BI Study Number: 1200-0316

UPSWING
Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®

STATISTICAL ANALYSIS PLAN

Version 1.1, 27/11/2020

Written by	[redacted]
Role	*Epidemiology and Outcome Research Specialist, CRO TSTAT*
Date	
Signature	
Reviewed by	[redacted]
Role	*Data Management & Statistics Unit* [redacted] *(CRO)*
Date	
Signature	
Approved by	[redacted]
Role	*Boehringer Ingelheim CTL*
Date	
Signature	
Approved by	[redacted]
Role	*Boehringer Ingelheim Principal Statistician*
Date	
Signature	

[redacted]

Boehringer Ingelheim

[redacted]

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Date	03-Dec-2020
Signature	[redacted]
Reviewed by	[redacted]
Role	*Data Management & Statistics Unit* [redacted] *(CRO)*
Date	04/12/2020
Signature	[redacted]
Approved by	[redacted]
Role	*Boehringer Ingelheim CTL*
Date	[redacted]
Signature	[redacted]
Approved by	[redacted]
Role	*Boehringer Ingelheim Principal Statistician*
Date	Dec 11, 2020
Signature	[redacted]

[redacted]

Boehringer Ingelheim

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACT	Anatomical Therapeutic Chemical
[redacted]	
BI	Boehringer Ingelheim
CA	Competent Authority
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTL	Clinical Trial Leader
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
EHR	Electronic Health Record
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
MAH	Marketing Authorization Holder
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
PFS	Progression free Survival
PD	Progressive Disease
PS	Performance Score
RDC	Remote Data Capture
RWD	Real World Data
[redacted]	
SOP	Standard Operating Procedures
SEAP	Statistical and Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
[redacted]	
TKI(s)	Tyrosine Kinase Inhibitor(s)
TMF	Trial Master File
WHO	World Health Organisation

1 STATISTICAL ANALYSIS PLAN OBJECTIVES

The UPSWING study is an observational (Real-World, non-interventional), multi-country, multi-center, retrospective study (based on existing data from medical records or electronic health records) on two cohorts of adult patients diagnosed with EGFR-TKI naïve advanced EGFR-mutated NSCLC, treated for EGFR mutated NSCLC within regular clinical practice. The two cohorts are the following:

- *Uncommon Mutation cohort*: patients who started at least 12 months prior to end of observation an EGFR-TKI treatment (ie. either afatinib, gefitinib, erlotinib, or osimertinib) in the first- or second-line setting within regular clinical practice in presence of uncommon or compound EGFR mutations. Patients treated with EGFR-TKI in interventional trials are excluded (to ensure the non-interventional setting of this study). Also patients treated with osimertinib with no further uncommon mutation than acquired T790M cannot be enrolled.
- *Sequencing cohort*: patients who were treated with first-line afatinib in presence of common EGFR mutations (ie. Del19 and/or L858R) and subsequently, after having acquired T790M mutation, with second-line osimertinib (which shall have been started at least 10 months prior to end of observation) within regular clinical practice or within an Early Access Program (EAP) / Compassionate Use Program (CUP). Patients who participated in GioTag study shall be excluded, as well as patients treated with afatinib and/or osimertinib in interventional trials (to ensure the non-interventional setting of this study).

For both cohorts, patients with active brain metastases at start of EGFR-TKI cannot be enrolled.

At least 200 eligible consecutive patients are planned to be enrolled for each cohort. Beside alive patients, also deceased and untraceable patients can be enrolled, in order to avoid selection bias.
It is planned that around 65 study centres in up to 11 countries will be participating.

The following documents were considered in order to write this Statistical Analysis Plan:

- the Study Protocol (version 1.0, 23 July 2019);
- the electronic case report form v. 1.5.3, 05/02/2020;
- the minutes of the customer meeting held on 12th November 2019;
- the slide kit of the Data Analysis Strategic Meeting on 21st January 2020;
- the email correspondence with the Sponsor until 27/11/2020,
- the slide kit and minutes of the conference call with Sponsor held on 17th June 2020,
- the slide kit and minutes of the conference call with Sponsor held on 26th November 2020.

The current Statistical Analysis Plan will define the statistical analyses foreseen for the Statistical Reports of the UPSWING study.

The **primary objective** of the study is to describe the time on treatment until its end or death. More specifically, this will be evaluated for each cohort as follows:

- *Uncommon mutation cohort*: To determine the time on treatment of EGFR-TKIs as first or second line therapy in NSCLC with uncommon Epidermal Growth Factor Receptor (EGFR) mutations. Time on treatment is defined from the start of EGFR-TKI until the end of EGFR-TKI treatment or death date by any cause.
- *Sequencing cohort*: 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. 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.

The **secondary objectives** of the study are the following:

1. To determine the overall response rate (for both cohorts).
2. To determine the overall survival (for both cohorts).
3. To describe the methodology and material (liquid vs tissue) used for detection of uncommon/T790M mutation (for both cohorts).
4. To determine the time on treatment until the end of the second-line treatment (for *Uncommon mutation cohort* only).

[redacted]

2 DEFINITION OF EVALUABLE PATIENTS

From the enrolled patients, the evaluable patients that will be considered for the analyses are those who meet the following criteria.

In this section, the eCRF fields are indicated as: "label of the field" [***name of the time point / name of the form. name of the eCRF variable***].

2.1 Inclusion and exclusion criteria

Criterion 1. Adult patient

- *"1. Adult patient" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_1**] = "Yes" AND*
- *"1. Adult patient" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC1**] is not flagged AND*
- *"Age at start of first-line treatment" [**PI. PI_age**] is not missing AND*
- *the age recorded in the field "Age at start of first-line treatment" [**PI. PI_age**] is coherent with the definition of adult patient which applies to the specific country (minimum age to be provided by the [redacted] according to the Data Validation Plan specifications).*

Criterion 2. Diagnosed with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) naïve advanced EGFR mutated non-small cell lung cancer (NSCLC)

- *"2. Diagnosed with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) naïve advanced EGFR mutated non-small cell lung cancer (NSCLC)" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_2**] = "Yes" AND*
- *"2. Diagnosed with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) naïve advanced EGFR mutated non-small cell lung cancer (NSCLC)" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC2**] is not flagged AND*
- *"Date of NSCLC diagnosis (dd/mmm/yyyy)" [**DIAG. DIAG_date**] is not missing (at least year shall be known)(*) AND*
- *"Date of NSCLC diagnosis (dd/mmm/yyyy)" [**DIAG. DIAG_date**] ≤ Start date of the Index EGFR-TKI therapy (as defined in Chapter 3) AND*
- *NSCLC stage at start of first-line treatment (as defined in Chapter 3) not missing*

(*) if the year is not provided, a query will be raised. If the year cannot be retrieved, the Sponsor will evaluate the opportunity to consider the patient as violator or not for this criterion.

Criterion 3. Treated for Epidermal Growth Factor Receptor (EGFR) mutated NSCLC within regular clinical practice.

- *"3. Treated for Epidermal Growth Factor Receptor (EGFR) mutated NSCLC within regular clinical practice)" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_3**] = "Yes" AND*
- *"3. Treated for Epidermal Growth Factor Receptor (EGFR) mutated NSCLC within regular clinical practice)" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC3**] is not flagged AND*
- *"Number of treatment lines for advanced EGFR-mutated NSCLC within date of data collection" [**PI. PI_num_lines**] is not missing (since all patients shall have received at least one line).*

Criterion 4. Informed and privacy consent signature obtained depending on local regulations

- *"4. Informed and privacy consent signature obtained depending on local regulations" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_4**] = "Yes" OR "Not applicable: ICF waiver/Opt-out/No opposition applies", AND*
- *"4. Informed and privacy consent signature obtained depending on local regulations" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC4**] is not flagged AND*
- *"Date of data collection (dd/mmm/yyyy)" [**PI. PI_date_coll**] is not missing.*

*Moreover, for patients with "4. Informed and privacy consent signature obtained depending on local regulations" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_4**] = "Yes, it will be also verified that:*

- *"Date of informed consent form signature by the patient or by next of kin* (dd/mmm/yyyy)" [**PI. PI_date_IC**] <= "Date of data collection (dd/mmm/yyyy)" [**PI. PI_date_coll**] AND*
- *"Date of privacy form signature by the patient or by next of kin* (dd/mmm/yyyy)" [**PI. PI_date_priv**] <= "Date of data collection (dd/mmm/yyyy)" [**PI. PI_date_coll**]*

During data elaboration this criterion will be critically reviewed and discussed, depending also on specificities of sites and countries local regulations.

Criterion 5 (UNCOMMON MUTATION COHORT). Patient harbouring uncommon or compound EGFR mutations

- *"Cohort" [**PI. PI_coh_ty**] = "Uncommon Mutation cohort" AND*
- *"5. Patient harbouring uncommon or compound EGFR mutations" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_5umc**] = "Yes" AND*
- *"5. Patient harbouring uncommon or compound EGFR mutations" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC5_umc**] is not flagged AND*
- *At least one uncommon mutation shall be present on the start date of the Index EGFR-TKI therapy (as defined in "Chapter 3"), according to the fields:*
  - *"EGFR mutations at start of first-line treatment" [**First-line treatment period / MUT1. MUT1_unc**]*
    OR
  - *"EGFR mutations at start of second-line treatment" in the MUTATIONS form of the [**Second-line treatment period / MUT2. MUT2_mut_start**]*

Criterion 5 (SEQUENCING COHORT). Patient with common EGFR mutations (Del19, L858R)

- *"Cohort" [**PI. PI_coh_ty**] = "Sequencing cohort" AND*
- *"5. Patient with common EGFR mutations (Del19, L858R)" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_5sc**] = "Yes" AND*
- *"5. Patient with common EGFR mutations (Del19, L858R)" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC5_sc**]" is not flagged AND*
- *"EGFR mutations at start of first-line treatment" [**First-line treatment period / MUT1. MUT1_seq**] = "Del19" OR "L858R"*

Criterion 6 (<u>UNCOMMON MUTATION COHORT</u>). Patient who started with either afatinib (Giotrif), gefitinib (Iressa), erlotinib (Tarceva), or osimertinib (Tagrisso) in the first- or second-line setting within regular clinical practice

- *"Cohort" [**PI. PI_coh_ty**] = "Uncommon Mutation cohort" AND*
- *"6. Patient who started with either afatinib (Giotrif®), gefitinib (Iressa), erlotinib (Tarceva), or osimertinib (Tagrisso) in the first- or second-line setting within regular clinical practice" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_6umc**] = "Yes" AND*
- *"6. Patient who started with either afatinib (Giotrif®), gefitinib (Iressa), erlotinib (Tarceva), or osimertinib (Tagrisso) in the first- or second-line setting within regular clinical practice" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC6_umc**] is not flagged AND*
- *"Type of treatment" [**First-line treatment period / TREAT. TREAT_ty**] = "EGFR-TKI" OR "Type of treatment" [**Second-line treatment period / TREAT. TREAT_ty**] = "EGFR-TKI" AND*
- *The EGFR-TKI ADMINISTRATION DETAILS form [**name of the form: EAD**] is not empty*

Criterion 6 (<u>SEQUENCING COHORT</u>). Patient was treated with afatinib (Giotrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line

- *"Cohort" [**PI. PI_coh_ty**] = "Sequencing cohort" AND*
- *"6. Patient was treated with afatinib (Giotrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_6sc**] = "Yes" AND*
- *"6. Patient was treated with afatinib (Giotrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC6_sc**]" is not flagged AND*
- *"Number of treatment lines for advanced EGFR-mutated NSCLC within date of data collection" [**PI. PI_num_lines**] = "2" OR ">2" AND*
- *The AFATINIB ADMINISTRATION DETAILS form [**name of the form: AAD**] is not empty AND earliest "Start date with this dose (dd/mmm/yyyy)" [**AAD. AAD_start_date**] is not missing, AND*
- *The OSIMERTINIB ADMINISTRATION DETAILS form [**name of the form: OAD**] is not empty AND earliest "Start date with this dose (dd/mmm/yyyy)" [**OAD. OAD_start_date**] is not missing, AND*
- *The earliest start date in the OSIMERTINIB ADMINISTRATION DETAILS form is greater than the earliest start date in the AFATINIB ADMINISTRATION DETAILS form, AND*
- *"EGFR mutations at start of second-line treatment" [**Second-line treatment period / MUT2. MUT2_mut_start**] includes "T790M"*

Criterion 7 (UNCOMMON MUTATION COHORT). Patient has started EGFR-TKI treatment at least 12 months prior to data entry

- *"Cohort" [**PI. PI_coh_ty**] = "Uncommon Mutation cohort" AND*
- *"7. Patient has started EGFR-TKI treatment at least 12 months prior to data entry" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_7umc**] = "Yes" AND*
- *"7. Patient has started EGFR-TKI treatment at least 12 months prior to data entry" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC7_umc**] is not flagged AND*
- *Start date of the Index EGFR-TKI therapy (as defined in "Chapter 3") is lower than or equal to ("Date of data collection (dd/mmm/yyyy)" [**PI. PI_date_coll**] – 11.50 months) (*)*

This line shall start in presence of at least one uncommon/compound mutation (as described in the definition of the calculated variable "Index EGFR-TKI therapy": see "Chapter 3").

(*) this means that if the start date of the index EGFR-TKI therapy is 11.49 months before date of data collection, the patient violates this criterion. This tolerance window has been agreed with the Sponsor during the Data Analysis Strategic Meeting, and will not be further discussed. Only in case exact day is not known and this makes the evaluation critical with the respect to the tolerance window, then case-by-case discussion will be done with the Sponsor.
In case the Index therapy line is an EGFR-TKI given in combination with chemotherapy, a query will be raised in order to ensure that the treatment line was administered according to regular clinical practice.

Criterion 7 (SEQUENCING COHORT). Patient has started osimertinib treatment at least 10 months prior to data entry

- *"Cohort" [**PI. PI_coh_ty**] = "Sequencing cohort" AND*
- *"7. Patient has started osimertinib treatment at least 10 months prior to data entry" in the ELIGIBILITY CRITERIA form [**EC. EC_IC_7sc**] = "Yes" AND*
- *"7. Patient has started osimertinib treatment at least 10 months prior to data entry" in the PROTOCOL DEVIATION FORM [**PDF. PDF_IC7_sc**] is not flagged AND*
- *Start date of the Index EGFR-TKI therapy (as defined in "Chapter 3") is lower than or equal to ("Date of data collection (dd/mmm/yyyy)" [**PI. PI_date_coll**] – 9.50 months) (*)*

This line shall start in presence of at least one common mutation (as described in the definition of the calculated variable "Index EGFR-TKI therapy": see "Chapter 3").

(*) this means that if the start date of the index EGFR-TKI therapy is 9.49 months before date of data collection, the patient violates this criterion. This tolerance window has been agreed with the Sponsor during the Data Analysis Strategic Meeting, and will not be further discussed. Only in case exact day is not known and this makes the evaluation critical with the respect to the tolerance window, then case-by-case discussion will be done with the Sponsor.

Criterion 8 (UNCOMMON MUTATION COHORT). Patient not treated for EGFR mutated NSCLC within a clinical trial

- *"Cohort" [**PI. PI_coh_ty**] = "Uncommon Mutation cohort" AND*
- *"1. Patient treated for EGFR mutated NSCLC within a clinical trial" in the ELIGIBILITY CRITERIA form [**EC. EC_EC_1_umc**] = "No" AND*
- *"1. Patient treated for EGFR mutated NSCLC within a clinical trial" in the PROTOCOL DEVIATION FORM [**PDF. PDF_EC1_umc**] is not flagged*

Criterion 8 (SEQUENCING COHORT). Patient not treated for EGFR mutated NSCLC within a clinical trial nor participated in GioTag study

- *"Cohort" [**PI. PI_coh_ty**] = "Sequencing cohort" AND*
- *"1. Patient treated for EGFR mutated NSCLC within a clinical trial or participated in GioTag study" in the ELIGIBILITY CRITERIA form [**EC. EC_EC_1_sc**] = "No" AND*
- *"1. Patient treated for EGFR mutated NSCLC within a clinical trial or participated in GioTag study" in the PROTOCOL DEVIATION FORM [**PDF. PDF_EC1_sc**] is not flagged*

Patients treated with osimertinib within an early access program/compassionate use program (EAP/CUP) are allowed.

Criterion 9. Patient without active brain metastases at start of EGFR-TKI therapy (independent of treatment line)

- *"2. Patient with active brain metastases at start of EGFR-TKI therapy (independent of treatment line)" in the ELIGIBILITY CRITERIA form [**EC. EC_EC_2**] = "No" AND*
- *"2. Patient with active brain metastases at start of EGFR-TKI therapy (independent of treatment line)" in the PROTOCOL DEVIATION FORM [**PDF. PDF_EC2**] is not flagged*

Criterion 10 (<u>UNCOMMON MUTATION COHORT only</u>). Patient not treated with osimertinib without further uncommon mutations than acquired T790M

- *"Cohort" [**PI. PI_coh_ty**] = "Uncommon Mutation cohort" AND*
- *"3. Patient treated with osimertinib with no further uncommon mutation than acquired T790M" in the ELIGIBILITY CRITERIA form [**EC. EC_EC_3_umc**] = "No" AND*
- *"3. Patient treated with osimertinib with no further uncommon mutation than acquired T790M" in the PROTOCOL DEVIATION FORM [**PDF. PDF_EC3_umc**] is not flagged AND*
- *If the first-line (as defined in "Chapter 3") is "Osimertinib", then the following condition shall NOT be verified: no options selected (excluding "Del19" and "L858R") in field "EGFR mutations at start of first-line treatment" [**First-line treatment period / MUT1. MUT1_unc**] AND only option "T790M" is selected in field "EGFR mutations at start of second-line treatment" [**Second-line treatment period / MUT2. MUT2_mut_start**]*
- *If the second-line (as defined in "Chapter 3") is "Osimertinib", then the following condition shall NOT be verified: no options selected (excluding "Del19" and "L858R") in field "EGFR mutations at start of first-line treatment" [**First-line treatment period / MUT1. MUT1_unc**] AND no options selected (excluding "Del19" and "L858R") in field "EGFR mutations at start of second-line treatment" [**Second-line treatment period / MUT2. MUT2_mut_start**] AND only option "T790M" is selected in field "EGFR mutations" at stop of second-line treatment/within end of observation [**Second-line treatment period / MUT2. MUT2_mut_stop**]*

2.2 Other criteria

None.

2.3 Analysis sets

ENROLLED PATIENTS: All patients entered in eCRF.

ELIGIBLE PATIENTS (UNCOMMON MUTATION COHORT): All enrolled patients meeting all the criteria described in section 2.1 (considering the UNCOMMON MUTATION COHORT version of criteria, where applicable) and in section 2.2.

ELIGIBLE PATIENTS (SEQUENCING COHORT): All enrolled patients meeting all the criteria described in section 2.1 (considering the SEQUENCING COHORT version of criteria, where applicable) and in section 2.2.

The analyses will be done on patients who respond to inclusion/exclusion criteria and are evaluable for primary analysis (i.e. patients without available data for the primary analysis will NOT be classified as "ELIGIBLE"), unless differently specified (see Chapter 4).

[redacted]

2.5 Hierarchy of violated criteria

The purpose of this algorithm is to assign an unique, major criteria violation to each enrolled patients, even in case a patient has more than one reason (ie. more than one criterion) for being excluded from the analysis.

2.5.1 UNCOMMON MUTATION COHORT

1) *Violation of **criterion 4** (as defined in Section 2.1) **for any reasons**: if informed consent/privacy consent was not provided where applicable by local regulations, patients' data cannot be used*
2) *Violation of **criterion 1** (as defined in Section 2.1) **for any reasons**: non-adult patients cannot be enrolled*
3) *Violation of **criterion 2** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
4) *Violation of **criterion 2** (as defined in Section 2.1) **for any other reason***
5) *Violation of **criterion 3** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
6) *Violation of **criterion 3** (as defined in Section 2.1) **for any other reason***
7) *Violation of **criterion 5** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
8) *Violation of **criterion 5** (as defined in Section 2.1) **for any other reason***
9) *Violation of **criterion 6** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
10) *Violation of **criterion 6** (as defined in Section 2.1) **for any other reason***
11) *Violation of **criterion 7** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
12) *Violation of **criterion 7** (as defined in Section 2.1) **for any other reason***
13) *Violation of **criterion 8** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
14) *Violation of **criterion 8** (as defined in Section 2.1) **for any other reason***
15) *Violation of **criterion 9** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
16) *Violation of **criterion 9** (as defined in Section 2.1) **for any other reason***
17) *Violation of **criterion 10** (as defined in Section 2.1) **where the violation is documented by the Investigator** (in the ELIGIBILITY CRITERIA form) **or in the PROTOCOL DEVIATION FORM***
18) *Violation of **criterion 10** (as defined in Section 2.1) **for any other reason***

2.5.2 SEQUENCING COHORT

The same algorithm will be used also for SEQUENCING COHORT, but criterion 10 will not be applicable.

3 COMPUTED VARIABLES

The following variables will be computed as described below.
In this section, the eCRF fields are indicated as: "label of the field" [***name of the time point / name of the form. name of the eCRF variable***].
In case of partial dates (i.e. day and/or month not known), the Biostatistician will estimate incomplete dates to be used in the statistical analysis as follows: if year is not unknown, missing days will be inputed as the first day of the month (01) and month will be inputed as "July" (07).
Moreover, if a patient is deceased and in the eCRF it is not reported that the patient stopped a specific treatment (ie. the treatment stop date is not provided), then the treatment stop date will be imputed with the date of death.

Number of NSCLC treatment lines and type of lines
For each patient, the total number of NSCLC treatment lines will be calculated as follows:

- If "Number of treatment lines for advanced EGFR-mutated NSCLC within date of data collection" [***PI. PI_num_lines***] = "1", this will correspond also to the total number of lines (this options is applicable only for UNCOMMON MUTATION COHORT). By definition, the line shall be an EGFR-TKI, and the type of treatment will be retrieved in field "Type of EGFR-TKI" [***EAD. EAD_EGFR***].
- If "Number of treatment lines for advanced EGFR-mutated NSCLC within date of data collection" [***PI. PI_num_lines***] = "2", depending on the type of cohort
    - *Uncommon mutation cohort*:
        1. the first-line treatment will be retrieved from the field [***First-line treatment period / TREAT. TREAT_ty***], and in case it is an "EGFR-TKI" the exact therapy will be retrieved from the field "Type of EGFR-TKI" [***EAD. EAD_EGFR***] of the record of the EGFR-TKI ADMINISTRATION DETAILS form having "Start date with this dose (dd/mmm/yyyy)" [***EAD. EAD_start_date***] equal to "Start date of this line (dd/mmm/yyyy)" [***First-line treatment period / TREAT. TREAT_start_date***];
        2. the second-line treatment will be retrieved from the field [***Second-line treatment period / TREAT. TREAT_ty***], and in case it is an "EGFR-TKI" the exact therapy will be retrieved from the field "Type of EGFR-TKI" [***EAD. EAD_EGFR***] of the record of the EGFR-TKI ADMINISTRATION DETAILS form having "Start date with this dose (dd/mmm/yyyy)" [***EAD. EAD_start_date***] equal to "Start date of this line (dd/mmm/yyyy)" [***Second-line treatment period / TREAT. TREAT_start_date***].
    - *Sequencing cohort*: by definition, "Afatinib" will be the first-line treatment, and "Osimertinib" will be the second-line treatment.
- If "Number of treatment lines for advanced EGFR-mutated NSCLC within date of data collection" [***PI. PI_num_lines***] = ">2", the first-line and second-line definition will correspond to those defined for patients with 2 lines only, while the subsequent lines will be retrieved from the records of the SUBSEQUENT LINES DETAILS form [***name of the form: SLD***]. In particular, each record will correspond to a single NSCLC therapy line, which will be identified on the basis of the field "Type of treatment" [***SLD. SLD_treat, SLD_EGFR***] after having ordered by "Start date of this line (dd/mmm/yyyy)" [***SLD. SLD_start_date***] (ascending order).

Start date of first-line therapy

- *Uncommon mutation cohort*: it will correspond to the therapy recorded in the NSCLC TREATMENT form at [***First-line treatment period***] according to the field: "Start date of this line (dd/mmm/yyyy)" [***First-line treatment period / TREAT. TREAT_start_date***]
- *Sequencing cohort*: it will correspond to the therapy recorded in the AFATINIB ADMINISTRATION DETAILS form, having the earliest non-missing date recorded in field "Start date with this dose (dd/mmm/yyyy)" [***AAD. AAD_start_date***].

Type of NSCLC treatment patterns for UNCOMMON MUTATION COHORT

Patient's treatment patterns will be defined according to the data recorded in the following forms:

- NSCLC TREATMENT at [***First-line treatment period***], considering the concatenation of fields [**TREAT. TREAT_ty** (*)**, TREAT_ty_sp, TREAT_radio_YN**]. The start date of this line will correspond to the field [***First-line treatment period / TREAT. TREAT_start_date***], while the stop date of this line (if any) will correspond to the field [***First-line treatment period / TREAT. TREAT_stop_date***];
- NSCLC TREATMENT at [***Second-line treatment period***] (if applicable, for patients with Number of NSCLC treatment lines (as defined before) >1), considering the concatenation of fields [**TREAT. TREAT_ty** (**)**, TREAT_ty_sp, TREAT_radio_YN**]. The start date of this line will correspond to the field [***Second-line treatment period / TREAT. TREAT_start_date***], while the stop date of this line (if any) will correspond to the field [***Second-line treatment period / TREAT. TREAT_stop_date***].
- SUBSEQUENT LINES DETAILS (if applicable, for patients with Number of NSCLC treatment lines (as defined before) >2), considering the concatenation of fields [**SLD. SLD_treat** (***)**, SLD_treat_sp, SLD_radio_YN**]. The start date of this line will correspond to the field [**SLD. SLD_start_date**], while the stop date of this line (if any) will correspond to the field [**SLD. SLD_stop_date**]. *The same patient could have more than one record: each record corresponds to a distinct line, which shall be ordered by start date.*

(*) in case it is an "EGFR-TKI", the exact therapy will be retrieved from the field "Type of EGFR-TKI" [***EAD. EAD_EGFR***] of the record of the EGFR-TKI ADMINISTRATION DETAILS form having "Start date with this dose (dd/mmm/yyyy)" [***EAD. EAD_start_date***] equal to "Start date of this line (dd/mmm/yyyy)" [***First-line treatment period / TREAT. TREAT_start_date***].

(**) in case it is an "EGFR-TKI" the exact therapy will be retrieved from the field "Type of EGFR-TKI" [***EAD. EAD_EGFR***] of the record of the EGFR-TKI ADMINISTRATION DETAILS form having "Start date with this dose (dd/mmm/yyyy)" [***EAD. EAD_start_date***] equal to "Start date of this line (dd/mmm/yyyy)" [***Second-line treatment period / TREAT. TREAT_start_date***].

(***) in case it is an "EGFR-TKI", the exact therapy will be retrieved from the field "Type of EGFR-TKI" [**SLD. SLD_EGFR**] of the same record.

Having defined the start and end dates of each line, the **Duration of treatment lines** will be calculated as the difference between the stop date of the line (^) and the start date of the line + 1 day.

(^) or the end of observation date (as defined later), in case the therapy line was not discontinued at the end of observation.

In particular, for each patient, the sequences of treatments will be defined taking into consideration the start dates of each line (as defined before). This way, it will be possible to calculate also the ***ordinal number*** *of each line*. Here below are provided some examples of the treatment line sequence that might be observed:

- EGFR-TKI (afatinib)
- Chemotherapy+Radiotherapy → EGFR-TKI (erlotinib)
- Chemotherapy+Targeted therapy → EGFR-TKI (gefitinib) → Chemotherapy+Immunotherapy
- etc.

Type of NSCLC treatment patterns for SEQUENCING COHORT

Patient's treatment patterns will be defined as follows:

- by definition, "Afatinib" will be the first-line treatment; the start date of the line will be the earliest start date of the field [**AAD. AAD_start_date**], while the stop date of the line will be the greatest stop date of the field [**AAD. AAD_stop_date**];
- by definition, "Osimertinib" will be the second-line treatment; the start date of the line will be the earliest start date of the field [**OAD. OAD_start_date**], while the stop date of the line will be the greatest stop date of the field [**OAD. OAD_stop_date**];
- subsequent lines will be defined according to the data recorded in the following forms SUBSEQUENT LINES DETAILS (if applicable, for patients with Number of NSCLC treatment lines (as defined before) >2), considering the concatenation of fields [**SLD. SLD_treat** (***)**, SLD_treat_sp, SLD_radio_YN**]. The start date of this line will correspond to the field [**SLD. SLD_start_date**]. *The same patient could have more than one record: each record corresponds to a distinct line, which shall be ordered by start date.*

(***) in case it is an "EGFR-TKI", the exact therapy will be retrieved from the field "Type of EGFR-TKI" [**SLD. SLD_EGFR**] of the same record.

Having defined the start and end dates of each line, the **Duration of treatment lines** will be calculated as the difference between the stop date of the line (^) and the start date of the line + 1 day.

(^) or the end of observation date (as defined later), in case the therapy line was not discontinued at the end of observation.

*In particular, for each patient, the sequences of treatments will be defined taking into consideration the start dates of each line (as defined before). This way, it will be possible to calculate also the **ordinal number** of each line.*

EGFR-TKI generation

- "Erlotinib" and "Gefitinib" will be classified as "1st generation EGFR-TKI";
- "Afatinib" will be classified as "2nd generation EGFR-TKI";
- "Osimertinib" will be classified as "3rd generation EGFR-TKI".

EGFR-TKI starting daily dose (mg) (first- and second-line treatment only)

The starting dose will be retrieved from the following fields of the following forms:

- from the AFATINIB ADMINISTRATION DETAILS form (only for the SEQUENCING COHORT), from the field [**AAD. AAD_dose**] of the record with earliest non-missing start date (recorded in field [**AAD. AAD_start_date**]);
- from the OSIMERTINIB ADMINISTRATION DETAILS form (only for the SEQUENCING COHORT), from the field [**OAD. OAD_dose**] of the record with earliest non-missing start date (recorded in field [**OAD. OAD_start_date**]);
- from the EGFR-TKI ADMINISTRATION DETAILS form (only for the UNCOMMON MUTATION COHORT), from the field [**EAD. EAD_dose**] of the record with earliest non-missing start date (recorded field [**EAD. EAD_start_date**]). The same patient could have one or two lines of EGFR-TKI recorded in this form, and each line is identified by the field "Type of EGFR-TKI" [**EAD. EAD_EGFR**]: therefore, for each line recorded in this form, it will be possible to identify the starting dose with the rule defined above.

Index EGFR-TKI therapy

- *Uncommon mutation cohort*: it will correspond to the therapy recorded in the NSCLC TREATMENT form, either at [***First-line treatment period***] or [***Second-line treatment period***] depending on the following conditions:
    - [***First-line treatment period***] is the time point to consider if:
        - "Type of treatment" [***First-line treatment period / TREAT. TREAT_ty***] = "EGFR-TKI" AND
        - "Start date of this line (dd/mmm/yyyy)" [***First-line treatment period / TREAT. TREAT_start_date***] is lower than or equal to ("Date of data collection (dd/mmm/yyyy)" [***PI. PI_date_coll***] – 11.50 months) AND
        - "EGFR mutations at start of first-line treatment" [***First-line treatment period / MUT1. MUT1_unc***] has at least one of the options selected (excluding "Del19" and "L858R") (*).
    - Otherwise, if the above-specified condition is not met, then the [***Second-line treatment period***] is the time point to consider if:
        - "Type of treatment" [***Second-line treatment period / TREAT. TREAT_ty***] = "EGFR-TKI" AND
        - "Start date of this line (dd/mmm/yyyy)" [***Second-line treatment period / TREAT. TREAT_start_date***] is lower than or equal to ("Date of data collection (dd/mmm/yyyy)" [***PI. PI_date_coll***] – 11.50 months) AND
        - "EGFR mutations at start of first-line treatment" [***First-line treatment period / MUT1. MUT1_unc***] OR "EGFR mutations at start of second-line treatment" in the MUTATIONS form of the [***Second-line treatment period / MUT2. MUT2_mut_start***] has at least one of the options selected (excluding "Del19" and "L858R") (*).

  The therapy recorded in the field "Type of EGFR-TKI" [***EAD. EAD_EGFR***] of the EGFR-TKI ADMINISTRATION DETAILS form, having "Start date with this dose (dd/mmm/yyyy)" [***EAD. EAD_start_date***] equal to the start date of the Index EGFR-TKI therapy (defined before), will correspond to the Index EGFR-TKI therapy.

  *(*) in case the option "Other EGFR mutation(s)" is selected, the Sponsor will evaluate plausibility (by means of a manual clinical review) of the specific mutation(s) recorded in the corresponding open field "If other EGFR mutation(s), please specify" [**First-line treatment period / MUT1. MUT1_unc_sp**], [**Second-line treatment period / MUT2. MUT2_mut_start_sp**]. The list of specified other EGFR mutations (if any) will be sent to Sponsor by the* [redacted]
- *Sequencing cohort*: it will correspond to the therapy recorded in the OSIMERTINIB ADMINISTRATION DETAILS form, having the earliest non-missing date recorded in field "Start date with this dose (dd/mmm/yyyy)" [***OAD. OAD_start_date***] lower than or equal to ("Date of data collection (dd/mmm/yyyy)" [PI. PI_date_coll] – 9.50 months). It is also required to have "EGFR mutations at start of second-line treatment" [***Second-line treatment period / MUT2. MUT2_mut_start***] including "T790M".

NSCLC stage at start of first-line treatment
It will correspond to the field "Stage of disease at start of first-line treatment (or at NSCLC diagnosis, in case stage was not re-evaluated)" [***DIAG. DIAG_stage***], when this field is not missing. If this field is missing, but there is evidence that the patient was diagnosed with stage III (ie. the Investigator confirmed in a query that could not classify the tumor as IIIB or IIIC, but that the stage was not IIIA), then the patient will be classified as "stage III (unspecified B/C)". As a result, the possible levels of this categorical variable will be:

- "stage IIIB"
- "stage IIIC"
- "stage III (unspecified B/C)"
- "stage IV".

Duration of NSCLC until start of first-line treatment (in months)
It will be calculated as the difference between Start date of first-line therapy (as defined before) and Date of NSCLC diagnosis [***DIAG. DIAG_date***] + 1 day, divided by 30.4375 days.
Duration of NSCLC until start of index EGFR-TKI therapy (in months)
It will be calculated as the difference between Start date of the Index EGFR-TKI therapy (as defined before) and Date of NSCLC diagnosis [***DIAG. DIAG_date***] + 1 day, divided by 30.4375 days.

Smoking duration (years) at start of first-line treatment
It will be calculated:

- For previous smokers (ie. patients with "Smoking status" [***SM.SM_status***] = "Previous smoker"): if smoking start year is not missing & smoking stop year is not missing, it will be calculated as Stop year [***SM.SM_stop_yyyy***] - Start year [***SM.SM_start_yyyy***]
- For current smokers (ie. patients with "Smoking status" [***SM.SM_status***] = "Current smoker"): if smoking start year is not missing, it will be calculated as YEAR(Start date of first-line therapy, as defined before) - Start year [***SM.SM_start_yyyy***]

BMI at start of first-line treatment
Considering the [***First-line treatment period***] time period, it will be computed as "Weight" (in Kg) **[CCPE.CCPE_weight_num, CCPE_weight_unit]**/"Height" (in centimeters) **[CCPE.CCPE_height_num, CCPE_height_unit]***100) ^ 2
In case weight is not reported in kg, a conversion will be performed; in case height is not reported in cm, a conversion will be performed.
BMI will also be reported as classes: underweight: BMI < 18.5, normal weight: BMI 18.5-24.9, overweight: BMI 25-29.9, obese: BMI >= 30.

Changes in ECOG PS at start of osimertinib from start of afatinib
Considering patients of the SEQUENCING COHORT with known ECOG PS both at afatinib start and at osimertinib start (ie. those with [***First-line treatment period*** / **CCPE. CCPE_ECOG**] ≠ UNK AND [***Second-line treatment period*** / **CCPE. CCPE_ECOG**] ≠ UNK), the difference in ECOG PS between [***Second-line treatment period***] and [***First-line treatment period***] will be computed, and the following patents groups will be defined:

- **No changes**: difference in ECOG PS = 0;
- **Improvements**: difference in ECOG PS <0;
- **Deteriorations of 1 step**: difference in ECOG PS = 1;
- **Deterioration of 2 or more steps**: difference in ECOG PS ≥2.

Changes in ECOG PS at start of second-line treatment with respect to start of first-line treatment
See previous algorithm, which will be applied for UNCOMMON MUTATION COHORT.

Sites of metastases at first-line treatment start
Considering the [***First-line treatment period***] time period,

- patients with "Presence of any metastases?" [**CCPE. CCPE_met_YN**] = "No" will be classified as patients with "No metastases";
- patients with "Presence of any metastases?" [**CCPE. CCPE_met_YN**] = "Yes" will be classified according to the options selected in field [**CCPE. CCPE_met_site, CCPE_met_site_sp**];
- patients with "Presence of any metastases?" [**CCPE. CCPE_met_YN**] = "UNK" will be classified as "UNK".

Sites of metastases at second-line treatment start
The same algorithm will be applied considering the [***Second-line treatment period***] time period, considering only patients with Number of NSCLC treatment lines (as defined previously) >1.
Sites of metastases at index EGFR-TKI therapy start
The same algorithm will be applied considering the time period (ie. either [***First-line treatment period***] or [***Second-line treatment period***]) corresponding to the index EGFR-TKI therapy (as defined before).

Patients with presence of brain metastases at start of EGFR therapy (either at first- or second-line)
They will be those patients having:

- [***First-line treatment period / CCPE. CCPE_met_site_3***] "Brain metastases" AND with first-line treatment corresponding to an EGFR-TKI

OR

- [***Second-line treatment period / CCPE. CCPE_met_site_3***] "Brain metastases" AND with second-line treatment corresponding to an EGFR-TKI.

Changes in metastatic sites at start of osimertinib from start of afatinib
Considering patients of the SEQUENCING COHORT with known presence/absence of metastases both at afatinib start and at osimertinib start (ie. those with [***First-line treatment period*** / **CCPE. CCPE_met_YN**] = ("Yes" OR "No") AND [***Second-line treatment period*** / **CCPE. CCPE_met_YN**] = ("Yes" OR "No")), the following algorithms will be computed considering separately all the possible sites of metastases listed in field [**CCPE. CCPE_met_site, CCPE_met_site_sp**]:

- **Patients with new metastatic sites**: considering all patients with no metastases in a specific site at [***First-line treatment period***] as denominator, it will be determined the absolute number and relative frequency of patients who have metastasis at the specific site at [***Second-line treatment period***]
- **Patients with resolved metastases**: considering all patients with presence of metastases in a specific site at [***First-line treatment period***] as denominator, it will be determined the absolute number and relative frequency of patients who do not have metastases at the specific site at [***Second-line treatment period***]

Changes in metastatic sites at start of second-line treatment from start of first-line treatment
See previous algorithm, which will be applied for UNCOMMON MUTATION COHORT.

EGFR mutational status at first-line treatment start

- For UNCOMMON MUTATION COHORT, it will be defined according to the fields [***First-line treatment period / MUT1. MUT1_unc, MUT1_unc_ex20_sp, MUT1_unc_sp***].
- For SEQUENCING COHORT, it will be defined according to the field [***First-line treatment period / MUT1. MUT1_seq***].

EGFR mutational status at second-line treatment start

It will be defined according to the following fields recorded in the MUTATIONS form of the [***Second-line treatment period***] time period (when applicable); for UNCOMMON MUTATION COHORT, only patients with Number of NSCLC treatment lines (as defined before) >1 should be considered:

- if "Was mutational status re-evaluated at start of second-line treatment?" [**MUT2. MUT2_reeval**] = "No" OR if "Any changes in EGFR mutations at start of second-line treatment with respect to start of first-line treatment?" [**MUT2. MUT2_changes**] = "UNK", patients will be classified as "Unknown EGFR mutational status"
- if "Any changes in EGFR mutations at start of second-line treatment with respect to start of first-line treatment?" [**MUT2. MUT2_changes**] = "No", then the patient's EGFR mutational status at second-line treatment start will be imputed as the same patient's EGFR mutational status at first-line treatment start (as defined before)
- if "Any changes in EGFR mutations at start of second-line treatment with respect to start of first-line treatment?" [**MUT2. MUT2_changes**] = "Yes", then the patient's EGFR mutational status at second-line treatment start will be retrieved from the fields [**MUT2. MUT2_mut_start, MUT2_mut_start_ex20_sp, MUT2_mut_start_sp, MUT2_concom_mut_start**]

Acquired EGFR mutations at second-line treatment start

For both cohorts, the mutations found at start of second-line treatment (ie. the options selected in the field [**MUT2. MUT2_mut_start**]) will be compared to the mutations found at start of first-line treatment (i.e. the options selected in the field [**MUT1. MUT1_mut_unc**] for the UNCOMMON MUTATION COHORT, or in the field [**MUT1. MUT1_mut_seq**] for the SEQUENCING COHORT). The mutations found at start of second-line treatment that were not present at first-line treatment start will be classified as acquired EGFR mutations.

EGFR mutational status at second-line treatment stop/end of observation

It will be defined according to the following fields recorded in the MUTATIONS form of the [***Second-line treatment period***] time period (when applicable):

- if "Was mutational status re-evaluated at at stop of second-line treatment (or within end of observation, in case
- second-line treatment was not discontinued)?" [**MUT2. MUT2_reeval_stop**] = "No" OR if "Any changes in EGFR mutations with respect to start of second-line treatment?" [**MUT2. MUT2_changes_stop**] = "UNK", patients will be classified as "Unknown EGFR mutational status"
- if "Any changes in EGFR mutations with respect to start of second-line treatment?" [**MUT2. MUT2_changes_stop**] = "No", then the patient's EGFR mutational status at second-line treatment stop/end of observation will be imputed as the same patient's EGFR mutational status at second-line treatment start (as defined before)
- if "Any changes in EGFR mutations with respect to start of second-line treatment?" [**MUT2. MUT2_changes_stop**] = "Yes", then the patient's EGFR mutational status at second-line treatment stop/end of observation will be retrieved from the fields [**MUT2. MUT2_mut_stop, MUT2_mut_stop_ex20_sp, MUT2_mut_stop_sp, MUT2_concom_mut_stop**]

Acquired EGFR mutations at second-line treatment stop/end of observation

For both cohorts, the mutations found at stop of second-line treatment/end of observation (ie. the options selected in the field [**MUT2. MUT2_mut_stop**]) will be compared to the mutations found at start of second-line treatment (i.e. the options selected in the field [**MUT2. MUT2_mut_start**]). The mutations found at second-line treatment stop/end of observation that were not present at start of second-line treatment will be classified as acquired EGFR mutations.

Classification of EGFR uncommon mutations (according to Yang's classification) for exploratory analyses
According to the MUTATIONS form, considering the EGFR mutational status at first- and second-line treatment start (but considering only lines containing EGFR-TKIs), the following definitions will be applied to classify patients' mutational status with respect to EGFR gene:

- **T790M-positive**: patients having T790M at start of either first- or second-line EGFR-TKI, but excluding patients developing acquired T790M at second-line osimertinib start;
- **Exon 20 insertion-positive**: patients having any type of exon 20 insertion at start of either first- or second-line EGFR-TKI, excluding patients included in group "a)";
- **Major uncommon mutations**: patients having either G719X and/or L861Q and/or S768I mutations at start of either first- or second-line EGFR-TKI, excluding patients included in groups "a)" or "b)";
- **Others**: patients not included in groups "a)", "b)", or "c)";
- **Compound mutations**: patients having more than one mutation of any type (including also common mutations).

The same patient cannot be included in more than one of the following groups, which are mutually exclusive: a), b), c), d). On the contrary, the same patient can be included in group e) and also in another group a) or b) or c) or d).
Source: Chih-Hsin Yang J, Schuler M, Popat S, Miura S, Heeke S, Park K, Märten A, Kim ES, Afatinib for the Treatment of Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Database of 693 Cases, Journal of Thoracic Oncology (2020), doi: https://doi.org/10.1016/j.jtho.2019.12.126.

Classification of EGFR uncommon mutations at first-line treatment start
The same 5 classes described above will be considered, but considering only EGFR mutational status at first-line treatment start (see algorithm described before), and without restrictions on type of treatment line.

Classification of EGFR uncommon mutations at second-line treatment start
The same 5 classes described above will be considered, but considering only EGFR mutational status at second-line treatment start (see algorithm described before), and without restrictions on type of treatment line.
In particular, "T790M-positive" group includes also patients developing acquired T790M at second-line osimertinib start, while excludes patients with T790M acquired only and treated with osimertinib. However, if the patient had also additional acquired mutations at start of second-line osimertinib (and not only acquired T790M), then the patient will not be excluded.
Only patients with Number of NSCLC treatment lines (as defined before) > 1 and [**MUT2. MUT2_reeval**] = "Yes" will be considered.
Patients without mutations at second line treatment start will not be included in "Others".

Classification of EGFR uncommon mutations at second-line treatment stop/end of observation
The same 5 classes described above will be considered, but considering only EGFR mutational status at second-line treatment stop/end of observation (see algorithm described before), and without restrictions on type of treatment line.
Only patients with Number of NSCLC treatment lines (as defined before) > 1 and [**MUT2. MUT2_reeval_stop**] = "Yes" will be considered.

Time on treatment with index therapy EGFR-TKI for UNCOMMON MUTATIONS COHORT

The following patients will be considered as having the event "treatment discontinuation":

- patients with discontinuation of index EGFR-TKI treatment, ie. those with discontinuation defined as "Treatment discontinued?" [**EAD. EAD_treat_disc**] = "Yes" in the latest record of the EGFR-TKI ADMINISTRATION DETAILS form referred to the index EGFR-TKI treatment (as defined before). For these patients, the time to event will be computed as the difference between the field "Stop date with this dose" [**EAD. EAD_stop_date**] of the above-mentioned record and the start date of the Index EGFR-TKI therapy (as defined before) + 1 day;
- deceased patients at time of inclusion in the study, ie. those with [**PI. PI_pt_class**] = "Deceased patient". For these patients, the time to event will be computed as the difference between the "Date of death" [**PI. PI_date_death**] and the start date of the Index EGFR-TKI therapy (as defined before) + 1 day.

The same patient could have multiple events, but for the purpose of the analysis only the earliest event will be considered.

Other patients will be considered as censored observations. The following situations might be observed:

- non-deceased patients with evidence of ongoing treatment at end of observation, ie. those with with [**PI. PI_pt_class**] = ("Living patient" OR "Untraceable patient") and with "Treatment discontinued?" [**EAD. EAD_treat_disc**] = "No" in the latest record of the EGFR-TKI ADMINISTRATION DETAILS form referred to the index EGFR-TKI treatment (as defined before). For these patients, the time to censoring will be computed as the difference between the end of observation date (as defined later) and the start date of the Index EGFR-TKI therapy (as defined before) + 1 day;
- non-deceased patients with unknown information on treatment interruption at end of observation, ie. those with [**PI. PI_pt_class**] = ("Living patient" OR "Untraceable patient") and with "Treatment discontinued?" [**EAD. EAD_treat_disc**] = "UNK" in the latest record of the EGFR-TKI ADMINISTRATION DETAILS form referred to the index EGFR-TKI treatment (as defined before). For these patients, the time to censoring will be computed as the difference between the greatest start date [**EAD. EAD_start_date**] of the EGFR-TKI ADMINISTRATION DETAILS form referred to the index EGFR-TKI treatment (as defined before) and the start date of the Index EGFR-TKI therapy (as defined before) + 1 day.

Time on treatment for SEQUENCING COHORT

The following patients will be considered as having the event "osimertinib treatment discontinuation after switch from afatinib":

- patients with discontinuation of osimertinib treatment, ie. those with discontinuation defined as "Treatment discontinued?" [**OAD. OAD_treat_disc**] = "Yes" in the latest record of the OSIMERTINIB ADMINISTRATION DETAILS form. For these patients, the time to event will be computed as the difference between the field "Stop date with this dose" [**OAD. OAD_stop_date**] of the above-mentioned record and the start date of the first-line therapy (as defined before) + 1 day;
- deceased patients at time of inclusion in the study, ie. those with [**PI. PI_pt_class**] = "Deceased patient". For these patients, the time to event will be computed as the difference between the "Date of death" [**PI. PI_date_death**] and the start date of the first-line therapy (as defined before) + 1 day.

The same patient could have multiple events, but for the purpose of the analysis only the earliest event will be considered.

Other patients will be considered as censored observations. The following situations might be observed:

- non-deceased patients with evidence of ongoing treatment at end of observation, ie. those with with [**PI. PI_pt_class**] = ("Living patient" OR "Untraceable patient") and with "Treatment discontinued?" [**OAD. OAD_treat_disc**] = "No" in the latest record of the OSIMERTINIB ADMINISTRATION DETAILS form. For these patients, the time to censoring will be computed as the difference between the end of observation date (as defined later) and the start date of the first-line therapy (as defined before) + 1 day;
- non-deceased patients with unknown information on treatment interruption at end of observation, ie. those with with [**PI. PI_pt_class**] = ("Living patient" OR "Untraceable patient") and with "Treatment discontinued?" [**OAD. OAD_treat_disc**] = "UNK" in the latest record of the OSIMERTINIB ADMINISTRATION DETAILS form. For these patients, the time to censoring will be computed as the difference between the greatest start date [**OAD. OAD_start_date**] of the OSIMERTINIB ADMINISTRATION DETAILS form and the start date of the first-line therapy (as defined before) + 1 day.

Time to second-line treatment failure for UNCOMMON MUTATIONS COHORT

The algorithm will be computed only for patients with Number of NSCLC treatment lines (as defined previously) >1.
The time to event will be computed considering the time elapsed from start of first-line treatment (regardless the tipe of treatment) to stop of second-line (regardless the tipe of treatment) or death by any cause.
The following patients will be considered as having the event "treatment discontinuation":

- patients with discontinuation of second-line treatment, ie. those with non-missing "Stop date of this line" [**Second-line treatment period / TREAT. TREAT_stop_date**]. For these patients, the time to event will be computed as the difference between the stop date of the second-line treatment (as defined before) and the start date of the first-line therapy (as defined before) + 1 day;
- deceased patients at time of inclusion in the study, ie. those with [**PI. PI_pt_class**] = "Deceased patient". For these patients, the time to event will be computed as the difference between the "Date of death" [**PI. PI_date_death**] and the start date of the first-line therapy (as defined before) + 1 day.

The same patient could have multiple events, but for the purpose of the analysis only the earliest event will be considered.
Other patients will be considered as censored observations. The following situations might be observed:

- non-deceased patients with evidence of ongoing second-line treatment at end of observation, ie. those with with [**PI. PI_pt_class**] = ("Living patient" OR "Untraceable patient") and with "Ongoing at end of observation?" [**Second-line treatment period / TREAT. TREAT_ongoing**] = "Yes". For these patients, the time to censoring will be computed as the difference between the end of observation date (as defined later) and the start date of the first-line therapy (as defined before) + 1 day;
- non-deceased patients with unknown information on second-line treatment interruption at end of observation, ie. those with with [**PI. PI_pt_class**] = ("Living patient" OR "Untraceable patient") and "Ongoing at end of observation?" [**Second-line treatment period / TREAT. TREAT_ongoing**] = "UNK". For these patients, the time to censoring will be computed as the difference between the latest start date of the most recent regimen/posology(*) and the start date of the first-line therapy (as defined before) + 1 day.
  (*) it will correspond to the greatest start date among:
  - the field "Start date of this line" [**Second-line treatment period / TREAT. TREAT_start_date**]
  - the greatest start date [**EAD. EAD_start_date**] of the EGFR-TKI ADMINISTRATION DETAILS form.

Overall Survival for UNCOMMON MUTATION COHORT

For deceased patients at time of inclusion in the study (ie. those with [**PI. PI_pt_class**] = "Deceased patient"), the time to event will be computed as the difference between the "Date of death" [**PI. PI_date_death**] and the start date of the Index EGFR-TKI therapy (as defined before) + 1 day.

Other patients will be considered as censored observations. The following situations might be observed:

- alive patients at end of observation, ie. those with with [**PI. PI_pt_class**] = "Living patient". For these patients, the time to censoring will be computed as the difference between the end of observation date (as defined later) and the start date of the Index EGFR-TKI therapy + 1 day;
- untraceable patients at end of observation, ie. those with with [**PI. PI_pt_class**] = "Untraceable patient". For these patients, the time to censoring will be computed as the difference between the latest date when the patient was known to be alive (ie. [**PI. PI_date_alive**]) and the start date of the Index EGFR-TKI therapy + 1 day.

Overall Survival for SEQUENCING COHORT

For deceased patients at time of inclusion in the study (ie. those with [**PI. PI_pt_class**] = "Deceased patient"), the time to event will be computed as follows:

- for **OS from afatinib start**, as the difference between the "Date of death" [**PI. PI_date_death**] and the Start date of first-line therapy (as defined before, namely afatinib) + 1 day;
- for **OS from osimertinib discontinuation**, as the difference between the "Date of death" [**PI. PI_date_death**] and the Stop date of second-line therapy (as defined before, namely osimertinib) + 1 day. This algorithm will be computed only for patients with osimertinib discontinuation (ie. those with calculated stop date of second-line therapy).

Other patients will be considered as censored observations. The following situations might be observed:

- alive patients at end of observation, ie. those with with [**PI. PI_pt_class**] = "Living patient". For these patients, the time to censoring will be computed as the difference between the end of observation date (as defined later) and the start date of afatinib / stop date of osimertinib therapy (depending on the type of OS evaluated) + 1 day;
- untraceable patients at end of observation, ie. those with with [**PI. PI_pt_class**] = "Untraceable patient". For these patients, the time to censoring will be computed as the difference between the latest date when the patient was known to be alive (ie. [**PI. PI_date_alive**]) and the start date of afatinib / stop date of osimertinib therapy (depending on the type of OS evaluated) + 1 day.

End of observation date

- For alive patients (ie. those with [**PI. PI_pt_class**] = "Living patient"), it will correspond to the "Date of data collection (dd/mmm/yyyy)" [**PI. PI_date_coll**]
- For deceased patients (ie. those with [**PI. PI_pt_class**] = "Deceased patient") it will correspond to the "Date of death (dd/mmm/yyyy)" [**PI. PI_date_death**]
- For untraceable patients (ie. those with [**PI. PI_pt_class**] = "Untraceable patient") it will correspond to the "Date patient last known to be alive (dd/mmm/yyyy)" [**PI. PI_date_alive**]

Duration of observation window (in months) starting from the first-line treatment start

- For alive patients (ie. those with [**PI. PI_pt_class**] = "Living patient"), it will be calculated as the difference between the end of observation date (as defined before) and Start date of first-line therapy (as defined before) + 1 day
- For deceased patients (ie. those with [**PI. PI_pt_class**] = "Deceased patient") it will be calculated as the difference between the end of observation date (as defined before) and Start date of first-line therapy (as defined before) + 1 day
- For untraceable patients (ie. those with [**PI. PI_pt_class**] = "Untraceable patient") it will be calculated as the difference between the end of observation date (as defined before) and Start date of first-line therapy (as defined before) + 1 day

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The analyses will be performed on the Analysis set specified for each table.
Missing data will not be imputed and so patients with missing data will be excluded from the analyses of that variable(s).
If the investigator is unable to collect the requested information the data will be “NK” (Not Known) or “NA” (Not Available), if the investigator did not record the information the data will be “Not Recorded”.

The UPSWING study has descriptive objectives and no specific comparison will be performed. The estimation of confidence intervals limits will be performed, where relevant.

4.1 UNCOMMON MUTATION COHORT

4.1.1 Patient disposition, analysis sets and criteria violations

Table 1-UNC. Patient disposition (ENROLLED PATIENTS of the Uncommon Mutation Cohort)
For each center, the table will provide absolute and relative frequencies of:

- patients ENROLLED in the UPSWING study (as defined in Chapter 2.3) in the cohort
- patients ELIGIBLE for the UPSWING study (as defined in Chapter 2.3) in the cohort

Percentages will be calculated by column; percentages will be calculated by row only for "Overall in the cohort".

Figure 1-UNC. Workflow of analysis sets and reasons for violations (ENROLLED PATIENTS of the Uncommon Mutation Cohort)
A figure with the workflow of analysis sets and reasons for violations will be provided; the hierarchy of violated criteria specific for the cohort (as defined in Section 2.5) will be applied, so that each violator will be classified with only one major violation (even in case of multiple violations).

Table 2-UNC. Reasons for violations (ENROLLED PATIENTS of the Uncommon Mutation Cohort)
The table will describe the reasons for patient non-eligibility and non-evaluability (considering each criterion listed in Section 2.3).
Absolute and relative frequency distribution will be provided.
For each evaluability criterion, percentages will be computed out of the total number of enrolled patients in the cohort.

Table 3-UNC. Duration of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide main descriptive statistics (mean, standard deviation, quartiles, min, max) of duration of observation window (in months) starting from the first-line treatment start (see "Computed variables" chapter) Descriptives will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

4.1.2 Demographic and clinical characteristics

Table 4-UNC. Socio-demographics (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- descriptive statistics (mean, standard deviation, quartiles, min, max) of "Age at start of first-line treatment" [***PI. PI_age***];
- patients' distribution (absolute and relative frequency) by "Gender" [***PI. PI_gender***];
- patients' distribution (absolute and relative frequency) by "Ethnicity" [***PI. PI_ethn, PI_ethn_sp***], including also those cases when ethnicity was not provided (according to the field [***PI. PI_cons_ethn_YN***] = "No").

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 5-UNC. Physical examination and smoking habits at start of first-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- patients' distribution (absolute and relative frequency) by classes of BMI at start of first-line treatment (see "Computed variables" chapter)
- patients' distribution (absolute and relative frequency) by "Smoking status" [***SM. SM_status***];
- descriptive statistics (mean, standard deviation, quartiles, min, max) of "Estimated amount of cigarettes consumed on average each day" [***SM. SM_cig_num***];
- descriptive statistics (mean, standard deviation, quartiles, min, max) of smoking duration (years) at start of first-line treatment (see "Computed variables" chapter)

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 6-UNC. Clinical characteristics (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- patients' distribution (absolute and relative frequency) by "Patient's ECOG Performance Status" at start of first-line treatment [***First-line treatment period / CCPE. CCPE_ECOG***]
- patients' distribution (absolute and relative frequency) by "Patient's ECOG Performance Status" at start of second-line treatment [***Second-line treatment period / CCPE. CCPE_ECOG***], considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter)
- patients' distribution (absolute and relative frequency) by changes in ECOG PS at start of second-line treatment with respect to start of first-line treatment (see "Computed variables" chapter), considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter).

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, unless differently specified.

Table 7-UNC. NSCLC features (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- patients' distribution (absolute and relative frequency) by "Tumor histology" at NSCLC diagnosis [***DIAG. DIAG_hist, DIAG_hist_sp***]
- patients' distribution (absolute and relative frequency) by NSCLC stage at start of first-line treatment (see "Computed variables" chapter)
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of NSCLC until start of first-line treatment (in months) (see "Computed variables" chapter)
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of NSCLC until start of index EGFR-TKI therapy (in months) (see "Computed variables" chapter)

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

4.1.3 Mutational Status

[redacted]

Table 10-UNC. Approaches for detection of mutations at first-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3

The table will provide:

- absolute and relative frequency of patients by "Biologic sample(s) used for mutation testing" (according to the fields [***First-line treatment period / MUT1. MUT1_biol_samp, MUT1_biol_samp_sp***]);
- absolute and relative frequency of "Methodology used for mutation testing", with details of ARMS, sequencing, NGS (according to the fields [***First-line treatment period / MUT1. MUT1_meth, MUT1_meth_sp, MUT1_meth_ARMS, MUT1_meth_ARMS_sp, MUT1_meth_seq, MUT1_meth_seq_sp, MUT1_meth_NGS, MUT1_meth_NGS_sp***])

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

[redacted]

Table 12-UNC. Mutations at second-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

The table will provide:

- absolute and relative frequency of patients according to EGFR mutational status at second-line treatment start (see "Computed variables" chapter);
- absolute and relative frequency of patients according to Classification of EGFR uncommon mutations at second-line treatment start (see "Computed variables" chapter);
- absolute and relative frequency of patients according to acquired EGFR mutations at second-line treatment start (see "Computed variables" chapter);
- absolute and relative frequency of patients according presence/absence of other new mutated genes and detail of new mutations at second-line treatment start (according to the fields [***Second-line treatment period / MUT2. MUT2_oth_gene_start_YN*** (*), ***MUT2_oth_gene_start, MUT2_oth_gene_start_sp***]).

(*) in case [***MUT2_oth_gene_start_YN***] = "No", then the patient's mutational status for other genes at second-line treatment start will be imputed as the same patient's mutational status for other genes at first-line treatment.

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter).

Table 13-UNC. Approaches for detection of mutations at second-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3

The table will provide:

- absolute and relative frequency of patients by "Biologic sample(s) used for mutation testing" (according to the fields [***Second-line treatment period / MUT2. MUT2_biol_samp, MUT2_biol_samp_sp***]);
- absolute and relative frequency of "Methodology used for mutation testing", with details of ARMS, sequencing, NGS (according to the fields [***Second-line treatment period / MUT2. MUT2_meth_start, MUT2_meth_start_sp, MUT2_meth_ARMS, MUT2_meth_ARMS_sp, MUT2_meth_seq, MUT2_meth_seq_sp, MUT2_meth_NGS, MUT2_meth_NGS_sp***])

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter) with "Was mutational status re-evaluated at start of second-line treatment" [***Second-line treatment period / MUT2. MUT2_reeval***] = "Yes".

[redacted]

Table 15-UNC. Mutations at second-line treatment stop/end of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

The table will provide:

- absolute and relative frequency of patients according to EGFR mutational status at second-line treatment stop/end of observation (see "Computed variables" chapter);
- absolute and relative frequency of patients according to Classification of EGFR uncommon mutations at second-line treatment stop/end of observation (see "Computed variables" chapter);
- absolute and relative frequency of patients according to acquired EGFR mutations at second-line treatment stop/end of observation (see "Computed variables" chapter);
- absolute and relative frequency of patients according presence/absence of other mutated genes and detail of mutations at second-line treatment stop/end of observation (according to the fields [***Second-line treatment period / MUT2. MUT2_oth_gene_stop_YN*** (*)***, MUT2_oth_gene_stop, MUT2_oth_gene_stop_sp***]).

(*) in case [***MUT2_oth_gene_stop_YN***] = "No", then the patient's mutational status for other genes at second-line treatment stop/end of observation will be imputed as the same patient's mutational status for other genes at second-line treatment start.

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter) with "Was mutational status re-evaluated at stop of second-line treatment […]" [***Second-line treatment period / MUT2. MUT2_reeval_stop***] = "Yes".

Table 16-UNC. Approaches for detection of mutations at second-line treatment stop/end of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3

The table will provide:

- absolute and relative frequency of patients by "Biologic sample(s) used for mutation testing" (according to the fields [***Second-line treatment period / MUT2. MUT2_biol_samp_stop, MUT2_biol_samp_stop_sp***]);
- absolute and relative frequency of "Methodology used for mutation testing", with details of ARMS, sequencing, NGS (according to the fields [***Second-line treatment period / MUT2. MUT2_meth_stop, MUT2_meth_stop_sp, MUT2_meth_ARMS_stop, MUT2_meth_ARMS_stop_sp, MUT2_meth_seq_stop, MUT2_meth_seq_stop_SP, MUT2_meth_NGS_stop, MUT2_meth_NGS_stop_SP***])

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter) with "Was mutational status re-evaluated at stop of second-line treatment (or within end of observation […])?" [***Second-line treatment period / MUT2. MUT2_reeval_stop***] = "Yes".

4.1.4 NSCLC treatments

Table 18-UNC. NSCLC treatment patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- patients' distribution (absolute and relative frequency) by Number of NSCLC treatment lines (see "Computed variables" chapter);
- patients' distribution (absolute and relative frequency) by type of NSCLC treatment patterns (see "Computed variables" chapter);

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 19-UNC. First-line treatment details (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- absolute and relative frequency of patients by type of treatment (according to the field [***First-line treatment period / TREAT. TREAT_ty, TREAT_ty_sp***]), "Immune check-point inhibitors" and "Other immunotherapy" will be grouped together;
- absolute and relative frequency of patients by type of chemotherapy [***First-line treatment period / TREAT. TREAT_chemo, TREAT_chemo_sp***]); drug combinations will be shown in case of polychemotherapy regimens;
- absolute and relative frequency of patients undergoing radiotherapy (according to the field [***First-line treatment period /TREAT. TREAT_radio_YN***]);
- absolute and relative frequency of patients by type of targeted therapy (according to the field [***First-line treatment period /TREAT. TREAT_targTer, TREAT_targTer_sp***]);
- absolute and relative frequency of patients by type of immunotherapy (according to the field [***First-line treatment period /TREAT. TREAT_immuno, TREAT_immuno_sp***]).

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

[redacted]

Table 22-UNC. First-line treatment regimen (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
According to data distribution, it will be evaluated the opportunity to provide the absolute and relative frequency of patients by type of treatment (according to the field [***First-line treatment period / TREAT. TREAT_ty, TREAT_ty_sp***]) after having concatenated multiple options, in order to provide the frequency of combined treatments.
Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

[redacted]

Table 24-UNC. Response to first-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1

The table will provide:

- absolute and relative frequency of "Best response achieved" [***First-line treatment period / RESP. RESP_best***]
- absolute and relative frequency of patients achieving Overall Response (ORR), ie. those with [***First-line treatment period / RESP. RESP_best***] = "Complete response (CR)" or "Partial Response (PR)";
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of response (in months) [***First-line treatment period / RESP. RESP_dur_num, RESP_dur_unit***] for patients achieving Overall Response (ORR) (as defined before); all units will be reported to months.

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, unless differently specified..

Table 25-UNC. Second-line treatment details (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

The table will provide:

- absolute and relative frequency of patients by type of treatment (according to the field [***Second-line treatment period / TREAT. TREAT_ty, TREAT_ty_sp***]), "Immune check-point inhibitors" and "Other immunotherapy" will be grouped together;
- absolute and relative frequency of patients by type of chemotherapy [***Second-line treatment period / TREAT. TREAT_chemo, TREAT_chemo_sp***]); drug combinations will be shown in case of polychemotherapy regimens;
- absolute and relative frequency of patients undergoing radiotherapy (according to the field [***Second-line treatment period /TREAT. TREAT_radio_YN***]);
- absolute and relative frequency of patients by type of targeted therapy (according to the field [***Second -line treatment period /TREAT. TREAT_targTer, TREAT_targTer_sp***]);
- absolute and relative frequency of patients by type of immunotherapy (according to the field [***Second -line treatment period /TREAT. TREAT_immuno, TREAT_immuno_sp***]).

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter).

[redacted]

[redacted]

Table 28-UNC. Second-line treatment regimen (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
According to data distribution, it will be evaluated the opportunity to provide the absolute and relative frequency of patients by type of treatment (according to the field [***Second-line treatment period / TREAT. TREAT_ty, TREAT_ty_sp***]) after having concatenated multiple options, in order to provide the frequency of combined treatments.
Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter).

[redacted]

Table 30-UNC. Response to second-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1
The table will provide:

- absolute and relative frequency of "Best response achieved" [***Second-line treatment period / RESP. RESP_best***]
- absolute and relative frequency of patients achieving Overall Response (ORR), ie. those with [***Second -line treatment period / RESP. RESP_best***] = "Complete response (CR)" or "Partial Response (PR)";
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of response (in months) [***Second -line treatment period / RESP. RESP_dur_num, RESP_dur_unit***] for patients achieving Overall Response (ORR) (as defined before); all units will be reported to months.

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter), unless differently specified.

[redacted]

Table 32-UNC. Index-line treatment regimen (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
According to data distribution, it will be evaluated the opportunity to provide the absolute and relative frequency of patients by type of treatment (according to the fields [***First-line treatment period*** or ***Second-line treatment period / TREAT. TREAT_ty, TREAT_ty_sp***], depending on which is the index-line) after having concatenated multiple options, in order to provide the frequency of combined treatments.
Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 33-UNC. NSCLC treatments prior to index EGFR-TKI therapy patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- patients' distribution (absolute and relative frequency) by number of NSCLC lines prior to the index EGFR-TKI therapy (that will be obtained considering the ordinal number of the index EGFR-TKI therapy, as defined in the "Computed variables" chapter);
- patients' distribution (absolute and relative frequency) by pattern of NSCLC treatment prior to the index EGFR-TKI therapy (see "Computed variables" chapter) considering only the sequence of NSCLC treatments until the index EGFR-TKI therapy (excluded).

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 34-UNC. Index EGFR-TKI therapy patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
The table will provide:

- patients' distribution (absolute and relative frequency) by ordinal number of line of the index EGFR-TKI therapy (see "Computed variables" chapter);
- patients' distribution (absolute and relative frequency) by type of NSCLC treatment patterns (see "Computed variables" chapter) considering only the sequence of NSCLC treatments from the index EGFR-TKI therapy thereafter.

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 35-UNC. Response to index EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1
The table will provide:

- absolute and relative frequency of "Best response achieved" [***First-line treatment period*** or ***Second-line treatment period / RESP. RESP_best***, depending on which is the index-line];
- absolute and relative frequency of patients achieving Overall Response (ORR), ie. those with [***First-line treatment period*** or ***Second-line treatment period / RESP. RESP_best***] = "Complete response (CR)" or "Partial Response (PR)";
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of response (in months) [***First-line treatment period*** or ***Second-line treatment period / RESP. RESP_dur_num, RESP_dur_unit***] for patients achieving Overall Response (ORR) (as defined before); all units will be reported to months.

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort, unless differently specified.

4.1.5 Time on treatment

Table 36-UNC. Time on treatment with index therapy EGFR-TKI (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Primary objective

The table will provide the Kaplan-Meier estimates of quartiles of time on treatment with index therapy EGFR-TKI (with their 95% Confidence Intervals, using Greenwood's variance estimate) (see "Computed variables" chapter).
Moreover, a Kaplan-Meier survival curve will be provided. The analysis will be represented on a plot having the time to event on the horizontal axis and the percentage of event-free patients on the vertical axis.

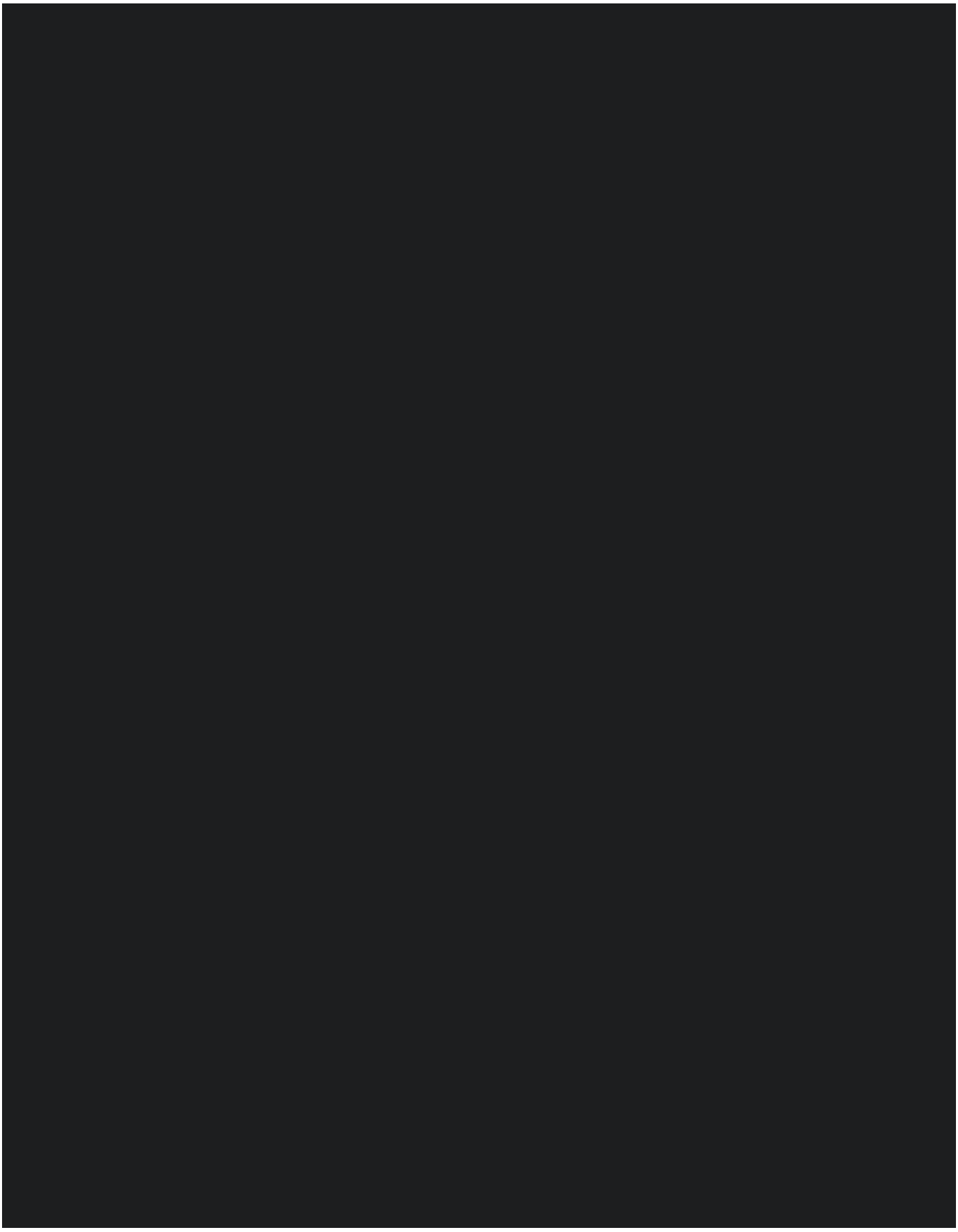
Table 37-UNC. Time to second-line treatment failure (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #4

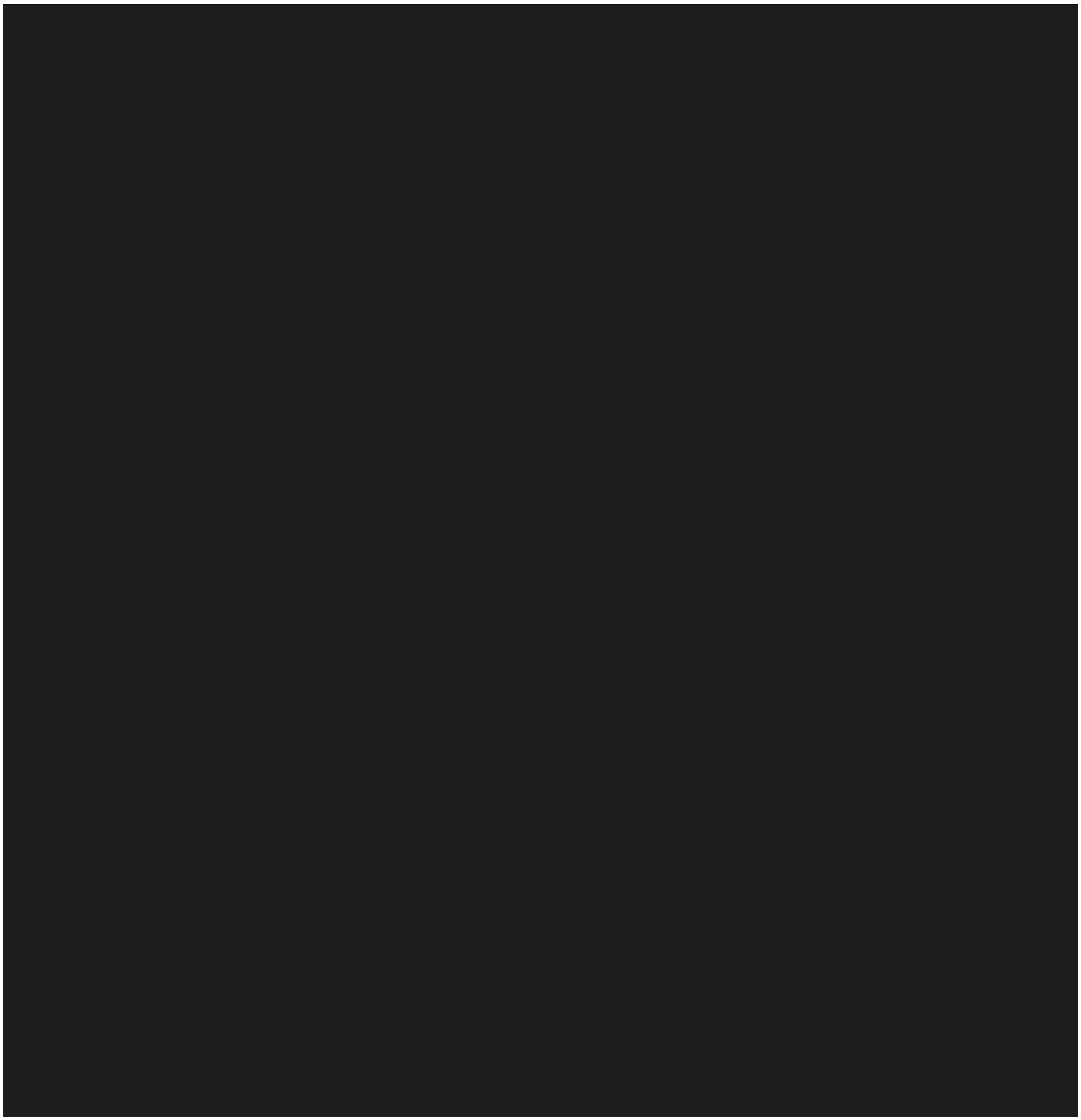
The table will provide the Kaplan-Meier estimates of quartiles of time to second-line treatment failure (with their 95% Confidence Intervals, using Greenwood's variance estimate) (see "Computed variables" chapter).
Moreover, a Kaplan-Meier survival curve will be provided. The analysis will be represented on a plot having the time to event on the horizontal axis and the percentage of event-free patients on the vertical axis.
The analysis will be performed on ELIGIBLE PATIENTS in the cohort, considering only patients with Number of NSCLC treatment lines >1 (see "Computed variables" chapter) while excluding those with mutation T790M acquired only at second-line osimertinib start.

4.1.6 Overall Survival – Secondary objective #2

Table 38-UNC. Overall Survival with index therapy EGFR-TKI (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

The table will provide the Kaplan-Meier estimates of quartiles of time to death (with their 95% Confidence Intervals, using Greenwood's variance estimate) (see algorithm for Overall Survival in the "Computed variables" chapter).
Moreover, a Kaplan-Meier survival curve will be provided. The analysis will be represented on a plot having the time to event on the horizontal axis and the percentage of event-free patients on the vertical axis.





4.2 SEQUENCING COHORT

4.2.1 Patient disposition, analysis sets and criteria violations

Table 1-SEQ. Patient disposition (ENROLLED PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Figure 1-SEQ. Workflow of analysis sets and reasons for violations (ENROLLED PATIENTS of the Sequencing Cohort)
See corresponding figure for the UNCOMMON MUTATION COHORT.

Table 2-SEQ. Reasons for violations (ENROLLED PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 3-SEQ. Duration of observation (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

4.2.2 Demographic and clinical characteristics

Table 4-SEQ. Socio-demographics (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 5-SEQ. Physical examination and smoking habits at start of first-line treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 6-SEQ. Clinical characteristics (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 7-SEQ. NSCLC features (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.
In this table, the "Duration of NSCLC until start of index EGFR-TKI therapy" will be renamed as "Duration of NSCLC until start of second-line treatment" (since the index EGFR-TKI of the Sequencing cohort corresponds to the osimertinib treatment, which is also the second-line treatment by definition).

Table 8-SEQ. Sites of metastases (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

4.2.3 Mutational Status

Table 9-SEQ. Mutations at first-line treatment (afatinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT. However, the variable "Classification of EGFR uncommon mutations at first-line treatment start" will not be analyzed because it is not applicable for this cohort at this time point.

Table 10-SEQ. Approaches for detection of mutations at first-line treatment (afatinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #3
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 11-SEQ. Mutations at second-line treatment (osimertinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 12-SEQ. Approaches for detection of mutations at second-line treatment (osimertinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #3
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 13-SEQ. Mutations at second-line treatment (osimertinib) stop/end of observation (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 14-SEQ. Approaches for detection of mutations at second-line treatment (osimertinib) stop/end of observation (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

4.2.4 NSCLC treatments

Table 15-SEQ. NSCLC treatment patterns (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT. However, the results will be focused on the 3rd or subsequent lines (if any), since the whole cohort will have in common the initial pattern "afatinib→osimertinib" by definition.

Table 16-SEQ. Details of first-line EGFR-TKI treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort)
The table will provide:

- absolute and relative frequency of afatinib starting daily dose (mg) (see "Computed variables" chapter).
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of afatinib treatment (see "Computed variables" chapter).

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 17-SEQ. Response to first-line treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #1
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 18-SEQ. Details of second-line EGFR-TKI treatment (osimertinib) (ELIGIBLE PATIENTS of the Sequencing Cohort)
The table will provide:

- absolute and relative frequency of osimertinib starting daily dose (mg) (see "Computed variables" chapter)
- patients' distribution (absolute and relative frequency) by "Which programme was used for patient treatment with osimertinib?" [***Second-line treatment period / TREAT. TREAT_osim_progr***]
- descriptive statistics (mean, standard deviation, quartiles, min, max) of Duration of osimertinib treatment (see "Computed variables" chapter)

Descriptives and percentages will be calculated over the number of ELIGIBLE PATIENTS in the cohort.

Table 19-SEQ. Response to second-line treatment (osimertinib) (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #1
See corresponding table for the UNCOMMON MUTATION COHORT.
Moreover, the table will provide patients' distribution (absolute and relative frequency) by "Presence of brain metastases at the end of osimertinib treatment line?" [***Second-line treatment period / RESP. RESP_brain_met***].

4.2.5 Time on treatment

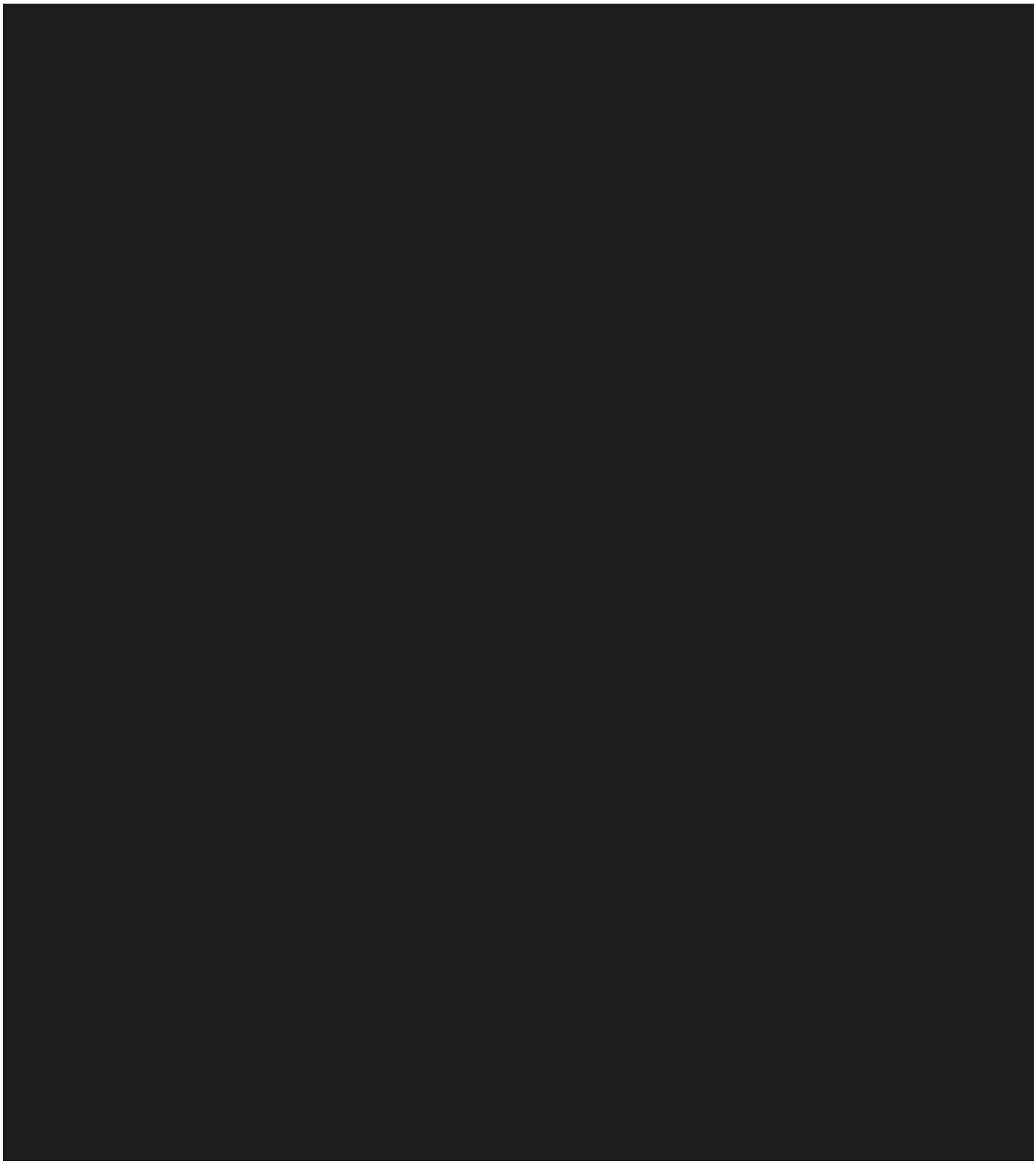
Table 20-SEQ. Time on treatment (ELIGIBLE PATIENTS of the Sequencing Cohort) – Primary objective
The table will provide the Kaplan-Meier estimates of quartiles of time on treatment with the pattern afatinib-osimertinib (with their 95% Confidence Intervals, using Greenwood's variance estimate) (see "Computed variables" chapter).
Moreover, a Kaplan-Meier survival curve will be provided. The analysis will be represented on a plot having the time to event on the horizontal axis and the percentage of event-free patients on the vertical axis.

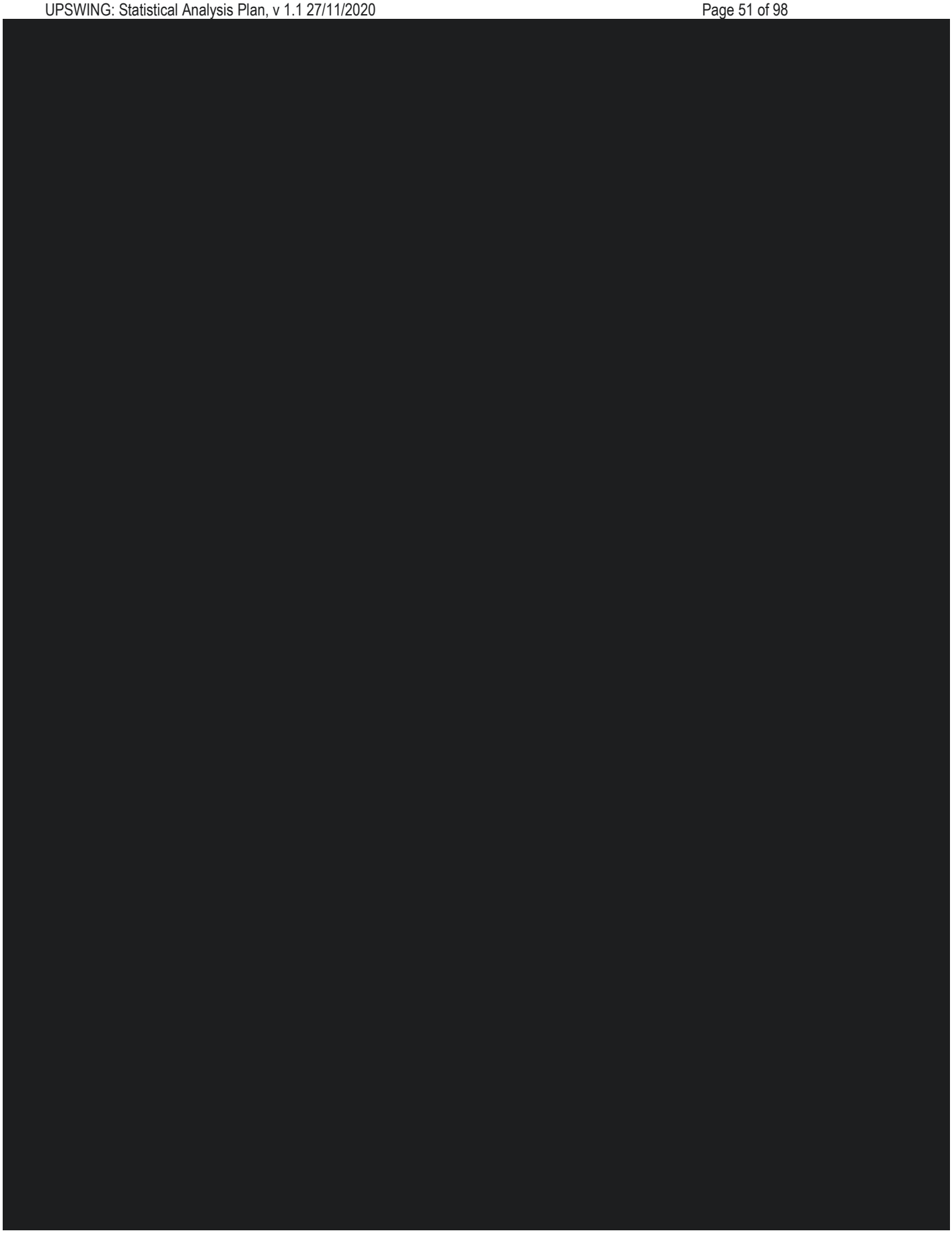
4.2.6 Overall Survival

Table 21-SEQ. Overall Survival from afatinib start (ELIGIBLE PATIENTS of the Sequencing Cohort) - Secondary objective #2
The table will provide the Kaplan-Meier estimates of quartiles of time to death from afatinib start (with their 95% Confidence Intervals, using Greenwood's variance estimate) (see algorithm for Overall Survival in the "Computed variables" chapter).
Moreover, a Kaplan-Meier survival curve will be provided. The analysis will be represented on a plot having the time to event on the horizontal axis and the percentage of event-free patients on the vertical axis.

Table 22-SEQ. Overall Survival from osimertinib discontinuation (ELIGIBLE PATIENTS of the Sequencing Cohort)
The table will provide the Kaplan-Meier estimates of quartiles of time to death from osimertinib discontinuation (with their 95% Confidence Intervals, using Greenwood's variance estimate) (see algorithm for Overall Survival in the "Computed variables" chapter).
Moreover, a Kaplan-Meier survival curve will be provided. The analysis will be represented on a plot having the time to event on the horizontal axis and the percentage of event-free patients on the vertical axis.
In this analysis, only patients who discontinued osimertinib (see "Computed variables" chapter) will be considered.

4.2.7 Per-Protocol Subgroup analysis for SEQUENCING COHORT





5 TABLES LAYOUT

5.1 UNCOMMON MUTATION COHORT

5.1.1 Patient disposition, analysis sets and criteria violations

Table 1-UNC. Patient disposition (ENROLLED PATIENTS of the Uncommon Mutation Cohort)

	Total number of enrolled patients		Total number of eligible patients	
	N	%	N	%
Overall	**xxx**	**100.0**	**xxx**	**xx.x**
Country - Center 1 – City	xxx	xx.x	xxx	xx.x
Country - Center 2 – City	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x

Note. Eligible patients are defined as those who satisfy inclusion and exclusion criteria described in Chapter 2.
Note. For each center, percentages will be calculated by column; percentages will be calculated by row only for "Overall".
Note. Results will be sorted by descending frequency of enrolled patients.

Figure 1-UNC. Workflow of analysis sets and reasons for violations (ENROLLED PATIENTS of the Uncommon Mutation Cohort)

A figure with the workflow of analysis sets and reasons for violations will be provided; the hierarchy of violated criteria specific for the cohort (as defined in Section 2.5) will be applied, so that each violator will be classified with only one major violation (even in case of multiple violations).

Table 2-UNC. Reasons for violations (ENROLLED PATIENTS of the Uncommon Mutation Cohort)

	N	%
Criterion 1. Adult patient		
Evaluable	xxx	xx.x
Not Evaluable – reason	xxx	xx.x
Criterion 2. Diagnosed with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) naïve advanced EGFR mutated non-small cell lung cancer (NSCLC)		
Evaluable	xxx	xx.x
Not Evaluable – reason	xxx	xx.x
Criterion 3. Treated for Epidermal Growth Factor Receptor (EGFR) mutated NSCLC within regular clinical practice.		
Evaluable	xxx	xx.x
Not Evaluable – reason	xxx	xx.x
Criterion 4. Informed and privacy consent signature obtained depending on local regulations		
Evaluable	xxx	xx.x
Not Evaluable – reason	xxx	xx.x
…	…	…
Total number of enrolled patients	**xxx**	**100.0**

Note. The same patient might violate more than one criterion.

Table 3-UNC. Duration of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

	N	Mean	SD	25th percentile	Median	75th percentile	Min	Max
Duration of observation window (months)	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

5.1.2 Demographic and clinical characteristics

Table 4-UNC. Socio-demographics (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Age at start of first-line treatment (in years)	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x
Gender	Male	xxx (xx.x%)
	Female	xxx (xx.x%)
Ethnicity	White	xxx (xx.x%)
	Black or African American	xxx (xx.x%)
	Asian	xxx (xx.x%)
	American Indian or Alaska Native	xxx (xx.x%)
	Native Hawaiian or other Pacific Islander	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)
	Not collected (*)	xxx (xx.x%)

(*) ethnicity cannot be collected in France. In Germany, Republic of Korea and Spain, ethnicity can be collected if consent is provided, or if consent is not necessary.

Table 5-UNC. Physical examination and smoking habits at start of first-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
BMI	Underweight: BMI < 18.5	xxx (xx.x%)
	Normal weight: BMI 18.5-24.9	xxx (xx.x%)
	Overweight: BMI 25-29.9	xxx (xx.x%)
	Obese: BMI >= 30	xxx (xx.x%)
	UNK	xxx (xx.x%)
Smoking status	Never-smoker	xxx (xx.x%)
	Previous smoker	xxx (xx.x%)
	Smoker	xxx (xx.x%)
	UNK	xxx (xx.x%)
Estimated amount of cigarettes consumed on average each day	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x
Smoking duration (years) at start of first-line treatment	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x

Table 6-UNC. Clinical characteristics (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Patient's ECOG Performance Status at start of first-line treatment	0	xxx (xx.x%)
	1	xxx (xx.x%)
	2	xxx (xx.x%)
	3	xxx (xx.x%)
	4	xxx (xx.x%)
	UNK	xxx (xx.x%)

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Patient's ECOG Performance Status at start of second-line treatment	0	xxx (xx.x%)
	1	xxx (xx.x%)
	2	xxx (xx.x%)
	3	xxx (xx.x%)
	4	xxx (xx.x%)
	UNK	xxx (xx.x%)

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Changes in ECOG PS at start of second-line treatment with respect to start of first-line treatment	No changes	xxx (xx.x%)
	Improvement	xxx (xx.x%)
	Deterioration of 1 step	xxx (xx.x%)
	Deterioration of 2 or more steps	xxx (xx.x%)
	UNK	xxx (xx.x%)

Table 7-UNC. NSCLC features (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Tumor histology at NSCLC diagnosis	Adenocarcinoma	xxx (xx.x%)
	Squamous-cell carcinoma	xxx (xx.x%)
	Large-cell carcinoma	xxx (xx.x%)
	Mixed	xxx (xx.x%)
	Not otherwise specified (NOS)	xxx (xx.x%)
	Other	xxx (xx.x%)
NSCLC stage at start of first-line treatment (*)	IIIB	xxx (xx.x%)
	IIIC	xxx (xx.x%)
	IV	xxx (xx.x%)
Duration of NSCLC until start of first-line treatment (in months)	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x
Duration of NSCLC until start of index EGFR-TKI therapy (in months)	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x

(*) or at NSCLC diagnosis, in case stage was not re-evaluated.

Table 8-UNC. Sites of metastases (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Sites of metastases at first-line treatment start	No metastases	xxx (xx.x%)
	Adrenal glands	xxx (xx.x%)
	Bones	xxx (xx.x%)
	Brain	xxx (xx.x%)
	Liver	xxx (xx.x%)
	Lung contralateral	xxx (xx.x%)
	Lung ipsilateral	xxx (xx.x%)
	Pleura	xxx (xx.x%)
	Spine	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Sites of metastases at second-line treatment start	No metastases	xxx (xx.x%)
	Adrenal glands	xxx (xx.x%)
	Bones	xxx (xx.x%)
	Brain	xxx (xx.x%)
	Liver	xxx (xx.x%)
	Lung contralateral	xxx (xx.x%)
	Lung ipsilateral	xxx (xx.x%)
	Pleura	xxx (xx.x%)
	Spine	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

		ELIGIBLE PATIENTS (N=xxx)
Sites of metastases at index EGFR-TKI therapy start	…	…
	….	…

Changes in metastatic sites at start of second-line treatment from start of first-line treatment

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Patients with new metastatic sites	No metastases	xxx (xx.x%)
	Adrenal glands	xxx (xx.x%)
	Bones	xxx (xx.x%)
	Brain	xxx (xx.x%)
	Liver	xxx (xx.x%)
	Lung contralateral	xxx (xx.x%)
	Lung ipsilateral	xxx (xx.x%)
	Pleura	xxx (xx.x%)
	Spine	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Patients with resolved metastatic sites	No metastases	xxx (xx.x%)
	Adrenal glands	xxx (xx.x%)
	Bones	xxx (xx.x%)
	Brain	xxx (xx.x%)
	Liver	xxx (xx.x%)
	Lung contralateral	xxx (xx.x%)
	Lung ipsilateral	xxx (xx.x%)
	Pleura	xxx (xx.x%)
	Spine	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

5.1.3 Mutational Status

Table 9-UNC. Mutations at first-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
EGFR mutational status at first-line treatment start	Del19	xxx (xx.x%)
	L858R	xxx (xx.x%)
	L858X (with X being unequal to R)	xxx (xx.x%)
	T790M de novo	xxx (xx.x%)
	G719X	xxx (xx.x%)
	L861Q	xxx (xx.x%)
	S768I	xxx (xx.x%)
	E709X	xxx (xx.x%)
	L747P/S	xxx (xx.x%)
	Q787Q	xxx (xx.x%)
	Exon 20 insertion (*)	xxx (xx.x%)
	Other EGFR mutation(s) (*)	xxx (xx.x%)
Classification of EGFR uncommon mutations at first-line treatment start	T790M-positive	xxx (xx.x%)
	Exon 20 insertion-positive	xxx (xx.x%)
	Major uncommon mutations	xxx (xx.x%)
	Others	xxx (xx.x%)
	Compound mutations	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

		ELIGIBLE PATIENTS (N=xxx)
Other genes alterations at start of first-line treatment?	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	UNK	xxx (xx.x%)
Other known genes alterations	ALK	xxx (xx.x%)
	HER2	xxx (xx.x%)
	KRAS	xxx (xx.x%)
	MET amplification	xxx (xx.x%)
	PI3KCA	xxx (xx.x%)
	PTEN	xxx (xx.x%)
	ROS1	xxx (xx.x%)
	Other gene(s) mutated (*)	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

Table 10-UNC. Approaches for detection of mutations at first-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3

		ELIGIBLE PATIENTS (N=xxx)
Biologic sample(s) used for mutation testing	Tissue, Histological sample (solid biopsy)	xxx (xx.x%)
	Cytological sample	xxx (xx.x%)
	Blood (liquid biopsy)	xxx (xx.x%)
	Other (*)	xxx (xx.x%)
	UNK	xxx (xx.x%)
Methodology used for mutation testing	Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
	- ADx	xxx (xx.x%)
	- Qiagen	xxx (xx.x%)
	- Roche	xxx (xx.x%)
	- Super ARMS	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	ddPCR	xxx (xx.x%)
	BEAMing	xxx (xx.x%)
	Sequencing	xxx (xx.x%)
	- Sanger seguencing	xxx (xx.x%)
	- Pyrosequencing	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	Next-Generation Sequencing (NGS)	xxx (xx.x%)
	- Targeted NGS	xxx (xx.x%)
	- Whole-exome sequencing	xxx (xx.x%)
	- Whole-genome sequencing	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

Table 11-UNC. Summary of type of mutation detected by technique at first-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

	T790M-positive ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	Exon 20 insertion-positive ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Major uncommon mutations (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	Other (not included in the previous groups) ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Compound mutations (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

Table 12-UNC. Mutations at second-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
EGFR mutational status at second-line treatment start	Del19	xxx (xx.x%)
	L858R	xxx (xx.x%)
	L858X (with X being unequal to R)	xxx (xx.x%)
	T790M de novo	xxx (xx.x%)
	G719X	xxx (xx.x%)
	L861Q	xxx (xx.x%)
	S768I	xxx (xx.x%)
	E709X	xxx (xx.x%)
	L747P/S	xxx (xx.x%)
	Q787Q	xxx (xx.x%)
	Exon 20 insertion (*)	xxx (xx.x%)
	Other EGFR mutation(s) (*)	xxx (xx.x%)
	Unknown EGFR mutational status	xxx (xx.x%)
Classification of EGFR uncommon mutations at second-line treatment start	T790M-positive	xxx (xx.x%)
	Exon 20 insertion-positive	xxx (xx.x%)
	Major uncommon mutations	xxx (xx.x%)
	Others	xxx (xx.x%)
	Compound mutations	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Acquired EGFR mutations at second-line treatment start	Del19	xxx (xx.x%)
	L858R	xxx (xx.x%)
	…	…

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Other new genes alterations at start of second-line treatment?	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	UNK	xxx (xx.x%)
Other known genes alterations	ALK	xxx (xx.x%)
	HER2	xxx (xx.x%)
	KRAS	xxx (xx.x%)
	MET amplification	xxx (xx.x%)
	PI3KCA	xxx (xx.x%)
	PTEN	xxx (xx.x%)
	ROS1	xxx (xx.x%)
	Other gene(s) mutated (*)	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

Table 13-UNC. Approaches for detection of mutations at second-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3

		ELIGIBLE PATIENTS with >1 NSCLC line with re-evaluated mutational status (N=xxx)
Biologic sample(s) used for mutation testing	Tissue, Histological sample (solid biopsy)	xxx (xx.x%)
	Cytological sample	xxx (xx.x%)
	Blood (liquid biopsy)	xxx (xx.x%)
	Other (*)	xxx (xx.x%)
	UNK	xxx (xx.x%)
Methodology used for mutation testing	Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
	- ADx	xxx (xx.x%)
	- Qiagen	xxx (xx.x%)
	- Roche	xxx (xx.x%)
	- Super ARMS	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	ddPCR	xxx (xx.x%)
	BEAMing	xxx (xx.x%)
	Sequencing	xxx (xx.x%)
	- Sanger seguencing	xxx (xx.x%)
	- Pyrosequencing	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	Next-Generation Sequencing (NGS)	xxx (xx.x%)
	- Targeted NGS	xxx (xx.x%)
	- Whole-exome sequencing	xxx (xx.x%)
	- Whole-genome sequencing	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

Table 14-UNC. Summary of type of mutation detected by technique at second-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

	T790M-positive ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	Exon 20 insertion-positive ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Major uncommon mutations (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	Other (not included in the previous groups) ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Compound mutations (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

Table 15-UNC. Mutations at second-line treatment stop/end of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
EGFR mutational status at second-line treatment stop/end of observation	Del19	xxx (xx.x%)
	L858R	xxx (xx.x%)
	L858X (with X being unequal to R)	xxx (xx.x%)
	T790M de novo	xxx (xx.x%)
	G719X	xxx (xx.x%)
	L861Q	xxx (xx.x%)
	S768I	xxx (xx.x%)
	E709X	xxx (xx.x%)
	L747P/S	xxx (xx.x%)
	Q787Q	xxx (xx.x%)
	Exon 20 insertion (*)	xxx (xx.x%)
	Other EGFR mutation(s) (*)	xxx (xx.x%)
	Unknown EGFR mutational status	xxx (xx.x%)
Classification of EGFR uncommon mutations at second-line treatment stop/end of observation	T790M-positive	xxx (xx.x%)
	Exon 20 insertion-positive	xxx (xx.x%)
	Major uncommon mutations	xxx (xx.x%)
	Others	xxx (xx.x%)
	Compound mutations	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Acquired EGFR mutations at second-line treatment stop/end of observation	Del19	xxx (xx.x%)
	L858R	xxx (xx.x%)
	…	…

		ELIGIBLE PATIENTS with >1 NSCLC line (N=xxx)
Other new genes alterations at second-line treatment stop/end of observation?	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	UNK	xxx (xx.x%)
Other known genes alterations	ALK	xxx (xx.x%)
	HER2	xxx (xx.x%)
	KRAS	xxx (xx.x%)
	MET amplification	xxx (xx.x%)
	PI3KCA	xxx (xx.x%)
	PTEN	xxx (xx.x%)
	ROS1	xxx (xx.x%)
	Other gene(s) mutated (*)	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

Table 16-UNC. Approaches for detection of mutations at second-line treatment stop/end of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3

		ELIGIBLE PATIENTS with >1 NSCLC line with re-evaluated mutational status (N=xxx)
Biologic sample(s) used for mutation testing	Tissue, Histological sample (solid biopsy)	xxx (xx.x%)
	Cytological sample	xxx (xx.x%)
	Blood (liquid biopsy)	xxx (xx.x%)
	Other (*)	xxx (xx.x%)
	UNK	xxx (xx.x%)
Methodology used for mutation testing	Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
	- ADx	xxx (xx.x%)
	- Qiagen	xxx (xx.x%)
	- Roche	xxx (xx.x%)
	- Super ARMS	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	ddPCR	xxx (xx.x%)
	BEAMing	xxx (xx.x%)
	Sequencing	xxx (xx.x%)
	- Sanger seguencing	xxx (xx.x%)
	- Pyrosequencing	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	Next-Generation Sequencing (NGS)	xxx (xx.x%)
	- Targeted NGS	xxx (xx.x%)
	- Whole-exome sequencing	xxx (xx.x%)
	- Whole-genome sequencing	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	- UNK	xxx (xx.x%)
	Other	xxx (xx.x%)
	UNK	xxx (xx.x%)

Table 17-UNC. Summary of type of mutation detected by technique at second-line treatment stop/end of observation (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

	T790M-positive ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	Exon 20 insertion-positive ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Major uncommon mutations (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	Other (not included in the previous groups) ELIGIBLE PATIENTS (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Compound mutations (N=xxx)
Methodology used for mutation testing	
Amplification Refractory Mutation System (ARMS)	xxx (xx.x%)
ddPCR	xxx (xx.x%)
BEAMing	xxx (xx.x%)
…	…

5.1.4 NSCLC treatments

Table 18-UNC. NSCLC treatment patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Number of NSCLC treatment lines	1	xxx (xx.x%)
	2	xxx (xx.x%)
	3	xxx (xx.x%)
	…	…
Type of NSCLC treatment patterns	<pattern A>	xxx (xx.x%)
	<pattern B>	xxx (xx.x%)
	…	…

Table 19-UNC. First-line treatment details (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Type of treatment	EGFR-TKI	xxx (xx.x%)
	Other targeted therapy	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	Chemotherapy	xxx (xx.x%)
	Immune check-point inhibitors or immunotherapy	xxx (xx.x%)
	- Atezolizumab	xxx (xx.x%)
	- Nivolumab	xxx (xx.x%)
	- Pembrolizumab	xxx (xx.x%)
	- Other (*)	xxx (xx.x%)
	Other treatment (*)	xxx (xx.x%)
Patients undergoing radiotherapy		xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

		ELIGIBLE PATIENTS (N=xxx)
Type of chemotherapy	Carboplatin alone	xxx (xx.x%)
	Cisplatin alone	xxx (xx.x%)
	…	…
	<combination A>	xxx (xx.x%)
	<combination B>	xxx (xx.x%)
	…	…
	Other(s) (*)	xxx (xx.x%)

(*) listing might be provided depending on the number of cases observed.

Table 20-UNC. Type of first-line targeted therapy according to type of uncommon mutations (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

	T790M-positive ELIGIBLE PATIENTS (N=xxx)
Type of targeted therapy	
Afatinib	xxx (xx.x%)
Gefitinib	xxx (xx.x%)
Erlotinib	xxx (xx.x%)
Osimertinib	xxx (xx.x%)
…	…

	Exon 20 insertion-positive ELIGIBLE PATIENTS (N=xxx)
Type of targeted therapy	
<as above>	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Major uncommon mutations (N=xxx)
Type of targeted therapy	
<as above>	xxx (xx.x%)
…	…

	Other (not included in the previous groups) ELIGIBLE PATIENTS (N=xxx)
Type of targeted therapy	
<as above>	xxx (xx.x%)
…	…

	ELIGIBLE PATIENTS with Compound mutations (N=xxx)
Type of targeted therapy	
<as above>	xxx (xx.x%)
…	…

Table 21-UNC. Duration of first-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

	N	Mean	SD	25th percentile	Median	75th percentile	Min	Max
Duration of first-line treatment (overall)	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Duration of first-line EGFR-TKI	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Duration of first-line targeted therapy	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Duration of first-line chemotherapy	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Duration of first-line immunotherapy	xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
…	…	…	…	…	…	…	…	…

Table 22-UNC. First-line treatment regimen (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Type of treatment	Chemotherapy alone	xxx (xx.x%)
	Chemotherapy+Radiotherapy	xxx (xx.x%)
	Chemotherapy+Immune check-point inhibitors	xxx (xx.x%)
	<combination x>	xxx (xx.x%)
	…	…

Table 23-UNC. Details of first-line EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

		ELIGIBLE PATIENTS receiving an EGFR-TKI as first-line treatment (N=xxx)
Type of first-line EGFR-TKI	Afatinib	xxx (xx.x%)
	Erlotinib	xxx (xx.x%)
	Gefitinib	xxx (xx.x%)
	Osimertinib	xxx (xx.x%)
EGFR-TKI by generation	1st generation	xxx (xx.x%)
	2nd generation	xxx (xx.x%)
	3rd generation	xxx (xx.x%)

		ELIGIBLE PATIENTS receiving an EGFR-TKI as first-line treatment (N=xxx)
Afatinib starting daily dose (mg)	50 mg	xxx (xx.x%)
	40 mg	xxx (xx.x%)
	30 mg	xxx (xx.x%)
	…	…
Gefitinib starting daily dose (mg)	…	…
…	…	…

Table 24-UNC. Response to first-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1

		ELIGIBLE PATIENTS (N=xxx)
Best response achieved	Complete response (CR)	xxx (xx.x%)
	Partial Response (PR)	xxx (xx.x%)
	Stable Disease (SD) or Non-CR/Non PD	xxx (xx.x%)
	Disease Progression	xxx (xx.x%)
	UNK	xxx (xx.x%)
Overall Response (ORR)		xxx (xx.x%)
Duration of response (in months)	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x

Table 25-UNC. Second-line treatment details (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 26-UNC. Type of second-line targeted therapy according to type of uncommon mutations (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 27-UNC. Duration of second-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 28-UNC. Second-line treatment regimen (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 29-UNC. Details of second-line EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 30-UNC. Response to second-line treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1
Similar layout will be provided.

Table 31-UNC. Details of index EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 32-UNC. Index-line treatment regimen (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 33-UNC. NSCLC treatments prior to index EGFR-TKI therapy patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 34-UNC. Index EGFR-TKI therapy patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)
Similar layout will be provided.

Table 35-UNC. Response to index EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1
Similar layout will be provided.

5.1.5 Time on treatment

Table 36-UNC. Time on treatment with index therapy EGFR-TKI (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Primary objective

Quartiles Estimates			
		95% Confidence Interval	
%	Point Estimate	[Inferior	Superior)
75	xx.xx	xx.xx	xx.xx
50	xx.xx	xx.xx	xx.xx
25	xx.xx	xx.xx	xx.xx

Total	Failed	Censored	Percent Censored
xx	xx	xx	xx.xx

A Kaplan-Meier survival curve will be provided.

Table 37-UNC. Time to second-line treatment failure (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #4

Similar layout will be provided.

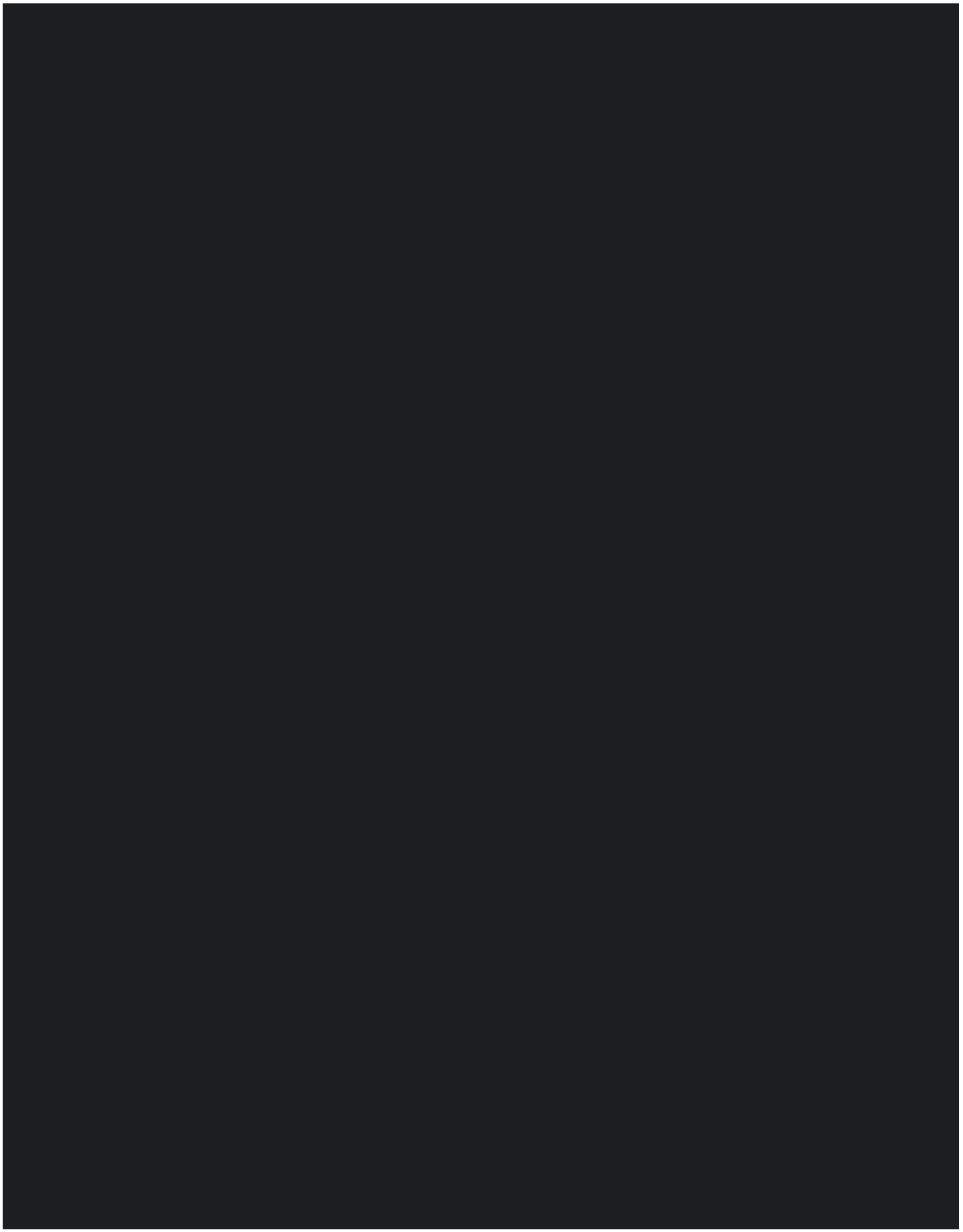
5.1.6 Overall Survival – Secondary objective #2

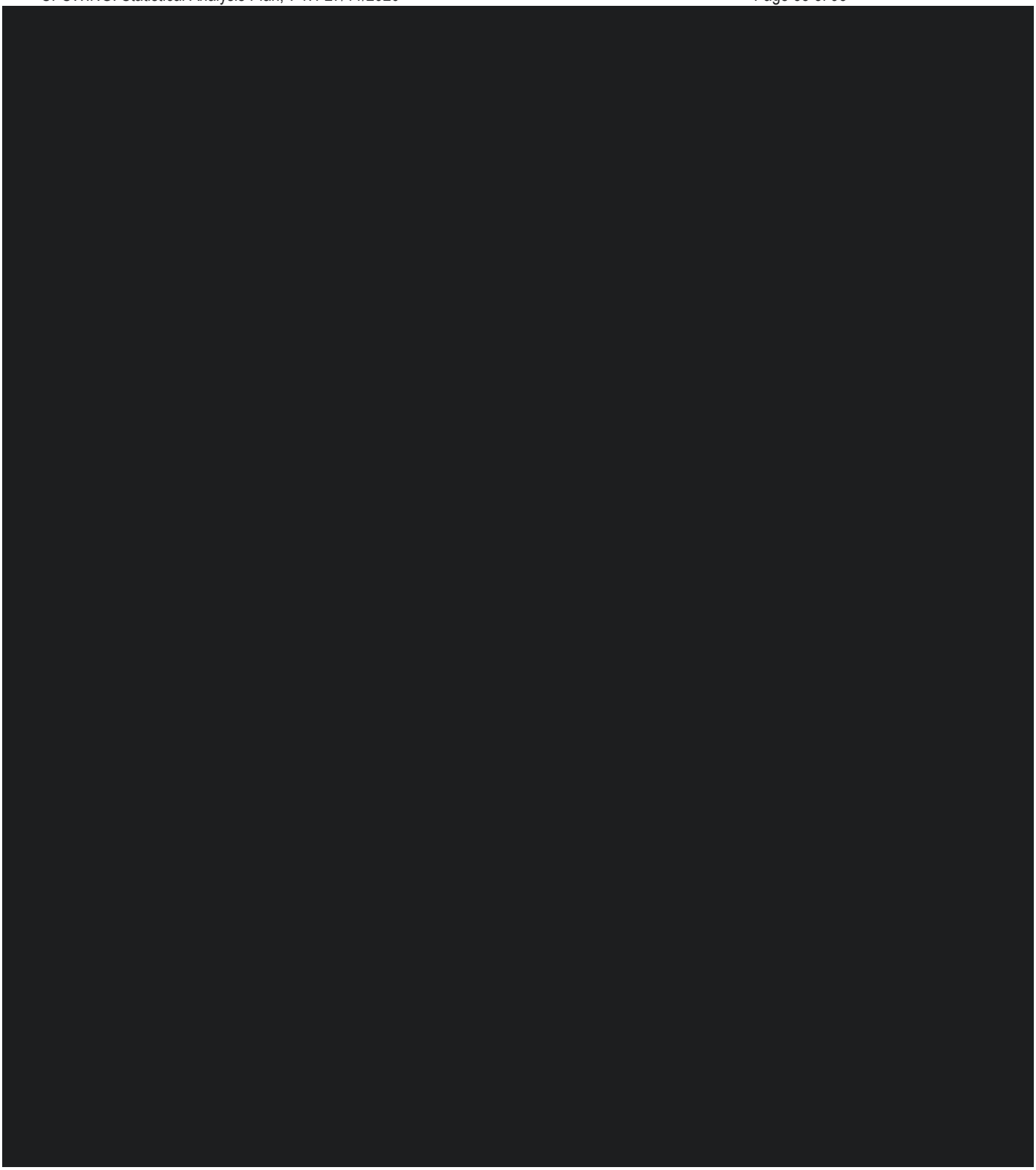
Table 38-UNC. Overall Survival with index therapy EGFR-TKI (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort)

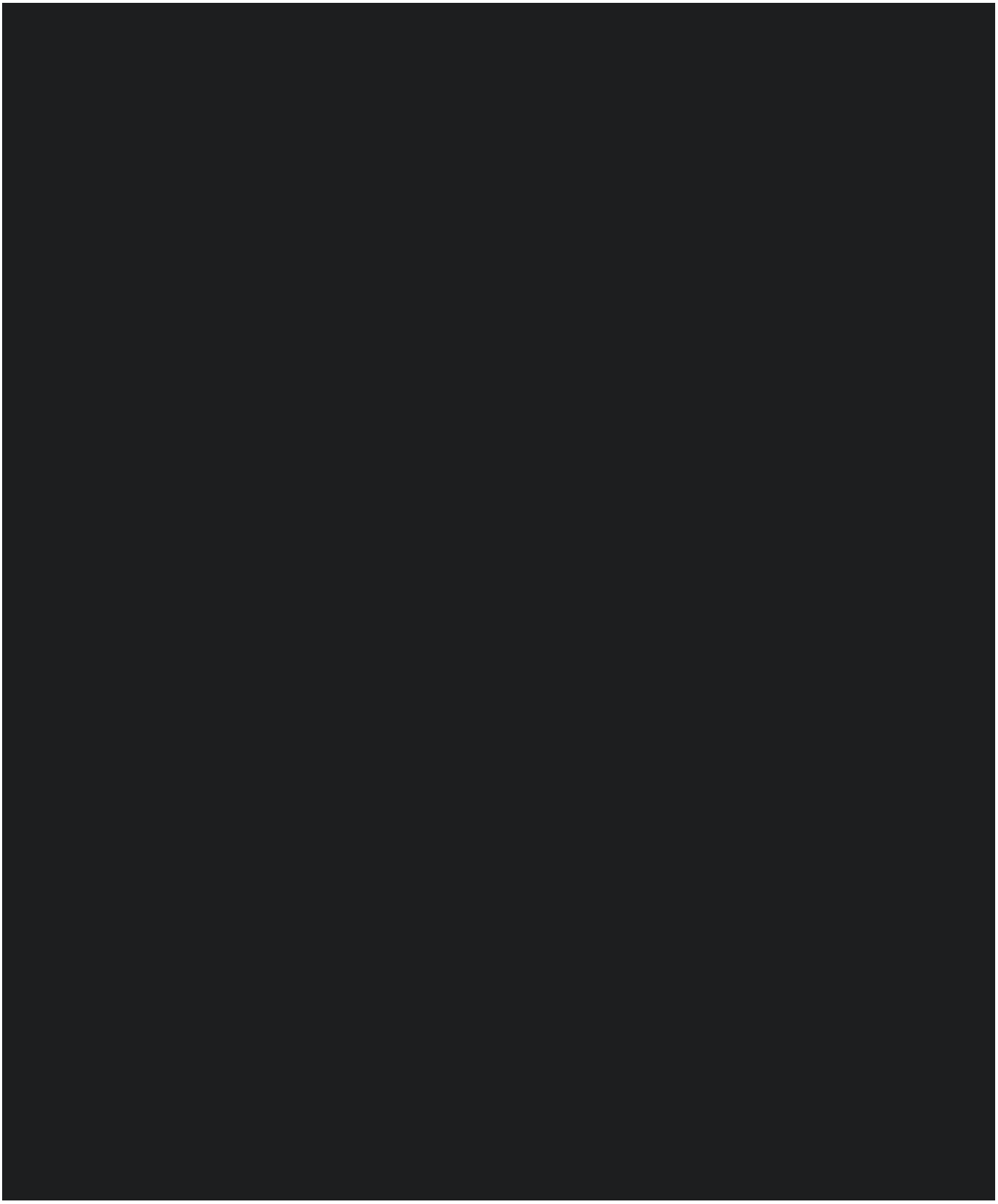
Quartiles Estimates			
		95% Confidence Interval	
%	Point Estimate	[Inferior	Superior)
75	xx.xx	xx.xx	xx.xx
50	xx.xx	xx.xx	xx.xx
25	xx.xx	xx.xx	xx.xx

Total	Failed	Censored	Percent Censored
xx	xx	xx	xx.xx

A Kaplan-Meier survival curve will be provided.







5.2 SEQUENCING COHORT

5.2.1 Patient disposition, analysis sets and criteria violations

Table 1-SEQ. Patient disposition (ENROLLED PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Figure 1-SEQ. Workflow of analysis sets and reasons for violations (ENROLLED PATIENTS of the Sequencing Cohort)
See corresponding figure for the UNCOMMON MUTATION COHORT.

Table 2-SEQ. Reasons for violations (ENROLLED PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 3-SEQ. Duration of observation (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

5.2.2 Demographic and clinical characteristics

Table 4-SEQ. Socio-demographics (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 5-SEQ. Physical examination and smoking habits at start of first-line treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 6-SEQ. Clinical characteristics (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 7-SEQ. NSCLC features (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.
In this table, the "Duration of NSCLC until start of index EGFR-TKI therapy" will be renamed as "Duration of NSCLC until start of second-line treatment" (since the index EGFR-TKI of the Sequencing cohort corresponds to the osimertinib treatment, which is also the second-line treatment by definition).

Table 8-SEQ. Sites of metastases (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

5.2.3 Mutational Status

[redacted]

Table 10-SEQ. Approaches for detection of mutations at first-line treatment (afatinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #3
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 11-SEQ. Mutations at second-line treatment (osimertinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 12-SEQ. Approaches for detection of mutations at second-line treatment (osimertinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #3
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 13-SEQ. Mutations at second-line treatment (osimertinib) stop/end of observation (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 14-SEQ. Approaches for detection of mutations at second-line treatment (osimertinib) stop/end of observation (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT.

5.2.4 NSCLC treatments

Table 15-SEQ. NSCLC treatment patterns (ELIGIBLE PATIENTS of the Sequencing Cohort)
See corresponding table for the UNCOMMON MUTATION COHORT. However, the results will be focused on the 3rd or subsequent lines (if any), since the whole cohort will have in common the initial pattern "afatinib→osimertinib" by definition.

Table 16-SEQ. Details of first-line EGFR-TKI treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Afatinib starting daily dose (mg)	50 mg	xxx (xx.x%)
	40 mg	xxx (xx.x%)
	30 mg	xxx (xx.x%)
	…	…
Duration of afatinib treatment	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x

Table 17-SEQ. Response to first-line treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #1
See corresponding table for the UNCOMMON MUTATION COHORT.

Table 18-SEQ. Details of second-line EGFR-TKI treatment (osimertinib) (ELIGIBLE PATIENTS of the Sequencing Cohort)

		ELIGIBLE PATIENTS (N=xxx)
Osimertinib starting daily dose (mg)	80 mg	xxx (xx.x%)
	40 mg	xxx (xx.x%)
Programme used for patient treatment	Regular Clinical Practice	xxx (xx.x%)
	Through EAP/CUP	xxx (xx.x%)
Duration of osimertinib treatment	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x

Table 19-SEQ. Response to second-line treatment (osimertinib) (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #1

		ELIGIBLE PATIENTS (N=xxx)
Best response achieved	Complete response (CR)	xxx (xx.x%)
	Partial Response (PR)	xxx (xx.x%)
	Stable Disease (SD) or Non-CR/Non PD	xxx (xx.x%)
	Disease Progression	xxx (xx.x%)
	UNK	xxx (xx.x%)
Overall Response (ORR)		xxx (xx.x%)
Duration of response (in months)	N	xxx
	Mean	xx.x
	SD	xx.x
	25th percentile	xx.x
	Median	xx.x
	75th percentile	xx.x
	Min	xx.x
	Max	xx.x
Presence of brain metastases at the end of osimertinib treatment line?	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	UNK	xxx (xx.x%)

5.2.5 Time on treatment

Table 20-SEQ. Time on treatment (ELIGIBLE PATIENTS of the Sequencing Cohort) – Primary objective

Quartiles Estimates			
		95% Confidence Interval	
%	Point Estimate	[Inferior	Superior)
75	xx.xx	xx.xx	xx.xx
50	xx.xx	xx.xx	xx.xx
25	xx.xx	xx.xx	xx.xx

Total	Failed	Censored	Percent Censored
xx	xx	xx	xx.xx

A Kaplan-Meier survival curve will be provided.

5.2.6 Overall Survival

Table 21-SEQ. Overall Survival from afatinib start (ELIGIBLE PATIENTS of the Sequencing Cohort) - Secondary objective #2

Quartiles Estimates			
		95% Confidence Interval	
%	Point Estimate	[Inferior	Superior)
75	xx.xx	xx.xx	xx.xx
50	xx.xx	xx.xx	xx.xx
25	xx.xx	xx.xx	xx.xx

Total	Failed	Censored	Percent Censored
xx	xx	xx	xx.xx

A Kaplan-Meier survival curve will be provided.

Table 22-SEQ. Overall Survival from osimertinib discontinuation (ELIGIBLE PATIENTS of the Sequencing Cohort)
Similar layout will be provided.

6 QUALITY CHECKS ON THE STATISTICAL REPORT

The statistical analysis of the UPSWING study will be managed by 3 main figures in [redacted]: the Biostatistician (BS), the [redacted]. In particular, in this context, [redacted] of data cleaning, database creation, management and lock, while BS is the owner of Statistical Analysis Plan and Statistical Report redaction.
BS and [redacted] of the UPSWING study have performed an annual training of at least 30 hours and an induction training concerning knowledge and skills required for the management of observational studies with a focus on their role. Furthermore they are coordinated by R-DMS who possesses qualifications necessary for her job.
Moreover, regarding instruments, database management and data analysis will be performed using SAS Enterprise Guide v. 7.1 and SAS 9.4.
Actions to improve the quality of data are taken in different moments during the study and using various tools, as described in [redacted] Standard Operating Procedures concerning data cleaning and statistical analysis.
Data validation (see Data Validation Plan) foresees both on-line (electronic CRF allows to verify data at the moment they are entered by means of automated edit checks, out of range controls, etc.) and off-line checks. Subsequently, quality control continues at the moment of the database lock when, as requested by [redacted] procedure, the [redacted] can lock the database only if, among other conditions, BS and Sponsor approve the quality of data (i.e In defining if the obtained quality of data is sufficient, the impact of possible missing/inconsistent data remained after all possible efforts to fix are done, will be based on the impact of these data on the primary and the secondary study objectives).
Finally, a quality control of the data analysis process focused on the detection of possible calculation errors or inconsistent data is performed. To observe the recommendation about the detection of priorities in order to make the process more efficient, the type of statistical report quality control is defined on the basis of the risk analysis conducted for the study.
The following quality controls will be performed on the statistical report of the UPSWING study.

- All the tables described in this document will be programmed and verified by a BS.
- R-DMS will perform an overall conceptual review of results, in order to evaluate their coherence and plausibility. Moreover, all the tables in this report will be independently reviewed to verify their consistency.
- Moreover, the following tables will be reprogrammed or independently verified (by another [redacted], as detailed for each point):

  For UNCOMMON MUTATION COHORT report:
  - Table 1-UNC. Patient disposition (ENROLLED PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate frequencies
  - Table 2-UNC. Reasons for violations (ENROLLED PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate frequencies and check the algorithms for each criterion for 100% of enrolled patients
  - Table 8-UNC. Sites of metastases (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate descriptive statistics and check the algorithm for 10% of analyzed patients
  - Table 10-UNC. Approaches for detection of mutations at first-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #3: formatted table will be checked against the raw output
  - Table 12-UNC. Mutations at second-line treatment start (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate descriptive statistics and check the algorithm for 10% of analyzed patients
  - Table 18-UNC. NSCLC treatment patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate descriptive statistics and check the algorithm for 10% of analyzed patients
  - Table 31-UNC. Details of index EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort): [redacted]another BS will independently recalculate descriptive statistics and check the algorithm for 10% of analyzed patients
  - Table 34-UNC. Index EGFR-TKI therapy patterns (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate descriptive statistics and check the algorithm for 10% of analyzed patients

- Table 35-UNC. Response to index EGFR-TKI treatment (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #1: formatted table will be checked against the raw output
- Table 36-UNC. Time on treatment with index therapy EGFR-TKI (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Primary objective: [redacted]/another BS will independently recalculate and check the algorithm for 100% of analyzed patients
- Table 37-UNC. Time to second-line treatment failure (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort) – Secondary objective #4: [redacted]/another BS will independently recalculate and check the algorithm for 100% of analyzed patients
- Table 38-UNC. Overall Survival with index therapy EGFR-TKI (ELIGIBLE PATIENTS of the Uncommon Mutation Cohort): [redacted]/another BS will independently recalculate and check the algorithm for 20% of analyzed patients

For SEQUENCING COHORT report:

- Table 1-SEQ. Patient disposition (ENROLLED PATIENTS of the Sequencing Cohort): [redacted]/another BS will independently recalculate frequencies
- Table 2-SEQ. Reasons for violations (ENROLLED PATIENTS of the Sequencing Cohort): [redacted]/another BS will independently recalculate frequencies and check the algorithms for each criterion for 100% of enrolled patients
- Table 12-SEQ. Approaches for detection of mutations at second-line treatment (osimertinib) start (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #3: formatted table will be checked against the raw output
- Table 16-SEQ. Details of first-line EGFR-TKI treatment (afatinib) (ELIGIBLE PATIENTS of the Sequencing Cohort): [redacted]/another BS will independently recalculate descriptive statistics and check the algorithm for 10% of analyzed patients
- Table 19-SEQ. Response to second-line treatment (osimertinib) (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #1: formatted table will be checked against the raw output
- Table 20-SEQ. Time on treatment (ELIGIBLE PATIENTS of the Sequencing Cohort) – Primary objective: [redacted]/another BS will independently recalculate and check the algorithm for 100% of analyzed patients
- Table 21-SEQ. Overall Survival from afatinib start (ELIGIBLE PATIENTS of the Sequencing Cohort) – Secondary objective #2: [redacted]/another BS will independently recalculate and check the algorithm for 20% of analyzed patients
- Table 22-SEQ. Overall Survival from osimertinib discontinuation (ELIGIBLE PATIENTS of the Sequencing Cohort): [redacted]/another BS will independently recalculate and check the algorithm for 20% of analyzed patients

7 REVISION HISTORY

Table	SAP version and date	Change description	Applicant	Note
Table 6-UNC	Vers. 1.0 FINAL, 03/07/2020	Analysis added	[redacted] (on behalf of BI CTL)	
Table 8-UNC	Vers. 1.0 FINAL, 03/07/2020	Analysis added	[redacted] (on behalf of BI CTL)	
Table 11-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 12-UNC	Vers. 1.0 FINAL, 03/07/2020	Analysis added	[redacted] (on behalf of BI CTL)	
Table 14-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 15-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 16-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 17-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 20-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 26-UNC	Vers. 1.0 FINAL, 03/07/2020	Table added	[redacted] (on behalf of BI CTL)	
Table 39-UNC – Table 43-UNC	Vers. 1.0 FINAL, 03/07/2020	Tables added	[redacted] (on behalf of BI CTL)	
Table 44-UNC – Table 48-UNC	Vers. 1.0 FINAL, 03/07/2020	Tables modified	[redacted] (on behalf of BI CTL)	
Table 22-SEQ, Table 27-SEQ	Vers. 1.0 FINAL, 03/07/2020	Tables modified	[redacted] (on behalf of BI CTL)	
Table 23-UNC	Vers. 1.0 FINAL, 03/07/2020	Analysis modified	[redacted] (on behalf of BI TSTAT)	
Table 29-UNC	Vers. 1.0 FINAL, 03/07/2020	Analysis modified	[redacted] (on behalf of BI TSTAT)	
Table 31-UNC	Vers. 1.0 FINAL, 03/07/2020	Analysis modified	[redacted] (on behalf of BI TSTAT)	
Table 16-SEQ	Vers. 1.0 FINAL, 03/07/2020	Analysis modified	[redacted] (on behalf of BI TSTAT)	
Table 18-SEQ	Vers. 1.0 FINAL, 03/07/2020	Analysis modified	[redacted] (on behalf of BI TSTAT)	
Tables in which classification of EGFR uncommon mutations is analysed	Vers. 1.1, 27/11/2020	Algorithm modified	[redacted] (on behalf of BI CTL)	
Table 19-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 21-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 24-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 25-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 27-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 30-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 35-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	
Table 37-UNC	Vers. 1.1, 27/11/2020	Table modified	[redacted] (on behalf of BI CTL)	

8 APPENDIX

Not applicable