TITLE PAGE

Protocol Title: EMERGE-201: A phase 2, multicenter, open-label study of lurbinectedin efficacy and safety in participants with advanced or metastatic solid tumors

Protocol (and Amendment) Number: JZP712-201-02

Compound: Lurbinectedin (JZP712, also known as PM01183)

Brief Title: Lurbinectedin monotherapy in participants with advanced or metastatic solid tumors

Study Phase: Phase 2

Acronym: EMERGE-201

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	Refer to the appended electronic signature page for date
Amendment 01	12 August 2021
Original Protocol	14 July 2021

Amendment 02

Overall Rationale for the Amendment:

The overall rationale for the changes in this protocol amendment was to 1) align with the updated approved lurbinectedin IB to include safety updates and 2) broaden enrollment criteria and assess antitumor activity in a wider population. The following is a list of important changes in Amendment 02; editorial changes are not included in this list.

Section # and Name	Description of Change	Brief Rationale
Global	Changed the patient inclusion criteria from LCNET to PD-NEC.	To identify the signal of efficacy in PD-NECs.
Global	Updated the nomenclature of the former HRD-positive tumor agnostic malignancies cohort to the HRD-positive malignancies agnostic cohort.	For consistency in naming and presentation.
1.3 Schedule of Activities; 5.5.1 Dose Adjustment Due to Changes in Body Surface Area	Regarding BSA, updated (in Section 1.3)/added (in new Section 5.5.1) language to indicate that "dose of study intervention should be recalculated if the participant's BSA has a ≥ 10% change (higher or lower) compared with the predose Cycle 1 Day 1 value or the BSA recorded for dosing calculation at the previous cycle."	To clarify that dose adjustments per BSA changes will be based on the predose Cycle 1 Day 1 value *or the BSA recorded for dosing calculation at the previous cycle*.
1.3 Schedule of Activities	Regarding hematology, biochemistry-A, and biochemistry-B assessments, updated description of the	To clarify the sampling window and ensure Screening laboratory results are reviewed prior to first dosing.

Section # and Name	Description of Change	Brief Rationale
	sampling windows. Also added statement that "Screening laboratory results must be reviewed before first dosing on C1D1." Hematology and biochemistry-B samples no longer required on C1D1.	
1.3 Schedule of Activities; 8.6.1 Required Analyses	Revised "blood sample for ctDNA somatic mutational analysis (required)" to "Baseline blood for mutational analysis (required in all cohorts)."	To monitor for changes and/or emergence of resistance mutations and to clarify this is required for all cohorts.
1.3 Schedule of Activities; 8.6.1 Required Analyses; 8.6.2 Optional Analyses	Revised "blood sample for longitudinal ctDNA somatic mutational analysis" to "blood for longitudinal mutational analysis." Also revised this assessment as required for the HRD-positive malignancies agnostic cohort.	To monitor for changes and/or emergence of resistance mutations and to clarify this is required only for the HRD-positive malignancies agnostic cohort
1.3 Schedule of Activities; 4.1 Overall Design; 6.6 Prophylactic Medication; 6.7 Study Intervention Dose Delay and Reduction Rules; 6.10.1 Allowed Concomitant Medications	To specify administration of G-CSF or GM-CSF as mandatory from Cycle 1 onwards.	To align with the known safety profile of lurbinectedin as well as the updated, approved lurbinectedin IB.
2.2.2 Poorly Differentiated Neuroendocrine Carcinomas	Modified introductory text for the LCNET cohort to a broader PD-NEC population.	To provide accurate background information regarding the study cohorts.
2.2.3 Homologous Recombination Deficient-positive Malignancies Agnostic Cohort	Updated introductory text relative to the HRD-positive malignancies agnostic cohort and added additional clarification on enrollment of participants previously exposed to PARPi.	To provide clarification on background information, particularly related to PARPi usage.
2.3.1 Risk Assessment	Added text describing the risk of rhabdomyolysis.	To align with the updated approved lurbinectedin IB.
4.1 Overall Design	Added text regarding preferential enrollment; applicable only to	To clarify enrollment procedures for the HRD-positive malignancies agnostic cohort and ensure adequate

Section # and Name	Description of Change	Brief Rationale
	the HRD-positive malignancies agnostic cohort.	and even enrollment across the various tumor types under study.
4.4 End of Study Definition	Revised EOS definition.	To clarify the definition of the EOS.
5.1 Inclusion Criteria	Revised inclusion criteria for former LCNET cohort to criteria for to PD-NEC cohort. Revised inclusion criteria for the HRD-positive malignancies agnostic cohort relative to PARPi and germline/somatic pathogenic mutations.	To ensure inclusion of appropriate participant population per updated protocol.
5.2 Exclusion Criteria	Added criterion regarding PARPi for the HRD-positive malignancies agnostic cohort.	To ensure inclusion of appropriate participant population.
5.5 Criteria for Treatment Continuation	Added information for treatment continuation (Cycle 2 and after) relative to events of rhabdomyolysis.	To align with the updated approved lurbinectedin IB.
6.1.1 Precautions During Study Treatment Administration	Added this new subsection to include information regarding extravasation and co-administration of lurbinectedin and other IV drugs.	To align with the updated approved lurbinectedin IB.
6.7 Study Intervention Dose Delay and Reduction Rules	Added information regarding Grade ≥ 3 rhabdomyolysis.	To align with the updated approved lurbinectedin IB.
7.1 Discontinuation of Study Intervention	Added language regarding continuation of radiographic assessment for participants who discontinued treatment due to reasons other than disease progression, death, withdrawal of consent from study, or lost to follow-up. Language in "radiological tumor assessment" row of 1.3 Schedule of Activities revised accordingly. Added Grade ≥ 3 hypersensitivity reaction and Grade ≥ 3 rhabdomyolysis as reasons a participant must be discontinued from study intervention.	To clarify radiographic imaging procedures for participants who discontinue treatment and to align with the updated approved lurbinectedin IB.

Section # and Name	Description of Change	Brief Rationale
8.6 Genetics and/or Mutational Analyses	Revised description of analyses which may be performed on blood and tumor samples.	For consistency with changes made in Section 1.3.
8.6.2 Optional Analyses	Regarding pretreatment and on-treatment tumor samples, added text that "every effort should be made to collect archival or post-treatment tissue samples from all PD-NEC participants."	To ensure collection of all necessary study samples.
9.4 Statistical Analyses	Added text regarding planned timing of the primary analysis.	To clarify timing of the primary analysis.
9.5 Interim Analysis	Added text that "there will be no pause in enrollment during the interim analysis of the first 12 evaluable participants of a cohort…"	To clarify that the interim analysis will not affect enrollment.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: EMERGE-201: A phase 2, multicenter, open-label study of lurbinectedin efficacy and safety in participants with advanced or metastatic solid tumors

Brief Title: Lurbinectedin monotherapy in participants with advanced or metastatic solid tumors

Rationale: Lurbinectedin is a novel alkylating agent that inhibits oncogenic transcription through the preferential binding of guanines located in GC rich regulatory areas. To date, over 1700 participants with advanced tumors have been treated with lurbinectedin in clinical trials. Lurbinectedin has been studied in multiple advanced tumors, including SCLC. In a lurbinectedin phase 2 study (PM1183-B-005-14), antitumor activity of lurbinectedin monotherapy was assessed in participants with several advanced solid tumors including the second-line SCLC participant cohort. The data demonstrated a substantial clinical benefit with an acceptable and manageable safety profile, which led to accelerated approval of lurbinectedin for patients with extensive-stage SCLC with disease progression on or after platinum-based chemotherapy. The proposed study is designed to assess the safety and efficacy of lurbinectedin monotherapy in 3 cohorts of participants with high-unmet medical need: advanced (metastatic and/or unresectable) UC, advanced (metastatic and/or unresectable) PD-NEC, and an HRD-positive malignancies agnostic cohort.

Objectives and Endpoints:

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the antitumor activity of lurbinectedin in the selected advanced solid tumors	Investigator-assessed ORR according to RECIST v1.1
Secondary	
To evaluate the overall safety profile of lurbinectedin in the selected advanced solid tumors	AEs and SAEs as graded by NCI CTCAE v5.0
To assess other antitumor efficacy parameters of lurbinectedin in the selected advanced solid tumors.	Investigator-assessed PFS, TTR, DOR, and DCR as assessed per RECIST v1.1
To assess OS in participants treated with lurbinectedin in the selected advanced solid tumors.	OS
[redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: AE = adverse event; DCR = disease control rate; DOR = duration of response; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time-to-response;

Brief Summary: This is an open-label, multicenter, phase 2 study of lurbinectedin monotherapy in participants with advanced (metastatic and/or unresectable) solid tumors.

Overall Design:

- The participant population comprises participants in 3 cohorts with advanced (metastatic and/or unresectable) UC, advanced (metastatic and/or unresectable) PD-NEC, and an HRD-positive malignancies agnostic cohort.
- Participants will receive lurbinectedin 3.2 mg/m^2 IV on Day 1 of Q3W cycle. Study intervention will continue until confirmed disease progression, withdrawal of participant consent, participant lost to follow-up, unacceptable toxicity, or the study or individual cohort is terminated by the sponsor, whichever comes first.
- This is a signal-seeking study of lurbinectedin 3.2 mg/m^2 monotherapy. Review of the safety and efficacy data will be performed on an ongoing basis by the sponsor. The sponsor may decide to close a cohort or cohorts due to safety concerns, lack of efficacy or any other reasons. A cohort or cohorts may be expanded at the sponsor's discretion to greater than 20 participants if an efficacy signal is observed without any safety concerns.
- This study includes up to a total of 60 participants in the initial assessment of efficacy in which each tumor cohort includes up to 20 participants. If there is evidence of efficacy, enrollment beyond 20 participants in the individual cohort may be considered. Each cohort will have up to 4 stages: stage 1 at n = 12 and stage 2 at n = 20 for futility testing (see Section 9.5); if a cohort enrolls beyond 20 participants, the study may enroll stage 3 with an interim analysis to assess efficacy at n = 35, and a final stage 4 at n = 100 for the final analysis.

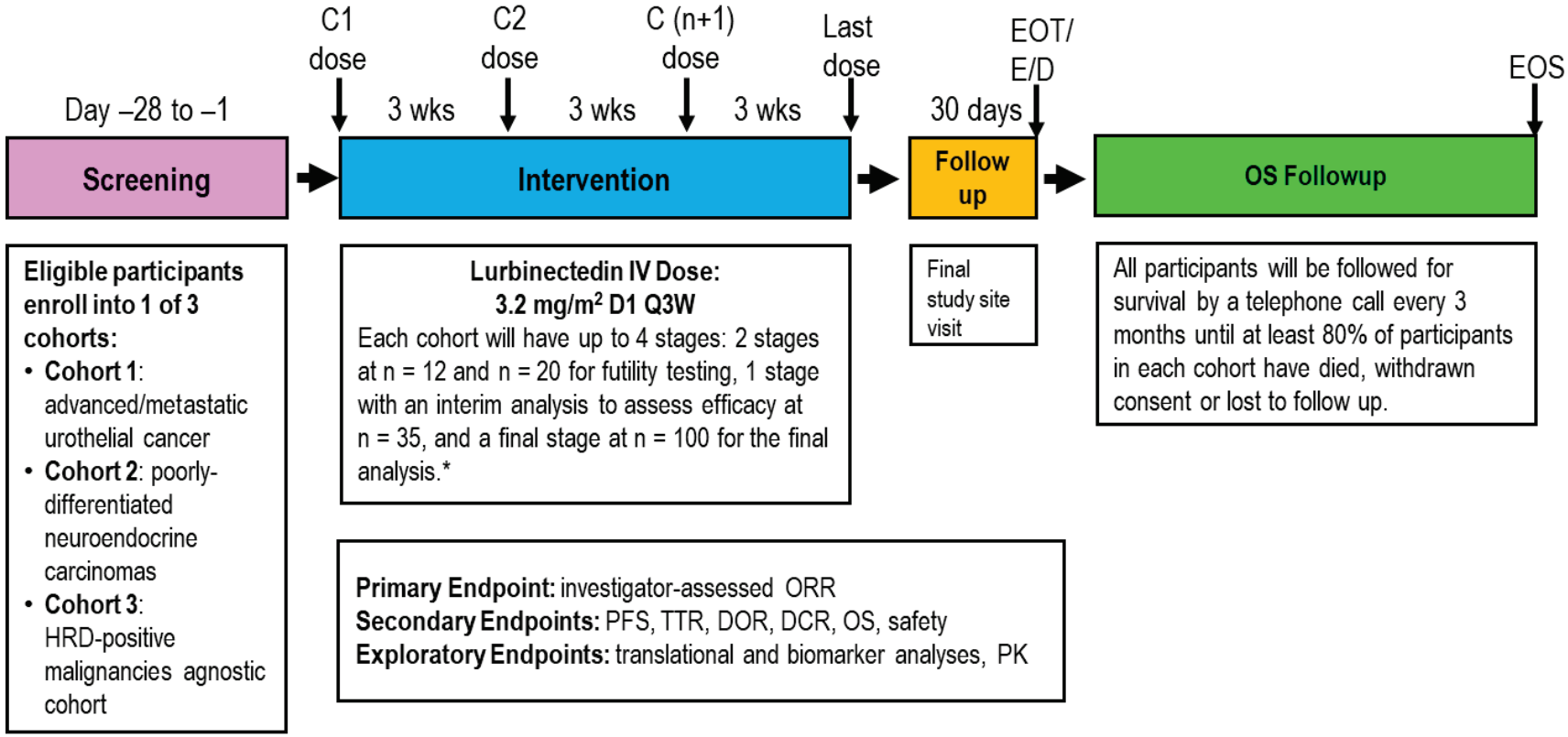
Table 2: Overall Study Design

Overall Design	
Study Phase	2
Clinical Indication	Advanced (metastatic and/or unresectable): urothelial cancer poorly differentiated neuroendocrine carcinoma homologous recombination deficient-positive malignancies agnostic cohort

Overall Design	
Study Type	Interventional
Type of Design	Open-label, multicenter study of lurbinectedin monotherapy
Type of Control	None
Study Blinding	Open-label
Population	Participants with 1 of the following advanced (metastatic and/or unresectable) tumors (as per eligibility criteria): urothelial cancer poorly differentiated neuroendocrine carcinoma homologous recombination deficient-positive solid tumor malignancy
Number of Participants	Approximately 12 to 20 participants/cohort with approximately 60 total participants to be enrolled in the study for evidence of efficacy. The study may be expanded to up to 100 participants/cohort for a total approximately 300 total participants, see Section 9.5.
Duration of Participation	Each participant will participate in the study from the time he/she signs the informed consent form through the end-of-the-study visit. The study comprises a Screening Period, Intervention Period, a Safety Follow-up Period, and an OS Follow-up Period. The overall duration of study participation for each participant is projected to be approximately 17 months, comprising 28 days for screening, 10 months for treatment and safety follow-up and approximately 6 additional months of follow-up over the telephone for survival assessment.
Number of Treatment Cohorts	3
Treatment Group	Lurbinectedin 3.2 mg/m^2 IV on Day 1 of Q3W cycle until confirmed disease progression, withdrawal of participant consent, participant lost to follow-up, unacceptable toxicity, or the study or individual cohort is terminated by the sponsor
Data Monitoring Committee	Not applicable

1.2. Schema

Figure 1: Study Schematic



Abbreviations: C = cycle; D = day; DCR = disease control rate; DOR = duration of response; E/D = early discontinuation; EOS = end of study; EOT = end of treatment; HRD = homologous recombination deficient; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; [redacted] Q3W = every 3 weeks; TTR = time-to-response; wks = weeks.
*Note: See Section 9 of the protocol for details on sample size and futility analysis.

1.3. Schedule of Activities

Table 3: Schedule of Activities

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
Informed consent	X (–28 to -1)										
Inclusion and exclusion criteria	X (–28 to -1)										Note: for the HRD-positive malignancies agnostic cohort, participants without mutational analysis results are not eligible for participation
Demography	X (–28 to -1)										
Primary diagnosis and prior treatment(s)	X (–28 to -1)										
Medical and cancer history/past and current medical conditions	X (–28 to -1)										

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
Full physical examination including height, weight, and BSA	X (–7 to -1)	X			X			X	X		BSA will be recalculated on Day 1 of each treatment cycle. The dose of study intervention should be recalculated if the participant's BSA has a ≥ 10% change (higher or lower) compared with the predose C1D1 value or the BSA recorded for dosing calculation at the previous cycle (see Section 5.5.1). Height is only required at Screening.
Performance status (ECOG)	X (–7 to -1)	X			X			X	X		–1 day window (except in Cycle 1)
Single 12-lead ECG	X (–7 to -1)	Repeat if clinically indicated									ECG: cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate (HR) and QRS complex.
Highly sensitive serum OR urine pregnancy test (WOCBP only)	X (–7 to -1)	X			X			X	X		Beta subunit-human chorionic gonadotropin (β-hCG) (urine or serum). In WOCBP, if a urine pregnancy test is positive a serum test must be performed and confirmed negative prior to administering IP. See Section 8.4.5 for pregnancy reporting requirements.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
HIV (antibody), Hepatitis B (surface antigen), and Hepatitis C (surface antigen, and RNA if positive by antibody) screening	X (–28 to -1)										All participants will be tested for HIV prior to the enrollment into the study and HIV-positive participants will be excluded from the study. Participants with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Participants with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible; HBV DNA should be obtained in these participants prior to enrollment. Participants with HCV will be excluded from the study; participants who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
Coagulation tests	X (–7 to -1)				X			X	X		–3 day window (except in Cycle 1). Clinical laboratory tests are detailed in Appendix 3.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
Hematology	X (–7 to -1)		X	X	X	X	X	X	X		–3 day window (from C1D8). Screening laboratory result must be reviewed before first dosing on C1D1. Clinical laboratory tests are detailed in Appendix 3. Any participants with febrile neutropenia of any grade, Grade 4 neutropenia, and/or Grade 4 thrombocytopenia, should have relevant tests repeated daily until recovery to Grade ≤ 3 and through the day after fever resolution, if applicable. **For Cycle 3 and after, Hematology and Biochemistry "A" tests on Days 8 and 15 are to be performed only in participants with Grade ≥ 3 biochemical Grade 4 hematological treatment-related toxicities, or who required dose adjustments due to hematological or biochemical abnormalities in the preceding cycle.**
Biochemistry-A	X (–7 to -1)		X	X	X	X	X	X	X		–3 day window (from C1D8). Screening laboratory result must be reviewed before first dosing on C1D1. Clinical laboratory tests are detailed in Appendix 3.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
Biochemistry-B	X (–7 to -1)				X			X	X		–3 day window (from C2D1). Screening laboratory result must be reviewed before first dosing on C1D1. Albumin, total proteins, Ca^{++} and Mg^{++}. Total proteins, Ca^{++} and Mg^{++} will be measured at Screening and repeated thereafter only in those participants with abnormal baseline values. Clinical laboratory tests are detailed in Appendix 3.
Vital signs (HR, BP, temperature, respiratory rate)	X (–7 to -1)	X			X			X	X		–1 day window (except in Cycle 1)
[redacted]		[redacted]									[redacted]
AAGP		X									One blood sample for the evaluation of AAGP will be collected at the end of the lurbinectedin infusion (± 5 min) from all participants.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
HRD-positive malignancies agnostic cohort only: blood for confirmation of any pre-identified germline and/or somatic pathogenic mutations	X (–28 to -1)										Blood will be collected before lurbinectedin administration in Cycle 1 from all participants in the HRD-positive malignancies agnostic cohort.
HRD-positive malignancies agnostic cohort only: blood for longitudinal mutational analysis (required)					X		X		X		Required only for the HRD-positive malignancies agnostic cohort.
Baseline blood for mutational analysis (required in all cohorts)		X									Blood should be collected before lurbinectedin administration.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
Radiological tumor assessment	X (–28 to -1)	Every 6 weeks (±7 days) from the C1D1 for 36 weeks (±7 days). After completion of the Week 36 tumor assessment, every 12 weeks (±14 days) thereafter. The assessments will be performed at these time points until PD, start of a new anticancer therapy, death, withdrawal of consent from the study, EOT visit, lost to follow up, or study termination, whichever occurs first.							X (if not performed within 7 days of last treatment evaluation visit for participants who discontinue treatment, see Section 7.1)		Evaluation by contrast enhanced helical CT-scan or MRI, as clinically indicated, of all measurable sites of disease involvement and of all nonmeasurable sites of disease should be done prior to the first lurbinectedin administration. While on treatment, evaluation of all original sites of disease involvement should be done per RECIST v1.1. The same initial method must be used throughout the study. For all PD-NEC participants, CT-scan or MRI of brain will be requested before the planned treatment onset to rule out CNS involvement. Participants showing a response must have a confirmatory assessment at least 4 weeks after initial response. See Appendix 8 for tumor assessment guidelines.
Pretreatment tumor sample (optional)	X (–28 to -1)	Tumor samples may be submitted at any time during the study.									Pretreatment tumor sample from primary tumor and/or metastasis, either obtained at diagnosis or at any time before the first lurbinectedin administration. Any tumor sample, sample from primary tumor and/or metastasis, (either formalin fixed paraffin-embedded tumor tissue or cytology slides) will be acceptable. Archived tumor samples, if available, can be submitted at any time during the study.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
Administer colony-stimulating factors (eg, G-CSF or GM-CSF)		X			X			X			Refer to Section 6.10.1. A mandatory window of at least 24 hours and up to 72 hours must be allowed from the last dose of study intervention administration until G-CSF or GM-CSF prophylaxis is started.
Administer lurbinectedin		X			X			X			± 3 day window (except in Cycle 1). Refer to criteria for treatment continuation (Section 5.5) and dose delay and reduction rules (Section 6.7) prior to each administration of lurbinectedin. Note that the dose of study intervention should be recalculated if the participant's BSA has a ≥ 10% change (higher or lower) compared with the predose C1D1 value or the BSA recorded for dosing calculation at the previous cycle (see Section 5.5.1).
[redacted]		[redacted]									[redacted]
OS										X	
AE review		←═══════════→									Adverse events resulting in study discontinuation will be followed until satisfactory resolution per the investigator. See Section 8.4.1.

Procedure	Screening (window)	Intervention Period [Days]							EOT (30± 7D after last dose) or E/D	OS telephone call every 3 months	Comments
		C1			C2			≥ C3			
		D1	D8	D15	D1	D8	D15	D1			• D–1 is the calendar day before C1D1. • Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window. • EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy. • The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity.
SAE review		←═══════════════→									All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. During the OS Follow-up, any spontaneous treatment-related SAEs will be collected and reported.
Prior/concomitant medications	←═══════════════→										

Abbreviations: AAGP = alpha-1 acid glycoprotein; AE = adverse event; β-hCG = beta subunit-human chorionic gonadotropin; BP = blood pressure; BSA = body surface area; C = cycle; CNS = central nervous system; CT = computed tomography; D = day; ECG = electrocardiogram; E/D = early discontinuation; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HBcAb = hepatitis B core antibody; HBsAg = hepatis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; HRD = homologous recombination deficient; ICF = informed consent form; IP = investigational product; MRI = magnetic resonance imaging; OS = overall survival; PCR = polymerase chain reaction; PD = progressive disease; PD-NEC = poorly differentiated neuroendocrine carcinoma [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = woman of childbearing potential.

2. INTRODUCTION

The proposed study is a multicenter, phase 2 clinical trial to evaluate the efficacy and safety of lurbinectedin monotherapy in participants in 3 cohorts: advanced (metastatic and/or unresectable) UC, advanced (metastatic and/or unresectable) PD-NEC, and HRD-positive malignancies agnostic.

2.1. Study Rationale

Lurbinectedin is a novel alkylating agent that inhibits oncogenic transcription through the preferential binding of guanines located in GC rich regulatory areas (Deaton, 2011; Nuñez, 2016). Lurbinectedin also exerts immunomodulatory activity by inhibiting transcription in macrophages in the tumor microenvironment (Belgiovine, 2017; Cespedes, 2016), which may contribute to its antitumor efficacy.

To date, over 1700 participants with multiple types of advanced solid tumors have been treated in clinical trials with lurbinectedin monotherapy or in combination with chemotherapy, and antitumor efficacy has been shown across multiple indications (Data on file, Pharma Mar PBRER/PSUR, 2021). In Study PM1183-B-005-14, antitumor activity of lurbinectedin monotherapy was assessed in participants across several advanced solid tumors (Trigo, 2020), namely advanced SCLC, head and neck carcinoma, NETs, biliary track carcinoma, endometrial carcinoma, carcinoma of unknown primary site, GCTs, and Ewing's family of tumors. Among these participants, a dose of 3.2 mg/m^2 lurbinectedin in the second-line SCLC cohort demonstrated a substantial clinical benefit with an acceptable and manageable safety profile. Based on these data, lurbinectedin was granted accelerated approval by the FDA (FDA, 2020). In addition to this trial, objective responses have been observed in participants with several other advanced tumors, including ovarian cancer, pancreatic cancer, breast cancer, NSCLC, SCLC, NETs, endometrial carcinoma, bladder carcinoma, and soft tissue sarcoma (Pharma Mar IB, 2022), suggesting antitumor activity of lurbinectedin either as monotherapy or in combination with other therapeutic agents in many advanced tumors.

The proposed study is designed to assess the efficacy and safety of lurbinectedin monotherapy in 3 cohorts of participants with high-unmet medical need: (1) advanced (metastatic and/or unresectable) UC, (2) advanced (metastatic and/or unresectable) PD-NEC, and (3) HRD-positive malignancies agnostic.

2.2. Background

Treatment failures are very common in patients with advanced or metastatic disease, especially in patients with disease progression after treatment with one or more lines of anticancer therapies. Their prognosis is poor and could benefit from participating in clinical trials. In recent years, immune CPIs have been tested in many new tumors, including advanced or metastatic diseases, with a remarkable long-term efficacy (La-Beck, 2015). However, this long-term benefit is limited to only a small percentage of patients and most of these patients eventually progress.

Cytotoxic chemotherapy remains a crucial component of the therapeutic armamentarium for many of these advanced cancer patients; lurbinectedin is a novel transcription inhibitor that may offer a

treatment benefit to these patients. Lurbinectedin has previously shown antitumor activity in many advanced cancers, including tumors with DNA damage repair deficiencies (Cruz, 2018) and histological variants such a neuroendocrine tumors; a detailed description of the chemistry, pharmacology, efficacy, and safety of lurbinectedin is provided in the IB (Pharma Mar IB, 2022).

This study includes up to a total of 60 participants in the initial assessment of efficacy in which each tumor cohort includes up to 20 participants. If there is evidence of efficacy, enrollment beyond 20 participants in the individual cohort may be considered. The study may be expanded to up to 100 participants/cohort for a total approximately 300 total participants, see Section 9.5. The following 3 cohorts with specific histologically or cytologically or pathogenic germline and/or somatic mutation tumors:

- **Cohort 1:** UC
- **Cohort 2:** PD-NEC
- **Cohort 3:** HRD-positive malignancies agnostic cohort

2.2.1. Urothelial Cancer

In recent years, the treatment paradigm for UC has evolved rapidly. Significant increases in OS and PFS were shown following avelumab maintenance treatment of patients with locally advanced or metastatic UC who had not progressed with first-line platinum-containing chemotherapy or who had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Powles, 2020). These data led to recent FDA approval of avelumab in this indication, and avelumab is now the standard of care as the first-line maintenance treatment of advanced or metastatic UC (Bavencio, 2020). Enfortumab vendotin, an ADC that targets Nectin-4, which is highly expressed in UC, was granted an accelerated approval by the FDA for the treatment of patients with locally advanced or metastatic UC who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy; and is being used as the standard of care for second-line therapy for these patients (Padcev PI, 2021). More recently, sacituzumab govitecan, another ADC, was granted fast track designation and subsequently granted an accelerated approval by the FDA based on the phase 1/2 data for heavily pretreated bladder cancer patients (median number of prior therapies: 3; range 2 to 6; Trodelvy PI, 2021).

Despite several new treatment options for patients with advanced or metastatic UC, an unmet need remains because few approved treatment options are available for these patients who progress beyond second or third-line therapies. These patients mainly receive monotherapy chemotherapies, such as taxane or vinflunine, in the salvage setting with a modest response (Bellmunt, 2009; Petrylak, 2017).

In a mouse model with xenografted human-derived bladder cancer (Pharma Mar, data on file), lurbinectedin exhibited antitumor activity. In previously completed phase 1 studies either as lurbinectedin monotherapy or in combination with other chemotherapeutic agents, 2 participants with UC demonstrated stable disease (Pharma Mar IB, 2022). The proposed study will be the first to assess the efficacy and safety of lurbinectedin monotherapy in participants with advanced or metastatic UC.

2.2.2. Poorly-Differentiated Neuroendocrine Carcinoma

Poorly differentiated neuroendocrine carcinomas are rare and aggressive neuroendocrine neoplasms with distinct clinical and pathological features with a high grade, high proliferative index, and either small or large cell morphology. Patients progressing from frontline platinum-based chemotherapy have limited options in the second and later lines of chemotherapy, and there is a high unmet medical need for patients with advanced/refractory PD-NECs.

Lurbinectedin is an alkylating agent that inhibits oncogenic transcription through preferential binding to guanine residues in the DNA minor groove, triggering a cascade of events that can perturb the cell cycle and potentiate eventual cell death. In an earlier study, lurbinectedin monotherapy exhibited an ORR of 6.5% (95% CI, 0.8% to 21.4%) in patients with advanced/refractory (second line and beyond) Grade 2 and 3 NETs. Most patients had gastroenteropancreatic NETs (n = 20/32; 62.5%) and non-functioning NETs (n = 23/32; 71.9%). Thirty-one of 32 treated patients were evaluable for efficacy. Two out of 31 evaluable patients had PR, with a median DoR of 4.7 months, PFS of 1.4 months, and median OS of 7.4 months. The DCR in the evaluable patients (confirmed CR + PR + SD ≥ 4 months) was 29.0% (95% CI, 14.2% to 48.0%). Lurbinectedin showed an acceptable, predictable, and manageable safety profile. The most common Grade 3/4 toxicity was neutropenia (40.6%; Grade 4, 12.4%; febrile neutropenia, 3.1%). Although a heterogeneous patient population with Grade 2 and 3 NETs were enrolled in this study, the study met its primary endpoint, exhibiting a signal of efficacy (Longo-Muñoz, 2022).

While most PD-NECs (~90%) originate from the lung, namely small cell lung cancer (SCLC; ~86%) and large cell pulmonary NETs (~4%), a minority (~10%) arise from other anatomical sites and are generally termed extrapulmonary neuroendocrine carcinomas. Large cell neuroendocrine tumor of the lung is an uncommon, aggressive, and preoperatively difficult-to-diagnose malignancy. Large cell neuroendocrine tumor represents a subtype of PD-NECs and has a poor prognosis, similar to SCLC. Data demonstrated that first-line platinum-based chemotherapies, especially platinum and etoposide, showed similar efficacy in patients with LCNET and SCLC (Derks, 2017). However, most of these patients progress rapidly and subsequent treatments with chemotherapies are not very effective (Russo, 2016).

The FDA recently approved lurbinectedin for the treatment of adult patients with extensive-stage SCLC who progressed on prior platinum-containing regimens. Thus, lurbinectedin may show similar therapeutic benefit in patients with advanced/refractory LCNET or PD-NECs of other histological origin. Therefore, based on the available clinical data with an acceptable safety profile of lurbinectedin, a cohort of this study is designed to explore lurbinectedin monotherapy in patients with advanced/refractory PD-NEC of any origin, including LCNET of lung.

2.2.3. Homologous Recombination Deficient-Positive Malignancies Agnostic Cohort

Homologous recombination deficiency encompasses a broad spectrum of tumors with pathogenic mutations in the HR-DDR pathway. Such mutations and the associated cancer risk are well described (Radhakrishnan, 2014; Heeke, 2018). Loss of function mutations in *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* or *PALB2*, and/or promoter hypermethylation of the *BRCA1* gene promoter (leading to loss of expression of BRCA1) have been associated with cancer development and may predict responsiveness to therapy, including PARP inhibitors. Several other DNA repair proteins

are involved in HR-DDR (eg, ATM, ARID1A, ATR, BAP1, CHEK2, RAD50, RAD54), and mutations or alterations to other less defined pathways can also lead to HRD (Miller, 2020).

Heeke et al. reviewed the molecular profiles of 52,426 tumors and showed that in tumors that underwent NGS600 testing (n = 17,566), the overall frequency of HR-DDR mutations detected was 17.4%. The most commonly mutated lineages were endometrial (34.4%; n = 1,475), biliary tract (28.9%; n = 343), bladder (23.9%; n = 201), hepatocellular (20.9%; n = 115), gastroesophageal (20.8%; n = 619), and ovarian (20.0%; n = 2,489). Other lineages with a significant proportion of tumors that tested positive for HR-DDR deficiency by NGS included melanoma (18.1%; n = 670), breast (15.6%; n = 1,625), pancreatic (15.4%; n = 833), and colorectal cancer (15.0%; n = 2,454) (Heeke, 2018). Examination of mutations in these genes using publicly available data in The Cancer Genome Atlas database (10,967 samples) aligns closely with these frequencies (NCI, 2021).

Limited data are available from lurbinectedin clinical studies for malignancies associated with the HR-DDR pathway genes. Lurbinectedin is a selective inhibitor of the active transcription of protein-coding genes, and its mechanism of action involves the irreversible stalling of elongating RNA polymerase II on the DNA template followed by degradation by the ubiquitin/proteasome machinery. This results in recruitment of DNA repair factors, including XPF nuclease, and induces the accumulation of double-strand breaks and apoptosis as downstream events. Due to the inability to repair these breaks, effects are increased in homologous recombination repair-deficient cells (Cruz, 2018). In another study, Tumini et al reported that trabectedin and lurbinectedin were more sensitive in cancer cells with high levels of R-loops, which may be caused by loss of function of BRCA1/2 proteins or FANC family proteins (Tumini, 2019).

In an earlier Phase 2 study, monotherapy lurbinectedin was evaluated in a cohort of 89 evaluable female patients with advanced or metastatic breast cancer, consisting of Arm A (n = 54) with germline BRCA-mutated patients and Arm B (n = 35) with unselected advanced or metastatic breast cancer patients. Lurbinectedin exhibited higher objective responses in participants with deleterious BRCA1/2 mutations compared to BRCA1/2 unselected participants, with ORR of 41% (95% CI, 27.6% to 55.0%) and 9% (95% CI, 1.9% to 23.7%), respectively. In Arm A, median PFS was 4.6 months (95% CI, 3.0 to 6.0 months), and median OS was 20.0 months (95% CI, 11.8 to 26.6 months); 57% and 43% of patients carried deleterious BRCA1 and BRCA2 mutations, and 56% and 44% patients had triple-negative and HR+ disease, respectively. In contrast, median PFS was 2.5 months (95% CI, 1.3 to 3.4 months) and median OS was 12.5 months (95% CI, 6.6 to 17.9 months) in Arm B patients (Cruz, 2018).

In a small cohort of 20 advanced or metastatic breast cancer patients with deleterious BRCA1/2 mutations who received prior PARPi, monotherapy lurbinectedin had relatively lower antitumor activity with one patient achieving objective response (ORR 5%; 95% CI, 0.1% to 24.9%) and 4 patients having SD for ≥ 4 months (Pharma Mar IB, 2022). No further pharmacogenomic o molecular analysis was performed to determine the mechanisms of antitumor activity of lurbinectedin in these patients, specifically if there is any relationship with prior administration of PARPi or platinum compounds. Therefore, the current study is designed with a cohort of patients with malignancies consisting of both germline or somatic pathogenic mutations (a mutation that significantly affects the functions of genes associated with oncogenesis [NCI, 2022]) of HR-DDR pathways to explore the antitumor efficacy of lurbinectedin and conduct further

pharmacogenomic and molecular analyses. In addition, until further knowledge is gathered to understand the mechanism of action of lurbinectedin in patients who have received prior PARPi, patients with HRD deficient-positive malignancies who are primary resistant/refractory to PARPi (progression within ≤ 3 months of the first dose of PARPi) will be excluded in this cohort of the study.

2.3. Benefit/Risk Assessment

The approved dose regimen for lurbinectedin is 3.2 mg/m^2 administered as a 1-hour IV infusion on Day 1 and Q3W (Pharma Mar IB, 2022). This dose regimen provides the optimal benefit to the participants and minimizes the potential risk/toxicity of lurbinectedin (Pharma Mar IB, 2022).

2.3.1. Risk Assessment

Potential risks to participants in this study are anticipated to be consistent with the known pharmacology and safety profile of lurbinectedin in previous clinical studies, as described in the lurbinectedin IB (Pharma Mar IB, 2022). The main risks associated with lurbinectedin are AEs related to reversible myelosuppression. There is also a risk of hepatotoxicity and gastrointestinal toxicity (specifically nausea and vomiting). Episodes of rhabdomyolysis were reported in 2 patients treated with single-agent lurbinectedin, although none of them occurred at the recommended dose of 3.2 mg/m^2 Q3W. A small number of reports of rhabdomyolysis have been received in the postmarketing setting. Based on animal studies and its mechanism of action, lurbinectedin may cause embryo-fetal toxicity, and effective methods of contraception are recommended to be used by study participants.

2.3.2. Benefit Assessment

The following potential benefits of lurbinectedin are anticipated:

- Receiving lurbinectedin may provide treatment benefit to study participants.
- All participants will contribute to the process of developing new therapies in protocol-specified advanced and metastatic solid tumors.
- Participants will receive comprehensive clinical examinations and clinical monitoring associated with the study.

2.3.3. Overall Benefit: Risk Conclusion

Lurbinectedin has an acceptable, predictable, and manageable safety profile, (Pharma Mar IB, 2022). Enrolled participants will be monitored closely for any safety signal on an ongoing basis throughout the study. Lurbinectedin has also exhibited antitumor activity in several other advanced tumors, including ovarian cancer, pancreatic cancer, breast cancer, NSCLC, SCLC, NETs, endometrial carcinoma, bladder carcinoma, and soft tissue sarcoma (Pharma Mar IB, 2022), suggesting antitumor activity of lurbinectedin either as a monotherapy or in combination with other therapeutic agents in many advanced tumors. Based on available safety and efficacy data from the ongoing and completed trials, overall, lurbinectedin has a positive benefit-risk profile for these participants.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the antitumor activity of lurbinectedin in the selected advanced solid tumors	Investigator-assessed ORR according to RECIST v1.1
Secondary	
To evaluate the overall safety profile of lurbinectedin in the selected advanced solid tumors	AEs and SAEs as graded by NCI CTCAE v5.0
To assess other antitumor efficacy parameters of lurbinectedin in the selected advanced solid tumors.	Investigator-assessed PFS, TTR, DOR, and DCR as assessed per RECIST v1.1
To assess OS in participants treated with lurbinectedin in the selected advanced solid tumors.	OS
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

- This is an open-label, multicenter, phase 2 study of lurbinectedin monotherapy in participants with advanced (metastatic and/or unresectable) solid tumors.
- The participant population comprises participants in 3 cohorts: advanced (metastatic and/or unresectable) UC, advanced (metastatic and/or unresectable) PD-NEC, and an HRD-positive malignancies agnostic cohort (specific criteria are presented in Section 5.1).
  - Note that for the HRD-positive malignancies agnostic cohort only, the sponsor may preferentially enroll participants with certain tumor types at any time during the study to ensure adequate and even enrollment across the various tumor types under study.
- Participants will receive lurbinectedin 3.2 mg/m^2 IV on Day 1 of Q3W cycle. Study intervention will continue until confirmed disease progression, withdrawal of participant consent, participant lost to follow-up, unacceptable toxicity, or the study or individual cohort is terminated by the sponsor, whichever comes first.
- This is a signal-seeking study of lurbinectedin 3.2 mg/m^2 monotherapy. Review of the safety and efficacy data will be performed on an ongoing basis by the sponsor. The sponsor may decide to close a cohort or cohorts due to safety concerns, lack of efficacy or any other reasons. A cohort or cohorts may be expanded at the sponsor's discretion to greater than 20 participants if an efficacy signal is observed without any safety concerns.
- This study includes up to a total of 60 participants in the initial assessment of efficacy in which each tumor cohort includes up to 20 participants. If there is evidence of efficacy, enrollment beyond 20 participants in the individual cohort may be considered. Each cohort will have up to 4 stages: stage 1 at n = 12 and stage 2 at n = 20 for futility testing (see Section 9.5); if a cohort enrolls beyond 20 participants, the study may enroll stage 3 with an interim analysis to assess efficacy at n = 35, and a final stage 4 at n = 100 for the final analysis.
- Beginning on Cycle 1 Day 1, participants still on study treatment will undergo tumor assessments every 6 weeks (± 7 days) through Week 36, regardless of treatment dose delays. After Week 36, tumor assessments will be required every 12 weeks (± 14 days). Participants will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, lost to follow-up, study termination by the sponsor, or death, EOT visit, or study termination, whichever occurs first. After the EOT visit, all participants will be followed for survival by a telephone call every 3 months until at least 80% of participants in each cohort have died or withdraw consent or are lost to follow-up. If a cohort closes due to futility, the OS follow-up for that cohort will end.

- Administration of primary prophylaxis of colony-stimulating factors such as G-CSF or GM-CSF is mandated starting from Cycle 1 and during all subsequent cycles, in addition to the mandatory prophylactic medications listed in Section 6.6. The type, dose, and scheme to be used may vary according per institutional/standard practices or guidelines (see Section 6.6 for details).
- The projected study duration for each participant is approximately 17 months (including Screening Period [28 days], Intervention Period [9 months], Safety Follow-up Period [30 days]), and OS Follow-up Period (6 months).

4.2. Scientific Rationale for Study Design

This is an open-label, nonrandomized, multi-cohort, signal-seeking study in advanced (metastatic and/or unresectable) tumors. The primary endpoint is the tumor response rate for each of 3 tumor cohorts. The ORR of each cohort will be assessed for a clinically meaningful improvement (see Section 9.5). The ORR is a direct measure of a drug antitumor activity, which can be evaluated in a single-arm study (FDA, 2018). If a cohort meets the predefined threshold of clinical efficacy, it may be further expanded to more than 20 participants and a discussion may be conducted with the FDA and other regulatory agencies for further clinical development of lurbinectedin in these tumors.

There is no statistical hypothesis testing in this signal-seeking study. However, desired response rates are defined as 20% or more for each cohort for further exploration in these participants with selected advanced (metastatic and/or unresectable) solid tumors with lurbinectedin monotherapy (Section 9.2).

4.3. Justification for Dose

Lurbinectedin was granted accelerated approval by FDA for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. The approved dose regimen for lurbinectedin is 3.2 mg/m^2 administered as a 1-hour IV infusion on Day 1 and Q3W) (Zepzelca, 2022). This dose regimen provides the optimal benefit to the participants and minimizes the potential risk/toxicity of lurbinectedin (Fudio, 2021).

In an exposure-response analysis of data for lurbinectedin in SCLC participants, the recommended lurbinectedin dosing regimen of 3.2 mg/m^2 Q3W provided the maximum benefit in SCLC participants with disease progression on or after platinum-based chemotherapy. Lowering the dose resulted in reduced efficacy, whereas increasing it led to high incidence of severe hematological toxicity without improvement of efficacy (Fudio, 2021). Therefore, lurbinectedin 3.2 mg/m^2 Q3W was selected for the maximum benefit for these participants.

4.4. End of Study Definition

The EOS occurs when all dosed participants have been followed until at least 80% of participants in each cohort have died, withdrawn consent, or are lost to follow-up. After EOT, further follow-up of all participants will take place for an assessment of OS via a telephone call every 3 months after their EOT visit until the EOS. The EOS for each participant is defined as the date of the last OS follow-up telephone call as shown in the SoA (Table 3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Disease Characteristics for Each Cohort

Participants with advanced (metastatic and/or unresectable) cancer who meet the following criteria for individual cohorts.

1. **Urothelial Cancer Cohort:**
    a. Has histologically or cytologically documented advanced (metastatic and/or unresectable) urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis (mixed histology tumors is allowed if predominant histology is urothelial carcinoma. Small cell or NEC is NOT allowed if predominant).
    b. Has progressed on a platinum-containing regimen (cisplatin ineligible participants who have received only an immune CPI as their first-line treatment are allowed).
        – Prior therapies may include but are not limited to immune CPI, enfortumab vendotin, or sacituzumab govitecan.
        – Platinum followed by avelumab maintenance is considered as one line of therapy.
        – Prior cytotoxic therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy in the relapsed or metastatic setting if administered > 12 months prior to enrollment.
2. **Poorly Differentiated Neuroendocrine Carcinomas Cohort:**
    a. Has histologically or cytologically confirmed advanced (metastatic and/or unresectable) PD-NEC of any origin.
        – SCLC patients are not eligible in this cohort.
        – Histologically defined LCNET of lung are eligible regardless of their previous diagnosis and treatment (as an example, patient may be diagnosed earlier as NSCLC or SCLC and treated accordingly, but later biopsy results confirm the diagnosis as LCNET).
    b. Received at least 1 prior line of therapy.
3. **Homologous Recombination Deficient-positive Malignancies Agnostic Cohort:**

Note: participants must have previous mutational and genomic analysis results that will confirm the following eligibility criteria for potential participation.

    a. Has histologically or cytologically confirmed advanced (metastatic and/or unresectable) endometrial, biliary tract, urothelial, breast (TNBC or HR+HER2–

breast cancer), pancreas, gastric, or esophageal solid tumor, irrespective of PD-L1 status.

b. Has a pre-identified germline and/or somatic pathogenic mutation (a mutation that significantly affects the functions of genes associated with oncogenesis [NCI, 2022]) in one of the following genes: *BRCA1/2, PALB2, RAD51/51B/51C/51D, ATR, ATM, ARID1A, BAP1, CHEK2, RAD50, RAD54.*
c. Received at least 1 prior line of therapy.
d. Patients who have received prior PARPi are allowed **unless** they progressed within ≤ 3 months after the first dose with PARPi

Informed Consent

4. Is capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Age

5. Is ≥ 18 years of age at the time of signing the informed consent.

Safety Parameters

6. Has ECOG performance status of 0 or 1.
7. Has a life expectancy of ≥ 3 months.
8. Has adequate bone marrow function, as follows:
   a. ANC ≥ 1500/mm^3 or ≥ 1.5 × 10^9/L,
   b. Platelets ≥ 100,000/mm^3 or ≥ 100 × 10^9/L,
   c. Hemoglobin ≥ 9 g/dL (note: may have been transfused).
9. Has as adequate renal function, defined as estimated creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation or by 24-hour urine collection for creatinine clearance or according to the local institutional standard method.
10. Has adequate liver function, as follows:
    a. Total serum bilirubin ≤ 1.5 × ULN,
    b. Aspartate aminotransferase and alanine aminotransferase ≤ 3 × ULN, or for participants with documented metastatic liver disease, AST and ALT levels ≤ 5 × ULN.

Tumor Assessment requirement

11. Has measurable disease in accordance with RECIST v1.1.

Sex and Contraceptive/Barrier Requirements

12. Male and female

a. Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 4 months after the last dose of study intervention:

- Refrain from donating sperm.

  PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below.
  - Agree to use a male condom [with female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year as described in Appendix 5 Contraceptive and Barrier Requirements] when having sexual intercourse with a woman of childbearing potential who is not currently pregnant. Note: male participants who are azoospermic (vasectomized or due to a medical cause) are still required to follow the protocol-specified contraception/barrier criteria.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-childbearing potential as defined in Appendix 5 Contraception and Barrier Guidance.

    OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 5 Contraception and Barrier Guidance during the study intervention period and for at least 6 months after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 7 days before the first dose of study intervention, see Section 8.3.6: Pregnancy Testing.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.6 Pregnancy Testing.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

5.2. Exclusion Criteria

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

Medical Conditions

1. Has persisting toxicity (NCI CTCAE v5.0 Grade > 1) related to prior therapy; however, alopecia, sensory neuropathy, hypothyroidism and rash Grade ≤ 2 are acceptable, and other Grade ≤ 2 AEs not constituting a safety risk based on the investigator's judgement are acceptable.
2. Has known symptomatic CNS metastases requiring steroids. Participants with previously diagnosed CNS metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to enrollment, have discontinued high dose corticosteroid treatment for these metastases for at least 2 weeks, and are neurologically stable (≤ 10 mg prednisone mg daily or ≤ 2 mg dexamethasone daily are allowed).
3. Has a diagnosis of any other malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, low grade (Gleason ≤ 6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration), or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms. Other cancers not expected to affect health or survival over 2 years may be approved by the medical monitor after case review.
4. Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
5. Has significant neurological or psychiatric disorders that could harm participant ability or compliance with the study assessments.
6. Has an active infection requiring systemic therapy.
7. Has significant non-neoplastic liver disease (eg, cirrhosis, active chronic hepatitis).
8. Has any other major illness that, in the investigator's judgment, could substantially increase the risk associated with the patient's participation in this study.
9. Has any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the participant at high risk for treatment complications.
10. Has illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures.

Prior/Concomitant Therapy

11. Received prior treatment with lurbinectedin or trabectedin.

12. Received prior treatment with any IP within 4 weeks of the study IP first infusion. Observational studies are permitted.
13. Received live vaccines within 4 weeks of the first dose of study treatment or plans to receive live vaccines during study participation. Administration of inactive vaccines or mRNA vaccines (for example, inactivated influenza vaccines or COVID-19 vaccines) are allowed.
14. Has major surgery ≤ 4 weeks or major radiation therapy ≤ 2 weeks prior to enrollment unless fully recovered. Prior palliative radiotherapy is permitted, provided it was completed at least 2 weeks prior to participant enrollment.
15. Received prior allogeneic bone marrow transplantation or solid organ transplant.
16. Patients who have progressed on prior PARPi within 3 months after initiation of PARPi treatment are excluded for the HRD-positive malignancies agnostic cohort.

Diagnostic Assessments

17. HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).
18. Human immunodeficiency infection at screening (positive anti-HIV antibody).

Other Exclusions

19. Has a known or suspected hypersensitivity to any of the components of the drug product.
20. Is an investigational site staff member directly involved in the conduct of the study or a family member, site staff member otherwise supervised by the investigator, or participant who is a Jazz employee directly involved in the conduct of the study

5.3. Lifestyle Considerations

Not applicable. No restrictions are required.

5.3.1. Meals and Dietary Restrictions

The lurbinectedin population [redacted] detected several covariates that affected lurbinectedin [redacted] (Pharma Mar IB, 2022). [redacted] any food or fruits rich with CYP3A inhibitors or inducers (eg, grapefruit or grapefruit juice and Seville oranges) should be avoided during lurbinectedin treatment.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be automatically assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Treatment Continuation

Further treatment cycles (ie, Cycle 2 and after) will be administered Q3W if the participant fulfills all the retreatment criteria within 3 days prior to the scheduled lurbinectedin infusion (Table 3) and defined in Table 4.

Table 4: Criteria for Treatment Continuation (Cycle 2 and After)

Variable	Retreatment Criteria (Day 1)
Hemoglobin[a]	≥ 9 g/dL
ANC	≥ 1.5 × 10^9/L
Platelets	≥ 100 × 10^9/L
AST/ALT	≤ 3 × ULN; for participants with documented metastatic liver disease, AST and ALT levels ≤ 5 × ULN
Total serum bilirubin	≤ 1.5 × ULN
Serum creatinine	≤ 1.5 × ULN or creatinine clearance ≥ 30 mL/min
Events of rhabdomyolysis	Withhold for Grade 2; resume at same dose if Grade ≤ 1
Other nonhematological treatment-related AEs (except isolated increased GGT and/or AP; Grade 2 asthenia, constipation, alopecia, peripheral neuropathy, or nonoptimally treated nausea and/or vomiting)	Grade ≤ 1
Active infection (including sepsis) and/or bleeding (any grade)	Absence

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal.

[a] Participants may receive packed red blood cells transfusion and/or erythropoietin treatment, if clinically indicated, to increase or maintain adequate hemoglobin levels.

If a participant does not meet the requirements for treatment continuation on Cycle 2 Day 1 or subsequent cycles, reassessments will be performed at least every 48 to 72 hours for evaluation of treatment continuation. Treatment can be withheld up to a maximum of 3 weeks. Lurbinectedin dose delay and reduction rules are presented in Section 6.7.

5.5.1. Dose Adjustment Due to Changes in Body Surface Area

Body surface area will be recalculated on Day 1 of each treatment cycle. The dose of study intervention should be recalculated if the participant's BSA has a ≥ 10% change (higher or lower)

compared with the predose Cycle 1 Day 1 value or the BSA recorded for dosing calculation at the previous cycle. Refer to Section 6.7 for additional guidance regarding dose adjustment criteria.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention/treatment is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s)/Treatment(s) Administered

Refer to Table 5 for details regarding the study intervention.

Table 5: Study Treatment/Intervention

Treatment Arm	Intervention/Treatment Name	Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	Sourcing	Pkg	Labeling	Storage Conditions
1	lurbinectedin (JZP712) Also known as PM01183	Lyophilized powder for concentrate for solution for infusion	4.0 mg/vial 0.5 mg/mL after reconstitution	3.2 mg/m^2 every 3 weeks	Infusion/IV	Experimental	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee.	Study intervention will be provided in 4-mg/vial, sterile 30-mL, single-dose, type I clear-glass vials and labeled as required per country requirement. Child resistant packaging as required	Open labeling	If not used immediately after reconstitution or dilution, the lurbinectedin solution can be stored prior to administration for up to 24 hours following reconstitution, including infusion time, at either room temperature/ ambient light or under refrigeration at 2ºC-8ºC (36ºF - 46ºF) conditions.

6.1.1. Precautions During Study Treatment Administration

If extravasation of lurbinectedin occurs, immediately discontinue the infusion, remove the infusion catheter, and monitor for signs and symptoms of tissue necrosis. Administer supportive care per the institutional guidelines as needed. Administer subsequent infusion at a site that was not affected by extravasation. Consider use of a central venous catheter to reduce the risk of extravasation, particularly in patients with limited venous access. Monitor patients for signs and symptoms of extravasation during the lurbinectedin infusion.

Do not co-administer lurbinectedin and other IV drugs concurrently within the same IV line.

6.2. Preparation/Handling/Storage/Accountability

1. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site Binder.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Preparation of Study Intervention

Before use, the vials are reconstituted with water for injection (8 mL) to obtain a solution containing 0.5 mg/mL lurbinectedin. For administration to participants as IV infusion, the reconstituted vials are diluted with glucose 50 mg/mL (5%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion.

In order to obtain reliable [redacted] information during the first dosing, the infusion rate should not be modified once the infusion begins, especially during the first cycle. Lurbinectedin is administered as a 1-hour IV infusion.

6.4. Measures to Minimize Bias

Specific measures to minimize bias are not applicable to this open-label, nonrandomized study. All participants who sign the ICF will receive a participant number. The participant number identifies the participant for all study procedures that occur throughout the study. This number is unique and once assigned, cannot be reassigned to another study participant.

6.5. Study Intervention/Treatment Compliance

Participants who are dosed at the site 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 eCRF. The dose of study intervention and study participant identification should be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6. Prophylactic Medication

All participants will receive mandatory prophylactic medications as indicated below. The IV formulation of these agents must be used in this setting:

- Corticosteroids (dexamethasone 8 mg or equivalent)
- Serotonin (5-HT_3) antagonists (ondansetron 8 mg or equivalent)
- Extended treatment with oral 5-HT_3 antagonists and oral dexamethasone for 2 consecutive days
- If necessary, and in addition to the above, administration of 10 mg of oral or IV metoclopramide (or equivalent) every 8 hours.
- Administration of primary prophylaxis of colony-stimulating factors such as G-CSF or GM-CSF is mandated starting from Cycle 1 and during all subsequent cycles. The type, dose, and scheme to be used may vary according to institutional/standard practices or guidelines. A mandatory window of at least 24 hours and up to 72 hours must be allowed from the last dose of study intervention administration until G-CSF or GM-CSF prophylaxis is started.

6.7. Study Intervention Dose Delay and Reduction Rules

For any treatment delay due to treatment-related AEs lasting more than 1 week, a dose reduction should be implemented upon recovery.

Participants may continue the study treatment at a reduced dose if they present any of the following:

- Grade ≥ 3 treatment-related nonhematological toxicity. Exceptions are Grade ≥ 3 nausea and/or vomiting not optimally treated, Grade 3 asthenia lasting ≤ 3 days, Grade 3 diarrhea lasting ≤ 2 days or not optimally treated, Grade 3 transient ALT/AST elevations that are rapidly reversible and not leading to subsequent delays, and nonclinically relevant biochemical abnormalities
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia concomitantly with Grade ≥ 3 bleeding
- Grade 4 neutropenia, any grade febrile neutropenia or neutropenia associated with infection/sepsis
  - Note: All participants receive mandatory colony-stimulating factors such as G-CSF or GM-CSF starting from Cycle 1 and during all subsequent cycles.

However, if the episode of neutropenia persists despite supportive care with G-CSF or GM-CSF, then the dose must be reduced

- Frequent or prolonged (> 1 week) dose delays due to treatment-related AEs
- Unacceptable toxicity in the judgement of the investigator

Participants who experience Grade ≥ 3 hypersensitivity reactions or Grade ≥ 3 rhabdomyolysis will be discontinued from study intervention.

Dose reduction levels are shown in Table 6.

Table 6: Lurbinectedin Dose Reduction Levels

Dose Reduction	Lurbinectedin Dose (mg/m^2)
1 (starting dose)	3.2
–1	2.6
–2	2.0

Up to 2 dose reductions are allowed per participant. Participants who continue to experience treatment-related toxicity and/or frequent dose delays after permitted dose reductions should be discontinued from the study. However, they can continue receiving the study intervention if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Once the dose has been reduced for an individual participant, it will not be re-escalated under any circumstance.

Participants not meeting criteria for continuation after a maximum of 3-week delay should be discontinued from the study. For delays > 3 weeks, retreatment can be considered on case-by-case basis after discussion with the medical monitor.

Details related to required follow-up laboratory tests to be performed after reporting of specific AEs are presented in Section 8.3.4.

6.8. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.9. Treatment of Overdose, Medication Errors, or Misuse

Overdose (defined as any dose administered or received that was higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study drug), and misuse of the study drug are considered reportable experiences.

There is currently no specific treatment in the event of an overdose with lurbinectedin, and possible symptoms of overdose have not been established. Lurbinectedin must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 14 days.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.10. Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency, and route

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.10.1. Allowed Concomitant Medications

The following medications are allowed during study participation:

- Colony-stimulating factors such as G-CSF or GM-CSF
  - Primary G-CSF or GM-CSF is mandated during the first and all subsequent cycles. The type, dose, and scheme to be used may vary according to institutional/standard practices or guidelines. A mandatory window of at least 24 hours and up to 72 hours must be allowed from the last dose of study intervention administration until G-CSF or GM-CSF prophylaxis is started.
- Therapies for pre-existing and treatment-emergent medical conditions, including pain management
- Blood products and transfusions, as clinically indicated
- Bisphosphonates
- Primary and secondary prophylaxis and/or symptomatic treatment for emesis according to ASCO guidelines for nausea or vomiting (see Section 6.6; Hesketh, 2017)
- Erythropoietin treatment according to ASCO guidelines
- Anticoagulation therapy.

In addition to the above, all treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the

community standards of medical care. All concomitant medication will be recorded in the case eCRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of the medication as per Section 6.10 may also be included in the eCRF.

6.10.2. Prohibited Concomitant Medications

The following medications are prohibited during study participation:

- Any other antineoplastic therapy
- Any other investigational agents
- Immunosuppressive therapies other than corticosteroids for antiemetic prophylaxis and/or pain control
- Aprepitant, fosaprepitant or related compounds (other NK-1 antagonists)
- Radiotherapy

6.10.3. Lurbinectedin Drug-Drug Interactions

In vitro studies with human liver microsomes have shown that CYP3A4 is a major metabolic enzyme involved in lurbinectedin metabolism, followed by CYP2E1, CYP2D6, and CYP2C9. The contribution of other CYP isoenzymes is negligible. Thus, concomitant drugs which induce or inhibit CYP3A4 should be carefully monitored or avoided, whenever possible (Appendix 7). A significant interaction with aprepitant (CYP3A4 inhibitor) is suggested by available lurbinectedin phase 2 data from ovarian cancer patients and a phase 1 Study PM1183-A-008-13 in patients with advanced solid tumors, where lurbinectedin clearance was reduced by 42%, approximately, in the presence of aprepitant and resulted in unusually long-lasting neutropenia, as well as thrombocytopenia with a worse outcome. Although all patients eventually recovered, the use of aprepitant is not permitted.

Based on in vitro study results, lurbinectedin was shown to inhibit CYP2C8, CYP3A4, and CYP2B6. However, according to guidelines from European Medicines Agency and FDA (US), the calculated in vivo impact of lurbinectedin on those CYP isoenzymes was insignificant. Therefore, no potential drug-drug interaction is expected between lurbinectedin and drugs which are metabolized by CYP3A4, CYP2C8, or CYP2B6.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation from study *intervention* does not represent discontinuation from the *study* (Section 7.2). Participants may discontinue from study intervention at any time for any reason, or at the discretion of the investigator. In addition, a participant may be discontinued from study intervention by the investigator or sponsor for safety, behavioral, compliance, and/or administrative reasons. For participants that discontinue study intervention, all effort should be made to complete the procedures listed in the *EOT visit* (Table 3).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will return to the site 30 days (± 7 days) later for an EOT visit, and the participant will be followed for OS. For participants who discontinue treatment due to reasons other than disease progression, death, withdrawal of consent from study, or lost to follow-up, radiographic assessment should continue until disease progression, initiation of new anticancer therapy, death, withdrawal of consent from study, EOT Visit, lost to follow-up, or study termination. A radiological tumor assessment will be performed at the EOT visit for these participants if not performed within 7 days of the last treatment assessment visit. See the SoA (Table 3) for 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.

A participant must be discontinued from study intervention for any of the following reasons:

- The participant requests to discontinue study intervention
- The participant has an AE that may compromise the participant's continued participation (see Section 8.4.3 for follow-up guidelines)
- The participant experiences a Grade ≥ 3 hypersensitivity reaction
- The participant experiences Grade ≥ 3 rhabdomyolysis
- The participant has any of the clinical conditions as noted in Section 6.7, which cannot be resolved with either of the following attempts:
  - The participant requires > 2 dose reductions
  - The participant requires a treatment delay > 3 weeks from the due date because of treatment-related toxicity (except if objective clinical benefit is observed, with the Sponsor's agreement)
- The participant has a positive serum pregnancy test or becomes pregnant during the study (Appendix 5 and Section 8.4.5)
- The participant is noncompliant with study intervention or procedures
- The sponsor decides to terminate the study or an individual cohort for any reason
- The investigator determines the participant should not continue on study intervention

- The participant has confirmed radiological disease progression as per RECIST v1.1

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, or compliance reasons.
- At the time of discontinuing from the study, if possible, an E/D visit should be conducted within 30 days, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
  - The participant will be permanently discontinued from both the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow-up.
  - The rules for handling missing data for an individual participant will be specified in Section 9 and the SAP for the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Study and Site Start and Closure Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be 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 must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator should maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 415 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. General Administrative Procedures

8.1.1. Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant/legal representative prior to participation in this study. A signed copy of the ICF should be given to the participant and the original should be placed in the participant's medical records.

8.1.2. Assignment of Participant Number

Each participant who signs the ICF will be assigned a unique number that will identify the participant throughout the study. Once a number has been assigned, it cannot be reassigned to another study participant. See Section 5.4 for handling of participant numbers for screen failures who are rescreened.

8.1.3. Primary Diagnosis and Prior Treatment

The primary diagnosis and prior treatment(s), including best response and time to progression, if available should be recorded.

8.1.4. Medical History

A medical history will be obtained by the investigator or a medically qualified designee (consistent with local regulations). All active conditions should be recorded and any condition diagnosed within the last 1 year that the investigator deems clinically significant.

8.1.5. Demographics

Demographics will include race, ethnicity, age, and sex.

8.1.6. Medication Review (Prior and Concomitant Medications)

The investigator or medically qualified designee should review the participant's prior medication use within 30 days of the Screening assessment. All medication currently taken by the participant should be recorded.

8.1.7. Inclusion and Exclusion Criteria Review

All inclusion and exclusion criteria should be reviewed by the investigator to ensure the participant qualifies for the study.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA. The efficacy assessments will measure antitumor activity and include:

- ORR, PFS, TTR, DOR, DCR
- OS

Antitumor activity will be assessed by radiological tumor assessments and will be based on RECIST v1.1 criteria.

The details related to tumor assessments are presented in Appendix 8.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. The safety assessments include:

- AEs and SAEs
- Laboratory measurements
- Other laboratory measurement (AAGP)
- Physical examination findings
- Vital signs
- ECG findings

Any clinically significant changes in laboratory findings, PE findings, vital sign measurements, and ECG findings occurring during the study must be reported as an AE.

8.3.1. Physical Examinations

- A complete PE will be conducted according to the SoA (Table 3). Weight will be collected at Day 1 of each cycle. Height will be collected at Screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
  - Any abnormalities identified at the screening PE should be recorded as medical history.
  - Any abnormalities identified after the screening PE should be recorded as an AE.

8.3.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and BP will be assessed per institutional guidelines.
- If not otherwise directed by institutional guidelines, BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.3.3. Electrocardiograms

- A single 12-lead ECG will be obtained as outlined in the SoA (Table 3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (Table 3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with abnormal values considered clinically significant during participation in the study and/or considered by the investigator to be related to study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 3, must be conducted in accordance with the SoA (Table 3).

- Any participants with febrile neutropenia of any grade, Grade 4 neutropenia, and/or Grade 4 thrombocytopenia, should have relevant tests repeated daily until recovery to Grade ≤ 3 and through the day after fever resolution, if applicable.
- For Cycle 3 and after, Hematology and Biochemistry "A" tests on Days 8 and 15 are to be performed only in participants with Grade ≥ 3 biochemical or Grade 4 hematological treatment-related toxicities, or who required dose adjustments due to hematological or biochemical abnormalities in the preceding cycle (Table 3).

8.3.5. Other Laboratory Assessment

Levels of serum AAGP will be assessed.

8.3.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted according to the SoA (Table 3).
- Pregnancy testing (urine or serum as required by local regulations) should be repeated 30 days after last dose of lurbinectedin.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 4.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

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

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the start of intervention until the EOT or E/D visit as specified in the SoA (Table 3) and per Section 8.4.3. Participants' discontinuation from study treatment with an ongoing treatment-related AE should be followed until satisfactory resolution per the investigator. Any spontaneous reporting of treatment-related SAE during the OS follow-up will be also collected and reported.

Note: All SAEs that occur after the consent form is signed but before study intervention/treatment must be reported by the investigator if they cause the participant to be

excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to diet, placebo treatment, or a procedure.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and within 24 hours of first knowledge of the event by study personnel, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. All treatment-related deaths will be reported as SAEs. Deaths due to progression of disease are not SAEs and should not be reported as SAEs.

Investigators are not obligated to actively seek information on new AEs or SAEs after conclusion of the 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 should promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

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.

8.4.3. Follow-up of AEs and SAEs

Adverse events resulting in study termination will be followed to the satisfactory resolution and determination of outcome as ascertained by the investigator.

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). Further information on follow-up procedures is provided in Appendix 4.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE 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, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigator safety reports will be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The RSI for the determination of expectedness of lurbinectedin can be found in the IB (Pharma Mar IB, 2022).

8.4.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 30 days of the last dosing of the study participant.
- If a pregnancy is reported during treatment or within 30 days after the last dose of IP, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- 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.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, 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.

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

The following DREs are common in participants with advanced or metastatic solid tumors:

- Disease progression
- Death

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the

event may meet the definition of an SAE. These DREs will be monitored by a medical monitor on a routine basis.

NOTE: However, if the following condition applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

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

8.4.7. Overdose, Medication Errors, and Misuse

Overdose (defined as any dose administered or received that was higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study drug), and misuse of the study drug are considered reportable experiences. The method for completing and transmitting reports of these experiences are provided in Appendix 4.

If any overdose, medication error, or misuse of the study drug results in an AE, this must be recorded. If the AE is serious, it must also be reported as described in Appendix 4.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

[redacted]

8.6. Genetics and/or Mutational Analyses

- In the HRD-positive malignancies agnostic cohort, blood and (optional) tumor samples may be tested to confirm pre-identified germline and/or somatic mutations.
- In all cohorts, blood may be tested for pathogenic somatic mutations in DNA and/or expression changes in RNA relevant to the mechanism of action of lurbinectedin and to evaluate and association with observed clinical response.
- [redacted]
- Samples may also be used for research to develop methods, assays, prognostics and/or companion diagnostics related to lurbinectedin.

- See Appendix 6 for information regarding genetic research. Details on processes for collection and storage and destruction of these samples can be found in the laboratory manual.

8.6.1. Required Analyses

The following samples will be collected for analysis before lurbinectedin administration in Cycle 1:

- **Homologous recombination deficient-positive malignancies agnostic cohort:**
  - Blood for confirmation of any pre-identified germline and/or somatic pathogenic mutations.
  - Blood for longitudinal mutational analysis.
- **All cohorts:**
  - Baseline blood for mutational analysis.

[redacted]

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This nonrandomized multi-cohort signal finding study will use estimation rather than hypothesis testing to characterize the ORR for each cohort.

9.2. Sample Size Determination

This study is designed to assess the antitumor activity of lurbinectedin in terms of the ORR according to the RECIST v1.1 in 3 different advanced (metastatic and/or unresectable) solid tumors cohorts. This study includes up to a total of 60 participants in the initial assessment of efficacy in which each tumor cohort includes up to 20 participants. If there is evidence of efficacy, enrollment beyond 20 participants in the individual cohort may be considered.

Each cohort will have up to 4 stages: stage 1 at n = 12 and stage 2 at n = 20 for futility testing (see Section 9.5); if a cohort enrolls beyond 20 participants, the study may enroll stage 3 with an interim analysis to assess efficacy at n = 35, and a final stage 4 at n = 100 for the final analysis. If there are ≥ 4 responses (a target of 20% ORR) out of 20 participants in a cohort, the lower bound of 70% CI of ORR (10.5% to 33.4%) will exclude a 10% ORR (Table 7) and the cohort may continue. This will provide approximately 85% confidence that the true ORR rate is > 10%, where a 10% or lower response rate is not clinically meaningful. If there are ≥ 8 responses (22.9% ORR) out of 35 participants in a cohort, the lower bound of 95% CI of ORR (10.4% to 40.1%) will exclude a 10% ORR (Table 8) and the cohort may continue enrollment up to a total of 100 participants. If there are ≥ 20 responses (20% ORR) out of 100 participants in a cohort, the lower bound of 95% CI of ORR (12.7% to 29.2%) will exclude a 10% ORR (Table 8).

Table 7: Two-sided, Exact CI of ORR Under Varying Scenarios for n = 20

Sample Size	No of Responders	Observed ORR (%)	70% CI of ORR (%)	80% CI of ORR (%)	90% CI of ORR (%)	95% CI of ORR (%)
	4	20	(10.5, 33.4)	(9.0, 36.1)	(7.1, 40.1)	(5.7, 43.7)
	5	25	(14.4, 38.8)	(12.7, 41.5)	(10.4, 45.6)	(8.7, 49.1)
	6	30	(18.5, 44.0)	(16.6, 46.7)	(14.0, 50.8)	(11.9, 54.3)
	7	35	(22.8, 49.1)	(20.7, 51.8)	(17.7, 55.8)	(15.4, 59.2)
	8	40	(27.2, 54.1)	(24.9, 56.7)	(21.7, 60.6)	(19.1, 63.9)

Abbreviations: CI = confidence interval; ORR = objective response rate.

Table 8: Two-sided, Exact CI of ORR Under Varying Scenarios for n = 35 and n = 100

Sample Size	No of Responders	Observed ORR (%)	95% CI of ORR (%)
35	7	20.0	(8.4, 36.9)
	8	22.9	(10.4, 40.1)
	9	25.7	(12.5, 43.3)
100	18	18.0	(11.0, 26.9)
	19	19.0	(11.8, 28.1)
	20	20.0	(12.7, 29.2)

Abbreviations: CI = confidence interval; ORR = objective response rate.

9.3. Analysis Sets

Participant Analysis Set	Description
Enrolled	All participants who sign the informed consent form
Safety	All participants who take at least 1 dose of study treatment. This is the primary set for safety analyses
Efficacy-evaluable	Participants in the Safety analysis set with measurable disease at baseline and one of the following: (a) at least 1 post-baseline evaluable tumor assessment, (b) clinical progression, or (c) death
[redacted]	[redacted]
[redacted]	[redacted]

9.4. Statistical Analyses

The SAP will be finalized prior to DBL, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

The primary analysis is planned to take place when the last enrolled participant in a cohort has had 6 months of treatment and follow up. The primary analysis may be performed separately for each cohort based on enrollment.

9.4.1. General Considerations

9.4.1.1. Definition of Study Periods for Analysis

9.4.1.1.1. Baseline

Baseline evaluations (eg, disease assessments, laboratory tests, vital signs, and ECOG performance status) will be defined as evaluations with a date on or prior to the date of first dose of study intervention. If there are multiple valid observations in the Screening Period, then the latest non-missing observation on or before the first dose of study intervention will be used as the baseline in the analyses.

Detailed instructions for assigning baseline values will be given in the SAP.

9.4.1.1.2. Post-baseline

Post baseline evaluations will be defined as evaluations taken after the date of the first dose of study treatment.

The post-baseline period is further characterized into a treatment period, a 30-day safety follow-up period after the last dose of study treatment, and an OS Follow-up Period.

Treatment-emergent adverse events are defined as AEs with an onset date on or after the date of the first dose of study treatment. An AE is a TEAE if it occurs up to 30 days after the last dose of study intervention. TEAEs can be pre-treatment AEs that worsen in CTCAE grade after the start of study treatment.

9.4.1.2. Statistical Methods

The efficacy analyses will be performed on the Efficacy-evaluable analysis set, separately for each cohort. The safety analyses will be performed on the Safety analysis set.

Unless otherwise noted, discrete measurements will be tabulated by the frequency and proportion of participants falling into each category within each cohort. Continuous measurements will be summarized using the sample size, mean, standard deviation, median, minimum, and maximum values for each cohort.

Time-to-event measurements will be summarized using K-M estimates. This will be done for the following endpoints: TTR, DOR, PFS, and OS. The TTR will also be analyzed using summary statistics such as mean, standard deviation, median, minimum, and maximum values. Median survival time will be reported along with 95% CIs constructed based on a log-log transformed CI for the survivor function (Brookmeyer, 1982). Rates at fixed times (3, 6, 9, and 12 months) will be derived from the K-M estimates if the data allow, and the corresponding CIs will be calculated based on Greenwood formula for variance derivation and on a log-log transformation applied to the survivor function (Greenwood, 1926; Kalbfleisch, 1980).

9.4.1.3. Dropouts and Missing Data

9.4.1.3.1. Imputation of Non-date Missing Data

Data used for evaluating efficacy and safety endpoints may be missing for technical reasons (eg, unreadable scan, participant missed appointment).

The primary efficacy analysis will be performed on the Efficacy-evaluable analysis set in this study. For participants without any post baseline disease assessment, the response of this participant will be imputed as non-responder for sensitivity analyses of ORR in the Safety analysis set.

Participants with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes."

The details of analyses with missing data will be specified in the SAP.

9.4.1.3.2. Imputation of Partial Dates

Imputed dates will not be used to derive study day or duration. In addition, imputed dates are not used for deriving the last contact date for OS. Imputed dates will be displayed in listings and identified as imputed.

AEs with partial dates will have imputed dates used to identify treatment emergent AEs and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is completely missing, then the duration of the AE will be set to missing.

Algorithms for imputing partial dates will be provided in the SAP.

9.4.2. Primary Endpoint(s)

Best overall response is defined as the best response recorded between the date of first dose and the date of objectively documented progression per RECIST v1.1, or the date of subsequent anticancer therapy, death due to any cause, loss to follow-up, or study discontinuation, whichever occurs first. BOR will be determined programmatically in the analysis of the study results.

The ORR is defined as the proportion of participants whose BOR is investigator-assessed confirmed CR or PR using the RECIST v1.1 criteria. ORR will be summarized by a binomial response rate for each cohort and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method (Clopper, 1934).

9.4.3. Secondary Endpoint(s)

The investigator-assessed objective response will be further characterized by the TTR and DOR. DOR and TTR will be evaluated for responders (confirmed CR and PR) only.

TTR is defined as the time from first dosing date to the date of the first confirmed response (CR or PR), as assessed by the investigators.

Duration of response is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST v1.1 criteria or death due to any cause, whichever occurs first.

The below censoring rules are applicable to both DOR and PFS. Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who started a new anticancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment on or prior to the initiation of first subsequent anticancer therapy. Participants who are lost to follow-up or discontinued from the study without a prior reported progression and without start of subsequent anticancer therapy will be censored on the date of their last evaluable tumor assessment on or prior to the date of loss to follow-up or study discontinuation.

PFS is defined as the time from the first dosing date to the date of first documented disease progression or death due to any cause, whichever occurs first. Participants who did not have any on-study tumor assessments and did not die will be censored on their first dosing date. If a participant is to permanently discontinue study intervention before disease progression, the participant will be followed for survival by telephone visits every 3 months.

The DCR is define as the proportion of participants whose BOR is confirmed CR, or PR, or stable disease using the RECIST v1.1 criteria. The point estimate and 95% CI of DCR will be calculated using the same method as the primary endpoint ORR.

Overall survival is defined as the time from the first dosing date to the date of death from any cause. A participant who has not died will be censored at the last known alive date.

9.4.4. Safety Analyses

All safety analyses will be performed on the Safety analysis set.

9.4.4.1. Adverse Events

Adverse events will be coded using MedDRA to classify events under primary system organ class and preferred term; the severity will be graded using the NCI CTCAE v5.0.

The number and percentage of participants who experienced TEAEs, treatment emergent SAEs, TEAEs by maximum severity, TEAEs leading to discontinuation of study drug, Grade 3 and 4 TEAEs, treatment-related TEAEs, treatment-related SAEs, treatment-related TEAEs leading to discontinuation of study drug, treatment-related Grade 3 and 4 TEAEs, and Grade 5 TEAEs will be summarized using the Safety analysis set. Results will be presented by SOC and preferred term, or preferred term only. Summary will be separate and in an overview.

All deaths will be summarized and listed.

For all AE summaries, if a participant has more than 1 AE within a preferred term, the participant is counted only once at the maximum severity and with the closest relationship to study drug. If a participant has more than 1 AE within a SOC, the participant is similarly counted once when reporting results for that SOC.

All AE data will be listed. Listing of AEs will include all enrolled participants as pretreatment SAEs and deaths are collected. The information presented will include participant number,

primary SOC and preferred term, date of onset, severity, relationship to study drug, action taken, and stop date (if available).

9.4.4.2. Vital Signs, Clinical Laboratory Results, and ECOG Performance Status

Vital signs, clinical laboratory results, and ECOG performance status measures will be summarized and listed.

9.4.4.3. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary and will be summarized using descriptive statistics.

[redacted]

9.5. Interim Analysis

Review of the safety and efficacy data will be performed by the sponsor on an ongoing basis in this study. Assessment of the observed responses will be performed after enrollment of approximately 12 and 20 efficacy-evaluable participants for treatment benefit. If no confirmed response per RECIST v1.1 is observed in approximately the first 12 evaluable participants of a cohort, the recruitment of participants in that cohort will be stopped. If there are ≤ 3 confirmed responses in the first 20 evaluable participants of a cohort, the recruitment of participants in the cohort will be stopped. There will be no pause in enrollment during the interim analysis of the first 12 evaluable participants of a cohort, and the futility boundary will be adjusted based on the actual number of participants at each stage.

Interim futility monitoring will be implemented through the BPP approach with the prior distribution for ORR assumed to be Beta (0.5, 0.5). Table 10 has the operating characteristics for futility of stopping at 12 and 20 participants. If no response is observed in the first 12 participants of a cohort, there is an 89% posterior probability that the actual response rate is

no more than 10%. If there are ≤ 3 responses in the first 20 participants of a cohort, there is a 70% posterior probability that the actual response rate is no more than 20%.

Table 10: Posterior Probability for Interim Futility Monitoring

No Participants	Futility Stopping	Prob (ɵ≤10%|r, n)	Prob (ɵ≤15%|r, n)	Prob (ɵ≤20%|r, n)
12	0	89%	95%	98%
20	1	76%	91%	97%
20	2	46%	72%	87%
20	3	21%	47%	70%

ɵ = True response rate; r = the observed responses; n = the number of participants

The SAP will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator, reviewed and approved by the IRB/IEC, and submitted to the national regulatory authority (as applicable), before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval and submission to the national regulatory authority before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must 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 must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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

[redacted]

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Safety Monitoring

Throughout the study, the sponsor will perform safety assessments of all enrolled participants on an ongoing basis. A thorough evaluation of the safety and efficacy will be performed after enrollment of the first 12 participants to determine whether to continue or stop a cohort.

10.1.6. Dissemination of Clinical Study Data

As the sponsor of the study, Jazz Pharmaceuticals is solely responsible for disclosing results on ClinicalTrials.gov, EudraCT, and other public registries in accordance with applicable global laws and regulations. By signing this protocol, the investigator acknowledges that all posting requirements are solely the responsibility of the sponsor, and agrees not to submit any information about the study or its results.

10.1.7. Data Quality Assurance

- Investigators and site staff will be trained on protocol procedures and eCRF completion prior to enrolling participants in the study.
- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy are described in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or institution/site as applicable, for the period of time established in the clinical study agreement entered into by the investigator's study site unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the first participant has the first study-related procedure (typically signing the ICF).

10.1.9.2. Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been accounted for and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient 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 but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- 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 at least 30 days prior to submission. This allows the sponsor to protect proprietary information and to provide comments. In addition, this allows the sponsor to protect the publication rights of other investigators in multicenter trials.
- The sponsor will comply with the requirements for publication of study results. In accordance with 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 mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 1. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Description
AAGP	alpha-1 acid glycoprotein
ADC	antibody-drug conjugate
AE	adverse event
ANC	absolute neutrophil count
BP	blood pressure
BOR	best overall response
BPP	Bayesian Posterior Probability
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPI	checkpoint inhibitor
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBL	database lock
DCR	disease control rate
DOR	duration of response
DRE	disease-related event
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Description
eCRF	electronic case report form
E/D	early discontinuation
EOS	end-of-study
EOT	end of treatment
EU	European Union
EV	enfortumab vendotin
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GCT	germ cell tumor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRD	homologous recombination deficient
HR-DDR	homologous recombination deficient DNA damage repair
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
K-M	Kaplan-Meier
LCNET	large cell neuroendocrine tumor

Abbreviation	Description
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEC	neuroendocrine carcinoma
NET	neuroendocrine tumor
[redacted]	[redacted]
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PARP	poly-ADP ribose polymerase
PARPi	poly-ADP ribose polymerase inhibitor
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PD-NEC	Poorly differentiated neuroendocrine carcinoma
PE	physical examination
PFS	progression-free survival
[redacted]	[redacted]
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
Q3W	every 3 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SoA	Schedule of Activities

Abbreviation	Description
SUSARS	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TTR	time-to-response
UC	urothelial cancer
US	United States
USPI	United States Prescribing Information
WOCBP	woman of childbearing potential

APPENDIX 2. REFERENCES

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Zepzelca (lurbinectedin) for injection, for intravenous use. US Prescribing Information. Jazz Pharmaceuticals Inc. CA, US. April 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213702s004lbl.pdf.

APPENDIX 3. CLINICAL LABORATORY TESTS

- The tests detailed in Table 11 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters		
Hematology	Platelet Count	White blood cell count with differential: Neutrophils Lymphocytes Monocytes	
	Red blood cell Count		
	Hemoglobin		
	Hematocrit		
Biochemistry-A	Serum electrolytes (Na^+, K^+, Cl^-)	AST/ALT	GGT
	AP[a]	Total bilirubin (and direct if total is > 1.5 × ULN)	LDH
	Creatinine	CPK	Glucose (random)
Biochemistry-B	Albumin	Total proteins	Ca^{++} Mg^{++}
Coagulation	PT/INR	PTT	
Pregnancy testing	Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential)		
Other Screening Tests	Serology[b] (HIV antibody, HBsAg, and hepatitis C virus antibody)		

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphokinase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAg = hepatis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

[a] If alkaline phosphatase is elevated, consider fractionating.

[b] All participants will be tested for HIV prior to the inclusion enrollment into the study and HIV-positive participants will be excluded from the study. Participants with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Participants with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible; HBV DNA should be obtained in these participants prior to randomization. Participants with HCV will be excluded from the study; participants who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

Investigators must document their review of each laboratory safety report.

APPENDIX 4. AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: 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.

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 (ie, 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 intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, 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.

Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
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.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (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 should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

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 (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the SAE required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- 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.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only
  - Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  - Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. An AE/SAE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
  - Life-threatening: life-threatening consequences; urgent intervention indicated.
  - Fatal: death related to AE
- When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- Adverse events will be classified by the investigator using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0. A copy of this version can be downloaded from the cancer therapy evaluation program at http://ctep.cancer.gov. If the CTCAE grade is not specified for a particular event or if the event term does not appear in the CTCAE, general guidelines are provided for grading the AE in the table below.

Grade	Symptoms
1	Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate, minimal local or noninvasive intervention indicated; limiting, age-appropriate instrumental activities of daily living (ADL[a])
3	Severe or medically significant but not immediately life threatening; hospitalization or

	prolongation of hospitalization indicated; disabling limiting self-care ADL[b].
4	Life threatening consequences; urgent intervention indicated
5	Death related to adverse event

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothing, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing and undressing, self-feeding, using the toilet, taking medications, and not bedridden.
Note: a semicolon indicates "or" within the description of the grade.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an 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 is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor (or designee) 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.

Follow-up of AEs and SAEs
• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor a copy of any post-mortem findings including histopathology report, if performed. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to sponsor or designee via a Data Collection Tool
• SAEs must be reported to the sponsor (or designee) using an SAE Reporting system within 24 hours of first knowledge of the event by study personnel. • The site will enter the SAE data into the SAE reporting system as soon as it becomes available. • Details regarding the SAE Reporting system, instructions on completion, and contact information can be found in the Investigator trial binder. • The SAE Reporting should be completed as much as possible before transmittal. • Contacts for SAE reporting can be found in the Investigator trial binder.

APPENDIX 5. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

          Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
    - If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]

• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual 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 and the preferred and usual lifestyle of the participant.

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

APPENDIX 6. GENETICS

Use/Analysis of DNA

- Inclusion in the HRD-positive malignancies agnostic cohort requires a pre-identified germline and/or somatic pathogenic mutation. Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease.
- DNA samples from blood will be used for confirmation of any pre-identified germline and/or somatic pathogenic mutations. They may also be used to develop tests/assays including diagnostic tests related to lurbinectedin's mechanism of action.
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to lurbinectedin or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses will be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on lurbinectedin continues but no longer than 15 years or other period as per local requirements.

APPENDIX 7. CYP3A INHIBITORS AND INDUCERS

Table 12: Examples of Clinical Inhibitors for P450-mediated Metabolisms (for Concomitant Use Clinical DDI Studies and/or Drug Labeling) (03/06/2020)

Endpoint	Strongest Inhibitors (≥ 10-Fold Increase)	Strong Inhibitors (< 10 to ≥ 5-Fold Increase)	Moderate Inhibitors (≤ 2 to <5-Fold Increase)	Weak Inhibitors (≥ 1.25 to < 2-Fold Increase)
Inhibitors				
CYP3A4	boceprevir, cobicistat[a], danoprevir and ritonavir[b], elvitegravir and ritonavir[b], grapefruit juice[c], indinavir and ritonavir[b], itraconazole[a], ketoconazole, lopinavir and ritonavir[a,b], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b], posaconazole, ritonavir[a,b], saquinavir and ritonavir[a,b], telaprevir[a], tipranavir and ritonavir[a,b], telithromycin, troleandomycin, voriconazole	Clarithromycin[b], idelalisib, nefazodone, nelfinavir[a]	aprepitant, ciprofloxacin, conivaptan[d], crizotinib, cyclosporine, diltiazem[e], dronedarone[a], erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil[a]	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor[a], lomitapide, ranitidine, ranolazine[a], ticagrelor[a]
Inducers				
Endpoint	**Strong Inducers (≥80%)**		**Moderate Inducers (≥50% to <80%)**	**Weak Inducers (≥20% to <50%)**

CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[f]	bosentan, efavirenz, etravirine, phenobarbital, primidone	armodafinil, modafinil[g], rufinamide

Abbreviations: AUC = area under the concentration-time curve.
This table is prepared to provide examples of clinical inhibitors and inducers and is not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].
[a] Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥ 1.25-fold).
[b] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
[c] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
[d] The classification is based on studies conducted with intravenously administered conivaptan.
[e] Diltiazem increased AUC of certain sensitive CYP3A substrates (eg, buspirone) more than 5-fold.
[f] The effect of St. John's wort varies widely and is preparation-dependent.
[g] Based on effect of 200 mg/day modafinil. A higher dose (400 mg/day) modafinil had larger induction effect on CYP3A.
Source: FDA Drug Development and Drug Interactions: Table of Substrates Inhibitors and Inducers 2020

APPENDIX 8. TUMOR ASSESSMENTS GUIDELINES

The full RECIST version 1.1 guideline is contained in the following:

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009 Jan 1;45(2):228-47.

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Bone scans or 18-Fluorodeoxyglucose Positron Emission Tomography (18FDG-PET) and brain CT or MRI scans are also required at baseline (28-day screening period) if brain metastasis is suspected or if participants have symptoms of brain metastasis except in patients with lung cancer. All patients with lung cancer will require brain scan.

Bone lesion(s) identified at baseline by bone scan will be further assessed by CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by CT or MRI as per the tumor assessment schedule as an alternative to bone scans. Bone scans will only be repeated during study as clinically indicated (eg, participant describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), at the time of CR confirmation, and at every other tumor assessment visit (every 12 weeks) if considered local standard of care.

MRI brain scans must be included in subsequent tumor assessments if a participant has brain metastases at baseline; otherwise, brain will be evaluated only when clinically indicated.

CR and PR must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. For equivocal findings of progression (eg, 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. In the absence of clinical deterioration, participants with PD can remain on the current study treatment until PD is confirmed by subsequent scan at PI's discretion.

Baseline and all scans performed for treatment evaluation will be collected and stored for future evaluation if a cohort or cohorts for further expansion and/or regulatory submission. Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless an increase in size has been observed following completion of radiation therapy.

The same radiographic procedure used to assess disease sites at screening should be used throughout the study (eg, the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 criteria. The same evaluator, if possible, should perform assessments to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

If a participant starts a new anticancer therapy before documented disease progression, then tumor assessments should be continued per the SoA (if feasible) until documentation of disease progression or death, whichever occurs first.

APPENDIX 9. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01: 12 August 2021

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The overall rationale for the changes in this protocol amendment was to include Agency-requested feedback. Following is a list of important changes in Amendment 01; editorial changes are not included in this list.

Section # and Name	Description of Change	Brief Rationale
5.1/Inclusion Criteria, Disease Characteristics for Each Cohort; Criterion 9a; Criterion10a	Added “advanced (metastatic and/or unresectable)”	To provide additional clarity that participants in all cohorts must have advanced disease
5.1/Inclusion Criterion 11a	Changed “...pancreas or gastric/esophageal solid tumors” to “...pancreas, gastric, or esophageal solid tumors”	To provide additional clarity
5.1/Inclusion Criterion 11b	Changed “no more than 3 prior lines of systemic therapies” to “no more than 3 prior lines of chemotherapy” and updated the supporting text for this criterion	To allow hormone therapies, targeted therapies, and/or other biological agents
6.7/Study Intervention Dose Delay and Reduction Rules	Deleted “and any grade febrile neutropenia” as a reason participants may continue with secondary G-CSF prophylaxis instead of dose reduction	For alignment with the approved Lurbinectedin USPI

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[redacted]
Signer Name: [redacted]
Signing Reason: I approve this GxP document
Signing Time: Oct-06-2022 | 2:23 PM PDT
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