TRIAL STATISTICAL ANALYSIS PLAN (MASTER)

c38787852-01

BI Trial No.:	1381.9
Title:	An open-label, Phase II, platform trial evaluating safety and efficacy of multiple BI 754091 anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
Investigational Product(s):	BI 754091 (anti-PD-1)
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	20 APR 2022 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the Master TSAP

Term	Definition / description
AE	Adverse Event
BHM	Bayesian Hierarchical Model
CR	Complete Response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DC	Disease Control
DLT	Dose Limiting Toxicity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DoR	Duration of Response
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FL	Follicular Lymphoma
ICH	International Conference on Harmonisation
IPD	Important Protocol Divations
iRECIST	Immune Response Evaluation Criteria in Solid Tumours
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
O*C	Oracle Clinical
OR	Objective Response
OS	Overall Survival
PD	Progression of Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response

Term	Definition / description
PSTAT	Project Statistician
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RPM	Report Planning Meeting
SA	Statistical Analysis
SAE	Serious Adverse Event
SD	Stable Disease
StD	Standard Deviation
SMQ	Standardised 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

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 Master Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the Master TSAP is based on the planned analysis specification as written in Master CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, Master TSAP readers may consult the Master 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.

SAS® Version 9.4 or the latest version will be used for analyses.

R v3.5.1 and JAGS v4.3.0 or the latest versions will be used for BHM analysis.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In Section 2.2.2 of master CTP, Duration of immune-response (DOiR) is defined as the duration from the date of first documented iPR or iCR according to iRECIST, if applicable, as assessed by the Investigator to the date of iCPD or death among patients with iOR.

Change: Duration of iOR (DOiR), is defined as the time from first documented iCR or iPR until the earliest of disease progression (immune unconfirmed progressive disease (iUPD) that is confirmed at a later radiological assessment) or death among patients with iOR.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of the trial is objective response (OR), defined as best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the Investigator.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

This section is not applicable because no key secondary endpoints have been defined in the Master CTP.

5.2.2 Secondary endpoint(s)

The secondary endpoints of the trial will include:

- Duration of response (DoR), defined as the time from first documented CR or PR (RECIST v1.1) until the earlier of disease progression or death among patients with OR.
- Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) according to RECIST v1.1 as assessed by the Investigator.
- Progression-free survival (PFS), defined as the time from first treatment until Progression of Disease (PD) or death from any cause, whichever occurs earlier.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is an open-label study. Specific dosing and treatment regimens for each of the BI 754091 combinations are described in the individual Modules.

Table 6.1: 1 Definition of treatment periods

Analysing Treatment Period	Start Date (including)	Stop Date (including)
Screening	Date of informed consent	Date/Time of the first administration of trial treatment -1 day
On-treatment	Date/Time of the first administration of trial treatment	Date of the last administration of trial treatment + REP
Follow up	Date of the last administration of trial treatment + REP + 1 day	Date of the last per protocol visit

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. AE reported within REP after the last trial medication will be considered on treatment. Detailed rule for assigning AEs to these time periods are listed below:

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way.

No per protocol set is defined for this phase II 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	**Inclusion criteria not met**			
	A1.1	No confirmed diagnosis of module-specified tumor types.	Inclusion criterion (IN) 2 not met	None	Automatic
	A1.2	Prior irAEs not resolved to a degree for patients moving from one module to another.	IN 3 not met	None	Automatic
	A1.3	Patient < 18 years of age at the time of signature of ICF	IN 4 not met	None	Automatic
	A1.4	ECOG score >1	IN 5 not met		
	A1.5	Women of child-bearing potential and men able to father a child are not willing or able to use highly effective methods of birth control during trial participation and for at least 6 months after the last administration of trial medication.	IN 8 not met	None	Automatic
	A2	**Exclusion criteria met**			
	A2.1	Use of investigational or anti-tumour treatment within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initial administration of trial treatment.	Exclusion criterion (EX) 1 met	None	Automatic
	A2.2	More than one anti-PD-(L)1-based treatment regimen prior to entering the study.	EX 2 met	None	
	A2.3	Major surgery performed within 12 weeks prior to first trial treatment or planned within 12 months after screening	EX 3 met	None	Automatic
	A2.4	Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated	EX 4 met	None	Automatic

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
		basal-cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or other local tumours considered cured by local treatment.			
	A2.5	Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial.	EX 5 met	None	Automatic
	A2.6	Allogenic bone marrow or solid organ transplant.	EX 6 met	None	
	A2.7	Inadequate organ function or bone marrow reserve as demonstrated by the laboratory values presented in CTP Table 3.2.3: 1.	EX 7 met	None	Automatic
	A2.8	Any of the following cardiac criteria specified in CTP Exclusion criterion 7	EX 8 met	None	Automatic
	A2.9	Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection.	EX 9 met	None	Automatic
	A2.10	Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy. Patients removed from previous IO therapy because of a severe immune-related adverse event (irAE).	EX 10 met	None	Automatic
	A2.11	Known history of severe hypersensitivity reactions to other mAbs or known hypersensitivity to the trial drugs or their excipients.	EX 11 met	None	Automatic
	A2.12	Known presence of symptomatic central nervous system (CNS) metastases, unless asymptomatic and off corticosteroids and/or anti-convulsant therapy	EX 12 met	None	

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
		for at least 2 weeks prior start of treatment.			
	A2.13	Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment.	EX 13 met	None	Automatic
	A2.14	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 14 met	None	Automatic
	A2.15	Chronic alcohol or drug abuse or any condition that, in the Investigator's opinion, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures.	EX 15 met	None	Automatic
	A2.16	Women who are pregnant, nursing, or who plan to become pregnant while in the trial and for at least 6 months after the last administration of trial medication.	EX 16 met	None	Automatic
	A2.17	Men who plan to father a child while in the trial and for at least 6 months after the last administration of trial medication.	EX 17 met	None	
B		**Informed consent**			
	B1	Informed consent not available/not done	Inclusion criteria 1 not met	All	Automatic
	B2	Informed consent too late	Informed consent obtained later than the initiation of treatment	None	Automatic
C		**Trial medication**			
	C1.1	Non-compliance per protocol	Incorrect trial medication dose taken or wrong dose schedule; (in fusion time, program) decision at MQRM	None	Automatic and manual

Category / Code		Description	Comment / Example	Excluded from	Automatic/ 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 4.2.2.1 of master the protocol or related sections in each module	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

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 trial medications in at least one module. The TS is used for both efficacy analysis and safety analyses.

PK Analysis Set (PKS):
This patient set includes all patients in the TS with at least one valid plasma concentration. PKS will be used for all pharmacokinetic analyses

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

In general missing efficacy data will not be imputed and all reasonable efforts will be taken during the trial to obtain such data. Patients with unknown vital status, missing tumour imaging data will be censored for time-to-event analyses as detailed below.

Table 6.6: 1 describes how patients will be classified for the analysis of PFS.

Table 6.6: 1 Derivation rules for PFS

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

*Refers to Table 6.7:1 in module TSAPs for first planned post-baseline radiological assessment window.

For endpoints related to OR and DC the rules defined above, where applicable, will be followed.

Table 6.6: 2 describes how patients will be classified for the analysis of death. Patients will be censored at the date of last contact if the investigator is no longer able to contact a patient or caregiver, and vital status cannot be determined otherwise, provided that no other information indicates that the patient was near death at that point.

Table 6.6: 2 Derivation rules for OS

Status at time of analysis	**Outcome**	**Date of outcome**
Death and the date of death is known	Event	Date of death
Death and date of death is unknown	Event	Date of last contact when the patient is known to be alive + 1 day
Alive	Censored	Date of last contact when the patient is known to be alive
Unknown	Censored	Date of last contact when the patient is known to be alive

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") [2].

Missing data and outliers of PK data are handled according to [2]. PK parameters that cannot be reasonably calculated, based on the available drug concentration-time data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first administration of study drug in each module.

Study day will be calculated relative to the date of the first administration of study drug in each module. 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.

Refers to module TSAPs for specific time windows.

7. PLANNED ANALYSIS

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.

For plasma concentrations as well as for all PK parameters the following descriptive statistics will additionally be calculated, CV (arithmetic coefficient of variation), gMean (geometric mean) and gCV (geometric coefficient of variation).

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 (25th percentile), median, P75 (75th 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.

The data from each module will be analysed and reviewed together with the data from other studies in the same combination project to evaluate the safety and efficacy benefit in explored indications/patient populations. Decisions on further development will be made based on an analysis of the aggregated data for each combination via a meta-analytic approach implementing quantitative Go-NoGo rules. Results of the meta-analytic approach will be summarised as an internal research report and will be used to support the rationale and the benefit-risk assessment for future development trials, if applicable.

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

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. 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

Refer to module TSAPs for treatment cycles details.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis

For the primary endpoint objective response, will be analysed in terms of ORR, defined as the proportion of patients with best overall response of CR or PR determined according to RECIST v1.1 until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

A BHM approach (Berry et. al., 2013) [3] will be used to derive the posterior distribution of the ORR of each patient cohort within each Module if applicable. The description of BHM approach refers to Section 7.1 in the master protocol. All calculations for the shrinkage estimator are performed using the statistical software R v3.5.1 and JAGS v4.3.0. Please refer to section 9 for more details of calculations.

Only confirmed ORR will be used for the primary analysis of the primary endpoint. Descriptive statistics regarding e.g., observed objective response rate (both confirmed and unconfirmed) for each cohort within each Module will be displayed additionally.

Confirmed best overall response will be derived according to the following derivation rules:

- If CR or PR: look at subsequent visits, if there is another CR or PR >=28 days and <= 84 days then the patient has a confirmed response. If there is not another CR or PR >=28 days and <= 84 days then the patient can be a confirmed stable disease (SD) if the CR or PR is assessed at >=35 days from the start of study treatment.
- If SD: to be confirmed SD, the measurement must have been taken at >=35 days from the start of study treatment (only one reading is necessary).
- Additional details are provided in Table 7.4.1: 1.

Table 7.4.1: 1 Details of confirmed BOR derivation rules

Overall response (time point 1)	Overall response (>=28 and <= 84 days from time point 1)	Confirmed BOR
CR	CR	CR
CR	PD	SD as long as assessed at >=35 days,, otherwise, PD

CR	NE/Missing	SD as long as assessed at >=35 days, otherwise NE
PR	CR	PR
PR	PR	PR*
PR	SD	SD as long as assessed at >=35 days, otherwise PD
PR	PD	SD as long as assessed at >=35 days, otherwise PD
PR/SD	NE/Missing	SD as long as assessed at >=35 days, otherwise NE
NE	NE/Missing	NE

* In a scenario: PR-SD-PR, the best overall response will be derived as PR if the time window between the two PRs >=28 days and <= 84 days,.

The primary analysis will include patients who entered the trial with their initially assigned treatment, and additional analyses may be performed taking into account the patients who cross-over from different Modules if applicable.

7.4.2 Interim analysis

Interim analysis will be performed when deemed necessary. Final/primary analysis for a specific treatment combination or cohort will be considered as interim analysis. A cohort or Module may be closed, if determined to be appropriate based on results on interim analyses. Note that interim analysis will not lead to any modifications within the running trial unless otherwise stated in a Module.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable because no key secondary endpoints have been defined in the CTP.

7.5.2 (Other) Secondary endpoint(s)

Duration of objective response
For all patients with OR the duration of OR (DOR) will be calculated as follows:

For patients with disease progression or death or without disease progression or death (censored):

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

The censoring rules for duration of OR (i.e. outcome and date of outcome) are shown in Table 6.6:1.

Kaplan-Meier estimates will be used to calculate median duration of OR for each cohort within each Module.

Disease control
DC will be analysed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, SD. The same method for the analysis of primary endpoint will be used for the analysis of DC using the BHM approach. The median and 95% credible interval will be used to summarize the shrinkage estimator of DCR.

Descriptive statistics regarding e.g., observed disease control rate for each cohort within each Module will be displayed additionally.

Progression-free survival
For patients with 'event', or with "censored" as an outcome for PFS:

PFS [days] = date of outcome – date of first treatment administration + 1

The censoring rules for PFS (i.e. outcome and date of outcome) are described in Table 6.6: 1. The time frame for the primary assessment of PFS will be from first treatment administration until the earliest of disease progression, death or the time point of the PFS analysis.

Kaplan-Meier (KM) estimates will be used to display the distribution of PFS for each cohort on a KM curve. To support the plot estimated survival probabilities at specific time points of interest (scheduled imaging time-points) will be tabulated along with 95% confidence intervals, using Greenwood's variance estimate. In addition the survival distribution will be used to provide estimates of the median, 25th and 75th percentiles.

7.7 EXTENT OF EXPOSURE

The total number of cycles initiated and the numbers of cycle initiated will be summarized descriptively for each cohort. Refer to module TSAPs for details.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS). Analysis will be performed as defined in Section 7.3.4 of the CTP.

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 patients with AEs and not on the number of AEs. The severity of AEs will be scaled according to the Common Terminology Criteria for Adverse Events (CTCAE) latest version.

AEs are collected and analysed as per the standard BI AE guideline (001-MCG-156: Handling and summarisation of adverse event data for clinical trial reports and integrated summaries) [4].

Missing and incomplete AE dates are handled as per standard BI internal guidelines (001-MCG-156_RD-01: Handling of missing and incomplete AE dates) [2].

The analyses of adverse events will be based on the concept of treatment-emergent adverse events. That means that all adverse events occurring between the first treatment administration until the end of the REP will be assigned as “on treatment”.

Adverse events will be displayed by the initial dose of study medication administered on the first day of treatment.

The overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- All AEs by highest CTCAE grade,
- Serious AEs by highest CTCAE grade
- Investigator assessed related AEs by highest CTCAE grade
- Investigator assessed related SAEs by highest CTCAE grade
- Investigator assessed immune-related AEs by highest CTCAE grade
- Investigator assessed immune-related AEs through the whole trial
- AEs with CTCAE grade >=3 by highest CTCAE grade
- Investigator assessed related AEs with CTCAE grade >=3 by highest CTCAE grade
- AEs leading to treatment discontinuation by highest CTCAE grade
- AEs leading to death

Special search categories will be defined in the module TSAPs if applicable and displayed by treatment, highest CTCAE grade and PT.

Tables including only SOC without PT or the opposite may also be produced if needed.

For tables containing SOC, the sorting will be done by frequency in SOCs then frequency in PTs within SOCs. Otherwise, the tables will be sorted by frequency in PTs.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards [5]. The following analyses will be performed for selected lab tests shown in table 9.2: 1:

- Descriptive statistics, including changes from baseline to worst laboratory value and from baseline to last laboratory value
- Frequency of patients with possible clinically significant abnormalities
    - Possible clinically significance will be defined as listed in Tables 9.2: 1.

Analyses of descriptive statistics should use normalized lab values.

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 between the first treatment administration until the end of the REP will be considered as on-treatment. All lab tables should be footnoted to indicate that values were excluded if they were collected after the REP.

Liver Function tests and potential Hy's Law

Time to initial onset of liver enzyme elevations and frequency of patients with liver enzyme elevations will be produced.

7.8.3 Vital signs

N/A

7.8.4 ECG

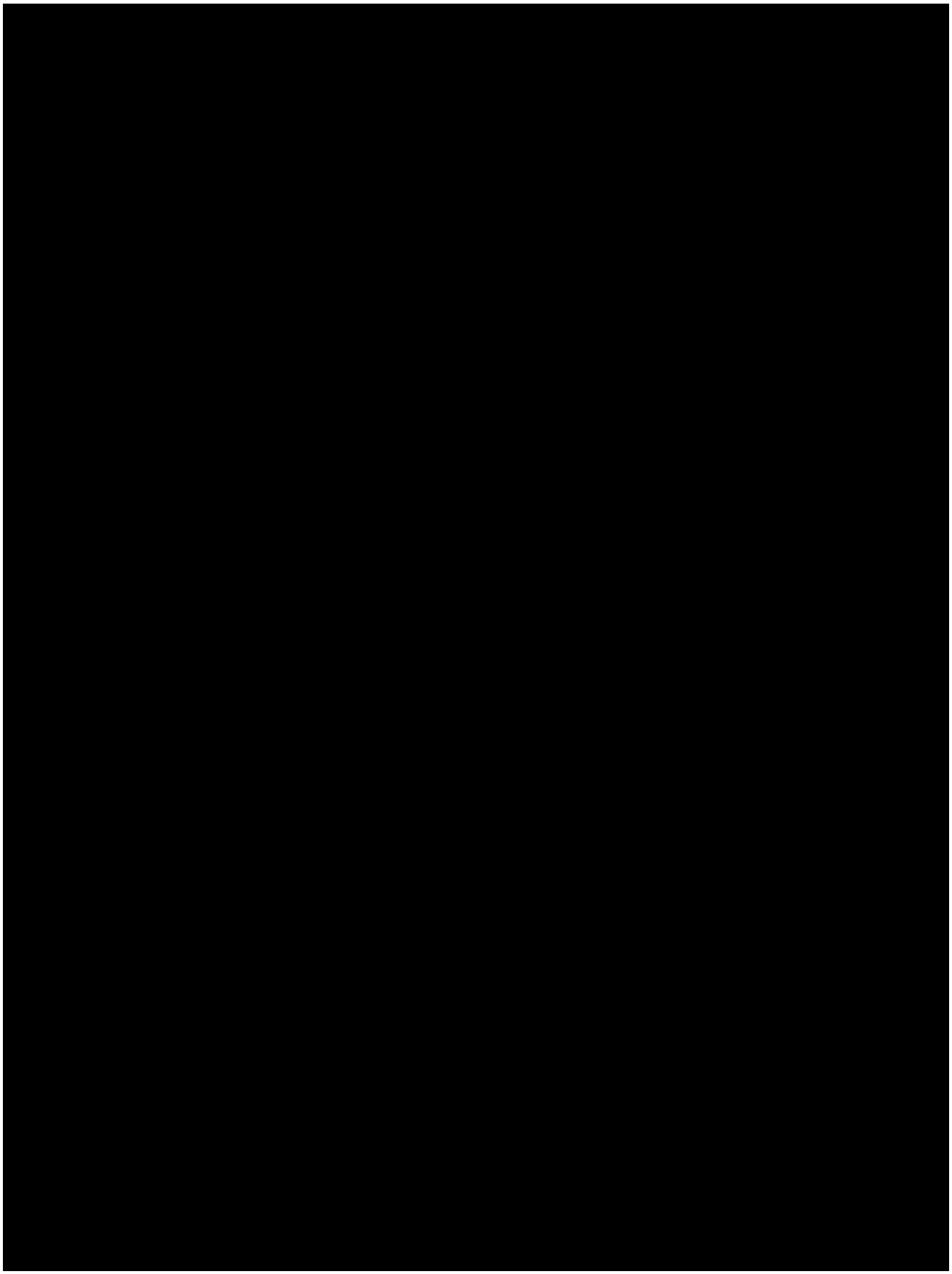
N/A

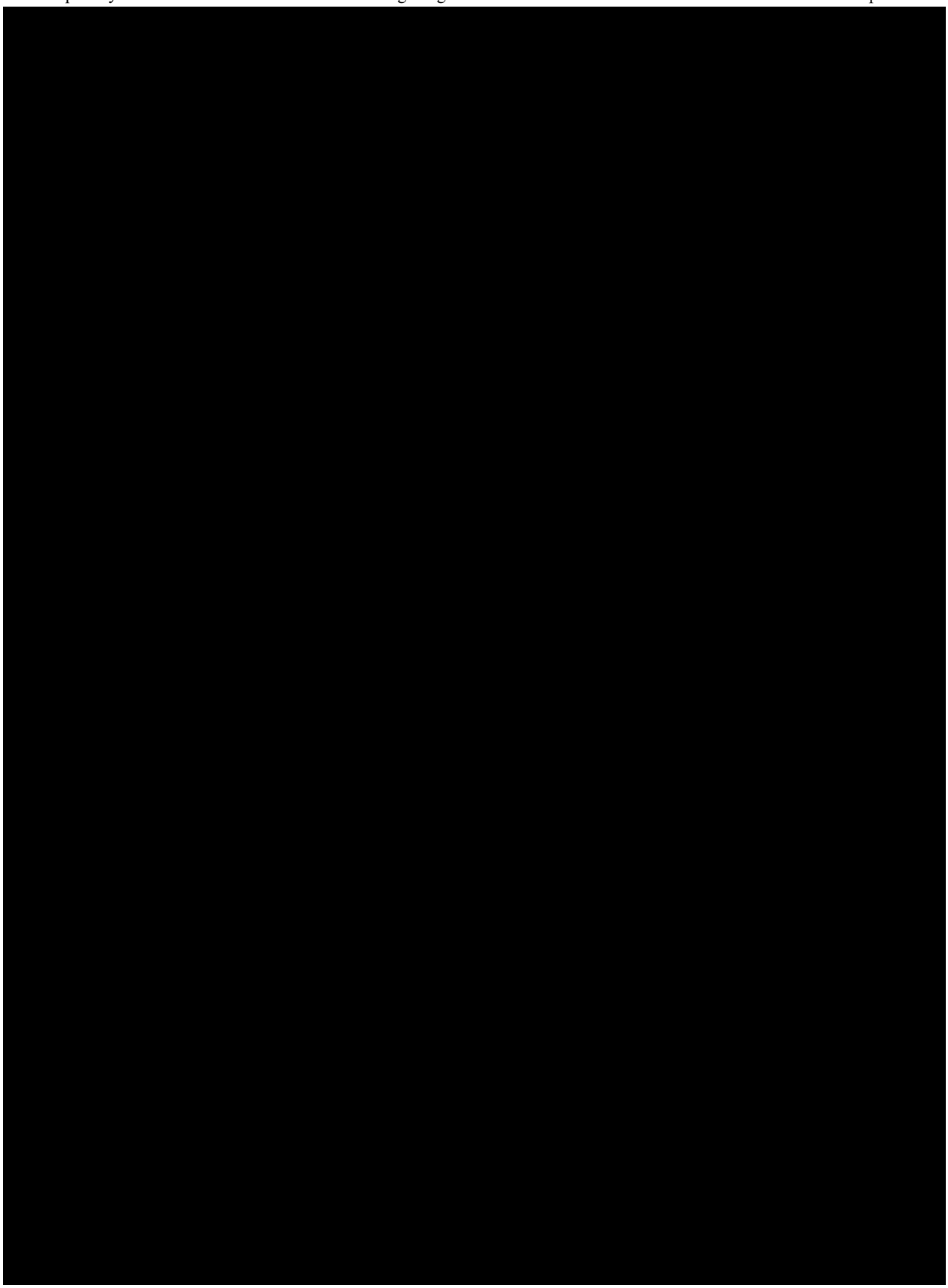
7.8.5 Others

Refer to module TSAPs for PK and biomarkers analyses.

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-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3.	Berry SM, Broglio KR, Groshen S, Berry DA. Bayesian hierarchical modeling of patient subpopulations: Efficient designs of Phase II oncology clinical trial. Clinical Trials 10 (5), 720-734 (2013) [R18-2260].
4.	001-MCG-156: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5.	*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	**02-NOV-20**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**21-FEB-21**		None	This is the final TSAP
Revised	**20-APR-22**		6.3 7.4.1	Added definition of PK Analysis Set (PKS) Updated confirmed best overall response derivation rule

APPROVAL / SIGNATURE PAGE

Document Number: c38787852 **Technical Version Number:1.0**

Document Name: 08-01-tsap-master-core1

Title: An open-label, Phase II, platform trial evaluating safety and efficacy of multiple BI 754091 anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author	[redacted]	21 Apr 2022 14:49 CEST
Approval-Biostatistics		21 Apr 2022 14:54 CEST
Approval-Team Member Medicine		21 Apr 2022 15:08 CEST
Approval-Clinical Program [redacted]		21 Apr 2022 16:14 CEST
Approval-Clinical Trial Leader		26 Apr 2022 15:08 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed