Statistical and Epidemiological Analysis Plan

BI Trial No.:	1200-0318 **Document number:c44182243-01**
Title:	Real-world study on afatinib as first-line treatment in patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC)
Investigational product(s):	Giotrif®(afatinib)
Responsible trial statistician:	[redacted]
Responsible project epidemiologist:	[redacted]
Date of statistical and epidemiological analysis plan:	05 Feb 2024
Version:	V2.0
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1. TABLE OF CONTENTS

[redacted]

2. LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADR	Adverse Drug Reaction
AE	Adverse Event(s)
AESI	Adverse Event of Special interest
AITS	Afatinib + investigator's choice treated set
BOR	Best overall response
BMI	Body Mass Index
CI	Confidence interval
CR	Complete response
CRF	Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
ES	Enrolled set
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIS	Non-Interventional Study
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PR	Partial response
PT	Preferred Term
SAE	Serious adverse event
SD	Stable disease
SEAP	Statistical and Epidemiological Analysis Plan
SOC	System Organ Class

Abbreviation / Acronym	Definition / Expansion
T790M	Thr790Met
TEAE	Treatment-emergent adverse event
TKI	Tyrosine Kinase Inhibitor
TLF	Tables, Listings and Figures
TOT	Time on treatment
TS	Treated set
WHO-DD	World Health Organization - Drug Dictionary

3. INTRODUCTION

This is a NIS to be conducted at approximately 10 sites in China where real world data are from EGFR mutation positive NSCLC patients who will initiate afatinib as first-line treatment and receiving subsequent therapy.

The primary objective of this study is to assess the time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment or death date by any cause.

This SEAP describes the detailed statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for Tables, Listings and Figures (TLF). It includes the variables and analysis dataset, and manipulations as well as other types of analyses that was not mentioned in the protocol.

The analyses described in this SEAP are based upon the following study documents:

Study Protocol, Version 3.0 (Mar 08, 2022)

Electronic Case Report Form (eCRF), Version 2.0 (DEC 24, 2019)

SAS® Version 9.3 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No changes of the planned analysis of the study.

5. OUTCOMES

5.1 PRIMARY OUTCOMES

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

5.2 SECONDARY OUTCOMES

- Overall survival (OS) from the start of afatinib until the date of death, loss to follow-up (including patient withdrawal) or end of study period

- Objective response rate (ORR) [objective response is defined as best overall response of CR and PR] according to RECIST 1.1[1] with afatinib first-line treatment

- Adverse events (AEs), serious AEs (SAEs), afatinib-related AEs (ADRs) as indicated by incidence seriousness and intensity graded according to United States (US) national cancer institute's (NCI) (CTCAE Version 5.0)

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 EXPOSURE

Afatinib:

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

3rd generation TKI or other subsequent treatment:

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

Refer to Section 7.6 and 7.7 for analysis details.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No formal protocol deviation specification were documented in this study. Subjects who missed main informed consent, unable to provide written informed consent or not fulfil eligibility criteria will be excluded from all analysis set.

6.3 PATIENT SETS ANALYSED

Enrolled set (ES)

The enrolled set consists of all patients who signed informed consent and fulfilled all eligibility criteria.

Treated set (TS)

Treated Set (TS) includes all patients from ES and who were dispensed medication and are documented to have taken at least one dose of first-line treatment afatinib.

6.5 POOLING OF CENTRES

This section is not applicable because there will be no pooling of centres or countries and no modelling thereof.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The details of imputation for partial and missing data for date of adverse event and concomitant therapy are stated at section 7.10.1 and 7.2 below, respectively. The details of imputation for partial and missing data for date of TOT event and OS event are stated at section 7.6 and 7.7.1 below, respectively. Other missing data will be recorded as missing/unknown, and no other imputation of missing data will be performed unless otherwise stated.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, 'Baseline' values are defined as the last non-missing value prior to first administration of Afatinib.

The time window is 28 -7/+2 days for subsequent clinic visits during first-line treatment period, first visit ⩽1 month followed by regular visits according to institution standards after start of second line treatment, regular visits according to institution standards after start further subsequent treatments.

'Study Day' will be calculated relative to the date of first administration of Afatinib.

- Study Day = Assessment Date – Date of first administration of Afatinib for visit (or event) prior to first study treatment.
- Study Day = Assessment Date – Date of first administration of Afatinib + 1 day for visit (or event) at or after first study treatment.

7. PLANNED ANALYSIS

Continuous data will be summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations, unless otherwise stated. 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 will be reported to one more decimal place than the raw data recorded in the database. The standard deviation 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.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. The category missing will be displayed only if there are actually missing values. When necessary, continuous variables also will be categorized into intervals, with the distribution of patients (n, N, %) for each interval provided.

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

Raw data collected in eCRF will also be listed.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic and baseline characteristic parameters collected and to be presented include:

- Age [years]
- Age class (<65, ⩾65 years)
- Gender (Male, Female)
- Race (as defined in the eCRF)
- Height [cm]
- Weight [kg]
- Body mass index (BMI) [kg/m^2] (defined as weight [kg]/ (height [cm]/100)^2)
- Smoking status (Former, Current, Never)
- Baseline ECOG score
- EGFR mutation type
- Comorbidity history
- Surgery history
- Tumor histology classification
- Disease stage at the start of afatinib

- Metastases at the start of afatinib
- Afatinib starting dose at baseline
- Medical history
- Prior therapy

In addition, to assess the presence of channeling bias, the data from study 1200-0066 will be used to assess potential channeling and to put the results into perspective. The baseline characteristics listed above (Except for Race) in this study and in study 1200-0066 will be presented separately. Patient characteristics will be compared between the two studies using absolute standardized differences (ASD), where an ASD of at least 10% will be considered a meaningful difference.

For continuous variable:

$$\text{ASD} = \frac{|(mean_1 - mean_2)|}{\sqrt{({s_1}^2 + {s_2}^2)/2}}$$

- $mean_1$ is the arithmetic average of the analysed variable for study 1200-0318.
- $mean_2$ is the arithmetic average of the analysed variable for study 1200-0066.
- s_1 is the standard deviation of the analysed variable for study 1200-0318.
- s_2 is the standard deviation of the analysed variable for study 1200-0066.

For binary categorical variable:

$$ASD = \frac{|(p_1 - p_2)|}{\sqrt{(p_1(1-p_1) + p_2(1-p_2))/2}}$$

- $p_1$is the rate of the analysed variable for study 1200-0318.
- $p_2$is the rate of the analysed variable for study 1200-0066.

For categorical baseline variables with levels, Dalton (2008) proposed to use a multivariate Mahalanobis distance method to generalize the standardized difference metric to handle a multinomial sample [3]:

$$\mathrm{T} = (p_{12}, p_{13}, \ldots p_{1k})'$$

$$\mathrm{C} = (p_{22}, p_{23}, \ldots p_{2k})'$$

$$p_{jk} = Pr(\text{category } k \mid \text{treatment group } j), j \in \{1, 2\}, \text{and } k \in \{2, 3, \ldots, k\}$$

$$\text{ASD} = \sqrt{(T - C)'S^{-1}(T - C)}$$

Where S is a $(k-1)\times(k-1)$ covariance matrix defined as:

$$S = [S_{kl}] = \begin{cases} \dfrac{[p_{1k}(1-p_{1k}) + p_{2k}(1-p_{2k})]}{2}, k = l \\ \dfrac{[p_{1k}p_{1l} + p_{2k}p_{2l}]}{2}, k \neq l \end{cases}$$

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for concomitant therapy collected in eCRF. Medications will be coded by World Health Organization Drug Dictionary (WHO-DD) version Sep 2019.

Medication collected in eCRF "Concomitant therapy" will be classified as Prior only if start and stop prior to the date of first dose of study medication, if a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Incomplete dates of medication/therapy will be imputed as detailed below:

Start Date: If start date is completely missing and end date is not prior to first dosing, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to first dosing, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant. If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing, then set day to last day of the month.

Note: if both start and end dates are missing, then the medication will be classified as concomitant only if there is no other evidence to indicate medication start before first study treatment, and classified as prior and concomitant if there is evidence to indicate medication start before first study treatment.

The following summary will be provided:

- A summary of prior therapy for study 1200-0318 (Analysis set: Treated Set)
- A summary of prior therapy compared between study 1200-0318 and 1200-0066 (Analysis set: Treated Set)
- A summary of concomitant therapy (Analysis set: Treated Set))

7.3 TREATMENT INITIATION

A summary of number of subjects with at least one afatinib dose modification and number of afatinib modifications will be provided.

7.4 METHODS ADDRESSING BIAS

As described in Section 7.1, channelling bias can occur due to preferential prescribing in relation to different risks for the events of interest. For example, if the sequential therapy would be prescribed more often compared with other treatments to high risky Chinese patients with EGFR mutation positive NSCLC (e.g., patients in this study are more severe than other Chinese EGFR mutation positive NSCLC patients or with more comorbidities at baseline). Thus, more incidences of outcome events were expected in the group with the sequential therapy (e.g., the incidence rates of AEs/ADRs will be affected). To assess the presence of the bias, we plan to use the data from study 1200-0066 to put the results into perspective to compare baseline demographic and clinical characteristics of the NSCLC patients. Through this, we can verify that safety or efficacy difference is due to patient baseline characteristics or the sequential therapy.

7.5 METHODS ADDRESSING CONFOUNDING / EFFECT MEASURE MODIFICATION

Not applicable.

7.6 PRIMARY ANALYSES

All patients treated with afatinib will be included in the analysis of the primary outcome, Time on Treatment (TOT) on afatinib.

The TOT with afatinib is defined as time from the start of afatinib to last dose date of afatinib or death date by any cause, which comes first.

Refer to Table 7.6: 1for the rules for determining TOT with afatinib event or censoring date. The analysis of TOT with afatinib will be performed on Treated Set (TS). Those analyses will be conducted as one of the interim analyses mentioned in section 7.11.

Table 7.6: 1 Rules for determining TOT event or censoring date

Rule #	Situation	Outcome	Date of event of censoring
1	Patients lost to follow up without providing end date of treatment during afatinib treatment period	censor	Date of last known date of contact during afatinib treatment period
2	Patients still receive ongoing first-line afatinib treatment at end of study period	censor	Date of last known date of contact during first line afatinib treatment period

Rule #	Situation	Outcome	Date of event of censoring
3	Other situations	event	Date of last treatment during first line afatinib treatment period

The last known date of contact will derive as follows:

For subjects who withdrew from study or became lost to follow-up, the date last known of contact will be based on the last assessment date/visit date or the date of the last dose of study drug or end of study date, whichever occurs later.

If last known of contact date is later than cut-off date, use cut-off date as last known of contact date.

Kaplan-Meier estimates and two-sided 90% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated, the Brookmeyer-Crowley method[4] based on log-log transformation will be used to construct the 90% CI, the standard error of the Kaplan-Meier quartile estimates will be estimated using Greenwood's formula. Kaplan-Meier curves will also be produced.

For the purpose of calculating TOT, incomplete first line afatinib treatment end dates will be imputed as below:

If month and year are present and day is missing:

- If year=year of first dosing and
  - If month = month of first dose then set day to day of first dose
  - If month > month of first dose then set day to first day of month
- If year > year of first dose then set day to first day of month

For all other cases, the missing dates will not be imputed and the subject will censored at last known of contact date and censored situation will be missing treatment end date.

7.7 SECONDARY ANALYSES

7.7.1 OS from the start of afatinib until the date of death

OS is defined as the time from the start of afatinib until death for any reason. Subjects who have not died at the time of the statistical analysis will be censored at the time they were last known contact.

OS will be analyzed in a similar fashion with primary analysis. Analysis will be provided for population set TS.

The swimlane plot of overall survival by subsequent treatment will be provided.

For the purposes of displaying the subsequent treatment duration in plot, incomplete second line treatment start/end and third line treatment start dates will be imputed as below:

If month and year are present and day is missing for treatment start date:

- Set day to the first day of month

If month and year are present and day is missing for treatment end date:

- If year=year of treatment start date and
  - If month = month of treatment start date then set day to last day of month
  - If month > month of first dose then set day to first day of month

For all other cases, the missing dates will not be imputed and partial dates will not be displayed on plot.

7.7.2 ORR according to RECIST 1.1[1] with afatinib in first-line treatment

ORR defined as percentage of subjects with a best overall response of CR or PR according to RECIST 1.1. Response is only recorded when RECIST 1.1 criteria is used.

The best overall response (BOR) calculated based on the overall visit responses from each RECIST assessment during first-line treatment period (defined as start of afatinib to start of second-line treatment). It is the best response a subject has had during first-line treatment period, from start of afatinib until earliest RECIST progression (PD or death) or the last evaluable assessment in the absence of RECIST progression (PD or death).

Categorization of BOR will be based on the RECIST 1.1[1] criteria using the following response categories: CR, PR, stable disease (SD), progressive disease (PD) and not evaluable (NE) (CR>PR>SD>PD>NE).For subjects whose progression event is death, BOR will be calculated based on data up until the last evaluable RECIST assessment prior to death. If no evaluable RECIST assessments prior to death, then BOR will be assigned as PD.

To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 42 days. If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative patients lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered NE.

Progression events that have been censored due to start second line treatment or other subsequent treatments before reporting PD after the last evaluable assessment will not contribute to the BOR derivation.

The Clopper-Pearson method[2] will be used to provide an estimation of ORR with 95% Cis. BOR will analyzed in terms of frequency and proportions. All those analyses will be performed on the Treated Set (TS).

7.8 OTHER ANALYSES

7.8.1 Resistance mechanisms

Type and proportion of Resistance mechanisms (T790M, etc.) after afatinib first-line treatment will be summarized for Treated Set (TS).

7.8.2 Disposition of Subjects

A summary of the number of subjects enrolled, the number of subjects treated (with at least one dose of study medication afatinib) and the number and percentage of subjects withdrawing from the study will be provided. Subjects withdrawing from study will also be summarized by major reason. (Analysis set: ES).

7.9 EXPOSURE TIME

See Section 7.6, Section 7.7.1 and Section 7.8.

7.10 SAFETY ANALYSIS

All the safety analysis will be performed on Treated Set (TS).

7.10.1 Adverse events

All AEs will be collected and documented on the eCRF from the day of signing informed consent up to 30 days after the last dose of afatinib administration. In addition, all ADRs associated with afatinib and AEs with fatal outcome must be collected and documented on the eCRF after the end of residual effect period (30 days after the last dose of afatinib administration) up to the end of study.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher.

Treatment-emergent adverse events will be tabulated and are defined as those adverse events that start on or after the date/time of first dose of Afatinib until 30 days after last dose of Afatinib, all AEs related to Afatinib after 30 days from last dose of Afatinib will be analysed as treatment-emergent AEs.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment.

For the purpose of calculating treatment emergent AEs, incomplete onset dates will be imputed as below:

If onset date is completely missing, onset date is set to the date of first dose of trial medication.

If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dosing, then set month and day to month and day of first dosing
- If year < year of first dosing, then set month and day to December 31.
- If year > year of first dosing, then set month and day to January 1.

If month and year are present and day is missing:

- If year=year of first dosing and
    - If month = month of first dose then set day to day of first dose
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to first day of month

- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to first day of month

For all other cases, set onset date to date of first dosing.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, and then alphabetically for SOC, and PT within SOC.

ADRs are defined as TEAEs related to study treatment Afatinib, missing causality will be assumed as related to Afatinib.

The AE severity are assessed by intensity graded according to United States (US) national cancer institute's (NCI) (CTCAE Version 5.0), for each subject and each adverse event, the worst severity (CTCAE Grade) recorded will be attributed and used in the by-severity summaries. If severity is missing, the worst case will be assumed.

The Following summaries will be provided:

- An overview of any AEs, TEAEs, ADRs, serious TEAEs, serious ADRs, and TEAEs leading to withdrawals, all AEs leading to death, and TEAEs leading to death will be presented.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by SOC, and PT
- A summary of the most common treatment-emergent adverse events by SOC, and PT (> 5% will be reported).
- A summary of the number and percentage of subjects reporting a serious treatment-emergent adverse event by SOC and PT.
- A summary of the number and percentage of subjects reporting a drug related treatment-emergent adverse event (ADR) by SOC and PT
- A summary of the number and percentage of subjects reporting a drug related serious TEAEs by SOC and PT
- A summary of the number and percentage of AEs leading to death during the study by SOC and PT.
- A summary of the number and percentage of TEAEs leading to death during the study by SOC and PT.
- A summary of the number and percentage of subjects with TEAEs leading to discontinuation of study treatment by SOC and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by CTCAE Grade, SOC and PT

7.10.2 Laboratory data

Clinical Laboratory Safety Evaluation will be performed at Baseline and first-line treatment visit. The frequency of worst laboratory abnormalities shift from baseline for all parameters will be provided.

7.10.3 Vital signs

Vital signs are not collected in this study.

7.10.4 ECG

ECG are not collected in this study.

7.10.5 Others

Not applicable.

7.11 INTERIM ANALYSES

No interim analyses will be performed for this study.

Final analysis

The final analysis after all patients end of study and database lock of stage 2 will include the OS assessment.

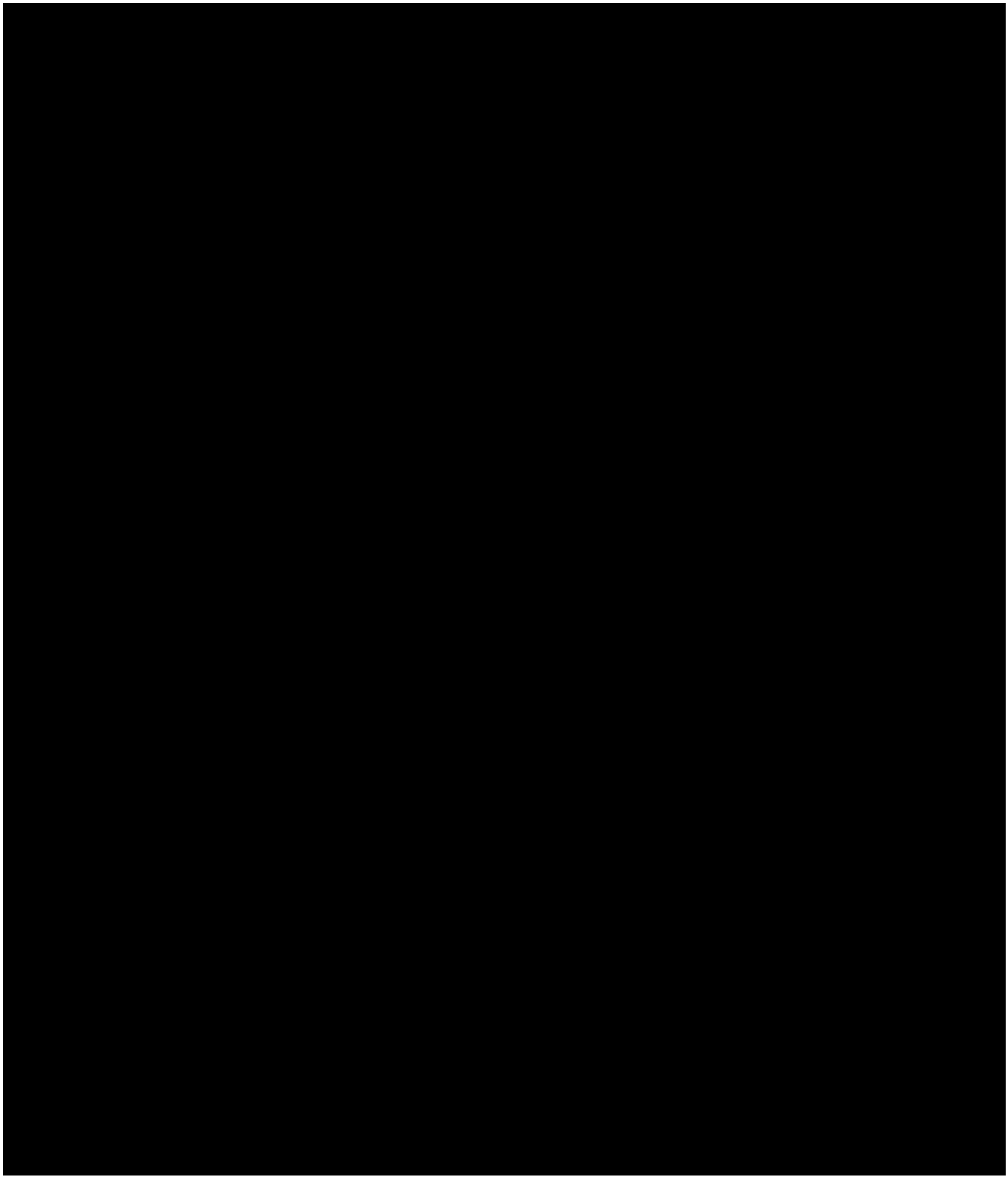
8. REFERENCES

[1] Eisenhauer, E.A., et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2): p. 228-47.

[2] Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.

[3] Dalton, J.E. (2008) A new standardized difference metric for multinomial samples. Unpublished work.

[4] Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 – 41



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
V1.0	26-Dec-19	[redacted]	None	Final V1.0
V1.1	06-Feb-20		7.1	For categorical baseline variables with levels, a multivariate Mahalanobis distance method to generalize the standardized difference metric is added
V1.1	06-Feb-20		7.7.4	"Progression events that have been censored due to start second line treatment or other subsequent treatments before reporting PD without documented PD after the last evaluable assessment will not contribute to the BOR derivation." Was changed to "Progression events that have been censored due to start second line treatment or other subsequent treatments before reporting PD after the last evaluable assessment will not contribute to the BOR derivation."
V1.1	06-Feb-20		7.8.2	"Subjects withdrawing from study treatment will also be summarized by major reason." Was changed to "Subjects withdrawing from study will also be summarized by major reason."
V1.1	06-Feb-20		7.10.1	"A summary of the most common treatment-emergent adverse events by treatment group and overall, and PT (Incidence rate > 5%). " was changed to "A summary of the most common treatment-emergent adverse events by SOC, and PT (Incidence rate > 5%). "
V1.1	06-Feb-20		8	Add new reference: [3] Dalton, J.E. (2008) A new standardized difference metric for

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
				multinomial samples. Unpublished work.
V1.**1**	16-Nov-20	[redacted]	7	Add "Raw data collected in eCRF will also be listed."
V1.1	21-Jan-21		7.7.4	Removed confirmed response definition, as this is NIS study and no scheduled assessment will be performed to confirm the CR or PR response during 28 days. In addition, ORR is not the primary endpoint for this study.
V1.1	22-Jan-21		7.7.4	Add definition of BOR for SD
V1.1	28-Apr-21		7.6	Kaplan-Meier estimates and two-sided 95% confidence intervals was change to Kaplan-Meier estimates and two-sided 90% confidence intervals.
V1.2	15-Jun-22		5.1	Primary outcome change to :To assess the time on treatment of afatinib as first-line therapy in advanced non-small cell lung cancer patients with EGFR mutation. Time on treatment (TOT) is defined from the start of afatinib treatment until the end of the afatinib treatment or death date by any cause.
	15-Jun-22		5.2 5.3	Delete DCR, PFS analyses for secondary outcome, and move Resistance mechanisms from secondary outcomes to other outcomes
	15-Jun-22		7.6	Patients from the population set TS will be included in the analysis of the primary outcome instead of population A3TS
	15-Jun-22		7.6	Rules for determining TOT censoring date from last known date

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
				of taking this treatment modified to time of last known contact.
	15-Jun-22	[redacted]	7.7	Delete secondary analyses of TOT, PFS and DCR
	15-Jun-22		7.71	Rules for determining OS censoring date from last known date to be alive modified to time of last known contact.
	15-Jun-22		7.8	Delete TOT analyses, move Resistance mechanisms from section 7.7 to 7.8
	15-Jun-22		7.11	Interim analysis change from 3 times to 1.