TRIAL STATISTICAL ANALYSIS PLAN

c38727127-02

BI Trial No.:	1381.2
Title:	An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumours Including Protocol Amendment 8
Investigational Products:	BI 754111 and BI 754091
Responsible trial statistician:	[redacted] Phone: [redacted]
Date of statistical analysis plan:	18 APR 2022 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ATC	Anatomical Therapeutic Chemical
AE	Adverse event
BLRM	Bayesian logistic regression model
BOR	Best overall response
CR	Complete Response
CTC	Common Terminology Criteria
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data base lock
DC	Dendritic Cells
DLT	Dose limiting toxicity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
EMA	European Medicines Agency
EOT	End of treatment
ICH	International Conference on Harmonization
irAE	Immune-related Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum tolerated dose
O*C	Oracle Clinical
OR	Overall response
PK	Pharmacokinetics
PSTAT	Project Statistician
PT	Preferred term
PD	Progression of disease
PD	Protocol deviation
Q1	Lower quartile
Q3	Upper quartile
(i)RECIST	(immuntherapeutics) Response Evaluation Criteria in Solid Tumours
RPM	Report planning meeting
SA	Statistical analysis
SD	Stable Disease
StD	Standard deviation
SMQ	Standardized MedDRA query
SOC	System organ class
TESS	Treatment emergent signs and symptoms
ToC	Table of contents
TMW	Trial Medical Writer

TS	Treated Set
TSAP	Trial statistical analysis plan
WHO	World Health Organization

3. INTRODUCTION

As per ICH E9 [1], 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., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

Phoenix TM WinNonlin® version 8.1 will be used for PK analyses. SAS® Version 9.4 or a newer version will be used for PK and all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

NA

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary endpoint of Part I (dose escalation) of the trial is the:

- Maximum tolerated dose (MTD) of the BI 754111 plus BI 754091 combination
- Number of patients experiencing Dose Limiting Toxicities (DLTs) during the combination MTD evaluation period (first cycle of BI 754111 plus BI 754091 combination therapy) in patients with solid tumours.

The primary endpoint of Part II (dose expansion cohorts) of the trial is:

- Confirmed objective Response (OR), defined as the best overall response of confirmed complete response (CR) or partial response (PR) according to RECIST v. 1.1 assessed by the Investigator, where the best overall response is the best time point response recorded from the first administration of BI 754091 until the earliest of disease progression according to RECIST v1.1, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow- up or withdrawal of consent.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

No key secondary endpoints specified in CTP

5.2.2 Secondary endpoints

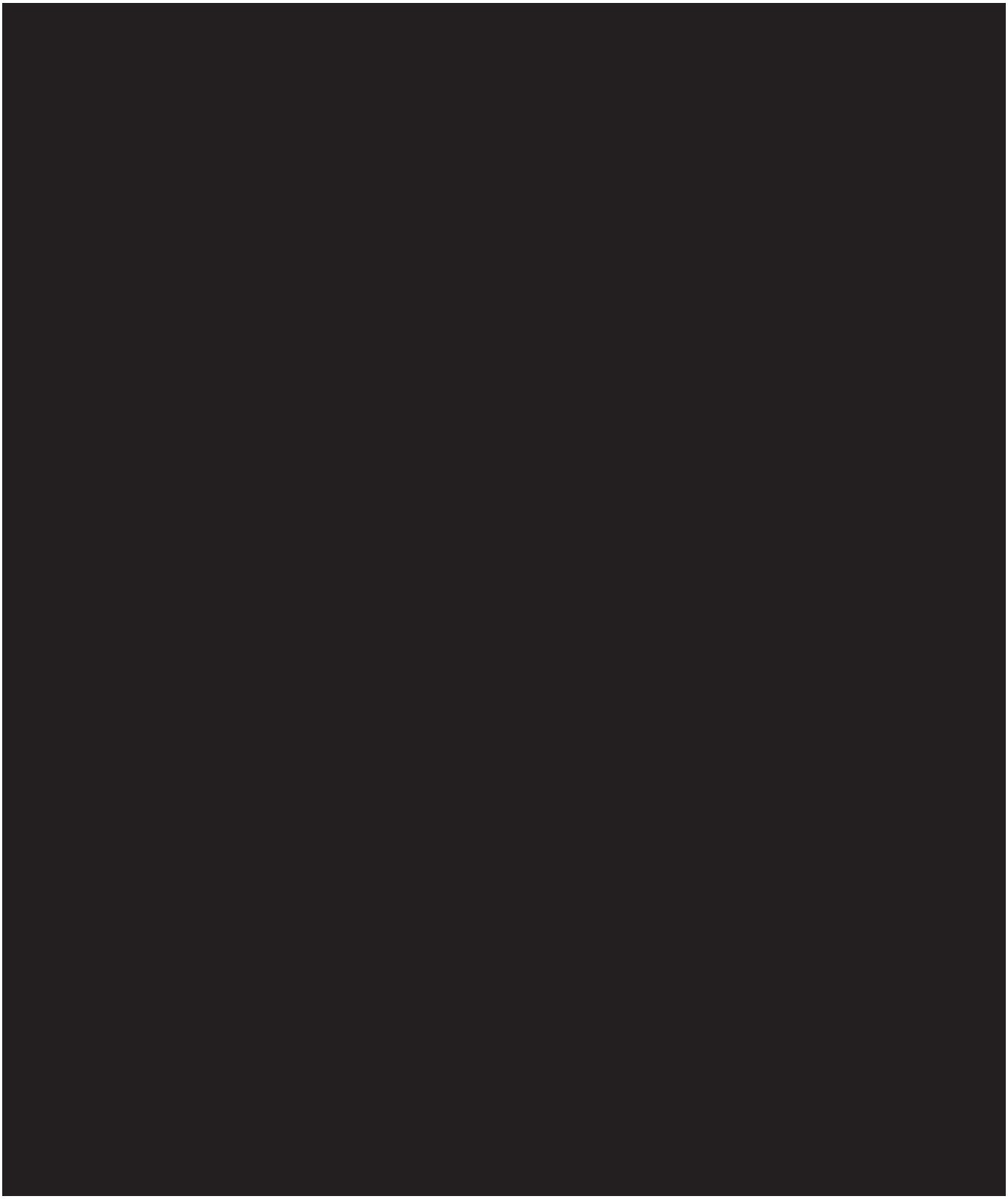
The secondary endpoints of Part I (dose escalation) of the trial are the following:

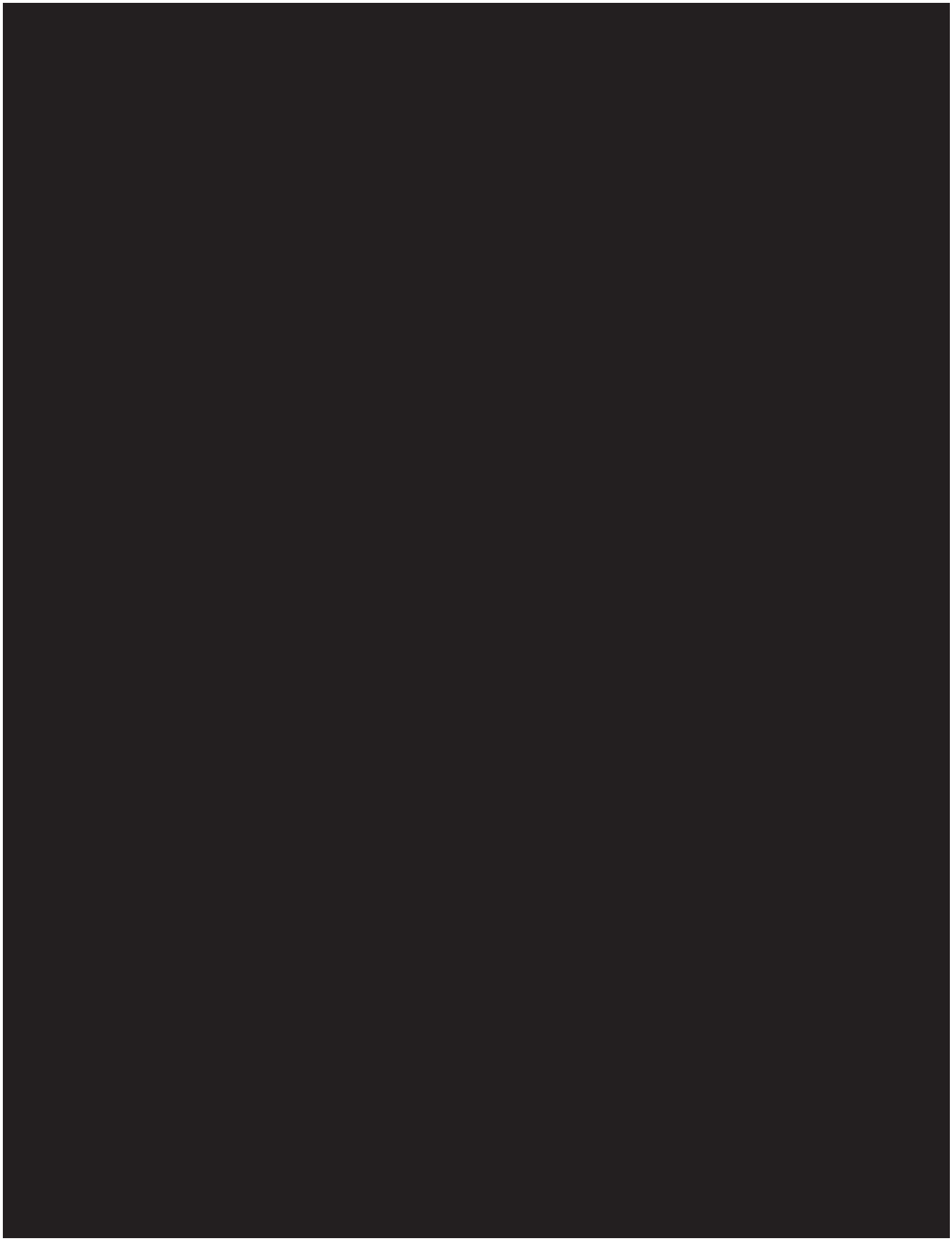
- PK parameters to be calculated for BI 754111 after single and multiple doses of BI 754111 in combination with BI 754091, and also for BI 754091 after single and multiple doses of combination therapy include:
  - C_{max}: maximum measured concentration of BI 754111/ BI 754091 in plasma
  - AUC_{0-504}: area under the concentration-time curve of BI 754111 / BI 754091 in plasma over the time interval from 0 to 504 hours
- Number of patients experiencing DLTs from start of treatment until end of treatment (in all cycles)
- OR for patients with solid tumours: confirmed CR and PR according to RECIST Version 1.1 as assessed by the Investigator until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow- up or withdrawal of consent.

The secondary endpoints of Part II (dose expansion) of the trial are the following:

- Duration of response is the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD, up until anti-cancer therapy, or death
- Disease control (CR, PR, or SD according to RECIST Version 1.1) as assessed by the Investigator

- Progression-free survival (PFS) is the duration from the date of first treatment to the date of PD, up until anti-cancer therapy, or death
- Number of patients experiencing DLTs from start of treatment until end of treatment





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In this Phase I trial, treatments are not randomized. Different dose levels of BI 754091 / BI 754111 will arise in Part I and there is only one dose level in Part II.

For Part I, the initial trial medication (*i.e.* dose level) assigned at the beginning of the first treatment cycle will be used as label of the analysing treatment.

Table 6.1: 1 Definition of analyzing treatment periods for safety analysis

Analysing Treatment Period	**Start Date**	**Stop Date**
Screening	Date of informed consent	Date/Time of the first administration of trial treatment
On-treatment	Date/Time of the first administration of trial treatment	Date of the last administration of trial treatment + 30 days (residual effect period)
Follow-up	Date of the last administration of trial treatment + 31 days	Date of the last per protocol visit

Note: a 30-day residual effect period (REP) is defined for this trial.

For safety analyses, adverse events (AEs) will be classified to one of the following time periods: “Screening”, “On-treatment” or “Follow-up”. This will be applied for all adverse events. It is indicated in CTP Section 5.3.6.8.1 that the residual effect period of this trial is 30 days, and thus AE reported within 30 days of the last trial medication will be considered on treatment. Detailed rules for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤ AE onset date < date/time of first administration of BI 754091 or BI 754111, then the AE is assigned to “Screening”
- If date/time of first administration of BI 754091 or BI 754111 ≤ AE onset date ≤ date of last administration of BI 754091 or BI 754111 + 30 days, then the AE is assigned to “On-treatment”
- If AE onset date > date of last administration of BI 754091 or BI 754111 + 30 days, then the AE is assigned to “Follow-up”

6.2 IMPORTANT PROTOCOL DEVIATIONS

According to [2] important safety protocol deviations (PDs) are those that potentially affect the rights or safety of study subjects. Important protocol deviations (IPDs) are those that can potentially influence the primary outcome measure(s) for the respective patients in a way that is neither negligible nor in accordance with the study objectives.

No per protocol set is defined for this phase I trial, but patients with IPDs will be identified and reported in the clinical trial report (CTR). Potential IPDs are defined in Table 6.2: 1. The final list of IPDs will be confirmed at the last report planning meeting (RPM) before data base lock (DBL).

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A1.1	Patient < 18 years of age at the time of signature of ICF	Inclusion criterion (IN) 2 not met	None	Automatic
	A1.2	(Dose escalation part) Patients without a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours or any requirements of measureable disease / previous treatment status not met	IN 3 not met	None	Automatic
	A1.3	(Dose expansion part) Patients without measurable disease per RECIST v1.1 criteria, or without at least 1 tumour lesion amenable to biopsy, or not medically fit and willing to undergo a biopsy before first treatment and, unless clinically contraindicated, after 6 weeks on therapy, or with any of the other cohort-specific requirements not met	IN 4 not met	None	Automatic
	A1.4	ECOG score > 1	IN 5 not met	None	Automatic
	A1.5	Women of child-bearing potential and men able to father a child must be ready and able to use highly effective methods of birth control.	IN 7 not met	None	Automatic
	A2	**Exclusion criteria not met**			
	A2.1	Major surgery performed within 12 weeks prior to first trial treatment or planned within 12 months after screening	Exclusion criterion (EX) 1 met	None	Automatic

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
	A2.2	Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	EX 2 met	None	Automatic
	A2.3	Previous enrolment in this trial	EX 3 met	None	Automatic
	A2.4	Use of investigational or anti-tumour treatment within 4 weeks or 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment	EX 4 met	None	Automatic
	A2.5	Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with exception of alopecia and Grade 2 neuropathy due to prior platinum-based therapy	EX 5 met	None	Automatic
	A2.6	Prior treatment with anti-LAG-3 agents	EX 6 met	None	Automatic
	A2.7	Patients with NSCLC that has epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements	EX 7 met	None	Automatic
	A2.8	Presence of other active invasive cancers others than the one treated in this trial, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma *in situ* of the cervix, or other local tumours considered cured by local treatment	EX 8 met	None	Automatic
	A2.9	Untreated brain metastasis(es) that may be considered active	EX 9 met	None	Automatic
	A2.10	Inadequate organ function or bone marrow reserve as demonstrated by the laboratory values in CTP Table 3.3.3:1	EX 10 met	None	Automatic
	A2.11	Any of the following cardiac criteria specified in CTP Exclusion criterion 11	EX 11 met	None	Automatic

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
	A2.12	History of pneumonitis with in the last 5 years	EX 12 met	None	Automatic
	A2.13	History of severe hypersensitivity reactions to other mAbs	EX 13 met	None	Automatic
	A2.14	Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment	EX 14 met	None	Automatic
	A2.15	Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy	EX 15 met	None	Automatic
	A2.16	Active infection requiring systemic treatment at start of treatment in this trial	EX 16 met	None	Automatic
	A2.17	Known history of human immunodeficiency virus infection or active hepatitis B or C virus infection	EX 17 met	None	Automatic
	A2.18	Interstitial lung disease	EX 18 met	None	Automatic
B		**Informed consent**			
	B1	Informed consent not available/not done	Inclusion criteria 1 not met	Treated Set	Automatic
	B2	Informed consent too late	Informed consent obtained later than the initiation of treatment	None	Automatic
C		**Trial medication**			
	C1.1	Non-compliance with BI 754091 or BI 754111 per protocol	Incorrect trial medication dose taken or wrong dose schedule; (infusion time, program) decision at MQRM	None	Automatic and manual
	C1.2	Discontinuation of trial medication not following the protocol	Decision at MQRM	None	Automatic and manual
D		**Concomitant medication**			
	D1.1	Prohibited medication use	Review concomitant medications for prohibited medication use; also refer to Section 4.2.2.2 of the protocol	None	Manual
E		**Study Specific**			
	E1	Incorrect study procedures performed.	Any deviation from protocol not defined above deemed important to document in study report by trial team.	TBD	Manual

Note: MQRM – Medical and Quality Review Meeting; TBD – to be determined

6.3 SUBJECT SETS ANALYSED

Screened Set:
This patient set includes all patients who have signed the informed consent. The screened set will be used for patient disposition tables.

Treated Set (TS):
This patient set includes all patients who were documented to have received at least one dose of BI 754091 or BI 754111. The TS is used for both efficacy analysis, safety analyses and biomarker analysis.

MTD set:
This patient set includes all patients enrolled in Part I who were not replaced within the MTD evaluation period. Patients who were replaced during the MTD evaluation period will not be considered for MTD determination.

PK Analysis Set (PKS):
This patient set includes all patients in the TS who provide at least one evaluable observation for at least one PK endpoint and no PK relevant protocol violation. PKS will be used for all pharmacokinetic analyses.

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No imputation will be performed on missing efficacy data. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs, with particular emphasis on potential DLTs.

Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) [3].

Missing data and outliers of PK data are handled according to Boehringer internal SOPs.

In general, missing data not discussed in (3) and BI standards will not be imputed unless required for the following analyses and definitions. Then the rules as described below apply.

1) **Partial date for Time from First Diagnosis**

   If date is partial, which is allowed, then imputation will be based on below logic:

   - if missing day, then imputation will use the first day of the month;

- if missing both day and month then imputation will use January 1st ;
- if missing completely, then report to DM for querying the site. If the date is completely missing at the site, no imputation will be made.

2) Partial Start Dates of Duration of Chemotherapy or Prior Radiation

- If day is missing, then imputation will use the first day of the month;
- If month and day are missing, imputation will use January 1st.

3) Partial End Dates of Duration of Chemotherapy or Prior Radiation

- If day is missing, then imputation will use the later of last day of the month and the available start date;
- If month and day are missing, imputation will use the later of last day of the year and the available start date**.**

4) Partial or missing start date of subsequent anti-cancer therapy/subsequent radiotherapy

If the day of the start date of subsequent systemic therapy/subsequent radiotherapy is missing, then the 1st of the month will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed.

If day and month, or day and month and year are missing, it will be distinguished whether the start date of subsequent systemic therapy/subsequent radiotherapy is required for censoring of PFS or for other descriptive statistics:

- <u>For censoring of PFS or DoR:</u> If only the year is reported, the 1st of January of this year will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed. In case of a completely missing start date of subsequent anti-cancer therapy/subsequent radiotherapy and the patient did not have any post-baseline tumour assessment or did not progress or die, the PFS of this patient will be censored at the day of first administration of BI 754091 or BI 754111. Additionally, all imputed start dates of subsequent anti-cancer therapy/subsequent radiotherapy should be before the death date, if available.
- <u>For descriptive statistics:</u> Dates will not be imputed if more than only the day of the date is missing.

5) Partial death date / end of study date

If the day of the death/end of study date is missing, then the 1st of the month will be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified baseline is defined as the time point closest to but prior to the first administration of any study medication. If no time is specified and the date is the same as the first administration date, then it will still be considered baseline if not specified otherwise. If there is no measurement earlier than the first administration of study medication, then no baseline will be derived.
Study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be 'Day -1' and the day of first administration of study drug will be 'Day 1'; therefore 'Day 0' will not exist.

Imaging time windows:
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.

For the presentation of tumour response data which will follow a calculated visit approach based on the protocol specified tumour imaging schedule. Imaging will be performed at screening and every 6 weeks after BI 754091 infusion (i.e. Week 6, 12, 18 …etc.), then every 9 weeks after 6 months of treatment; image data will be slotted to Week 6, 12, 18 etc. based on their relative day (from start of treatment) and using a ±3 week window (images taken in the first 3 weeks from start of treatment will be assigned to Week 6). If two or more images for a patient are assigned to one interval then the last assessment will be used to ensure progressive disease is not missed.
In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point (i.e. Week 6, 12, 18 … etc.) will be assigned to each and every image. This is achieved by creating windows for every radiological response assessment. These windows are defined in Table 6.7: 1.

Table 6.7: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study medication)	**Due date of scans (days)***	**Window (days)**
6	43	1 to ≤ 64
12	85	65 to ≤ 106
18	127	107 to ≤ 148
24	169	149 to ≤ 200

* The date of the first dose of study medication is Day 1

Table 6.7: 2 Nominal time points and windows for imaging (cont.)

Nominal time point (weeks from start of study medication)	**Due date of scans (days)***	**Window (days)**
33	232	201 to ≤ 263
42	295	264 to ≤ 326
51	358	327 to ≤ 389
Etc., 9 week interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

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.

Laboratory values:
Baseline is defined as the latest time point before the very first administration of any study medication. For laboratories where not only the examination date but also time are recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first administration of study medication is considered as baseline value if and only if the time of laboratory assessment is before or the same as the time of first study drug administration.

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

Laboratory time windows:
Time windows and visits will be calculated to determine the planned day of laboratory assessment, based on the protocol-specified laboratory assessment schedule.

For the presentation of a descriptive summary analysis over time for a laboratory parameter the laboratory data will be displayed by calculated visit instead of actual visit reported to ensure a common handling of all laboratory assessments and to account for unscheduled visits representing a repeated laboratory measurement. As Phase Ia and Phase Ib have a different laboratory assessment schedule, the time windows for the calculated visits will be different for Phase Ia and Phase Ib.

Table 6.7: 2 Calculated visits, nominal time points and windows for laboratory assessments in Phase Ia

Calculated visit	**Nominal time point (day from start of study medication)***	**Window (days)**
Cycle 1 Day 1	1	1 to ≤ 4
Cycle 1 Day 8	8	5 to ≤ 11
Cycle 1 Day 15	15	12 to ≤ 18
Cycel 2 Day 1	22	19 to ≤ 32
Cycle 3 Day 1	43	33 to ≤ 53
Cycle 4 Day 1	64	54 to ≤ 74
Etc., 21 days interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

Table 6.7: 3 Calculated visits, nominal time points and windows for laboratory assessments in Phase Ia

Calculated visit	**Nominal time point (days from start of study medication)***	**Window (days)**
Cycle 1 Day 1	1	1 to ≤ 11
Cycel 2 Day 1	22	12 to ≤ 32
Cycle 3 Day 1	43	33 to ≤ 53
Cycle 4 Day 1	64	54 to ≤ 74
Cycel 5 Day 1	85	75 to ≤ 95
Cycle 6 Day 1	106	96 to ≤ 116
Cycle 7 Day 1	127	117 to ≤ 137
Cycel 8 Day 1	148	138 to ≤ 158
Cycle 9 Day 1	169	159 to ≤ 179
Cycle 12 Day 1	232	180 to ≤ 1263
Cycel 15 Day 1	295	264 to ≤ 326
Cycle 18 Day 1	358	327 to ≤ 389
Etc., 21 days interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

Biomarker time windows:
The time windows used for biomarker analysis are defined as follows.

Cytokine / flow cytometry:

C1D1 (BL): before 1st treatment (1T)
C1D2: 24h post 1T +/-18 h
C1D8: 168 h post 1T +/- 48 h
C1D15: 336 h post 1T +/- 48 h

C2D1: before 2nd treatment (2T) -24 h
C2D2: 24h post 2T +/-18 h
C2D8: 168h post 2T +/- 48 h

C3D1: before 3rd treatment (3T) -24 h

C4D1: before 4th treatment (4T) -24 h
C4D2: 24h post 4T +/-18 h
C4D8: 168h post 4T +/- 48 h

C5D1: before 5th treatment (5T) -24 h

Biopsies (Immunohistochemistry, RNAseq):

C1D1: before 1st treatment (1T)
C3D1: 1008 h post 1st Treatment +/- 168 h

7. PLANNED ANALYSIS

For End-Of-Text 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.

For time-to-event analysis tables the set of statistics is: number of patients [N(%)], number of patients with event [N(%)], <time to event> [months] followed by P25 (25^{th} percentile), median, P75 (75^{th} percentile) and number of patients censored [N(%)]. If not specified otherwise the duration as well as the 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 (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). 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

Descriptive statistics are planned for demographic characteristics, disease history, prior therapies, medical history, alcohol and tobacco use, baseline ECOG PS, and baseline disease assessment.

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 (CTs) will be coded according to World Health Organization (WHO) Drug Dictionary (actual version). CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorize 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 3 category will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Not applicable in this study.

7.4 PRIMARY ENDPOINTS

In order to identify the MTD and the recommended dose for Part II, the number of patients with DLTs at each dose level during Part I (first three weeks) must be presented. Patients who discontinue during the first treatment course for reasons other than a DLT will be excluded from the determination of the MTD.

The analysis of the MTD is based on a BLRM guided by the escalation with overdose control principle. The MTD is defined as the highest dose for a given schedule that is expected to cause less than 25% risk of the true DLT rate being above or equal to 33% during the MTD evaluation period. Estimation of the MTD during the dose escalation phase of the study will be based upon the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients. The model to be used is specified in CTP Section 7.

In addition, the number of patients with DLTs that occurred during Part I and Part II will be summarized at each dose level. The BLRM will be rerun to re-evaluate the MTD and RP2D together with all relevant data collected during Part II.

For Part II, OR according to RECIST Version 1.1 will be summarized descriptively with exact 95% Clopper-Pearson CIs. Response data collected after the EOT, after PD, or the start of subsequent anti-cancer therapy will not be used. This applies to other endpoints based on the response data. Confirmed best overall response (BOR) will be derived according to the following derivation rules:

Table 7.4: 1 Details of confirmed best overall response derivation rules

Overall response (time point 1)	Overall response (>=28 days from time point 1)	Confirmed BOR
CR	CR	CR
CR	PD	SD as long as >=39 days, otherwise, PD
CR	NE/Missing	SD as long as >=39 days, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD as long as >=39 days, otherwise, PD
PR	PD	SD as long as >=39 days, otherwise, PD
PR/SD	NE/Missing	SD as long as >=39 days, otherwise, NE

NE: not evaluable

- If CR or PR: Look at all subsequent visits, if there is another CR or PR >=28 days and no more than one missing visit (defined by time window Table 6.7.1) in between then the patient has a confirmed response. If there is not another CR or PR >=28 days and/or more than one missing visit between the two responses, then the patient can be a confirmed SD if the CR or PR is >=39 days from start of combination therapy.
- If SD: To be confirmed SD, the measurement must have been taken >=39 days from start of combination therapy (only one reading is necessary).
- Additional details are provided in Table 7.4: 1.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Other secondary endpoints

7.5.2.1 Other secondary endpoints in Part I

PK parameters evaluated after the single and after multiple administrations of BI 754111 in combination with BI 754091, and also for BI 754091 after single and multiple doses of combination therapy

The PK parameters will be evaluated using noncompartmental analysis methods according to 001-MCS-36-476 [4]. Tables and figures for concentration values and PK parameters will be created according to Boehringer internal SOPs.

Descriptive statistics will be calculated for all concentration time points and PK parameters. The following descriptive statistics will be calculated for BI 754111 and BI 754091 concentrations and for PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, tenth percentile (P10), Q1, Q3, ninetieth percentile (P90), arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation.

Treated and evaluable patients will be included in the PK analysis. A patient is considered not evaluable if the patient had an important protocol violation relevant to the evaluation of PK or had insufficient PK data. Non evaluable patients will be listed with their individual PK parameters, but such data will not be included when calculating descriptive statistics. If the data suggest a PK / PD relationship of special parameters (e.g. PK vs. RO), a detailed analysis may be performed and documented in a separate report.

Number of patients experiencing DLTs from the start of treatment until end of treatment

Number of patients with DLT(s) which occurred during the entire treatment period will be summarized for each dose cohort.

OR for patients with solid tumors according to RECIST Version 1.1 as assessed by the investigator

OR will be summarized descriptively with exact 95% Clopper-Pearson CIs.

7.5.2.2 Other secondary endpoints in Part II

Duration of response according to RECIST Version 1.1 as assessed by the Investigator

Duration of response is defined as the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD, up until anti-cancer therapy, or death. Duration of response will be provided in a listing.

Duration of OR according to RECIST v1.1:

Duration of OR can only be calculated for patients with OR.
For patients with disease progression or death:

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

For patients without disease progression or death:

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

Censoring rules and applicable dates of outcome for duration of OR according to RECIST v1.1 are specified in Table 7.5.2.2:1

Table 7.5.2.2:1 Censoring rules for duration of objective response according to RECIST v1.1

Situation	**Outcome (event or censored)**	**Date of outcome**
No other anti-cancer therapy		
Alive and not progressed according to RECIST v1.1, no missed radiological assessment window*	Censored	Date of last radiological assessment
Alive and not progressed according to RECIST v1.1, one or more consecutively missed radiological assessment window*	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed according to RECIST v1.1, no missed radiological assessment window* prior to progression	Event	Date of radiological assessment of progression
Progressed according to RECIST v1.1, one or more consecutively missed radiological assessment window* prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression according to RECIST v1.1, no missed radiological assessment window* prior to death	Event	Date of death

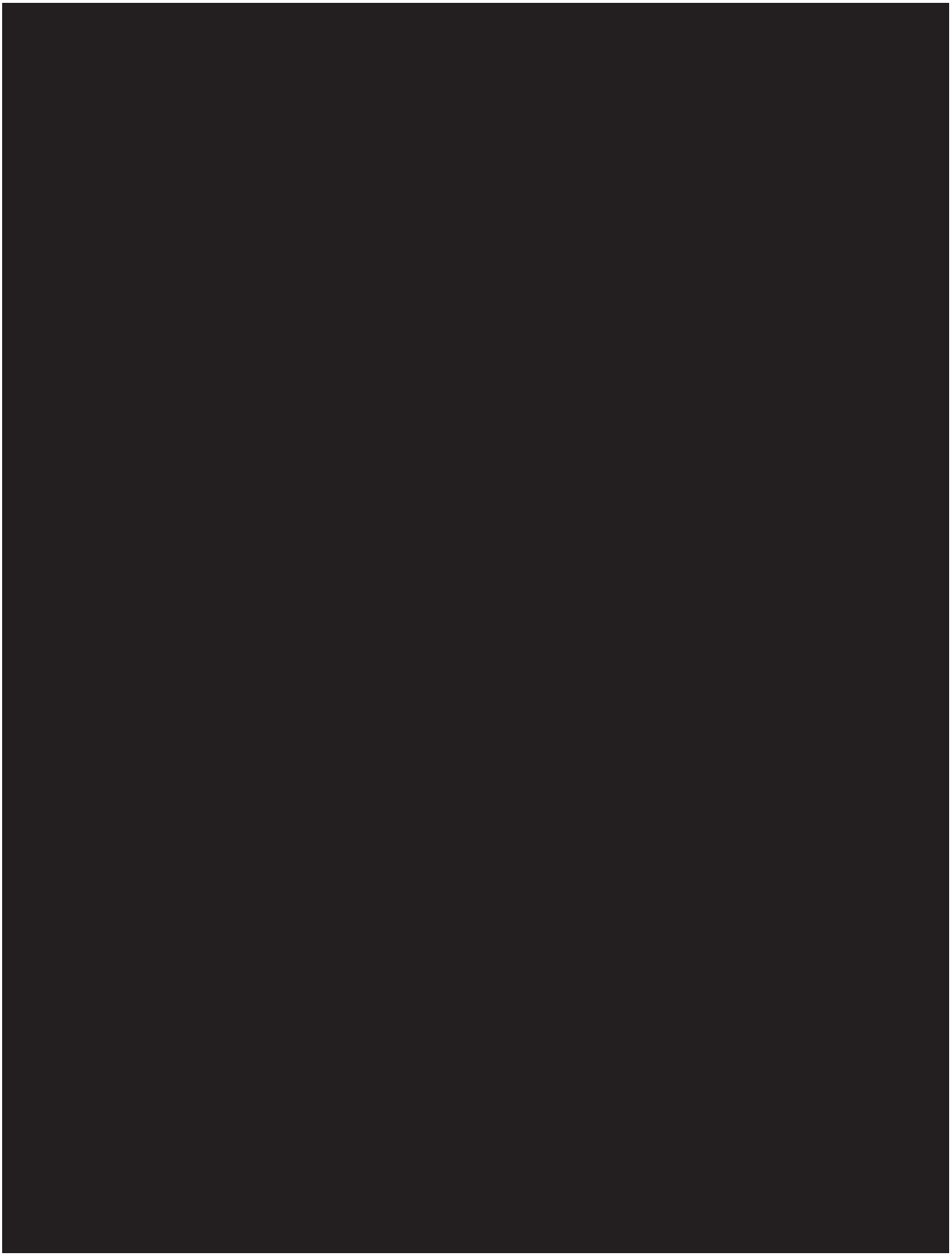
Table 7.5.2.2:1 Censoring rules for duration of objective response according to RECIST v1.1 (cont.)

Situation	Outcome (event or censored)	Date of outcome
Death without progression according to RECIST v1.1, but one or more consecutively missed radiological assessment window* 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 according to RECIST v1.1 or death, no missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

[redacted]

Censoring rules and applicable dates of outcome for duration of OR according to RECIST v1.1 are specified in Table 7.5.2.2:2.

[redacted]



Disease control according to RECIST Version 1.1 as assessed by the Investigator

Disease control is defined as a BOR of CR, PR or SD. Disease control rates will be presented with exact 95% Clopper-Pearson CIs.

PFS

[redacted]

PFS [days] = date of outcome – date of first administration of any trial medication + 1.
A patient has an evaluable response assessment if CR, PR, stable disease (SD), or progressive disease (PD) according to RECIST v1.1 has been assigned by the investigator. PFS will be summarized descriptively by quartiles with 95% confidence interval (based on the Greenwood's method) calculated from Kaplan-Meier estimate. Kaplan-Meier plots will also be produced. Rules to determine censoring, PFS events and applicable dates of outcome are specified in Table 7.5.2.2: 3 below.

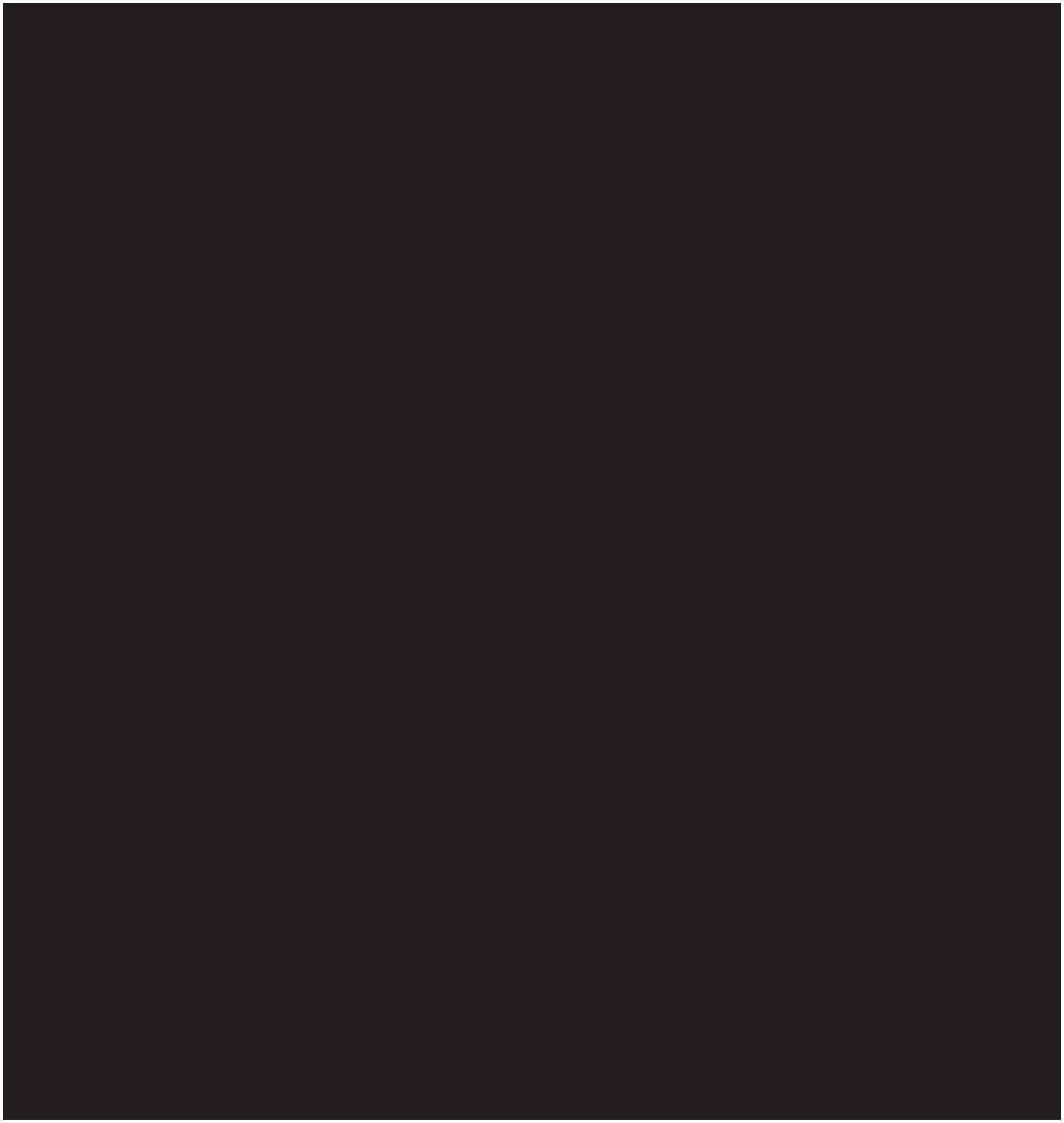
If patients would have their radiological examinations over a number of days, (*i.e.* target lesions assessed on day x, non-target lesions assessed on day y and new lesion (if applicable) on day z), the earliest date of the multiple assessments should be considered.

Table 7.5.2.2:3 Censoring rules for progression-free survival according to RECIST v1.1

Situation	**Outcome**	**Date of outcome**
No baseline radiological assessment		
Patient with death on or before first planned post-baseline radiological assessment (≤ Day 64)	Event	Date of death
Patient without death or patient with death after first planned post-baseline radiological assessment (> Day 64)	Censored	First treatment administration
Without post-baseline radiological assessments		
Vital status is unknown or patient is known to be alive	Censored	First treatment administration
Death prior to or on the first planned post-baseline radiological assessment (≤ Day 64)	Event	Date of death

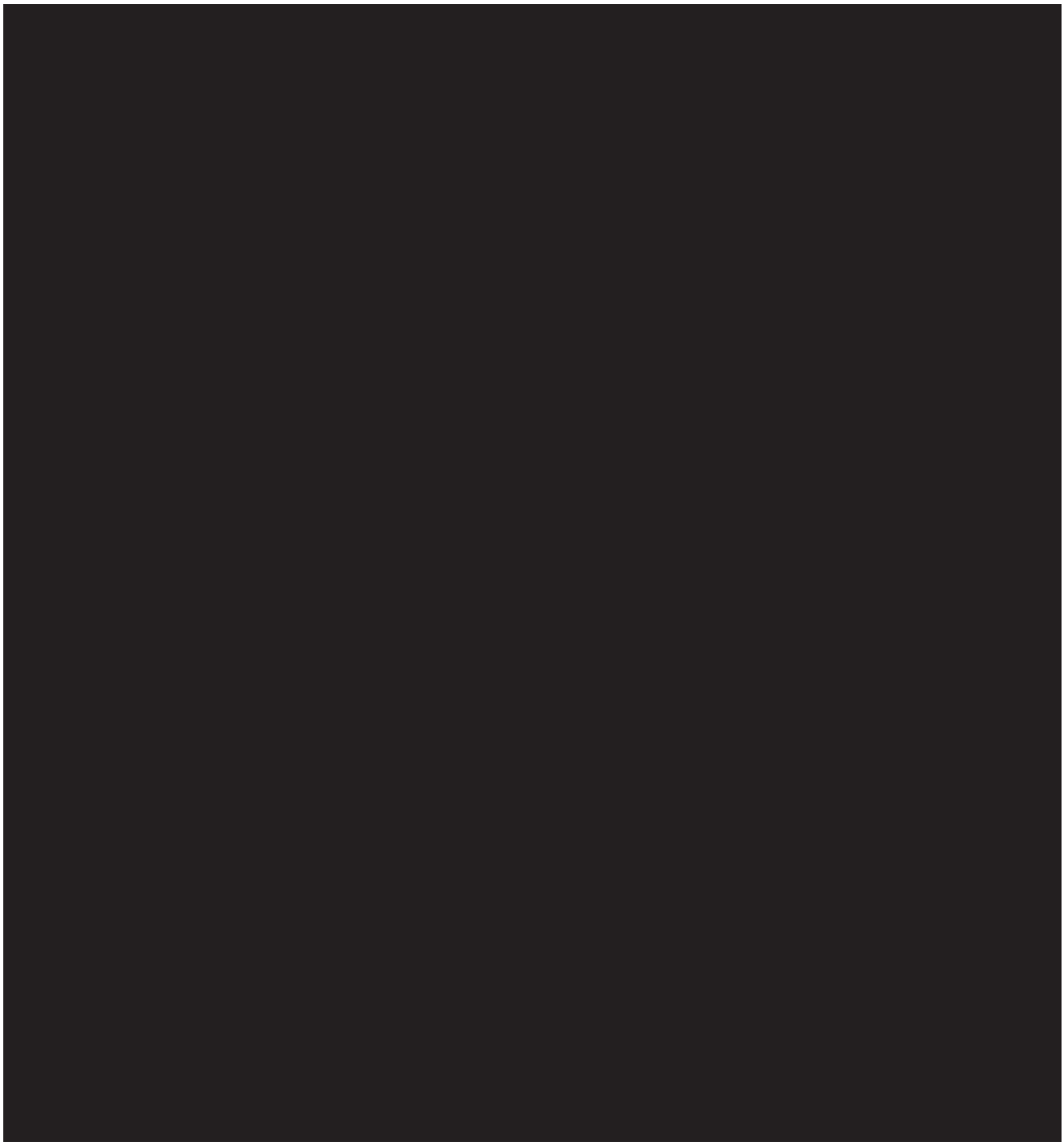
Situation	Outcome	Date of outcome
Death beyond the first planned post-baseline radiological assessment (> Day 64)	Censored	First treatment administration
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed	Censored	Date of last evaluable radiological assessment
Progressed, no missed radiological assessment window* prior to progression	Event	Date of radiological assessment of progression
Progressed, but one or more consecutively missed radiological assessment window* prior to progression	Censored	Date of last evaluable radiological assessment prior to missed assessment (or first treatment administration if no post-baseline assessment prior to missed assessment)
Death but no progression, no missed radiological assessment window* prior to death	Event	Date of death
Death without progression, but one or more consecutively missed radiological assessment window* prior to death	Censored	Date of last evaluable radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to death	Censored	First treatment administration

* Windows for radiological assessments are defined in Table 6.7: 1



Number of patients experiencing DLTs from start of treatment until end of treatment

Number of patients with DLT(s) which occurred during the entire treatment period will be summarized for each expansion cohort.



7.7 EXTENT OF EXPOSURE

The total number of cycles initiated and the numbers of cycle initiated will be summarized descriptively for each dose cohort. Results from Part I and Part II will be presented separately.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

Patients who were replaced within the MTD evaluation period will be excluded from the determination of the MTD but will be considered for all other safety evaluations.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs. The reporting and analyses of AEs will follow the BI guideline [5]. AEs will be coded with the most recent version of MedDRA®. The severity of AEs will be scaled according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Unless otherwise specified, the analysis of adverse events will be based on the concept of treatment emergent adverse events. For details on the treatment definition, see Section 6.1.

An overall summary of AEs will be presented with an additional entry for patients with DLT(s) and will also include the number of patients with AEs by the worst CTCAE grade.

The frequency of patients with AEs will be summarized by treatment, primary system organ class and/or preferred term, and will be sorted by the highest CTCAE grade. Separate tables will be provided for patients with:

- DLTs
- All adverse events
- Serious adverse events
- Drug-related AEs
- Drug-related serious AEs
- AEs leading to permanent discontinuation of trial treatment
- AEs leading to death
- Treatment emergent immune-related AEs (irAEs)
- irAEs through the whole trial
- Infusion-related AEs

The system organ classes will be sorted by frequency, and preferred terms will be sorted by frequency (within system organ class).

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards [6]. The same on-treatment period as considered for the analysis of adverse events will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in a new category “missing CTCAE grade at baseline” for those laboratory parameters where CTCAE grading is applicable. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE Version 5.0.

7.8.2.1 Analysis

The Laboratory tests will be classified into the following categories:

- Primary- full analysis
- Secondary- listing of possible clinically significant values
- Diagnostic- listing of all observed values
- Not analysed

The following outputs will be presented for primary laboratory tests:

- Descriptive statistics, including changes from baseline
- Frequency of patients with shifts from baseline
    - Shifts will be defined in terms of
        - CTCAE grades will be used for laboratory tests with CTCAE grades defined
        - The upper and lower reference limits will be used for laboratory tests without CTCAE grades
- Frequency of patients with possible clinically significant abnormalities (definitions see Section 7.8.2.2)

The analysis of secondary laboratory tests will be limited to tabulation of the frequency of patients with possible clinically significant abnormalities (definitions see Section 7.8.2.2).

Laboratory tests classified as “diagnostic” are recorded as a follow-up to abnormalities of associated lab tests for diagnostic purposes i.e. amylase and lipase would be measured to investigate possible pancreatitis. These values will be presented in a separate listing. No other analyses will be performed

Analyses of descriptive statistics should use normalized lab values and will be displayed by calculated visit instead of actual visit reported to ensure a common handling of all laboratory assessments and to account for unscheduled visits representing a repeated laboratory measurement (see Table 6.7: 2 and Table 6.7: 3).

Analyses of frequencies of patients with potential clinical significance, analyses of shift, and liver function categories tables should use converted values.

Baseline for safety laboratory parameters will be the last available measurement before the start of study drug. Laboratory measurements taken up to 30 days after the last administration of study drug will be considered as on-treatment.

Primary laboratory test results will be presented in CTR section 15.
Laboratory test that are not analysed will be listed in Appendix 16.2.8.

Handling of CTCAE grade -1 and -9 laboratory parameters:
Generally, in case only one direction of worsening (high or low laboratory value) is specified in the CTCAE document, there is no need to examine the other direction. Therefore, for calculating the change in CTCAE grade, patients with a CTCAE grade of -9 (no CTCAE grade defined) will be automatically treated as CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as -9.
There are certain parameters for which CTCAE grades can only be differentiated by taking physiological consequences into account. These laboratory values will be coded as -1. As these definitions aggregate laboratory data and adverse events or concomitant therapies no analyses based on CTCAE grades will be done. Instead standard laboratory analyses as for laboratory parameters without CTCAE grade definitions will be done.

Corrected calcium:
The grading of hypocalcemia is based on corrected calcium as calcium can be falsely low if hypoalbuminemia is present. The following corrective calculation will be performed:

Corrected calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) - 4g/dL]

No correction of the reference range has to be done. The reported reference range of total calcium will be used for analyses.
Corrected calcium can be only derived at a certain time point in case both laboratory values total calcium and albumin have been reported for the patient in the same laboratory sample.

Differential blood count:
Differential blood counts were to be measured in absolute values according to the CTP. In case a subject's differential blood count is reported in percentage, the following conversion will be applied:

Differential [10^9/L] = Differential [%] * (White blood cell count value / 100)
The corresponding reference ranges of the converted differential blood values are not allowed to be converted like the individual laboratory measurements. The reference range is taken from the BI standard reference range definition.

Liver Function tests and potential Hy's Law
A listing of all liver function tests will be provided for all patients who meet the following criteria at any time:

- ALT or AST ≥3xULN and elevation of total bilirubin ≥2xULN at within +/- 30 days

In addition, tables of liver function test abnormalities will be produced.

7.8.2.2 Classification of laboratory tests

Table 7.8.2.2: 1 Primary Laboratory tests[1]

Label	Lab test name	Direction of interest	Potential Clinical significance rule
ALKP	Alkaline Phosphatase	High	CTCAE Grade 2 or higher[4]
BILI	Total Bilirubin	High	CTCAE Grade 2 or higher[4]
BILDIR	Direct Bilirubin	High	CTCAE Grade 2 or higher[4] using grades defined for Total Bilirubin
CK	Creatinine Kinase	High	A[2,3]
CREJIDMS	Creatinine	High	>1.5xULN and >baseline ambiguous CTCAE not used[4]
FT3	Triiodothyronine, Free	Low[5], High[5]	<LLN and <baseline or >ULN and >baseline No CTCAE defined
FT4V	Thyroxine, Free	Low[5], High[5]	<LLN and <baseline or >ULN and >baseline No CTCAE defined
GLUB	Glucose	Low, High[5]	Low: A[2,3] High: >10mmol/L and > baseline No CTCAE defined
HGB	Hemoglobin	Low	A[2,3] (listed in CTCAEv5 as "Anemia")
K	Potassium	Low[5], High	Low: < 3 mmol/L and <baseline High: A[2,3]
LDH	Lactate Dehydrogenase	High[5]	≥ 3xULN and > baseline No CTCAE defined
LYMABS	Lymphocytes	Low	A[2,3]
NA	Sodium	Low[5], High	High: A[2,3] Low: < 130mmol/L and < baseline
NEUABS	Neutrophils	Low	A[2,3]
PLTCT	Platelets	Low	A[2,3]
SGOT	Aspartate Aminotransferase	High	CTCAE Grade 2 or higher[4]
SGPT	Alanine Aminotransferase	High	CTCAE Grade 2 or higher[4]
TPONI	Troponin I	High[5]	>ULN and > baseline CTCAE based upon AE
TPONTULT	Troponin T	High[5]	>ULN and > baseline CTCAE based upon AE
TSH	Thyrotropin	Low[5], High[5]	<LLN and <baseline or >ULN and >baseline No CTCAE defined
UREAN	Blood Urea Nitrogen	High[5]	> 10 mmol/L and > baseline No CTCAE defined
WBC	Leukocytes	Low	A[2,3]

[1] Shift tables, descriptive statistics, and potential clinically significant values will be presented.

[2] A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[3] Separate shift tables for the low and high directions, when both directions are specified. Shift tables compare baseline vs. on-treatment CTCAE grades. CTCAE grading will not consider symptoms.
[4] CTCAE grades will not be defined for baseline values for ALKP, SGPT, SGOT, BILI (Total and Direct) and baseline and post-baseline values for CREJIDMS. Special categories are defined for shift tables.
[5] Separate shift tables for the low and high directions, when both directions are specified. Shift tables compare baseline vs. on-treatment using the three categories 1.) below reference range, 2.) within reference range, and 3.) above reference range.

Table 7.8.2.2: 2 Secondary Laboratory tests[1]

Label	**Lab test name**	**Direction of interest**	**Potential Clinical significance rule**
ALB	Albumin	Low	A[2]
CA	Calcium	Low, High	A[2]
CHOL	Cholesterol	High	A[2]
CL	Chloride	Low, High	<80 mmol/L and <baseline or >120 mmol/L and >baseline No CTCAE defined
CPEP	C-peptide	Low	<LLN and <baseline No CTCAE defined
EOSABS	Eosinophils	High	>1.0 10**9/L and > baseline No CTCAE defined
P	Phosphate	Low, High	H: > 1.7 mmol/L and >baseline, L: < 0.7 mmol/L and <baseline
PROT	Serum Protein	Low	<LLN and <baseline No CTCAE defined
TRIGL	Triglycerides	High	A[2]
UREA	Urea	High	> 1.5 x ULN and > baseline No CTCAE defined
URIC	Uric Acid	High	Females: > 600umol/L and >baseline Males: > 650umol/L and >baseline CTCAE based upon AE

[1] The frequencies of potential clinically significant values will be tabulated, and values that meet the criteria will be listed. No other analyses will be performed.
[2] A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[3] CTCAE grading will not consider symptoms such as presence of bleeding or use of anticoagulation.

Table 7.8.2.2: 3 Diagnostic Laboratory tests[1]

Label	Lab test name	Direction of interest	Potential Clinical significance rule
AMYL	Amylase	High	> 2x ULN and > baseline
LIPASE	Lipase	High	> 2x ULN and > baseline

[1]Values will be displayed in a listing. No other analysis will be performed.

Table 7.8.2.2: 4 Laboratory tests that will not be analyzed

Label	Lab test name
BASABS	Basophils
BICARBV	Bicarbonate
CKMBABS	Creatinine Kinase MB
HCT	Hematocrit
HDL	HDL Cholesterol
LDL	LDL Cholesterol
MCV	Ery. Mean Corpuscular Volume
MONABS	Monocytes
PREG	Choriogonadotropin Beta
RBC	Erythrocytes
UGLU	Urine Glucose
UNIT	Urine Nitrite
UPH	Urine pH
UPRO	Urine Protein
URBCZ	Urine Erythrocytes
UWBCZ	Urine Leukocytes

7.8.3 Vital signs

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

7.8.4 ECG

Clinically significant abnormal ECG findings (as assessed by the investigator) will be provided in the form of patient level listing.

7.8.5 Others

[redacted]

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.	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
5.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
6.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**21-JUN-17**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct.
Final	**DD-MMM-19**	[redacted]	None	This is the final TSAP
Draft 3.2	**18-APR-22**	[redacted]	6.6	Added imputation rules for partial dates

APPROVAL / SIGNATURE PAGE

Document Number: c38727127 **Technical Version Number:2.0**

Document Name: 8-01-tsap-core-3

Title: An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author	[redacted]	19 Apr 2022 14:19 CEST
Approval-Biostatistics		19 Apr 2022 15:19 CEST
Approval-Clinical Program [redacted]		19 Apr 2022 16:20 CEST
Approval-Clinical Trial Leader		22 Apr 2022 10:54 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed