Trial Statistical Analysis Plan

c27745069-01

BI Trial No.:	1200.283
Title:	LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung Including protocol amendment version 3.0 **[c13055147-03]**
Investigational Product:	Afatinib in combination with pembrolizumab
Responsible trial statistician(s):	Telephone: Fax: Email:
Date of statistical analysis plan:	14 May 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
RPM	Report Planning Meeting
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria Adverse Events
CTP	Clinical Trial Protocol
DCR	Disease Control Rate
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor, also known as ERBB1
EMA	European Agency for the Evaluation of Medicinal Products
ERBB2	Second member of the ERBB family of proteins
ERBB3	Third member of the ERBB family of proteins
HLT	High Level Term
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IPD	Important Protocol Deviations
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NCI	National Cancer Institute
NE	Not Evaluable
NN	Non-CR/Non-PD
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDL1	Programmed Death Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetics
PSTAT	Project Statistician
PR	Partial Response
PT	Preferred Term

Term	Definition / description
PV	Protocol Violation
RECIST	Response Criteria for Solid Tumours
SD	Stable Disease
SMQ	Standardised MedDRA query
TOC	Table of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

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 Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

The validated SAS® version will be used that is in place on the BI system at the time of analyses. Currently Version 9.4 is being used.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The phase II, single arm trial was originally designed with two parts: i) Safety run-in to decide the RP2D of the combination therapy for the main part and ii) main part of phase II. At the end of safety run-in, after careful consideration of benefit-risk assessment and current available treatment options, SMC recommended to stop the trial. Below are some of the main changes compared to planned analysis in study protocol version 2.0, considering that the trial will not go to the main part:

- Analysis and decision on RP2D was not conducted as the trial will not go to the main part of the phase II.

- Analysis of duration of response will not be done, as there are not enough number of responses to do this analysis.

- No extensive subgroup analysis for primary endpoint will be done for PD-L1 expression, and for subgroups defined by the biomarkers related to immune status.

- Subgroup analysis for other efficacy endpoint e.g. PFS, OS, ORR, DOR involving PD-L1 expression and subgroups defined by the biomarkers related to immune status will not be done due to small number of patients.

- No analysis, except a listing, will be done for irRECIST criteria.

- The analysis of PK assessment, mentioned in section 7.3.3 of the protocol, will not be done. A listing with the information on actual time of collection of PK-sample with the values of plasma concentration will be reported.

5. ENDPOINT(S)

This trial is an open-label, single arm phase II study assessing the tolerability and anti-tumour activity of afatinib when given in combination with a fixed dose of pembrolizumab in patients with squamous NSCLC, who progressed during or after first line platinum-based standard therapy and had no prior treatment with an immune checkpoint inhibitor or EGFR targeted therapy.

This trial consists of two parts:

1) Safety run-in: Maximum of 24 patients will be treated in the first part.

    a) At first 12 patients will be treated, for at least one full cycle, at the starting dose of 40 mg of afatinib and 200 mg of pembrolizumab. Along with the results from Bayesian logistic model (BLRM), safety-monitoring committee (SMC) will assess the overall safety and tolerability of this dose. If the starting dose is tolerable and safe, it will be declared as RP2D.

    b) If the starting dose of afatinib (40 mg) is intolerable, 12 more patients will be included in the safety run-in and they will receive a starting dose of afatinib of 30 mg along with 200 mg of pembrolizumab. After they have been treated for at least one full cycle, the SMC will assess the overall safety profile along with results from BLRM to confirm this combination as RP2D and the study will go to main part.

        If this reduced dose (30 mg afatinib with 200 mg of pembrolizumab) is also too toxic no additional patients will be enrolled and the study will be stopped and will not go to main part.

        Note that this safety run-in is to determine the safe dose of afatinib in combination with standard dose of pembrolizumab.

2) Main part: Once the RP2D has been established, this will be the starting dose of afatinib for future patients entered to the main part of the trial. In total, 38 patients will be included in the main part to assess efficacy and safety of this treatment combination.

If the RP2D is defined as the original starting dose of afatinib (40 mg daily) in combination with pembrolizumab, the trial will include 12 patients from the safety run in and 38 patients from the main part, leading to 50 patients in total. However if the RP2D is defined as 30 mg of afatinib in combination with pembrolizumab, the trial will include 62 patients in total (12 patients at 40 mg and 50 patients at 30 mg).

Decision after safety run-in: Safety monitoring committee reviewed safety and efficacy data of 24 patients from two cohorts of safety run-in phase. In the first cohort, 12 patients were treated with a starting dose of 40 mg of afatinib and 200 mg of pembrolizumab and in the second cohort, 12 additional patients were treated with a starting dose of 30 mg of afatinib

and 200 mg of pembrolizumab. After careful assessment of benefit-risk, and considering current available treatment options for the population, the committee advised to stop the trial. The analysis for this trial will include patients from the safety run-in phase.

5.1 PRIMARY ENDPOINT(S)

The primary endpoint for this study is to assess the efficacy of afatinib in combination with pembrolizumab as measured by Objective Response rate (ORR). ORR is defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR) from first drug intake until the earliest of disease progression, death, or last evaluable tumour assessment before start of any new subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent.

RECIST 1.1 (2) will be used to determine all response and progression endpoints.

Note: As the study will not go to the second stage, protocol mentioned "supportive analysis with summaries" will not be done with supplemented immune-related RECIST (irREICST (9)) criteria; though a detailed listing will report all the assessments, following RECIST and irRECIST criteria, done in this study.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

The key secondary objectives are to confirm the recommended phase II dose (RP2D) of daily afatinib when combined with pembrolizumab given in 3-weekly cycles and assess the safety profile of the combination treatment.

5.2.2 Other secondary endpoint(s)

Other secondary endpoints are:

- Disease control rate (best overall response of CR, PR (confirmed) or SD).
- Progression-free survival (PFS), defined as the time from the treatment start date to the date of disease progression, or to the date of death from any cause, whichever occurs earlier.
- Overall survival (OS), defined as the time from the date of treatment start date to the date of death.
- Tumour shrinkage.

Note: As the trial will not go to the main part, no formal analysis will be done for protocol specified secondary endpoint "Duration of (confirmed) objective response" and no decision/ analysis on "Recommended Phase II Dose (RP2D)" will be done as well for this trial.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

All outputs will be presented by the starting dose of afatinib (30 mg or 40 mg) in combination with pembrolizumab, with patients grouped according to their actually assigned treatment. A "Total" treatment column will be introduced if different afatinib starting doses should be used within the trial.

The following definitions and study periods based on actual start and stop dates of afatinib and pembrolizumab administration are defined:

- **First administration of study treatment:** Date when first dose of afatinib or pembrolizumab, whichever occurs earlier, been administered.

- **Last administration of study treatment:** Date when last dose of afatinib or pembrolizumab, whichever occurs later, been administered.

- **Screening:** Day of informed consent to day prior to the first administration of study treatment.

- **On-treatment period:** Day of first administration of study treatment to (the last administration of study treatment + 30 days).

- **Residual effect period:** day after last administration of study treatment to the 30th day after last administration of study treatment.

- **Post-study:** on or after the 31st day after last administration of study treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Patients with potentially important protocol deviations (IPDs) will be documented. The following list of potentially IPDs will be used; note that this is a working list and may not be finalised until the final Report Planning Meeting (BRPM) prior to database lock.

Table 6.2: 1 Important protocol deviations

Category/code		Description	Comment	Manual/ Automatic
A		**Entrance criteria not met**		Automatic
	A1	Diagnosis of trial disease questionable	Refer to IN 1, 2, 3	Manual
	A2	Patient not eligible	Refer to IN 4,5	Automatic for IN 4 and Manual for IN5
	A3	Prohibited baseline condition, diagnosis or treatment	Refer to IN 6, 7, 8 or EX 1-24	Automatic for IN 6, 7, 8. Manual for EX24.
	A4	Not reached legal age of consent	Refer to IN 9	Automatic
	A5	Pregnancy	Violation of IN 11 or EX 25	Manual
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent not signed	Automatic
	B2	Informed consent too late	Informed consent date after screening visit date	Automatic
C		**Trial medication**		
	C1	Incorrect trial medication taken	Treatment was not paused, dose reduced, or discontinued according to protocol. This will be collected manually and reviewed at MQRMs.	Manual
	C2	Non-compliance	Overall Afatinib compliance rate < 80%	Manual
D		**Concomitant medication**		
	D1	Use of prohibited concomitant medications	Review concomitant medications for prohibited medication use. Refer to section 4.2.2.1	Manual
E		**Trial specific**		
	E1	Prohibited anticancer interventions	Patient received therapeutic radiation or another anti-cancer treatment before termination of study treatment	Manual

6.3 PATIENT SETS ANALYSED

Treated set: this includes all patients who received at least one dose of afatinib or pembrolizumab.

The "treated set" will be used for all efficacy and safety analyses.

Note: Safety monitoring committee reviewed safety and efficacy data for 24 patients from safety run-in phase. After careful assessment, of benefit-risk and considering current available treatment option for the population, the committee advised to stop the trial. The analysis for this trial will include patients treated in "safety run in" phase only.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing efficacy data will not be imputed and all reasonable efforts will be taken during the study to obtain such data. Patients with unknown vital status or time to progression will be censored for time to event analyses; further details are provided in Section 7.

Missing or incomplete AE dates will be imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (3)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first dose of study treatment (refer to section 6.1 for definition).

Study day will be calculated relative to the date of the first administration of study treatment. The day, prior to first administration of study treatment, will be 'Day -1' and the day of first administration of study treatment will be 'Day 1'; therefore 'Day 0' will not exist.

Time windows and visits will be calculated to determine the planned day of tumour measurement and response status, based on the protocol-specified tumour imaging schedule. Imaging data will be displayed as screening, Week 9, 18, 27… etc. First imaging is scheduled to be performed at week 9 (56-63 days after C1_V1) and every 9-weeks intervals (63 ± 7 days, 126 days ± 7 days etc.) thereafter until PD/start of subsequent anti-cancer treatment.

After first documentation of PD, as per RECIST 1.1, repeat imaging is needed at ≥ 4 weeks to confirm PD as per irRECIST.

7. PLANNED ANALYSIS

In general the display format of the analysis results will follow BI guideline (7, 8) as much as possible.

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (StD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to Mean, StD, Min and Max.

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. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

- Gender (Male, Female)
- Race and ethnicity (as defined in the eCRF)
- Age [years]
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] (defined as weight [kg]/(height [cm]/100)^2)
- Smoking history (Never-smoked, Ex-smoker, Currently smokes)
- Alcohol History (Non-drinker, drinks – no interference, drinks – possible interference)
- Country

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics using standard summary tables for all treated patients are planned for this section of the report.

7.3 TREATMENT COMPLIANCE

Descriptive statistics using standard summary tables for the treated set of patients are planned for this section of the report. A summary of whether patients took study drugs, afatinib and pembrolizumab, according to the protocol and whether they missed any doses will be

produced for each planned visit. In addition, a summary of overall percentage compliance will be produced using visit dates and the total number of doses missed during the study.

7.4 PRIMARY ENDPOINT(S)

The primary endpoint for this study is Objective Response rate (ORR), defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) from first drug intake until the earliest of disease progression, death, or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent. Confirmation of the response is needed with a repeat assessment at the next imaging time point (or ≥4 weeks later). Table 7.4:1 describes different best overall responses.

Table 7.4: 1 Rules to determine Best overall response

Item	Best Overall Response	Definition
1	Complete response (CR)	At least two determinations of CR at least 4 weeks apart before progression, death or start of new anticancer therapies.
2	Partial response (PR)	At least two determinations of PR at least 4 weeks apart before progression, death or start of new anticancer therapies. Some examples: 1) PR-SD-PR: BOR will be PR provided 4 weeks gap between two PR-determinations. 2) PR-CR-PD: BOR will be PR provided 4 weeks gap between PR and CR determinations.
3	Stable Disease (SD)	At least one SD assessment (or better) > 6 weeks after treatment start date and not qualifying for CR or PR.
4	Progressive Disease (PD)	Progression < 12 weeks and not qualifying for CR, PR and SD.
5	UNKNOWN (UNK)	If not satisfied above 4 items.
Note: Use “else if” conditions starting from Item 1.		

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

The key secondary objectives are to confirm the recommended phase II dose (RP2D) of daily afatinib when combined with pembrolizumab given in 3-weekly cycles and assess the safety profile of the combination treatment.

7.5.2 Other Secondary endpoint(s)

- Disease control rate (DCR) is defined as the proportion of patients with best overall response of CR, PR, or stable disease (SD) from first administration of study

treatment until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent.
A summary of disease control rate using the investigator assessment of response will be produced.

- Progression-free survival (PFS), defined as the time (months) from the date of first administration of study treatment to the date of disease progression, or to the date of death from any cause, whichever occurs earlier. The date of progression for the primary analyses will be determined based on assessments made by the investigators. All treated patients will be included.

  Kaplan–Meier curve and associated summary table will be produced for PFS.

  Table 7.5.2: 1 describes rules that can be used for sensitivity analyses to determine whether or not patients have had a PFS event (progression or death) along with the date of event or date of censoring (for those with no event).

- Overall survival (OS), defined as the time from the date of treatment start date to the date of death.

Kaplan–Meier curve and associated summary table will be produced for overall survival.

- Tumour shrinkage

Waterfall plots (and associated tables) of the maximum percentage reduction from baseline sum of target lesion diameters will be presented for each cohort.

Table 7.5.2: 1 Rules to determine events and censoring for sensitivity analyses of PFS

Rule #	Situation	Outcome (event or censored)	Date of PFS event or censoring
1	No baseline tumour assessment (no death before second scheduled assessment)	censored	Date of the start of study treatment
2	Progressed from imaging (no missed radiologic assessments)	event	Date of PD
3a	Non-PD from imaging[1], death before next scheduled assessment	event	Date of death
3b	Non-PD from imaging[1], one missed assessment, death or progression after date of missed assessment, but before a second scheduled assessment	event	Date of PD or death
3c	Non-PD from imaging[1], more than one consecutive missed assessment, death or progression after date of second missed assessment	censored	Date of last imaging before missed assessment
3d	Non-PD from imaging[1], more than one consecutive missed assessment, non-PD according to imaging after missed assessments	censored	Date of last non-PD imaging
4	New anti-cancer medication before progression or death	censored	Date of last imaging before new anti-cancer medication
5	Death before the scheduled date of first imaging	event	Date of death
6a	No imaging performed post-baseline, patient dies between first and second scheduled assessments	event	Date of death
6b	No imaging performed post-baseline, patient dies after second scheduled assessment	censored	Date of the start of study treatment
6c	No imaging performed post-baseline, vital status is unknown or patient known to be alive	censored	Date of the start of study treatment
7	Alive and not progressed from imaging (no missed assessments)	censored	Date of last imaging

[1] From the last assessment at which CR, PR or SD was assessed.

7.7 EXTENT OF EXPOSURE

Total treatment time (days and number of courses) will be calculated for each patient; off-drug periods due to non-compliance or toxicity prior to permanent discontinuation will be included as treatment time. In addition, the total treatment time will be summed over all patients and transformed to patient years. Standard descriptive summaries of these data will be provided for the treated set of patients.

Further summaries will also be produced:

- Treatment time (days) broken down by each dose level of study treatment (40 mg and 30 mg of afatinib with pembrolizumab).
- Number and proportion of patients on each dose level over time.
- Time to first dose reduction and duration (days) of off-drug periods prior to first dose reduction.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

The analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

The analyses will be based on BI standards. Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to CTCAE version 4.05.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences.
- 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).
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries'. (4)

For further details on summarization of AE data, please refer to (3, 4).

The analysis of AEs will include all events with onset in the on-treatment period (between treatment start date and (last date of trial medication + 30 days)) and residual effect period. Events occurring before first drug intake will be assigned to ‘screening', and all events occurring after the residual effect period will be assigned to ‘Post-study/follow-up’.

- An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by highest CTC grade (grade 3, 4, 5 and all grades to allow both cohorts to fit on one page), treatment, primary system organ class and preferred term (PT). Separate tables will be provided for patients with each of the following AE categories:

- AEs by treatment, highest CTCAE grade, using SOC and PT
- Drug related AEs, as assessed by investigators, by treatment, highest CTCAE, using SOC and PT
- AEs leading to dose reduction by treatment, highest CTCAE, using SOC and PT
- AEs leading to discontinuation of either study drug by treatment, highest CTCAE, using SOC and PT
- AEs leading to discontinuation of afatinib by treatment, highest CTCAE, using SOC and PT
- AEs leading to discontinuation of pembrolizumab by treatment, highest CTCAE, using SOC and PT
- Serious AEs by treatment, highest CTCAE, using SOC and PT
- Non-serious AEs by treatment, highest CTCAE, using SOC and PT
- Drug related serious AEs by treatment, highest CTCAE, using SOC and PT
- AEs leading to death by treatment, SOC and PT
- Other significant AEs using SOC and PT (see definition below)
- Protocol specified adverse events of special interest(discussed below)
- AEs of special search category (discussed below)

The system organ classes will be sorted according to the standard sort order specified by European Medicines Agency (EMA), preferred terms will be sorted by frequency (within system organ class).

Protocol defined adverse events of special interest

Some pre-defined AEs are considered to be of special interest (AESIs). The following are considered as AESIs:

- **Hepatic injury**

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
For patients with normal liver function (ALT, AST, bilirubin within normal limits) at baseline:

i) An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

For patients with abnormal liver function at baseline (AST and/or ALT>ULN)):

ii) An elevated AST or ALT lab value that is greater than or equal to 5X the upper limit of normal and an elevated total bilirubin lab value greater than or equal to 2X upper limit of normal measured in the same blood draw sample, with the exclusion of causes due to underlying diseases.

- **Dose Limiting Toxicities**

  Dose Limiting Toxicities (DLT) occurring during the first cycle in patients included in the safety run in will be considered protocol specified AESI. Please refer to section 5.2.5 in clinical trial protocol.

Separate summary tables will be reported for hepatic injury and dose limiting toxicity. A separate listings will be prepared for patients who are identified as having experienced any of the following AEs.

AEs of special search category

A separate summary and listing will be reported for "AEs of special search category".

Identification will be based upon modified MedDRA SMQ and HLT groupings. Details of AESI are provided in table 7.8.1: 1.

Table 7.8.1: 1 Adverse event of special search category

Search Category	Search criterion
1. Diarrhoea	- PT Diarrhoea - PT Diarrhoea in association with PT dehydration - PT Diarrhoea in association with SMQ (broad) Acute renal failure
2. Skin toxicity, including rash/acne	**2.1. Severe skin reactions** - SMQ (narrow) Severe cutaneous adverse reactions

Table 7.8.1: 1 Adverse event of special search category (Contd.)

Search Category	Search criterion
Skin toxicity, including rash/acne (contd.)	**2.2. Rash/acne (contd.)** - PT Acne - PT Acne conglobata - PT Acne cystic - PT Acne fulminans - PT Acne infantileTria - PT Acne pustular - PT Acne varioliformis - PT Dermatitis acneiform
Skin toxicity, including rash/acne (contd.)	- PT Blister - PT Dermatitis - PT Dermatitis bullous - PT Dermatitis exfoliative - PT Dermatitis exfoliative generalised - PT Dermatosis - PT Drug eruption - PT Eczema
Skin toxicity, including rash/acne (contd.)	- PT Epidermal necrosis - PT Erythema - PT Exfoliative rash - PT Folliculitis - PT Generalised erythema - PT Mucocutaneous rash - PT Oedema blister
Skin toxicity, including rash/acne (contd.)	- PT Rash - PT Rash erythematous - PT Rash follicular - PT Rash generalised - PT Rash macular - PT Rash maculo-papular - PT Rash maculovesicular - PT Rash morbilliform - PT Rash papular - PT Rash papulosquamous - PT Rash pruritic
Skin toxicity, including rash/acne (contd.)	- PT Rash pustular - PT Rash rubelliform - PT Rash scarlatiniform - PT Rash vesicular - PT Skin disorder - PT Skin erosion - PT Skin exfoliation - PT Skin fissures
Skin toxicity, including rash/acne	- PT Skin induration - PT Skin irritation - PT Skin lesion - PT Skin necrosis - PT Skin reaction - PT Skin swelling - PT Skin toxicity - PT Skin ulcer

Table 7.8.1: 1 Adverse event of special search category (Contd.)

Search Category	Search criterion
3. Pneumonitis / ILD like events	- SMQ (broad) for Interstitial lung disease
4. Hepatic impairment	- SMQ (Broad) Liver related investigations, signs and symptoms - SMQ (Broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions - SMQ (Broad) Hepatitis, non-infectious - SMQ (Broad) Cholestasis and jaundice of hepatic origin
5. Paronychia	- PT Nail bed infection - PT Nail infection - PT Paronychia
6. Pyrexia	- PT Pyrexia - PT Body temperature increased - PT Hyperthermia

Other significant AEs

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.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). CTCAE version 4.05 grades will be applied to laboratory parameters using the current BI oncology standard as detailed in the document 'Conversion of laboratory parameters to CTCAE grades within BI' (5).

Primary laboratory tests are defined as:

Table 7.8.2: 1 List of laboratory tests

Category	Parameters
Hematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, reticulocytes, white blood cell count (WBC) with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalised Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Electrolytes	Sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO3)
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea (preferred) or blood urea nitrogen (BUN), creatinine; creatinine clearance at screening
Pancreatic function parameters	Amylase, Lipase
Other	Glucose, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatine phosphokinase (CPK)
Urinalysis	pH, protein, glucose, blood, leucocytes, nitrite; in case of pathological finding further evaluation should be performed and results documented
Pregnancy test	β -HCG testing in urine or serum in women of childbearing potential (WOCBP)
Thyroid function testing	Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4), Thyroid stimulating hormone (TSH)

The following analyses will be presented for the primary laboratory tests:

- Descriptive statistics at each planned assessment.
- Frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment.
- Frequency of patients with possible clinically significant abnormalities.

Possible clinically significant abnormalities are defined as CTCAE grade of 2 or greater, with an increase of at least one grade from baseline.

Frequency and time of onset of liver enzyme elevations will be tabulated. Additional, more in-depth analyses will be performed as needed. These analyses will examine the influence of extent of exposure and time to event onset.

Note: **Section 5.2.3** in protocol has detailed list of lab parameters which will be summarized beside important lab parameter mentioned above.

7.8.3 Vital signs

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

7.8.4 ECG

ECG data will be collected as described in CTP section 5.2.4. Clinically significant findings in ECG data will be reported under “Adverse events” if applicable and will be analysed accordingly.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D et al.: New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247 [R09-0262].
3	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4	*001-MCG-156:* "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5	BI Guidance document “Conversion of laboratory values to CTCAE grades within Boehringer Ingelheim”.
6	*001-MCG-157:* "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
7	*001-MCG-159:* “Reporting of Clinical Trials and Project Summaries”, current version; IDEA for CON.
8	*001-MCG-159_RD-03:* “Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)”, current version; IDEA for CON.
9	Bohnsack O, Ludajic K, Hoos A. “Adaptation of the immune-related response criteria: irRECIST. 39th Ann Cong of the European Society for Medical Oncology (ESMO)”, Madrid, 26 - 30 Sep 2014 (Poster)

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final V1.0	14-May-19		None	This is the final TSAP without any modification