Trial Statistical Analysis Plan

c02542327 -02

BI Trial No.:	1280.16
Title:	A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab(BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors. Including Protocol Amendment 03 [c02190401-06]
Investigational Product(s):	Xentuzumab (BI 836845)
Responsible trial statistician(s):	 Tel.: Fax: Tel. Fax:
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2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical, Therapeutic, Chemical (classification system)
ANOVA	Analysis of Variance
BI	Boehringer Ingelheim
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
BSA	Body Surface Area
CR	Complete Response
CRF	Case Report Form
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DC	Disease Control
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMG	Dictionary Maintenance Group

Term	Definition / description
DMS	Data Management and Statistics
ECG	Electrocardiogram
ECGS	ECG set
eCRF	Electronic Case Report Form
ENR	Enrolled Set
EOTV	End of Treatment Visit
FDA	Food and Drug Administration
FU	Follow Up
ICH	International Conference on Harmonisation
IGF	Insuline-Like Growth Factor
IPV	Important Protocol Violation
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MS	MTD Set
NE	Not Evaluable
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival

Term	Definition / description
PPS	Per Protocol Set
PR	Partial Response
PR interval	ECG interval from the onset of the P wave to the beginning of the QRS complex
PT	Preferred Term
PV	Protocol Violation
Q1	25^{th} percentile
Q3	75^{th} percentile
QRS	Combination of the Q, R and S waves
QT	ECG interval from the beginning of the QRS complex to the end of the T wave
QTc	Generic term for QTcF and QTcB intervals
QTcB	QT interval, corrected by Bazett's formula
QTcF	QT interval, corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
RP2D	Recommended Phase II Dose
RS	Randomised Set
SAE	Serious Adverse Event
SD	Stable Disease
SDL	Subject Data Listings
SIR	Synoptic Interim Report
SOC	System Organ Class
SOP	Standard Operating Procedure
TCM	Trial Clinical Monitor
TMCP	Translational Medicine and Clinical Pharmacology
TSAP	Trial Statistical Analysis Plan
TTP	Time to Progression
TS	Treated Set

Term	Definition / description
ULN	Upper Limit of Normal
WHO-DD	World Health Organisation - Drug Dictionary

3 INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP (see in section "Statistical Methods and Determination of Sample Size"). Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation. This TSAP follows Boehringer Ingelheims (BI) internal reference (1).

The trial consists of two parts, the first part is the dose confirmation part (Part A) and second part is an expansion cohort (Part B).

The TSAP describes the analysis for both parts of the trial. After the first part, safety analyses outputs were performed and documented.(see Section 9.1).

In general, study or trial medication refers to the combination of xentuzumab with afatinib.

SAS Version 9.4 or later version will be used for all analyses unless otherwise specified.

4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

4.3 CLARIFICATIONS

The following points warrant further clarification:

- If not stated otherwise, date of randomisation will be replaced by first treatment administration of any study medication in the outputs .
- The terms “progression”, “progressive disease” (PD) and “disease progression” will be used interchangeably within this document.
- The terms “treatment cycle” or “treatment course” will be used interchangeably throughout this document.
- The terms “study medication” and “trial medication” will be used interchangeably throughout this document. These terms may be used for the combination of xentuzumab and afatinib, or any of these medications alone. Clarification is given when necessary.
- The terms “Part A” and “first part” will be used interchangeably throughout this document. The terms “Part B” or “second part” will be used interchangeably throughout this document.

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

5.1.1 First part

The primary endpoints are the maximum tolerated dose (MTD) of trial medication based on the occurrence of dose limiting toxicity (DLT) during the first treatment course. The planned treatment course consists of 28 days.

MTD:

MTD is defined as the highest dose level examined of trial medication, at which no more than 1 out of 6 patients experienced a DLT during the MTD evaluation period. The MTD evaluation period is defined as the time from the first administration of xentuzumab up to start of cycle 2. That means that the exact duration of this period will be derived for each patient. If the patient does not start cycle 2, a fixed duration of 28 days will be used.

The MTD and the safety profile (including DLTs occurring after first treatment course), pharmacokinetic and pharmacodynamics parameters will be the basis to define the recommended phase II dose (RP2D) to be used for further trials in the development of xentuzumab in combination with afatinib.

5.1.2 Second part

Objective response (OR)

The primary endpoint for the second part of the study is objective response (OR).

OR is defined as best overall response of complete response (CR) or partial response (PR). Best overall response to trial medication will be determined according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 (see Appendix 10.5 of the CTP) recorded from first administration of trial medication until the earliest of disease progression, death or last adequate tumour assessment before start of subsequent anti-cancer therapy.

Note that an adequate tumour assessment includes an assessment of target lesions, as well as radiological tests to evaluate non-target lesions and to search for new lesions, i.e. a RECIST tumour evaluation. If no RECIST tumour evaluation has been performed, the assessment will be set to missing.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Other secondary endpoints

5.2.2.1 First part

There are no secondary endpoints.

5.2.2.2 Second part

Time to OR

Time to objective response is defined as the time from first treatment administration until first documented CR or PR.

Time to objective response will only be calculated for patients with an objective response:

- Time to OR [days] = date of first documented CR or PR - date of first treatment administration +1.

Duration of OR

Duration of objective response is defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with objective response.

Duration of objective response will only be calculated for patients with an objective response. For patients with disease progression or death:

- Duration of objective response [days] = date of outcome – date of first assessment indicating OR + 1.

For patients without disease progression or death:

- Duration of objective response (censored) [days] = date of outcome – date of first assessment indicating objective response + 1

The censoring rules for duration of OR are given in Table 5.2.2.2: 1.

Table 5.2.2.2: 1 Derivation rules for Duration of Objective Response

Situation	**Outcome (event or censored)**	**Date of outcome**
No other anti-cancer therapy		
Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments

Table 5.2.2.2: 1 Derivation rules for Duration of Objective Response (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death, no more than one consecutively missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

Only radiological assessments after first assessment indicating objective response will be taken into consideration.

Disease control (DC)

DC is defined as best overall response of CR or PR or SD where best overall response is defined according to RECIST version 1.1 (see Appendix 10.5 of the CTP) from first administration of trial medication until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

Note that an adequate tumour assessment includes an assessment of target lesions, as well as radiological tests to evaluate non-target lesions and to search for new lesions, i.e. a RECIST tumour evaluation. If no RECIST tumour evaluation has been performed, the assessment will be set to missing.

5.4.2 Treatment exposure

Total treatment duration [days]:

Date of last administration of any trial medication – date of first administration of any trial medication + 1.

Total treatment duration therefore includes time when treatment was temporarily discontinued and subsequently reintroduced.

Duration of specific medication exposure [days]:

Date of last administration of specific medication – date of first administration of specific medication + 1.

Duration of specific medication exposure will be calculated separately for xentuzumab and afatinib.

Number of courses initiated [N]:

Course initiated means that the patient received at least one administration of trial medication in the initiated course.

Total number of xentuzumab infusions [N]:

Sum of xentuzumab infusions calculated across all courses.

It will be calculated for each patient who received at least one infusion of xentuzumab.

Number of patients with at least one dose reduction [N]

Number of patients with at least one dose reduction will be counted.

The number of patients with at least one dose reduction will first be calculated for any medication and then separately for each specific medication for which dose reduction is allowed. This means that it will be calculated separately for xentuzumab and afatinib.

Time to first dose reduction of specific medication [days]:

Date of first administration of the first reduced dose of specific medication – date of first administration of specific medication + 1.

Time to first dose reduction will be calculated only for patients who had a dose reduction.

This will also be calculated separately for patients with a dose reduction of xentuzumab or afatinib.

Total dose of specific trial medication [mg]:

Total dose of trial medication will be calculated separately for xentuzumab and afatinib.

For xentuzumab, this is the sum of the administered doses calculated across all courses. This takes into account the dose reductions.

For afatinib, this is calculated as the total duration of treatment with this medication in days multiplied by the actual dose taken (using the actual dose recorded on the Case Report Form (CRF)) for the days the medication was taken. This takes into account the dose reductions of afatinib. This calculation is only an approximation of the total dose taken, since the way the data are collected do not allow a more precise calculation.

Dose intensity of specific trial medication during all treatment duration (%):

Dose intensity of trial medication will be calculated separately for xentuzumab and afatinib.

100*(Total dose of specific trial medication actually received by a patient / Planned total dose of specific trial medication during the entire duration of treatment).

The planned total dose is calculated as the total dose of the medication a patient should have received from the date of first administration of the medication to the date of last administration.

The planned total dose of xentuzumab for each patient is calculated using the following formula: planned dose per infusion (e.g. 1000 mg) multiplied by number of visits with administration of xentuzumab.

For afatinib, the planned total dose for each patient is calculated using the following formula: total duration of treatment with this medication in days multiplied by the planned daily dose (e.g. 40 mg, using the dose the patient was initially assigned to).

This is done assuming that the initial dose was taken throughout, and dose reduction as specified in the protocol will not be considered in the calculation. This means that if a patient had protocol-defined dose reduction due to an Adverse Event (AE), the reduced dose will not be used in the calculation of the denominator.

For afatinib, this calculation is only an approximation of the dose intensity, since the way the data are collected does not allow a more precise calculation.

6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Part A and part B: Patients will be analysed according to the cohort initially assigned. All planned analysis will be presented by this cohort, unless specified otherwise. Handling of patients where cohort assignment has not been followed will be handled on a case-by-case basis, to be agreed at report planning meetings or DBL meeting (but prior to database lock).

For safety summaries data recorded during the Residual Effect Period (REP) will be considered as on-treatment. For this trial, the length of the REP is 42 days.

The actual study periods and treatment codes are defined in a document entitled "8-07-other-sdtm-trial-arms-trial-elements", which can be found in Data Management and Statistics (DMS) folder, Section 8, within BIRDS.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol set (PPS) analysis will be performed for this study, hence, no patient will be excluded from the analyses (except those with missing informed consent or not adhering to age limit). However patients with potentially important protocol violations (IPVs) will be documented. The following list of potentially IPVs in Table 6.2: 1 will be used; note that this is a working list and may not be finalised until the final Blinded Report Planning Meeting (BRPM) or DBL meeting (but prior to database lock for the primary analysis). Potentially important protocol violations will be handled according to BI standards (6).

During the study conduct, protocol deviation should be monitored and guidance for improving / teaching the respective sites should be discussed during the study Medical Quality Review Meetings (MQRMs).

Table 6.2:1 Important protocol violations

Category/ Code		**Description**	**Requirements**	**Excluded from**
A [1]		**Entrance criteria not met**		
	A1	Diagnosis of trial disease questionable	Inclusion criteria IN2-IN4 not met. or Indicated by medical review of oncological history and baseline tumour assessment details from investigator.	None

Table 6.2:1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	A2	Prohibited baseline condition, diagnosis or treatment	At least one of inclusion criteria IN6-IN9 or IN13 is not met or At least one of exclusion criteria EX3, EX7-EX8, EX10-EX12, EX14-EX16, or EX18-EX20 is met. or Indicated by medical review of baseline conditions. or Prohibited medication use (or surgery) before the treatment period of the trial, that is, At least one of exclusion criteria EX1, EX2, EX4-EX6, EX9, EX22, or EX24 is met or Indicated by medical review of concomitant therapy use before start of study treatment.	None
	A3	Laboratory result indicating inadequate organ function at screening	Inclusion criteria IN11 or IN12 not met or Both screening and baseline (defined in Section 6.7 of this document) laboratory results are missing.	None
	A4	Adequate archival tumour tissue not available	IN5 not met.	None
B [1]		**Legal Criteria**		
	B1	Informed consent not available / not done	Inclusion criterion IN14 is not met. or Date of informed consent is missing.	All

Table 6.2:1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	B2	Informed consent too late	Informed consent date was after Screening Visit date	None
	B3	Age limit for patient inclusion not adhered to	Patient's age < 18 as in IN1	All
C [2]		**Trial medication and randomisation**		
	C1	Time window violation for procedures performed at screening	Baseline disease assessment not within 30 days prior to first treatment. Create listing, decision at MQRM / RPM.	None
	C2	Trial medication not given according to protocol	Dose reduction scheme not followed (see CTP section 4.1.4.3); Administration of trial medication(s) not compliant. Indicated by medical review (i.e. where Administration of xentuzumab according to the protocol = 'No' and associated comments, or compliance data from afatinib with associated comments) Please note: This excludes the investigational treatment given outside the boundaries specified in the CTP (covered in Category C3).	None
	C3	Infusion time for the investigational treatment outside of CTP specific boundaries	Infusion duration of xentuzumab given < 50 minutes or > 200 minutes (Infusion time should be from 60 to 180 minutes, but the thresholds above are accepted). The exact duration of the infusion should be calculated taking interruptions into account. In case of missing administration times, the violation will not be considered important if administration according to protocol = 'Yes'.	None

Table 6.2:1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	C4	Patient assignment not followed	Patients do not receive the initial treatment they were allocated to.	None
D [2]		**Concomitant medication**		
	D1	Prohibited treatment during trial conduct phase	Exclusion criterion EX17 met or Indicated by medical review of concomitant therapy use during study treatment.	None
E [2]		**Missing Data**		
	E1	Imaging assessments not done according to CTP instructions	Imaging assessment should be performed at screening and several time points thereafter (see TSAP Section 6.7.2).	None
	E2	Pregnancy test not done according to CTP instructions	Only for studies where pregnancy tests are required.	None
F [2]		**Trial Specific protocol violations**		
	F1	Other protocol violations affecting patient rights or safety	Manual PVs will be collectively captured.	None

[1] IPV will be derived automatically .
[2] IPV will be identified via individual review at MQRM/RPM/DBL.

6.3 PATIENTS SETS ANALYSED

The following analysis sets will be defined for this trial:

- Enrolled set (ENR)

This patient set includes all patients with informed consent given. The enrolled set will be used for patient disposition tables.

- Treated set (TS)

This patient set includes all patients who are documented to have received and taken at least one dose of any study medication during the treatment cycles (from day 1).

The TS will be used for all planned safety and efficacy analyses.

- MTD Set (MS)

The MTD set defines the set of patients in the first part of the trial that are fully evaluable for determination of the MTD in the first treatment course. The MTD set will be used for some safety analyses in the first part, this is specified in the technical TSAP.

Patients in the TS who were replaced within the MTD evaluation period in the first part of the trial will be excluded from the determination of the MTD. Replacement of patients in the first part of the study is defined in Section 3.3.4.3 of the CTP. The final list of replaced patients is supplied by the Trial Clinical Monitor (TCM) no later than the last report planning meeting before the database lock for the safety analysis.

6.5 POOLING OF CENTRES

This section is not applicable because there are no inferential statistics, and therefore there is no statistical model in which centre/country can be included.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed, unless required for the following analyses and definitions. Then the rules as described below apply.

Missing dates that affect the evaluation of endpoints specified in previous sections of this TSAP will be imputed utilising a "worst case" approach, which will be applied on a case-by-case basis (depending on the affected endpoint) and agreed to by the trial team members at the final BRPM before database lock at the latest.

The rules in the table 6.6: 1 below have been agreed by the trial and project teams, and will be used in this trial, if applicable.

Table 5.3.2.2:1 Rules for imputations of missing or incomplete dates

Date	**Imputation rule**
Date of birth	In case only the year is given: 1st of January
Date of death	Date last known to be alive. If only year and month are given: this will be imputed with 1st of the month for the analysis of OS
Date of first histological diagnosis	1st of month if day is missing 1st of January if month also missing
Date of start of concomitant medication	No imputation required
Date of end of concomitant medication	No imputation required
Date of start of subsequent anti-cancer therapy (imputation required only for censoring of PFS)	If the day (respectively day and month) of the start date of subsequent anti-cancer therapy is missing, then the first of the month (respectively 1st January) will be imputed unless this date leads to a date before the stop date of study medications. In this case, the study medications stop date + 1 day will be imputed. Additionally, all imputed start dates of subsequent anti-cancer therapy should be before death date if available.
Date of stop of subsequent anti-cancer therapy	No imputation required
Date of end of treatment (only for patients still ongoing at time of snapshot/DBL)	Date of snapshot If date of death before this date, use date of death

6.6.1 Adverse events

Missing or incomplete AE dates are imputed according to BI standards (2).

6.6.2 Laboratory values at baseline

For missing laboratory data at Cycle 1 Visit 1 (before the very first administration of study medication) data from preceding visits will be used.

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

6.7.1 Baseline

The last measurement observed prior to start of trial medication will be assigned to baseline. Note that for some trial procedures (for example body weight, vital signs, laboratory tests) this may be the value measured on the same day trial medication was started. In these cases it will be assumed that the measurements were taken prior to the intake of any study medication. For tumour assessment, baseline evaluations must be based on Magnetic Resonance Imaging (MRI) or Computed Tomography scans performed no more than 30 days prior to start of trial medication.

Study days and visits will be labelled according to the flow chart of the CTP.

Unless otherwise specified, baseline is defined as the latest time-point before the very first administration of any study medication. If this criterion is not fulfilled then no baseline will be derived .

Laboratory values:

Baseline is defined as the latest time-point before the very first administration of any study medication.

If any of these times are missing and the date of laboratory value is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

6.7.2 Time windows for every RECIST assessment

In order to identify whether consecutive imaging time-points are missing for a given patient, a nominal time point [4, 8, 16, 24, 32, 40, 48, 56, 68 weeks and every 12 weeks thereafter] will be assigned to each and every image. This is achieved by creating windows for every RECIST assessment. The windows are defined in Table 6.7.2: 1 below. Day 1 corresponds to the date of first drug intake of xentuzumab or afatinib.

Table 6.7.2:1 Nominal time-points and windows for imaging

Nominal time-point [weeks from start of therapy]	**Due date of scans [days]**	**Window [days]**
4	29	1 to =< 43

8	57	44 to =< 85
16	113	86 to =< 141
24	169	142 to =< 197
32	225	198 to =< 253
40	281	254 to =<309
48	337	310 to =<365
56	393	366 to =<435
68	477	436 to =<519
every 12 week interval	etc (1)	etc (1)

(1) Due date of imaging = (nominal time point * 7) + 1. To calculate the lower bound of the window, use the middle point between the due date of the previous time point and the current due date + 1. To calculate the upper bound of the window, use the middle point between the due date of the next time point and the current due date.

If a patient does not have an image in one of the windows described above, he/she will be said to have 'missed an assessment' for that time-point. In case a patient has more than one assessment in one window, the assessment with the latest outcome will be used for the analysis unless a PD has been recorded earlier then PD will be used.

7 PLANNED ANALYSES

The labelling and display format of statistical parameters will follow BI standards (7).

Unless otherwise specified, outputs will be displayed separately for each part of the trial.

With protocol amendment 4, starting doses of xentuzamab 1000mg + afatinib 30mg and xentuzamab 1000mg + afatinib 20mg are also allowed in part B. For part B, sections for trial subjects and safety analyses will be displayed by starting dose and total. Efficacy analyses will be done for part B patients, and RP2D patients (defined as pooled patients of all the patients in part B and the patients starting with xentuzumab 1000mg + afatinib 40mg in part A excluding squamous carcinoma patients).

Descriptive statistics for continuous variables will generally contain N (number of patients in that patient set with non-missing values), Mean, Standard Deviation, Minimum (Min), Q1 (25^{th} percentile), Median, Q3 (75^{th} percentile), Maximum (Max). In general, means, standard deviations, medians, Q1 and Q3 will be presented to one more decimal place than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

For time-to-event analysis tables, the set of statistics is: number of patients [N (%)], Number of patients with event [N (%)], Number of patients censored [N (%)], <Time to event> [months] followed by P25 (25^{th} percentile), Median, P75 (75^{th} percentile). If not specified otherwise, the duration as well as time to event will be displayed in months.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group total. Percentages will be rounded to one decimal place.

In general a category “missing” will be displayed, if there are missing data for the corresponding variable. Percentages will also generally be based on all patients in the respective patient set whether they have non-missing values or not.

Sort order for general categorical variables: If categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the “default ordering” defined by the eCRF is to be used in such cases. If categories are derived the ordering as specified in the table shell document should be used; in general ordinal data (e.g. categorised continuous data) are to be displayed in ascending order.

The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be indented and “[N (%)]” to be displayed only for the main category.

If a table includes only categorical data, “[N (%)]” is to be displayed in the column header.

In general, a “Total” column will not be displayed for post-baseline displays. Tables that display the status of patients for a primary or secondary endpoint with number of events and number censored will contain a total column.

Abbreviations (e.g., Wors.) or acronyms (e.g., PD) should not be displayed in tables and patients data listings without any explanation. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = days ÷ 7
- Months = days × 12 ÷ 365.25
- Years = days ÷ 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.1.1 Disposition of patients

For patient disposition the standard descriptive table from the EOT catalogue will be populated. Additionally, patients with discontinuations by initial treatment and the reasons will be listed and tabulated, overall and and for each treatment separately. The same output will also contain an overview of discontinued and non-discontinued, as well as completed and non-completed patients.

7.1.2 Important protocol violations

A table and a listing of patients with important protocol violations based on Table 6.2: 1 will be created in Section 15.1.3 and Appendices 16.2.3 and 16.1.9.2.3 (if needed) respectively, of the CTR.

7.1.3 Demographic and other baseline characteristics

Standard descriptive analysis and summary tables for all patients treated by initial treatment will be created for demographic data, oncological history and baseline conditions.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies will be coded according to World Health Organisation - Drug Dictionary (WHO-DD). Concomitant therapies (CT) will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

Concomitant medications will be presented according to whether they are concomitant with the reception of study medication, or whether they were given prior to study medication. In case start and stop dates of the medications are completely missing, they are assigned as given prior to study medication.

7.3 TREATMENT COMPLIANCE

Compliance was not analysed separately, but assessed in terms of exposure (including dose intensity). Refer to Section 7.7 for further details on exposure analysis.

7.4 PRIMARY ENDPOINTS

7.4.1 First part

The primary endpoints are the MTD and the occurrence of DLT. The MTD is determined from the occurrences of DLTs during the MTD evaluation period (this period is defined in Section 5.1.1). An overall summary of the DLTs (see CTP Section 5.2.6 for definitions of DLT) which occurred during the MTD evaluation period and the on-treatment period will be provided for each dose cohort.

Patients that were treated but replaced for the MTD evaluation (see CTP Section 3.3.4.3) will be excluded from the MTD determination. Replacement of patients will be determined on a case by case basis; exclusion of these patients from the MTD evaluation will be confirmed by the trial team at the report planning meeting prior to database lock.

A listing of patients with DLTs by initial treatment will be performed.

At the end of the dose escalation phase, a safety analysis will be performed to determine the RP2D. The results will be documented for internal use and communication with the participating investigators. (see also in Section 9.1)

7.4.2 Second part

Objective response (OR)

OR as assessed by investigators is defined as a best overall response of CR or PR and will be analysed. Descriptive statistics including number of treated patients, number of patients with objective response as best overall response and the corresponding percentages will be presented and evaluated.

The same analysis will also be done for RP2D patients (defined as pooled patients of all the patients in part B and the patients starting with xentuzumab 1000mg + afatinib 40mg in part A excluding squamous carcinoma patients).

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other secondary endpoints

7.5.2.1 First part

This section is not applicable as no secondary endpoint has been specified in the protocol.

7.5.2.2 Second part

Disease control

Disease control (DC) is defined as best overall response of complete response (CR) or partial response (PR) or stable disease (SD) (defined in Section 5.2.2.2). Only descriptive statistics are planned for this section of the report.

Time to OR

For patients with objective response, time to objective response will be shown on patient level. If applicable a set of summary statistics for time to objective response on cohort level will also be produced.

Duration of OR

For patients with objective response, duration of objective response will be shown on patient level. If applicable a set of summary statistics for duration of objective response on cohort level will also be produced.

The same analysis will also be done for RP2D patients (defined as pooled patients of all the patients in part B and the patients starting with xentuzumab 1000mg + afatinib 40mg in part A excluding squamous carcinoma patients).

7.7 EXTENT OF EXPOSURE

The variables defined in Section 5.4.2 will be summarised descriptively for each dose cohort.

7.8 SAFETY ANALYSES

All safety analyses will be performed on the TS (unless otherwise specified; for example, the MTD Set will be used for some safety outputs). Patients in the first part of the trial who were replaced within or before the first treatment cycle will be excluded from the determination of the MTD.

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature. All analyses will be based on the number of patients with AEs (not the number of AEs).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (Lowest Level Term (LLT), Common Terminology Criteria for Adverse Events (CTCAE) grade, action taken with trial medication, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

For further details on summarisation of AE data, please refer to (2) and (4).

Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to CTCAE (CTCAE version 4.03 (10)).

The analyses of adverse events will be based on the concept of treatment-emergent adverse events. That means that all adverse events with an onset between first treatment administration until end of the REP will be assigned as ‘on treatment’. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after the residual effect period will be assigned to ‘post-treatment’; these AEs will be displayed in listings only. Adverse events will be displayed by the initial dose of study medication administered on the first day of treatment .

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term.

Separate tables will be provided for patients with drug-related adverse events, adverse events leading to dose reduction, adverse events leading to discontinuation, serious adverse events, serious drug-related serious adverse events, adverse events leading to death, other significant adverse events, adverse events of special interest, and adverse events fulfilling the DLT definition (for part A only), and drug-related adverse events leading to discontinuation.
Sorting order:

In tables presenting System Organ Classes (SOCs) and Preferred Terms (PTs), SOCs will be sorted alphabetically and PTs (within SOC) by descending frequency.

Reporting of CTCAE grades in tables:

In tables showing AEs by worst CTCAE grade, AEs with missing CTCAE grade will only be displayed under the category "All grades", but no category "Missing grade" will be displayed. Therefore the categories "Grade 1" to "Grade 5" might not add up to the category "All grades"; a footnote will explain this handling.

Displaying of CTCAE grades in AE tables (Section 15) will be “All grades”, “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4”, and “Grade 5” separately.

Listings of adverse events

Adverse events will be reported with start and end day as calculated from the first day of treatment with study medication.

Incidence and severity of adverse events

The incidence of AEs overall (irrespective of relatedness to study medication), related AEs, and serious AEs (SAE) will be reported by severity according to CTCAE grades.

Other significant adverse events

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades.

A listing of patients who developed ‘other significant’ AEs will be provided and a flag for serious and non-serious will be included.

AEs leading to dose reduction or permanent discontinuation will include:

- AEs leading to dose reduction of xentuzumab
- AEs leading to dose reduction of afatinib
- AEs leading to permanent discontinuation of xentuzumab
- AEs leading to permanent discontinuation of afatinib

AEs leading to death

AEs leading to death during the on-treatment period will be tabulated in a separate table. In this table no CTCAE grades will be shown. For fatal AEs without CTCAE grade 5 or missing grade, the grade will be imputed as CTCAE grade 5. Reported fatal AEs that occurred in the follow-up period will be listed.

Protocol-specified Adverse Events of Special Interest (AESI)

Protocol-specified AESIs are specified in the CTP Section 5.2.2.1. Their incidence will also be reported.

Adverse events by user defined AE categories (UDAEC)

User defined adverse events categories (UDAEC) as defined on project level by the pharmacovigilance working group will be derived and the latest version will be used for the analysis.The most recent version of the categories is defined in a document entitled "8-02-sap-safety-core", which can be found in the Project Data Management and Statistics folder, section 8 (project level), within BIRDS. The incidence of AE by UDAEC will be analysed.

7.8.2 Laboratory data

7.8.2.1 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). The same on-treatment periods as considered for the analysis of adverse events will be applied for laboratory values except for that the baseline laboratory value will be included in the 'on-treatment' period. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE version 4.03 (10). The following outputs will be presented:

- Worst CTCAE grade experienced during the on-treatment phase.
- Transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value during the on-treatment phase, and from baseline to last laboratory value.

Patients with missing CTCAE grade at baseline or no baseline value but post baseline values will be displayed in the category “Missing CTCAE grade at baseline”. Laboratory values without CTCAE grading will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment.

Analysis of potentially clinically significant abnormal laboratory values, and handling of CTCAE grade -1 and -9 laboratory parameters, are described in the SOP for "Display and analysis of laboratory data" (5), Reference Document 9.

7.8.2.2 Laboratory values of special interest

Hepatic enzyme elevations (potential Hy’s law cases):

These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3ULN with total bilirubin ≥ 2ULN and ALKP < 2 ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc.

Patients with missing laboratory values for liver enzymes will be excluded from these analyses but will be presented separately in a listing. Tabulations of hepatic enzyme elevations and liver laboratory values (see Section 5.2.2.1 of the CTP), including flags of true DILI cases, are created in accordance with the Food and Drug Administration (FDA) DILI guidance (8).

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

ECGs are done throughout the trial, and changes in analysis results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator.

8 REFERENCES

1	*001-MCG-160_RD-06:* "Trial Statistical Analysis Plan - Template", current version; IDEA for CON.
2	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
4	*001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5	*001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.
6	*001-MCS-50-413*: “Handling of Protocol Violations in Clinical Trials and Projects”, current version; IDEA for CON.
7	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
8	Guidance for industry: drug-induced liver injury: premarketing clinical evaluation U.S. Departement of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), 2009.[P09-12413]
9	Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45: 228-247 [R09-0262]
10	Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (2010) [R10-4848]
11	Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, Quarmby V, Richards S, Schneider CK, Subramanyam M, Swanson S, Vethelyi D, Yim S. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J 16 (4), 658 - 673 (2014) [R15-1067]

9 ADDITIONAL SECTIONS

9.1 SAFETY ANALYSIS

After 12 evaluable patients treated at the designated MTD dose have completed at least the first course of treatment in part A, a safety analysis will be performed. For this purpose a database snapshot will be performed. The safety analysis will summarise results regarding safety and will be used for recommendation of the dose of trial medication to be taken forward as recommended phase II dose. The selection of the RP2D will consider overall safety observed during available treatment cycles for all treated patients, including the ones that were replaced for the determination of the MTD.

Disposition of patients, demographic characteristics and oncological history, previous therapies (listing), concomitant therapies (listing), exposure (total duration of treatment, patients with dose reduction), adverse events and laboratory parameters (listing of laboratory values, table of frequency of patients with transitions of CTCAE grades at baseline and worst grade on treatment) will be shown in the safety analysis.

10 HISTORY TABLE

Table 7.8.2.2: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	27-Sep-17		None	This is the final TSAP without any modification