Title: A PHASE II PILOT CLINICAL TRIAL OF LURBINECTEDIN (ZEPZELCA™ PM01183) IN PATIENTS WITH ADVANCED GASTROINTESTINAL MALIGNANCIES WITH DNA REPAIR MUTATIONS

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A PHASE II PILOT CLINICAL TRIAL OF LURBINECTEDIN (ZEPZELCA™ PM01183) IN PATIENTS WITH ADVANCED GASTROINTESTINAL MALIGNANCIES WITH DNA REPAIR MUTATIONS

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IND Exempt 160388

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INVESTIGATOR'S PROTOCOL AGREEMENT

Protocol No.: HRI-Lurbinectedin-001

Study Title: A Phase II Pilot Clinical Trial of lurbinectedin (Zepzelca™ PM01183) in Patients with Advanced Gastrointestinal malignancies with DNA Repair Mutations

Version Date: Version 4.0 June 11, 2024

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the study specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on Form FDA 1572 and on other document(s) required by local regulatory authority.
- Retain records and documents related to this trial for at least 7 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 7 years have elapsed since the formal discontinuation of clinical development of the investigational products.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of HonorHealth Research Institute (HRI), and Jazz Pharmaceuticals confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB informed of adverse events and periodically report the status of the study to them.
- Not implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the trial has read, understands, and has signed the Informed Consent.
- Ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths (within 1 business day of learning of the death and 2 business days of learning of the SAE) to HRI as indicated in Section 7 of the protocol.
- Assure access to study monitors.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- Cooperate fully with any study-related GCP audit as performed by quality assurance group specified by the sponsor.
- Abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the study.

Investigator's Printed Name: _____

Investigator's Signature: _____ Date: _____

SAE REPORTING

All SAEs must be reported via Medwatch Form 3500A along with the SAE Report Form Cover letter promptly to HRI Drug Safety after the Investigator recognizes/classifies the event as a SAE.

For life-threatening or fatal events, the Investigator must report initial information on the SAE **within 1 business day** of becoming aware of the event, preferably by email or alternatively by fax or email (Refer to protocol section 7.9 Investigator Reporting Serious Adverse Events).

All SAEs including life-threatening and death, regardless of the causal relationship to study drug must be reported via Medwatch Form 3500A promptly to Jazz Pharmaceuticals within 1 business day after received by study sponsor.

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List of Abbreviations	
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (SGPT)
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Aminotransferase (SGOT)
ATM	Ataxia-Telangiesctasia Mutated
ATR	ataxia telangiectasia and Rad3-related kinase
ARID1A	Adenine-thymine (AT)–rich interactive domain-containing protein 1A
β-hCG	Beta subunit of human chorionic gonadotrophin (hCG)
BPI	Brief Pain Inventory
BRCA1	BReast CAncer gene 1
BRCA2	BReast CAncer gene 2
BRIP1	BRCA1 interacting protein C-terminal helicase 1
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA-125	Cancer antigen 125
CA19-9	Carbohydrate antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CHEK2	CHK2 checkpoint homolog
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Hanzel
CNV	Copy Number Variants
CNS	Central Nervous System
CRF	Case Report Form
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
EMSY	EMSY
FANC	Fanconi anaemia complementation group
FDA	Food and Drug Administration
^{18}F-FDG	Fluorine-18 Fluoro-D-Glucose
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factors
HIPPA	Health Insurance Portability and Accounting Act
HIV	Human Immunodeficiency Virus
HRI	HonorHealth Research Institute
HUS	Hemolytic Uremia Syndrome

List of Abbreviations	
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
KPS	Karnofsky Performance Status
LD	Longest Diameter
MDASI	MD Anderson Symptom Inventory
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MRE11	Meiotic recombination 11
Nab	Nanoparticle albumin bound
NBN	nibrin
NCI	National Cancer Institute
NRS	Numeric Rating Scale
NS	Normal Saline
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PALB2	Partner and localizer of BRCA2
PD	Progressive Disease
PDA	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
PO	Orally
PR	Partial Response
PTEN	phosphatase and tensin homolog
QC	Quality Control
RAD51	Restriction-site associated DNA
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamate Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvic Transaminase
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SPARC	Secreted Protein Acidic and Rich in Cysteine
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGen	Translation Genomic Research Institute
ULN	Upper Limit of Normal
WBC	White Blood Cells

TRIAL SYNOPSIS

Title and No: A Phase II Pilot Clinical Trial of lurbinectedin (Zepzelca™ PM01183) in Patients with Advanced Gastrointestinal malignancies with DNA repair Mutations
Protocol # HRI-Lurbinectedin-001
IND Exempt 160388
Version 3.0 dated November 14, 2023

Sponsor: HonorHealth Research Institute, 10510 N. 92nd Street Scottsdale, AZ 85258
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Clinical Phase: Phase II

Objectives:

Primary: To evaluate the antitumor activity of lurbinectedin in terms of overall response rate (ORR), according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, in patients with advanced gastrointestinal malignancies with DNA repair mutations.

Secondary:

1. To assess the duration of response (DOR) and the clinical benefit (defined as patients with response or stable disease [SD] ≥ 4 months)
2. To determine the evolution of tumor markers (e.g., CA19-9, CEA, or CA125, whichever is being followed) during treatment
3. To determine the progression-free survival (PFS) and the progression-free survival rate at three months (PFS3)
4. To determine the overall survival (OS) and the overall survival rate at six and 12 months (OS6 and OS12)
5. To explore the antitumor activity of lurbinectedin according to clinical parameters (e.g., patient or disease characteristics, prior therapy, etc.) and genomic/molecular parameters (whole exome) if they were obtained as part of their prior care
6. To evaluate the safety profile of this lurbinectedin administration schedule (Day 1 every three weeks [q3wk]) in this patient population, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5)

Trial Design: Open-label, single arm, phase II study

No. Patients: Total of nineteen (19) evaluable (e.g. received at least 1 dose of lurbinectedin and a baseline and follow up scan) patients in the selected dose for efficacy with advanced gastrointestinal malignancies with DNA repair mutations will be enrolled.

Investigational Product: lurbinectedin (Zepzelca™ PM01183)

Formulation: lurbinectedin drug product (DP) is presented as a lyophilized powder for concentrate for solution for infusion in 4 mg vials, which will be supplied by Jazz Pharmaceuticals for the purposes of this study.

Before use, the 4 mg vial should be reconstituted with 8 mL of sterile water for injection, USP, to give a solution containing 0.5 mg/mL lurbinectedin. For administration to patients as an intravenous (IV) infusion, reconstituted vials should be diluted either with dextrose 50 mg/mL (5%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion.

The full composition of the lurbinectedin 4 mg vials and the reconstituted solution per mL is shown in Table S1.

Table S1. Composition of lurbinectedin vials.

Component	lurbinectedin 4 mg	Concentration per vial after reconstitution
lurbinectedin	4.00 mg	0.50 mg/mL
Sucrose	800.00 mg	100.00 mg/mL
Lactic acid	22.08 mg	2.76 mg/mL
Sodium hydroxide	5.12 mg	0.64 mg/mL

Administration: Intravenously (IV) as a one-hour infusion.

lurbinectedin will be administered with a minimum total volume of 100 mL of solution for infusion (either on 5% dextrose or 0.9% sodium chloride) through a central catheter or over a minimum total volume of 250 mL if through a peripheral line, always over one hour (±10 min) at a fixed infusion rate.

Dose and Schedule:

lurbinectedin 3.2 mg/m2 will be administered IV on Day 1 q3wk (three weeks ± 48 hours = one treatment cycle). BSA will be calculated according to standard practice at each center.

lurbinectedin intravenously as a 1 hour (±10 min) infusion on Day 1 q3wk through peripheral or central lines at a dose of 3.2 mg/m2 will be administered.

A lower lurbinectedin starting dose of 2.6 mg/m2 may be implemented after six treated patients, in case of severe related toxicities (according to dose reduction criteria) are observed in more than 33% of patients in the first two cycles. In that circumstance, decision will be taken upon agreement with the Sponsor and Investigators.

Doses will have to be recalculated for patients showing a ≥ 10% variation in total body weight from baseline or from last dose adjustment.

Granulocyte colony-stimulating factors (G-CSFs) prophylaxis:

Patients will receive secondary prophylaxis subcutaneously with G-CSFs if indicated. Filgrastim subcutaneous dose of 5 µg/kg/day for 5 days is the preferred option, although other agent can be used [type, dose and time will be used according to American Society of Clinical Oncology (ASCO) guidelines]. G-CSFs prophylaxis should start at least 24 hours after lurbinectedin infusion

Antiemetic prophylactic medication:

All patients will receive standard antiemetic prophylaxis before each treatment infusion, as follows:

- Intravenous corticosteroids (dexamethasone 8 mg, or equivalent, or at institutional antiemetic doses).
- Intravenous serotonin (5-HT3) antagonists (ondansetron 8 mg or equivalent).

Apart from the mandatory prophylaxis described above, it is recommended that patients continue treatment with corticosteroids and 5-HT3 antagonists for at least three days. Nevertheless, depending on the patient's condition or the tolerability of the study treatment, antiemetic regimen

or agents (other than those described above), dose, and time could be modified according to the Investigator's criteria.

If necessary and in addition to the above, any of the following could apply:

- Administration of 10 mg of metoclopramide (or equivalent) every eight hours.
- Olanzapine 10 mg orally daily (Day 1-4).

Note: Aprepitant and equivalent agents (e.g., fosaprepitant) are forbidden in patients treated with lurbinectedin.

Patient Population: Adult patients with advanced gastrointestinal malignancies with DNA repair mutations at study entry

Duration of Study: The total duration of the study will be approximately 26 months.

Planned start date (first patient on study): Third quarter 2022.
Planned enrollment period: 24 months.
Planned end-of-study date (clinical cut-off): estimated to occur about 12 months after the last evaluable patient is enrolled.

Duration of Treatment

Patients will be individually evaluated at scheduled visits in three study periods:

- **Screening:** From signature of the informed consent to first infusion of lurbinectedin.
- **Treatment:** From the first infusion of lurbinectedin to **end of treatment** (EOT). EOT is defined as 30 days (± 7 days) after the date of lurbinectedin last administration, unless the patient starts a new antitumor therapy or dies within those 30 days, in which case the date of administration of this new antitumor therapy or the date of death will be considered as EOT.
- **Follow-up:** after EOT, patients will be followed every four weeks until recovery to at least grade 1 or stabilization of symptoms of all treatment-related adverse events (AEs), if any, or until start of a new antitumor therapy. Patients who finish treatment without disease progression will be followed every six weeks until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. A (±)1-week window is allowed for tumor assessments during follow-up. After disease progression is documented or a new antitumor therapy is started, patients will be followed at least every three months until death of any cause or date of study termination, whichever occurs first. For the purpose of collecting information on patient's survival exclusively, a documented telephone call would be acceptable. Information about further therapies will be collected during this follow-up period.

Patients will be considered to be **on-study** from the signature of the ICF until death or study termination. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of EOT, immediately before the start of the follow-up period.

Patients will receive the study treatment while it is considered to be in their best interest. Specifically, treatment will continue until:

- Disease progression.
- Unacceptable toxicity (except in case of clear clinical benefit, with the Sponsors' approval), after appropriate dose reduction.
- Intercurrent illness of sufficient magnitude to preclude safe continuation of the study.
- Patient refusal (follow-up has to be continued for those patients who refuse treatment, but do not withdraw consent). Non-compliance with the study requirements.
- Investigator's decision.
- Protocol deviation with an effect on the management of the patient's risk/benefit ratio.
- Treatment delay >3 weeks from the treatment due date (except in case of clear clinical benefit, with the Sponsors' approval).

- Requirement of >2 dose adjustments.
- Clinical cutoff. Patients could continue treatment under compassionate use agreement after study termination.

Endpoints:
Primary: Overall response rate (ORR), according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1

Secondary:

- Duration of response (DOR), defined as the time from the date when the response criteria (PR or CR) are fulfilled to the date of PD, recurrence or death.
- Clinical benefit, defined as the percentage of patients with ORR or SD ≥4 months, according to RECIST v.1.1.
- CA19-9, CEA, or CA125 (whichever is being followed) evolution during treatment.
- Progression-free survival (PFS), defined as the time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation.
- Progression-free survival rate at three months (PFS3), defined as the percentage of patients who are alive and progression-free three months after the first infusion.
- Overall survival (OS), defined as the time from the date of first infusion to the date of death (of any cause) or last patient contact.
- Overall survival rate at six months (OS6), defined as the percentage of patients who were alive six months after the first infusion
- Overall survival rate at 12 months (OS12), defined as the percentage of patients who were alive 12 months after the first infusion
- Treatment safety: AEs, serious AEs (SAEs) and laboratory abnormalities graded according to the NCI-CTCAE v.5.
- Pharmacogenomic analysis in tumor samples

Inclusion criteria:

1. Voluntary written informed consent form (ICF) of the patient obtained before any study-specific procedure.
2. Age ≥ 18 years of age; male or female.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤1
4. Histologically or cytologically confirmed gastrointestinal carcinoma
5. Locally advanced unresectable or metastatic disease at study entry
6. Known deleterious or suspected deleterious (or equivalent interpretation) mutations in DNA repair in ATM, ATR, CHEK2, BRCA1, BRCA2, RAD51, BRIP1, PALB2, PTEN, FANC, NBN, EMSY, MRE11, or ARID1A prior to study entry
7. Progressive disease to prior treatment. Patients no longer able to continue prior treatment due to intolerable toxicity may be considered for study participation provided that radiology assessment confirms either stable disease or disease progression (i.e., no response to treatment).
8. Measurable tumor lesions according to RECIST 1.1 criteria.
9. Adequate hematological, renal, metabolic and hepatic function, defined as:
    a. Hemoglobin ≥9 g/dL (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥1.5 x 10^9/L, and platelet count ≥100 x 10^9/L.
    b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 x upper limit of normal (ULN).
    c. Total bilirubin ≤ ULN.

d. Albumin ≥3.0 g/dL.
e. Calculated creatinine clearance (CrCL) ≥30 mL/min (according to the Cockcroft and Gault´s formula).

11. Washout periods prior to Day 1 of Cycle 1:
    a. At least three weeks since last prior chemotherapy and/or investigational drugs'.
    b. At least four weeks since the last radiotherapy (RT) > 30 Gy.
    c. At least two weeks since the last palliative RT (≤ 10 fractions or ≤ 30 Gy total dose).
12. Patients with prior malignancy successfully treated who are currently stable and on no active treatment are eligible.
13. Recovery to grade ≤1 from any adverse event (AE) derived from previous anticancer treatment (excluding alopecia and/or skin toxicity of any grade and grade ≤2 peripheral neuropathy) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.5).
14. Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure* during the trial and up to six weeks after treatment discontinuation, and fertile male patients with WOCBP partners must agree to refrain from fathering a child or donating sperm during the trial and up to four months after treatment discontinuation.

*Effective methods: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence.

Exclusion criteria:

1. Prior treatment with lurbinectedin or trabectedin
2. Neuroendocrine differentiation subtype in histology
3. Known brain metastases or leptomeningeal disease involvement
4. Concomitant diseases/conditions:
   a. History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrollment; or pain history of left ventricular ejection fraction (LVEF) ≤ 50% assessed by multiple-gated acquisition scan (MUGA) or equivalent by ultrasound (US); or symptomatic arrhythmia.
   b. Generalized edema, and/or ascites clinically evident or requiring drainages within three weeks prior to study entry. Permanent external drainages due to ascites are also excluded.
   c. Immunocompromised patients, including those known to be infected by human immunodeficiency virus (HIV).
   d. Known chronically active hepatitis B virus (HBV) or hepatitis C virus (HCV). For hepatitis B, this includes positive tests for both hepatitis B surface antigen and quantitative hepatitis B polymerase chain reaction (PCR). For hepatitis C, this includes positive tests for both hepatitis C antibody and quantitative hepatitis C PCR.
   e. Active uncontrolled infection.
   f. Limitation of the patient's ability to comply with the treatment or to follow-up the protocol.
   g. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study.
5. Patients acutely ill and/or in immediate vital distress, including those with rapidly deteriorating clinical condition or who may require unscheduled hospitalizations due to uncontrolled disease symptoms within the prior two weeks to treatment registration.
6. Pregnant or breastfeeding women.
7. Live vaccine administration within 3 weeks of study entry

Replacement of Patients:
Patients will be replaced if they are not evaluable for the primary endpoint of the study (ORR as per RECIST v.1.1), specifically, if they have not been treated or have not received a complete lurbinectedin infusion (plus baseline and one follow up scan). All replaced patients who received treatment will be included in the general safety analysis, if appropriate.

Statistical Methods:

Sample Size:
This is a pilot phase II trial which is of interest because lurbinectedin has demonstrated activity against breast cancer in patients with no prior PARP inhibitor (41%).
The main objective of this trial is to determine the efficacy of the study treatment, in terms of ORR, in patients with advanced relapsed gastrointestinal malignancies with DNA repair mutations.
Up to 19 evaluable patients will be recruited to the study to test the null hypothesis that 5% or less patients will show a response to treatment with lurbinectedin versus the alternate hypothesis that 25% or more will respond to treatment. If at most 1 of the first 12 patients respond, the study will be stopped. If there are ≥ 2 responses, the study will be continued to 19 patients. If at least 3 respond, lurbinectedin will be considered promising for future trials.

Statistical Analysis Plan:
The overall response rate will be estimated as the percentage of evaluable patients with a response, either complete (CR) or partial (PR), with exact 95% confidence interval. Percentage of patients with clinical benefit, progression-free survival (PFS) at 3 months, and overall survival (OS) at 6 and 12 months will be evaluated similarly. Duration of response will be summarized using descriptive statistics. The evolution of tumor markers (CA19-9, CEA, or CA125) will be plotted for each patient across time. PFS and OS will be estimated using the Kaplan-Meier estimate.

Table of Contents

1 BACKGROUND 16

2 STUDY POPULATION 19

3 STUDY TREATMENT 23

4 STUDY ASSESSMENTS 27

4.3.1 Day 1 of each cycle (except where noted) 29
4.3.2 Day 8 of each cycle 29
4.3.3 Day 15 of each cycle 30
4.3.4 Tumor Assessments every three cycles (Prior to Cycles 4, 7, 10, etc.) 30
4.3.5 End of Treatment 30
4.3.6 Follow-Up Assessments after End of Study or Early Termination 31

5 EVALUATION OF RESPONSE 31

5.6.2 Methods of Measurement 33
5.6.3 Baseline Documentation of “Target” and “Non-target” Lesions 34

6 SAFETY 36

7 STATISTICAL CONSIDERATIONS 43

Up to 17 evaluable patients will be recruited to the study to test the null hypothesis that 5% or less patients will show a response to treatment with lurbinectedin versus the alternate hypothesis that 25% or more will respond to treatment. If none of the first 9 patients respond, the study will be stopped. If there are ≥1 responses, the study will be continued to 17 patients to obtain the true response rate. Statistical Analysis Plan 43
Laboratory Assessments 45
Hematology Parameters 45
Clinical Chemistry 46
Disclosure of Data 47
Confidentiality 47
Publication 48
Trial Registration and Results Posting Requirements 48
Quality Assurance 48
Study Data Monitoring Plan 48
Data Safety and Monitoring 48
On-site Audits 48
Investigator Documentation 49
Investigator Protocol Agreement 49
Financial Disclosures 49
Laboratory Certification and Normal Ranges 50
Records Retention 50

8 DATA MANAGEMENT 50

Case Report Forms 50
Source Documents 50

REFERENCES 51

APPENDIX A: SCHEDULE OF TREATMENT AND EVALUATIONS 51

APPENDIX B: ECOG PERFORMANCE STATUS 55

APPENDIX C: REVISED NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE), VERSION 5.0 (PUBLISHED 27 NOVEMBER 2017) 55

APPENDIX D: LURBINECTEDIN STUDY DRUG PREPARATION, DOSING, ADMINISTRATION AND STORAGE 56

LIST OF TABLES

Table 1. Dose Reduction Schema.....25
Table 2. Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity) .....**Error! Bookmark not defined.**
Table 3. Dose Modification for Day 8 of Each Cycle (Hematologic Toxicity)*.....**Error! Bookmark not defined.**
Table 4. Nab-paclitaxel and gemcitabine Dose Modifications for Day 1 of Each Cycle (Non-hematologic Toxicity)* .....**Error! Bookmark not defined.**
Table 5. Nab-paclitaxel and gemcitabine Dose Modifications Day 8 Each Cycle (Non-hematological Toxicity).....**Error! Bookmark not defined.**
Table 6. RECIST 1.1 Target Lesion Response Criteria.....34
Table 7. RECIST 1.1 Non-target Lesion Response Criteria 34
Table 8. RECIST Overall Response Criteria.....35

1 BACKGROUND

1.1 DNA Repair in Gastrointestinal malignancies

Gastrointestinal malignancies , remains a difficult disease to treat. In the United States in 2021, there is estimated to be 338,090 cases of gastrointestinal malignancies with 169,280 deaths, making gastrointestinal malignancies the leading cause of cancer related deaths [Siegel et al 2021]. DNA repair is important throughout gastrointestinal malignancies as ability to perform molecular analysis has revealed [Ruiz-Banobre and Goel 2019Additionally, the findings of mismatch-repair deficient tumors that are sensitive to checkpoint inhibition therapy, regardless of tumor of origin suggests that certain mutations are highly senstivie to targeted therapy [Le et al 2015]. A genomicsubtype that has been elucidated termed “unstable” is significant for the presence of DNA damage repair deficiency and can be targeted by several old and emerging therapies. Individuals in DNRA repair genes such as DNA repair genes BRCA2, ATM, FANCA, CHEK2, BRCA1, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11, NBN can be targeted by agents that focus on exploiting the DNA repair pathway [Mateo J et al 2015].

1.2 lurbinectedin (also named as PM01183 or PM1183). as Zepzelca™

lurbinectedin is an alkylating drug approved by the FDA as Zepzelca™ for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. lurbinectedin was selected for clinical development based on its in vitro activity against human solid and non-solid tumor cell lines, its in vivo activity in xenografted human tumors, as well as an acceptable non-clinical toxicology profile.

lurbinectedin is a new Chemical Entity that inhibits active transcription by binding guanine-rich sequences in the regulatory regions of actively transcribed genes, evicting oncogenic transcription factors from their binding sites. Secondary to this activity, lurbinectedin could also induce the specific degradation of transcribing RNA Pol II, inhibit DNA damage repair and subsequently favor DNA double strand breaks and apoptosis.

lurbinectedin demonstrated antiproliferative effects in vitro against a broad selection of tumor types with values of IC_{50} in the range of 1-10 nM. and exhibited in vivo antitumor activity against different murine models of xenografted human-derived tumor types.

1.2.1 Clinical Trial Experience

lurbinectedin has been studied as a single agent and in combination with other anti-cancer agents across several Phase I through Phase III clinical trials in solid tumors. A total of 2474 patients were included in clinical trials (cutoff date of 15 January 2020). Of these, 1872 patients were treated with lurbinectedin alone or combined with other drugs: 573 in phase I trials, 601 in phase II trials 521 in phase III trials, and 177 in Investigator Sponsored Trials (ISTs).

In addition to the patients treated in clinical trials, 170 patients received lurbinectedin under compassionate use agreements.

The pooled safety data that led to the FDA approval included lurbinectedin as a single agent at a dose of 3.2 mg/m^2 intravenously every 21 days in 554 patients with advanced solid tumors. Among 554 patients who received lurbinectedin, including 105 patients with small cell lung cancer (SCLC) in PM1183-B-005-14 (Study B-005).

All patients in this study received a pre-specified anti-emetic regimen consisting of a

corticosteroid and serotonin antagonist. Patients could receive G-CSF for secondary prophylaxis (i.e., after patients had an initial decrease in WBC), but not primary prophylaxis.

Among patients who received lurbinectedin, 29% were exposed for 6 months or longer and 6% were exposed for greater than one year.

Serious adverse reactions occurred in 34% of patients who received lurbinectedin. Serious adverse reactions in ≥ _3% of patients included pneumonia, febrile neutropenia, neutropenia, respiratory tract infection, anemia, dyspnea, and thrombocytopenia.

Permanent discontinuation due to an adverse reaction occurred in two patients (1.9%) who received lurbinectedin which included peripheral neuropathy and myelosuppression.

Dosage interruptions due to an adverse reaction occurred in 30.5% of patients who received lurbinectedin which included neutropenia, and hypoalbuminemia. Dose reductions due to an adverse reaction occurred in 25% of patients who received lurbinectedin and included neutropenia, febrile neutropenia and fatigue.

The most common adverse reactions including laboratory abnormalities, were leukopenia, lymphopenia, fatigue, anemia, neutropenia, increased creatinine, increased alanine aminotransferase, increased glucose, thrombocytopenia, nausea, decreased appetite, musculoskeletal pain, decreased albumin, constipation, dyspnea, decreased sodium, increased aspartate aminotransferase, vomiting, cough, decreased magnesium and diarrhea.

lurbinectedin has shown efficacy against various malignancies; especially those individuals who tumor harbors mutations in DNA repair. In individuals with BRCA mutated metastatic breast cancer, the ORR was 41%. In individuals with small cell lung cancer who have progressed through one line of therapy the ORR was 35% [lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial
Trigo, José et al.
The Lancet Oncology, Volume 21, Issue 5, 645 – 654].

1.3 Drug Administration and Rationale

Due to the high response rate and clinical activity in lurbinectedin in malignancies driven by DNA repair, we propose to examine the clinical benefit of individuals with gastrointestinal malignancies who harbor mutations in DNA repair.

1.4 Primary Objective

To evaluate the antitumor activity of lurbinectedin in terms of overall response rate (ORR), according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, in patients with advanced gastrointestinal malignancies with DNA repair mutations.

1.5 Secondary Objectives

The secondary objectives of this study are to:

- Assess the duration of response (DOR) and the clinical benefit (defined as patients with response or stable disease [SD] ≥3 months).

- Determine the evolution of tumor markers (e.g., CA19-9, CEA, or CA125, whichever is being followed) during treatment.

- Determine the progression-free survival (PFS) and the progression-free survival rate at three months (PFS3).

- Determine the overall survival (OS) and the overall survival rate at six and 12 months (OS6 and OS12).

- Explore the antitumor activity of lurbinectedin according to clinical parameters (e.g., patient or disease characteristics, prior therapy, etc.) and genomic/molecular parameters (whole exome) if they were obtained as part of their prior care.

- Evaluate the safety profile of this lurbinectedin administration schedule (Day 1 every three weeks [q3wk]) in this patient population, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5).

- Evaluate changes in the tumor (if available) through genomic analysis.

1.6 Overview

This is a open-label, single-arm phase II clinical trial to evaluate the activity and safety of lurbinectedin in adult patients with advanced gastrointestinal malignancies with DNA repair mutations at study entry that have been previously treated with up to three systemic chemotherapy lines for advanced disease.

Known deleterious or suspected deleterious DNA repair mutations (ATM, ATR, CHEK2, BRCA1, BRCA2, RAD51, BRIP1, PALB2, PTEN, FANC, NBN, EMSY, MRE11, or ARID1A) will be required prior to study entry for all patients.

Nineteen (19) evaluable (eg received at least 1 dose of lurbinectedin and a baseline and follow up scan) patients in the selected dose for efficacy with advanced gastrointestinal malignancies with DNA repair mutations will be enrolled.

The primary endpoint of the trial is ORR (confirmed response) per RECIST v.1.1.

Toxicity (adverse events) will be recorded using the NCI CTCAE, version 5.0 (see Appendix C).

1.7 Primary Endpoints

- Overall response rate (ORR), defined as the percentage of patients with confirmed complete (CR) or partial response (PR) according to RECIST v.1.1.

1.8 Secondary Endpoints

To evaluate the following:

- Duration of response (DOR), defined as the time from the date when the response criteria (PR or CR) are fulfilled to the date of PD, recurrence or death.

- Clinical benefit, defined as the percentage of patients with ORR or SD ≥3 months, according to RECIST v.1.1.

- CA19-9, CEA, or CA125 (whichever is being followed) evolution during treatment.

- Progression-free survival (PFS), defined as the time from the date of first infusion to the

date of PD, death (of any cause), or last tumor evaluation.

- Progression-free survival rate at three months (PFS3), defined as the percentage of patients who are alive and progression-free three months after the first infusion.
- Overall survival (OS), defined as the time from the date of first infusion to the date of death (of any cause) or last patient contact.
- Overall survival rate at six months (OS6), defined as the percentage of patients who were alive six months after the first infusion.
- Overall survival rate at 12 months (OS12), defined as the percentage of patients who were alive 12 months after the first infusion.
- Treatment safety: AEs, serious AEs (SAEs) and laboratory abnormalities graded according to the NCI-CTCAE v.5.

2 STUDY POPULATION

2.1 Patient Selection and Study Duration

Up to 40 patients will be recruited from up to 2 study centers in the United States with the goal of 17 evaluable patients. Evaluable patient is defined as having received at least 1 dose of lurbinectedin and a baseline and a follow up scan. Those patients who are considered not evaluable will be replaced (see section 5.3). The expected duration of this study is 26 months; 14 months for accrual and 12 months follow-up. Enrollment into the screening or treatment phase of the study will be stopped when the anticipated or actual patient numbers have been achieved across all study sites or in the event that any of the stopping rules as defined in Section XX. are met.

2.2 Eligibility

2.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to participate in the study:

1. Voluntary written informed consent form (ICF) of the patient obtained before any study-specific procedure
2. Age ≥ 18 years of age; male or female
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤1
4. Histologically or cytologically confirmed gastrointestinal carcinoma
5. Locally advanced unresectable or metastatic disease at study entry

6. Known deleterious or suspected deleterious mutations in DNA repair in ATM, ATR, CHEK2, BRCA1, BRCA2, RAD51, BRIP1, PALB2, PTEN, FANC, NBN, EMSY, MRE11, or ARID1A prior to study entry

7. Progressive disease to prior treatment. Patients no longer able to continue prior treatment due to intolerable toxicity may be considered for study participation provided that radiology assessment confirms either stable disease or disease progression (i.e., no response to treatment)

8. Measurable tumor lesions according to RECIST 1.1 criteria

9. Adequate hematological, renal, metabolic and hepatic function, defined as:
   a. Hemoglobin ≥9 g/dL (patients may have received prior red blood cell [RBC] transfusion, if clinically indicated); absolute neutrophil count (ANC) ≥1.5 x 10^9/L, and platelet count ≥100 x 10^9/L.
   b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 x upper limit of normal (ULN).
   c. Total bilirubin ≤ ULN.
   d. Albumin ≥3.0 g/dL.
   e. Calculated creatinine clearance (CrCL) ≥30 mL/min (according to the Cockcroft and Gault´s formula).

10. Washout periods prior to Day 1 of Cycle 1:
    a. At least three weeks since last prior chemotherapy and/or investigational drugs'.
    b. At least four weeks since the last radiotherapy (RT) > 30 Gy.
    c. At least two weeks since the last palliative RT (≤ 10 fractions or ≤ 30 Gy total dose)

11. Patients with prior malignancy successfully treated who are currently stable and on no active treatment are eligible

12. Recovery to grade ≤1 from any adverse event (AE) derived from previous anticancer treatment (excluding alopecia and/or skin toxicity of any grade and grade ≤2 peripheral neuropathy) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.5)

13. Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure* during the trial and up to six weeks after treatment discontinuation, and fertile male patients with WOCBP partners must agree to refrain from fathering a child or donating sperm during the trial and up to four months after treatment discontinuation.

*Effective methods: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; progestogen-only hormonal contraception associated

with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence.

2.2.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria will be excluded from study participation:

1. Prior treatment with lurbinectedin or trabectedin

2. Neuroendocrine differentiation subtype in histology

3. More than three prior systemic chemotherapy lines for advanced disease

4. Known brain metastases or leptomeningeal disease involvement

5. Concomitant diseases/conditions:
    a. History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrollment; or history of left ventricular ejection fraction (LVEF) ≤ 50% assessed by multiple-gated acquisition scan (MUGA) or equivalent by ultrasound (US); or symptomatic arrhythmia.
    b. Generalized edema, and/or ascites clinically evident or requiring drainages within three weeks prior to study entry. Permanent external drainages due to ascites are also excluded.
    c. Immunocompromised patients, including those known to be infected by human immunodeficiency virus (HIV).
    d. Known chronically active hepatitis B virus (HBV) or hepatitis C virus (HCV). For hepatitis B, this includes positive tests for both hepatitis B surface antigen and quantitative hepatitis B polymerase chain reaction (PCR). For hepatitis C, this includes positive tests for both hepatitis C antibody and quantitative hepatitis C PCR.
    e. Active uncontrolled infection.
    f. Limitation of the patient's ability to comply with the treatment or to follow-up the protocol.
    g. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study.
6. Patients acutely ill and/or in immediate vital distress, including those with rapidly deteriorating clinical condition or who may require unscheduled hospitalizations due to uncontrolled disease symptoms within the prior two weeks to treatment registration

7. Pregnant or breastfeeding women

8. Live vaccine administration within 3 weeks of study entry

2.3 Patient Enrollment

All patients must have a signed and dated current, IRB approved informed consent and HIPAA Authorization prior to any study specific screening procedures being performed.

A trial and site specific screening number will be assigned by the site when the patient signs the Informed Consent Form. Once all screening procedures have been completed and laboratory values have been reported, the investigator will register the patient into the study as follows:

1. Completion of all data entry into the required screening eCRFs
2. Provide HRI with the completed patient eligibility forms signed by the Investigator to HRI via email or fax.

HRI will review the screening eCRFs within 48 hour and confirm eligibility of the patient and assign the trial specific patient enrollment number.

If the patient is determined NOT eligible for the study, the patient will be determined a screen failure and the reason noted on the patient eligibility form and sent to the Investigator for the study records. The Investigator, or delegated study team member, is responsible for entering all patients consented to the study in the EDC, including screen failures.

2.4 Study Periods

Patients will be individually evaluated at scheduled visits in three study periods:

1. **Screening Period:** Defined from signature of the ICF to first infusion of lurbinectedin.

2. **Treatment Period :** Defined from the first infusion of lurbinectedin to **end of treatment** (EOT). **EOT** is defined as 30 days (± 7 days) after the date of lurbinectedin last administration, unless the patient starts a new antitumor therapy or dies within those 30 days, in which case the date of administration of this new antitumor therapy or the date of death will be considered as EOT.

3. **Follow-up Period :** Defined after EOT, patients will be followed every four weeks until recovery to at least grade 1 or stabilization of symptoms of all treatment-related adverse events (AEs), if any, or until start of a new antitumor therapy. Patients who finish treatment without disease progression will be followed every six weeks until disease progression or start of a new antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. A (±)1-week window is allowed for tumor assessments during follow-up. After disease progression is documented or a new antitumor therapy is started, patients will be followed at least every three months until death of any cause or date of study termination, whichever occurs first. For the purpose of collecting information on patient's survival exclusively, a documented telephone call would be acceptable. Information about further therapies will be collected during this follow-up period.

2.5 Patients will be considered to be **on-study** from the signature of the ICF until death or study termination. Patients will be considered to be **on-treatment** for the duration of their treatment and until the day of EOT, immediately before the start of the follow-up period.

2.6 Patient Discontinuation

Patients will receive the study treatment while it is considered to be in their best interest. Specifically, treatment will continue until:

1. Disease progression.
2. Unacceptable toxicity (except in case of clear clinical benefit, with the Sponsors' approval), after appropriate dose reduction

3. Intercurrent illness of sufficient magnitude to preclude safe continuation of the study.
4. Patient refusal (follow-up has to be continued for those patients who refuse treatment, but do not withdraw consent).
4. Non-compliance with the study requirements.
5. Investigator's decision.
6. Protocol deviation with an effect on the management of the patient's risk/benefit ratio.
7. Treatment delay > 3 weeks from the treatment due date (except in case of clear clinical benefit, with the Sponsors' approval).
8. Requirement of > 2 dose adjustments.
9. Clinical cutoff. Patients could continue treatment under compassionate use agreement after study termination.

3 STUDY TREATMENT

Study treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other outpatient setting appropriate for chemotherapeutic infusions.

No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the patient's malignancy.

3.1 Administration and Dosing

3.2 lurbinectedin

lurbinectedin drug product (DP) is presented as a lyophilized powder for concentrate for solution for infusion in 4 mg vials, which will be supplied by Jazz Pharmaceuticals for the purposes of this study.

The solution for infusion will be prepared at each investigational site. Before use, the 4 mg vial should be reconstituted with 8 mL of sterile water for injection, USP, to give a solution containing 0.5 mg/mL lurbinectedin. For administration to patients as an intravenous (IV) infusion, reconstituted vials should be diluted either with dextrose 50 mg/mL (5%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion.

The full composition of the lurbinectedin 4 mg vials and the reconstituted solution per mL is shown in Table 1.

Table 1. Composition of lurbinectedin vials.

Component	lurbinectedin 4 mg	Concentration per vial after reconstitution
lurbinectedin	4.00 mg	0.50 mg/mL
Sucrose	800.00 mg	100.00 mg/mL
Lactic acid	22.08 mg	2.76 mg/mL
Sodium hydroxide	5.12 mg	0.64 mg/mL

Lurbinectedin will be administered with a minimum total volume of 100 mL of solution for infusion (either on 5% dextrose or 0.9% sodium chloride) through a central catheter or over a minimum total volume of 250 mL if through a peripheral line, always over 60 minutes (±10 min) at a fixed infusion rate.

The starting dose of lurbinectedin will be 3.2 mg/m2 on Day 1 q3wk (three weeks ± 48 hours = one treatment cycle). BSA will be calculated according to standard practice at each center.

A lower lurbinectedin starting dose of 2.6 mg/m2 may be implemented after six treated patients, in case of severe related toxicities (according to dose reduction criteria) are observed in more than 33% of patients in the first two cycles. In that circumstance, decision will be taken upon agreement with the Sponsor and Investigators.

Doses will have to be recalculated for patients showing a ≥ 10% variation in total body weight from baseline or from last dose adjustment.

Detailed guidelines for the preparation and administration of lurbinectedin are provided in the lurbinectedin Investigator Brochure.

3.3 Granulocyte colony-stimulating factors (G-CSFs) prophylaxis

Patients will receive primary prophylaxis subcutaneously with G-CSFs. Either pegfilgrastrim at 6 mg once per cycle or filgrastim subcutaneous dose of 5 µg/kg/day for 5 days can be used [type, dose and time will be used according to American Society of Clinical Oncology (ASCO) guidelines]. G-CSFs prophylaxis should start at least 24 hours after lurbinectedin infusion.

3.4 G-CSFs prophylaxis should start at least 24 hours after lurbinectedin infusion.

3.5 Antiemetic prophylactic medication

All patients will receive standard antiemetic prophylaxis before each treatment infusion, as follows:

- Intravenous corticosteroids (dexamethasone 8 mg, or equivalent, or at institutional antiemetic doses).
- Intravenous serotonin (5-HT_3) antagonists (ondansetron 8 mg or equivalent).

Apart from the mandatory prophylaxis described above, it is recommended that patients continue treatment with corticosteroids and 5-HT_3 antagonists for at least three days. Nevertheless, depending on the patient's condition or the tolerability of the study treatment, antiemetic regimen or agents (other than those described above), dose, and time could be modified according to the Investigator's criteria.

If necessary and in addition to the above, any of the following could apply:

- Administration of 10 mg of metoclopramide (or equivalent) every eight hours.
- Olanzapine 10 mg orally daily (Day 1-4).

Note: Aprepitant and equivalent agents (e.g., fosaprepitant) are forbidden in patients treated with lurbinectedin.

3.6 Dose Modification for Toxicity

Toxicities will be graded using the NCI CTCAE v5.0 (see Appendix C). If toxicity occurs during or after any treatment cycle, the toxicity will be graded and appropriate supportive care treatment

may be administered to decrease the signs and symptoms (e.g. antiemetics, antidiarrheals, antipyretics, antihistamines).

A maximum of a 3-week treatment delay is permitted to allow recovery of toxicities or other illness that prevents the patient from receiving chemotherapy.

After Cycle 1, in order to be re-treated, patients will have to fulfill the criteria defined in Table 2.

If a patient does not meet the requirements for treatment continuation on Day 1 of any cycle after Cycle 1 due to toxicity and/or abnormal laboratory values, re-assessments will be performed within one week, and treatment will be withheld until appropriate recovery, for a maximum of three weeks after the treatment due date.

If there is no recovery after a 3-week delay, the patient must be withdrawn from the treatment, except if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Then, treatment may continue after appropriate dose reduction (Section 3.6). Delays >3 weeks due to reason different to toxicity issues should be discussed with the Sponsor before resuming treatment.

Table 2. Criteria for Treatment Continuation

	Day 1
Variable	**Re-treatment**
	Day 1
ECOG PS	≤1
Hemoglobin [a]	≥9.0 g/dL
ANC	≥1.5 x 10^9/L
Platelets	≥90 x 10^9/L
AST/ALT	≤3.0 x ULN
Total bilirubin, or **----------** **direct bilirubin (when total bilirubin >1.5 x ULN)**	≤1.5 x ULN, or ---------- ≤ ULN
Albumin	≥3.0 g/dL [b]
Calculated CrCL (Cockcroft and Gault's formula)	≥30 mL/min
Other non-hematological drug-related AEs (except isolated increased GGT and/or AP [c]**, grade 2 alopecia, constipation, fatigue, neuropathy, or non-optimally treated nausea).**	Grade ≤1

[a] Patients may receive PRBC transfusion and/or EPO treatment, if clinically indicated, to increase/maintain adequate hemoglobin levels.

[b] Albumin infusion is not allowed to reach albumin levels required per protocol.

[c] Any grade accepted for non-drug-related increase of GGT and/or AP.

AE(s), adverse event(s); ANC, absolute neutrophil count; AP, alkaline phosphatase; AST/ALT, aspartate aminotransferase/alanine aminotransferase; CrCL, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; EPO, erythropoietin; GGT, gamma-glutamyltransferase; PRBC, packed red blood cells; PS, performance status; ULN, upper limit of normal.

3.7 Dose Reduction Criteria

Patients who experience any grade ≥ 3 treatment-related non-hematological toxicity (according to the NCI-CTCAE, v.5) and/or any grade febrile neutropenia, neutropenic infection or sepsis, grade 4 neutropenia or grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with grade ≥3 bleeding, and/or prolonged (> 2 weeks) dose delays due to treatment-related toxicity will continue treatment after appropriate dose reduction (see Table 3).

Exceptions for dose reduction are: grade ≥3 nausea and/or vomiting not optimally prevented; grade 3 asthenia lasting ≤3 days; grade 3 diarrhea lasting ≤2 days or not optimally treated; transient grade 3 ALT/AST elevations that are rapidly reversible and not leading to subsequent delays; and/or not clinically relevant biochemical abnormalities (i.e., in gamma-glutamyltransferase [GGT], lactate dehydrogenase [LDH] and/or alkaline phosphatase [AP] levels), none of which require dose reduction to be implemented.

The guidelines for dose reduction are shown in Table 3.

Table 3. Dose reduction levels.

Dose reduction level	lurbinectedin dose (mg/m^2) [a]
1	3.2 [b] every 21 days
−1	2.6 [b] every 21 days
−2	2.0 [b] every 21 days

[a] BSA will be calculated according to standard practice at each center.

[b] **With G-CSF prophylaxis.**

BSA, body surface area; G-CSF, granulocyte colony-stimulating factor.

Up to two dose reductions are allowed per patient. Patients who continue to experience treatment-related toxicity after two dose reductions must be withdrawn from the study.

Once the dose has been reduced for an individual patient, it will not be re-escalated under any circumstances. Patients who experience treatment-related grade 3 or 4 hypersensitivity will immediately discontinue treatment without any dose reduction.

3.8 Intended Dose Delays

Intended cycles may be delayed for non-toxicity reasons for up to 21 days (for reasons such as scheduling conflicts), but only with documentation and explanation in the CRF.

3.9 Concomitant Therapy

Necessary supportive measures for optimal medical care may be given throughout the study, including:

- Therapies for pre-existing and treatment-emergent medical conditions, including pain management.

- Blood products and transfusions, as clinically indicated.
- In case of nausea or vomiting, the use of secondary prophylaxis and/or symptomatic treatment for emesis, if required, will be according to ASCO guidelines.
- Erythropoietin (EPO) according to ASCO guidelines.
- Oral anticoagulation and/or low molecular weight heparin (LMWH) for the treatment or secondary prophylaxis of deep venous thrombosis (DVT).
- Megestrol acetate for appetite stimulation, if appropriate for management of emerging wasting syndrome.

3.10 Prohibited Concomitant Therapies

The following medications/therapies are prohibited throughout the study treatment period:

- Concomitant administration of any other antineoplastic therapy.
- Any other investigational agents.
- Immunosuppressive therapies, other than corticosteroids. Corticosteroids are allowed provided that they are not being used with immunosuppressive intention.
- Aprepitant, fosaprepitant, and directly related compounds.
- Radiotherapy (RT), except for limited-field bone radiation for pain control purposes.
- Strong and moderate CYP3A inhibitors
- Strong and moderate CYP3A inducers
- Aprepitant

Furthermore, intake of medicinal herbs (e.g., milk thistle, *Silybum marianum)* or grapefruit juice is not recommended during lurbinectedin treatment.

4 STUDY ASSESSMENTS

4.1 Laboratory Assessments

All hematology, blood chemistries, urinalyses, and serum or urine pregnancy tests (if applicable) will be performed by the local laboratory for each investigational site.

Prior to study enrollment, each patient will have the following assessments completed (see Appendix A). Assessments that have been completed as part of standard medical care, but *prior to obtaining consent,* may be used for the purposes of screening and do not need to be repeated if they have been completed within 21 days prior to cycle 1, day 1.

4.2 Screening (Within 21 Days Prior to First Dose on C1/D1)

1. Written informed consent to be obtained prior to any study specific screening procedures being performed.

2. Review inclusion/exclusion criteria

3. Medical history including concurrent baseline conditions (using NCI CTCAE version 5.0; Appendix C), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy)

4. Complete physical examination including height (cm) and weight (kg)

5. ECOG Performance Status - see Appendix B

6. Vital signs (blood pressure, pulse, respiratory rate, and temperature)

7. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. (see RECIST 1.1 criteria in Section 6)

8. Electrocardiogram (ECG)

9. Complete blood count (CBC) with differential and platelet count

10. Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance (the Cockcroft-Gault equation may be used to calculate the creatinine clearance at any of the time points in this protocol), total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)

11. CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)

12. PT/INR

13. Urinalysis (lab): protein, specific gravity, glucose, and blood

14. Serum pregnancy test (if applicable)

15. Concomitant medication notation (to include all medications taken within 30 days prior to study enrollment)

16. Acquisition of archival tumor tissue (if available) or obtaining new tumor tissue. Note- if tumor tissue acquisition not possible per the investigator this will not be pursued.

Once eligibility is confirmed by the Investigator, the site is to register the patient following the procedures outlined in Section 3.4.

4.3 On-Study Assessments

Patients must begin Cycle 1 within 21 days of signing the informed consent document and after the screening assessments. Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other out-patient setting appropriate for chemotherapeutic infusions. All assessments should be performed within 72 hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted within 24 hours (except those noted), or if medical or scheduling conditions require a delay. Note- while safety visits are mandated in days 8 and 15 of cycles 1 and 2 and are optional afterwards, they may be conducted

at the discretion of the investigator.

4.3.1 Day 1 of each cycle (except where noted)

- Inclusion/exclusion review (Cycle 1 only)
- Medical history review (Cycle 1 only)
- Directed physical exam (within 72 hours prior to Cycle 1 Day 1 treatment)
- Vital Signs (blood pressure, pulse, respiratory rate, and temperature) to be collected ≤ 24 hours prior to treatment.
- Measurement of weight (kg) and BSA calculation prior to dosing (BSA will be calculated before each new cycle, based on the actual height and weight of the patient. After Cycle 1, if there has been a > 10% weight change from baseline (Cycle 1 Day 1), the drug doses will be recalculated based on the new BSA value.) (See Section XX).
- ECOG Performance Status - see Appendix B
- Hematology: CBC with differential and platelet count within 72 hours prior to Cycle 1 treatment)
- Serum chemistries (see Section 5.2) (within 72 hours prior to Cycle 1 treatment)
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9) (within 72 hours prior to Cycle 1 treatment)
- PT/INR required only If patient is on anticoagulation with warfarin.
- Urinalysis (within 72 hours prior to Cycle 1 treatment)
- Serum Pregnancy if applicable (within 72 hours prior dosing on day 1 of each cycle). Negative result must be confirmed prior to dosing.
- AEs using the NCI CTCAE (see Appendix C)
- Concomitant medication notation
- Antiemetic prophylaxis (Section 3.5)
- lurbinectedin (Section 3.2)
- G-CSFs prophylaxis should start at least 24 hours after lurbinectedin infusion.

4.3.2 Day 8 of each cycle (cycles 1 and 2)

- Directed physical exam
- Vital Signs (blood pressure, pulse, respiratory rate, and temperature) to be collected
- Measurement of weight (kg)

- ECOG
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- AEs using the NCI CTCAE (see Appendix C)
- Concomitant medication notation

4.3.3 Day 15 of each cycle (cycles 1 and 2 only)

Cycle 1 day 15 clinic visit can be conducted by telemedicine (video teleconference or phone call). Lab tests on day 15 of each cycle can be done at a local lab if the patient is unable to visit the site. Lab results are to be available to the investigator within 1 day to allow evaluation of potential adverse events and patient safety.

- Directed physical exam
- Vital Signs (blood pressure, pulse, respiratory rate, and temperature) to be collected ≤ 24 hours prior to treatment.
- ECOG Performance Status (see Appendix B)
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- AEs using the NCI CTCAE (see Appendix C)
- Concomitant medication notation

4.3.4 Tumor Assessments every three cycles (Prior to Cycles 4, 7, 10, etc.)

- In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.
- Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements.

4.3.5 End of Treatment

When the patient completes all cycles of study medication, or withdraws from treatment prior to completing all cycles, the following assessments will be performed with 30 days after completing the last dose of study medication:

- Directed physical exam, if deemed necessary

- Measurement of weight (kg)
- ECOG Performance Status (see Appendix B)
- Vital signs (see Section 5.2)
- Hematology: CBC with differential and platelet count
- Serum chemistries (see Section 5.2)
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Urinalysis (see Section 5.2)
- Serum pregnancy if applicable
- Concomitant medication notation
- CT/MRI scan to evaluate disease status (using same imaging method as Baseline)
- AEs using the NCI CTCAE version 5.0 (see Appendix C)
- Confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted monthly for survival status for up to 12 months from time of enrollment.
- Tumor biopsy if possible. Note- if tumor tissue acquisition not possible per the investigator this will not be pursued

4.3.6 Follow-Up Assessments after End of Study or Early Termination

Follow-up assessments for survival, in person or by telephone, will be conducted for all patients 30 days after the End of Study or Early Termination Visit and then monthly for up to 12 months from the time of enrollment. In the event that a patient cannot be reached during the follow-up period, a designated family member may be contacted.

5 EVALUATION OF RESPONSE

5.1 Best Overall Response

Best overall response is defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for tumor progression, the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

5.2 Overall Tumor Response

The overall tumor response rate is defined as the total proportion of patients who have an objective tumor response (CR + PR). Rates for the individual categories of response (CR, PR, SD, and PD) will also be determined.

5.3 Not Evaluable

Patients will be defined as being not evaluable for response if a radiological assessment cannot be made. These patients will be counted as treatment failures in the analysis of tumor response data.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by PET scan, fine needle aspirate or biopsy when possible before confirming the CR status.

5.4 Progression-free Survival

Progression-free survival (PFS) is defined as the time from enrollment (i.e. assignment of patient ID number) to first documentation of objective tumor progression , clinical progression, or to death due to any cause. In the absence of previous documentation of objective tumor progression will be censored at the last date the patient was known to be progression-free in patients who do not have objective tumor progression and who are: 1) still on study at the time of an analysis; 2) are given anti-tumor treatment other than the study treatment; or 3) are removed from study follow-up prior to documentation of objective tumor progression.

5.5 Survival

Survival is defined as the time from enrollment (i.e. assignment of patient ID number) to date of death. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

5.6 Guidelines for Measuring Disease

Antitumor activity will be evaluated by RECIST 1.1 criteria (Eisenhauer 2009). These response criteria are widely recognized and accepted as the standard criteria for determining response in patients with solid tumors.
https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

5.6.1 Disease Definitions

Measurable disease is defined as the presence of ≥1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

At Baseline, tumor lesions will be categorized as:

Measurable Lesions: lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.
- Malignant lymph nodes: to be considered pathologically enlarged and measureable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At Baseline and follow-up, only the short axis will be measured and followed.

Or

Non-measurable Lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

For special considerations regarding lesion measurability for bone lesions, cystic lesions and lesions with prior local treatment, consult the RECIST 1.1 guidelines.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before beginning of treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, either a CT scan or documentation by color photography, including a ruler to estimate the size of the lesion, is to be done.

5.6.2 Methods of Measurement

Tumor measurements should be performed using the same method as well as the same staff member per patient, if possible, throughout the study. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of ≤5 mm in slice thickness contiguously. This applies to tumors of the chest, abdomen, and pelvis.

As a rule, the minimum size of the lesion should be no less than double the slice thickness.

Lesions on chest x-rays are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is necessary.

Tumor markers *alone* cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors) if required by protocol.

5.6.3 Baseline Documentation of "Target" and "Non-target" Lesions

Target Lesions: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]), be representative of all involved organs, and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum of the LD will be used as reference to further characterize the objective tumor response.

Non-target Lesions: all other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and will also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

5.7 Response Criteria

Table 1. RECIST 1.1 Target Lesion Response Criteria

Target Response Criteria	Definition
Complete Response (CR)	The disappearance of all target lesions and no new sites or disease-related symptoms confirmed at least 4 weeks after initial documentation. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm. All sites must be assessed, including non-measurable sites, such as effusions, or markers.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference the baseline sum of the diameters confirmed at least 4 weeks after initial documentation. PR is also recorded when all measurable disease has completely disappeared, but a non-measurable component (i.e., ascites) is still present but not progressing.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters recorded since on study (this includes the baseline sum if that is the smallest on study), which must also demonstrate an absolute increase of at least 5 mm; or the appearance of one or more new lesions;

Non-target lesion response will be classified according to the RECIST Non-Target Lesion Response Criteria in the following table.

Table 2. RECIST 1.1 Non-target Lesion Response Criteria

Non-Target Response Criteria	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level confirmed at least 4 weeks after initial

	documentation. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-Complete Response/Non- Progressive Disease (Non-CR/Non-PD)	Persistence of one or more non-target lesions and/or the maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more non-target lesions and/or unequivocal progression of existing non-target lesions ("unequivocal progression" is defined as an overall level of substantial worsening in non-target disease that is of magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy).

5.8 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be classified as having "symptomatic deterioration." Every effort will be made to document the objective evidence of disease progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Table 3. RECIST Overall Response Criteria

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

NE = inevaluable

5.9 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively

documented, taking as reference for PD the smallest measurements recorded since the treatment started.

5.10 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

For the purposes of this trial, the minimal time interval required between 2 measurements for determination of SD is 6 weeks (at least 2 consecutive assessments 6 weeks apart revealing SD). This time interval takes into account the expected clinical benefit that such a status may bring to the population under study.

6 SAFETY

The investigator is responsible for monitoring the safety of patients who have enrolled in the study. All adverse events (AEs) occurring after any administration of the study medication will be followed until the event resolves, until the patient begins alternative treatment, or until the end of the study. Investigators will grade AEs using the NCI CTCAE, version 5.0 (see Appendix C).

Investigators are required to document all AEs regardless of causality, observed during the study period, starting with initial dose of study drug and ending at the time the patient goes off study or 30 days after patient's last dose of study drug, whichever is later per Section 7.9.

AEs occurring following the signature of the informed consent, but prior to the first dose of study drug, will not be reported as AEs. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious. Serious adverse events (SAEs), as defined below, must be reported to Sponsor within 24 hours of knowledge of their occurrence.

6.1 Adverse Events

An AE is any unfavorable medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the CRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs.

Patients should be instructed to report any AE that they experience to the Investigator, starting from the time of their first dose. Investigators should assess AEs at each visit. AEs occurring during the clinical trial, starting at the time of the initial study drug infusion, and the follow-up period should be recorded on the appropriate AE page of the CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention;
- or is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

6.2 Serious Adverse Events

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Life-threatening is defined as an event with immediate risk of death from the event as it occurred. It does not include an event that might have caused death if it occurred with a greater severity.
- In-patient hospitalization or prolongation of existing hospitalization, except for the following:
    - A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
    - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
    - The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
    - A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
    - Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.

Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

- Results in a persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other listed outcomes above.

6.3 Adverse Event Severity

AE will be graded according to the NCI CTCAE, Version 5.0 (see Appendix C)

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI CTCAE grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

6.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

6.5 Action Taken

The Investigator will report the action taken for the trial treatment as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or dose reduction of specified study treatment, as appropriate) and report if concomitant and/or additional treatments were given for the event.

6.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the patient's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, not recovered or death (due to the SAE).

6.7 Causality Assessment

All adverse events regardless of CTCAE grade must also be evaluated for relationship (in regards to study treatment including/ trial interventions).

The determination of the likelihood that trial treatment caused the adverse event will be provided by an investigator. The Investigator must determine the relationship between the administration of study treatment and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Relationship	**Attribution**
Not Suspected	Not Related
	Unlikely
Suspected	Possibly
	Probably
	Definite

Not suspected: Means a causal relationship of the adverse event to IP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a reasonable possibility that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

The Medical Monitor will make the final determination of relationship between the administration of study treatment and the occurrence of the reported AEs/SAEs.

6.8 Patient Reporting of AEs and SAEs

Patients are to be encouraged to call the site to report any unexpected symptoms or problems they encounter between office visits. These events should be considered in the same fashion as if they had been reported at a scheduled office visit. At each scheduled office visit, after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the following standard questions

- Have you had any (other) medical problems since your last clinic visit?
- Have you taken any new prescribed or over-the-counter medicines or herbal/vitamin preparations, other than those given to you in this study, since your last visit/assessment?

- Have any new procedures been performed since your last study visit?

6.9 Investigator Reporting Adverse Events

The Investigator is responsible for recording and following all Grade ≥3 AEs, regardless of causality, observed during the study period, starting with initial dose of study drug and ending at the time the patient goes off study or 30 days after patient's last dose of study drug, whichever is later. The Investigator should follow AEs until the event is resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained. Events occurring within 30 days prior to study drug administration should be recorded as pre-treatment signs and symptoms. The only exception to this is for an AE that occurs prior to the first dose of study drug but is due to a procedure associated with assessments carried out to determine eligibility or to permit participation in this protocol – this should be recorded as an AE (rather than a pre-treatment sign or symptom).

The Investigator or designee must completely and promptly record each AE in the source documentation, regardless of relationship to study drug as determined by the Investigator.

The Investigator must assess AE/SAE causality for any patients treated at his/her site. The Investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Clinically significant laboratory abnormalities present at the baseline visit will be recorded as pre-treatment signs and symptoms.

For the purposes of this study, only the following adverse events are to be recorded in the eCRFs:

- Grade ≥ 3 AEs
- All grade neuropathy adverse events
- Any AE that leads to study treatment discontinuation
- Any AE that is associated with and contributing to an SAE as determined by the Investigator

In addition, all SAEs must be reported promptly to Sponsor **after the Investigator recognizes/classifies the event as a SAE.** The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE within 24 hours/ 1 business day of becoming aware of the event, preferably by fax or alternatively by phone or email; at a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. If an SAE is reported by phone or by e-mail, the Investigator must fax a completed SAE report form to Sponsor within 1 business days. For an event that is not life-threatening or fatal, the Investigator must fax a completed SAE report form within 2 business days after he/she recognizes/classifies the event as an SAE.

The Investigator should follow all AEs/SAEs observed during the study until the AE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies.

All SAEs including life-threatening and death, regardless of the causal relationship to study drug must be reported via Medwatch Form 3500A promptly to Jazz Pharmaceuticals (AEReporting@jazzpharma.com) **within 1 business day** after received by study sponsor.

6.10 Expedited Reporting by Investigator to (Sponsor)

Serious adverse events (SAE) are defined above in Section 7.2.

The investigator must inform the Sponsor and in writing using a MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The MEDwatch 3500A form along with the SAE Report Form Cover letter must be completed and supplied to the Sponsor via email (preferred method) or facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and study treatment. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH 3500A form. A final report to document resolution of the SAE is required. A copy of the email or fax transmission confirmation of the SAE report to the Sponsor should be attached to the SAE and retained with the patient records.

HRI Oncology Drug Safety
Email: oncologydrugsafety@honorhealth.com
Fax: 480-323-1560
Telephone: 480-323-1350

6.11 IRB Notification of SAEs

The Investigator is responsible for promptly notifying the IRB of all SAEs, including any follow-up information per local IRB guidelines, occurring at his/her site and any SAE regulatory reports and Investigational New Drug Safety Reports that he/she receives from Sponsor.

6.12 SAE Follow-Up

For all SAEs occurring after first dose of study medication or within 30 days of the last administration of study medication, the investigator must submit follow-up reports to Sponsor and Jazz Pharmaceuticals regarding the status of the SAE and the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies.

6.13 Sponsor Notification of Post-Study SAEs

The Investigator should notify Sponsor of any death or SAE occurring after a patient has withdrawn from the study, or after 30 days of the last study drug dose, whichever is later, when such death or SAE may reasonably be related to the medication used in the study. However, Investigators are not obligated to actively seek AEs in former study participants.

6.14 Pregnancy

While not considered a SAE unless a serious criterion is met, pregnancies occurring in patients enrolled on the study or in their partners must be reported. The investigator should complete the pregnancy report form and fax it to (Sponsor/CRO) within 24 hours of knowledge of the pregnancy. The Study Sponsor will send the completed pregnancy report form to Jazz Pharmaceuticals (AEReporting@jazzpharma.com) within 1 business day after learning of the pregnancy.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on study treatment, or within 30

days of the patient's last dose study treatment, are considered immediately reportable events. Study treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female patient may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female patient until completion of the pregnancy, and must notify Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Sponsor immediately by email, facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to the Sponsor immediately by email, facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

The Study Sponsor will in turn report the above information to Jazz Pharmaceuticals (AEReporting@jazzpharma.com) within 1 business day of awareness.

Male Patients

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

6.15 Overdose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Any sequela of an accidental or intentional overdose of study treatment should be reported as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on a Medwatch 3500A form and as an AE. The overdose resulting in the SAE should be identified as the cause of the event on the Medwatch 3500A form submitted to Jazz Pharmaceuticals (AEReporting@jazzpharma.com) within 1 business day of awareness. The
CRF but should not be reported as an SAE itself.

In the event of overdose, the patient should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for lurbinectedin overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

7 STATISTICAL CONSIDERATIONS

7.1 Trial Design

This is a phase II open-label trial, with the identity of the treatment known to the patients, Investigators and Sponsor.

7.2 Sample Size Considerations

This is a pilot phase II trial which is of interest because lurbinectedin has demonstrated some activity against breast cancer in patients with no prior PARP inhibitor (44%) and in patients with advanced small cell lung cancer (35%).

The main objective of this trial is to determine the efficacy of the study treatment, in terms of ORR, in patients with advanced relapsed gastrointestinal malignancies with DNA repair mutations.

Up to 19 evaluable patients will be recruited to the study to test the null hypothesis that 5% or less patients will show a response to treatment with lurbinectedin versus the alternate hypothesis that 25% or more will respond to treatment. If at most 1 of the first 12 patients respond, the study will be stopped. If there are ≥ 2 responses, the study will be continued to 19 patients. If 3 or more respond, lurbinectedin will be considered promising for future study. The sample size justification is based on a Simon minimax two stage design, with alpha = 0.05 and power = 0.80.

Statistical Analysis Plan

7.3 Analysis of the Conduct of the Trial

Enrollment, major protocol deviations, and discontinuations for the trial will be summarized using a CONSORT diagram.

7.4 Patient Disposition

A detailed description of patient disposition will include:

- A summary of data on patient discontinuation from treatment.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol deviations.

All patients enrolled in the study will be included in the summation. Patients will be evaluable for safety if they received at least one full lurbinectedin infusion. The number of patients who do not qualify for analysis, who die or discontinue before treatment begins, will be specified.

7.5 Analysis of Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments

Other patient characteristics will be summarized as appropriate.

7.6 Efficacy Analysis

Patients will be evaluable for efficacy if they received at least one complete infusion of lurbinectedin (with a baseline and follow up scan). Those patients who are considered not evaluable will be replaced (see section “Replacement of patients”).

The primary objective of this study is to assess the antitumor activity of lurbinectedin as the **overall response rate (ORR)**, defined as the percentage of evaluable patients with a response, either complete (CR) or partial (PR). The ORR will be assessed using RECIST v.1.1, on a set of measurable lesions identified at baseline as target lesions, and non-target lesions (if any) and followed until progressive disease (PD) by an appropriate method (computed tomography [CT] scan or magnetic resonance imaging [MRI]).

Radiological and/or clinical (whenever appropriate) tumor assessment will be performed at baseline and every six weeks until evidence of PD. If an objective response is observed, according to RECIST v.1.1, it must be confirmed by the same method at least four weeks after the date of the first documentation of response.

ORR is defined as the percentage of patients with confirmed response, either CR or PR, from the start of treatment to the date of disease progression or the start of a subsequent therapy or end of patient’s follow-up, whichever comes first. The proportion will be estimated with a 95% exact confidence interval.

Tumor marker CA19-9, CEA, or CA125 (whichever is being followed) will be measured every three weeks prior to each new cycle. The obtained values will be correlated with RECIST v.1.1 evaluation, whenever possible. CA19-9, CEA, or CA125 values will not be used alone to guide clinical treatment decisions. Tumor markers will be plotted across time for each patient.

The date of response, the date of clinical and/or radiological PD and the date of death will be registered and documented (as appropriate).

A copy of the imaging tests conducted on all patients during this clinical trial may be requested by the Sponsor.

Progression-free survival (PFS), defined as the time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation. PFS will be estimated using the Kaplan-

Meier method with median PFS reported.

Progression-free survival rate at three months (PFS3), defined as the percentage of patients who are alive and progression-free three months after the first infusion. The proportion will be estimated with an exact 95% confidence interval.

Overall survival (OS), defined as the time from the date of first infusion to the date of death (of any cause) or last patient contact. OS will be estimated using the Kaplan-Meier method with median OS reported.

Overall survival rate at six months (OS6), defined as the percentage of patients who were alive six months after the first infusion. Overall survival rate at 12 months (OS12), defined as the percentage of patients who were alive 12 months after the first infusion. The proportions will be estimated with exact 95% confidence intervals.

Continuous variables will be summarized using the mean (SD) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics on response and toxicity rates. The distribution of time-to-event endpoints (e.g. response duration, progression-free survival, overall survival) will be estimated using the Kaplan and Meier method. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

7.7 Safety and Tolerance Analysis

Patients will be evaluable for safety if they received at least one full lurbinectedin infusion. All AEs will be graded according to the NCI-CTCAE v.5.

The safety profile of patients will be monitored throughout the treatment and up to 30 days (±7 days) after the last lurbinectedin infusion (End of Treatment, EOT), until the patient starts a new antitumor therapy or until the date of death, whichever occurs first.

Treatment delays, dose reduction requirements, transfusions requirements and reason for treatment discontinuation will be monitored throughout the study.

Any treatment-related AEs will be followed until recovery to grade ≤1 or baseline values, or stabilization of symptoms, whenever possible.

The incidence of grade 3 AEs (regardless of causality) and grade 3 treatment-related AEs (those AEs thought to be suspected related to study drug) will be summarized by NCI CTCAE version 5.0 term and maximum grade. The incidence of SAEs and AEs that lead to discontinuation of study drug will also be summarized. Listings of patients who discontinue study drug due to an AE and patients with SAEs and deaths will be presented. Narratives will be provided for patients who experience an SAE.

7.8 Laboratory Assessments

Hematology Parameters

To investigate the maximal degree of myelosuppression, the NCI CTCAE version 5.0 grade for WBC, ANC, platelet count, and hemoglobin concentration will be summarized by the most severe

grade in the first treatment cycle and by the most severe grade during the therapy for each treatment group; testing of treatment group differences will be performed using a CMH test. The incidence of patients with NCI CTCAE version 5.0 hematology values of Grade 3 or 4 that occurred after the first dose of study drug will be presented. Data for patients with Grade 3 or 4 hematology values will be listed.

Clinical Chemistry

Liver and renal function will be summarized using the NCI CTCAE version 5.0 for alkaline phosphatase, ALT, AST, total bilirubin, BUN and creatinine. The number and percentage of patients who have more than one NCI CTCAE version 5.0 grade will be summarized using the most severe Grade for the first cycle of therapy and for anytime during therapy for each treatment group; testing of treatment group differences will be performed using a Cochran-Mantel-Hanzel test. The incidence of patients with NCI CTCAE version 5.0 chemistry values of Grade 3 or 4 that occurred after the first dose of study drug will be presented. Data for patients with Grade 3 or 4 chemistry values will be listed.

7.8 Replacement of Patients

Patients will be replaced if they are not evaluable for the primary endpoint of the study (ORR as per RECIST v.1.1), specifically, if they have not been treated or have not received a complete lurbinectedin infusion (plus baseline and one follow up scan).

All replaced patients who received treatment will be included in the general safety analysis, if appropriate.

7.9. Tumor analysis

If possible per the investigator prior tumor tissue will be obtained at baseline and on progression for genomic analysis.

8.0 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

Ethics

Institutional Review Board/Ethics Committee Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by (Sponsor/CRO) prior to submission to the IRB. The Investigator will forward to (CRO or Sponsor) -nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CFR 56 of the *Code of Federal Regulations,* as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S.

In addition, the Investigator will be responsible for forwarding to (CRO or Sponsor) -nominated designee a description of the IRB board members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA and other appropriate

regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB for informational purposes.

7.9 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

Informed Consent

Written informed consent of the patient to participate in the study must be obtained and documented by the Investigator in accordance with the FDA regulations set forth in 21 CFR 50 as well as the applicable regulatory bodies in all other participating countries outside the United States.

The Investigator must provide the patient with a copy of the informed consent form in a language understandable to the patient. Written consent should be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care (e.g., withdrawal of current medications).

Changes made by a participating site to the recommended informed consent must be forwarded to HRI for approval prior to submission to the corresponding IRB. A copy of the signed informed consent will be given to the patient or their legal representative and a copy must be retained in the Investigator's study records.

Disclosure of Data

Confidentiality

The Investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other study personnel. Such information shall remain the confidential and proprietary property of HRI and shall be disclosed only to the Investigator or other designated study personnel.

The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the Investigator or other study personnel; and,
- information after such time that it is disclosed to the Investigator by a third party entitled to disclose such information.
- If the study site is a 'covered site' under the definitions of the Health Insurance Portability and Accounting Act (HIPAA), the Investigator will ensure that the patient consents to the use of data by the Sponsor and its designees for the purposes of regulatory submissions, study publications, and drug approval.

Publication

Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are patient to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

Quality Assurance

Study Data Monitoring Plan

Data monitoring procedures will be carried out by HRI for all participating sites and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documentation (including radiology review), review of study related regulatory documents and logs (e.g., enrollment, study site staff training and delegation) and review of drug infusion records will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the site monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The Principal Investigator and Clinical Research Coordinator responsible for the study will be provided with a follow-up letter for resolution of the findings.

The CRO site monitor will complete a written monitoring report and forward it to the HRI. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to HRI Administration and the site monitor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's study file for follow-up at the next monitoring session.

Data Safety and Monitoring

This treatment regimen combines 3 chemotherapeutic agents with known toxicity profiles. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities are considered to have an acceptable risk profile. Data reported to the sponsor will be received by the Lead Principal Investigator on a regular basis and not less than once a month. In addition, SAEs will be reported to the Sponsor immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the Lead Principal Investigator and the site Principal Investigators who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. The Sponsor will provide listings of toxicities on a regular basis.

On-site Audits

Regulatory authorities, the IEC/IRB, HRI may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

7.10 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the Lead Principal Investigator or HRI there is sufficient reasonable cause.

HRI has the right to discontinue the study under the conditions specified in the clinical trials agreement. Written notification documenting the reason for study termination will be provided to the site investigator by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to HRI.

Investigator Documentation

Form FDA 1572

The Investigator must provide HRI with a fully executed Form FDA 1572. Any additions to the study must be provided via a new fully executed Form FDA 1572. Others should follow FDA guidance “Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs”.

Curriculum Vitae

The Investigator must provide HRI with his/her current signed and dated curriculum vitae and a current signed and dated curriculum vitae for each sub-Investigator listed on Form FDA 1572. Current signed and dated curriculum vitae is defined as updated within 2 years of study start up.

Investigator Protocol Agreement

The Investigator must sign the Investigator’s Protocol Agreement. The original must be kept on file at the Investigator site and a copy provided to HRI The completed Investigator’s Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator’s Protocol Agreement must be signed if and when a protocol amendment is issued by (Sponsor/CRO).

Financial Disclosures

The Investigator and sub-Investigator(s) must complete a Clinical Investigator Financial Certification/Disclosure Statement to report financial interests and arrangements that may be of concern to FDA per 21 CFR 54.

Laboratory Certification and Normal Ranges

The Investigator will indicate on the Form FDA 1572 the name and location of any local laboratories that will be used for laboratory assessments. The Investigator will provide a copy of all clinical laboratory certifications, certification numbers, and dates of certifications, and. Normal ranges for all laboratory tests will be included with all reported results. Updated versions of these documents must be provided to HRI as appropriate. In the event the clinical laboratory is changed during the study HRI will be promptly notified, and the Form FDA 1572 will be updated. Appropriate documentation will be submitted to HRI to verify the certification of the new laboratory.

All radiology facilities being utilized outside the investigative site must be pre-approved by HRI.

Records Retention

In accordance with applicable regulatory requirements, following closure of the study, the Investigator will maintain a copy of all site study records in a safe and secure location. HRI will inform the Investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

HRI reserves the right to terminate the study for refusal of the Investigator and/or investigational site to comply with any requirements stated in this study protocol.

8 DATA MANAGEMENT

Case Report Forms

All the clinical data will be captured by the site on electronic case report forms (eCRFs). The eCRFs will be used for all consented patients. The investigator and trained trial personnel will enter and edit the data via a secure network, with secure identification and password requirement. A complete electronic audit trial will be maintained. The investigator will be required to provide approval of all data to confirm accuracy. Copies of the eCRFs will be provided to the investigator at the conclusion of the trial.

HRI will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCP guidelines as well as other applicable regulations and guidelines.

Source Documents

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor or assigned clinical monitor.

Data captured on the eCRFs is to be transcribed from source document and must be consistent with any discrepancies explained and documented.

REFERENCES

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

2. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015 Jun 25;372(26):2509-20. doi: 10.1056/NEJMoa1500596. Epub 2015 May 30. PMID: 26028255; PMCID: PMC4481136.

3. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015 Oct 29;373(18):1697-1708.

4. Ruiz-Bañobre J, Goel A. DNA Mismatch Repair Deficiency and Immune Checkpoint Inhibitors in Gastrointestinal Cancers. Gastroenterology. 2019 Mar;156(4):890-903. doi: 10.1053/j.gastro.2018.11.071. Epub 2018 Dec 19. PMID: 30578781; PMCID: PMC6409193.

5. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7-33. doi: 10.3322/caac.21654. Epub 2021 Jan 12. PMID: 33433946.

APPENDIX A: SCHEDULE OF TREATMENT AND EVALUATIONS

	Screening Within 21 Days	Cycle 1 and 2					Cycle 3+					Prior to Cycles 4, 7, 10, etc.	End of Study or Early Termination[11]	Follow-up
Assessment		**Day 1**	**Day 2**	**Day 8**	**Day 9**	**Day 15**	**Day 1**	**Day 2**	**Day 8**	**Day 9**	**Day 15**			
Window		+7 days[16]		+ 1 day			+7 days[16]							
Signed informed consent	X													
Review inclusion/exclusion	X	X												
Medical history[1]	X	X												
Physical examination	X	X[2]		X[3]		X	X						X	
Height (cm)	X													
Weight (kg)	X	X		X[3]			X[3]						X	
BSA calculation		X					X[4]							

Vital signs	X	X[3]		X[3]		X	X[3]						X	
ECOG PS	X	X[3]		X[3]		X	X[3]						X	
CT/ MRI scan / tumor measurements[5]	X											X	X	
ECG	X													
CBC w/differential & PLTs	X	X[2]		X[3]		X	X						X	
Serum chemistries [6,14]	X	X[2]		X[3]		X	X						X	
PT/INR	X	X[19]					X[19]							
CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)	X	X[2]					X						X	
Urinalysis[7]	X	X[2]					X						X	

Fresh Tissue and/or Archived blocks of tumor[8]	X[8]													
Serum pregnancy	X	X[2]					X						X	
Concomitant medications[9]	X	X		X		X	X						X	
Adverse events[10]		X		X		X	X						X	
Contact Information Review													X	X
Telephone follow-up[12]														X

Assessment	Screening Within 21 Days	Cycle 1 and 2					Cycle 3+					Prior to Cycles 4, 7, 10, etc.	End of Study or Early Termination[11]	Follow-up
		Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 9	Day 15			
Window		+7 days[16]		+ 1 day			+7 days[16]							
TREATMENT														
lurbinectedin		X					X							
Pegfilgrastim/filgrastrim[15]				X					X					

Schedule of Events footnotes:

1. To include concurrent baseline conditions (using NCI CTCAE, version 5.0), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2. Within 72 hours prior to Cycle 1 Day 1.
3. Should be performed ≤ 24 hours prior to the treatment day.
4. BSA only needs to be changed if there has been a change >10% in body weight from Cycle 1-Day 1 (See Section 4.2).
5. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, a brain scan is required to exclude brain metastases if clinically indicated only. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 5 days of starting chemotherapy. In addition to the CT / MRI scan, tumor size may also be assessed utilizing visual or palpable lesions on physical examination including full assessment of all known metastases (see RECIST 1.1 criteria in Section 6). Follow-up scans are due every 3 cycles (prior to cycle 4, 7, 10)
6. To include BUN, phosphorus, magnesium, creatinine, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, and electrolytes (chloride, sodium, potassium, and bicarbonate) and CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9).
7. Lab urinalysis to include protein, specific gravity, glucose, and blood.
8. Archived paraffin block of tumor specimen, metastatic tumor sample preferred. If patient is scheduled to undergo a tumor biopsy for standard of care purposes at any time. .
9. To include all medications taken within 30 days prior to study enrollment.
10. Patient will be followed until resolution of any drug-related AE or SAE occurring during the study, including, within 30 days of last administration of study medication, or when the patient begins alternative therapy; whichever is sooner.
11. End of Study or Early Termination assessments can be completed 14-28 (+/- 2) days from the last dose of study medication.
12. Follow-up assessments for survival in person or by telephone will be conducted in all patients 30 days after the End of Study or Early Termination Visit and then monthly for up to 12 months from the time of enrollment.
13. The Cockcroft-Gault equation may be used in calculating the creatinine clearance at any of the time points in this protocol.
14. Intended cycles may be delayed for non-toxicity reasons for up to 21 days (for reasons such as scheduling conflicts), but only with documentation and explanation in the CRF.

15. GCSF will be given after 24 hours after day 1 of every cycle .
16. PT/INR required only If patient is on anticoagulation with warfarin.

APPENDIX B: ECOG PERFORMANCE STATUS

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair

APPENDIX C: REVISED NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE), VERSION 5.0 (PUBLISHED 27 NOVEMBER 2017)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 can be viewed on-line at the following NCI web site:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

APPENDIX D: LURBINECTEDIN PACKAGE INSERT FOR STUDY DRUG PREPARATION, DOSING, ADMINISTRATION AND STORAGE

See links below to website access:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213702s000lbl.pdf