Clinical Study Protocol

Title Page

Clinical Study Protocol 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 Number:	MS201923_0050
Protocol Version:	21 June 2021/Version 4.0
Merck Compound:	Berzosertib (M6620)
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	II
Short Title:	Berzosertib + topotecan in relapsed platinum-resistant SCLC
Acronym or Abbreviation:	**DDRi**ver SCLC 250
Coordinating Investigator:	PPD , MD PPD
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA

	Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Acro Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2020-004231-25

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original protocol	07-Oct-2020
2.0	Global amendment	20-Nov-2020
3.0	Global amendment	23-Dec-2020
3.1-JPN	Country-specific amendment	25-Mar-2021
3.2-USA	Country-specific amendment	27-Apr-2021
3.3-BEL	Country-specific amendment	27-Apr-2021
4.0	Global amendment	21-Jun-2021

Protocol Version 4.0 (21 June 2021)

Overall Rationale for the Amendment

The high-level rationale for the changes implemented in this amendment are to include:

- All country-specific changes into a single global amendment (see Appendix 9 for descriptions and rationale of changes)
- Clarification of weak DDI potential of berzosertib via CYP3A4 inhibition and recommendations on precautions for coadministration of certain CYP3A4 substrates
- Merck standards updates.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	• Clarify medical history assessment should include smoking history • Clarify cycle start may be delayed up to 7 days for scheduling conflicts	Text is amended to clarify study procedures.
2.3.1 Risk Assessment, Table 3 6.5.3 Prohibited Medicines and Precautions	Include text to describe DDI potential due to CYP3A4 inhibition and to recommend precautions when berzosertib is coadministered with sensitive CYP3A4 substrates with narrow therapeutic index	Berzosertib is a weak inhibitor of CYP3A4 at the dose of 210 mg/m^2 and precautions are recommended when berzosertib is co-administered with sensitive CYP3A4 substrates with a narrow therapeutic index.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria, item 2	Reduce the imaging time interval for assessment of stable disease from 4 weeks to 2 weeks for patients with known, but stable, brain metastases	Time is reduced to eliminate delay to start study intervention in patients with actual stable brain metastases.
Section 5.3.1 Meals and Dietary Restrictions (pertains only to Japan)	Pertaining only to the country-specific V3.1-JPN amendment, restriction of Grapefruit Juice etc. are removed in this version.	Drug interactions by grapefruit and Seville oranges or other citrus fruits and their juices are predominantly by the inhibition of intestinal CYP3A4 activity without an apparent inhibition of hepatic CYP3A4. Since berzosertib is administered intravenously, its pharmacokinetics should not be affected by citrus fruits like grapefruit and Seville oranges. Hence, restriction of grapefruit juice, etc., are not included in this protocol.
Throughout	Minor editorial revisions for clarity, consistency, and to address Merck standards updates.	Minor; therefore, have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol 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

Short Title: Berzosertib + topotecan in relapsed platinum-resistant small-cell lung cancer (SCLC)

Rationale: The purpose of this study is to assess efficacy, safety, tolerability, and pharmacokinetics (PK) of berzosertib in combination with topotecan in participants with relapsed, platinum-resistant SCLC.

Objectives and Estimands (Main Part):

Objectives	Estimand Attributes
Primary	
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 IRC **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 • Progression according to RECIST 1.1: while not progressed strategy, i.e., assessments up to the intercurrent event **Population Level Summary:** Objective response rate
Secondary	
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 IRC. Measured by time from first documentation of objective response to progressive disease (PD) or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention **Population:** Patients with relapsed, platinum-resistant SCLC with a confirmed objective response 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., will be considered as event of interest • Discontinuation of treatment: treatment-policy strategy, i.e., ignoring the intercurrent event

Objectives	Estimand Attributes
	• 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
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:** Patients 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
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:** Patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent anticancer treatment **Intercurrent Event Strategy:** • 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 OS time • Kaplan-Meier estimates

Objectives	Estimand Attributes
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 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 (EORTC) 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:** Patients 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 treatment: 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 changes from baseline analysis for multi-item scales in EORTC questionnaires (i.e., physical functioning and dyspnea) and VAS • Proportion of patients with ≥ 1 category improvement and proportion of patients with ≥ 1 category worsening in single-item symptoms (i.e., cough and chest pain)
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 **Population:** Patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan

In case DL2 is declared RP2D, data for participants receiving DL2 will in addition be analyzed as part of the main study.

Objectives and Estimands (Safety Run-in Part in Japan):

Objectives	Estimand Attributes
Primary	
To confirm whether the regimen and recommended Phase II dose (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:** • Dose Level 1 (DL1): Japanese patients with advanced solid tumors, for which no effective standard therapy exists, or standard therapy has failed • Dose Level 2 (DL2): Japanese patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan
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 patients with advanced solid tumors • DL2: Japanese 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 • Progression according to RECIST 1.1: while not progressed strategy, i.e., assessments up to the intercurrent event **Population Level Summary:** Objective response rate
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 objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention **Population:** • DL1: Japanese patients with advanced solid tumors with a confirmed objective response according to RECIST 1.1 as assessed by the Investigator • DL2: Japanese patients with relapsed, platinum-resistant SCLC with a confirmed objective response according to RECIST 1.1 as assessed by the Investigator **Treatment:** Berzosertib + topotecan

Objectives	Estimand Attributes
	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
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 patients with advanced solid tumors • DL2: Japanese patients 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
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 patients with advanced solid tumors • DL2: Japanese patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent anticancer treatment **Intercurrent Event Strategy**: • 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

Objectives	Estimand Attributes
	Population Level Summary: • Median OS time • Kaplan-Meier estimates
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 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 **Population:** • DL2: Japanese patients 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 treatment: 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 changes from baseline analysis for multi-item scales in EORTC questionnaires (i.e., physical functioning and dyspnea) and VAS • Proportion of patients with ≥ 1 category improvement and proportion of patients with ≥ 1 category worsening in single-item symptoms (i.e., cough and chest pain)
To characterize the pharmacokinetic (PK) profile of berzosertib	**Endpoint:** PK parameters of berzosertib in plasma by non-compartmental analysis (NCA) **Population:** • DL1: Japanese patients with advanced solid tumors • DL2: Japanese patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan

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

Overall Design: This is a multicenter, Phase II, open-label, single-arm study designed to assess the efficacy and safety of berzosertib in combination with topotecan in participants with relapsed, platinum-resistant SCLC (platinum-free interval [PFI] < 90 days) with only 1 prior line of systemic treatment. In Japan, a Safety Run-in Part will be conducted before enrollment into the Main Part of the Phase II study.

Number of Arms: 1

Blinding: No blinding

Number of Participants: Approximately 80 participants are planned to be assigned to study intervention. In the Safety Run-in Part in Japan, 3 to 9 participants at each dose level are planned.

Study Intervention Groups and Duration: For this single-arm Phase II study, all participants will be assigned to receive berzosertib at a dose of 210 mg/m^2 via intravenous (IV) administration on Day 2 and Day 5 of each 21-day cycle and topotecan at a dose of 1.25 mg/m^2 via IV administration on Days 1 through 5 of each 21-day cycle.

For the Safety Run-in Part in Japan, the dose of berzosertib in Dose Level (DL) 1 will be 105 mg/m^2. Berzosertib and topotecan doses at DL2 will be the same as in the Main Part of the Phase II study. Details are shown in Section 1.2 and Section 4.1.

For each participant, the study will include a Screening Period lasting up to 28 days, a Study Intervention Period consisting of 21-day cycles of berzosertib + topotecan until disease progression or other criteria for study intervention discontinuation are met, an End-of-Treatment Visit, a Safety Follow-up Period of 30 days after last study intervention dose, and Efficacy and Survival Follow-up Visits every 12 weeks from last study intervention administration. During the Survival Follow-up, survival information and subsequent anticancer therapy given to the participant should be recorded. The Survival Follow-up Visits can occur as clinic visits or by telephone contact until death, lost to follow-up, study withdrawal of consent, or End of Study. Additionally, participants who discontinue study intervention for reasons other than disease progression or death will continue with regular imaging assessments until disease progression, addition of subsequent anticancer therapy, death, withdrawal of consent, lost to follow-up, or End of Study.

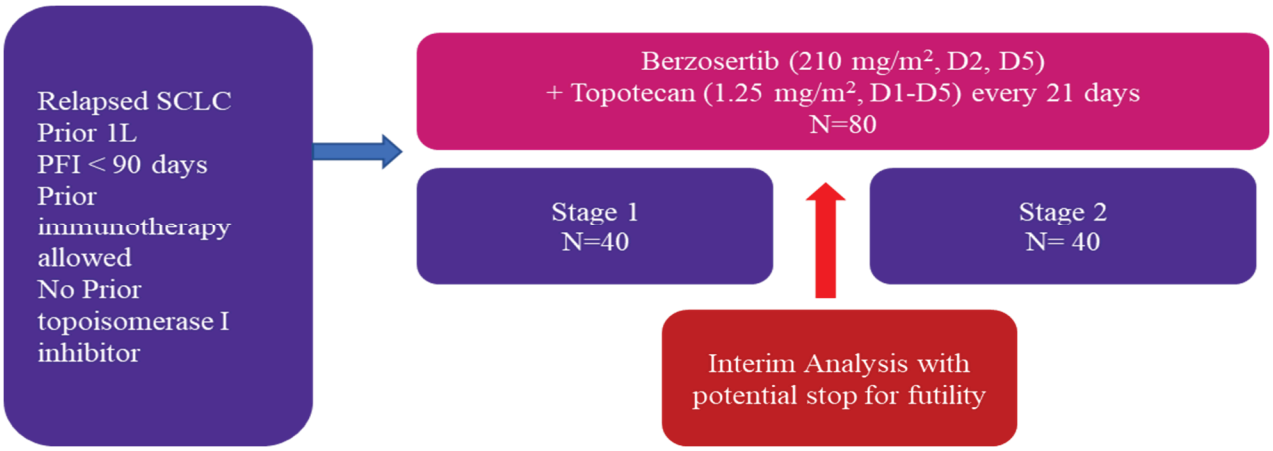
Involvement of Special Committees: Yes

An Independent Review Committee will perform blinded determinations as to whether the criteria for tumor response or progression are met according to Response Evaluation Criteria in Solid Tumors version 1.1. In addition, the study will be monitored regularly by an internal Safety Monitoring Committee. The Safety Run-in Part in Japan will additionally be regularly monitored by a Local Safety Monitoring Committee.

1.2 Schema

The Main Part of this study will enroll participants with relapsed SCLC who received 1 prior line of platinum-based treatment, and whose disease is considered to be resistant to platinum-based treatment, defined as platinum-free interval < 90 days. The schematic structure of the Main Part of this study is shown in Figure 1 below (see details in Section 5.1).

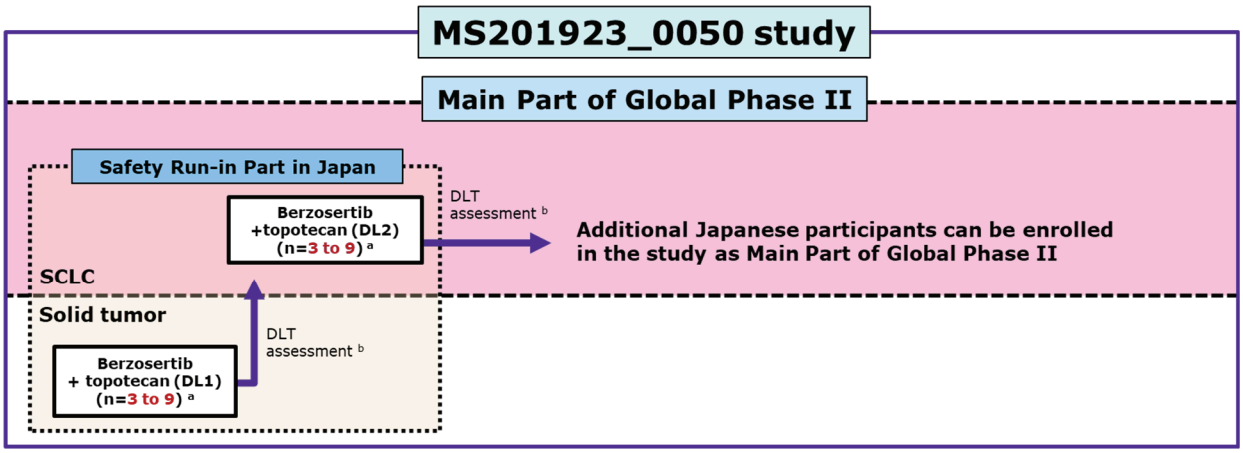
Figure 1 Main Part of Global Phase II Study Schema



1L = 1 prior line; D = day; PFI = platinum-free interval; SCLC = small-cell lung cancer.

The schematic structure of the study and its Safety Run-in Part in Japan is shown in Figure 2 below. Section 4.1.1 presents more details of the Safety Run-in Part in Japan.

Figure 2 Schematic Structure Depicting the Safety Run-in Part in Japan



Dosages and schedule

- DL1: berzosertib **105** mg/m² Day 2 and Day 5, topotecan 1.25 mg/m² Day 1-5, 21 days/cycle
- DL2: berzosertib **210** mg/m² Day 2 and Day 5, topotecan 1.25 mg/m² Day 1-5, 21 days/cycle

DL = dose level; DLT = dose-limiting toxicity; SCLC = small-cell lung cancer.

[a] The participants may continue the study treatment after DLT evaluation period per Clinical Study Protocol.

[b] If DL2 is considered safe by Safety Monitoring Committee, it can be the recommended Phase II dose. See Section 9.4.2.1 for details.

1.3 Schedule of Activities

The Schedule of Activities (SoA) is presented in Table 1. The schedule for triplicate digital electrocardiograms (ECGs) and pharmacokinetic (PK) blood sample collection is provided in Table 2.

If a decision to permanently discontinue study intervention is made at a scheduled or unscheduled visit, that visit becomes the End-of-Treatment Visit with all relevant assessments conducted per Table 1. Otherwise, an End-of-Treatment Visit must occur within 7 days of last study intervention administration.

Survival follow-up may be conducted at the study site or via phone every 12 weeks until death, lost to follow-up, withdrawal of consent, or End of Study.

Table 1 Schedule of Activities: Treatment, End of Treatment, and Follow-up Period

Assessments and Procedures	Screening	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up		Notes (Cycle start may be delayed up to 7 days to accommodate scheduling conflicts, with approval from the Medical Monitor)
	D -28 to -1	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)		Safety Follow-up 30 Days after Last Dose (± 7D)	Efficacy and Survival every 12 Weeks from Last Dose (± 2 weeks)	
Informed Consent	X											
Inclusion and Exclusion Criteria; Medical History	X											Confirm inclusion/exclusion before first study intervention dose based on Section 5. Medical history to include verification of smoking status.
Hepatitis B (HBV)	X											Required at screening: • HBsAg • Total anti-HBc • Anti-HBsAg • HBV DNA: if HBsAg/anti-HBc or anti-HBc is positive Required during Study Intervention Period, if past HBV or current HBV infection: • HBsAg and HBV-DNA every 12 weeks
Hepatitis C (HCV)	X											Required at screening: • anti-HCV • HCV RNA: if anti-HCV is positive Required during Study Intervention Period, if past or current HCV infection: • HCV RNA every 12 weeks
Physical Examination	X	X							X	X		Symptom-directed physical examinations performed as clinically indicated per Investigator's judgment.

Assessments and Procedures	Screening	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up		Notes (Cycle start may be delayed up to 7 days to accommodate scheduling conflicts, with approval from the Medical Monitor)
	D -28 to -1	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)		Safety Follow-up 30 Days after Last Dose (± 7D)	Efficacy and Survival every 12 Weeks from Last Dose (± 2 weeks)	
Height	X											
Weight	X	X							X	X		
Vital Signs	X	X							X	X		Predose on all visits
Standard 12-lead ECG	X								X	X		Standard 12-lead ECG – paper readout, see Section 8.2.3 for additional details
Hematology	X	X		X			X	X	X	X		Required at D3 at Cycle 1 in the Safety Run-in Part Recommended at D8 and D15 at Cycle 1 only; optional at subsequent cycles. Baseline neutrophils should be ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3 prior to C1; for subsequent cycles, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL See Table 17 for required Assessments
Serum Chemistry	X	X		X					X	X		Required at D3 at Cycle 1 in the Safety Run-in Part See Table 17 for required Assessments
Coagulation	X	X							X			From Cycle 1 onwards, only if clinically indicated. See Table 17 for required Assessments
β-HCG, serum/urine (WOCBP only)	X	X							X	X		Serum test at Screening and EOT, urine test on D1 of each cycle and at Safety Follow-up

Assessments and Procedures	Screening	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up		Notes (Cycle start may be delayed up to 7 days to accommodate scheduling conflicts, with approval from the Medical Monitor)
	D -28 to -1	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)		Safety Follow-up 30 Days after Last Dose (± 7D)	Efficacy and Survival every 12 Weeks from Last Dose (± 2 weeks)	
Imaging Disease Assessment	X	At the end of every 6 weeks (± 1 week) after first dose (C1D1) until Week 36, then every 9 weeks (± 2 weeks) until PD as assessed by the IRC, death, withdrawal of consent, lost to follow-up, or End of Study, whichever comes first, regardless of study intervention modifications/discontinuation										Tumor assessment according to RECIST Version 1.1 (see Appendix 7) Measurable disease at screening must be confirmed by the IRC prior to start of treatment. Not required for DL1 in Safety Run-in Part. Locally assessed PD must be verified by the IRC (see Section 8.1.1).
Brain scan	X	As clinically indicated until PD or new treatment starts										Baseline brain imaging by brain MRI (preferred) or CT, with contrast
ECOG PS	X	X							X	X		See Appendix 8
Karnofsky Scale	X											See Appendix 8
Concomitant Medications and Procedures	X											From time of signing ICF through Safety Follow-up Visit. See Table 2 for concomitant medication information collection on PK assessment days
AEs and SAEs												

Assessments and Procedures	Screening	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up		Notes (Cycle start may be delayed up to 7 days to accommodate scheduling conflicts, with approval from the Medical Monitor)
	D -28 to -1	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)		Safety Follow-up 30 Days after Last Dose (± 7D)	Efficacy and Survival every 12 Weeks from Last Dose (± 2 weeks)	
Study Intervention Dispensation/Administration												
Berzosertib Dosing		**Global Phase II:** 210 mg/m^2 IV on Day 2 and Day 5 every 21 days **Safety Run-in Part in Japan:** DL1 105 mg/m^2 IV on Day 2 and Day 5 every 21 days DL2: 210 mg/m^2 IV on Day 2 and Day 5 every 21 days										Participants from DL1 in Safety Run-in part may escalate to DL2 at the discretion of Investigator once the DL2 is confirmed to be tolerable in the Safety Run-in part.
Topotecan Dosing		1.25 mg/m^2 IV on Days 1 through 5 every 21 days										
PRO questionnaires: EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L		X							X	X	X	Details of PRO assessments are included in Section 8.1.3. Not applicable in DL1 in the Safety Run-in Part.
Pharmacokinetic Assessments												
Plasma PK Collection: berzosertib and topotecan		See Table 2										Plasma PK samples for analysis of berzosertib (and [redacted]) and/or topotecan collected as outlined in Table 2.

Assessments and Procedures	Screening	Cycle Duration = 21 Days							EOT (within 7 days after last dose)	Follow-up		Notes (Cycle start may be delayed up to 7 days to accommodate scheduling conflicts, with approval from the Medical Monitor)
	D -28 to -1	D1 (± 3)	D2	D3	D4	D5	D8 (± 3)	D15 (± 3)		Safety Follow-up 30 Days after Last Dose (± 7D)	Efficacy and Survival every 12 Weeks from Last Dose (± 2 weeks)	
CCI												
CCI												
CCI												
CCI												

AEs = adverse events; β-HCG = β-human chorionic gonadotropin; C = cycle; CT = computed tomography; D = Day(s); DL = dose level; CCI ; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EORTC = European Organization for the Research and Treatment of Cancer; EOT = end-of-treatment; EQ-5D-5L = EuroQol 5 Dimension 5 Level Scale; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IRC = Independent Review Committee; IV = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire; QLQ-LC13 = lung cancer specific questionnaire; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; WOCBP = women of childbearing potential.

Table 2 CCI **Assessments and Pharmacokinetics Sampling Schedule**

Visit			C1D1	C1D2	C1D3	C1D4	C1D5	C2D1	C2D2	C4D2 and every 4th cycle thereafter[a]
CCI /PK timing relative to EOI of study drug[b]										
Timepoint	Predose[c]	CCI		CCI			CCI			
		PK	T	T+B			T+B	T	T+B	T+B
	EOI (+ 15 minutes)	CCI		CCI			CCI			
		PK	T	T+B			T+B	T	T+B	T+B
	1 h after EOI[b] (± 15 minutes)	CCI		CCI						
		PK	T	T+B				T		
	2 h after EOI[b, †] (± 15 minutes)	PK only		T+B						
	3 h after EOI[b], (± 30 minutes)	CCI		CCI						
		PK		T+B						
	7 h after EOI[b, †] (± 30 minutes)	PK only		T+B						
	1 sample any time after EOI	CCI			CCI					
		PK			T+B‡	T+B‡				
	≥ 30 minutes after last sample	PK only					T+B		T+B	T+B
Concomitant medications[e]			X	X	X	X	X	X	X	X

B = sample for berzosertib; C = Cycle; D = Day; DL = dose level; EOI = end of infusion; ECG = electrocardiogram; eCRF = electronic case report form; h = hour; PK = pharmacokinetic; T = sample for topotecan.

[a] That is: C8D2, C12D2, C16D2, etc.

[b] PK Sampling times are relative to EOI of topotecan for T samples on C1D1, C1D3, C1D4 and C2D1, or relative to EOI for berzosertib for T + B samples on C1D2, C1D5, C4D2 and thereafter. ‡ For Safety Run-in Part in Japan, PK sampling for topotecan and berzosertib are to be scheduled for 23 h ± 2 hours (C1D3) and 47 h ± 2 hours (C1D4) after EOI for berzosertib. For main part, topotecan and berzosertib PK samples are to be taken at any time after EOI of topotecan. Exact time of sample collection should be recorded in the eCRF. See Section 6.1 for details of dose timing of topotecan and berzosertib.

[c] Predose is up to 60 minutes before start of topotecan infusion.

CCI [redacted]

[e] Record time and dose for each concomitant medication taken.

† Only for the Safety Run-in Part in Japan.

‡ For Safety Run-in Part in Japan, PK sampling are to be scheduled for 23 h ± 2 hours (C1D3) and 47 h ± 2 hours (C1D4) after EOI for berzosertib. For main part, PK samples are to be taken at any time after EOI of topotecan.

2 Introduction

Berzosertib (formerly known as M6620) is a free base drug substance that acts as a potent inhibitor of the ataxia telangiectasia mutated and Rad3-related (ATR) protein that is being developed for the treatment of malignancies as a single agent or in combination with chemotherapy and/or ionizing radiation or other anticancer agents.

Detailed information on the chemistry, pharmacology, efficacy, and safety of berzosertib is in the Investigator's Brochure (IB) and details regarding topotecan are in the topotecan product information.

2.1 Study Rationale

The purpose of this study is to assess efficacy, safety, tolerability, and PK of berzosertib in combination with topotecan in participants with relapsed, platinum-resistant SCLC.

The results from a Phase I/II study of berzosertib + topotecan demonstrated clinical activity that suggested a potential benefit of the combination in participants with platinum-resistant SCLC in comparison with historical data of single agent topotecan (see Section 2.3.2) and a toxicity profile that largely mirrored that of topotecan as single agent (Thomas 2018; confidential data); thus, the berzosertib and topotecan combination has the potential of providing clinical benefit in this population with poor outcomes and high unmet medical need. This study may potentially support the indication of berzosertib in combination with topotecan as a standard of care treatment in patients with relapsed, platinum-resistant SCLC.

To date, there is no experience with berzosertib in Japanese patients. Therefore, a Japan-only Safety Run-in Part will take place to evaluate the safety, tolerability, and PK profile of berzosertib in combination with topotecan in Japanese participants. The rationale to have a safety run-in for the berzosertib and topotecan combination, instead of a classical Phase I dose escalation, is based on the assessment of expected low ethnic sensitivity in berzosertib PK and lack of plausible basis for PK interaction in Japanese patients. Accordingly, no added toxicity in Japanese participants is expected. The Safety Run-in Part consisting of 2 dose levels (DLs) will be conducted at Japanese sites in parallel with the Main Part of the Global Phase II study. Japanese sites will continue the Main Part of Phase II after completion of the Safety Run-in Part, including the dose-limiting toxicity (DLT) evaluation and confirmation of tolerability at the recommended Phase II dose (RP2D). Participants enrolled into the Safety Run-in Part will follow the same eligibility criteria, study procedures and participants withdrawal criteria as outlined in the Phase II study, unless otherwise specified. The schematic structure of study and its Safety Run-in Part is shown in Figure 2 in Section 1.2. Section 4.1.1 presents more details of the Safety Run-in Part in Japan.

2.2 Background

Chemotherapeutic agents that induce DNA damage are an effective and common treatment option for patients with many types of solid tumors; however, many cancers, despite displaying initial sensitivity and clinical response to these agents, ultimately progress. One mechanism that has been proposed to protect tumor cells from DNA damage is the DNA damage response (DDR) pathway

regulated by the ataxia telangiectasia mutated (ATM) and ATR kinases. Theoretically, small molecule-mediated inhibition of ATR should enhance the effect of DNA damaging chemotherapy on cancer cells.

Berzosertib is a potent inhibitor of ATR that blocks ATR activity in cells, with a concentration resulting in 50% maximal inhibition of 20 nM. Based on nonclinical observations (refer to the latest IB), berzosertib has the potential to have a substantial therapeutic impact on a number of malignancies, including SCLC, in which defects in the DDR are known to be prevalent and in which cytotoxic chemotherapy is a standard of care.

An estimated 1.6 million new lung cancers are diagnosed worldwide each year, approximately 15% of which are SCLC, the most aggressive form of lung cancer, characterized by a rapid doubling time and widespread metastases (Byers 2015). Small-cell lung cancer is a heterogeneous disease, including extremely chemosensitive and chemoresistant clones. While patients with extensive SCLC initially exhibit high response rates to first-line chemotherapy regimens and immunotherapy, typically consisting of a platinum, etoposide, and PD-L1 inhibitors (e.g., atezolizumab, durvalumab), most patients relapse with a median survival of 10 to 12 months (Horn 2018; Paz-Ares 2019). If the relapse is early, i.e., the chemotherapy-free interval is < 90 days (resistant disease), the prognosis is poorer, with response to most regimens ≤ 10% (NCCN 2020, von Pawel 2014). Worldwide, topotecan was the only approved agent in the second-line setting until recently. Based on a single-arm Phase II study with 105 participants, the US Food and Drug Administration granted lurbinectedin an accelerated approval (15 June 2020) as second-line treatment in SCLC. Nonetheless, participants with early relapse (chemotherapy-free interval < 90 days) had poorer outcomes, with a median overall survival (OS) time of 5 months, a median progression-free survival (PFS) time of 2.6 months, and an objective response rate (ORR) of 22% (Trigo 2020).

The berzosertib + topotecan combination has shown promising clinical activity and a favorable safety profile in participants with solid tumors, including participants with platinum-resistant SCLC. A Phase I/II study with the berzosertib + topotecan combination established the recommended Phase II dose, with topotecan at 1.25 mg/m^2 administered from Day 1 to Day 5, and berzosertib at 210 mg/m^2 administered on Day 2 and Day 5, in cycles of 21 days. The toxicity profile of this regimen largely mirrored that of topotecan as single agent. The most common Grade 3 and 4 toxicities were hematological, such as anemia, leukopenia, and neutropenia (40% to 50% each) and thrombocytopenia (25%); however, with most participants having received granulocyte colony-stimulating-factor (G-CSF) prophylactically, complications such as febrile neutropenia were uncommon, and no treatment-related deaths occurred (Thomas 2018; confidential data). In terms of efficacy, there were 2 partial responses (PR) of ≥ 18 months, and ≥ 7 months and 7 stable disease (SD) responses lasting ≥ 3 months (median: 9 months; range, 3 to 12 months). Three of 5 participants with SCLC, all of whom had platinum-resistant disease, had a PR or prolonged SD of ≥ 6 months. In the subsequent Phase II portion of the study of berzosertib in combination with topotecan in participants with relapsed SCLC, there was an overall response rate of 36%: 30% in participants with platinum-resistant disease (n = 20) and 60% in participants with platinum-sensitive disease (n = 5). The median PFS time was 4.8 months (4.3 in platinum-resistant and 7.4 in platinum-sensitive; confidential data). These results suggest a potential benefit of the combination in participants with platinum-resistant disease, defined by disease recurrence within 90 days from the last dose of platinum given in prior lines, in comparison with historical

data of single agent topotecan; thus, the berzosertib and topotecan combination has the potential of providing clinical benefit in this patient population with poor outcomes, few treatment options, and high unmet medical need.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of berzosertib are found in Section 4.2 and the IB.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

2.3.1 Risk Assessment

In the Phase I (Thomas 2018) and Phase II (confidential data) berzosertib and topotecan combination studies, the toxicity profile of berzosertib + topotecan was similar to that of topotecan when given as a single agent. The combination of berzosertib with topotecan will be further assessed and evaluated for exacerbated toxicities or unforeseen AEs, as compared with historical data from berzosertib and topotecan as single agents, and from berzosertib in combination with topotecan.

Identified and potential risks of the study intervention and procedures are presented in Table 3.

Table 3 Berzosertib and Topotecan - Identified and Potential Risks with Mitigation Strategies

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Berzosertib		
Identified Risks for berzosertib in combination with chemotherapy		
Gastrointestinal disorders such as nausea and vomiting	Refer to the berzosertib IB.	Continuous safety monitoring is performed during the study per the SoA (Sections 1.3 and 8.1.3).
Hypersensitivity, including infusion-related reactions[a]	Refer to the berzosertib IB	Exclusion criteria are in place to prohibit enrollment of participants with known hypersensitivity to the study interventions, a similar structural compound, or to one or more excipients used. Continuous safety monitoring is performed during the study. Premedication is permitted for participants who have experienced an infusion-related reaction (Section 6.5.2).

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential Risk for berzosertib in combination with chemotherapy		
Risks associated with drug-drug interactions	No formal drug interaction studies have been conducted with berzosertib in humans; however, in a Phase I/II study of berzosertib in combination with topotecan, no drug interactions were reported with authorized concomitant medications and/or with topotecan. The toxicity profile of the study drugs combination largely mirrored that of topotecan as single agent. Berzosertib is primarily metabolized by CYP3A4. Inhibitors of CYP3A4 might be expected to decrease berzosertib's clearance and inducers of CYP3A4 might be expected to increase its clearance. Berzosertib is a weak inhibitor of CYP3A4. Concomitant administration of sensitive CYP3A4 substrates with a narrow therapeutic index should be considered with caution and careful monitoring for safety. Based on in vitro data, berzosertib has the potential to be an inhibitor of BCRP and OATP1B3 at clinically relevant concentrations and may increase exposure of BCRP and OATP1B3 substrates. For further information, refer to the berzosertib IB.	Concomitant administration with potent inhibitors or inducers of CYP3A4 is prohibited in this study. Concomitant administration with sensitive CYP3A4 substrates with a narrow therapeutic index, BCRP and OATP1B3 substrates should be carefully considered. Clinical protocol-specific instructions should be closely followed (see Sections 5.3 and 6.5).
Pregnancy, fertility, and lactation	There is a potential risk, based on its mechanism of action, that administration of berzosertib during pregnancy could cause fetal harm. For further information, refer to the berzosertib IB.	A negative serum pregnancy test is required for inclusion. Participants who get pregnant during the study must discontinue the study intervention (see Section 7.1). Refer to the berzosertib IB for guidance regarding pregnancy, lactation, contraception and fertility and see protocol Section 5.1 and Appendix 3 for contraception requirements. Further, strict use of contraception is required; participants should be informed that fertility might be impaired long term and may opt to cryopreserve sperm or ova prior to treatment. Male participants must also use a condom with pregnant female partners during the study, since exposure to the study intervention through the ejaculate could harm an existing fetus.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Topotecan (SmPC 2019)		
Anemia	Moderate to severe (Hb ≤ 8.0 g/dL) in 37% of patients (14% of courses).	Adverse events are continually monitored during the study (see Section 8.1.3) and managed clinically, as indicated, including by study intervention interruption, dose modification or discontinuation.
Leukopenia (including neutropenia)	Abnormally low white blood cell count (leucopenia, neutropenia) that may be accompanied with fever and signs of infections (febrile neutropenia). Severe neutropenia (neutrophil count < 0.5 x 10^9/L) during Course 1 in 55% of patients, with duration ≥ 7 days in 20% and overall in 77% of patients (39% of courses). In association with severe neutropenia, fever or infection occurred in 16% of patients during Course 1 and overall in 23% of patients (6% of courses). Median time to onset of severe neutropenia was 9 days and the median duration was 7 days.	Adverse events are continually monitored during the study (see Section 8.1.3) and managed clinically, as indicated, including by study intervention interruption, dose modification or discontinuation.
Thrombocytopenia	Severe (platelets < 25 x 10^9/L) in 25% of patients (8% of courses); moderate (platelets between 25.0 and 50.0 x 10^9/L) in 25% of patients (15% of courses). Median time to onset of severe thrombocytopenia was Day 15 and the median duration was 5 days.	Adverse events are continually monitored during the study (see Section 8.1.3) and managed clinically, as indicated, including by study intervention interruption, dose modification or discontinuation.
Study Procedures		
Blood sampling	Blood sampling is required for participants as detailed in the SoA and are considered essential for the study's scientific objectives. Blood sampling carries a risk of AEs including pain, bruising, bleeding, redness and swelling of the site/vein, and infection.	Minimization of blood sampling was thoughtfully considered during protocol development weighing risk to participants versus achievement of the study's scientific objectives. Blood samples will be taken by qualified professional and every effort will be made to minimize any discomfort.
Tumor biopsies	Fresh tumor biopsies may be required for some participants as detailed in the SoA and inclusion criteria. Biopsies carry a risk of AEs including bleeding and infection.	Investigators are to use clinical judgment and not proceed with a biopsy if is clinically contra-indicated or there is high risk of AEs.
Imaging procedures	Imaging disease assessments are required for all participants as detailed in the SoA to monitor disease progression. These are associated with a risk of allergic reactions to contrast agents, exposure to ionizing radiation for some types of imaging (e.g., CT scans, bone scintigraphy), nephrogenic systemic fibrosis, and intracranial gadolinium deposition for	Imaging procedures in this study will be conducted at a similar frequency to that in routine clinical practice. Participants will be monitored for allergic reactions, as per routine clinical practice. Selection of imaging modality will be guided by any identified risk factors, as described in the Imaging Manual.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	gadolinium and contrast induced renal damage for iodinated contrast.	

AEs = adverse events; CT = computed tomography; CYP3A4 = cytochrome P450 3A4; BCRP = breast cancer resistance protein; Hb = hemoglobin; IB = Investigator's Brochure; OATP1B3 = organic anion transporting polypeptide 1B3; SoA = Schedule of Activities.

[a] Infusion-related reactions have been reported using a variety of terms to describe the same biologic event, including erythema, eyelid edema, face edema, flushing, hypersensitivity, infusion-related reaction, pruritus, pruritus allergic, rash, rash erythematous, rash macular, rash pruritic, and rhinitis allergic.

2.3.2 Benefit Assessment

- Patients with relapsed, platinum-resistant SCLC have few treatment options. All participants in the current study will receive a current standard of care + berzosertib, which has the potential to improve their treatment outcome (see Section 2.2).
- Participants in this study will be contributing to the process of developing new therapies in an area of unmet need, expanding the current standard of care by displacing the existing standard of care for recurrent platinum-resistant SCLC.
- The medical evaluations and assessments in the current study protocol, with regular physical examinations, monitoring of AEs, and laboratory assessments, in many instances go beyond the local standard of care.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize the risk to participants in this study as outlined in Table 3, the risks (potential and identified) associated with berzosertib in combination with topotecan are justified by the anticipated benefits that may be afforded to participants with relapsed, platinum-resistant SCLC, for which there are few treatment options.

3 Objectives and Estimands

Objectives and estimands are outlined in Table 4 and Table 5.

Table 4 Objectives and Estimand Attributes (Main Part)

Objectives	Estimand Attributes
Primary	
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 IRC. **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 • Progression according to RECIST 1.1: while not progressed strategy, i.e., assessments up to the intercurrent event **Population Level Summary:** Objective response rate
Secondary	
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 IRC. Measured by time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention. **Population:** Patients with relapsed, platinum-resistant SCLC with a confirmed objective response 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., 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

Objectives	Estimand Attributes
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 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:** Patients 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
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:** Patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent anticancer treatment **Intercurrent Event Strategy**: • 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 OS time • Kaplan-Meier estimates

Objectives	Estimand Attributes
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 EORTC 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-5L **Population:** Patients 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 treatment: 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 changes from baseline analysis for multi-item scales in EORTC questionnaires (i.e., physical functioning, dyspnea) and VAS • Proportion of patients with ≥ 1 category improvement and proportion of patients with ≥ 1 category worsening in single-item symptoms (i.e., cough and chest pain)
To evaluate the safety and tolerability of berzosertib + topotecan	**Endpoint:** Occurrence of AEs and treatment-related AEs and occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead ECG findings **Population:** Patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan

Objectives	Estimand Attributes
CCI	[redacted]

Objectives	Estimand Attributes
CCI	

AEs = adverse events; CYP = cytochrome P450; 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; IRC = Independent Review Committee; OS = overall survival; PD = progressive disease; PFS = progression-free survival; CCI ; CCI ; PRO = patient-reported outcome; QLQ-LC13 = lung cancer specific questionnaire; QLQ-C30 = Quality of Life Questionnaire; CCI ; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SCLC = small-cell lung cancer; VAS = visual analogue scale.

In case DL2 is declared RP2D, data for participants receiving DL2 will in addition be analyzed as part of the main study.

Table 5 Objectives and Estimand Attributes (Safety Run-in Part in Japan)

Objectives	Estimand Attributes
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 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 patients with advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed • DL2: Japanese patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan
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 patients with advanced solid tumors • DL2: Japanese 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 • Progression according to RECIST 1.1: while not progressed strategy, i.e., assessments up to the intercurrent event **Population Level Summary:** Objective response rate

Objectives	Estimand Attributes
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 objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention. **Population:** • DL1: Japanese patients with advanced solid tumors with a confirmed objective response according to RECIST 1.1 as assessed by Investigator • DL2: Japanese patients with relapsed, platinum-resistant SCLC with a confirmed objective response according to RECIST 1.1 as assessed by Investigator **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

Objectives	Estimand Attributes
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 patients with advanced solid tumors • DL2: Japanese patients 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
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 patients with advanced solid tumors • DL2: Japanese patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent anticancer treatment **Intercurrent Event Strategy**: • 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 OS time • Kaplan-Meier estimates

Objectives	Estimand Attributes
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 EORTC 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-5L **Population:** • DL2: Japanese patients 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 treatment: 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 changes from baseline analysis for multi-item scales in EORTC questionnaires (i.e., physical functioning and dyspnea) and VAS • Proportion of patients with ≥ 1 category improvement and proportion of patients with ≥ 1 category worsening in single-item symptoms (i.e., cough and chest pain)
To characterize the PK profile of berzosertib	**Endpoint:** PK parameters of berzosertib in plasma by NCA **Population:** • DL1: Japanese patients with advanced solid tumors • DL2: Japanese patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan

Objectives	Estimand Attributes
CCI	

Objectives	Estimand Attributes
CCI	

AEs = adverse events; CYP = cytochrome P450; DL = dose level; DLT = dose-limiting toxicity; CCI ; EORTC = European Organization for the Research and Treatment of Cancer; HRQoL = health-related quality of life; NCA = non compartmental analysis; 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; CCI ; 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.

4 Study Design

4.1 Overall Design

This is a multicenter, Phase II, open-label, single-arm study designed to assess the efficacy and safety of berzosertib in combination with topotecan in participants with relapsed, platinum-resistant SCLC (platinum-free interval [PFI] < 90 days) with only 1 prior line of systemic treatment. An Independent Review Committee (IRC) will perform blinded determinations as to whether the criteria for tumor response or progression are met according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; see Appendix 2 for additional IRC details).

For each participant, the study will include a Screening Period lasting up to 28 days, a Study Intervention Period consisting of 21-day cycles of berzosertib + topotecan until disease progression or other criteria for study intervention discontinuation are met (see Section 7), an End-of-Treatment Visit, a Safety Follow-up Period of 30 days after the last study intervention dose, and Efficacy and Survival Follow-up Visits every 12 weeks from the last study intervention administration. During the Survival Follow-up, survival information and subsequent anticancer therapy given to the participant should be recorded. The Survival Follow-up Visits can occur as clinic visits or by telephone contact until death, lost to follow-up, study withdrawal of consent, or End of Study. Additionally, participants who discontinue study intervention for reasons other than disease progression or death, will continue with regular imaging assessments (see Table 1 for details) until disease progression, start of subsequent anticancer therapy, death, withdrawal of consent, lost to follow-up, or End of Study.

An interim analysis 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).

Section 1.2 presents the Study Schema, Section 1.3, the Schedule of Activities, Section 4.4, the End of Study definition, and Section 6.7 study intervention after the end of study.

4.1.1 Safety Run-in Part (Japan-only)

The Safety Run-in Part will be conducted at Japanese sites concurrently with the Main Part of the global Phase II study according to a Bayesian Optimal Interval Design (BOIN) (Yuan 2016). Japanese sites will continue the Main Part of Phase II after completion of Safety Run-in Part, including the DLT evaluation and confirmation of tolerability at the DL2. The starting dose of berzosertib and topotecan in the Safety Run-in Part is determined based on the safety data from the Phase I/II combination study of berzosertib and topotecan, Phase I study of single agent berzosertib as well as available safety data of single agent topotecan in Japanese and non-Japanese (PMDA 2011, Thomas 2018, confidential data).

Participants enrolled into the Safety Run-in Part will follow the same eligibility criteria, study procedures (unless otherwise specified), and participants withdrawal criteria as outlined in the global Phase II study.

The Safety Run-in Part will consist of the combination therapy of berzosertib with topotecan, up to 2 DLs, with a BOIN design, enrolling cohorts of 3 participants. Participants in DL1 will receive berzosertib at a dose of 105 mg/m^2 intravenous (IV) every 21 days on Days 2 and 5, and topotecan at a dose of 1.25 mg/m^2 IV every 21 days on Day 1 to 5. At DL2, participants will receive the same dose regimen as in the Main Part of the Phase II study (see Section 4.1). Participants enrolled on the DL1 may escalate to DL2 once the tolerability at DL2 is confirmed.

Of note, in the Safety Run-in Part, participants with advanced solid tumors will enroll in the DL1. Participants with relapsed platinum-resistant SCLC will enroll in the DL2. In case safety and tolerability of DL2 is confirmed, participants enrolled in the DL2 will be included in all study objectives, including efficacy evaluation, in the global Phase II Part of the study. The discontinued participants will remain in the overall safety and efficacy analyses as long as the Main Part of Phase II stipulates.

Dose-limiting toxicities (DLTs) are defined in Section 6.8.

Details on the BOIN design and escalation decisions are outlined in Section 9.4.2.

4.2 Scientific Rationale for Study Design

The selection of this study design (i.e., a single-arm, non-randomized, Phase II study) is based on the fact that topotecan in platinum-resistant SCLC yields a response rate of ≤ 10%, according to medical literature (NCCN 2020, von Pawel 2014); therefore, it is thought that a single-arm study in this specific patient population may serve as a confirmation of clinical proof-of-concept that the combination of berzosertib with topotecan adds clinical value to topotecan, as a single agent, according to historical controls. In addition, new drugs have been recently granted accelerated approval based on single-arm open-label Phase II studies, when able to demonstrate a positive benefit-risk ratio for diseases with high unmet medical need, such as relapsed SCLC.

The primary endpoint of objective response is a clinically relevant measure of tumor control, particularly in SCLC, which is usually a malignancy with fast growth leading to dismal prognoses. In addition, other drugs in this setting obtained recent regulatory accelerated approvals by means of studies where objective response was the primary endpoint (e.g., lurbinectedin). The secondary efficacy endpoints of duration of response, PFS, OS, and patient-reported outcomes (PROs) are standard measures of efficacy and will be supportive of the overall efficacy determination.

Berzosertib administration as single agent is well tolerated. Because there is no experience with berzosertib in Japanese patients, Japan-only Safety Run-in Part will be conducted to evaluate the safety, tolerability and PK of berzosertib in combination with topotecan in Japanese participants. The rationale to have a safety run-in for the berzosertib and topotecan combination, instead of a classic Phase I dose escalation, is based on the assessment of expected low ethnic sensitivity in berzosertib PK and lack of plausible basis for PK interaction in Japanese patients. Accordingly, no added toxicity in Japanese participants is expected (Paller 2014).

4.3 Justification for Dose

4.3.1 Main Part of Global Phase II

Based on the reported Phase Ib study (Thomas 2018), the starting study intervention doses for the combination in this study are as follows:

- Berzosertib by IV administration at a dose of 210 mg/m^2 on Day 2 and Day 5 of each 21-day cycle
- Topotecan by IV administration at a dose of 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle.

Section 6.6 provides the dose selection and modification information for this study.

4.3.2 Safety Run-in Part (Japan-only)

Two dose levels are planned in the Safety Run-in Part as shown below. The dose levels are designed based on the Phase I/II combination study of berzosertib and topotecan, Phase I studies of single agent berzosertib as well as available safety data of single agent topotecan in Japanese and non-Japanese (PMDA 2011, Thomas 2018, confidential data).

DL1:

- Berzosertib by IV administration at a dose of 105 mg/m^2 on Day 2 and Day 5 of each 21-day cycle
- Topotecan by IV administration at a dose of 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle.

DL2 (same as the Main Part of global Phase II):

- Berzosertib by IV administration at a dose of 210 mg/m^2 on Day 2 and Day 5 of each 21-day cycle
- Topotecan by IV administration at a dose of 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts as defined in Section 1.3 (Schedule of Activities) and fulfilled at least 1 of the following criteria:

- Minimum follow-up of 12 months after the last study intervention administration
- Withdrawal of consent from the study
- Lost to Follow-up
- Died.

The end of the study is defined as the date of completion for all participants (i.e., the last visit of the last participant).

The Sponsor may terminate the study at any time once access to berzosertib or topotecan for participants still benefiting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥ 18 years of age at the time of signing the informed consent. In Japan, if a participant is < 20 years, the written informed consent from his/her parent or guardian will be required in addition to the participant's written consent. Once the participant reaches 20 years of age, participant's written consent will be obtained.

Type of Participant and Disease Characteristics – Safety Run-in Part in Japan - DL1 Only

2. Histologically proven advanced solid tumors, for which no effective standard therapy exists, or standard therapy has failed or cannot be tolerated
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 and Karnofsky Scale ≥ 70% (see Appendix 8)

Type of Participant and Disease Characteristics – Main Part of Global Phase II and DL2 of Safety Run-in Part in Japan

4. ECOG PS ≤ 2 and Karnofsky Scale ≥ 60% (see Appendix 8)
5. Histologically confirmed SCLC
6. Radiologically confirmed progression after first-line or chemoradiation platinum-based treatment (carboplatin or cisplatin), with or without immunotherapy, for treatment of limited or extensive stage SCLC, with a PFI < 90 days. The PFI is measured by the elapsed time

from the last day of the regimen of a platinum-based treatment until the first day of documented disease progression

7. Measurable disease according to RECIST 1.1 at Screening. Evidence of measurable disease must be confirmed by the IRC prior to start of treatment
8. Tumor tissue provision: archival (collected within 12 months before date of informed consent form [ICF]) signature for Screening) or fresh biopsy specimen, if medically feasible

Type of Participant and Disease Characteristics - All Parts

9. Have adequate hematologic function as indicated by:

- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9.0 g/L. Prior red blood transfusions are allowed
- Absolute neutrophil count ≥ 1,500/µL with no growth factor treatment within 14 days of obtaining the screening blood sample
- Total bilirubin level ≤ 1.5 × upper limit of normal (ULN), except in the case of known Gilbert syndrome, in which case total bilirubin must be ≤ 2 × ULN, an aspartate aminotransferase (AST) and an alanine aminotransferase (ALT) level ≤ 3.0 × ULN or ≤ 5 × ULN in presence of liver metastases
- Adequate renal function defined as creatinine clearance ≥ 60 mL/min by calculation using the Cockcroft-Gault formula or measured by 24-hour urine collection. The Cockcroft-Gault formula is (l40 - age) × weight [kg]) / (72 × serum creatinine [mg/dL]) × 0.85 (if female)

Sex

10. Are male or female
11. Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies

Male participants:

Agree to the following during the Study Intervention Period and for at least 6 months after the last study intervention dose:

- Refrain from donating sperm

PLUS, either:

- Abstain from any activity that allows for exposure to ejaculate

OR

- Use a male condom: When having sexual intercourse with a woman of childbearing potential (WOCBP), who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.
- Male participants must use a condom with pregnant female partners

Female participants:

Are **not** pregnant or breastfeeding (for sites in Japan, the participant is not eligible even if breastfeeding is suspended), and at least 1 of the following conditions applies:

- **Not** a WOCBP

OR

- If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
  - Before the first dose of the study intervention, if using hormonal contraception:
    - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

    OR

    - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay

  AND

  A barrier method, as described in Appendix 3.
  - During the Study Intervention Period
  - After the Study Intervention Period (i.e., after the last study intervention dose is administered) for at least 6 months after the last study intervention dose and agree not to donate eggs (ova, oocytes) for reproduction during this period

  The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - Have a negative serum pregnancy test, as required by local regulations, within 24 hours before the first study intervention dose.

Additional requirements for pregnancy testing during and after study intervention are in Appendix 5.

Informed Consent

12. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Clinically relevant (i.e., active), uncontrolled intercurrent illness including, but not limited to, severe active infection including, severe acute respiratory syndrome coronavirus-2

infection/coronavirus disease 2019, immune deficiencies, uncontrolled diabetes, uncontrolled arterial hypertension, symptomatic congestive heart failure (New York Heart Association Classification ≥ Class III), unstable angina pectoris, myocardial infarction, uncontrolled cardiac arrhythmia, and cerebral vascular accident/stroke. Calculated QTc average (using the Fridericia correction calculation) of > 450 msec for males and > 470 msec for females. Any psychiatric illness/social situations that would limit compliance with study requirements.

The following exceptions apply:

a. Participants with human immunodeficiency virus infection are eligible if they are on effective antiretroviral therapy with undetectable viral load within 6 months, provided there is no expected drug-drug interaction. Human immunodeficiency virus testing is not mandated for study inclusion. If performed, the participant must be consented for testing as per local standard guidance.
b. Participants with evidence of chronic hepatitis B virus (HBV) infection are eligible if the HBV viral load is undetectable on suppressive therapy (if indicated), and if they have ALT, AST, and total bilirubin levels < ULN, and provided there is no expected drug-drug interaction. See the Schedule of Assessments (SoA; Table 1) for tests required at screening and during Study Intervention Period.
c. Participants with a history of hepatitis C virus (HCV) infection are eligible if they have been treated and cured. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load, and if they have ALT, AST, and total bilirubin levels < ULN. See the SoA (Table 1) for tests required at screening and during Study Intervention Period.

2. Unstable brain metastases; however, participants with known brain metastases may be enrolled in this clinical study if they are clinically stable (without evidence of progression by imaging for at least 2 weeks prior to the first study intervention dose and any neurologic symptoms have returned to baseline), have no evidence of new brain metastases, and are on a stable or decreasing dose of steroids for at least 14 days prior to study intervention. Participants with carcinomatous meningitis are excluded regardless of clinical stability. Screening central nervous system imaging is not mandatory.
3. Prior malignant disease within the last 3 years. Exceptions include fully resected basal cell carcinoma of the skin or squamous cell carcinoma of the skin, in situ cervical cancer, fully resected ductal carcinoma in situ of the breast, superficial or noninvasive bladder cancer, and Stage IA, Grade I endometrioid endometrial cancer with no myometrial invasion, that has undergone curative therapy. Participants with other localized malignancies treated with curative intent need to be discussed with the Medical Monitor.
4. Participants with known history of Li-Fraumeni Syndrome and Ataxia Telangiectasia.
5. Participants not recovered from AEs Grade > 1 from prior anticancer therapies, including surgeries. Exception: Grade 2 AEs not constituting a safety risk (e.g., alopecia), based on the Investigator's judgment; must consult with the Medical Monitor prior to enrollment.

Prior/Concomitant Therapy

6. For participants in the Main Part of global Phase II and DL2 of Safety Run-in Part in Japan: 2 or more lines of prior systemic anticancer treatment, including retreatment with a platinum-based regimen
7. Prior treatment with topoisomerase I inhibitor, including topotecan and irinotecan
8. Prior treatment with an ATR inhibitor
9. Prior or concurrent treatment with a nonpermitted drug/intervention:

    - Participants who may have received any of the following anticancer therapy(ies) within the following time windows from the first day of study interventions administration:
        - Small molecule inhibitor therapy (including investigational) within 2 weeks or 5 half-lives, whichever is longer
        - Any type of anticancer antibody or antibody drug conjugates within 3 weeks
        - Systemic chemotherapy within 4 weeks (within 6 weeks for nitrosoureas/ mitomycin C)
        - Prior curative-intent high-dose radiotherapy within 4 weeks. Prior palliative radiotherapy to metastatic lesion(s) is permitted provided it was completed at least 1 week prior to first day of study interventions administration and toxicities recovered to Grade ≤ 1.
        - Any other type of anticancer therapy, not listed above, within 4 weeks.
    - Concomitant use of strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) enzymes that cannot be discontinued for at least 1 week prior to administration of study intervention and for the duration of study intervention.
    - Other prohibited concomitant medications as listed in Section 6.5.3.

Prior/Concurrent Clinical Study Experience

10. Concurrent participation in another interventional clinical study is not permitted. There are no restrictions on prior clinical study participation provided the above washout periods are followed.

Other Exclusions

11. Known hypersensitivity to the study interventions, a similar structural compound, or to one or more excipients used.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions on caffeine, modest alcohol, or tobacco use apply during this study.

5.3.3 Activity

Electrocardiograms will be obtained after the participant has rested in a semi-supine position (Section 8.2.3).

Participants will abstain from strenuous exercise for 2 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities.

Based on in vitro and in vivo assays, berzosertib has a phototoxic potential as it absorbs in the UV-visible radiation spectrum, and is widely distributed in tissues, including skin. Therefore, participants should be cautioned to minimize exposure to the sun and other sources of visible and UV radiation, and to take protective measures when necessary.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once within 14 days, after the reason for the screening failure has been addressed. Rescreened participants will be assigned a new participant number and will undergo Screening procedures as planned in the protocol. Any previous screening tests can be used for rescreening, provided they are within the new screening window of -28 days.

6 Study Interventions

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol. Study intervention is used instead of "study drug, Investigational Medicinal Product, or study treatment".

For this study, both berzosertib and topotecan are considered study interventions.

6.1 Study Interventions Administration

Berzosertib at a dose of 210 mg/m^2 will be via IV administration over 60 minutes (± 10 minutes) and start approximately 15 minutes 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 will be via IV administration over 30 minutes on Days 1 through 5 of each 21-day cycle. Study intervention details are provided in Table 6.

Specific to DL1 in the Safety Run-in Part in Japan, the dose of berzosertib will be 105 mg/m^2.

Specific to the Safety Run-in Part in Japan, all participants, in principle, should undergo inpatient observation during Cycle 1 until at least Day 5 of study intervention. Inpatient observation could be extended on a case by case basis, as assessed by the Investigator.

All other conditions will be the same as above.

Prior to study intervention administration, baseline neutrophils should be ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3 prior to Cycle 1. For subsequent cycles, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

Investigators should prophylactically premedicate participants with corticosteroid and antihistamine before the first 2 berzosertib infusions. Premedication should be administered for subsequent berzosertib infusions based upon clinical judgment and presence/severity of prior infusion -related reactions to berzosertib. See Table 6 for suggested premedication regimen with corticosteroids and antihistamine.

Prophylactic G-CSF will be administered according to local practice and topotecan label. Its administration as primary or secondary prophylaxis is highly recommended and can be adjusted according to institutional guidelines and clinical judgment. G-CSF may be used from Day 6, at least 24 hours after the last dose of topotecan.

Participants are planned to continue with study intervention until documented disease progression, discontinuation due to AEs, death, or withdrawal from the study, whichever occurs earlier.

Additional details of sourcing, packaging, including quantity per container, anticipated length of supply per container, and labeling of the study interventions will be defined in a separate Pharmacy Manual.

Table 6 Study Interventions

Intervention Name	Berzosertib	Topotecan
Type	Drug	Drug
Dose Formulation	Solution for infusion	Concentrate for solution for infusion
Unit Dose Strength	20 mg/mL	1 mg/mL topotecan free base
Dose Amount	Main Part: 210 mg/m^2 Safety Run-in Part in Japan: DL1: 105 mg/m^2 DL2: 210 mg/m^2	1.25 mg/m^2
Premedication	Suggested premedication regimen: hydrocortisone (200 mg IV) and diphenhydramine (25 mg IV) approximately 60 minutes before study intervention infusions. The regimen may be modified based on local treatment standards and guidelines, as appropriate, as long as not prohibited by the protocol (see Section 6.5.3)	Prophylactic or therapeutic use of antiemetic medication according to the topotecan product information is recommended, unless the specific medication is prohibited for other reasons, e.g., the antiemetic is also a strong CYP3A4 inhibitor (see Table 6)
Frequency	On Day 2 and Day 5 of each 21-day cycle	Days 1 through 5 of each 21-day cycle
Route of Administration	IV infusion	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	SoC/IMP depending on local law

Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Packaging and Labeling	Study Intervention will be provided in CCI Each C will be labeled per country requirements.	Depending on the local regulations, topotecan may be either sourced from a local hospital pharmacy or supplied by the Sponsor (or designated service provider) and will be packaged/labeled according to local requirements.
Current/Former Name(s) or Alias(es)	Substance code MSC2527093A, M6620, VX-970	

DL = dose level; IMP = Investigational Medicinal Product; IV = intravenous; NIMP = Non-Investigational Medicinal Product; SoC = standard of care.

6.2 Study Interventions Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the Head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study interventions, the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Study Reference Manual.
- Only participants enrolled in the study may receive study interventions and only authorized site staff may supply it. All study interventions will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study interventions accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose each participant used during the study.
  - The disposition (including return, if applicable) of any unused study interventions.
  - Dates, quantities, batch numbers, container numbers, expiry dates, formulations, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study interventions provided were fully reconciled.

- Unused study interventions will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study interventions accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

This is a single-arm study, all participants will receive the same study interventions. In the Safety Run-in Part in Japan, participants at DL1 will receive a lower berzosertib dose (105 mg/m^2).

6.3.2 Blinding

Not applicable as this is a single-arm study.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information. Additionally, on berzosertib PK and/or ECG assessment days and the day before (see Table 2), date, time, and dose amount of each concomitant therapy administration (e.g., each individual administration when a drug is taken twice daily) is to be recorded in addition to the regular collection of start and stop dates. Furthermore, the time for all meals taken up until the last triplicate digital ECG measurements on each ECG day are to be recorded. CCI [redacted]

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

There is no specific treatment or medicine available to counteract the inhibition of ATR intended by berzosertib or topotecan. For any unwanted events during treatment with berzosertib and/or topotecan, the oncological standards in supportive care should be applied.

6.5.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Permitted premedications are described in Section 6.1.

6.5.3 Prohibited Medicines and Precautions

Any inadvertent use of prohibited medications during the Study Intervention Period will be reported as protocol deviations. These will be reviewed by the Sponsor and proportionate action taken. In cases where prohibited medication use is judged to significantly affect the participant's safety or compromise the study's scientific objectives, study participants will be permanently discontinued from the study.

Participants must not receive concurrent anticancer therapy (see Section 6.5.4 for details of concurrent palliative radiation therapy).

Based on nonclinical findings, the concomitant administration of berzosertib with sensitive CYP3A4 substrates with a narrow therapeutic index, substrates of breast cancer resistance protein (BCRP), or organic anion transporting polypeptides (OATP) 1B3 should be considered with caution and careful monitoring for safety.

Because berzosertib is primarily metabolized by CYP3A4, inhibitors of CYP3A4 might be expected to decrease berzosertib's clearance and inducers of CYP3A4 might be expected to increase its clearance.

The Investigator should refer to the topotecan summary of product characteristics (SmPC) or Package Insert for guidance on prohibited mediations during treatment.

Prohibited concomitant medications and precautions during berzosertib treatment are listed in Table 7.

Table 7 Prohibited Concomitant Medications and Precautions During Berzosertib Treatment

Restricted Medication	Study Period	
	Screening Period	Treatment Period
Strong CYP3A4 inhibitors or inducers • Examples of strong CYP3A4 inhibitors include clarithromycin, diltiazem, idelalisib, cobicistat, HIV protease inhibitors, itraconazole, ketoconazole, posaconazole, voriconazole and nefazodone*. • Examples of strong CYP3A4 inducers include carbamazepine, enzalutamide, mitotane, phenytoin, rifampin and St. John's wort.	None allowed within 7 days before the first dose of study intervention	None allowed until the permanent discontinuation of berzosertib
Precautions for Concomitant Medication		
Sensitive CYP3A4 substrates with a narrow therapeutic index, substrates of BCRP, and OATP1B3 • Examples of sensitive CYP3A4 substrates with a narrow therapeutic index include alfentanil, everolimus, sirolimus, and tacrolimus • Examples of substrates of BCRP include rosuvastatin and sulfasalazine • Examples of substrates of OATP1B3 include asunaprevir, atorvastatin, bosentan, danoprevir, docetaxel, fexofenadine, glyburide, imatinib, nateglinide, paclitaxel, pravastatin, repaglinide, simvastatin acid, and telmisartan	The use of sensitive CYP3A4 substrates with a narrow therapeutic index, substrates of BCRP and OATP1B3 should be considered with caution and careful monitoring for safety	

BCRP = breast cancer resistance protein; CYP3A4 = cytochrome P450 3A4; HIV = human immunodeficiency virus; OATP1B3 = organic anion transporting polypeptide 1B3.

* Not approved in Japan.

6.5.4 Other Interventions

Radiation therapy is allowed on this study for palliative treatment e.g., for lesions that cause symptoms that cannot be adequately controlled by other means e.g., analgesics; however, the use of radiation therapy during the Study Intervention Period should be discussed with the Medical Monitor on a case by case basis considering the influence on imaging assessments of target/nontarget lesions.

In addition, the Investigator should ensure that tumor assessments are recently obtained and reported as per RECIST 1.1, before initiation of radiation therapy. Berzosertib and topotecan should be withheld at least 1 day before the administration of radiation therapy; both drugs can be resumed after radiation therapy is completed, provided the participant has recovered from potential radiation therapy toxicities (Grade < 2 or back to baseline) and will derive benefit from resuming study treatment, as assessed by the Investigator. In case whole brain radiation therapy is administered, a wash-out period of ≥ 14 days is required before resuming study treatment.

6.6 Dose Selection and Modification

Participants will receive berzosertib in combination with topotecan as per the initial treatment assignment (see Table 6) until the criteria are met as outlined in Section 4.4 (End of Study Definition) and/or Section 7.1 (Discontinuation of Study Intervention).

The justification for study intervention dose is presented in Section 4.3. Berzosertib and topotecan should be administered in combination, including during dose modifications and interruptions, unless one agent is permanently discontinued.

In case a dose reduction is necessary, berzosertib and topotecan will be administered as outlined in Section 6.6.1. See Section 6.8 for specifics regarding dose modification during the Safety Run-in Part.

6.6.1 Study Intervention Dose Modifications

6.6.1.1 Berzosertib Dose Modifications

In the DL1 of the Safety Run-in Part in Japan, dose reduction from 105 mg/m^2 is not allowed. Therefore, berzosertib should be discontinued if toxicity requiring dose modification is observed in DL1.

In the Main Part of the global Phase II and in the DL2 of the Safety Run-in Part, the dose of berzosertib may be reduced for the occurrence of drug-related toxicity using the following toxicity-dependent guidelines:

- **For Grade 4 hematologic toxicity:** The dose of berzosertib will be reduced by 1 dose level (first dose reduction).
- **For Grade 3 nonhematologic toxicity:** The dose of berzosertib will be reduced by 1 dose level (first dose reduction).
- **For Grade 4 nonhematologic toxicity:** The dose of berzosertib will be reduced by 2 dose levels (equivalent to second dose reduction).

For liver function toxicity, please also see Section 7.1 as it may indicate potential severe liver injury (possible Hy's Law) and study intervention discontinuation.

For pulmonary toxicity, study intervention should be interrupted in case of suspected interstitial lung disease (ILD), and permanently discontinued if ILD is confirmed.

Based on the criteria above, a maximum of 2 dose reductions will be permitted. Once the berzosertib dose has been reduced, it should not be re-escalated to the starting dose. If a second Grade 4 nonhematologic toxicity were to recur, treatment will be discontinued. Dose reduction levels are provided in Table 8.

Table 8 Berzosertib Dose Modifications

Dose modifications for Grade 4 hematologic and Grade 3 nonhematologic drug-related adverse events	
Starting dose	210 mg/m^2
First dose reduction (1 dose level)	160 mg/m^2
Second dose reduction (2 dose levels)	105 mg/m^2
Dose modifications for Grade 4 nonhematologic drug-related adverse events	
Starting dose	210 mg/m^2
First dose reduction (2 dose levels)	105 mg/m^2

In case of hematological toxicity during any cycle, treatment may be interrupted. Prior to initiation of the next cycle, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

In addition, in case of non-hematologic Grade 3 or higher toxicity during any cycle, treatment should be interrupted and may be resumed when all toxicities have returned to Grade ≤ 2; resumption may be at the discretion of the Investigator.

Treatment interruptions due to a study intervention-related AE may occur for a maximum of 21 days.

Participants who develop intolerance to berzosertib may continue on single agent topotecan at the discretion of the Investigator, administered every 3 weeks (on Days 1 to 5) at the same dose administered in combination therapy, until disease progression or other criteria for discontinuation are met (Section 7.1).

6.6.1.2 Topotecan Dose Modifications

The dose of topotecan may be reduced for drug-related toxicity using the toxicity-dependent guidelines in Table 9 and Table 10. Topotecan dose reductions will be accomplished by decreasing the dose of topotecan for each of the 5 days.

Based on the below criteria, a maximum of 2 dose reductions will be permitted. Once the topotecan dose has been reduced, it should not be re-escalated to the starting dose.

Table 9 Topotecan Dose Modifications for Hematologic and Nonhematologic Toxicities

	Topotecan 1st Dose Reduction (mg/m^2)	Topotecan 2nd Dose Reduction (mg/m^2)
Dose Modifications for Hematologic Toxicities		
Toxicity		
Grades 1 and 2	No adjustment	Not applicable
Grades 3 neutropenia persisting after Day 21	1	0.75
Grade 4 thrombocytopenia or Grade 4 neutropenia with fever or infection or of duration ≥ 7 days	1	0.75
Dose Modifications for Nonhematologic Toxicities		
Toxicity		
Grades 1 and 2	No adjustment	Not applicable
Grades 3 and 4 (except Grade 3 nausea)	1	0.75

Table 10 Topotecan Dose Modifications for Renal Function (Regardless of Drug Relationship)

Creatinine Clearance (Cockcroft-Gault Formula)	Topotecan 1st Dose Reduction (mg/m^2)
≥ 60 mL/min	No adjustment
40-59 mL/min	1
20-39 mL/min	0.75
< 20 mL/min	Discontinue

For liver function toxicity, please also see Section 7.1 as it may indicate potential severe liver injury (possible Hy's Law) and study intervention discontinuation.

For pulmonary toxicity, study intervention should be interrupted in case of suspected ILD, and permanently discontinued if ILD is confirmed.

In case of hematological toxicity during any cycle, treatment may be interrupted. Prior to initiation of the next cycle, neutrophils should be > 1,000/mm^3, platelets > 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

In addition, in case of non-hematologic Grade 3 or higher toxicity during any cycle, treatment should be interrupted and may be resumed when all toxicities have returned to Grade ≤ 2; resumption may be at the discretion of the Investigator.

Treatment interruptions due to a drug-related AE may occur for a maximum of 21 days.

Participants who develop intolerance to topotecan may continue single agent berzosertib at the discretion of the Investigator, administered at the same schedule in combination therapy (on Days 2 and 5 of 21-day cycles), until disease progression or other criteria for discontinuation are met (Section 7.1).

6.7 Study Intervention After the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study (outside of potential continued treatment as described in Section 4.4) because such care would not differ from what is normally expected for patients with SCLC.

6.8 Definition of Dose-limiting Toxicity (Safety Run-in Part Only)

Participants enrolled in the Safety Run-in Part will be monitored for DLTs during the first cycle. DLT will be defined as any of the following AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, assessed as drug-related by the Investigator and/or the Sponsor at any dose and judged not to be related to the underlying disease or any previous or concomitant medication or concurrent condition occurring during the DLT evaluation period (Cycle 1, 21 days).

Study accrual will be halted, pending discussions with the Safety Monitoring Committee (SMC) or the study Sponsor, if there is an occurrence of a Grade 5 AE attributable to the study treatment. The SMC must confirm any DLT.

A DLT is defined as drug-related:

- Neutropenia Grade 4 for > 7 days' duration*
- Febrile neutropenia (i.e., absolute neutrophil count < 1000/mm^3 with single temperature of > 38.3 °C [101 °F] or a sustained temperature of ≥ 38 °C [100.4 °F] for more than one hour)
- Infection (documented clinically or microbiologically) with Grades 3 or 4 neutropenia (absolute neutrophil count < 1.0×10^9/L)
- Thrombocytopenia ≥ Grade 3;
  - associated with clinically significant bleeding
  - requiring platelet transfusion
- Any Grade ≥ 3 non-hematological AEs, excluding the following:
  - Single laboratory values out of normal range that have no clinical correlate and resolve to Grade ≤ 1 or to baseline within 7 days with adequate medical management or asymptomatic Grade 3 lipase or amylase elevation (> 5 × ULN) not associated with clinical manifestation of pancreatitis.
  - Nausea or vomiting Grade 3 of ≤ 72 hours duration with adequate and optimal therapy.
  - Diarrhea Grade 3 persisting ≤ 72 hours after initiation of medical management.
  - Transient (≤ 72 hours) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache, hypertension that resolves to Grade ≤ 1 with adequate treatment.
  - Nonrecurrent Grade 3 skin toxicity that resolves to Grade ≤ 1 in less than 7 days after initiation of medical management.

- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 2 within 6 days.
- Infusion-related reaction resolving within 6 hours from the end of infusion and controlled with medical management.
- Any death clearly due to the underlying disease or extraneous causes.

- Death due to drug-related AEs
- Any drug-related toxicity including toxicities:
  - that cause interruption of treatment for > 3 weeks (21 successive days). If a participant is deemed fit to restart treatment on Day 21 then this is not a DLT.
  - that prevent the administration of ≥ 80% of the planned dose of berzosertib or topotecan.
  - that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk.

* Note: In the event of a Grade 4 neutropenia, a full blood count must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. The participant will be closely monitored until resolution to Grade 3 or less.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, efficacy, and survival follow-up. The SoA (Table 1) indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants will be withdrawn from study intervention for any of the following reasons:

- A participant may withdraw from the study intervention at any time at his/her own request, and without giving a reason. The participant will continue follow-up, unless consent to study was withdrawn as well
- Upon documentation of disease progression per RECIST 1.1 as determined by the Investigator and verified by the IRC, as outlined in Section 8.1.1.
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the judgment of the Investigator
- Unequivocal clinical progression
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- Pregnancy

- Confirmed ILD
- Liver injury:

  The Investigator will consider discontinuation of study intervention for abnormal liver function when a participant meets 1 of the conditions outlined in the algorithm or if the Investigator believes that it is in best interest of the participant.

  - All events of ALT or AST > 8 × ULN
  - All events of ALT or AST > 5 × ULN for more than 2 weeks
  - All events of ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT > 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

  These may indicate potential severe liver injury (possible Hy's Law) and will be reported as a serious adverse event (SAE).

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the SoA (Table 1). The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed. A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records.

Additional participants must be enrolled for each participant who withdraws from the study after signing consent and successfully meeting entry criteria but did not receive study intervention.

The Investigator will secure the safety of the study participants and make every attempt to collect data.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.

- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (see Section 1.3).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

A maximum of 134 mL of blood will be collected in any 1-month period from each participant in the study, including any extra assessments that may be required.

8.1 Efficacy Assessments and Procedures

8.1.1 Tumor Response

A central imaging laboratory/IRC will be used to read and interpret all computed tomography (CT), magnetic resonance imaging (MRI) data, will confirm measurable disease at screening (see Section 5.1), and will independently verify progressive disease (PD). Radiographic images and clinical findings (such as physical assessments and biopsies) will be used by the Investigators for the local determination of disease progression and participant treatment decisions. See Appendix 7 for additional information.

Participants will have a chest/abdomen/pelvis imaging scan (e.g., CT, MRI) and, if clinically indicated, imaging scans of other body areas (e.g., neck) or other modalities (e.g., bone scan, positron emission tomography-CT [PET-CT]). A brain scan with contrast (MRI [preferred] or CT, with contrast) should be performed during screening and subsequently, as clinically indicated. Participants should have a repeat imaging scan as described in the SoA in Section 1.3. All imaging scans to assess disease progression should be performed using similar CT/MRI platforms and imaging techniques, including the use or absence of contrast, and should be of consistent anatomic locations with prior imaging scans, whenever possible.

Imaging scans will be locally read. The applicable overall response category for each visit that includes disease assessment, based on evaluation of imaging scan, will be recorded in the eCRF.

Imaging scans must also be uploaded or copied to the selected Imaging Research Organisation, as well as any relevant clinical information and study procedure (e.g., cytology and biopsy results). A central IRC, managed by an Imaging Research Organisation, will additionally read and interpret all radiographic scans for this study (see Appendix 2 for details of the IRC).

If PD has been determined locally at a time point, an expedited review by the IRC must be sought to verify the PD. Results of the IRC review will be communicated to the Investigator. While the Investigator is awaiting the results of the IRC review, the participant should not be discontinued from the study intervention, if judged feasible by the Investigator.

If the IRC review verifies PD, the participant should discontinue study intervention and subsequent tumor assessments are no longer required. If the IRC review does not verify PD, the participant should continue receiving the study intervention unless there is a medical reason for a change in therapy or discontinuation (e.g., clinical deterioration, or other criteria as specified in Section 7.1) as per Investigator's clinical judgment. Participants will continue to have tumor assessments until the IRC determines PD.

Tumor assessments per protocol will be performed until PD is verified by the IRC, regardless of study intervention discontinuation or start of subsequent anticancer treatment.

For assessment time points and procedures for primary, secondary, and CCI efficacy endpoints, see Section 1.3 for the SoA.

8.1.2 Survival Follow-up

Survival Follow-up Visits will be completed until End of Study (see Table 1 and Section 4.4). During Survival Follow-up, further anticancer treatment should be recorded.

8.1.3 Patient-Reported Outcomes

Patient-reported outcomes will be assessed by the EuroQol 5 Dimension 5 Level Scale (EQ-5D-5L), European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), and module QLQ-LC13 (lung cancer specific questionnaire), according to schedule specified in the SoA (see Table 1). The PROs questionnaires should be completed by the participant preferably prior to any of the other

trial-related assessments being performed, such as physical examinations, blood draws, and study intervention administration. Participants will use a validated electronic tablet or validated site pad to record their responses to these questionnaires. In rare and extenuating circumstances when an electronic tablet or site pad is not available or not working properly, collection on validated paper questionnaires may be allowed to ensure data are collected and not lost.

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 to 4 where 1 represents "Not at All" and 4 represents "Very Much", and questions 29 and 30 are measured in a range from 1 to 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." Data will be collected by the clinical research organization and housed in a database.

For Safety Follow-up Visit that occurs within 7 days after End-of-Treatment Visit, PRO assessment can be skipped at the Safety Follow-up Visit. However, if the PRO assessment at End-of-Treatment Visit is missed, then PROs should be collected at the Safety Follow-up Visit.

Patient-reported outcome assessments at Efficacy and Survival Follow-up will be conducted at 12 weeks and 24 weeks from last dose and can be conducted either at the study site or remotely, if permitted. As soon as a participant starts subsequent anticancer treatment, PRO will not be collected.

The PRO assessments are not applicable to DL1 in the Safety Run-in Part in Japan.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, ECGs, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

Participants should be observed for potential infusion-related reactions according to local practice.

8.2.1 Physical Examinations

Physical examinations will be performed and the ECOG PS and Karnofsky Scale should be recorded according to the SoA (Table 1). Symptom-directed physical examinations may be performed as clinically indicated per Investigator's judgment.

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological systems as well as head/neck, lymph nodes, and abdomen.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular and respiratory systems, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses and the study disease.

8.2.2 Vital Signs

- Height (screening only) and weight at visits specified in the SoA (Table 1) will be measured and recorded.
- Temperature (method of acquisition should be recorded), pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests if feasible) will be measured at the time points specified in the SoA (Table 1) with the participant in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3 Electrocardiograms

Safety ECGs

A standard single 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine with paper readouts that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the SoA (Table 1). All samples will be clearly identified.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

The tests will be performed by local laboratories.

The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention. Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.

The Investigator will review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports will be filed with the source documents.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are provided in Appendix 4.

The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.3.

Requests for follow-up will usually be made via the Study Monitor, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until the 30-day follow-up visit as specified in the SoA (Table 1). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.

All AEs will be collected from the signing of the ICF until the 30-day follow-up visit as specified in the SoA (Table 1).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.

Investigators are not obligated to actively solicit AEs or SAEs after the end of study participation; however, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is provided in Appendix 4.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and then file it along with the IB in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study, or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a SAE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 6 months after the last study intervention administration.

If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Collection of Pregnancy Information

Male participants with partners who become pregnant:

- The Investigator will attempt to collect pregnancy information on any male participant's female partner, who becomes pregnant while the participant is in this study. This applies only to participants who receive study intervention.
- After obtaining signed consent from the pregnant female partner directly, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant:

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with SCLC and can be serious/life threatening:

- Progressive disease

Because PD is typically associated with the disease under study it will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the applicable eCRF page.

However, if either of the following conditions applies, then the event will be recorded and reported as an SAE:

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.7 Adverse Events of Special Interest

No AEs of special interest have been identified.

8.4 Treatment of Overdose

For this study, any dose of berzosertib or topotecan > 10% over the planned daily dose included in this study protocol or planned for an individual participant enrolled in the study will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose of either berzosertib or topotecan. If an overdose is suspected, monitor the participant for bone marrow suppression and institute supportive-care measures (such as prophylactic G-CSF and antibiotic therapy) as appropriate. Refer to the berzosertib IB and the topotecan product information for additional information.

Even if not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 4, the section on Reporting SAEs.

8.5 Pharmacokinetics

Blood sampling for PK analysis will be collected according the Schedule in Table 2. PK results from NCA will be included in Safety-Run-in Part. Population PK and exposure-response results will be reported separately in a stand-alone report that may also include data from other studies.

The following PK parameters will be calculated for berzosertib and [redacted], when appropriate:

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 quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}tlast}$/Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. 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 area under the concentration-time curve (AUC) from time zero (= dosing time) to 48 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}48h}$/Dose	The area under the concentration-time curve (AUC) from time zero (= dosing time) to 48 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). Normalized using actual dose, using the formula $AUC_{0\text{-}48h}$ /Dose.
$AUC_{0\text{-}72h}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to 72 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}72h}$/Dose	The area under the concentration-time curve (AUC) from time zero (= dosing time) to 72 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). 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.
C_{eoi}	The observed concentration at the end of the infusion period.
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)

Symbol	Definition
CL	The apparent total body clearance of study intervention following extravascular administration, CL = Dose/$AUC_{0-\infty}$.
CCI [redacted]	[redacted]
[redacted]	[redacted]
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration until steady state is reached. $R_{acc(Cmax)}$ = (C_{max} after multiple dose)/(C_{max} after single dose)
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.

Whole blood samples of approximately 2 mL will be collected at each time point for measurement of plasma concentrations of berzosertib and its CCI [redacted]. For the determination of topotecan in plasma, whole blood samples of approximately 2 mL will be collected at each required time point. Collection times are specified in the SoA (Table 2). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The quantification of berzosertib in plasma and quantification of topotecan will be performed using validated assay methods. CCI [redacted] Concentrations will be used to evaluate the PK of study intervention.

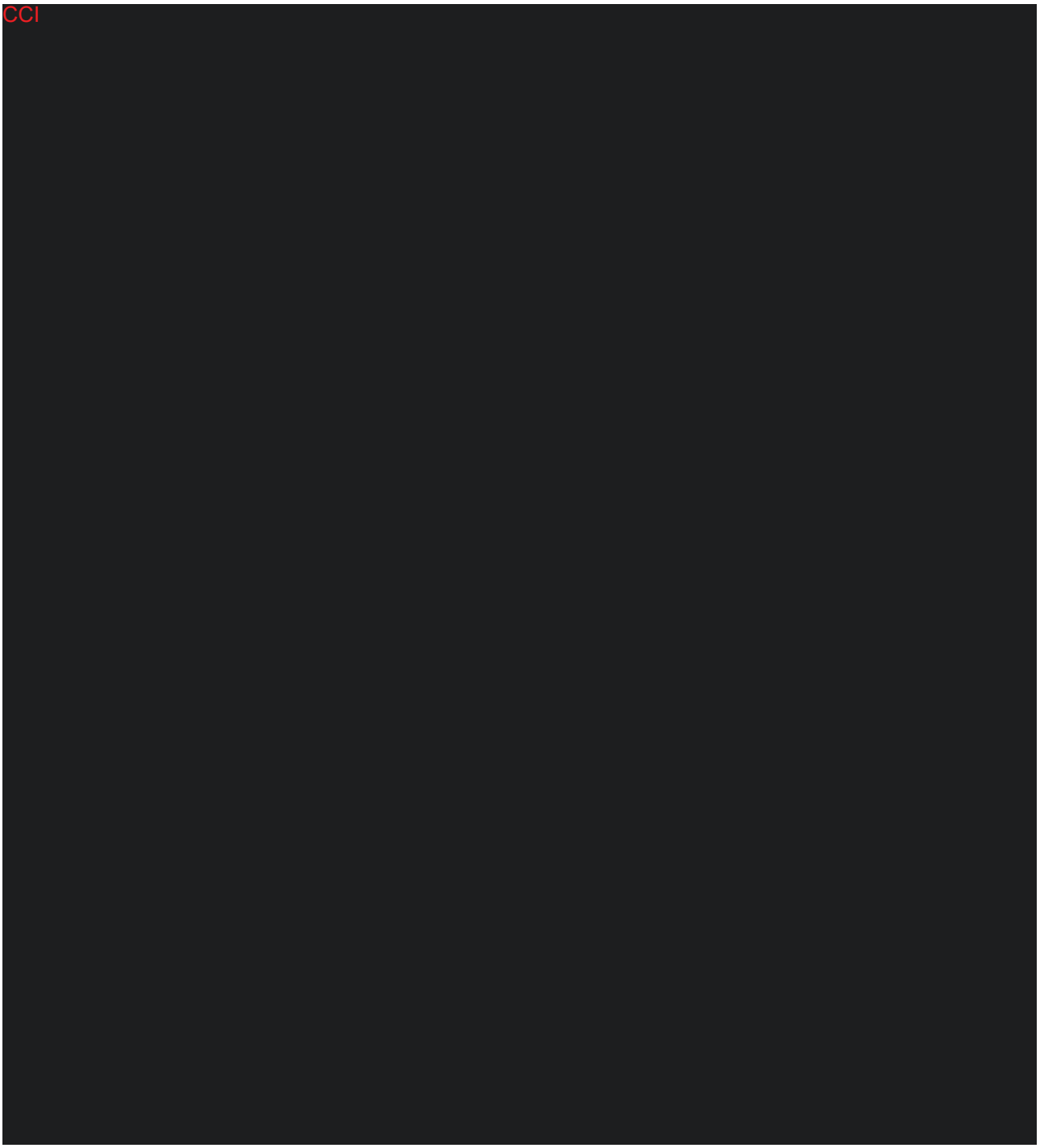
Remaining samples collected for analyses of study intervention concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF, according to local regulations.

8.6 Pharmacodynamics

Not applicable for this study.

CCI



CCI

[redacted]

8.9 Immunogenicity Assessments

Not applicable for this study.

8.10 Medical Resource Utilization and Health Economics

Not applicable for this study.

9 Statistical Considerations

This section outlines the statistical analysis strategy and procedures for the study. Full details of all planned analyses will be described in the study Integrated Analysis Plan (IAP).

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[redacted]

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[redacted]

CCI

[redacted]

9.3 Populations for Analyses

The analysis populations are specified in Table 12. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Table 12 Populations for Analyses

Analysis Set	Description
Screening Analysis Set (SCR)	All participants who provided informed consent, regardless of the participant's study intervention status in the study.
Full Analysis Set (FAS)/ Safety Analysis Set (SAF)	All participants who were administered any dose of any study intervention

Analysis Set	Description
DLT Analysis Set in Safety Run-in Part	All participants who were administered any dose of any study intervention and were evaluable for DLT in the Safety Run-in Part in Japan. For DLT analysis, participants are evaluable if at least one of the following criteria is fulfilled: • Received at least 80% of the planned cumulative dose of study interventions during the DLT period and completed the DLT period. • Experienced at least 1 DLT during the DLT period, regardless of the administered cumulative dose of study interventions and completion of the DLT period.

DLT = dose-limiting toxicity.

9.4 Statistical Analyses

In case DL2 is declared RP2D, i.e., Japanese participants to join in main part of study, data of DL2 will be analyzed together with the main study part. A subgroup analysis will be performed to evaluate Japanese participants. Analyses for the Safety Run-in Part will include both DL1 and DL2 separately by dose level.

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

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, minimum, maximum, 25% quartile and 75% quartile. Categorical variables will be summarized using frequency counts and percentages. Proportions are calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the IAP. If not explicitly stated, no imputation will be used in the analyses.

9.4.1 Efficacy Analyses

All analyses on efficacy estimands will be conducted on the Full Analysis Set (FAS). The estimands framework is used in Table 13 to describe the analysis of primary and secondary efficacy estimands.

Table 13 Efficacy Analyses and Estimands (Main Part)

Endpoint	Statistical Analysis Methods/Further Estimand Attributes
Primary	
Objective Response	**Endpoint:** Objective Response according to RECIST 1.1 as assessed by IRC **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 • Progression according to RECIST 1.1: While not progressed strategy, i.e., assessments up to the intercurrent event **Population Level Summary:** Objective response rate: The ORR will be determined as the proportion of patients with confirmed objective response of either PR or CR. Confirmation of the response according to RECIST 1.1 is required no sooner than 4 weeks after the initial documentation of CR or PR. The 95% CI for the ORR will be calculated using the Clopper-Pearson method.
	Sensitivity Analysis: As main estimator, but using Investigator assessment instead of IRC assessment
	Supplementary Analysis: As main estimator, but using unconfirmed objective response instead of confirmed objective response
Secondary	
Duration of Response	**Endpoint:** Duration of response according to RECIST 1.1 as assessed by IRC, measured by time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention **Population:** Patients with relapsed, platinum-resistant SCLC and confirmed objective response according to RECIST 1.1 as assessed by IRC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention: 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
	Sensitivity Analysis: As main estimator, but using Investigator assessment instead of IRC assessment

Endpoint	Statistical Analysis Methods/Further Estimand Attributes
PFS	**Endpoint:** Progression-free survival measured by time from first study intervention to PD according to RECIST 1.1 (by IRC) or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or first study intervention **Population:** Patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan **Intercurrent Event Strategy:** • Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention: 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
	Sensitivity Analyses: **1.** As main estimator, but considering all deaths as events, irrespective of time of last tumor assessment. **2.** As main estimator, but using Investigator assessment instead of IRC assessment **3.** As main estimator, but using while not on subsequent anticancer therapy strategy for IE start of subsequent anticancer treatment
OS	**Endpoint:** OS as measured by time from first study intervention to death **Population:** Patients with relapsed, platinum-resistant SCLC **Treatment:** Berzosertib + topotecan followed by subsequent therapy **Intercurrent Event Strategy:** The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • 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 OS time • Kaplan-Meier estimates

Endpoint	Statistical Analysis Methods/Further Estimand Attributes
Physical functioning; cough, dyspnea, and chest pain; and overall health state	**Endpoint:** Change from baseline in physical functioning measured by the EORTC QLQ-C30; cough, dyspnea, and chest pain measured by EORTC QLQ-LC13; and health state as measured by VAS as a component of the EQ-5D-5L **Population:** Patients 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 treatment: 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 changes from baseline analysis for multi-item scales in EORTC questionnaires (i.e., physical functioning, dyspnea) and VAS • Proportion of patients with ≥ 1 category improvement and proportion of patients with ≥ 1 category worsening in single-item symptoms (i.e., cough and chest pain)
	Sensitivity Analysis: • Discontinuation of treatment: treatment-policy strategy, i.e., regardless of the intercurrent event
CCI	[redacted]

CI = confidence interval; CR = complete response; DL = dose level; EORTC = European Organization for the Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5 Dimension 5 Level Scale; IRC = Independent Review Committee; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire; QLQ-LC13 = lung cancer specific questionnaire; 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.
In case DL2 is declared RP2D, data for participants receiving DL2 will in addition be analyzed as part of the main study.

Efficacy of the Safety Run-in Part in Japan will be analyzed similarly to the main study part for the following populations:

- DL1: Japanese participants with advanced solid tumors
- DL2: Japanese participants with relapsed, platinum-resistant SCLC.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set, except for evaluation of DLT in the Safety Run-in Part in Japan.

The on-treatment period is defined as the time from first study intervention to the last study intervention date + 30 days.

Further details on safety analyses are summarized in Table 14 and Table 16.

Table 14 Safety Endpoints (Main Part)

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	
AEs	The definitions, procedures for recording, evaluating, follow-up, and reporting of AEs are described in Appendix 4. AEs will be coded according to the latest available version of the MedDRA. Missing classifications concerning study intervention relationships will be considered related to the study interventions. Analysis will be based on TEAEs, which are events with onset dates during the on-treatment period, or events with onset dates before the on-treatment period and worsening during the on-treatment period. The following TEAEs will be presented in summaries by incidence and type according to MedDRA SOC and Preferred Term: • TEAEs • SAEs • TEAEs related to study interventions • NCI-CTCAE Grade ≥ 3 TEAEs • NCI-CTCAE Grade ≥ 3 study intervention-related TEAEs • TEAEs leading to temporary interruption of study interventions • TEAEs leading to permanent discontinuation of study interventions • TEAEs leading to dose modification • TEAEs leading to death.
Deaths	Death and primary reason for death, overall and during the treatment period, will be tabulated.
Laboratory Values	Baseline values are defined as the last value prior to first administration of study intervention. Only on-treatment values will be summarized. Laboratory values will be graded using NCI-CTCAE (Version 5.0), if applicable. Non-gradable parameters will be classified as normal, high, or low. Summary statistics for: • Absolute values • Change from baseline • Worst on-treatment grade Shift tables (baseline versus worst on-treatment)
Vital Signs	• Summary statistics for baseline and on-treatment values • Shift tables (baseline versus minimum/maximum on-treatment)
ECGs	• Summary statistics for baseline and on-treatment values • Shift tables (baseline versus worst on-treatment)
CCI [redacted]	[redacted]

AEs = adverse events; ECGs = electrocardiograms; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs = serious adverse events; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Table 15 Safety Endpoints (Safety Run-in Part in Japan)

Endpoint	Statistical Analysis Methods
Primary	

Endpoint	Statistical Analysis Methods
Dose-limiting toxicity	The number and proportion of participants experiencing a DLT (see Section 6.8) confirmed by the SMC during the DLT period will be reported by dose level. Analysis will be based on the DLT Analysis Set in the Safety Run-in Part.
AEs, Deaths, Laboratory Values, Vital Signs, ECGs	Endpoints will be analyzed as described in Table 14.

AEs = adverse events; DLT = dose-limiting toxicity; ECGs = electrocardiograms; SMC = Safety Monitoring Committee.

9.4.2.1 Safety Run-in Part in Japan

In the Safety Run-in Part in Japan, a BOIN design (Yuan 2016) will support DL decisions. Upon review of emerging data available, the Local SMC may recommend to the Sponsor approaches such as stop the Safety Run-in part or establish the RP2D in participants in Japan. The target DLT rate for the BOIN model will be 30%, leading to tolerability boundaries as shown in Table 16.

Table 16 Tolerability Judgment Boundaries for Target Toxicity Rate = 30%

Judgment	Number of DLT evaluable participants treated at the current DL						
	3	4	5	**6**	7	8	**9**
Tolerability is confirmed in case the number of DLTs is ≤	**0**	0	1	**1**	1	1	**2**
Tolerability is not confirmed, in case the number of DLTs is ≥	**2**	2	2	**3**	3	3	**4**

DL = dose level; DLT = dose-limiting toxicity.

Cohorts of 3 participants will be enrolled. At least 3 DLT evaluable participants on a dose level are required to confirm the tolerability at DL1 or DL2. The maximum number of participants per dose level is 9.

Example Readout (assuming all 3 participants in each cohort are DLT evaluable)

Decision Criteria on DL1:

- If 0/3 participants with DLT: DL1 is considered safe. Escalate to DL2
- If 1/3 participants with DLT: Enroll 3 additional participants on DL1
  - If 1/6 participants with DLT: DL1 is considered safe. Escalate to DL2
  - If 2/6 participants with DLT: Enroll 3 additional participants on DL1
    - If 2/9 participants with DLT: DL1 is considered safe. Escalate to DL2
    - If 3/9 participants with DLT: The Local SMC will provide recommendations based on emerging data available.
    - If ≥ 4/9 participants with DLT: Stop the Safety Run-in Part
  - If ≥ 3/6 participants with DLT: Stop the Safety Run-in Part

- If ≥ 2/3 participants with DLT: Stop the Safety Run-in Part

Decision criteria on DL2:

- If 0/3 participants with DLT: DL2 is considered safe
- If 1/3 participants with DLT: Enroll 3 additional participants on DL2
  - If 1/6 participants with DLT: DL2 is considered safe
  - If 2/6 participants with DLT: Enroll 3 additional participants on DL2
    - If 2/9 participants with DLT: DL2 is considered safe
    - If 3/9 participants with DLT: The Local SMC will provide recommendations based on emerging data available.
    - If ≥ 4/9 participants with DLT: Stop the Safety Run-in Part
  - If ≥ 3/6 participants with DLT: Stop the Safety Run-in Part
- If ≥ 2/3 participants with DLT: Stop the Safety Run-in Part

If the Local SMC declares DL2 safe, it will be the RP2D in Japan, and Japanese sites may continue the study in the Main Part of Phase II.

Participants are enrolled in cohorts of three and the decision whether a toxicity is indeed considered DLT is taken by the Local SMC. The SMC meetings are planned after each cohort, i.e., after the first three enrolled participants, after the first six enrolled participants, and so on. If, however, any concerns on safety/tolerability arise during the safety run-in, an ad hoc SMC meeting may be held at any time, and the local SMC may decide on holding or discontinuation of the Safety Run-in Part.

The final decision on evaluability will be made by the Local SMC (e.g., considering relevant deviations from dosing schedule).

9.4.3 Other Analyses

Baseline characteristics will be analyzed on the FAS. Summary statistics will be provided as described for continuous/categorical variables in Section 9.4.

Details on the PK analyses will be in the IAP that will be finalized before database lock. Integrated analyses across studies, such as the population PK analysis will be presented separately from the main clinical study report.

Noncompartmental PK analysis will be used to characterize the PK of berzosertib (and CCI, if applicable) in participants from the Safety Run-in Part in Japan. Details will be described in the IAP.

9.4.4 Sequence of Analyses

Main Part of Global Phase II:

The study will be monitored regularly by an internal SMC (see Appendix 2). 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)
- The primary analysis will be performed once all 80 participants have been followed for at least 3 months (or dropped-out/died prematurely)
- A follow-up analysis will be performed once the end of study has been reached.

Safety Run-in Part in Japan:

The study will be monitored regularly by the Local SMC (see Appendix 2). Safety analysis will be performed after completion of the DLT evaluation period of each cohort in DL1 and DL2.

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11 Appendices

Appendix 1 Abbreviations

AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3-related
BCRP	Breast cancer resistance protein
β-HCG	β-human chorionic gonadotropin
BOR	Best overall response
CI	Confidence interval(s)
CR	Complete response
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DDR	DNA damage response
DL	Dose level
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EORTC	European Organization for the Research and Treatment of Cancer
EOT	End-of-Treatment
EQ-5D-5L	EuroQol 5 Dimension 5 Level Scale
FAS	Full Analysis Set
FDG-PET	Fludeoxyglucose positron emission tomography
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

G-CSF	Granulocyte colony-stimulating-factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HRT	Hormonal replacement therapy
HRQoL	Health-related quality of life
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-Investigational Medicinal Product
OATP	Organic anion transporting polypeptides
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET-CT	Positron emission tomography- computed tomography

PFI	Platinum-free interval
PFS	Progression-free survival
CCI	[redacted]
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PRO	Patient-reported outcome
QLQ-C30	Quality of Life Questionnaire
QLQ-LC13	Lung cancer specific questionnaire
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase II dose
SAE(s)	Serious adverse event(s)
SD	Stable disease
SCLC	Small-cell lung cancer
SMC	Safety Monitoring Committee
SmPC	Summary of product characteristics
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEAE(s)	Treatment-emergent adverse event(s)
ULN	Upper limit of normal
VAS	Visual analogue scale
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with enough, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.

Participants will be informed that their participation is voluntary.

Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; International Council for Harmonisation (ICH) guidelines; Health Insurance Portability and Accountability Act requirements, where applicable; and the IRB/IEC or study center.

The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.

If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.

A copy of the ICF(s) will be provided to the participant or the participant's legally authorized representative (where allowed by local laws and regulations).

The original signed and dated consent will remain at the Investigator's site and will be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Participants who are rescreened are required to sign a new ICF.

There will be additional informed consent for optional pharmacogenetic sample collection and storage and for optional future research.

Data Protection

The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.

The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.

The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH Good Clinical Practice (GCP). The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries: EudraCT number 2020-004231-25, www.ClinicalTrials.gov, and Japan Registry of Clinical Trials (jRCT).

The study will be conducted at approximately 41 study sites in Asia, Europe, and North America, including approximately 13 study sites in the US.

The Sponsor will be responsible for supply and manufacture of berzosertib. Depending on the local regulations, topotecan may be either sourced from a local hospital pharmacy or supplied by the Sponsor (or designated service provider).

A 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 composition and specific working procedures of the SMC will be described in a SMC Charter, which will be established prior to the start of recruitment.

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 pharmacokinetic (PK) data. The local SMC shall also confirm any DLT reported by Investigators and make recommendations to the Sponsor regarding possible changes to the conduct of the study such as suspension/discontinuation of enrollment, and modifying the study including additional enrollment beyond the six participants. In addition to the regular SMC meetings, ad hoc meetings will be held as needed.

An IRC will perform a blinded determination as to whether the criteria for tumor response or progression according to RECIST 1.1 are met. The role of the IRC will be to review radiographic image findings and relevant clinical information (e.g., cytology or biopsy results) for the determination of the time point overall response according to RECIST 1.1 for each participant. The IRC membership, assessment criteria details, mandate, and processes of the IRC will be defined in the IRC Charter.

Details of structures and associated procedures will be defined in a separate Study Reference Manual, which will be prepared under the supervision of the Clinical Study Leader.

Refer to the Study Organization and the Study Sites in Japan in supporting document.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- The Japanese ministerial ordinance on GCP
- Applicable laws and regulations

The Investigator will submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them before the study is initiated.

The Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.

Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
- Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating

in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant.

The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with any Steering Committee or other relevant study-appointed committees or groups.

Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

The first publication will include the results of the analysis of at least the primary endpoints and will include data from the study site. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the

results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication but maintains the right to delay publication to protect intellectual property rights.

Posting of data on the European Clinical Trial Database (EudraCT), www.ClinicalTrials.gov and jRCT is planned and will occur 12 months after the last visit, or scheduled procedure, or another appropriate date to meet applicable requirements.

Data Quality Assurance

All participant study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF. Details for managing eCRFs are in the Study Reference Manual.

The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.

The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan (within the Clinical Operations Plan).

The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.

Study Monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, the Japanese ministerial ordinance on GCP, and all applicable regulatory requirements.

The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:

- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e., the Sponsor's study number) and participant's study number.
- Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.

Data recorded on printed or eCRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.

The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file.

Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator or a record retainer designated by the Head of the study site ensures that no destruction of medical records is performed without the Sponsor's written approval.

Definition of what constitutes source data is found in the CRF guidelines.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.

- The first act of recruitment is the date the first participant signs an ICF and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor’s compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

Woman of Childbearing Potential (WOCBP):

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3. A postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
- A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency • Implantable progestogen-only hormone contraception associated with inhibition of ovulation* • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.
Highly Effective Methods That Are User Dependent - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation o Oral o Intravaginal* o Transdermal* o Injectable* • Progestogen-only hormone contraception associated with inhibition of ovulation o Oral o Injectable* • Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study. * Not approved in Japan
Notes: Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants. Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for the his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.1.

Other Adverse Events to be Reported Using a Specialized Procedure or Form

- All pregnancies occurring during the study and their outcome will be documented on the Pregnancy report form and Parent-Child/Fetus Adverse Event Report form as outlined in Section 8.3.5.
- Overdoses associated with an AE or a SAE are recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses not related to an AE/SAE (without signs or symptoms) are recorded in eCRF on treatment forms and are reported to Drug Safety using SAE paper form.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. • However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- As needed, Sponsor/designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to the Sponsor/designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the eCRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Sponsor/designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the Sponsor or its designee will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool, specified below, to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department. • By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.
SAE Reporting by a Paper Form
• SAE reporting on a paper report form is used as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available. • Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event. • Additional documents (e.g., laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the eCRF may be required in addition (e.g., medical history, concomitant medication). The data provided will be consistent with the information in the eCRF.

Reporting of Adverse Events of Special Interest

Not applicable; no adverse events of special interest have been identified.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 5 Clinical Laboratory Tests

Clinical Laboratory assessments are provided in Table 17.

Table 17 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
			Mean corpuscular hemoglobin	
	Hemoglobin			
	Hematocrit			
Coagulation	Prothrombin time/INR		Activated partial thromboplastin time	
Biochemistry	Blood urea nitrogen or urea (if blood urea nitrogen cannot be performed)	Potassium	Aspartate aminotransferase	Bilirubin (total and direct)
	Creatinine	Sodium	Alanine aminotransferase	Total protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
		Lipase	Amylase	Magnesium
				Phosphate
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.				
Other Tests	• Serum and urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential). • Safety laboratory assessments, e.g., hematology, chemistry, will be performed locally. CCI will be tested in specialized laboratories/contract research organizations (to be determined).			
Serology	Hepatitis B virus (HBV) Screening: • HBV surface antigen (HBsAg) • Total hepatitis B core antibody (anti-HBc) • Hepatitis B surface antigen antibody (anti-HBsAg) • HBV DNA: if HBsAg/anti-HBc or anti-HBc is positive Required during Study Intervention Period if past HBV or current HBV infection: • HBsAg and HBV-DNA every 12 weeks Hepatitis C virus (HCV) Screening: • anti-HCV • HCV RNA: if anti-HCV is positive Required during Study Intervention Period if past HBV or current HBV infection: • HCV RNA every 12 weeks			

CCI

Appendix 7 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The text below was obtained from Eisenhauer 2009 and Schwartz 2016.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

No photographs, no skin lesion measurement by calipers and no measurements on chest X-ray will be done in this study.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit; however, they must normalize for a participant to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and

prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in 1st-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse event (AE) of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Electronic Case report forms (eCRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the

measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

When the participant also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants

for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the participant who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, e.g., because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fludeoxyglucose positron emission tomography (FDG-PET) response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET

at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study intervention until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 the 'BOR'.

The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of complete or PR IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
See text for more details.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be

based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the eCRF.

In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies, it is reasonable to consider a participant with time point responses of partial response-NE-partial response as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Conditions that define 'early progression, early death, and inevaluability' are study-specific and should be clearly described in each protocol (depending on treatment duration, and treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e., in randomized studies (Phase II or III) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Appendix 8 Performance Scales

Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Karnofsky Scale

Percent	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent
20	Very sick, hospitalization indicated. Death not imminent
10	Moribund, fatal processes progressing rapidly
0	Dead

Appendix 9 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Version 3.3-BEL (27 April 2021)

Overall Rationale for the Amendment

The high-level rationale for the changes implemented in this country-specific amendment in Belgium are as follows:

- Based on in vitro data and static modeling predictions, the drug-drug interaction (DDI) potential of berzosertib was updated by removing "sensitive P-gp substrates" and adding "OATP1B3 substrates". In addition, the instructions for concomitant use of breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP) 1B3 substrates with berzosertib are provided.
- The removal of sensitive P-gp substrates is also to align with the berzosertib Investigator's Brochure Version 10.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment; Table 3	The summary of data/rationale for risk and mitigation strategy for drug-drug interactions was updated to include additional information CYP3A4 inhibitors and BCRP and OATP1B3 substrates.	To clarify the potential risks associated with concomitant administration of berzosertib with BCRP and OATP1B3 substrates and recommended precautions.
6.5.3 Prohibited Medicines and Precautions, Table 7	Text and table were updated to include additional information for the administration of berzosertib with BCRP and OATP1B3 substrates. Sensitive P-gp substrates was removed.	To clarify the recommended precautions of concomitant administration of berzosertib with BCRP and OATP1B3 substrates. To align with berzosertib Investigator's Brochure, Version 10.
Throughout	Minor clerical and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 3.2-USA (27 April 2021)

Overall Rationale for the Amendment

The high-level rationale for the changes implemented in this amendment are to include:

- Implementation of verification of locally assessed disease progression by an Independent Review Committee (IRC) to secure an accurate progressive disease (PD) assessment. Investigators will be requested to continue imaging until PD is verified by IRC in order to potentially reduce the number of censored observations for duration of response (DoR)/progression-free survival (PFS) according to IRC.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Assessments,	Revised Imaging Disease Assessment text to read: "…until disease progression ***as assessed by the IRC."*** Added the following note: "Locally assessed PD must be verified by the IRC (see Section 8.1.1)."	To implement IRC verification of Investigator-assessed PD.
7.1 Discontinuation of Study Intervention	Second bullet is revised to read: • "Upon documentation of disease progression per RECIST 1.1 ***as determined by the Investigator and verified by the IRC, as outlined in Section 8.1.1***."	To implement IRC verification of Investigator-assessed PD.
8.1.1 Tumor Response	Text has been added to specify the tumor assessment requirements in the event of disease progression.	To implement IRC verification of Investigator-assessed PD.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized

Protocol Version 3.1-JPN (25 March 2021)

Overall Rationale for the Amendment

The high-level rationale for the changes implemented in this amendment are to further ensure participant's safety.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria Age	Added a description that participant's written consent will be obtained when participants reaches 20 years of age.	In Japan, ≥ 20 years of age is legally considered adult.
5.1 Inclusion Criteria Female participants	Added a description that the participant is not eligible even if breastfeeding is suspended.	To clarify the eligibility for breastfeeding women.
6.1 Study Interventions Administration	Added a description that all participants, in principle, should undergo inpatient observation during Cycle 1 until at least Day 5 of study intervention in the Safety Run-in Part in Japan.	In accordance with a Japanese local guideline, "Revision of 'Guidelines for Clinical Evaluation of Anticancer Drugs' " (PFSB/ELD Notification No. 1101001).
6.5.3 Prohibited Medicines Table 7 5.3.1 Meals and Dietary Restrictions	Added a description that consumption of grapefruit/grapefruit juice, Seville or blood oranges is prohibited.	To show examples of prohibited food.
6.6.1 Study Intervention Dose Modifications	Added a description on dose interruption and discontinuation of berzosertib (Section 6.6.1.1) and topotecan (Section 6.6.1.2) when interstitial lung disease (ILD) is suspected and confirmed.	For participant's safety.

7.1 Discontinuation of Study Intervention	Added confirmed ILD to the criteria for discontinuation of study intervention.	For participant's safety.
8.3.5 Pregnancy	The period of reporting pregnancy is set to 6 months after the last study intervention administration.	To align with the required period for contraception after the last study intervention administration.

PFSB = Pharmaceutical and Food Safety Bureau; ELD = Evaluation and Licensing Division.

Protocol Version 3.0 (23 December 2020)

Overall Rationale for the Amendment

The high-level rationale for the changes implemented in this amendment are to include:

- The Safety Run-in Part in Japan
- Assessments of patient-reported outcomes (PROs)
- An additional exclusion criterion for QTc, modification on the exclusion criterion regarding New York Heart Association Classification and the wash-out period for previous anticancer antibody or antibody drug conjugates
- Additional minor Sponsor modifications.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema Table 1 Schedule of Activities 2.1 Study Rationale 3 Objectives and Estimands 4.1.1 Safety Run-in Part (Japan-only) 4.2 Scientific Rationale for Study Design 4.3.2 Safety Run-in Part (Japan-only) 5.1 Inclusion Criteria 6.1 Study Interventions Administration 6.3.1 Study Intervention Assignment 6.6.1.1 Berzosertib Dose Modifications 6.8 Definition of Dose-limiting Toxicity (Safety Run-in Part Only) CCI 9.3 Populations for Analyses 9.4.2 Safety Analyses 9.4.3 Other Analyses 9.4.4 Sequence of Analyses	The following were added regarding the Safety Run-in Part in Japan: Figure 2 to show the schematic structure. In Table 1, berzosertib dosing for Dose Level (DL) 1 and DL2 and description that external confirmation of measurable disease and PROs are not applicable for DL1. In Section 2.1, rationale. In Section 3, objectives and estimands. In Sections 4.1.1, 4.2 and 4.3.2, study design, rationale and dose justification. In Section 5.1, an inclusion criterion. In Sections 6.1, 6.3.1 and 6.6.1.1, specified the dose and dose modification of berzosertib. Section 6.8, definition of dose limiting toxicity (DLT). In Section 8.8, tumor biopsy is optional for participants in DL1. CCI In Section 9.3, definitions of analysis sets. In Section 9.4.2, an endpoint for DLT in Table 15. In Section 9.4.3, other analyses. In Section 9.4.4, sequence of analyses.	To implement Safety Run-in Part in Japan to join the Main Part of global Phase II study.
1.1 Synopsis	Added “To assess health-related quality of life (HRQoL) based on patient-reported outcomes (PROs) when treated with berzosertib + topotecan” as a secondary objective with its estimand attributes.	To collect information regarding participants’ perspective of their functioning and symptoms.
1.3 Schedule of Activities	Added the PRO assessments with necessary notes to the schedule of activities.	To specify the PRO assessment schedule.
3 Objectives and Estimands	Added “To assess health-related quality of life (HRQoL) based on PROs when treated with berzosertib + topotecan” as a secondary objective as well as an CCI objective with its estimand attributes. Additionally, the underlined phrase was added to the following sentence: “CCI f CYPs/transporters, in plasma, may be conducted”.	To add PRO assessment objectives. CCI
4.2 Scientific Rationale for Study Design	Specific rationale for PRO assessments is provided.	For clarification of rationale.
5.2 Exclusion Criteria	Added exclusion criterion for the upper limit of QTc interval, modified the exclusion criterion regarding New York Heart Association Classification	To ensure participant safety and clarify.
8.1.1 Tumor Response	Inserted a new subheading ‘Tumor Response’.	To assist with the structure of the document.

Section # and Name	Description of Change	Brief Rationale
8.1.2 Patient-Reported Outcomes	Inserted a new subheading 'Patient-Reported Outcomes' with the required information regarding the assessment.	PROs complement objective clinical endpoints such as tumor response, duration of response and progression-free survival.
CCI		
9.4.1 Efficacy Analyses	Added the PROs endpoint in Table 13 with its statistical analysis methods/further estimand attributes.	To add statistical considerations for PRO endpoint analysis.
Throughout	Applied country-specific adaptation to comply with regulatory requirements in Japan.	To conduct the study in Japan.
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized.

Protocol Version 2.0 (20 November 2020)

Overall Rationale for the Amendment

The high-level rationale for the changes implemented in this amendment are to update the eligibility criteria and to provide clarification on study intervention aspects (premedication, G-CSF use, and treatment interruption/resumption).

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added exclusion for participants with known history of Li-Fraumeni Syndrome and Ataxia Telangiectasia.	To eliminate the potential risk for increased toxicity in participants with such history.
Table 1 Schedule of Activities 6.1 Study Interventions Administration 6.6.1.1 Berzosertib Dose Modifications 6.6.1.2 Topotecan Dose Modifications	Hematologic criteria for neutrophils, platelets, and hemoglobin for subsequent dosing of berzosertib and topotecan were added. In Sections 6.6.1.1 and 6.6.1.2 only, revised sentence from: "In addition, in case of Grade 3 or higher toxicity during any cycle, treatment may be interrupted and may be resumed when all toxicities have returned to Grade ≤ 2, at the discretion of the Investigator" To: "In addition, in case of non-hematologic Grade 3 or higher toxicity during any cycle, treatment should be interrupted and may be resumed when all toxicities have returned to Grade ≤ 2; resumption may be at the discretion of the Investigator".	To provide additional instructions for guidance prior to dosing, treatment interruption and resumption.
5.3.3 Activity	Added statement regarding berzosertib phototoxic potential with cautionary instructions of protective measures.	For clarification.

Section # and Name	Description of Change	Brief Rationale
6.1 Study Interventions Administration	Added the following: - A specific statement regarding prophylactic premedication of corticosteroids and antihistamines - Specific recommendations regarding the use of G-CSF as primary prophylaxis	To provide more specific guidance about premedication and G-CSF administration
6.5.4 Other Interventions	Added a requirement of a ≥ 14-day wash-out period in case whole brain radiation therapy was administered.	For clarification, given the potential for increased neurotoxicity.
Throughout	Minor document formatting revisions	Minor; therefore, have not been summarized

Appendix 10 Sponsor Signature Page

Study 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
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2020-004231-25
Clinical Study Protocol Version:	21 June 2021/Version 4.0

I approve the design of the clinical study:

PPD

23Jun2021

Signature Date of Signature

Name, academic degree:	PPD, MD
Function/Title:	PPD
Institution:	
Address:	
Telephone number:	PPD
E-mail address:	PPD

Appendix 11 Coordinating Investigator Signature Page

Study 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
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2020-004231-25
Clinical Study Protocol Version:	21 June 2021/Version 4.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature PPD

PPD

Date of Signature

Name, academic degree:	PPD, MD
Function/Title:	Coordinating Investigator
Institution:	PPD
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 12 Principal Investigator Signature Page

Study 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
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2020-004231-25
Clinical Study Protocol Version:	21 June 2021/Version 4.0
Site Number:	

I, the undersigned approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: