Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201923_0050
Title	A Phase II, open-label, single-arm study of berzosertib (M6620) in combination with topotecan in participants with relapsed platinum-resistant small-cell lung cancer
Study Phase	II
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Approval Page

Integrated Analysis Plan: MS201923_0050

A Phase II, open-label, single-arm study of berzosertib (M6620) in combination with topotecan in participants with relapsed platinum-resistant small-cell lung cancer

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within ELDORADO via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
BMI	Body Mass Index
AUC	The area under the concentration-time curve
$AUC_{0\text{-}tlast}$	The AUC from time zero (= dosing time) to the last sampling time (t_{last})
$AUC_{0\text{-}tlast}$/Dose	Dose-normalized $AUC_{0\text{-}tlast}$
$AUC_{0\text{-}\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}
$AUC_{0\text{-}\infty}$/Dose	Dose-normalized $AUC_{0\text{-}\infty}$
$AUC_{0\text{-}48h}$	The AUC from time zero (= dosing time) to 48 hours
$AUC_{0\text{-}48h}$/Dose	Dose-normalized $AUC_{0\text{-}48h}$
$AUC_{0\text{-}72h}$	The AUC from time zero (= dosing time) to 72 hours
$AUC_{0\text{-}72h}$/Dose	Dose-normalized $AUC_{0\text{-}72h}$
BOR	Best Overall Response
BSA	Body Surface Area
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
C_{max}	Maximum observed concentration
C_{max}/Dose	Dose-normalized Cmax
C_{eoi}	The observed concentration at the end of the infusion period
C_{trough}	The concentration observed immediately before next dosing
COVID-19	2019 Novel Coronavirus Disease
CR	Complete Response
CL	The apparent total body clearance
CV	Coefficient of variation
(e)CRF	(electronic) Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DL	Dose Level

DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 Dimension 5 Level Scale
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FU	Follow-up
GBS	Global Biostatistics
GeoCV%	Geometric coefficient of variation
GeoMean	Geometric mean
HRQoL	Health Related Quality of Life
IA	Interim Analysis
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IRC	Independent Review Committee
KM	Kaplan-Meier
LOCF	Last Observation Carried Forward
LLOQ	Lower limit of quantitation
LSmean	Least squares mean
Min	Minimum
Max	Maximum
MR(C_{max})	Metabolic ratio of C_{max}
MR(AUC)	Metabolic ratio of AUC
MCIC	Minimal Clinically Important Change
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
n	Number of non-missing observations
N	Number of subjects
OR	Objective Response

ORR	Objective Response Rate
OS	Overall Survival
PA	Primary Analysis
PD	Progressive Disease or Protocol Deviation or Pharmacodynamics
PFS	Progression Free Survival
PT	Preferred Term
CCI	[redacted]
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-Reported Outcome
QLQ	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
REML	Restricted maximum likelihood
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCLC	Small Cell Lung Cancer
SCR	Screening analysis set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval
$t_{1/2}$	Apparent terminal half-life
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantitation
VAS	Visual Analogue Scale
V_Z	The apparent volume of distribution during the terminal phase following intravenous administration
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	28Jun2021	PPD	NA – First version

2.0	27Apr2022	PPD	• Fixed typos.
			• Section 8.1: Added wording related to which subjects will be included in IA.
			• Section 11.3: Removed the +1 from "Time since initial cancer diagnosis" as per Merck standards.
			• Section 13: Clarified planned dose calculation and dose compliance formula. Added new subsection for permanent dose reduction.
			• Section 14.2.1:
			  ○ Removed PFS from table 4 title.
			  ○ Updated DoR text and table 4 to match the estimands approach and remove redundancies.
			• Section 14.3: Added table for censoring rules and removed reference to DoR section.
			• Section 14.5.1: Clarified completion rate wording.
			• Section 15.2.1: Removed "by severity" wording from TEAEs, Grade >=3, Grade >=4. Removed Non-Serious TEAEs. Added Infusion-related reactions. Added Chinese sites outputs.

3.0	24Nov2022	PPD	• Sections 6, 6.3, 6.4, 7, 8.1, 14.5 and 15.8: reworded as per SMC decision to stop for futility, updated PA timing and reduced the scope of what will be analyzed. ○ Removed: HRQoL analyses, PK listings, PK main part analyses and CCI [redacted] analyses. These won't be part of the CSR. • Section 9.6: added missing day imputation and laboratory assessments. Created new section (9.11.8) with the imputation instructions. • Section 9.7 and tables 3 and 4: added time window description for efficacy analyses (DoR and PFS) and updated the respective tables accordingly. • Section 10.2: added comment about COVID-related PDs. • Sections 14.1.1, 14.3.1 and 14.4.1: added a summary table for intercurrent events. • Section 14.2.1: specified that is case of less than 6 responders only listings will be provided. • Tables 3 and 4: updated time windowing. • Section 14.5.2: updated completion and compliance calculations as shells. • Section 15.2.1: added site code "71" to identify Chinese sites. • Section 15.3 and appendix 4: added infusion site reactions. Section 15.7: added criteria for missing data imputation, updated PK parameters descriptions, specified Phoenix WinNolin output will be provided by Sponsor and removed Main part analysis.
4.0	07Dec2022	PPD	• Section 11.3: updated categories for number of organs involved in the disease.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			• Updated section 14.5 to specify the ePRO analyses to be performed at final DBL.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the analysis of data collected for protocol MS201923_0050. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

This IAP is based on Section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments, with the exception of CCI [redacted], CCI [redacted] which will be described in subsequent versions of this document or in distinct documents. Details of the Local Safety Monitoring Committee (SMC) analyses for review of the Japanese participants' safety without formal statistical analysis are provided in a separate IAP, whereas details of the Global SMC analysis are provided in Appendix 17.1.

5 Objectives and Estimands

5.1 Main Part

Objectives	Estimand Attributes	IAP section
Primary		
To assess efficacy of intervention in terms of objective response (OR) with berzosertib + topotecan	**Endpoint:** Objective response according to RECIST 1.1 as assessed by the Independent Review Committee (IRC) **Population:** Participants with relapsed, platinum-resistant small-cell lung cancer (SCLC) **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Discontinuation of treatment: treatment-policy strategy, i.e. regardless of the intercurrent event • Start of subsequent anticancer treatment: while not treated with subsequent anticancer therapy strategy, i.e. ignoring tumor assessments after the intercurrent event • Progression according to RECIST 1.1: while not progressed strategy, i.e. assessments up to the intercurrent event **Population Level Summary:** Objective response rate (ORR)	Section 14.1
Secondary		
To assess efficacy of intervention in terms of Duration of Response (DoR) with berzosertib + topotecan	**Endpoint:** Duration of Response according to RECIST 1.1 as assessed by the IRC. Measured by time from first documentation of OR to progressive disease (PD) or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention. **Population:** Participants with relapsed, platinum-resistant SCLC and confirmed OR according to RECIST 1.1 assessed by IRC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Death within 2 scheduled tumor assessments: composite strategy, i.e. will be considered as event of interest • Discontinuation of treatment: treatment-policy strategy, i.e. ignoring the intercurrent event • Start of subsequent anticancer treatment: treatment-policy strategy, i.e. ignoring the intercurrent event **Population Level Summary:** • Median duration of response • Kaplan-Meier estimates, including the Kaplan-Meier estimate at 6 months	Section 14.2

Objectives	Estimand Attributes	IAP section
To assess efficacy of intervention in terms of Progression-free survival (PFS) with berzosertib + topotecan	**Endpoint:** Progression-free survival according to RECIST 1.1 as assessed by the IRC. Measured by time from first study intervention to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention **Population:** Participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Death within 2 scheduled tumor assessments: composite strategy, i.e. will be considered as event of interest • Discontinuation of treatment: treatment-policy strategy, i.e. ignoring the intercurrent event • Start of subsequent anticancer treatment: treatment-policy strategy, i.e. ignoring the intercurrent event **Population Level Summary:** • Median PFS time • Kaplan-Meier estimates	Section 14.3
To assess efficacy of intervention in terms of Overall Survival (OS) with berzosertib + topotecan followed by subsequent therapy	**Endpoint:** Overall survival. Measured by time from first study intervention to death **Population:** Participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent anticancer treatment **Intercurrent Event Strategy:** • Discontinuation of treatment: treatment-policy, i.e. ignoring the intercurrent event • Start of subsequent anticancer therapy: treatment-policy, i.e. ignoring the intercurrent event **Population-Level Summary:** • Median OS time • Kaplan-Meier estimates	Section 14.4

Objectives	Estimand Attributes	IAP section
To assess the efficacy of intervention in terms of physical functioning, cough, dyspnea and chest pain, and overall health-related quality of life (HRQoL) based on patient-reported outcomes (PROs) when treated with berzosertib + topotecan	**Endpoint:** Change from baseline in physical functioning measured by the European Organization for the Research and Treatment of Cancer (EORT) Quality of Life Questionnaire (QLQ-C30); cough, dyspnea, and chest pain measured by EORTC QLQ-LC13 (lung cancer specific questionnaire); health state as measured by visual analogue scale (VAS) as a component of the EuroQol 5 Dimension 5 Level Scale (EQ-5D-5L) **Population:** Participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Discontinuation of treatment: while on treatment strategy, i.e. ignoring PRO assessments after the intercurrent event • Start of subsequent anticancer therapy: while not treated with subsequent anticancer therapy strategy, i.e. ignoring PRO assessments after the intercurrent event • Death: while alive strategy, i.e. considering PRO assessments before the intercurrent event. **Population-Level Summary:** • Mean change from baseline analysis for multi-item scales in EORTC questionnaires (i.e. physical functioning, dyspnea and VAS) • Proportion of participants with ≥ 1 category improvement and proportion of participants with ≥ 1 worsening in single-item symptoms (i.e. cough and chest pain)	Section 14.5
To evaluate the safety and tolerability of berzosertib + topotecan	**Endpoint:** Occurrence of adverse events (AEs) and treatment-related AEs, and occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead ECG findings	Section 15

CCI [redacted]

CCI

[redacted]

ECG = electrocardiogram; EORTC = European Organization for the Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5 Dimension 5 Level Scale; HRQoL = health-related quality of life; CCI ; PK = pharmacokinetics; PRO = patient-reported outcome; QLQ-LC13 = lung cancer specific questionnaire; QLQ-C30 = Quality of Life Questionnaire; QTc = corrected QT interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; VAS = visual analogue scale.

5.2 Safety Run-in Part in Japan

Objectives	Estimand Attributes	IAP section
Primary		
To confirm whether the regimen and RP2D of berzosertib in combination with topotecan that were established in the Phase I study in non-Japanese can be safely applied to Japanese participants	**Endpoint:** Occurrence of dose limiting toxicities (DLTs) until the end of Cycle 1 in Japanese participants, occurrence of AEs and treatment-related AEs, and occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead ECG findings **Population:** • DL1: Japanese participants with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan	NA – see IAP for Safety Run-in SMC

Objectives	Estimand Attributes	IAP section
Secondary		
To assess efficacy of intervention in terms of objective response with berzosertib + topotecan	**Endpoint:** Objective response according to RECIST 1.1 as assessed by the Investigator **Population:** • DL1: Japanese participants with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Discontinuation of treatment: treatment-policy strategy, i.e. regardless of the intercurrent event • Start of subsequent anticancer treatment: while not treated with subsequent anticancer therapy strategy, i.e. ignoring tumor assessments after the intercurrent event • Progression according to RECIST 1.1: while not progressed strategy, i.e. assessments up to the intercurrent event **Population Level Summary:** Objective response rate	Section 14.1
To assess efficacy of intervention in terms of duration of response with berzosertib + topotecan	**Endpoint:** Duration of Response according to RECIST 1.1 as assessed by the Investigator. Measured by time from first documentation of OR to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention. **Population:** • DL1: Japanese participants with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Death within 2 scheduled tumor assessments: composite strategy, i.e. will be considered as event of interest • Discontinuation of treatment: treatment-policy strategy, i.e. ignoring the intercurrent event • Start of subsequent anticancer treatment: treatment-policy strategy, i.e. ignoring the intercurrent event **Population Level Summary:** • Median duration of response • Kaplan-Meier estimates, including the Kaplan-Meier estimate at 6 months	Section 14.2

Objectives	Estimand Attributes	IAP section
To assess efficacy of intervention in terms of PFS with berzosertib + topotecan	**Endpoint:** Progression-free survival according to RECIST 1.1 as assessed by the Investigator. Measured by time from first study intervention to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention **Population:** • DL1: Japanese participants with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Death within 2 scheduled tumor assessments: composite strategy, i.e. will be considered as event of interest • Discontinuation of treatment: treatment-policy strategy, i.e. ignoring the intercurrent event • Start of subsequent anticancer treatment: treatment-policy strategy, i.e. ignoring the intercurrent event **Population Level Summary:** • Median PFS time • Kaplan-Meier estimates	Section 14.3
To assess efficacy of intervention in terms of OS with berzosertib + topotecan followed by subsequent therapy	**Endpoint:** Overall survival. Measured by time from first study intervention to death **Population:** • DL1: Japanese participants with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent anticancer treatment **Intercurrent Event Strategy:** • Discontinuation of treatment: treatment-policy, i.e. ignoring the intercurrent event • Start of subsequent anticancer therapy: treatment-policy, i.e. ignoring the intercurrent event **Population-Level Summary:** • Median OS time • Kaplan-Meier estimates	Section 14.4

Objectives	Estimand Attributes	IAP section
To assess the efficacy of intervention in terms of physical functioning, cough, dyspnea and chest pain, and overall HRQoL based on PROs when treated with berzosertib + topotecan	**Endpoint:** Change from baseline in physical functioning measured by the EORT QLQ-C30; cough, dyspnea, and chest pain measured by EORTC QLQ-LC13; health state as measured by VAS as a component of the EQ-5D-L **Population:** • DL2: Japanese participants with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Discontinuation of treatment: while on treatment strategy, i.e. ignoring PRO assessments after the intercurrent event • Start of subsequent anticancer therapy: while not treated with subsequent anticancer therapy strategy, i.e. ignoring PRO assessments after the intercurrent event • Death: while alive strategy, i.e. considering PRO assessments before the intercurrent event. **Population-Level Summary:** • Mean change from baseline analysis for multi-item scales in EORTC questionnaires (i.e. physical functioning, dyspnea and VAS) • Proportion of participants with ≥ 1 category improvement and proportion of participants with ≥ 1 worsening in single-item symptoms (i.e. cough and chest pain)	Section 7
To characterize the PK profile of berzosertib	**Endpoint:** PK parameters of berzosertib in plasma by NCA **Population:** • DL1: Japanese participants with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese participants with relapsed, platinum-resistant SCLC	Section 15.7

CCI [redacted]

Objectives	Estimand Attributes	IAP section
CCI		

DL = dose level; DLT = dose limiting toxicity; ECG = electrocardiogram; EORTC = European Organization for the Research and Treatment of Cancer; HRQoL = health-related quality of life; OS = overall survival; PD = progressive disease; PFS = progression-free survival; CCI PK = pharmacokinetics; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire; QLQ-LC13 = lung cancer specific questionnaire; QTc = corrected QT interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RP2D = recommended Phase II dose; SCLC= small-cell lung cancer; VAS = visual analogue scale.

Analyses for the Safety Run-in Part will include both DL1 and DL2 separately by dose level.

6 Overview of Planned Analyses

Main Part of Global Phase II:

The study will be monitored regularly by an internal SMC (Appendix 2 of the CSP). The following analyses will be conducted:

- An interim analysis for futility will be conducted after the first 40 participants have completed their second on-treatment tumor assessment (or dropped-out/died prematurely)

Given the decision to stop for futility (analysis performed in May 2022):

- The primary analysis will be performed once all participants have completed the study (or dropped-out/died prematurely).
- No follow-up analysis will be performed.

Safety Run-in Part in Japan:

The study will be monitored regularly by the Local SMC (Appendix 2 of the CSP). Safety analysis will be performed after completion of the DLT evaluation period of each cohort in DL1 and DL2 and also a final analysis after all follow-up is complete.

The IAP will be approved prior to database lock.

6.1 Analyses for SMC Meetings

6.1.1 Main Part

An internal SMC will review the emerging safety profile during review of the safety data and will monitor for any new safety signal observed during the conduct of the study. The SMC will also review the results of the interim analysis to assess the benefit of continuing the study (see Section 6.2).

SMC analyses (as per SMC Charter) will be performed after the first 15 treated participants have completed their second on-treatment tumor assessment, and after the first 40 treated participants have completed their second on-treatment tumor assessment.

The Global SMC will include a subset of the full set of safety analysis described in this IAP, as specified in Appendix 17.1 and in the tables, listings, and figures (TLFs) table of contents. In addition, after the first 40 participants, the SMC analysis will include efficacy analyses (see Section 6.2).

6.1.2 Safety Run-in Part

An additional local SMC is organized for the Safety Run-in Part in Japan. The local SMC will periodically review all accumulating safety data and available PK data. Once the last participants of the respective cohort have completed the DLT assessment period (i.e. 21 days) or discontinued from the trial prematurely, a data snapshot will be taken for provision of SMC outputs. Local SMC outputs will include only data from Japanese participants.

Details of analysis for SMC meetings are specified in the Local SMC Charter and in a separate IAP.

6.2 Interim Analysis

The Main Part of the study has a single-arm, two-stage design with a total of 80 planned participants. An interim analysis (IA) with potential stop for futility will be conducted after the first 40 participants have completed their second on-treatment tumor assessment or

dropped-out/died prematurely (i.e. end of Stage 1). The study will continue to Stage 2 if at least 6 participants out of the first 40 participants are observed with a confirmed objective response (complete response [CR] or partial response [PR] according to IRC). If ≤ 5 participants in Stage 1 are observed with an objective response, the study will stop for futility.

The IA results will be reviewed by the Global SMC and will include a subset of the full set of efficacy outputs (efficacy endpoints: OR, DoR, PFS and OS) described in this IAP, as specified in Appendix 17.1 and in the TLFs table of contents.

6.3 Primary Analysis

The primary analysis (PA) will include all planned analyses identified in the Clinical Study Protocol and in this IAP. The PA will be performed once all participants have completed the study or dropped-out/died prematurely, and the database is locked for the analysis. The PA will also include the Japanese participants with relapsed plat-r SCLC enrolled on DL2 in the Safety Run-in.

6.4 Follow-up Analysis

Follow-up analysis will not be performed.

7 Changes to the Planned Analyses in the Clinical Study Protocol

HRQoL based on Patient-reported outcomes (PROs) will not be evaluated for the Safety Run-in Part. Additionally with regards to ePRO data, in case of unavailability of Vendor data at the time of final DBL, analysis on ePRO data won't be included in CSR but might be analyzed separately and included in a future CSR addendum.

For the Main Part, only primary and secondary endpoints will be analyzed.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set (SCR)

The Screening analysis set includes all participants who signed the informed consent, regardless of the participant's study intervention status in the study.

Full Analysis Set (FAS)/ Safety Analysis Set (SAF)

The FAS/SAF will include all participants who were administered any dose of any study intervention.

For the outputs on OR and DoR that will be delivered at futility interim analysis, first 40 treated subjects from FAS/SAF analysis set will be included.

For Japanese subjects in the safety run-in, DL2 was declared safe by the SMC prior to the IA cut-off date, therefore these subjects will be considered for IA and other analyses performed for main part.

Dose Limiting Toxicity Analysis Set (DLT)

The Dose Limiting Toxicity analysis set (DLT) will include all participants who were administered any dose of any study intervention in the Safety Run-in Part in Japan and meet at least one of the following criteria:

- Received at least 80% of the planned cumulative dose of study intervention (i.e. 80% of each study intervention) during the DLT period (Day 1- Day 21) and completed the DLT period. The final decision on evaluability will be made by the SMC (e.g. considering relevant deviations from dosing schedule)
- Experienced at least one DLT during the DLT period, regardless of the administered cumulative dose of study intervention and completion of the DLT period.

Pharmacokinetic Analysis Set (PKS)

The PK Analysis Set will include all participants who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable postdose plasma concentration of berzosertib and/or its CCI was obtained.

Analyses per Analysis Set

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set			
Analyses	**Screening Analysis Set**	**Full Analysis Set /Safety Analysis Set**	**DLT Analysis Set**	**PKS**
Subject Disposition	✓			
Baseline Characteristics		✓		
Previous and Concomitant Therapies		✓		
Compliance and Exposure		✓		
Efficacy: Primary Endpoint/Estimand		✓		
Efficacy: Secondary Endpoint/Estimand		✓		
Pharmacokinetic Analysis – Safety Run-in				✓
Safety and Tolerability		✓	✓	

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on OR, PFS, and OS. All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed.

For the definition of subgroup level, data as documented in the electronic case report form (eCRF) will be taken. The category "missing" will not be included in any subgroup analysis.

In case of low number of participants within a category (< 4 participants, which is about 5% of the treated population), categories will be pooled when meaningful.

The following subgroups will be defined:

Age

- Age < 65 years
- Age ≥ 65 years

Gender

- Male
- Female

Race

- White
- Black or African American
- Asian
- Other

Ethnic origin

- Hispanic or Latino
- Not Hispanic or Latino

Region/Country

- North America
- Europe
- Japan
- China

Eastern Cooperative Oncology Group (ECOG) Performance status (PS)

- ECOG PS 0 or 1
- ECOG PS > 1

Stage at initial diagnosis

- Limited stage disease
- Extensive stage disease

Prior immunotherapy

- Yes
- No

Brain metastases at baseline, i.e. target and non-target lesions identified by IRC assessment

- Present
- Absent

Liver metastases at baseline, i.e. target and non-target lesions identified by IRC assessment

- Present
- Absent

Number of organs, including lung, with metastatic disease at baseline based on IRC assessment

- < 3
- ≥ 3

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

For the Main Part, the open-label study intervention is labelled as "Berzosertib+Topotecan". If the DL2 is declared RP2D, the Japanese participants enrolled in the Safety Run-in receiving DL2 will be pooled with the participants in the Main Part of the study.

A separate analysis will be performed on the participants of the Safety Run-in Part (presented by dose level and overall). Study intervention groups for the Safety Run-in Part are defined and labelled as "Berzosertib+Topotecan (DL1)" and "Berzosertib+Topotecan (DL2)".

For final CSR, data will be displayed in 3 columns in case of tables: Safety Run-in DL1 and DL2 and Main Part (note that DL2 participants will be also counted under Main Part column). In case of listings, cohort information will be displayed separately: Safety Run-in DL1, Safety Run-in DL2 and Main Part.

Listings

In the individual participant data listing all individual data will be listed as measured. Repeated and unscheduled measurements will be included in the listings. All listings will be sorted by treatment, subject ID, and/or nominal time point, as appropriate. Data which are measured before administration of study intervention will be sorted by participant number and nominal time point (if appropriate).

Tables and Descriptive Statistics

All data will be summarized by scheduled visit. Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), [the number of participants with missing values, (nmiss),] mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case statistics can't be calculated, for example due to low number of participants, not done abbreviation "nd" will be displayed.

In order to provide overall estimates of study intervention effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of participants treated at each site.

In order to provide overall estimates of treatment effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of participants treated at each site.

All analyses will be performed using SAS® Software version 9.4 or higher or R (www.r-project.org), Version 3.2.5 or higher.

9.1 Data Handling after Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations. Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

9.2 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the first study intervention administration will be used as the baseline measurement.

If an assessment that is planned to be performed before study intervention per protocol is performed on the same day as the start of study intervention, but the assessment time is not available, it will be assumed that it was performed prior to the first study intervention and will be considered as baseline.

Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on Study Day 1 will be considered to have been obtained after study intervention administration.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similar to an unscheduled post-dose measurement.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.3 Study Intervention Day

Day 1 is the day of start of study intervention, the day before is Day -1 (no Day 0 is defined). Study intervention day is defined relative to Day 1.

9.4 Definition of Duration and 'Time Since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first study intervention + 1) if not otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

9.5 Conversion Factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

9.6 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date among the following:

- Last known to be alive date collected on the 'Survival Follow-up' eCRF
    - In case of missing day in eCRF, last known to be alive date will be imputed as described in section 9.11.8.
- AE start and end dates
- Date of last study intervention
- Date of last tumor assessment
- Laboratory assessments (sample collection date)

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

9.7 Time Window

Descriptive statistics by visit or time point, e.g. for laboratory measurements, will include only data from scheduled visits. Unscheduled visits will be included in the derivation of baseline or worst on-treatment values.

For descriptive statistics over time by visit for HRQoL data and safety endpoints (laboratory, ECG, vital signs), only those visits that include at least 10 subjects will be printed in the summary tables and figures. However, "Discontinuation" and "End-of-Treatment" visits will always be included in the summary statistics despite the number of subjects who completed such visit.

For efficacy analyses (Duration of Response and Progression-Free Survival) described in Table 3~~Table 3~~ and Table 4~~Table 4~~, the following assessment windowing will be used:

- For all tumor assessments before week 29 use the 12-week interval (i.e. Day 202 or before).
- The 5th tumor assessment is followed by one 6-weekly assessment and 9 weekly assessments thereafter → taking +/-1 week into considerations, use the 15-week interval (6 weeks + 9 weeks) for all tumor assessment in week 29 and before week 35 (i.e. Day 203 – Day 244)
- The 6th tumor assessment is the first one followed by two subsequent 9-weekly tumor assessments → taking +/-1 week into considerations, use the 18-week interval for all tumor assessment in week 35 or later (i.e. Day 245 or later).

9.8 On-treatment Period

The on-treatment period is defined as the day of the first dose of study intervention to the last day of study intervention administration + 30 days, or the cut-off date or death, whichever occurs first.

9.9 Exposure Time

Refer to Section 13.

9.10 Follow-up Time

Different to exposure time, the follow-up time does not depend on the actual duration of treatment but rather provides an estimate for the potential to be treated for a certain period of time. This calculation provides a description on the maturity of data regardless of intercurrent events.

Follow-up time is defined in relation to the data cutoff based on participants enrollment (considering study cutoff date – start of study intervention +1), differentiated in categories of 6 months (= 180 days), 9 (= 270 days) and 12 months (360 days):

- ≤ 6 months vs > 6 months prior to data cutoff

- ≤ 9 months vs > 9 months prior to data cutoff
- ≤ 12 months vs > 12 months prior to data cutoff.

9.11 Imputation of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented and will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

9.11.1 Disease History

Incomplete dates for disease history (e.g. initial diagnosis date) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study intervention, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is the same as the year of the first study intervention, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

9.11.2 Adverse Events

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing).
- In all other cases, the missing onset day or missing onset month will be imputed by 1.
- Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

9.11.3 Previous and Concomitant Medication

Incomplete prior/concomitant medication start and stop dates will be imputed as presented in Table 1~~Table 1~~.

For the derivation of previous and concomitant medications following rules will be applied:

Previous Medication:

- Start date ≤ Start of study medication OR

- Start date = Missing

Concomitant Medication:

- End date ≥ Start of study medication AND (Start date ≤ End of study medication OR Start date=Missing) OR
- End date = Missing AND (Start date ≤ End of study medication OR Start date = Missing)

The derivation is based on the following principles

- Imputation leads to maximum reasonable duration
- Worst case: If medication is administered the same day as start of study medication, medication is classified as concomitant and previous

Table 1 Imputation rules for missing/incomplete start/end dates of medication

	Start Date	End Date
Day missing only	Day = 1	Day = Last day of month
Month missing	Day = 1 Month = Jan	Day = 31 Month = Dec
Year missing	Date = Missing No imputation	
All	if imputed date > date of death: imputation by date of death	

9.11.4 Dates of Study Intervention

Start date of study interventions:

- No imputation will be done.

End date of study interventions:

- In case the last date of study drug is missing or incomplete the date of last administration of study drug will be taken from the treatment termination eCRF pages.
- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the participant will be considered ongoing in the study and the cut-off date for the analysis will be used as the last dosing date.
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date) then the imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

= min (EOT date, death date), for all other cases

9.11.5 Death Date

For analysis of survival, partially missing death dates will be imputed as follows:

If only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last contact and the 15th day of the month.

Otherwise it will not be imputed.

Imputation of Death Date is used for survival analyses only. In the death listings, non-imputed data will be presented.

9.11.6 Tumor Assessments

All assessment dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the earliest of the scan dates associated with the evaluations will be used as the date of assessment.

If one or more tumor assessment dates for an evaluation are incomplete but other assessment dates are available, the incomplete date(s) are not considered as the assessment date and instead the earliest of all complete investigation dates is used (e.g. X-ray, CT-scan).

If all tumor assessment dates for evaluations have no day recorded, the 1st of the month is used.

If the month is not complete for a tumor assessment evaluation date, the month of the respective assessment will be considered as the date which is exactly between the previous and the following assessment. If both the previous and following assessments are not available, the respective assessment will not be used for any calculations.

9.11.7 Dates of Subsequent Anti-cancer Therapy

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses.

- If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anti-cancer therapy is before that date. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of the anti-cancer therapy.
- If both day and month are missing, no imputation will be performed.

Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

9.11.8 Last Known to be Alive Date

In case of missing day for date of last known to be alive collected on the ‘Survival Follow-up’ eCRF page, it will be imputed by using the first day of the month.

No other imputation will be done to last known to be alive date.

9.12 Scoring of HRQOL Data

Unless otherwise specified, HRQOL questionnaires (i.e., EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13) will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual. Missing data handling methods described in the scoring manual may be modified to implement the HRQoL estimand of interest and the associated sensitivity analyses. See Section 14.5 and Appendix 17.3 for details.

9.13 Age at Time of an Event

If Age at the Time of an Event is derived, the following algorithm will be used for the derivation

- Year of Event minus Year of Birth

9.14 Confidence Interval

Confidence intervals will be calculated as two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

9.15 Presentation of PK Concentration Data

Pharmacokinetic concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), Min, Median, and Max. Values below the lower limit of quantitation (LLOQ) will be imputed as zero.

Descriptive statistics of PK concentration data will be calculated using values with the same precision and same units as the source data and rounded for reporting purposes only.

Descriptive statistics will only be calculated for n>2 in which a measurement of BLQ represents a valid measurement. In case n ≤2, individual data will be presented (min, max) in summary tables.

The following conventions will be applied when reporting individual values and descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

9.16 Presentation of PK Parameters

Pharmacokinetic parameter data will be descriptively summarized using: n, Mean, standard deviation (SD), CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% CI for the GeoMean (LCI 95% GM, UCI 95% GM).

Pharmacokinetic parameter C_{max} will be reported with the same precision as the source data and All other PK parameters will be reported to 3 significant figures.

Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only. Descriptive statistics will only be calculated for a PK parameter when n>2. In case n ≤2, individual data will be presented (min, max) in summary tables.

The following conventions will be applied when reporting individual values and descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits

SD: 4 significant digits

CV%, GeoCV%: 1 decimal place

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented. Percentages will be presented with respect to the number of treated participants.

- Total number of participants screened (i.e. participants who gave informed consent)
- Number of participants who discontinued from the study prior to treatment overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, withdrawal of consent)
- Number and percentage of treated participants.

The end of study intervention status will be summarized by:

- Number and percentage of treated participants with ongoing study intervention
- Number and percentage of treated participants who completed study intervention (overall and by reason). A study treatment completer is a participant who discontinued study intervention due to death or disease progression.
- Number and percentage of treated participants who discontinued the study intervention (overall and by primary reason)

This block above will be repeated for each treatment component, i.e. Berzosertib and Topotecan.

The end of study status will be summarized by:

- Number and percentage of treated participants off-treatment and in follow-up

- Number and percentage of treated participants who completed or prematurely discontinued the study, grouped by main reason

A summary of participants who discontinued treatment and/or the study for reasons attributed to the COVID-19 pandemic will be provided.

In addition, the status after study treatment discontinuation/completion will be summarized by:

- Number and percentage of participants who started new anticancer therapy
- Number and percentage of participants with survival status alive/died/lost to follow-up

Disposition of participants by allocated study intervention group will be presented in a CONSORT Flow Diagram.

Additionally, the number of participants screened, and enrolled in each analysis set will be provided overall, by region (Europe, EEA (required by EudraCT), North America, and Asia), by country within region and by site.

A listing of discontinued participants will be provided.

A listing of pertinent participant disposition information for each participant will be provided, including first start date of new anti-cancer therapy.

10.2 Protocol Deviations / Exclusion from Analysis Sets

All protocol deviations, regardless if important or not, related to COVID-19 will be identified at SDTM level by using the Epi/Pandemic Related Indicator when the deviation description contains "COVID-19".

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive the wrong study intervention or an incorrect dose
- Participants that receive an excluded concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)

- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review or programming. The management of protocol deviations is outside the scope of this IAP document.

- Frequency tables as well as a listing will be provided based on the FAS/SAF for all important protocol deviations and the subset of protocol deviations that were attributed to the impact of the COVID-19 pandemic.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

If participants are excluded from the DLT Analysis Set, the reasons for exclusion will be listed.

10.3 COVID-19 Impact

An overview table and listing of the impact by COVID-19 will be prepared. The following aspects will be summarized:

- Any potential impact by COVID-19
- Adverse Events
- COVID-19 vaccinations
- Protocol deviations (important and non-important)
- Missed Visits (including number of missed visits)
- Missed efficacy evaluations (including number of missed efficacy evaluations)
- Tele-Visits performed (including number of Tele-Visits)
- Drug Administration - missed doses
- Drug Administration – dose interruptions
- Laboratory testing performed by external laboratory unit (only if at least 10 subjects are affected)
- Study Intervention Discontinuation

- Study Discontinuation
- Death

A listing will be generated using the MedDRA SMQ for COVID related terms. The following information will be provided:

- Study, Dose, Participant ID, Country
- Age, Gender, Race
- Date of first, last study intervention
- Covid-19 Guidance on Statistical Methods v2.0
- COVID-19 associated AE start date (day), COVID-19 associated AE stop date (day)
- AE-PT, verbatim,
- Toxicity Grade
- Seriousness
- Relationship to study intervention (investigator assessment)
- Action taken
- Outcome

COVID-19 related protocol deviations

- Summary of important COVID-19 related PDs by category and type of PD
- Summary of non-important COVID-19 related PDs by category of PD
- Listing of COVID-19 related PDs

Depending on the evaluation of the impact on the study objectives, further descriptive analyses may be considered

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the FAS/SAF.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Baseline Visit eCRF pages.

- The following demographic characteristics will be included:
  - Sex: Male, Female
  - Race: White, Black or African American, Chinese, Japanese, Korean, Other Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not permitted per local regulation, Other
  - Ethnic origin: Hispanic or Latino/Not Hispanic or Latino
  - Age (years)
  - Age categories:
    - < 65 years,
    - ≥ 65 years
      - 65-74,
      - 75-84,
      - ≥ 85 years
  - Pooled Region:
    - North America
    - Europe
    - Asia
  - Body Surface Area (BSA) (m^2) at Baseline
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2) at Baseline
  - ECOG Performance status (0,1,2) at Baseline
  - Karnofsky Performance status (0, 10, 20, …, 100%) at Baseline

Specifications for computation:

$$\text{BSA } [m^2] = \sqrt{\frac{height[cm] \times weight[kg]}{3600}}$$

BMI [kg/m²] = (weight [kg])/⟦height[cm]⟧^2 × 10000

Site codes will be used for the determination of the participant's geographic region.

Individual demographic characteristics and physical measurements will be listed.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term (PT) as event category and system

organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order. Individual medical history data will be listed.

11.3 Other Baseline Characteristics

Information on disease characteristics collected at baseline will be summarized. Summary statistics will be presented for:

- Time since initial cancer diagnosis [months] derived as (date of given informed consent – date of initial cancer diagnosis)/30.4375
- Stage at initial diagnosis: limited/extensive stage disease
- Prior use of immunotherapies
- Presence of brain metastases at baseline as per IRC data
- Presence of liver metastases at baseline as per IRC data
- Number of tumor sites at baseline: 1, 2, 3 or >3 as per IRC data

Baseline characteristics with respect to vital signs, physical examinations, and hematology/biochemistry are described in Section 15 (Safety Analyses).

Listing of disease history will be provided for all relevant data (as collected on the eCRF page for "Disease History") and derived variables used in the above text.

11.4 Prior Anti-cancer Therapy

Prior anti-cancer therapies are collected from the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details" and "Prior Anti-Cancer Surgeries Details" eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer treatment
- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer radiotherapy
- Participants with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- At least one prior anti-cancer drug therapy
- Type of prior anti-cancer therapy: Cytotoxic therapy, Endocrine therapy, Monoclonal antibodies therapy, Small molecules, Immunotherapy, Other.

- Intent of Therapy: Neo-Adjuvant, Adjuvant, Metastatic or Locally advanced
- Best response to last prior treatment: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD), Not evaluable, Unknown.
- Time from documented progressive disease date to the start of study treatment [months] derived as (start date of study treatment – documented progression disease date)/ 30.4375

The prior anti-cancer drugs will also be summarized based on the number and percentage of participants by the drug class and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. Prior anti-cancer drugs categorized as immunotherapies will also be summarized based on the number and percentage of participants by the preferred term.

The listings of prior anti-cancer treatments and procedures will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of prior anti-cancer drug therapies
- Listing of prior anti-cancer radiotherapy
- Listing of prior anti-cancer surgeries

12 Previous or Concomitant Medications/Procedures

The following analyses will be performed based on the FAS/SAF. The World Health Organization Drug dictionary (WHO-DD) will be used for coding of prior and concomitant medications and they will be described using Preferred Term (PT) as applicable.

Concomitant treatments are medications, other than study treatment, which are taken by participants any time during the on-treatment period, see Section 9.8.

Previous medications are medications, other than study treatment and pre-medications for study treatments, which started before first administration of study treatments.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date, see Section 9.11.3 for details on the classification of medications with partial start and end dates.

Concomitant and previous treatment each will be summarized by number and percentage of participants from the “Concomitant medication” eCRF. Preferred term will be tabulated as given from the WHO-DD dictionary most current version. The summary tables will be sorted by decreasing frequency of preferred term. In case of equal frequency regarding preferred term alphabetical order will be used. Each participant will only be counted once, even if he/she received the same medication at different times.

Concomitant and previous medication details will be included in a listing, along with a flag to indicate whether the medication was identified as a previous or concomitant medication.

All relevant details of **Concurrent procedures** captured on the CRF page "Concomitant Procedures" will be listed.

Subsequent anti-cancer therapy

Anti-cancer therapy after discontinuation will be summarized according to the respective eCRF pages. Treatments will be categorized by means of coding and medical review. The same approach as for concomitant medications will be applied based on preferred term.

Number and percentage of participants with any anti-cancer treatment post discontinuation and by type (Anti-cancer treatment [Cytotoxic therapy, Endocrine therapy, Monoclonal antibodies therapy, Small molecules, Immunotherapy, Other], Radiotherapy, Surgery) will be presented.

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on the FAS/SAF by treatment group/dose level.

All dosing calculations and summaries will be based on "Berzosertib Administration Details" and "Topotecan Administration Details" eCRFs pages.

Berzosertib at a dose of 210 mg/m^2 is administered IV after completion of topotecan administration on Day 2 and Day 5, of each 21-day cycle. Topotecan at a dose of 1.25 mg/m^2 is via IV administration on Days 1 through 5 of each 21-day cycle. Specific to DL1 in the Safety Run-in Part, the dose of Berzosertib is 105 mg/m^2.

No imputation for missing start dates of study interventions will be done. In case the last date of study intervention is incomplete the date of last study drug administration will be taken from the End of Treatment page. See Section 9.11.4 for further details.

Total number of infusions

For each study intervention, total number of infusions is calculated as the sum of the actual number of infusions that a participant received across cycles, regardless of infusion delays, interruptions, or any other types of deviations from the protocol required schedules. An infusion is regarded to be administered if either the actual dose received is > 0 or the duration of the infusion is > 0.

Cumulative dose

Cumulative dose (mg/m^2) per participant in a time period for both Berzosertib and Topotecan treatments is the sum of the BSA-adjusted actual dose amount that a participant received within that period. Cumulative dose will be calculated for each 21 day period/cycle, e.g. Day 1-21, 22-42, 43-64, etc. and also over the entire treatment period.

BSA-adjusted actual dose amount (mg/m^2) = actual dose amount (mg) / BSA (m^2)

The actual dose amount (mg) is taken at each dosing day from "Actual dose" on the CRF pages "Berzosertib Administration Details" and "Topotecan Administration Details" at each dosing day. BSA will be derived as defined in Section 11.1 using the most recent height and weight entries on the Vital Signs CRF pages.

In case the BSA is missing the latest BSA available will be used for calculation following the LOCF principle. If BSA cannot be derived due to missing weight and/or height data, data from the last available visit will be used instead.

Planned dose

For Berzosertib, the value for initial planned dose is 105 mg/m^2 for the DL1 cohort in the Safety Run-in and 210 mg/m^2 for DL2 cohort in the Safety Run-in and the Main study. The number of planned administrations per cycle is 2 (i.e. on Days 2 and 5). For Topotecan, the value for initial planned dose is 1.25 mg/m^2 and the number of planned administrations per cycle is 5 (i.e. on Days 1 through 5).

For each study intervention, planned dose (mg/m^2) per time period, i.e. cycle or overall, is calculated based on the initial planned dose (mg/m^2) and the number of planned administrations in the time period of interest, either cycle or overall, as follows:

Planned dose (mg/m^2) = initial planned dose x # of cycles x # of doses per cycle

Duration of therapy

Duration will be calculated differently based on the dosing days and frequency as follows.

Participants will receive 2 infusions of Berzosertib on Days 2 and 5 in each 21-day cycle. Hence, duration of Berzosertib therapy is calculated as follows:

$$Duration\ of\ Berzosertib\ (weeks) = \frac{(date\ of\ last\ dose - date\ of\ first\ dose + 18)}{7}$$

Participants will receive 5 infusions of Topotecan on Days 1 through Day 5 in each 21-day cycle. Hence, duration of Topotecan therapy is calculated as follows:

$$Duration\ of\ Topotecan\ (weeks) = \frac{(date\ of\ last\ dose - date\ of\ first\ dose + 17)}{7}$$

Actual Dose Intensity (DI)

The DI per week is calculated for each study intervention as follows:

$$Actual\ DI\ (mg/m^2/week) = \frac{total\ cumulative\ dose\ (mg/m^2)}{treatment\ duration\ (weeks)}$$

Relative Dose Intensity (RDI)

The RDI (%) is calculated for each study intervention by dividing the DI by the planned dose intensity per week of the appropriate study intervention.

Planned dose intensity per week will be derived by dividing planned dose (mg/m^2) by duration of therapy (weeks).

Dose reductions

A dose reduction is defined as a dose compliance < 90% at a single dose. Dose compliance is calculated, for each dose received, as the percentage of the BSA-adjusted actual non-zero dose (mg/m^2) received with respect to the initial planned BSA-adjusted dose on Cycle 1 Day 1 in case of Topotecan or Cycle 1 Day 2 for Berzosertib.

$$\text{Dose compliance (\%)} = \frac{actual\ non\ zero\ dose\ amount\ (mg/m^2)}{initial\ planned\ dose\ amount\ (mg/m^2)}$$

Minimum dose compliance will be derived for each participant by selecting the minimum dose compliance across all of that participant's non-zero doses received.

Participants with minimum dose compliance ≥ 90% are considered to have no dose reductions.

Summary of exposure

The summary of exposure will include the following information (as defined above) for each study intervention:

- Duration of therapy (weeks): overall distribution and by categories of ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 – 18 weeks, >18 – 24 weeks, >24 – 30, >30 – 36, and every 9 weeks after 36 weeks
- Total number of infusions received
- Total cumulative dose (mg/m^2)
- Dose intensity (mg/ m^2/week)
- Relative dose intensity (%): overall distribution and by categories of < 60%, ≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90% - ≤110%, >110%
- Participants with at least one dose reduction (dose compliance < 90%); and categories of minimum actual dose, with respect to initial planned dose, of ≥ 70% - < 90%, ≥ 50 - < 70%, and < 50%.

Number of participants with a change in dose due to COVID-19 will also be presented.

All relevant study drug exposure data will be presented in data listings, including reasons for dose adjustments and missed doses (e.g., due to adverse event or other reasons).

Time to permanent dose reduction

A dose reduction is defined as any reduction to the initial planned BSA-adjusted dose on Cycle 1 Day 1 in case of Topotecan or Cycle 1 Day 2 for Berzosertib of > 10%.

For the derivation of BSA (as described in Section 11.1) the most current available weight (in kg), and the height (in cm) will be used.

Only permanent dose reduction will be considered, i.e., dose reduction with a subsequent administration of ≥ 90% of planned dose will not be taken into account.

Time to permanent dose reduction of Berzosertib/Topotecan/any study treatment is defined by

- Date of 1st dose reduction of Berzosertib – Date of first study drug administration +1
- Date of 1st dose reduction of Topotecan – Date of first study drug administration +1
- Date of 1st dose reduction (any study treatment) – Date of first study drug administration +1

For patients without dose reduction, time to permanent dose reduction is censored at

- Date of last dose administration of Berzosertib – Date of first study drug administration + 17
- Date of last dose administration of Topotecan – Date of first study drug administration + 17
- Date of last dose administration of any study treatment – Date of first study drug administration + 17

Of note, although Berzosertib is administered on Day 2 the first time, the date of first drug administration is used as starting date for both drugs, i.e., for Berzosertib and Topotecan the same start date will be used.

Note: 17 days reflects the planned number of 16 days without any study treatment between two subsequent cycles plus 1 day.

Kaplan-Meier plots on time to dose reduction for each treatment component will be performed for the main part of the study. KM estimates at 21 days, 42 days, 63 days, and 84 days will be shown.

14 Efficacy Analyses

The following analyses will be performed based on the FAS/SAF.

14.1 Primary Objective: Objective Response

14.1.1 Primary Estimand

Endpoint

Objective Response (OR) according to RECIST 1.1, Eisenhauer EA, et. al., as assessed by IRC.

OR is defined as a confirmed BOR of complete response (CR) or partial response (PR). Confirmation of the response according to RECIST 1.1 is required no sooner than 4 weeks after the initial documentation of CR or PR. Patients with BOR of NE are considered as non-responders for OR.

Confirmed BOR is derived as follows:

- CR = at least two determinations of CR at least 4 weeks apart (with no PD in between)
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR), with no PD in between
- SD (applicable only to participant with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after start date (and not qualifying for CR or PR), i.e. Study Day 42 or later.
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks (42 days) after start date (and not qualifying for CR or PR).
- PD = PD ≤ 12 weeks (84 days) after start date (and not qualifying for CR, PR, non-CR/non-PD or SD). The condition PD in or out of the respective timeframe addresses a missing data situation in view of determining best overall response as PD or NE, respectively. Clinical deterioration will not be considered as documented disease progression.
- Not Evaluable (NE): all other cases.

SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the minimum duration for SD definition has been met.

The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

Population

Patients with relapsed, platinum-resistant SCLC.

Treatment

Berzosertib + topotecan

Intercurrent Event Strategy

- Discontinuation of treatment: Treatment-policy strategy, i.e., regardless of the intercurrent event
- Start of subsequent anticancer treatment: while not treated with subsequent anticancer therapy strategy; i.e., ignoring tumor assessments after the intercurrent event. If a tumor assessment was performed on the same day as start of new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR.
- Progression according to RECIST 1.1: While not progressed strategy, i.e., considering assessments up to the intercurrent event

Population Level Summary

The ORR by treatment group/dose level will be determined as the proportion of participants with objective response, along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the SAS FREQ procedure using the EXACT option).

Intercurrent Event overview

For Sections 14.1.1 and 14.1.2.1, the frequency of intercurrent events relevant to OR will be tabulated.

BOR

The frequency (number and percentage) of participants in each BOR category (CR, PR, SD, PD, and NE) will be tabulated. BOR will be presented in all summary tables where OR is provided (i.e. Sections 14.1.1, 14.1.2.1, and 14.1.3.1), according to the definition of CR, PR and SD in the corresponding section.

A summary table for intercurrent events based on IRC assessments will also be provided.

For the BOR according to IRC/INV (Sections 14.1.1 and 14.1.2.1) participants with BOR of NE will be summarized by reason for having NE status. The following reasons will be used in hierarchical order:

- No measurable disease at baseline assessment
- No post-baseline assessments due to death before first post-baseline assessment
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- Subsequent anticancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after start date)

- PD too late (>12 weeks after start date)

A swimmer plot displaying some key radiological milestones will be produced, sorted by decreasing follow-up time, using color code for OR. For each participant, the time from treatment start until end of follow-up.

14.1.2 Sensitivity Analyses

14.1.2.1 Objective Response according to Investigator

The sensitivity analysis for OR will be performed similar to the primary estimand (Section 14.1.1), however, the endpoint will be derived based on Investigator assessment instead of IRC assessment.

In addition, a summary of the IRC assessment versus investigator assessment will be provided including numbers of concordant and discordant assessments. Table 2~~Table 2~~ outlines the possible outcomes by investigator and IRC.

Table 2 Possible Outcomes for Investigator vs IRC

		IRC	
Investigator		Responder	Non-responder
	Responder	a	b
	Non-responder	c	d

N= a+b+c+d.
Non-responder includes participants with BoR of NE

The following measure of agreement and discordance will be calculated:

- Total Event Discrepancy Rate: (b+c) / N
- Total Event Agreement rate: (a+d) / N
- Proportion of responders assessed by investigator, but not confirmed by IRC: b / (a+b).

14.1.2.2 Subgroup Analyses

Subgroup analyses will be performed on the primary estimand based on the FAS/SAF for all subgroup levels defined in Section 8.2. All subgroup analyses are exploratory. No adjustment for multiplicity will be performed. In the case of a low number of participants within a category (<5% of the treated population), the categories will be pooled when meaningful.

ORR will be summarized at each subgroup level along with a 2-sided 95% CI using the Clopper-Pearson method.

The ORR and its corresponding 95% CI of all subgroups will also be presented in a forest plot together with the respective results for the primary analysis set.

14.1.3 Supplementary Analyses

14.1.3.1 Unconfirmed Objective Response (IRC)

Unconfirmed Objective Response will be derived similar to the primary estimand (Section 14.1.1), however, confirmation of CR/PR is not required.

Unconfirmed BOR is derived as follows:

- CR = at least one assessment of objective status of CR documented before progression.
- PR = at least one assessment of objective status of PR documented before progression (and not qualifying for CR).
- All other categories will be derived as for the primary estimand.

14.1.4 Further Endpoints

14.1.4.1 Disease Control

Disease control is defined similar to objective tumor response, but additionally to CR and PR also includes best overall response of SD. DCR will be calculated along with the two-sided 95% CI using the Clopper-Pearson method and will be presented in all summary tables where OR is provided (i.e. Sections 14.1.1, 14.1.2.1, and 14.1.3.1), according to the definition of CR, PR and SD in the corresponding section.

14.1.4.2 Tumor Shrinkage

Tumor shrinkage (%) is defined as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- [(Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline] × 100

The maximum tumor shrinkage (%) will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anticancer therapy, as:

- Minimum of [(sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline] × 100

The tumor shrinkage as well as the first occurrence of a new lesion and participant off treatment will be displayed against time point (weeks) in a line plot (spider plot).

A waterfall plot of maximum tumor shrinkage will be created, including all participants with measurable disease at baseline and at least one valid post-baseline assessment.

Tumor Shrinkage will be evaluated for tumor assessments according to IRC and investigator.

14.2 Secondary Objective: Duration of Response

14.2.1 Secondary Estimand

Endpoint: DoR according to RECIST 1.1 as assessed by IRC

DoR is defined for participants with confirmed objective response as time from first documentation of objective response (CR or PR) to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention.

For responders who do not have an event (PD or death) or with an event after two or more missing tumor assessments, DoR will be censored on the date of the last adequate tumor assessment (i.e. a tumor assessment with a result that is neither "NE" nor "NA").

DoR (months) = [date of event or censoring– first date of OR +1]/30.4375

The censoring and event date options to be considered for the DoR analysis are presented in Table 3~~Table 3~~.

Table 3 Outcome and event dates for DoR

Status		Outcome	Date of event / censoring
Responders who progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD	Event [part of composite intercurrent event strategy]	Minimum (Date of PD, Date of death)
	Otherwise[a]	Censored	Date of last tumor assessment with outcome CR, PR or SD
Responders who neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD

[a] Derivation of 2 or more missing tumor assessments according to the following rules:

Last Evaluable Scan Prior to Event (PD or Death), days since treatment start	Censor if Duration Between Last Scan and Event
[Study Day 1, Study Day 202]	> 84 days (12 weeks)
[Study Day 203, Study Day 244]	> 105 days (15 weeks)
> Study Day 245	> 126 days (18 weeks)

Population

Patients with relapsed, platinum-resistant SCLC and confirmed OR according to RECIST 1.1 as assessed by IRC.

Treatment

Berzosertib + topotecan.

Intercurrent Event Strategy

- Death within 2 scheduled tumor assessments: Composite strategy, i.e. death will be considered as event of interest.

- Discontinuation of treatment: Treatment Policy strategy, i.e. ignoring the intercurrent event.

- Start of subsequent anti-cancer treatment: treatment-policy strategy, i.e. ignoring the intercurrent event.

Population Level Summary

Median duration of response and Kaplan-Meier (KM) estimates.

Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics including the median DoR with two-sided 95% CIs. In particular, the DoR rate at 3, 6 and 12 months and estimates for every 6 months thereafter will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with each event type (PD or death) will be presented. The DoR or censoring time and the reasons for censoring will also be presented in a participant listing. Kaplan-Meier plots of DoR will also be provided.

If the number of participants with OR is small (less than 6 responders), the Kaplan-Meier method may not provide reliable estimates. In this case, only listings will be provided.

The frequency of participants with DoR

- < 3 months

- ≥ 3 months and < 6 months

- ≥ 6 months and < 9 months and

- ≥ 9 months

will be provided; additionally, the number of participants with DoR and at least one treatment ongoing in each category will be indicated.

14.2.2 Sensitivity analysis

The sensitivity analysis for DoR will be performed similar to the primary estimand (Section 14.2.1) but using Investigator assessment instead of IRC assessment for OR.

14.3 Secondary Objective: Progression-Free Survival

14.3.1 Secondary Estimand

Endpoint

Progression Free Survival (PFS) time is defined as the time from start date to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first.

PFS time (in months) = (Date of PD or death – study intervention start date + 1)/ 30.4375 (months)

The tumor response will be determined according to RECIST 1.1 and assessed by the IRC. Censoring rules for PFS are described in Table 4~~Table 4~~ below.

Table 4 Outcome and event dates for PFS

Status		Outcome	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or first study intervention	Event [part of composite intercurrent event strategy]	Minimum (Date of PD, Date of death)
	Otherwise[a]	Censored	Date of last tumor assessment with outcome CR, PR or SD or treatment start date (whatever occurs later)
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or treatment start date (whatever occurs later)

[a] Derivation of 2 or more missing tumor assessments according to the following rules:

Last Evaluable Scan Prior to Event (PD or Death), days since treatment start	Censor if Duration Between Last Scan and Event
[Day 1, Day 202]	> 84 days (12 weeks)
[Day 203, Day 244]	> 105 days (15 weeks)
> Day 245	> 126 days (18 weeks)

Treatment

Berzosertib + topotecan.

Intercurrent Event Strategy

- Death within 2 scheduled tumor assessments: Composite strategy, i.e. death will be considered as event of interest.
- Discontinuation of treatment: Treatment Policy strategy, i.e. ignoring the intercurrent event.
- Start of subsequent anti-cancer treatment: Treatment policy strategy, i.e. ignoring the intercurrent event.

Population Level Summary

Median duration of response and Kaplan-Meier (KM) estimates.

Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics including the median PFS with two-sided 95% CIs. In particular, the PFS rate at 3, 6 and 12 months and estimates for every 6 months thereafter will be estimated with corresponding two-

sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with each event type (PD or death) will be presented. The PFS or censoring time and the reasons for censoring will also be presented in a participant listing.

A summary table for intercurrent events based on IRC assessments will also be provided, as well as Kaplan-Meier plots of PFS.

14.3.2 Sensitivity Analysis

The following sensitivity analyses will be performed:

- As main estimator, but considering all deaths as events, irrespective of time of last tumor assessment.
- As main estimator, but using Investigator assessment instead of IRC assessment.
- As main estimator, but using While Not on subsequent anticancer therapy strategy for intercurrent event of start of subsequent anticancer treatment, meaning that tumor assessments after the intercurrent event start are ignored.

In addition, a summary of the IRC assessment versus investigator assessment of PFS will be provided including numbers of concordant and discordant assessments. Table 5~~Table 5~~ outlines the possible outcomes by investigator and IRC.

Table 5 Possible Outcomes for Investigator vs IRC

		IRC	
Investigator		Event	Censored
	Event	a [= a1 + a2 + a3]	b
	Censored	c	d

a1: number of agreements on timing and occurrence of event;
a2: number of times agreement on event status but investigator declares event later than IRC;
a3: number of times agreement on event status but investigator declares event earlier than IRC;
N= a+b+c+d.

The following measure of agreement and discordance will be calculated:

- Total Event Discrepancy Rate: (b+c) / N
- Total Event Agreement rate: (a+d) / N
- Rate of Unconfirmed Investigator Events: b / (a+b)
- Early Discrepancy Rate (EDR): (a3+b) / (a+b)
- Late Discrepancy Rate (LDR): (a2+c) / (a2+a3+b+c)

- Overall Discrepancy Rate: (a2+a3+b+c) / N

Subgroup analysis

The median PFS time and associated 2-sided 95% CI will also be summarized at each subgroup level defined in Section 8.2.

14.4 Secondary Objective: Overall Survival

14.4.1 Secondary Estimand

Endpoint

Overall survival (OS) is defined as the time from start date of first study intervention to the date of death due to any cause. OS for participants without death prior to cut-off will be censored at date of last contact (see Section 9.6). Overall survival in months is calculated as follows:

OS (months) = [date of death or censoring– study intervention start date +1]/30.4375

Population

Participants with relapsed, platinum-resistant SCLC.

Treatment

Berzosertib + topotecan

Intercurrent Event Strategy

- Discontinuation of treatment: Treatment-policy strategy, i.e., regardless of the intercurrent event
- Start of subsequent anti-cancer treatment: Treatment-policy strategy, i.e., regardless of the intercurrent event

Population Level Summary

Median OS time and KM estimates

OS will be displayed graphically and analyzed using Kaplan-Meier methodology analogous to that used for PFS as described in Section14.3. Additionally summary table for intercurrent events will also be provided.

14.4.2 Sensitivity Analysis

Subgroup analysis

The median OS time and associated 2-sided 95% CI will also be summarized at each subgroup level defined in Section 8.2.

14.5 Secondary Objective: Patient Reported Outcome

The analyses specified below will be performed for the FAS/SAF. Note that quality of life assessments were not collected for the Japanese Safety run-in DL1 participants so they are excluded from the analyses listed in this section.

PROs will be assessed by the EuroQol 5 Dimension 5 Level Scale (EQ-5D-5L), the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), and module QLQ-LC13 (lung specific).

The EQ-5D-5L comprises 5 questions and a visual analogue scale (VAS). The questionnaire is used to calculate the utility index, used in economic evaluations. The 5 items are mobility, self-care, usual activities of daily living, pain/discomfort, anxiety/depression with 5 descriptive levels ranging from "no problem to…" to "extreme…/unable to do…." The VAS ranges from 0 to 100 where 0 is "the worst health you can imagine" and 100 is "the best health you can imagine." The recall period is defined as "today."

The EORTC QLQ-C30 assesses the quality of life of cancer patients with 30 questions including the dimensions of activities of daily living, pain, fatigue, shortness of breath, appetite loss, nausea, vomiting, sleeping disturbances, diarrhea, difficulties to concentrate, anxiety and depression, memory loss, social activities, financial burden, impression of overall health and impression of overall quality of life. Questions 1-28 are measured in a range from 1-4 where 1 represents "Not at All" and 4 represents "Very Much", and questions 29-30 are measured in a range from 1-7 where 1 represents "Very poor" and 7 represents Excellent. The recall period is defined as "during the past week."

The EORTC QLQ-LC13 comprises 13 questions incorporated into 1 multi-item scale designed to evaluate lung cancer symptoms such as dyspnea, different types of pain, cough, hemoptysis, dysphagia, sore mouth, alopecia, and peripheral neuropathy. For each domain and item, a linear transformation is applied to standardize the raw score to a range from 0 to 100, with 100 representing the best possible function/quality of life, and highest burden of symptoms for symptom domains and single items. The recall period is defined as "during the past week."

For the purpose of analysis and reporting, PRO assessments until end of treatment will be considered. The end of treatment is defined as the first non-missing PRO assessment after last administration i.e., end of treatment visit or safety follow-up visit whichever comes earlier.

14.5.1 PRO Completion and Compliance

Compliance and completion rates will be displayed for the EORTC QLQ-C30, the EORTC QLQ-C13, and the EQ-5D-5L by the baseline assessment and subsequent assessments. The magnitude and reason for missingness, as collected on the 'Quality of Life Questionnaire' eCRF page, will be provided by scheduled assessment. The following measures will be provided per instrument:

- Number and percentage of treated participants with who returned the questionnaire (i.e. questionnaire with at least one non-missing item) by visit

- Number and percentage of missing questionnaires by visit and reasons

For all percentages mentioned above, denominator will be calculated as the number of participants for whom a scheduled PRO assessment is expected at the visit.

Additionally, completion and compliance rates will be calculated for each instrument at each scheduled visit as follows:

$$\%\ \text{Compliance} = 100 \times \frac{\text{number of subjects with at least one item of the PRO questionnaire available at the visit}}{\text{number of participants for whom a PRO score is expected at the visit}}$$

$$\%\ \text{Completion} = 100 \times \frac{\text{number of participants with evaluable PRO score available at the visit}}{\text{number of participants for whom a PRO score is expected at the visit}}$$

Evaluable PRO score will be based on the number of participants who completed the questionnaire (incomplete ones will be excluded) so that all relevant scores can be calculated according to the Scoring Manual (see Appendix 17.3).

14.5.2 Secondary Estimand

Endpoint

Change from baseline in physical functioning measured by the EORTC QLQ-C30; ; cough, dyspnea, and chest pain measured by EORTC QLQ-LC13 (lung cancer specific questionnaire); health state as measured by VAS as a component of the EQ-5D-5L.. Scores will be derived as described in Appendix 17.3..

Population

Participants with relapsed, platinum-resistant SCLC.

Treatment

Berzosertib + topotecan

Intercurrent Event Strategy

- Discontinuation of treatment: while on treatment strategy, i.e. ignoring PRO assessments after the intercurrent event
- Start of subsequent anticancer therapy: while not treated with subsequent anticancer therapy strategy, i.e. ignoring PRO assessments after the intercurrent event
- Death: while alive strategy, i.e., considering PRO assessments before the intercurrent event

Population Level Summary: Multi-item scales

Mean change from baseline will be calculated and presented for physical functioning, dyspnea and VAS. A summary table and a boxplot displaying mean change from baseline for each scheduled time-point will be provided.

Population Level Summary: Single-item scales

Proportion of participants with ≥ 1 category improvement and proportion of participants with ≥ 1 worsening in single-item symptoms (i.e. cough and chest pain)

PRO Responder's Analysis

For QLQ-LC13 cough and chest pain, the number and percentage (proportion) of participants in the following categories reflecting meaningful within-patient change from baseline will be summarized at each visit of the on-treatment period:

- Participants with at least 1 category improvement (i.e., a negative change from baseline in item score)
- Participants with no change (i.e., no change from baseline in item score)
- Participants with 1 category worsening (i.e., positive change from baseline in item score)
- Participants with more than 1 category worsening (i.e., positive change from baseline in item score)

Results will be displayed in a bar chart with scheduled time-points in x-axis and percentage of subjects by symptom in y-axis. Color code will be used for improvement, stable, worsening by 1 category and worsening by more than 1 category. The percentage will be calculated among participants for whom the QLQ-LC13 item of interest is available at both baseline and the visit.

Reference listings of QLQ-C30, QLQ-LC13 and EQ-5D-5L scores per visit will be provided.

15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

If not otherwise stated, safety analyses will be done on the FAS/SAF and according to the as-treated principle.

15.1 Dose Limiting Toxicity (Primary Endpoint – Safety Run-in Part)

The number and proportion of participants experiencing a DLT confirmed by the Local SMC of the Safety Run-in Part will be reported by dose level. Analysis will be based on the DLT Analysis Set in the Safety Run-in Part. A listing of DLTs will also be provided.

Details of DLT analyses for Local SMC are described in a separate IAP.

15.2 Adverse Events (Secondary Endpoint)

Treatment-emergent adverse events (TEAE) are those events with onset dates occurring within the on-treatment periods as defined in Section 9.8, or events with onset dates before the on-treatment period and worsening during the on-treatment period.

Adverse events related to study treatment are those events with relationship missing, unknown or yes.

Serious adverse events (SAEs) are AEs with the eCRF field "Serious adverse event" marked yes on the Adverse Events eCRF pages.

AEs leading to temporary treatment discontinuation are those with the action "Drug interrupted" selected on the Adverse Events eCRF pages.

AEs leading to permanent treatment discontinuation are those with the action "Drug withdrawn" checked on the Adverse Events eCRF pages.

AEs leading to dose modification are those with the action "Dose reduced" checked on the Adverse Events eCRF pages.

AEs leading to death are AEs with NCI-CTCAE toxicity Grade 5 or outcome "fatal".

All analyses described in this section will be based on TEAEs if not otherwise specified.

Treatment-emergent adverse events (TEAE) are those events with onset or worsening dates occurring within the on-treatment periods as defined in Section 9.8.

This includes also AEs ongoing at baseline, which first improve under study intervention and then worsen irrespective of baseline. Adverse events with changes in toxicity grade, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry, supported in eCRF v8.4 by 'AENEWID' in SUPPAE. Records of the same AE will be considered as one event in the analysis. If the severity of the reported event worsens after start of treatment, the TEAE flag will be re-evaluated for the worse and the subsequent records as per the TEAE definition. If the worse record starts outside of the on-treatment period, it will not appear on the summaries/listings of TEAEs, unless otherwise specified. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. The overall outcome of the adverse event is the outcome of the last event in the sequence. When such AEs are listed, start, end date and outcome should be provided together with change date, toxicity grade, and seriousness per episode.

The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listing. AEs attributed to the impact of COVID-19 will also be flagged in listing.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest, by treatment group/dose level, primary SOC and PT in alphabetical order.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category. In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

Incomplete AE start and stop dates will be handled as described in Section 9.11.2.

15.2.1 All Adverse Events

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following:
  - TEAEs
  - TEAEs, Grade ≥ 3, Grade ≥ 4,
  - Any Related TEAEs
  - Berzosertib Related TEAEs
  - Topotecan Related TEAEs
  - Any Related TEAEs, Grade ≥ 3, Grade ≥ 4
  - Berzosertib Related TEAEs, Grade ≥ 3, Grade ≥ 4
  - Topotecan Related TEAEs, Grade ≥ 3, Grade ≥ 4
  - Serious TEAEs
  - Related Serious AEs
  - Berzosertib Related Serious TEAEs
  - Topotecan Related Serious TEAEs
  - TEAEs leading to death
  - Berzosertib Related TEAEs leading to death
  - Topotecan Related TEAEs leading to death
  - Infusion-related reactions
- TEAEs by SOC and PT and worst grade
- Berzosertib Related TEAEs by SOC and PT and worst grade
- Topotecan Related TEAEs by SOC and PT and worst grade
- Any Related TEAEs by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Berzosertib Related TEAEs leading to death by SOC and PT

- Topotecan Related TEAEs leading to death by SOC and PT
- Any treatment Related TEAEs leading to death by SOC and PT
- TEAEs by SOC and PT: displaying in separate columns the All TEAEs / Related TEAEs / Grade ≥ 3 TEAEs / Related Grade ≥ 3 TEAEs
- TEAEs excluding SAEs, with frequency ≥ 5% in any treatment arm by SOC and PT

A horizontal bar chart will be produced to display TEAEs by worst grade. AE preferred terms will be displayed along the vertical axis and the percentage of subjects with an AE in each preferred term will be displayed on the horizontal axis. Within each bar, incidence of TEAEs of toxicity grade 3-5 will be shown in a darker shade and TEAEs of toxicity grade 1-2 will be displayed in a lighter shade. Only TEAEs occurring in at least 5% of participants will be included in the figure. Preferred terms will be sorted in order of descending frequency of incidence.

Additionally, a table and listing of AEs on participants from Chinese sites will be provided for IA. These sites will be identified among the FAS/SAF analysis set by selecting site code "70" and "71" included at the beginning of the participant identifier (e.g.: **70**10001).

- The table will contain all TEAEs by SOC and PTs.
- The listing will include all Grade ≥ 3 or serious AEs. It will display the following information: AE SOC and PT, cohort, dose level, participant identifier, age, sex, race, site of primary tumor, end of treatment date, AE start and end date (relative day to treatment start date), relationship to study treatment, grade, action on Berzosertib/topotecan, outcome, occurrence, seriousness (Y/N), during DLT period (Y/N), DLT as per investigator (Y/N).

15.2.2 Adverse Events Leading to Discontinuation of Study Treatment

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to discontinuation/dose modification of each study intervention. If indicated by *, tables by PT and primary SOC in alphabetical order will be provided:

Temporary discontinuation

- TEAEs leading to temporary discontinuation of Berzosertib*
- TEAEs leading to temporary discontinuation of Topotecan*
- TEAEs leading to temporary discontinuation of at least one study intervention
- TEAEs leading to temporary discontinuation of both study interventions
- Related TEAEs leading to temporary discontinuation of Berzosertib* (respective summary for Berzosertib and Topotecan)
- Related TEAEs leading to temporary discontinuation of Topotecan* (respective summary for Berzosertib and Topotecan)

Permanent discontinuation

- TEAEs leading to permanent discontinuation of Berzosertib*

- TEAEs leading to permanent discontinuation of Topotecan*
- TEAEs leading to permanent discontinuation of at least one study intervention*
- TEAEs leading to permanent discontinuation of both study interventions*
- Related TEAEs leading to permanent discontinuation of Berzosertib* (respective summary for Berzosertib and Topotecan)
- Related TEAEs leading to permanent discontinuation of Topotecan* (respective summary for Berzosertib and Topotecan)

Dose reduction

- TEAEs leading to dose reduction of Berzosertib*
- TEAEs leading to dose reduction of Topotecan*
- TEAEs leading to dose reduction of at least one study intervention
- TEAEs leading to dose reduction of both study interventions
- Related TEAEs leading to dose reduction of Berzosertib* (respective summary for Berzosertib and Topotecan)
- Related TEAEs leading to dose reduction of Topotecan* (respective summary for Berzosertib and Topotecan)

15.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events (Secondary Endpoint)

15.3.1 Deaths

All deaths, deaths within 30 days after last dose of study treatment, death within 60 days after first dose as well as reason for death, will be tabulated based on information from the "Death" and "Survival Follow-Up" CRFs.

- Number of Deaths
- Number of Deaths within 30 days after last dose of any study intervention
- Number of Deaths within 60 days after first dose of any study intervention
- Primary Reason of Death
  - Progressive disease and/or disease related condition
  - Event related to Berzosertib
  - Event related to Topotecan
  - Event related to Berzosertib and Topotecan
  - Event unrelated to study treatment
  - Unknown

In addition, date and cause of death will be provided in the individual participant data listing together with selected dosing information (date of first / last administration, dose and number of infusions separately for Berzosertib and Topotecan).

This listing will include:

- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)
- Flag for death within 30 days of last study intervention
- Flag for death within 60 days of first study intervention

15.3.2 Serious Adverse Events

The tabulation of serious TEAEs is described in Section 15.2.1. The listings of SAEs will also be provided with the relevant information such as AE SOC/PT, start/stop date, toxicity grade, relationship to study interventions, action taken with study interventions, and outcome, with a flag for SAEs with onset outside of the on-treatment period.

15.3.3 Other Significant Adverse Events

Infusion Related Reactions (IRR) are identified based on a list of MedDRA PTs (see Appendix 17.4) and divided into reactions versus signs and symptoms.

Reactions of IRR: should be considered onset is during Berzosertib and/or Topotecan infusion or within the next day of infusion and resolution on the same day or the day after onset for any infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or Type 1 hypersensitivity.

Signs and symptoms of IRRs and hypersensitivity/allergic reactions: should be considered when onset is during Berzosertib and/or Topotecan infusion or within the next day of infusion and resolution on the same day or the day after onset.

The frequency (number and percentage) of participants with each of the following will be presented for treatment emergent IRRs:

- IRRs, by PT
- IRRs, Grade ≥ 3, by PT
- Related IRRs, by PT
- Related IRRs, Grade ≥ 3, by PT
- IRRs leading to permanent discontinuation of any study intervention, by PT
- IRRs leading to permanent discontinuation of Berzosertib, by PT
- IRRs leading to permanent discontinuation of Topotecan, by PT
- Related IRRs leading to permanent discontinuation of any study intervention, by PT
- Related IRRs leading to permanent discontinuation of Berzosertib, by PT

- Related IRRs leading to permanent discontinuation of Topotecan, by PT
- Serious IRRs, by PT
- Related serious IRRs, by PT
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later)
- IRRs leading to death, by PT
- Related IRRs leading to death, by PT

The listing of all IRRs will also be provided with the relevant information.

Infusion site reactions (ISR) were considered as identified risk (non-important) and are likely associated with Berzosertib treatment if the infusion site reaction develops during infusion or within the next day of Berzosertib administration and resolution on the same day or the day after onset.

ISR have been reported using a variety of terms to describe the same biologic event, including catheter site pain, catheter site pruritus, catheter site rash, catheter site-related reaction, infusion site discomfort, infusion site erythema, infusion site extravasion, infusion site pruritus, infusion site rash, infusion site reaction, injection site rash, and injection site reaction. See Appendix 17.4 for the detailed MedDRA PTs.

The same frequency tables and listings described above for IRR will be provided for ISR.

15.4 Clinical Laboratory Evaluation (Secondary Endpoint)

All statistical analyses of laboratory values will be performed on the FAS/SAF using SI units.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived).

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the local laboratory normal ranges).

A complete list of laboratory tests to be analyzed along with the directions of abnormality for parameters with and without NCI-CTCAE grades are presented in Appendix 17.2.

For the definition of baseline measurement see Section 9.2.

Values below the detection limit will be imputed by half of the detection limit. In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g. "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and absolute changes from baseline to each scheduled visit over time. The End of treatment visit will be summarized separately. Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High). Abnormalities classified according to NCI-CTCAE toxicity grading version will be described using the worst on-treatment grade. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

Parameters with NCI-CTCAE grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants evaluable for NCI-CTCAE grading (i.e. those participants for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by NCI-CTCAE grade table will include number and percentage of participants with Grade 1, 2, 3, 4, 3/4, and any grade (1 to 4), laboratory abnormalities during the on-treatment period.
- The shift table will summarize baseline NCI-CTCAE grade versus the worst on-treatment NCI-CTCAE grade. The highest NCI-CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then sponsor-specific standard reference ranges will be used.

For **calcium**, CTCAE grading is based on Corrected Calcium. Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per NCI-CTCAE criteria will be summarized as frequency (number and row percentage) of participants with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

- Coagulation tests: activated partial thromboplastin time (aPTT) and prothrombin time (INR), collected at screening, baseline and end of treatment
- Pregnancy tests (urine collected at baseline and safety follow-up or serum collected at screening and end of treatment)
- Serology tests (HBV, HCV) collected at screening only

Following figures will be provided for each above-mentioned test:

- Boxplots of the laboratory values by timepoint.
- Boxplots of the change from baseline by timepoint.
- A plot of peak ALT versus peak total bilirubin, both relative to the upper limit of normal (ULN) will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxicity) will have reference lines at 3×ULN for ALT and at 2×ULN for total bilirubin.

In case multiple measures are reported at a given timepoint, the earliest assessment will be considered in boxplots.

Boxplots for laboratory parameters where toxicity grades are defined based on the ratio of the parameter values and the upper limit of normal (ULN) will not be displayed using the unit of measurement but instead using the ratio of the measured value over ULN. This comprises ALP, ALT, AST, bilirubin and creatinine. All graphical displays will be shown on a log-scale.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and CTCAE grades. Any out-of-range values that are identified by the investigator as being clinically significant will be shown in a data listing.

In addition, a listing displaying parameters with at least one value with grade ≥ 3 will be provided. For each participant, only parameters where at least one value has grade ≥ 3 will be displayed (all visits for the corresponding parameter will be displayed in the listing).

15.5 Vital Signs (Secondary Endpoint)

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

Following figures will be provided for each vital sign:

- Boxplots of the vital sign values by timepoint.
- Boxplots of the change from baseline by timepoint.

In case multiple measures are reported at a given timepoint, the earliest assessment will be considered in boxplots.

The maximum changes of vital sign measurements screening/baseline to maximum changes after start of 1st study treatment will be grouped as follows:

Body temperature increase	< 1°C , 1-< 2°C , 2-< 3°C, ≥ 3 °C
Pulse rate increase from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, > 20 – 40 bpm, > 40 bpm
Pulse rate decrease from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, > 20 – 40 bpm, > 40 bpm
SBP increase from baseline <140 mmHg; ≥ 140 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP increase from baseline <90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP decrease from baseline <90 mmHg; ≥ 90 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
Respiration rate increase from baseline <20 bpm ; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm
Respiration rate decrease from baseline <20 bpm ; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm

For each participant the worst on-treatment value will be calculated. For the definition of baseline values see Section 9.2. Missing values will define a separate category.

The following summaries will be prepared for vital sign parameters as grouped above:

- Maximal Shifts (changes in categories)
- Listing of highest change per participant

An additional participant data listing will present all changes from baseline reported in the highest categories.

15.6 Electrocardiograms (Secondary Endpoint)

Safety ECGs

A standard single 12-lead ECG will be obtained using an ECG machine with paper readouts that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Safety ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The QT interval corrected for heart rate by the Fridericia's formula (QTcF) as well as the QT interval corrected by the Bazett's formula (QTcB) are entered in the eCRF and will be analyzed as collected.

The following analyses will be performed for each applicable ECG parameters (heart rate, PQ/PR, QRS and QT durations, QTcB and QTcF) by treatment group/dose level, during the on-treatment

period. Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

- For each of the ECG parameters, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of participants with notable ECG values according to the following categories. The denominator to calculate percentages for each category is the number of participants evaluable for the category.
  - QT/QTc increase from baseline > 30 ms, > 60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

A shift table from baseline to the worst on-treatment observation, of the number and percentage of participants for each interpretation category (normal, abnormal/not clinically significant, abnormal/clinically significant, missing and total) will also be provided.

Complete ECG profiles will be listed for participants with at least one notable ECG interval value or change. Also, qualitative ECG abnormalities will be listed for each participant and time point and the corresponding notable values and abnormality findings will be included in the listings.

CCI [redacted]

[redacted]

15.7 Pharmacokinetics

15.7.1 Safety Run-In Part in Japan

Population: PK Analysis Set

Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 8.3, or higher (Certara, L.P., Princeton, New Jersey, USA). The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary North Carolina), Windows version 9.4 or higher will be used to produce tables, listings, and figures, where appropriate.

Pharmacokinetic parameters will be calculated using standard non-compartmental methods and the actual administered dose and actual sampling times. In cases actual dosing time is missing, scheduled time might be used for NCA after performance of adequate plausibility checks and agreement with the sponsor. Decision and rational should be included in the CSR. Otherwise, there will be no further imputation of missing data.

For each participant with PK data in the Safety Run-in Part, PK parameters will be calculated for berzosertib and its CCI [redacted] if estimable, as warranted by the data. Parameters are calculated following dosing on Cycle 1 Day 2 only unless otherwise indicated:

Symbol	**Definition**
$AUC_{0\text{-}tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantitation.
$AUC_{0\text{-}tlast}$/Dose	The Dose normalized AUC from time zero to t_{last} at which the concentration is at or above the lower limit of quantitation. Normalized using the actual dose, using the formula $AUC_{0\text{-}tlast}$ /Dose.
$AUC_{0\text{-}\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last\ pred}/ \lambda_z$
$AUC_{0\text{-}\infty}$ /Dose	The dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, using the formula $AUC_{0\text{-}\infty}$ /Dose.
$AUC_{0\text{-}48h}$	The AUC from time zero (= dosing time) to 48 hours.
$AUC_{0\text{-}48h}$/Dose	The AUC from time zero (= dosing time) to 48 hours. Normalized using actual dose, using the formula $AUC_{0\text{-}48h}$ /Dose.
$AUC_{0\text{-}72h}$	The AUC from time zero (= dosing time) to 72 hours.
$AUC_{0\text{-}72h}$/Dose	The AUC from time zero (= dosing time) to 72 hours. Normalized using actual dose, using the formula $AUC_{0\text{-}72h}$ /Dose.
C_{max}	Maximum observed concentration
C_{max}/Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max} /Dose.

Symbol	Definition
C_{eoi}	The observed concentration at the end of the infusion period. Calculated following dosing on Cycle 1 Day 2 and Cycle 1 Day 5 in the Safety Run-in Part
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing). Calculated on Cycle 1 Day 5 only before dosing for the Safety Run-in Part and on Day 2
CL	The apparent total body clearance following intravenous infusion, CL = Dose /$AUC_{0-\infty}$. Calculated for berzosertib only.
CCI [redacted]	[redacted]
[redacted]	[redacted]
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration following multiple dosing. $R_{acc(Cmax)}$ = (C_{max} after multiple dose)/ (C_{max} after single dose). Note: for C_{max} after multiple dose, the end-of-infusion (EOI) concentration on C1D5 will be used.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$.
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification.
V_Z	The apparent volume of distribution during the terminal phase following intravenous administration. V_Z = Dose/($AUC_{0-\infty}$*λ_z) following single dose. Calculated for berzosertib only.

Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If Cmax occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

In cases where the actual observation time is not equal to the scheduled observation time, AUC_{0-48h} and AUC_{0-72h} will be calculated by extrapolation to 48 hours and 72 hours provided λ_z is estimable. In case suitable regression cannot be performed, partial areas may be calculated using the concentration at 48 hours and 72 hours if actual sampling time is within 10% of the nominal sampling time.

In cases BLQ concentrations occur at the end of the collection interval, these concentrations might be set to missing for calculations of partial AUCs after agreement with the Sponsor. This is an exemption to the general BLQ handling rule and should be applied in case its application would result in estimation of implausible partial AUC values. Implausibility is considered in cases partial AUCs were greater than $AUC_{0-\infty}$.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- First (λ_z low) and last (λ_z up) time point of the time interval of the log-linear regression to determine λ_z.
- Number of data points ($N\lambda$) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (adjusted Rsq) for calculation of λ_z.
- AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. ($AUC_{extra\%}$)
- Span ratio of interval over which $t_{1/2}$ was estimated divided by $t_{1/2}$

The calculation of the AUC will be performed using the mixed log-linear trapezoidal method (linear up/log down). The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

No dose adjustment is needed for the calculation of dose dependent parameters. As such, the actual dose will be used.

If $AUC_{extra\%}$>20%, the coefficient of correlation (Rsq,adj) of λ_z is <0.8 or the observation period over which the regression line is estimated (span ratio) is less than 2-fold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL etc.) will be listed, flagged and included in the parameter outputs. In non-pivotal trials such values might be excluded from descriptive statistics and further statistical evaluation after discussion with the Sponsor. Should more than 10% of participants be flagged for $AUC_{extra\%}$ and/or Rsq,adj (for a particular analyte), a sensitivity analysis excluding flagged parameters may be performed after discussion with the Sponsor.

Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and displayed generally as “N.R.”.

15.7.2 General Specifications for PK Concentration and PK Parameter Data in Safety Run-in

Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration. The same applies to the predose (trough) sample of a multiple dose study.

Pre-dose samples which have been taken after the subsequent dosing will be reported as protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations.

Values below the LLOQ will be taken as zero for summary statistics of PK concentration data and for graphical presentations.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

Samples that are collected outside the specified time windows specified in the CSP will be excluded from the concentration summary and mean concentration plots.

Pharmacokinetic concentrations which are erroneous due to a protocol violation (as defined in the CSP), sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion must be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participant listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific CDISC data sets.

PK concentrations and PK parameters excluded from summary statistics will not be included in mean figures. Mean plots will only contain values where n>2. In case n≤2, individual participant profiles may be included in mean plots.

15.7.3 Presentation of PK Concentration and PK Parameter Data

Data from the Safety Run-in will be summarized in separate outputs.

15.7.3.1 Tables

- Individual plasma berzosertib and CCI concentrations and summary statistics by analyte, dose group, and day
- Individual plasma berzosertib and CCI PK parameters and summary statistics by analyte, dose group, and day
- Individual diagnostic berzosertib and CCI PK parameters

- Individual Plasma berzosertib and CCI and topotecan concentrations, actual Date/Time of sample collection, scheduled time, time deviation (by dose group, and day)

Additionally, Sponsor will provide the Phoenix WinNonlin NCA Core Output in a separate listing for it's inclusion in the CSR.

15.7.3.2 Figures

- Individual plasma berzosertib and CCI concentration-time profiles, dose group, and day; linear and Semi-Log Scale
- Mean and median plasma berzosertib and CCI concentration-time profiles, dose group, and day; linear and Semi-Log Scale (n>= 3)
- Boxplots for plasma berzosertib and CCI PK parameters (e.g. $AUC_{0-\infty}$/Dose, $AUC_{0-tlast}$/Dose, C_{max}/Dose) versus dose
- Individual plasma topotecan concentration-time profiles by dose group, and day; linear and Semi-Log Scale

All descriptive summaries of PK data will be performed using the PK Analysis Set.

15.8 Pharmacodynamics/Biomarkers

Analyses are described in a separate document and analyzed separately.

15.9 Population PK, PK-QTC Analysis, and Exposure-Response Analyses

Analyses are described in a separate document.

16 References

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17 Appendices

17.1 Appendix 1 – IAP for Global SMC (Main Part)

The principal objectives of the SMC are:

- To assess the safety and efficacy of the investigational treatment to safeguard the interests of study participants;
- To assess the benefit of continuing the study based on results of an interim analysis for futility that will be conducted after the first 40 participants have completed their second on-treatment tumor assessment (or dropped-out/died prematurely);
- To monitor the overall conduct of the clinical study to protect its validity and credibility.

Two SMC meetings are planned as follows. Further meetings may be scheduled by the SMC as needed.

- After the first 15 participants have completed their second on treatment tumor assessment or dropped-out/died prematurely
- After the first 40 participants have completed their second on treatment tumor assessment or dropped-out/died prematurely (IA with potential stop for futility)

Prior to each SMC meeting, a data snapshot will be taken, once the 15th or 40th participants have completed their 2nd on treatment tumor assessment scheduled 12 weeks after first study intervention and all data have been entered in the clinical database.

All data of all participants until the date when the data snapshot is taken will be included in the data snapshot.

Details of the SMC process (timelines and responsibilities) are provided in the SMC Charter.

Ongoing data cleaning will be performed, as described in the Integrated Data Review Plan.

Analysis Sets

The SCR and FAS/SAF Analysis Sets defined in Section 8.1 will be used for SMC analyses.

General Specifications for Data Analyses

Same specifications described in Section 9 will be used for SMC analysis.

Planned Analyses

- Disposition of participants and discontinuations using the SCR analysis set as described in Section 10.1.

- Summary of IPDs using the FAS/SAF analysis set as described in Section 10.2.1.
- Demographic characteristics, disease history and duration of study interventions as described in Sections 11.1, 11.3 and 13, respectively.
- Descriptive summaries of safety data using the FAS/SAF analysis set, presenting:
    - Adverse Events, as described in Sections 15.2 and 15.3 :
        - Overview of TEAEs
        - TEAEs by SOC and PT, Berzosertib/Topotecan Related TEAEs by SOC and PT
        - TEAEs by Worst Grade, SOC and PT, Berzosertib/Topotecan Related TEAEs by SOC and PT
        - SAEs by SOC and PT, Berzosertib/Topotecan Related SAEs by SOC and PT
        - TEAEs leading to death by SOC and PT
        - TEAEs leading to permanent discontinuation of Berzosertib/Topotecan by SOC and PT
        - Listing of death and SAEs
    - Clinical Laboratory Evaluation, as described in Section 15.4:
        - Summary by worst on-treatment for both hematology and biochemistry parameters
        - Summary by worst on-treatment NCI-CTCAE toxicity grade for both hematology and biochemistry parameters
        - eDISH plot
- For the IA with potential stop for futility (see Section 6.2), the following descriptive summaries of efficacy data using the FAS/SAF analysis set as described in Section 14 will be presented:
    - Objective Response: summary table, waterfall plot and spider plot
    - Kaplan-Meier plots of Overall Survival and Progression Free Survival
    - Listing of responders (OR, DR, PFS and OS)

17.2 Appendix 2 – Safety Laboratory Assessments

Directions of relevant abnormalities for all laboratory parameters are listed below:

NCI-CTCAE v5.0 gradable parameters

Category	Parameter	Name in NCI-CTCAE	Direction(s) of abnormality	Comments on derivation
		Serum chemistry		
Electrolytes	Calcium	Hypocalcemia	Low	Grading performed using corrected calcium
		Hypercalcemia	High	Grading performed using corrected calcium
Electrolytes	Potassium	Hypokalemia	Low	Grade 2 cannot be numerically distinguished from Grade 1. Grade 2 will not be derived.
		Hyperkalemia	High	
Electrolytes	Sodium	Hyponatremia	Low	
		Hypernatremia	High	
Enzymes/liver	Alanine Aminotransferase	Alanine Aminotransferase increased	High	
Enzymes/liver	Alkaline Phosphatase	Alkaline Phosphatase increased	High	
Enzymes/liver	Aspartate Aminotransferase	Aspartate Aminotransferase increased	High	
Enzymes/liver	Total bilirubin	Blood bilirubin increased	High	
Metabolism	Glucose	Hypoglycemia	Low	
Metabolism	Magnesium	Hypomagnesemia	Low	
		Hypermagnesemia	High	
Protein/liver	Albumin	Hypoalbuminemia	Low	
Renal/kidney	Creatinine	Creatinine increased	High	
		Hematology		
Platelets	Platelets Count	Platelet count decreased	Low	
Red blood cells	Hemoglobin	Anemia	Low	Grade 4 relies solely on clinical assessment and cannot be numerically derived
		Hemoglobin increased	High	
White blood cells/differential	White Blood Cell Count	White blood cell decreased	Low	
		Leukocytosis	High	Only Grade 3 numerically defined
White blood cells/differential	Absolute Lymphocytes Count	Lymphocyte count decreased	Low	
		Lymphocyte count increased	High	
White blood cells/differential	Absolute Neutrophils Count	Neutrophil count decreased	Low	
White blood cells/differential	Eosinophils	Eosinophilia	High	Only Grade 1 numerically defined

NCI-CTCAE v5.0 non-gradable parameters

Category	Parameter (LBTEST)	Abnormality Description	Direction(s) of abnormality
Serum chemistry			
Enzymes/liver	Alanine Aminotransferase *	Alanine Aminotransferase increased	High
Enzymes/liver	Alkaline Phosphatase *	Alkaline Phosphatase increased	High
Enzymes/liver	Aspartate Aminotransferase *	Aspartate Aminotransferase increased	High
Enzymes/liver	Total bilirubin *	Blood bilirubin increased	High
Enzymes/pancreas	Lipase	Lipase increased	High
Enzyme/pancreas	Amylase	Serum amylase increased	High
Metabolism	Glucose	Hyperglycemia	High
Metabolism	Phosphate	Phosphate low/high	Low/High
Plasma proteins	Total protein	Total protein low	Low
Renal/kidney	Blood Urea Nitrogen	Blood urea nitrogen high	High
Hematology			
Red blood cells	Hematocrit	Hematocrit low/high	Low/High
Red blood cells	Mean Corpuscular Hemoglobin	Mean corpuscular hemoglobin low/high	Low/High
Red blood cells	Mean Corpuscular Volume	Mean corpuscular volume low/high	Low/High
White blood cells/differential	Basophils	Basophils high	High
White blood cells/differential	Monocytes	Monocytes low/high	Low/High

* indicates parameter is NCI-CTCAE gradable with comparison to baseline and will therefore be included in the analysis of non-gradable parameters for this study.

17.3 Appendix 3 – PROs Scoring

This section will be included in a future version of this document.

The EQ-5D-5L scoring system will be converted into a single index value. The index value is country specific and is a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. The UK country specific value set will be used in deriving the index value which ranges from -0.594 (worst health state) to 1.000 (best health state).

The EORTC QLQ-C30 is a questionnaire developed to assess the general aspects of health-related quality of life of cancer patients. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer subjects (e.g. dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and financial impact of the disease.

The QLQ-LC13 questionnaire comprises 13 lung cancer-specific questions incorporated into one multi-item scale designed to evaluate lung cancer related symptoms [cough and hemoptysis (one item each), dyspnea (three items)], treatment related side-effects [sore mouth or tongue, dysphagia, hair loss, tingling hands, and feet (one item each)], pain (three items), and pain medication (one item). All items are rated on a 4-point scale, with 1 representing no symptom/problem at all, and 4 representing worst symptom/problem.

For both QLQ-C30 and QLQ-LC13 questionnaires, the scoring procedure for each multi-item scale and single item is the same and consists of computing the raw score (RS) and then computing the actual scale score (S) by making a linear transformation to standardize the score to values from 0 to 100 as shown below.

For **Functional scales**:

$$\text{Final Score} = 100 \times [1 - (RS - 1) / \text{Item range}]$$

For **Symptom scales / items** and **Global health status / QoL**:

$$\text{Final Score} = 100 \times [(RS - 1) / \text{Item range})]$$

Where RS is the raw score calculated as the mean of items contributing to the scale and Item range is the difference between the maximum possible value of RS and the minimum possible value. The range of RS equals the range of the item values. Most items are scored 1 to 4, giving Range = 3. The exceptions are the items contributing to the Global Health Status / QoL, which are 7-point questions with Range = 6.

All the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Therefore, a high score for a functional scale represents a

high/healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology / problems.

Questionnaire	Type of Scale	Scale	Number of items	Item numbers	Item range	Minimum number of non-missing items to calculate the 0-100 score
QLQ-C30	Global Health Status/QoL	Global Health Status/QoL	2	29, 30	6	1
	Functional scales	Physical functioning	5	1 to 5	3	3
		Role functioning	2	6, 7	3	1
		Emotional functioning	4	21 to 24	3	2
		Cognitive functioning	2	20, 25	3	1
		Social functioning	2	26, 27	3	1
	Symptom scales	Fatigue	3	10. 12,18		2
		Nausea and vomiting	2	14, 15	3	1
		Pain	2	9, 19	3	1
		Dyspnea	1	8	3	1
		Insomnia	1	11	3	1
		Appetite loss	1	13	3	1
		Constipation	1	16	3	1
		Diarrhea	1	17	3	1
		Financial Difficulties	1	28	3	1
QLQ-LC13	Symptom scales/items	Dyspnea	3	3, 4, 5	3	3
		Coughing	1	1	3	1
		Haemopsysis	1	2	3	1
		Sore mouth	1	6	3	1
		Dysphasia	1	7	3	1
		Peripheral neuropathy	1	8	3	1
		Alopecia	1	9	3	1
		Pain in chest	1	10	3	1
		Pain in arm or shoulder	1	11	3	1

Questionnaire	Type of Scale	Scale	Number of items	Item numbers	Item range	Minimum number of non-missing items to calculate the 0-100 score
		Pain in other parts	1	12	3	1
		Take any medication for pain	2	13	1 & 3 (*)	1

* "Take any medication for pain" has 2 questions: (1) "Did you take any medication for pain?" with range 1; (2) "If yes, how much did it help?" with range 3.

17.4 Appendix 4 - Criteria for infusion related reactions (IRRs) and infusion site reactions (ISRs)

Infusion related reactions	**Reactions - Considered when onset is on the day of Berzosertib and/or Topotecan infusion (during or after the infusion) or the day after the Berzosertib and/or Topotecan infusion (irrespective of resolution date):** • Hypersensitivity • Drug hypersensitivity • Type I hypersensitivity • Anaphylactic reaction • Infusion related reaction **Signs and Symptoms - occurring during Berzosertib and/or topotecan infusion or within 24h of infusion and resolved with end date within 2 days after onset** • Erythema • Rash • Rash erythematous • Rash macular • Rash pruritic • Pruritus • Pruritus allergic • Flushing • Chills • Urticaria • Headache • Bronchospasm • Dyspnoea • Hypotension • Hypertension • Pyrexia • Wheezing • Abdominal pain • Back pain
Infusion site reactions	**Infusion site reactions - are an identified risk (non-important) and likely associated with Berzosertib treatment if the infusion site reaction develops during infusion or within 24h of Berzosertib administration.** Catheter site pain Catheter site pruritus Catheter site rash

	Catheter site-related reaction Infusion site discomfort Infusion site erythema Infusion site extravasation Infusion site pruritus Infusion site rash Infusion site reaction Injection site rash

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