treated with osimertinib within an EAP/CUP or regular clinical practice
5. Age ≥ 18 years
6. Signed and dated written informed consent per regulations (Exemption of a written informed consent for NIS based on existing data in countries per local regulations and legal requirements)

3.1.3 Exclusion criteria

1. Patients who received drug(s) other than osimertinib as the second-line treatment and/or patients who received drug(s) other than afatinib (Gi(l)otrif®) as the first-line treatment
2. Patients with active brain metastases at start of treatment (either afatinib/Gi(l)otrif® or osimertinib)

Patients treated with afatinib (Gi(l)otrif®) and/or osimertinib in interventional trials are excluded to ensure the non-interventional setting of this study. Real-world studies such as ASTRIS are not affected by this exclusion (R17-0754). The threshold of start of

osimertinib at least 10 months prior to data entry was chosen based on the median PFS result of AURA-3 (R17-0221) to avoid early censoring and enable collection of mature data on adverse drug reactions (ADRs) and treatment duration. All patients fulfilling inclusion and exclusion criteria from a site will be entered to avoid bias.

3.2 Full Analysis Set

The full analysis set (FAS) includes all patients who were enrolled into the study, met all inclusion criteria and did not meet any exclusion criteria and provided a written and signed informed consent (if a written informed consent is required for this NIS by local regulation and legal requirement). The FAS will be used for all the analyses performed during this study.

3.3 Study Groups/Cohorts

3.3.1 Afatinib/Osimertinib Group

The afatinib/osimertinib group consists of all patients in FAS. This will be the only group in this study.

3.3.2 Comparison Group

This study has no comparator group.

3.4 Definition of Subgroups

Selected analyses will also be provided for some of the following subgroups:

- Ethnicity: Asia (Japan, Singapore and Taiwan) vs Non-Asia (Austria, Germany, Italy, Israel, Slovenia, Spain, Canada and US)
- Race: Asian vs Black or African American vs White (the other races – American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander and Other – will not be included in this subgroup)
- EGFR mutation at start of Afatinib: Del19 vs L858R
- Gender: Male vs Female
- Brain metastases at start of Afatinib: Presence vs Absence
- Brain metastases at any time: Presence vs Absence
- Age group 1 at start of Afatinib: <65 years vs ≥65 years
- Age group 2 at start of Afatinib: <75 years vs ≥75 years
- ECOG at start of Afatinib: Low ECOG (0 and 1) vs High ECOG (2, 3, 4 and 5)
- Data source: Cardinal Health vs Other Clinical Sites

3.5 Study Outcomes

3.5.1 Data Collected

The following data will be collected from medical records and will be recorded in the electronic case report form (eCRF) by investigators (or designees) during the study period:

- Informed consent
- Demographics: age at start of afatinib (Gi(l)otrif®) treatment, gender, ethnicity and race
- Type of mutations at initial diagnosis
- Stage of disease (IIIb or IV) at start of afatinib (Gi(l)otrif®) treatment
- Sites of metastases at start of afatinib (Gi(l)otrif®) treatment
- Eastern Cooperative Oncology Group (ECOG) performance score (PS) (if available) at start of afatinib (Gi(l)otrif®) treatment
- Body weight and height at start of afatinib (Gi(l)otrif®) treatment
- Date of start and end of afatinib (Gi(l)otrif®) treatment
- Starting dose of afatinib (Gi(l)otrif®)
- Afatinib (Gi(l)otrif®) dose modification(s) and respective date(s)
- Reason for discontinuation of afatinib (Gi(l)otrif®) treatment (e.g. progressive disease (PD), adverse event (AE))
- Type of mutations at start of osimertinib treatment
- Sites of metastases at start of osimertinib treatment
- ECOG PS (if available) at start of osimertinib treatment
- Type of mutations at stop of osimertinib if available (EGFR mutations: T790M, C797S [if positive: in cis or in trans], Del19, L858R, other EGFR sensitizing mutation (to be specified), non-EGFR: to be specified) (R16-1552, P15-11024)
- If osimertinib was provided within an EAP/CUP or prescribed as clinical practice
- Date of start and end of osimertinib treatment
- Starting dose of osimertinib
- Osimertinib dose modification(s) and date(s)
- Reason for discontinuation of osimertinib treatment (e.g. PD, AE)
- Subject status at data entry completion
- Date of death (if available) / Date patient was last known to be alive (if available)
- Date of consent withdrawal (if applicable)
- All ADRs (independently from the outcome) and AEs with fatal outcome with respective start and end dates, severity, outcome, seriousness and relationship to afatinib (Gi(l)otrif®)

3.5.2 Primary Outcome

Time on treatment with afatinib (Gi(l)otrif®) followed by osimertinib.
This will be assessed as the time from start of afatinib (Gi(l)otrif®) as first-line treatment until the end of the second-line treatment (last dose of osimertinib) or death date by any cause.

3.5.3 Secondary Outcome

Type and proportion of acquired resistance mutations after osimertinib.

4 DATA SOURCE

Data will be collected from patients' medical records and recorded in (e)CRFs.

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 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, current medical records must be available.

For (e)CRFs all data must be derived from source documents.

4.2 Records

The CRFs for individual patients will be provided via remote data capture (RDC) system or Electronic Data Capture (EDC) system.

4.3 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, Institutional Review Board (IRB) / Independent Ethics Committee (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 Boehringer Ingelheim (BI's) clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The clinical research associate (CRA)/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 4.1.

4.4 Storage of records

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

5 STATISTICAL METHODS

5.1 Data Quality Assurance

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.

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 data entry clerk/doctor.

If corrections are necessary after the data are saved, these will be documented in an audit trail.
For the further quality assurance of the documented patient observations, a sample-size based source data verification will be performed on about 30% of included patients.

Patient replacement may be considered if there are major quality issues (e.g. accuracy of the data or data validity cannot be trusted or enrolled the patient has too many missing data) identified from the collected data. The decision of whether or not to enforce a patient replacement will be made by BI and the 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 BI or BI's designees or by IRBs/IECs or 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.

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard procedures for analysis and reporting.

5.2 General Presentation Considerations

No study visits are expected on this study. The 'Date of Visit' page in eCRF will include only the information of the first day of data entry.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw

data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. The number of decimal places to be displayed in each output will be specified in the Tables, Listings and Figures (TLF) shells document.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. The number of patients with missing information for a specific variable will be displayed if applicable. Any planned collapsing of categories will be detailed in the SAP text and the data displays. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using non-missing data as the denominator.

Confidence intervals will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment. All report outputs will be provided to BI in a single Microsoft Word document.

5.3 Study Patients

A clear accounting of the disposition of all patients who enter the study will be provided.

- A summary of the number of patients checked for entry into the study and the number and percentage of patients not included by major reason – not meeting an Inclusion criterion or meeting an Exclusion criterion – and overall T14.1.1.1
- A summary of the number and percentage of patients included - per center, per country and region T14.1.1.2
- A summary of the number and percentage of dead patients and patients not completing the study, as well as the follow-up time in the study, calculated as below. T14.1.1.3

$$Follow-up\ Time\ (months) = (Data\ entry\ completion\ date - Start\ date\ of\ afatinib)/30.4375$$

Two by-patient listings will be provided:

- For all patients checked for entry, one listing will be presented with the date of first day of data entry, the Inclusion and Exclusion criteria and date of informed consent (if applicable) L16.2.1.1
- For all patients included in the study, one listing with the status at data entry completion will be presented. This listing will include at least the subject status and data of death / lost to follow-up (if applicable) L16.2.1.2

5.4 Demographic Characteristics

Baseline conditions and demographics will be analysed with descriptive statistics. Age at start of afatinib (Gi(l)otrif®) will be calculated as the number of complete years between a subject's birth date and the start date of initial dose of afatinib (Gi(l)otrif®). BMI will be calculated as follows:

$$BMI = \frac{weight\ (kg)}{height\ (m)^2}$$

- A summary of demographic variables (e.g. age at start of afatinib (Gi(l)otrif®), sex, ethnicity, race, country, region, height, weight and BMI at start of afatinib) will be provided. This summary will be repeated for Ethnicity and Race subgroups. T14.1.2.1 T14.1.2.2 T14.1.2.3

A by-patient listing with the demographic characteristics will be provided. L16.2.4

5.5 Disease Characteristics

The collection of data will be divided between first line treatment – afatinib (Gi(l)otrif®) – and second line treatment – osimertinib.

5.5.1 First Line Treatment – Afatinib

The frequency of the different types of mutations at the initial diagnosis – Del19 and L858R, others or both – and the stage of disease at start of afatinib (Gi(l)otrif®) will be summarized. T14.2.1.1

This analysis will be repeated for the Race subgroup. T14.2.1.2

The number and percentage of patients with metastases at start of afatinib (Gi(l)otrif®) will be provided by site of metastases. T14.2.1.3

The brain metastases summary will be repeated for the Race subgroup. T14.2.1.4

The ECOG PS at start of afatinib (Gi(l)otrif®) will be summarized in terms of number and percentage of patients with ECOG PS equal to 0, 1, 2, 3, 4, 5 or missing. T14.2.1.5

This analysis will be repeated for the Race subgroup. T14.2.1.6

The starting afatinib (Gi(l)otrif®) dose will be summarized through descriptive statistics. T14.2.1.7
This analysis will be repeated for the Race subgroup. T14.2.1.8

The frequency and number of dose modifications, reductions and increases of afatinib (Gi(l)otrif®) and the reason for change will also be summarized. T14.2.1.9

When a patient receives no drug for at least 14 days this will be considered a treatment interruption and will be derived using the end date of one dose and the start date of the next dose.

The frequency of treatment interruptions and the frequency and reason for treatment discontinuation will be provided. T14.2.1.10

By-patient listings with the following information will be provided:

- Type of mutations at the initial diagnosis, stage of disease, site of metastases and ECOG PS at start of afatinib. L16.2.6.1
- Start and end date of initial dose and the respective dose, start and end date of all modified doses and the respective doses and the reasons for dose modification(s); reason for treatment discontinuation. L16.2.6.2

5.5.2 Second Line Treatment – Osimertinib

The frequency of the different types of mutations at start and stop of osimertinib – Del19, L858R, both, T790M and other mutations – will be summarized. T14.2.2.1

This analysis will be repeated for the Race subgroup. T14.2.2.2

The type of mutations at stop of osimertinib will be analysed according to section 5.6.2.

The number and percentage of patients with metastases at start of osimertinib will be provided by site of metastases. T14.2.2.3

This analysis will be repeated for the Race subgroup. T14.2.2.4

The ECOG PS at start of osimertinib will be summarized in terms of number and percentage of patients with ECOG PS equal to 0, 1, 2, 3, 4, 5 or missing. T14.2.2.5

This analysis will be repeated for the Race subgroup. T14.2.2.6

The number and percentage of patients that, for treatment with osimertinib, used the regular clinical practice program or did it through EAP/CUP will be summarized. T14.2.2.7

The starting osimertinib dose will be summarized through descriptive statistics. T14.2.2.8

This analysis will be repeated for the Race subgroup. T14.2.2.9

The frequency and number of dose reductions and increases, and both of osimertinib and the reason for change will also be summarized. T14.2.2.10

The frequency of treatment interruptions and the frequency and reason for treatment discontinuation will be provided. T14.2.2.11

A summary analysis of patients for which metastases were developed or disappeared from start of Afatinib to start of Osimertinib will be provided. T14.2.2.12

A shift table of ECOG PS from start of Afatinib to start of Osimertinib will be displayed. T14.2.2.13

By-patient listings with the following information will be provided:

- Type of mutations, site of metastases and ECOG PS at start of osimertinib and the program used for treatment with osimertinib. L16.2.6.3
- Start and end date of initial dose and the respective dose, start and end date of all modified doses and the respective doses and the reasons for dose modification(s); reason for treatment discontinuation. L16.2.6.4
- Type of mutations at stop of osimertinib, before classification and categorization. L16.2.6.5

5.6 Statistical methods

5.6.1 Analysis of the Primary Outcome

The primary outcome is time on treatment, which is defined as time in months from the start date of afatinib (Gi(l)otrif®) treatment – 'start date of initial dose' for First Line Treatment – to the end date of osimertinib treatment – maximum between 'end date of initial dose' and the last 'end date of dose modification' for Second Line Treatment – or death date due to any cause – 'date of death'.

$$Time\ on\ treatment\ (months) = time\ on\ treatment\ (days) / 30.4375$$

Time on treatment will be analysed using Kaplan-Meier method, and the median along with two-sided 90% confidence interval will be displayed using the Greenwood's formula for estimation of standard errors.

The primary outcome will be analysed in SAS using the LIFETEST procedure as follows:

```
proc lifetest data=mydata alphaqt=0.1
 plots=survival(atrisk failure);
 time t*event(0);
run;
```

where **alphaqt** specifies the 90% confidence interval; the **t** variable is the time in months from the start date of afatinib (Gi(l)otrif®) treatment to the end date of osimertinib treatment or death; and the **event** variable specifies the subjects for which the whole information is present (=1) or were censored (=0). T14.2.3.1 F14.2.3.5 T14.2.3.7 F14.2.3.9 T14.2.3.11 F14.2.3.13

The time on treatment (afatinib, osimertinib and total) will be summarized through descriptive statistics and survival plots will be provided.

Both tables and plots will be repeated for the following subgroups: Ethnicity, Race, EGFR mutation, Gender, Brain metastases at start of Afatinib, Brain metastases at any time, Age group 1, Age group 2, ECOG and Data Source. T14.2.3.2 F14.2.3.6 T14.2.3.8 F14.2.3.10 T14.2.3.12 F14.2.3.14

For the subgroup analyses, the log-rank test results will be provided. These results may be obtained introducing the strata statement in the LIFETEST procedure as follows:

```
proc lifetest data=mydata alphaqt=0.1
 plots=survival(atrisk failure);
 time t*event(0);
 strata subgroup;
run;
```

For the total time on treatment, the information on the number and percentage of censored patients will also be summarized. T14.2.3.3

This table will be repeated for the following subgroups: Ethnicity, Race, EGFR mutation, Gender, Brain metastases at start of Afatinib, Brain metastases at any time, Age group 1, Age group 2, ECOG and Data Source. T14.2.3.4

Time between end of afatinib and start of osimertinib will be summarized through descriptive statistics. T14.2.3.15

Time between end of osimertinib and death will be analyzed in a similar way as the primary outcome. T14.2.3.16 F14.2.3.17

Swimmer plots displaying time on afatinib treatment, time between end of afatinib and start of osimertinib and time in osimertinib treatment for each patient will be provided. F14.2.3.18

By-patient listings will be provided including at least the time on treatment (afatinib, osimertinib and total), time between end of afatinib and start of osimertinib, time between end of osimertinib and death and information whether the patient was censored or not. L16.2.6.6 L16.2.6.7 L16.2.6.8

5.6.2 Analysis of the Secondary Outcome

Different types of resistance mutations identified at the time of discontinuation of osimertinib treatment will be systematically reviewed and categorized by the trial Medical Monitor. The proportion of patients with different types of mutations after categorization will be summarized descriptively through number and percentage of patients. T14.2.4.1

A pie chart with the different types of mutations after categorization will be provided. F14.2.4.3

Both table and plot will be repeated for the following subgroup: Ethnicity, Race, EGFR mutation, Gender, Brain metastases at start of Afatinib, Brain metastases at any time, Age group 1, Age group 2, ECOG and Data Source. T14.2.4.2 F14.2.4.4

A listing will be provided with the information on the resistance mutations at the time of discontinuation of osimertinib (before and after categorization). L16.2.6.9

5.7 Safety Data

There was no initial intention to analyze the safety data collected retrospectively in the study as part of the study analysis. The safety data from this study was reviewed and analysed as part of routine global pharmacovigilance processes but at a later point it was also requested by regulatory authorities that AE data is statistically analyzed.

An overview AE table containing at least number of patients and events with AEs, serious AEs, severe AEs will be produced. AE summary tables by severity, SOC and PT, SOC and PT or by PT only will be provided for all AEs, study treatment-related AEs, serious AEs, study treatment-related serious AEs, serious AEs with fatal outcome and study treatment-related serious AEs with fatal outcome. T14.3.1 T14.3.2 T14.3.3 T14.3.4 T14.3.5 T14.3.6 T14.3.7 T14.3.8

By-patient listings will be provided for all AEs and serious AEs, including AEs with fatal outcome. L16.3.1 L16.3.2

5.8 Handling of Missing and Incomplete Data

In case of missing data for any variable, the information on the number of patients with missing data will be displayed in the appropriate output(s). For categorical variables, the percentages will be calculated based on all available data (missing and non-missing). The subjects with missing information will be included in the calculations.

Regarding the analysis of the primary outcome, it is not expected to have missing information regarding the start date of afatinib (Gi(l)otrif®) treatment. For patients still on treatment, time on treatment will be censored at the date of completion of data collection. For patients lost to follow-up and still on treatment, time on treatment will be censored at the date the patient was last known to be alive.

The possibility of having missing date for ECOG PS is foreseen and no imputation rules will be applied.

5.8.1 Partial Dates

The following dates will be collected completed (no partial dates are accepted) in the CRF: ‘date of visit’ (date of the first day of data entry), ‘date of informed consent’, ‘date of date entry completion’ and ‘date of consent withdrawal’. For the other dates, the following rules will be applied.

In case the day is missing and the month and year are given:

- the 15th of the month for:
  - Start date of initial dose (afatinib (Gi(l)otrif®))

- the end day of last dose of afatinib (Gi(l)otrif®) if the month and year are same otherwise the 15th of the month for:
  - Start date of initial dose (osimertinib)
- the end day of the previous dose if the month and year are the same otherwise the 15th of the month for:
  - Start date of modified dose (afatinib (Gi(l)otrif®))
  - Start date of modified dose (osimertinib)
- the start day of the next dose if the month and year are the same otherwise the 15th of the month for:
  - End date of initial dose (afatinib (Gi(l)otrif®))
  - End date of initial dose (osimertinib)
  - End date of modified dose (afatinib (Gi(l)otrif®))
  - End date of modified dose (osimertinib)
- The day of last dose of osimertinib if the month and year are the same otherwise the 15th of the month for:
  - Date of death
  - Date patient was last known to be alive

If day and month are missing and year is given:

- The day and month of last dose of osimertinib if the year is the same otherwise the 1st of January for:
  - Date of death
  - Date patient was last known to be alive

In case the end date of one dose and start date of the next dose are partially given and they are the same (e.g. September 2017), is assumed the 15th day of the month for the former and the 16th day for the latter.
The same is assumed for the end date of afatinib (Gi(l)otrif®) and start date of osimertinib.

Patients with a substantial amount of missing and/or partial dates may be replaced according to section 5.1.

5.9 Determination of Sample Size

It is assumed that the median time on treatment from start of the first-line treatment until the end of the second-line treatment or death date by any cause is 24 months (based on: 13.6 months median PFS with afatinib (Gi(l)otrif®) in LUX-Lung 3, 13.7 months time to treatment failure with afatinib (Gi(l)otrif®) in LUX-Lung 7 plus 10.1 months median PFS of osimertinib in AURA-3, 13.2 months in the AURA study phase 2 extension component) (P17-01960, P17-03000). Based on the assumption that time on treatment follows an exponential distribution, a sample size of 171 patients are expected to ensure at 80% chance to observe a width of the 90% confidence interval of median time on treatment smaller or equal to 10 months, which is considered as a reasonable estimation precision. Assuming 10% of censored observations a total of 190 patients are included in the study.

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