Title: A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable, Recurrent **or** Metastatic Biliary Tract Cancer (BTC)

NCT Number: 03790111

Protocol Approval Date: November 23, 2020

Certain information within this protocol has been redacted (ie, Specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of TerSera or partners, personal information, or to otherwise protect the integrity of the clinical study.

The information contained in the following document is the property of TerSera Therapeutics LLC and should not be shared or used for any purpose other than for which it was provided.

CLINICAL STUDY PROTOCOL

Protocol Number:	LX1606.1-207-BTC LX1606.207 (Abbreviated number)
Investigational Phase:	2a
Protocol Title:	A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable, Recurrent **or** Metastatic Biliary Tract Cancer (BTC)
Study Name:	TELE-ABC (**T**elotristat **E**thyl for **A**dvanced **B**iliary Tract **C**ancer)
Amendment 3 Date	23 November 2020
Administrative Change	29 May 2020
Amendment 2 Date	08 August 2019
Amendment 1 Date	13 December 2018
Original Version Date:	24 October 2018
Sponsor:	TerSera Therapeutics LLC 520 Lake Cook Road, Suite 500 Deerfield, IL 60015
Medical Director:	CCI CCI CCI
Co-Coordinating Investigators	CCI CCI CC1 CCI CCI CC1

Investigator Signature Page

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Amendment 1 Date	13 December 2018
Amendment 2 Date	08 August 2019
Amendment 3 Date	15 November 2020
Original Version Date:	24 October 2018
Sponsor:	TerSera Therapeutics LLC 520 Lake Cook Road, Suite 500 Deerfield, IL 60015

CCI CCI CCI

By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the United States (US) Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to participants.

TerSera Executive Vice President R&D and Chief Medical Officer (Signature)

CCI CCI CCI

Date
11/23/2020

Principal Investigator

(Signature) Date

Principal Investigator (Printed Name)

TerSera Executive Director of Clinical Development

CCI CCI CCI

Date
11/23/2020

PROTOCOL AMENDMENT SUMMARY OF KEY CHANGES

1. Replaced former Sponsor name (Lexicon) and contact details, including Medical Director, Medical Monitor and Safety reporting contacts with new Sponsor (TerSera Therapeutics LLC) and contact details throughout the protocol.
2. Added Amendment 3 date.
3. Clarified in the Synopsis and throughout the protocol that efficacy, based on progression-free survival rate at Month 6 will also be assessed in the Per Protocol population and by treatment cycle.
4. Clarified in the Synopsis and within the protocol that Cycle 10 Day 1 is considered the Month 6 timepoint and Cycle 19 Day 1 is considered the Month 12 timepoint for analysis purposes.
5. Clarified that enrollment into Stage 2 will continue if greater than or equal to (≥) 60% of patients in the Safety Population and the Per-Protocol (PP) population survive and remain progression-free at Month 6.
6. Clarified in the Synopsis and throughout the protocol that certain [redacted]
7. Updated the synopsis and throughout the protocol which endpoints are exploratory endpoints.
8. Added new exploratory efficacy endpoint [redacted]
9. Added new exploratory subgroup analyses [redacted]
10. Included that patients who prematurely discontinued from Treatment Period or withdrew consent from Treatment Period prior to Month 6 of the Treatment Period, will be asked to reconsent to allow for images and or imaging reports, obtained locally, to be submitted to BICR.
11. Added a formal interim analysis to be conducted on the Stage 1 analysis group, i.e., the first 20 patients enrolled in the study. The interim analysis results will include safety,

efficacy (response rates) and pharmacodynamic (biomarker) data. These data will be used to help plan for future studies.

12. Outlined that C1D1 images do not need to be collected and submitted to BICR when images that were obtained within 6 weeks prior to Day 1 were submitted to BICR.
13. Clarified that Screening images obtained within 6 weeks prior to and including Cycle 1 Day 1 (C1D1), or whichever images were closest in date to C1D1, will be considered Baseline.
14. Minor grammatical edits have been incorporated throughout the protocol.
15. Added Appendix K detailing each edit within the document, except minor grammatical changes.

For a detailed summary of all changes, please refer to Appendix K.

1 SYNOPSIS

Name of Study Drug	XERMELO® (telotristat ethyl)
Protocol Number	LX1606.1-207-BTC LX1606.207 (Abbreviated number)
Protocol Title	A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (telotristat ethyl) plus First-line Chemotherapy in Patients with Unresectable, Locally Advanced, Recurrent or Metastatic Biliary Tract Cancer (BTC)
Primary Objective	The primary objective of the study is to assess the safety and efficacy (PFS rate at Month 6) in the Safety population receiving the combination of XERMELO plus 1L treatment with cis/gem combination chemotherapy. Efficacy (PFS rate at Month 6) will also be evaluated in the Per Protocol Population (PP) and by treatment cycle.
Secondary Objectives	To assess the effect of study treatment on the following: • Overall survival (OS) • OS rate at Months 6 and 12 • PFS rate at Month 12 and median PFS at Month 12 • Disease control rate (DCR); defined as complete response (CR) + partial response (PR) + stable disease (SD) at Months 6 and 12 and End of Study (EOS) • Objective response rate (ORR) defined as CR + PR at Months 6 and 12 and EOS • Local radiologist's assessment of PFS, ORR, and DCR • Change from Baseline in plasma 5-hydroxyindoleacetic acid (5-HIAA) and serum carbohydrate antigen 19-9 (CA 19-9) at Months 6 and 12 and EOS • Change from Baseline in body weight at Months 6 and 12 and EOS • Change from Baseline in serum albumin at Months 6 and 12 and EOS **Note**: Unless otherwise indicated, all radiologic endpoints will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as determined by blinded independent central review (BICR) and compared to published historical data of cisplatin/gemcitabine (cis/gem) alone.

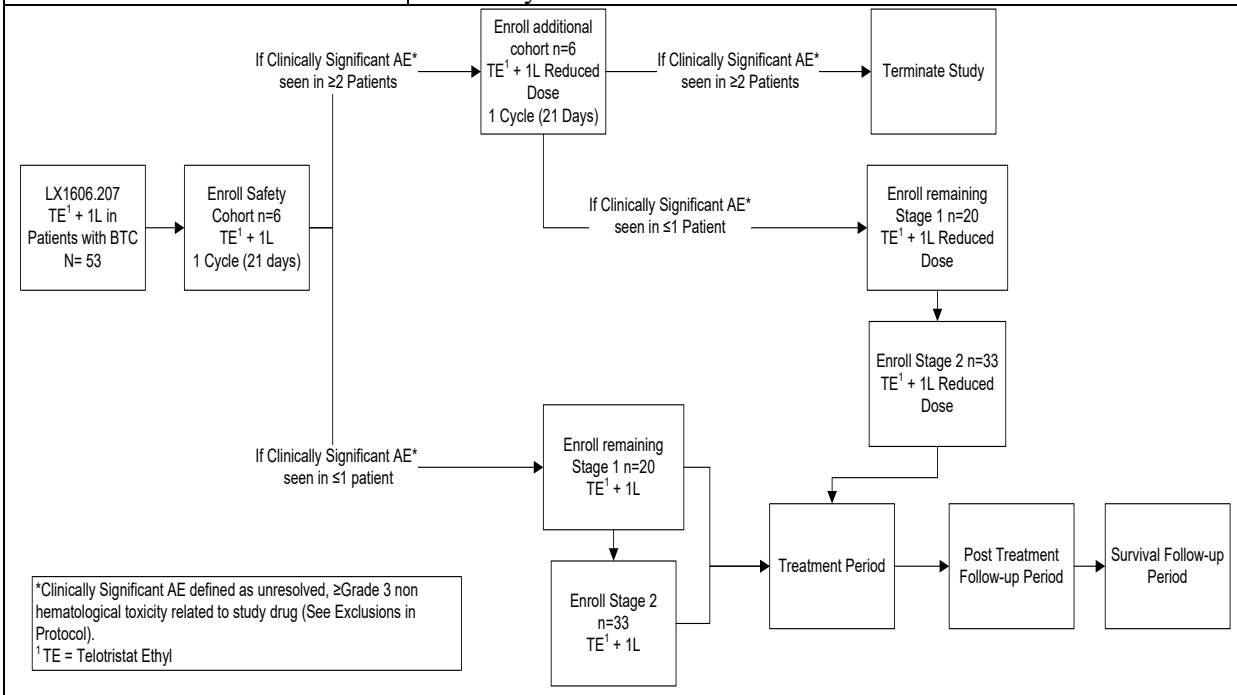
Exploratory Objectives	To assess the effect of study treatment on the following: • Changes in health-related quality of life (HRQoL) as measured by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21) items at Baseline, Months 6 and 12; • Change from Baseline in carcinogenic embryonic antigen (CEA) fragment at Months 6 and 12 and EOS; • Subgroup analyses of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment, based on categorical group of Baseline and change from Baseline at Months 6 and 12 and EOS in: CCI CCI CCI o body weight o serum albumin o correlation between Baseline neutrophil:lymphocyte ratio and OS • Subgroup analyses in: o Patients with changes in liver function tests o Patients with Biliary stents o Location of disease (intrahepatic, extrahepatic, or gallbladder) o Extent of disease o Demographic groups • Efficacy analyses by treatment cycles (such as in patients who completed CCI CCI with combination treatment)
Pharmacokinetic (PK) Objectives	To identify intrinsic and extrinsic factors contributing to variability in exposure of XERMELO and the active metabolite, LP-778902, when dosed as a combination treatment with cisplatin and gemcitabine, including but not limited to, age, sex, race, body mass index (BMI), as compared to historical data
Substudy Objectives	• To assess the effect of study treatment based on characterization of tumor tissue by immunohistochemical (IHC) staining (i.e., serotonin [5-HT] and tryptophan hydroxylase-1 [TPH-1]) • To determine the population PK profile among patients who participate in intensive PK sampling
Primary Safety Objectives	Evaluation of overall safety will be assessed by means of the following: • Incidence of treatment-emergent adverse events (TEAEs) and severity assessment using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0

	• Change from Baseline in clinical laboratory results including frequency of values meeting CTCAE severity Grades >1, laboratory data toxicities as defined by NCI CTCAE v5.0, physical examination (PE) findings, vital signs, and electrocardiogram (ECG) findings
Phase of Development	Phase 2a
Methodology	This study will be conducted as a multicenter, open-label, 2-stage study to assess the safety, tolerability, and efficacy of XERMELO in combination with first-line (1L) therapy (cisplatin plus gemcitabine) in patients with unresectable, locally advanced, recurrent or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer), who are naïve to tumor-directed therapy in the locally advanced or metastatic setting, and for which treatment with 1L therapy (defined as a combination of cis/gem) is planned. **Note**: 1L therapy will not be provided for this study by the Sponsor. **Note:** Efficacy (PFS rate at Month 6) will also be assessed in the Per Protocol population and by treatment cycle. **Note:** For statistical purposes and most analyses, Cycle 1 Day 1 is intended as Baseline, Cycle 10 Day 1 is intended as Month 6, and Cycle 19 Day 1 is intended as Month 12. <u>Study Overview:</u> <u>Stage 1</u> Stage 1 enrollment will include a Safety Run-in cohort. Safety and tolerability data of the combination treatment from the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment will be evaluated by the Coordinating Investigators, Sponsor, and Medical Monitor in accordance with established clinical stopping rules. This review will include all safety assessments from all patients obtained prior to the second chemotherapy cycle of the 6th patient enrolled. During this safety review, Stage 1 enrollment will continue as per the study schema outlined below. It is anticipated that a total of 20 patients will participate in Stage 1. If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug, and if efficacy in 12 (60%) or more of the 20 patients are deemed responders, in the Safety population, enrollment will continue to Stage 2. In addition, efficacy will be assessed in the Per-Protocol (PP) population and by treatment cycle. <u>Stage 2</u> Stage 2 may initiate enrollment once Stage 1 enrollment has been completed, in the absence of significant or unresolved Grade 3 or higher toxicities considered related to the study drugs. Approximately 33 additional patients are anticipated to participate in Stage 2. Study duration and assessments in this stage will be identical to Stage 1. From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 (>60%) or more responses are observed (i.e., patients are alive and progression-free at Month 6) in the Safety population, the study will

	be declared successful. Efficacy will also be assessed in the PP population and by treatment cycle. Study Treatment (Stage 1 and Stage 2) On Day 1 (D1), eligible patients are to initiate Cycle 1 (C1), a 21-day cycle of XERMELO plus 1L therapy (herein referred to as "combination treatment") as follows: o XERMELO 250 mg (1 x 250-mg tablet) given as an oral dose 3 times daily (tid) for 7 days, plus o Cisplatin 25 mg/m^2 administered intravenously (iv) over 60 to 90 minutes, followed by o Gemcitabine 1000 mg/m^2 administered iv over 30 minutes On Day 8, patients will receive combination treatment as follows: o XERMELO 500 mg (2 x 250-mg tablets) tid for 14 days, plus o Cis/Gem as described above Every 21 days thereafter, patients will initiate a new 21-day cycle (eg, Cycle 2 [C2], Cycle 3 [C3]) and will receive combination treatment, administered as o XERMELO 500 mg tid, plus o Cis/Gem regimen as described above on Day 1 and Day 8 of each cycle Dose modification(s) and/or delay in treatment may be permitted as described in the sections described below. During the Treatment Period, patients may discontinue cisplatin and continue treatment with XERMELO plus gemcitabine alone at the Investigator's discretion. Gemcitabine should be administered on the same schedule as described above. Active symptom control will be permitted during the study as clinically indicated. Radiological assessment of the tumor by computed tomography (CT) or magnetic resonance imaging (MRI) will be conducted prior to initiating treatment on Cycle 1 Day 1 (C1D1), then every 9 weeks (3 cycles) for the remaining duration of the Treatment Period. **Note:** If a radiological assessment has performed within 6 weeks prior to Day 1, a Day 1 assessment will not be required. All imaging will be evaluated by the local radiologist (or designee) for clinical management. If a change in response is noted by the local radiologist or Investigator at any time during the study a second radiological assessment should be performed within 4-6 weeks to confirm. All images will be sent to a central review facility for blinded, independent-parallel reading (i.e., BICR) for assessments of study endpoints. No information regarding results of progressive disease (PD) determination will be shared between central radiologic review and the local radiologist/Principal Investigator at any time during the study.

	Note: Management of biliary obstruction and/or ascending cholangitis will not be considered as PD in the absence of radiologically confirmed PD. Patients may continue to receive combination treatment as described above for as many cycles as possible until PD as determined by local review, unacceptable toxicity, or the patient withdraws from treatment. At this time, chemotherapy will be discontinued, the End-of-Treatment (EOT) assessments should occur, and the patient should enter the Follow-up Period. Visit dates for the Follow-up period are based off the EOT date. <u>Follow-up Periods:</u> All patients are expected to be followed for a total duration of 24 months after the Treatment Period unless they prematurely discontinue or voluntarily withdraw consent from future study visits or assessments. This 24-month phase is divided into 2 periods; the Post-treatment Follow-up Period (PTFP) where onsite visits occur every 3 months, and the Survival Follow-up Period, where survival status will be collected by phone and no onsite visits are required. <u>Post-treatment Follow-up</u> All patients are expected to enter a Post-treatment Follow-up Period (PTFP) at the time PD is confirmed locally or the patient experiences unacceptable toxicity, or the patient withdraws from chemotherapy in the absence of PD. During the Post-treatment Follow-up Period, patients may continue treatment with XERMELO at the discretion of the treating physician. Patients will complete scheduled study visits every 3 months for a total of 24 months or until the patient begins a new tumor-directed therapy, prematurely discontinues, declines further treatment after progression, or withdraws consent from future study visits or assessments. At this time, the End of Study (EOS) procedures should be performed and the patient should enter the Survival Follow-up (unless 24 months of follow-up after the last dose of chemotherapy has already occurred). **Note**: For those patients who enter the PTFP prior to PD confirmed locally (i.e., those who experience an unacceptable toxicity or withdraw from chemotherapy), routine imaging assessments will continue to be performed every 3 months until PD is confirmed by local review. **Note:** For those patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

	Survival Follow-up Once a new tumor-directed therapy begins, or a patient declines further treatment after progression, patients will enter the Survival Follow-up Period. All patients will be monitored until death, withdrawal of consent, loss to follow-up, or for a period of 24 months following the last dose of chemotherapy, whichever comes first. **Note:** Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study. The study scheme is as follows:



Number of Patients	A total of 20 patients are anticipated to be enrolled in Stage 1 and 33 patients in Stage 2, for a total of 53 patients enrolled in the study.
Patients	Eligible patients are defined as, adults of either sex (≥18 years of age) with unresectable, locally advanced, recurrent, or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer) naïve to tumor-directed therapy in the locally advanced or metastatic setting and are candidates to receive 1L therapy.
Number of Study Sites	Approximately 15 sites in the United States
Study Treatments	XERMELO (telotristat ethyl) tablets administered as 250 mg (1 x 250-mg tablet) tid for the first 7 days, then 500 mg (2 x 250-mg tablets) tid plus 1L therapy for the duration of the study

Route of Administration	XERMELO is administered orally, cisplatin and gemcitabine are administered intravenously.
Duration of Treatment	Approximately 6 months of combination treatment (XERMELO plus 1L therapy). **Note:** Patients may continue to receive treatment for as many cycles possible, until progressive disease (PD) (up to 19 cycles during the Treatment Period), and during the Post Treatment Follow-up Period (up to an additional 24 months) at the discretion of the Investigator.
Inclusion Criteria	Patients must meet **all** of the following criteria at Screening, or as otherwise indicated, to be considered eligible to participate in the study: 1. Adults of either sex, ≥18 years of age. Patients of childbearing potential must agree to use an adequate method of contraception during the study and for 30 days after the last dose of XERMELO. a. Childbearing potential is defined as those who have not undergone surgical sterilization (eg, documented hysterectomy, tubal ligation, or bilateral salpingo-oophorectomy) or those who are not considered postmenopausal (defined as 12 months of spontaneous amenorrhea). If necessary, follicular-stimulating hormone (FSH) results >35 IU/L at Screening are confirmatory in the absence of a clear postmenopausal history. b. Adequate methods of contraception, defined as having a failure rate of <1% per year, for patients or their partner include the following: condom with spermicidal gel, diaphragm with spermicidal gel, intrauterine device, surgical sterilization, vasectomy, oral contraceptive pill, depo-progesterone injections, progesterone implant (i.e., Implanon®), patch (Ortho Evra®), NuvaRing®, and abstinence. If a patient is not sexually active but becomes active, they or their partner should use medically accepted forms of contraception. 2. Histopathologically or cytologically-confirmed, unresectable, locally advanced, recurrent, or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer) 3. Naïve to tumor-directed therapy in locally advanced, unresectable, or metastatic setting. **Note**: Previous treatment with chemotherapy in the adjuvant setting (including previous exposure to 1L therapy) will be permitted if PD is confirmed >6 months following treatment. 4. Measurable disease, defined as the presence of at least 1 measurable lesion as determined by RECIST v1.1 using conventional imaging with CT or MRI 5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1

	6. Plans to initiate treatment with 1L therapy; defined as cis/gem: cisplatin 25 mg/m^2 administered iv over 60 to 90 minutes followed by gemcitabine1000 mg/m^2 administered iv over 30 minutes as standard of care 7. Ability to provide written informed consent prior to participation in any study-related procedure
Exclusion Criteria	Patients who meet **any** of the following criteria at Screening, or as otherwise indicated, will be excluded from participating in the study: 1. Prior exposure to XERMELO, telotristat ethyl, telotristat etiprate, LX1032, or LX1606 2. Primary tumor site in the ampulla of Vater 3. Treatment with photodynamic therapy for localized disease or to relieve biliary obstruction in the presence of metastatic disease within the past 30 days 4. Hematology laboratory values of: a. Absolute neutrophil count (ANC) ≤1,500 cells/mm^3; or b. Platelets ≤100,000 cells/mm^3; or c. Hemoglobin (Hgb) ≤9 g/dL; or d. White blood count (WBC) ≤3,000 cells/mm^3 5. Hepatic laboratory values of aspartate transaminase (AST) or alanine aminotransferase (ALT): a. >5 x upper limit of normal (ULN) if patient has documented history of hepatic metastases; or b. >2.5 x ULN if no liver metastases are present 6. Serum albumin <2.8 g/dL 7. Total bilirubin >1.5 x ULN or >1.5 mg/dL 8. Prothrombin time (PT) or international normalized ratio (INR) >1.5 x ULN. **Note:** Patients receiving therapeutic doses of anticoagulant therapy may be considered eligible if PT and INR are within the acceptable therapeutic limits for the institution. 9. Serum creatinine or serum urea >1.5 x ULN 10. Estimated glomerular filtration rate (eGFR) <50 mL/min 11. Positive pregnancy test, pregnant, or breastfeeding (female patients only) 12. Any other clinically significant laboratory abnormality that would compromise patient safety or the outcome of the study 13. Any clinically significant and/or uncontrolled cardiac-related abnormality that would compromise patient safety or the outcome of the study including, but not limited to: a. Arrhythmia b. Bradycardia c. Tachycardia d. Symptomatic valvular disease e. Symptomatic congestive heart failure classified by New York Heart Association (NYHA) as Class III or IV f. Evidence of ischemia on ECG

	g. Unstable angina pectoris 14. Myocardial infarction within the past 6 months 15. Active bleeding diathesis 16. Life expectancy ≤3 months 17. Current complaints of persistent constipation or history of chronic constipation, bowel obstruction or fecaloma within the past 6 months 18. Receiving chronic treatment with corticosteroids, ≥5 mg/day of prednisone (or equivalent), or other immunosuppressive agent(s) 19. Known history and/or uncontrolled hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus (HIV)-1 or HIV-2 **Note**: Because of the possibility of spontaneous resolution of and success of treatment for hepatitis C, a clarification is being provided. Patients who have a history of hepatitis C will be allowed if their HCV RNA load is below the range that reflects infection with the virus at a time point that is at least 12 weeks after a spontaneous remission or 24 weeks after the end of treatment for hepatitis C. Hepatitis B patients will continue to be excluded based on having history of the disease. 20. History of substance or alcohol abuse (Diagnostic and Statistical Manual of Mental Disorders 5th edition [DSM-V] Criteria for Substance-Related Disorders) within the past 2 years 21. History of galactose intolerance, deficiency of Lapp lactase, or glucose-galactose malabsorption 22. History of malignancy or active treatment for malignancy (i.e., radiation or chemotherapy, including monoclonal antibodies) within 5 years. **Note**: Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal breast cancer in situ, resected low-grade prostate cancer, or other malignancies that in the opinion of the Investigator and the Medical Monitor are considered cured, may participate. 23. Receipt of live, attenuated vaccine (eg, intranasal influenza, measles, mumps, rubella, varicella) or close contact with someone who has received a live, attenuated vaccine within the past 1 month. **Note**: Influenza vaccine will be allowed if administered >21 days prior to planned Day 1. 24. Receipt of any investigational agent or study treatment (i.e., any treatment or therapy not approved by the FDA for the treatment of BTC) within the past 30 days 25. Receipt of any protein or antibody-based therapeutic agents (eg, growth hormones or monoclonal antibodies) within the past 3 months 26. Treatment with any tumor-directed therapy including, but not limited to, chemotherapy or radiotherapy within the past 6 months with curative intent. **Note:** Treatment (i.e.,

	radiation, chemoembolization, radioembolization, or other local ablative therapies, or hepatic resection) is permitted if received ≥4 weeks from Screening and the patient has recovered to severity ≤Grade 1 toxicities as defined by NCI CTCAE v5.0. 27. Existence of any surgical or medical condition that, in the judgment of the Investigator, might compromise patient safety or the outcome of the study 28. Presence of any clinically significant findings (relative to the patient population) during review of medical history or upon PE that, in the Investigator's or Medical Monitor's opinion, would compromise patient safety or the outcome of the study (e.g., psychiatric illness/social situations that would limit compliance with study requirements) 29. Evidence of brain metastases 30. Unable or unwilling to communicate or cooperate with the Investigator for any reason 31. Employee of Sponsor or clinical site, or relative of any member of a clinical site's staff
Interim Analysis	A formal statistical interim analysis will be performed on patients included in the Stage 1 analysis. The interim analysis results will include safety, efficacy (PF responder rates), and pharmacodynamic (biomarker) data. These data will be used to help plan for future studies. Interim Analysis will be conducted: • In addition to (Stage 1 + Stage 2) analysis, after all 53 patients complete Month 6 • In addition to (Stage 1 + Stage 2) analysis after, all 53 patients complete Month 12
Statistical Methods	Three patient populations will be used for analyses. A Per-protocol (PP) population will consist of those patients that [redacted] and who have no major protocol violation(s) that would interfere with the collection or interpretation of the efficacy data. A Safety population will consist of all patients receiving any fraction of a dose of study drug. A PK population will be made up of all patients treated with at least 1 dose of study drug and who have adequate samples taken to reliably estimate the parameters of interest. The primary and secondary efficacy endpoints will be analyzed based on the Safety population. Additional analyses for the primary and secondary efficacy endpoints will be performed using the PP population. A Simon's 2-stage design algorithm will be used to assess whether the study is successful at each stage of the analysis. In the Stage 1 Safety population, if there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if 12 or more (≥60%) of the 20 patients enrolled are deemed responders per the definition below after the 20th patient is censored,

	is alive and progression-free at the Month 6 assessment, or has discontinued for any reason, the first stage of the study will be declared successful and enrollment will continue in Stage 2. Efficacy will also be assessed in the PP populations and by treatment cycle. **Note:** Patients are considered responders if they are alive and progression-free at the Month 6 assessment; otherwise, they are considered non-responders. In Stage 2, an additional 33 patients will be enrolled. If 34 (>60%) or more of the 53 patients enrolled (Stage 1 + Stage 2) are deemed responders, the study will be considered successful. Efficacy will also be assessed in the PP populations and by treatment cycle. For the primary endpoint, the distribution of PFS will be estimated using the Kaplan-Meier (KM) approach. The distribution of PFS from KM will be used to estimate the PFS rates and corresponding 95% confidence intervals (CI) at Month 6. In addition, the PFS rate at Month 12 and EOS visit along with their corresponding 95% CI will be presented. The median PFS value computed from this study will be compared with the historical/published median PFS time of cis/gem alone. Patients without PD or death will be censored at the last centrally confirmed radiographic assessment prior to study completion. In addition, patients who are lost to follow-up or discontinued from the study after receiving study treatment will be censored at the last date of contact prior to lost to follow-up or date of discontinuation, respectively. The same model will be applied to analyze the median OS and the OS rate at Months 6 and 12. Subgroup analyses may be performed based on the primary tumor site, prior therapy(ies), performance status, major demographic and prognostic subgroups, extent of disease, and Baseline biomarker levels. Descriptive statistics will be used to summarize the data for the response rates and pharmacodynamic endpoints. Continuous variables will be summarized by n, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by patient counts and percentages. All imaging for study endpoints will be assessed by the local radiologist and BICR. The BICR will supersede the local radiologist's assessment for the purpose of primary analysis of all applicable study objectives. A secondary analysis will be performed to further evaluate study objectives using the local radiologist assessments. For binary endpoints, such as ORR and DCR, the frequency and proportion of patients achieving the outcome in association with Fishers exact test will be presented at each assessed study time point. Other efficacy endpoints will be summarized descriptively by study time point. Change from Baseline for plasma CCI CCI CCI will be summarized descriptively and 1-sample t-tests may be performed to test for significance. In addition, descriptive

<table>
<tr><td></td><td>summaries of these endpoints will also be reported for responder and non-responder subgroups with respect to ORR and DCR.</td></tr>
<tr><td>Efficacy Assessments</td><td>Efficacy assessments include radiological study by CT or MRI and measurement of the tumor by RECIST v1.1 for the determination of PFS, ORR (CR+PR), and DCR (CR + PR + SD). In addition, HRQoL will be evaluated by EORTC QLQ-30 and QLQ-BIL21.</td></tr>
<tr><td>Safety Assessments</td><td>Safety and tolerability will be evaluated through the collection and review of TEAEs, including out-of-range laboratory parameters as graded by the CTCAE v5.0, vital signs measurement, 12-lead ECG findings, PE findings, and clinical laboratory parameters (chemistry, hematology, and urinalysis) including changes from Baseline and frequency of values meeting CTCAE Grades >1 for severity.</td></tr>
<tr><td>Pharmacodynamic and Pharmacokinetic Assessments</td><td>Pharmacodynamic assessments include the determination of CCI CCI CCI CCI
Pharmacokinetic (PK) assessments include the determination of concentrations of XERMELO and the active metabolite, LP-778902.</td></tr>
<tr><td>Dose Modification - XERMELO</td><td>In general, the following dose modification rules will be used with respect to potential toxicity and management of TEAEs believed to be related to XERMELO. Toxicity will be assessed according to the NCI CTCAE v5.0.
<table>
<tr><th>Grade of Event</th><th>Management/Next XERMELO Dose[2]</th></tr>
<tr><td>Grade 1</td><td>No change in dose</td></tr>
<tr><td>Grade 2</td><td>Hold until ≤Grade 1. Resume at same dose level.</td></tr>
<tr><td>Grade 3</td><td>Hold until ≤Grade 1. Resume at 1 dose level lower (250 mg tid).[1]</td></tr>
<tr><td>Grade 4</td><td>Discontinue treatment.</td></tr>
</table>
[1]Patients unable to tolerate 250 mg tid should be discontinued from XERMELO.
[2]Rechallenge may be permitted upon consultation with the Medical Monitor.
Recommended management for the following AEs:

Nausea and/or vomiting: treat with antiemetics
Diarrhea: treat as indicated for underlying cause
Gastrointestinal toxicity:

Monitor concomitant medication usage
Constipation (Grade 1 and above): initiate treatment as clinically indicated; examples of therapy(ies) include: laxatives, enemas, suppositories, psyllium hydration, over-the-counter (OTC) agents
Abdominal pain (Grade 1 and above): initiate treatment as clinically indicated; examples of therapy(ies) include: analgesics, anti-gas/bloating agents

</td></tr>
</table>

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<tr><td></td><td>

Hold XERMELO for Grade 2 constipation or abdominal pain until ≤Grade 1. Resume at 1 dose level lower (250 mg tid).
Discontinue XERMELO for Grade 3 constipation or abdominal pain.

• Suicidal ideation: discontinue XERMELO
</td></tr>
<tr><td>Dose Modification-Cisplatin/Gemcitabine</td><td>
In general, the following dose modification rules will be used with respect to potential toxicity and management of any TEAEs believed to be related to cisplatin or gemcitabine. Toxicity will be assessed according to the NCI CTCAE v5.0.

CCI CCI CCI
<table>
<tr><th>ANC</th><th></th><th>Platelet Count</th><th>Gemcitabine/Cisplatin</th></tr>
<tr><td>≥1,000/mm^3</td><td>and</td><td>≥100,000/mm^3</td><td>Treat as scheduled</td></tr>
<tr><td><1,000/mm^3</td><td>or/ and</td><td><100,000/mm^3</td><td>Defer treatment by 1 week. Reduce dose by 1 level for next treatment.</td></tr>
</table>
The following dose modification rules will be used with respect to hematologic toxicity on Day 8 of each treatment cycle believed to be related to cisplatin or gemcitabine:
<table>
<tr><th>ANC</th><th></th><th>Platelet Count</th><th>Gemcitabine/Cisplatin</th></tr>
<tr><td>≥1,000/mm^3</td><td>and</td><td>≥75,000/mm^3</td><td>Treat as scheduled</td></tr>
<tr><td><1,000/mm^3</td><td>or/ and</td><td><75,000/mm^3</td><td>Defer for 1 week. Reduce dose by 1 level for next treatment. If second deferral is needed, treatment will be omitted.</td></tr>
</table>
Note: Administration of granulocyte-colony stimulating factor (G-CSF) is allowed, but discontinuation is required at least 2 days prior to the next administration of chemotherapy. If symptoms do not resolve after 28 days of uninterrupted G-CSF, chemotherapy treatment should be stopped.

The following dose modification rules will be used with respect to nonhematologic toxicity on Day 1 of each treatment cycle believed to be related to cisplatin or gemcitabine.
</td></tr>
</table>

	<table><tr><th>Nonhematologic Toxicity[1]</th><th>Gemcitabine/Cisplatin</th></tr><tr><td>Grade 1 or 2</td><td>Treat as scheduled</td></tr><tr><td>Grade 3 or 4</td><td>Defer treatment until resolves to ≤Grade 1. Reduce dose by 1 level for next treatment.</td></tr></table> [1]Permissible exceptions to this rule are Grade 3 nausea, vomiting, hypertension, diarrhea, constipation, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care, and alopecia. The following dose modification rules will be used with respect to **nonhematologic toxicity on Day 8 of each treatment cycle** believed to be related to cisplatin or gemcitabine. <table><tr><th>Nonhematologic Toxicity[1]</th><th>Gemcitabine/Cisplatin</th></tr><tr><td>Grade 1 or 2</td><td>Treat as scheduled</td></tr><tr><td>Grade 3 or 4</td><td>Defer treatment until resolves to ≤Grade 1. Reduce dose by 1 level for next treatment. If deferral is needed for more than 1 week, treatment will be omitted.</td></tr></table> [1]Permissible exceptions to this rule are Grade 3 nausea, vomiting, hypertension, diarrhea, constipation, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care, and alopecia.
Clinical Stopping Rules	While the combination treatment in this study is assumed safe due to minimal overlapping toxicities, untoward side effects may occur. Therefore, assessment of the safety and tolerability data of all enrolled patients will occur once the 6th patient has completed 21 days of combination treatment and will include all safety assessments for all patients obtained prior to the second chemotherapy cycle of the 6th patient enrolled. The subsequent approach will be followed: • If ≤1 patient has a clinically significant (CS) adverse event (AE), the study will continue without a dose adjustment. • If ≥2 patients have CS AE, the dose level will be decreased to the Reduced Dose level in accordance with the table below, and 6 additional patients will be enrolled and treated with the Reduced Dose for 1 full cycle. o If ≤1 of these patients has a CS AE at the Reduced Dose for the 1st cycle, the Reduced Dose will be used for the study. o If ≥2 patients have a CS AE at the Reduced Dose, the study will be stopped. **Note:** A CS AE is considered an unresolved ≥Grade 3 nonhematological toxicity, which is related to the study drugs, excluding: controllable nausea, vomiting, hypertension, diarrhea, constipation, transient electrolyte abnormalities and alopecia; Grade 3 or higher febrile neutropenia.

	Dose Level / **Gemcitabine** / **Cisplatin** / **XERMELO** Starting Dose / 1000 mg/m^2 / 25 mg/m^2 / 500 mg tid Reduced Dose / 800 mg/m^2 / 20 mg/m^2 / 250 mg tid **Note:** If any patient experiences a Grade 4 toxicity during the Safety Run-in, the Sponsor, in consultation with the Investigator, will determine if additional patients should be enrolled at the Reduced Dose level.
Safety Data Analysis	Safety analysis will involve examination of the descriptive statistics and individual patient listings for any effects of XERMELO on clinical tolerability and safety. All safety data will be listed by patient. Summaries will be prepared by CTCAE grade for severity and, as needed, by cycle. The TEAE summaries will include the overall incidence (by System Organ Class [SOC] and Preferred Term [PT]), events by maximum intensity, event by relationship to each study drug, TEAEs by study drug exposure time, events leading to discontinuation of study drug, and serious adverse events (SAEs). Vital signs, ECG findings, PE findings, and laboratory variables (hematology, chemistry, and urinalysis) will be summarized descriptively at each time point. Actual and change from Baseline data will be calculated and summarized. In addition, shift tables will be generated for the laboratory variables including changes from Baseline and frequency of values meeting CTCAE Grades >1 for severity.
Pharmacokinetic Analysis	PK data will be summarized by n, arithmetic and geometric mean, standard deviation, median, minimum, and maximum values at various time points. Regression models may be used to evaluate the type and magnitude of associations between trough concentrations and clinical outcomes at selected time points. Based on intensive PK sampling from a subset of patients and sparse PK sampling (eg, trough concentrations) from the study population, population PK analyses will explore the effects of covariates including, but not limited to, age, sex, race, and body mass index (BMI) on the systemic exposure of XERMELO and the active metabolite, LP-778902, when dosed as a combination treatment with cisplatin and gemcitabine. PK data from this study may be integrated with PK data from other clinical trials to further enhance the population PK analysis. Details of population PK analysis plan will be prepared in a separate document. The data analysis plan and results from the population (cumulative) PK analysis will be documented in a separate report.

TABLE OF CONTENTS

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first-line
2L	second-line
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALKP	alkaline phosphatase
ALT	alanine aminotransaminase
ANC	absolute neutrophil count
AST	aspartate aminotransaminase
BICR	blinded independent central review
BMI	body mass index
BTC	biliary tract cancer
C1	Cycle 1
C1D1	Cycle 1, Day 1; Baseline (Baseline value is defined as the last non-missing data **on** **or** before the first dose of the study drug, unless otherwise specified)
C10D1	Cycle 10, Day 1 is intended as Month 6
C19D1	Cycle 19 Day 1 is intended as Month 12
CA 19-9	carbohydrate antigen 19-9
CBC	complete blood count
CCA	cholangiocarcinoma
CEA	carcinogenic embryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
cis	cisplatin
cis/gem	cisplatin/gemcitabine: cisplatin 25 mg/m^2 administered intravenously (iv) over 60 to 90 minutes followed by gemcitabine iv 1000 mg/m^2 administered iv over 30 minutes (also referred to as 1L therapy)
CMP	complete metabolic profile
CR	complete response
CRFg	Case Report Form guideline
CS	carcinoid syndrome or clinically significant
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (v 5.0)
D1	Day 1
DCR	disease control rate defined as CR+PR+SD
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th edition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End-of-Study
EOT	End-of-Treatment

Abbreviation	Definition
ERC	Ethics Review Committee
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
G-CSF	granulocyte-colony stimulating factor
GBC	gall bladder carcinoma
GCP	Good Clinical Practice
gem	gemcitabine
GGT	gamma-glutamyltransferase
GINA	Genetic Information Nondiscrimination Act of 2008
GLP	Good Laboratory Practice
HbsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus core antibody
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IAC	Independent Adjudication Committee
IB	Investigator Brochure
ICH	International Council for Harmonisation
IHC	immunohistochemical
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
iv	intravenously
KPS	Karnofsky Performance Scale
LDL	low-density lipoprotein
MAO-A	monoamino-oxidase A
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network®
NCI	National Cancer Institute
NCS	not clinically significant
NYHA	New York Heart Association
ORR	objective response rate defined as CR+PR
OTC	over-the-counter
OS	overall survival
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PHI	protected health information
PK	Pharmacokinetic
PP	per-protocol population
PR	partial response

Abbreviation	Definition
PT	Preferred Term or prothrombin time
QLQ-BIL21	Cholangiocarcinoma and Gallbladder Cancer Module
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	quality of life
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease or standard deviation
SFP	Survival Follow-up Period
SI	Le Système international d'unités (The International System of Units)
SOC	System Organ Class
SSA	somatostatin analog(s)
TEAE	treatment-emergent adverse events
TE	telotristat ethyl
tid	3 times daily
TPH	tryptophan hydroxylase
TPH-1	tryptophan hydroxylase-1
TTP	time to tumor progression
ULN	upper limit of the normal reference range
US	United States
v	version
WBC	white blood cell

Definitions of Investigational Product Terms

Term	Definition
LX1606 Hippurate or telotristat etiprate	salt form of the drug substance, LX1606 or telotristat ethyl
LP-778902 or telotristat or LX1033	active metabolite of LX1606 or telotristat ethyl
telotristat ethyl or LX1606	ethyl ester prodrug of the active metabolite LP-778902; XERMELO

3 INTRODUCTION

3.1 Background on XERMELO and Biliary Tract Cancer

Biliary tract cancer (BTC) is a group of malignancies that arise from the epithelium of the biliary tract. Classified by anatomical location, BTC includes cholangiocarcinoma (CCA), identified as intrahepatic or extrahepatic based on their location in relation to the liver, and gall bladder carcinoma (GBC) (Zhao, 2017). Approximately 10,000 new cases of BTC are diagnosed each year in the United States (US). Patients generally present with nonspecific abdominal symptoms that are bothersome, but not significantly burdensome for them to seek timely medical care. This most often results in a locally advanced, likely metastatic, BTC at the time of diagnosis (Marks, 2016). Demographically, the incidence of BTC increases with age. Patients are diagnosed later in life (between ages 40-70); there is a slight gender predominance in females for GBC and in males for CCA. A patient's geographic location plays a significant role in associated risk. The incidence of BTC is relatively rare in the Western world as compared to Asian countries where the liver fluke (a risk factor for BTC) is endemic but the overall incidence of BTC is rising; possibly due to increased recognition of the disease by physicians, improved diagnostic capabilities, and active screening of patients at high risk (Bergquist, 2015; Kanthan, 2015; Razumilava, 2014).

Management of risk factors and early detection of are key to improving survival in patients with BTC. Five years after diagnosis, 10% of patients with CCA and <5% with GBC remain alive. The 1-year survival rate for patients diagnosed with Stage 3 or 4 BTC is even lower. Only 10-15% of BTCs are amenable to surgery at initial presentation, and postresection recurrence rates remain at 50-60%. Given these statistics, it is apparent that these tumors are very aggressive malignancies with a very poor prognosis. Due to the rarity of this disease, evidence to support the role of adjuvant therapy is limited and available treatment options are not sufficient to address the poor survival rates in patients with locally advanced, recurrent, or metastatic BTC (Marks, 2016; Zhao, 2017).

Available Treatment Options

For patients presenting with unresectable BTC (locally advanced, recurrent, or metastatic) the current standard first-line (1L) therapy is a combination of cisplatin (cis) and gemcitabine (gem). The combination treatment (cis/gem) was found superior to gemcitabine alone in a randomized Phase 2 study (ABC-01) in 86 patients conducted in the United Kingdom (Valle, 2009). Treatment with cis/gem was associated with an improved disease control rate (DCR; complete response [CR] + partial response [PR] + stable disease [SD]; 75.0% vs 58.0%), time to tumor progression ([TTP]; 8.0 months vs 4.0 months) and 6-month

progression-free survival ([PFS]; 57.1% vs 45.5%) when compared to gemcitabine alone. Following the positive results, the ABC-01 trial was extended into a randomized, Phase 3 study (ABC-02) and powered to determine the effect of cis/gem or gemcitabine alone on overall survival (OS) and quality of life (QOL) (Valle, 2010).

In the ABC-02 study, the treatment regimens and eligibility criteria mirrored the ABC-01 study. A total of 410 patients were randomized (n=204 cis/gem vs. n=206 gem alone) and followed for a median of 8.2 months. Again, the combination treatment (cis/gem) was shown to be statically superior to gemcitabine alone; the median OS was 11.7 months vs 8.1 months, median PFS was 8.0 months vs 5.0 months, and DCR (CR + PR + SD) was 81.4% vs. 71.8%. Adverse events (AEs) were similar in the 2 groups with the exception of neutropenia, which was increased in the cis/gem group, although the number of neutropenia-associated infections was similar in the 2 groups (Valle, 2010).

A second randomized Phase 3 study (BT-22) was conducted in Japan and enrolled 84 Japanese patients (41 cis/gem vs 42 gem alone) with advanced BTC. For this study, the median OS was 11.2 vs 7.7 months, median PFS was 5.8 vs 3.7 months, and DCR (CR + PR + SD) was 68.3% vs 50.0% (Okusaka, 2010).

Treatment options for patients with unresectable BTC following the failure of 1L therapy remain limited and are not supported by Phase 3 data. Other chemotherapy combinations (eg, oxaliplatin, 5-FU, capecitabine) have demonstrated only marginal improvements in survival and targeted therapies, such as antiEGFR or antiVEGF antibodies, have produced limited success in early stage studies. As such, second-line (2L) treatment regimens are highly variable and are influenced by the physician's knowledge of available treatment options or, more likely, the availability of clinical trials (Zhao, 2017).

In February 2017, the US Food and Drug Administration (FDA) approved the oral drug telotristat ethyl (XERMELO) as a 2L therapy to be used in combination with somatostatin analogs (SSAs) to help address inadequate control of diarrheal symptoms in patients with carcinoid syndrome (CS). XERMELO has been shown to lower serotonin (5-HT) levels in the peripheral system by inhibiting tryptophan hydroxylase (TPH). Through inhibition of TPH, XERMELO reduces the production of peripheral 5-HT and the frequency of CS diarrhea. This intracellular mechanism of action complements the extracellularly mediated action of SSAs, providing a more complete inhibition of 5-HT overproduction than SSA therapy alone (Lexicon Pharmaceuticals, Inc., 2017).

3.2 XERMELO Pharmacology

A complete package of safety pharmacology has been conducted for XERMELO. Details may be found in the Investigator's Brochure (IB).

3.3 XERMELO Toxicology

A complete package of toxicology studies including Good Laboratory Practice (GLP)-compliant mammalian toxicology, genetic toxicology, and safety pharmacology has been conducted with XERMELO. Details may be found in the IB.

3.4 Clinical Trials of XERMELO in Humans

Detailed information regarding clinical studies may be found in the IB.

3.5 Rationale for Current Study

While XERMELO is indicated for the treatment of CS diarrhea in combination with SSA therapy in adults inadequately controlled by SSA therapy, its mediation of 5-HT may provide a larger benefit. Serotonin (5-HT) plays a critical role in regulating several major physiological processes including cell proliferation. Literature suggests cell proliferation is autoregulated by endogenously produced 5-HT and that high levels of circulating 5-HT may exert a direct mitogenic effect on tumor cells, leading to tumor growth. Further, by modulating the amount of 5-HT exposure, tumor growth may be inhibited through vasoconstrictive action on the arterioles feeding the malignant growth, an antiangiogenic effect (Sarrouilhe, 2015).

In vitro and in vivo studies have shown increased expression of TPH 1 and decreased expression of monoamino-oxidase A (MAO-A), the enzyme responsible for the degradation of serotonin, indicating that the metabolism of 5-HT is dysregulated. The result of this type of dysregulation is an increase in the production and secretion of 5-HT (Alpina, 2018; Huang, 2012; Sarroulilhe, 2015). In addition, treatment with 5-HT increased CCA cell growth in vivo and inhibition of 5-HT synthesis significantly blocked the growth of CCA in vivo and in vitro (Alpina, 2018; Huang, 2012; Sarroulilhe, 2015).

A novel treatment approach that inhibits 5-HT production may provide clinical benefit to the significant number of patients with unresectable BTC. Adding a TPH inhibitor, like XERMELO to the treatment paradigm in combination with 1L therapy, may improve the physician’s armamentarium and fulfill the unmet medical need for patients with advanced BTC.

The AE profiles of XERMELO and the cis/gem combination are largely distinct and do not overlap, except for events related to elevations of liver function tests (LFTs). This is not surprising, as liver involvement occurs often in the setting of advanced BTC and in patients with advanced NETs. In order to address a potential risk to patients with liver involvement, the study will exclude patients with aspartate transaminase (AST) or alanine aminotransaminase (ALT) levels >5 x upper limit of normal (ULN) who have a documented history of hepatic metastases. Moreover, a Safety Run-in has been included in the design of the study since this will be the first time that these 3 agents will be used concomitantly in patients. A total of 6 patients with advanced BTC will be enrolled and treated with XERMELO plus 1L therapy for 1 cycle (21 days) to assess the safety of the triple combination before enrolling additional patients. Liver function will be closely monitored throughout the study and dose adjustment/modification rules are described in Section 7.5.

The known and largely nonoverlapping safety profiles of XERMELO and the combination chemotherapy (cis/gem) suggest concomitant use is a rational approach to investigate the potential additive clinical benefit of XERMELO to 1L treatment, the current standard of care in eligible patients with advanced BTC.

This study is intended to assess the effect of XERMELO in combination with 1L chemotherapy on PFS in patients with locally advanced, unresectable, recurrent or metastatic BTC who are naïve to tumor-directed therapy in the locally advanced or metastatic setting and for which treatment with 1L therapy is planned.

3.6 Rationale for Selection of Dose

The dose level of XERMELO selected for this study is consistent with prior clinical study experience and is based upon clinical safety and pharmacodynamic (PD) data from Phase 2 and Phase 3 multiple ascending-dose studies in patients with symptomatic CS. Dosages of 1L therapy are consistent with standard of care established by the ABC-02 trial (Valle, 2010).

Based upon clinical study results, information for the XERMELO 500 mg tid dose level is more robust in terms of patient years of exposure and has an improved efficacy profile than the marketed dosage of 250 mg tid.

As such, it is anticipated that the combination of therapies, at the dose levels proposed in this protocol, will be safe and well tolerated and may provide clinical benefit to patients with BTC.

3.7 Rationale for Study Design

An open-label study will allow for the assessment of the safety, tolerability, and efficacy XERMELO plus 1L therapy, herein referred to as “combination treatment” in a transparent manner. Should an efficacy signal be identified, additional studies may be undertaken to further assess the effect of the combination treatment in a larger patient population.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of the study is to assess the safety and efficacy (PFS rate at Month 6) in the Safety population receiving the combination of XERMELO plus 1L treatment with cis/gem combination chemotherapy. Efficacy (PFS rate at Month 6) will also be evaluated in the Per Protocol Population (PP) and by treatment cycle.

4.2 Secondary Objectives

To assess the effect of study treatment on the following:

- Overall survival (OS)
- OS rate at Months 6 and 12
- PFS rate at Month 12 and median PFS at Month 12
- Disease control rate (DCR); defined as complete response (CR) + partial response (PR) + stable disease (SD) at Months 6 and 12 and End of Study (EOS)
- Objective response rate (ORR) defined as CR + PR at Months 6 and 12 and EOS
- Local radiologist's assessment of PFS, ORR, and DCR
- Change from Baseline in CCI CCI CCI CCI CCI Months 6 and 12 and EOS
- Change from Baseline in body weight at Months 6 and 12 and EOS
- Change from Baseline in serum albumin at Months 6 and 12 and EOS

Note: Unless otherwise indicated, all radiologic endpoints will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as determined by blinded independent central review (BICR) and compared to published historical data of cisplatin/gemcitabine (cis/gem) alone.

4.3 Exploratory Objectives

To assess the effect of study treatment on the following:

- Changes in health-related quality of life (HRQoL) as measured by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21) items at Baseline, Months 6 and 12
- Change from Baseline in CCI CCI CCI fragment at Months 6 and 12 and EOS
- Subgroup analyses of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment, based on categorical group of Baseline and change from Baseline at Months 6 and 12 and EOS in:

CCI

CCI

CCI

- body weight
- serum albumin
- correlation between Baseline neutrophil:lymphocyte ratio and OS

- Subgroup analyses in:
  - Patients with changes in liver function tests
  - Patients with Biliary stents
  - Location of disease (intrahepatic, extrahepatic, or gallbladder)
    - Extent of disease
    - Demographic groups
- Subgroup analyses of patients by treatment cycles (such as patients who completed C CCI CCI with combination treatment

4.4 Pharmacokinetic (PK) Objective

The pharmacokinetic (PK) objective is to identify intrinsic and extrinsic factors contributing to variability in exposure of XERMELO and the active metabolite, LP-778902, when dosed as a combination treatment with cisplatin and gemcitabine, including but not limited to, age, sex, race, and body mass index (BMI), as compared to historical data.

4.5 Substudy Objectives

- To assess the effect of study treatment based on characterization of tumor tissue by immunohistochemical (IHC) staining (i.e., serotonin [5-HT] and tryptophan hydroxylase-1 [TPH-1])
- To determine the population PK profile among patients who participate in intensive PK sampling

4.6 Safety Objectives

Evaluation of overall safety will be assessed by means of the following:

- Incidence of treatment-emergent adverse events (TEAEs) and severity assessment using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
- Change from Baseline in clinical laboratory results including frequency of values meeting CTCAE severity Grades >1, laboratory data toxicities as defined by NCI CTCAE v5.0, physical examination (PE) findings, vital signs, and electrocardiogram (ECG) findings

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This study will be conducted as a multicenter, open-label, 2-stage study to assess the safety , tolerability, and efficacy of XERMELO in combination with first-line (1L) therapy (cisplatin plus gemcitabine) in patients with unresectable, locally advanced, recurrent or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer), who are naïve to tumor-directed therapy in the locally advanced or metastatic setting, and for which treatment with 1L therapy (defined as a combination of cis/gem) is planned.

Note: 1L therapy will not be provided for this study by the Sponsor.

5.1.1 Screening

All patients are allowed a Screening Period of up to 21 days prior to Cycle 1 Day 1 (C1D1) when assessments for determining eligibility will be conducted per Appendix A. Written informed consent will be obtained from all patients before beginning any study related screening procedures. The collection of SAEs will begin after the patient has signed informed consent.

Note: If radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated at Day 1.

5.1.2 Study Overview

5.1.2.1 Treatment Period

Stage 1

Stage 1 enrollment will include a Safety Run-in cohort. Safety and tolerability data of the combination treatment from the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment will be evaluated by the Coordinating Investigators, Sponsor, and Medical Monitor in accordance with established clinical stopping rules. This review will include all safety assessments from all patients obtained prior to the second chemotherapy cycle of the 6th patient enrolled. During this safety review, Stage 1 enrollment will continue as per the study schema (Figure 5-1). It is anticipated that a total of 20 patients will participate in Stage 1.

Stage 2

Stage 2 may initiate enrollment once Stage 1 enrollment has been completed, in the absence of significant or unresolved Grade 3 or higher toxicities considered related to the study drugs.

Approximately 33 additional patients are anticipated to participate in Stage 2. Study duration and assessments in this stage will be identical to Stage 1. From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 or more (>60%) responses are observed (i.e., patients are alive and progression-free at Month 6), the study will be considered successful.

Study Treatment (Stage 1 and Stage 2)

On Day 1 (D1), eligible patients are to initiate Cycle 1 (C1), a 21-day cycle of XERMELO plus 1L therapy (herein referred to as "combination treatment") as follows:

- XERMELO 250 mg (1 x 250-mg tablet) given as an oral dose 3 times daily (tid) for 7 days, plus
- Cisplatin 25 mg/m^2 administered intravenously (iv) over 60 to 90 minutes, followed by
- Gemcitabine 1000 mg/m^2 administered iv over 30 minutes

On Day 8, patients will receive combination treatment as follows:

- XERMELO 500 mg (2 x 250-mg tablets) tid for 14 days, plus
- Cis/Gem as described above

Every 21 days thereafter, patients will initiate a new 21-day cycle (eg, Cycle 2 [C2], Cycle 3 [C3]) and will receive combination treatment, administered as:

- XERMELO 500 mg tid, plus
- Cis/Gem regimen as described above on Day 1 and Day 8 of each cycle

Dose modification(s) and/or delay in treatment may be permitted as described in Section 7.5. During the Treatment Period, patients may discontinue cisplatin and continue treatment with XERMELO plus gemcitabine alone at the Investigator's discretion. Gemcitabine should be administered on the same schedule as described above.

Active symptom control will be permitted during the study as clinically indicated.

Radiological assessment of the tumor by computed tomography (CT) or magnetic resonance imaging (MRI) will be conducted prior to initiating treatment on Cycle 1 Day 1(C1D1), then every 9 weeks (3 cycles) for the remaining duration of the Treatment Period. **Note:** If a radiological assessment has not been performed within 6 weeks prior to Day 1, a Screening assessment will also be required.

All imaging will be evaluated by the local radiologist (or designee) for clinical management. If a change in response is noted by the local radiologist or Principal Investigator at any time

during the study a second radiological assessment should be performed within 4-6 weeks to confirm.

All images will be sent to a central review facility for blinded, independent-parallel reading (i.e., BICR) for assessments of study endpoints (Section 8.2.1). No information regarding results of PD determination will be shared between central radiologic review and the local radiologist/Principal Investigator at any time during the study.

Note: Management of biliary obstruction and/or ascending cholangitis will not be considered as PD in the absence of radiologically confirmed PD.

Patients may continue to receive treatment as described above for as many cycles possible until progressive disease (PD) as determined by local review, unacceptable toxicity, or the patient withdraws from treatment. At this time, chemotherapy will be discontinued, End-of-Treatment (EOT) assessments should occur, and the patient should enter the Follow-up Period. The Follow-up visit dates will be based off of the EOT date.

5.1.2.2 Follow-up Periods

All patients are expected to be followed for a total duration of 24 months after the Treatment Period unless they prematurely discontinue or voluntarily withdraw consent from future study visits or assessments. This 24-month phase is divided into 2 periods; the Post-treatment Follow-up Period (PTFP) where onsite visits occur every 3 months, and the Survival Follow-up Period (SFP), where survival status will be collected by phone and no onsite visits are required.

Post-treatment Follow-up Period

All patients are expected to enter a PTFP at the time PD is confirmed locally or the patient is no longer able to tolerate chemotherapy plus XERMELO in the absence of PD. During the Post-treatment Follow-up Period, patients may continue treatment with XERMELO at the discretion of the treating physician.

Patients will complete scheduled study visits every 3 months for a total duration of 24 months or until the patient begins a new tumor-directed therapy, prematurely discontinues, declines further treatment after progression, or withdraws consent from future study visits or assessments. At this time, the End of Study (EOS) procedures should be performed and the patient should enter the SFP (unless 24 months of follow-up after the last dose of chemotherapy has already occurred).

Note: For those patients who enter the PTFP prior to PD confirmed locally (i.e., those who experience an unacceptable toxicity or withdraw from chemotherapy), routine imaging assessments will continue to be performed every 3 months during the Post-treatment Follow-up Period until PD is confirmed by local review.

Note: Patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

Survival Follow-up

Once a new tumor-directed therapy begins, or a patient declines further treatment after progression, patients will enter the SFP. During this period, all patients (or caregivers, where appropriate) will be contacted by phone every 3 months to obtain the patient's survival status until death, prematurely discontinue, withdrawal of consent, loss to follow-up, or for a period of 24 months following the last dose of chemotherapy, whichever occurs first. The site should make every attempt to document the date of death, if appropriate.

Note: Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

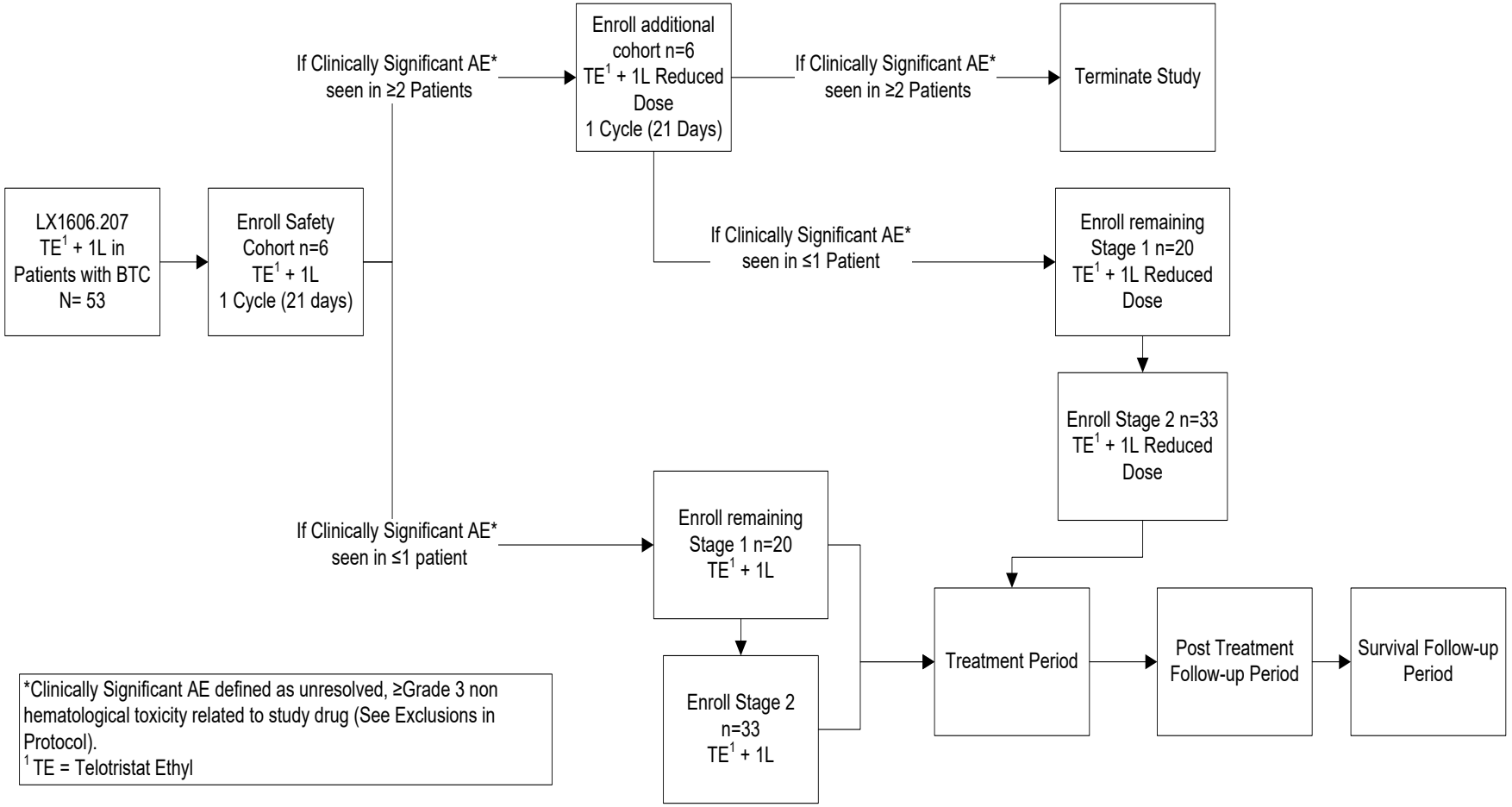
Note: The total duration of the PTFP and SFP combined should be no more than 24 months.

Reconsent

In cases when a patient has prematurely discontinued from the study and/or withdrawn consent from conducting further study assessments, these patients may be asked to re-consent to provide permission for their local imaging and imaging reports to be submitted to BICR.

The treatment schema is summarized in Figure 5-1.

Figure 5-1 Treatment Schema



6 STUDY POPULATION

It is anticipated that a total of 53 adult (>18 years of age) patients will be enrolled in 2 stages (n1=20 patients enrolled in Stage 1 and n2 = 33 patients enrolled in Stage 2) with unresectable, locally advanced, recurrent, or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer) naïve to tumor-directed therapy in the locally advanced or metastatic setting and are candidates to receive 1L therapy from approximately 15 centers in the United States over an 18-month period.

6.1 Inclusion Criteria

Patients must meet all of the following criteria at Screening, or as otherwise indicated, to be considered eligible to participate in the study:

1. Adults of either sex, ≥18 years of age. Patients of childbearing potential must agree to use an adequate method of contraception during the study and for 30 days after the last dose of XERMELO.
    a. Childbearing potential is defined as those who have not undergone surgical sterilization (eg, documented hysterectomy, tubal ligation, or bilateral salpingo-oophorectomy) or those who are not considered postmenopausal (defined as 12 months of spontaneous amenorrhea). If necessary, follicular-stimulating hormone (FSH) results >35 IU/L at Screening are confirmatory in the absence of a clear postmenopausal history.
    b. Adequate methods of contraception, defined as having a failure rate of <1% per year, for patients or their partner include the following: condom with spermicidal gel, diaphragm with spermicidal gel, intrauterine device, surgical sterilization, vasectomy, oral contraceptive pill, depo-progesterone injections, progesterone implant (i.e., Implanon®), patch (Ortho Evra®), NuvaRing®, and abstinence. If a patient is not sexually active but becomes active, they or their partner should use medically accepted forms of contraception.
2. Histopathologically or cytologically-confirmed, unresectable, locally advanced, recurrent, or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer)
3. Naïve to tumor-directed therapy in locally advanced, unresectable, or metastatic setting. **Note:** Previous treatment with chemotherapy in the adjuvant setting (including previous exposure to 1L therapy) will be permitted if PD is confirmed >6 months following treatment.
4. Measurable disease, defined as the presence of at least 1 measurable lesion as determined by RECIST v1.1 using conventional imaging with CT or MRI

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
6. Plans to initiate treatment with 1L therapy; defined as cis/gem: cisplatin 25 mg/m^2 administered iv over 60 to 90 minutes followed by gemcitabine1000 mg/m^2 administered iv over 30 minutes as standard of care
7. Ability to provide written informed consent prior to participation in any study-related procedure

6.2 Exclusion Criteria

Patients who meet any of the following criteria at Screening or as otherwise indicated, will be excluded from participating in the study:

1. Prior exposure to XERMELO, telotristat ethyl, telotristat etiprate, LX1032, or LX1606
2. Primary tumor site in the ampulla of Vater
3. Treatment with photodynamic therapy for localized disease or to relieve biliary obstruction in the presence of metastatic disease within the past 30 days
4. Hematology laboratory values of:
    a. Absolute neutrophil count (ANC) ≤1,500 cells/mm^3; or
    b. Platelets ≤100,000 cells/mm^3; or
    c. Hemoglobin (Hgb) ≤9 g/dL; or
    d. White blood count (WBC) ≤3,000 cells/mm^3
5. Hepatic laboratory values of aspartate transaminase (AST) or alanine aminotransferase (ALT):
    a. >5 x upper limit of normal (ULN) if patient has documented history of hepatic metastases; or
    b. >2.5 x ULN if no liver metastases are present
6. Serum albumin <2.8 g/dL
7. Total bilirubin >1.5 x ULN or >1.5 mg/dL
8. Prothrombin time (PT) or international normalized ratio (INR) >1.5 x ULN. **Note**: Patients receiving therapeutic doses of anticoagulant therapy may be considered eligible if PT and INR are within the acceptable therapeutic limits for the institution.
9. Serum creatinine or serum urea >1.5 x ULN
10. Estimated glomerular filtration rate (eGFR) <50 mL/min
11. Positive pregnancy test, pregnant, or breastfeeding (female patients only)

12. Any other clinically significant laboratory abnormality that would compromise patient safety or the outcome of the study
13. Any clinically significant and/or uncontrolled cardiac-related abnormality that would compromise patient safety or the outcome of the study including, but not limited to:
    a. Arrhythmia
    b. Bradycardia
    c. Tachycardia
    d. Symptomatic valvular disease
    e. Symptomatic congestive heart failure classified by New York Heart Association (NYHA) as Class III or IV (Criteria Committee of the NYHA, 1994)
    f. Evidence of ischemia on ECG
    g. Unstable angina pectoris
14. Myocardial infarction within the past 6 months
15. Active bleeding diathesis
16. Life expectancy ≤3 months
17. Current complaints of persistent constipation or history of chronic constipation, bowel obstruction or fecaloma within the past 6 months
18. Receiving chronic treatment with corticosteroids of ≥5 mg/day of prednisone (or equivalent), or other immunosuppressive agent(s)
19. Known history and/or uncontrolled hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus (HIV)-1 or HIV-2

    Note: Because of the possibility of spontaneous resolution of and success of treatment for hepatitis C, a clarification is being provided. Patients who have a history of hepatitis C will be allowed if their HCV RNA load is below the range that reflects infection with the virus at a time point that is at least 12 weeks after a spontaneous remission or 24 weeks after the end of treatment for hepatitis C.

    Hepatitis B patients will continue to be excluded based on having history of the disease.
20. History of substance or alcohol abuse (Diagnostic and Statistical Manual of Mental Disorders 5th edition [DSM-V] Criteria for Substance-Related Disorders) within the past 2 years (American Psychiatric Association, 2013)

21. History of galactose intolerance, deficiency of Lapp lactase, or glucose-galactose malabsorption
22. History of malignancy or active treatment for malignancy (i.e., radiation or chemotherapy, including monoclonal antibodies) within 5 years. **Note**: Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal breast cancer in situ, resected low-grade prostate cancer, or other malignancies that in the opinion of the Investigator and the Medical Monitor are considered cured, may participate.
23. Receipt of live, attenuated vaccine (eg, intranasal influenza, measles, mumps, rubella, varicella) or close contact with someone who has received a live, attenuated vaccine within the past 1 month. **Note**: Influenza vaccine will be allowed if administered >21 days.
24. Receipt of any investigational agent or study treatment (i.e., any treatment or therapy not approved by the FDA for the treatment of BTC) within the past 30 days
25. Receipt of any protein or antibody-based therapeutic agents (eg, growth hormones or monoclonal antibodies) within the past 3 months
26. Treatment with any tumor-directed therapy including, but not limited to, chemotherapy or radiotherapy within the past 6 months with curative intent. **Note**: Treatment (i.e., radiation, chemoembolization, radioembolization, or other local ablative therapies, or hepatic resection) is permitted if received ≥4 weeks from Screening and the patient has recovered to ≤Grade 1 toxicities as defined by NCI CTCAE v5.0.
27. Existence of any surgical or medical condition that, in the judgment of the Investigator, might compromise patient safety or the outcome of the study
28. Presence of any clinically significant findings (relative to the patient population) during review of medical history or upon PE that, in the Investigator's or Medical Monitor's opinion, would compromise patient safety or the outcome of the study (eg, psychiatric illness/social situations that would limit compliance with study requirements)
29. Evidence of brain metastases
30. Unable or unwilling to communicate or cooperate with the Investigator for any reason
31. Employee of Sponsor or clinical site, or relative of any member of a clinical site's staff

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may be discontinued from the study treatment and/or withdrawn from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including failure to adhere to the study requirements as in the study protocol, and/or lost to follow-up
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study (Section 6.4)
- Pregnancy (Section 9.3.1)
- Progressive disease based on RECIST v1.1
- Patient is unable to tolerate XERMELO following dosage reduction to 250 mg tid
- Patient experiences:
  - Unresolved Grade 3 constipation as graded by the NCI CTCAE v5.0; or
  - Development of severe, persistent, or worsening abdominal pain
  - Continuing or recurrent Grade 4 toxicity (with the exception of alopecia, inadequately treated nausea, vomiting, diarrhea, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care)
  - Suicidal ideation
  - Death

6.3.1 End-of-Treatment (EOT)/End-of-Study (EOS) Procedures

6.3.1.1 End-of-Treatment Procedures

The EOT procedures should occur as close to the last day of combination treatment whenever possible for all patients. Any assessments that have occurred <3 weeks prior to this visit will not be required to be repeated. See Appendix A for a list of all required EOT assessments. If a patient voluntarily withdraws consent from the study during the Treatment Period, or is discontinued prior to progressing, every attempt should be made to have the patient return to the clinic to complete all required EOT assessments and ask if the patient wishes to remain in the study by continuing into either Follow-up Period; PTFP where clinic visits occur every 3 months, or SFP where phone calls occur instead of on-site visits. The date the patient discontinues the treatment, the treatment(s) discontinued, the primary reason for discontinuation (eg, AE, PD, protocol deviation, withdrawal of consent, lost to follow-up,

death) and whether they will continue in either Follow-up Period must be recorded on the electronic case report form (eCRF). The patient must agree to report any AEs, including serious adverse events (SAEs), see Section 9.4, for 30 days following their last dose of any study drug.

Note: If the patient does not wish to enter the PTFP, EOS procedures should occur in the place of EOT procedures; see Appendix A for a list of all required EOS and EOT procedures.

For those patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint.

6.3.1.2 End-of-Study Procedures

The EOS procedures should occur at the final Post-treatment Follow-up visit whenever possible. Any assessments that have occurred ≤8 weeks prior to this visit will not be required to be repeated. See Appendix A for a list of all required EOS procedures. If a patient voluntarily withdraws or is discontinued from the study prior to completing the 24-month Follow-up Period, every attempt should be made to have the patient return to the clinic to complete the EOS assessments. Patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. See Appendix A for a list of all EOS assessments required. In addition, if a patient voluntarily ends participation in the study at any time, the primary reason for discontinuation (e.g., AE, PD, protocol deviation, withdrawal of consent, lost to follow-up, death) must be recorded on the eCRF and document whether the patient agrees to attend future study visits, allow contact by study personnel, and/or continued access to information and/or images about disease status and potential SAEs. The date the patient discontinues participation and the primary reason for discontinuation of participation (eg, AE, PD, protocol deviation, withdrawal of consent, lost to follow-up, death), must be recorded on the eCRF.

After the EOS visit occurs, patients who have not completed 24 months of follow-up will enter the SFP where all patients (or caregivers, where appropriate) will be contacted by phone every 3 months to obtain their survival status until death, premature discontinuation, withdrawal of consent, loss to follow-up, **or** for a total duration of 24 months after the last dose of chemotherapy (including the duration of the PTFP), whichever occurs first.

Note: Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to

consent to provide their local scans and/or local scan report closest to the 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

6.3.1.3 Lost to Follow-up

If a patient does not return to the clinic, attempts should be made to contact the patient (or a previously approved designee such as a caregiver, partner, or family member) to determine the reason for discontinuation. At minimum, 3 documented attempts, including 1 via certified mail, should be made to contact the patient before considering the patient lost to follow-up. If a patient is deemed lost to follow-up, every attempt should be made to obtain survival status through public records (eg, social security death index, obituaries) every 3 months for up to 24 months after the last documented patient visit and record this data in the eCRF.

6.4 Criteria for Termination of the Study

If the Sponsor, Investigator, study monitor, DSMB (if applicable), or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that a study site's participation in the study should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant such action include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or the FDA
- Insufficient adherence to protocol requirements

Study termination and follow-up would be performed in compliance with the conditions set forth in the following sections of the Code of Federal Regulations (CFR): 21 CFR 312.50 and 21 CFR 312.56.

6.5 Clinical Stopping Rules

While the combination treatment in this study is assumed safe due to minimal overlapping toxicities, untoward side effects may occur. Therefore, assessment of the safety and

tolerability data of all enrolled patients will occur once the 6th patient has completed 21 days of combination treatment and will include all safety assessments for all patients obtained prior to the second chemotherapy cycle of the 6th patient enrolled. The subsequent approach will be followed:

- If ≤1 patient has a clinically significant (CS) AE, the study will continue without a dose adjustment.
- If ≥2 patients have a CS AE, the dose level will be decreased to the Reduced Dose level in accordance with Table 6-1, and 6 additional patients will be enrolled and treated with the Reduced Dose for 1 full cycle.
    - If ≤1 of these patients has a CS AE at the Reduced Dose for the 1st cycle, the Reduced Dose will be used for the study.
    - If ≥2 patients have a CS AE on the Reduced Dose, the study will be stopped.

Note: A CS AE is considered an unresolved ≥Grade 3 nonhematological toxicity, which is related to the study drugs, excluding: controllable nausea, vomiting, hypertension, diarrhea, constipation, transient electrolyte abnormalities, and alopecia; Grade 3 or higher febrile neutropenia.

Table 6-1 Safety Run-in Dose Reduction

Dose Level	Gemcitabine	Cisplatin	XERMELO
Starting Dose	1000 mg/m^2	25 mg/m^2	500 mg tid
Reduced Dose	800 mg/m^2	20 mg/m^2	250 mg tid

Note: If any patient experiences a Grade 4 toxicity during the Safety Run-in, the Sponsor, in consultation with the Investigator, will determine if additional patients should be enrolled at the Reduced Dose level.

6.6 Method of Assigning Patients to Treatment

This is a nonrandomized study. Eligible patients will be assigned to treatment once eligibility has been confirmed.

6.7 Blinding and Unblinding of Study Drug

This is an open-label study.

6.8 Replacement of Patients

Patients who do not complete the study will not be replaced.

6.9 Rescreening of Patients

Patients who are excluded during the Screening Period may be allowed to rescreen once.

7 TREATMENT

The concomitant chemotherapy (cis/gem) will not be supplied by TerSera. Initial dosing will be as defined in Section 5.1. Any dosage modification(s) should be performed in accordance with Section 6.3 and Section 7.5.

7.1 XERMELO (telotristat ethyl)

For complete details on drug administration and storage, please refer to the IB.

7.1.1 Identity

Telotristat ethyl 250-mg tablets are white to off-white, coated, and oval with "T-E" debossed on 1 side and "250" debossed on the other side.

7.1.2 Packaging, Labeling, and Storage

Patients will receive 250-mg telotristat ethyl tablets packaged in 100-cc high-density polyethylene bottles with child-resistant polypropylene screw caps and heat-induction seal liners, as 100 tablet count per bottle. The drug product bottle contains desiccants.

Telotristat ethyl should be stored at 25°C (77°F); excursions are permitted 15°C to 30°C (59°F to 86°F).

7.2 Prior and Concomitant Medications

7.2.1 Prior Medication

All medications and other treatments taken within 30 days prior to Screening will be recorded on the eCRF.

7.2.2 Concomitant Medication

All concomitant medications and other treatments taken during the study, including modifications to dosage and/or frequency, will be recorded on the eCRF, including 1L therapy. Each component of the combination chemotherapy, (i.e., cisplatin, gemcitabine) for each cycle should be recorded as a separate entry.

Medical management of patients and their concomitant medications is allowed at the discretion of the Investigator. The list of concomitant medication therapy should be reviewed at each visit and continuance and/or adjustment of dosages should be evaluated based upon the patient's clinical presentation and contraindication(s) of the assigned treatment. Specific attention should be paid to additive effects of concomitant therapies that may increase a patient's risk of constipation and/or abdominal pain. Dosages of such concomitant treatments should be reduced or stopped, as appropriate, during the patient's participation on study.

7.3 Prohibited Medication or Concomitant Therapy

Medication and other treatments are prohibited if they are:

- Identified as contraindicated in the package insert for XERMELO (TerSera Therapeutics LLC, 2020), gemcitabine (Lilly USA, LLC, 2018), or cisplatin (Bristol-Myers Squibb Company, 2010) or in best practice during the administration of 1L therapy; respectively.
- Intended to produce an effect on tumor growth. No other tumor-directed therapy(ies) is (are) permitted while taking combination treatment.
- Chronic treatment with corticosteroids, ≥5 mg/day of prednisone (or equivalent), or other immunosuppressive agent(s)

7.4 Administration of Study Drug

All patients will be instructed to take XERMELO with food. "With food" means taking XERMELO tablets within 15 minutes before or within 1 hour after a meal or large snack. Patients will be instructed to take XERMELO tid during waking hours, with doses spaced approximately 6 hours apart.

Bottles of XERMELO and dosing instructions will be dispensed to patients on Day 1 of each cycle during the Treatment Period and at each visit during the Post-treatment Follow-up Period (if applicable), as described in Appendix A. Patients should be reminded to bring their bottles to the clinic on Day 8 of each cycle for dosing.

Cisplatin and/or gemcitabine will be administered iv as described in Section 5.1.2 in accordance with institutional practice guidelines.

7.4.1 Treatment Compliance

Patients will be asked to bring their unused or unopened bottles of XERMELO to each visit (Appendix A). At each visit and in the presence of the patient, study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. All dosages prescribed and dispensed to the patient, dose modification(s), and missed dose(s), including planned dose interruptions during the study must be recorded. Site personnel are to clarify any discrepancy and record this information within the eCRF.

Patients will be asked to keep a Medication Diary on an electronic, hand-held device provided for the study. The patients will enter the number of tablets of XERMELO taken at breakfast, lunch, and dinner on the device.

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited XERMELO dose, patients will take their subsequent dose at the

next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window for XERMELO should be considered missed. A dose delay of more than 1 week for cis and gem should also be considered missed. Missed or vomited doses of XERMELO will not be made up.

7.5 Dose Adjustment/Modification

For the purposes of this study the following definitions apply:

- Interruption: temporary stoppage of 1 or both treatments of the assigned combination treatment (XERMELO and/or 1L) but then resuming the treatment(s) within 3 weeks for XERMELO or at the next treatment cycle for 1L chemotherapy.
- Discontinuation: premature withdrawal from 1 or both treatments of the assigned combination treatment (XERMELO and/or 1L) defined as a dose interruption lasting for >3 weeks (XERMELO) or a missed cycle (cis/gem)
- **Note**: Discontinuation of cisplatin, but continuing treatment with gemcitabine alone, will not be classified as a discontinuation.

Note: If gem is deferred, cis will also be deferred. Day 8 treatment may be deferred for toxic effect by 1 week only. If a second deferral is needed, the treatment will be omitted, and the patient will move on to the next treatment cycle.

7.5.1 XERMELO (telotristat ethyl)

XERMELO reduces bowel movement frequency and constipation was observed in clinical studies in patients with CS diarrhea. Monitor for the development of constipation and/or severe, persistent, or worsening abdominal pain in patients taking XERMELO.

In general, CCI CCI CCI CCI CCI CCI Toxicity will be assessed according to the NCI CTCAE v5.0 (Appendix G).

Table 7-1 XERMELO Dose Modifications

Grade of Event	Management/Next XERMELO Dose[2]
Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1. Resume at same dose level.
Grade 3	Hold until ≤Grade 1. Resume at 1 dose level lower (250 mg tid).[1]
Grade 4	Discontinue treatment

[1]Patients unable to tolerate 250 mg tid should be discontinued from XERMELO.
[2]Rechallenge may be permitted upon consultation with the Medical Monitor.

Recommended management for the following AEs:

- Nausea and/or vomiting: treat with antiemetics
- Diarrhea: treat as indicated for underlying cause; examples of therapy(ies) include: antidiarrheal agents (eg, loperamide, over-the-counter [OTC]), pancrealipase for steatorrhea, cholestyramine for short gut syndrome
- Gastrointestinal toxicity:
    - Monitor concomitant medication usage as described in Section 7.2.2.
    - Constipation (Grade 1 and above): initiate treatment as clinically indicated; examples of therapy(ies) include: laxatives, enemas, suppositories, psyllium, hydration, OTC agents
    - Abdominal pain (Grade 1 and above): initiate treatment as clinically indicated; examples of therapy(ies) include: analgesics, anti-gas/bloating agents
    - Hold XERMELO for Grade 2 constipation or abdominal pain until ≤Grade 1. Resume at 1 dose level lower (250 mg tid).
    - Discontinue XERMELO for Grade 3 constipation or abdominal pain
- Suicidal ideation: Discontinue XERMELO

These dose modification rules should be followed for clinical laboratory abnormalities that are Clinically Significant as determined by the Investigator; the Investigator assessment can differ from the CTCAE severity grading stated on the laboratory report.

Clinical interpretation is especially important for hepatic enzyme abnormalities. These may be elevated at Baseline, and CTCAE severity grades provided on the laboratory report may not account for this. Furthermore, GGT changes have been commonly observed with telotristat ethyl in patients with carcinoid syndrome, and these have been of uncertain clinical significance.

Mean GGT changes in an oncology study were +130 U/L and +242 U/L on 250 mg tid and 500 mg tid, respectively, of telotristat ethyl at Week 12. Increases in GGT were observed soon after telotristat initiation, and values remained elevated throughout the course of treatment (Kulke, 2017).

In the same study, elevations in ALT were only +7 U/L and +17 U/L, respectively on these doses. No increase from Baseline in mean value of bilirubin levels was observed in any treatment group. Most adverse events of hepatic enzyme elevation were mild or moderate in intensity, the rate did not increase with long-term treatment, and a review concluded that these increases did not lead to Clinically Significant outcomes (Lexicon, 2018).

If there are laboratory changes without Clinical Significance, the Investigator can maintain treatment and continue to monitor. The drug may be interrupted at the Investigator's discretion in consultation with the Medical Monitor.

7.5.2 Cisplatin/Gemcitabine

In general, [redacted]

Toxicity will be assessed according to the NCI CTCAE v5.0.

Table 7-2 Dose Reduction

Dose Level	Gemcitabine	Cisplatin
Starting Dose	1000 mg/m^2	25 mg/m^2
Reduced Dose	800 mg/m^2	20 mg/m^2

The following dose modification rules (Table 7-3) will be used with respect to **hematologic toxicity on Day 1 of each treatment cycle** believed to be related to cisplatin or gemcitabine:

Table 7-3 Dose Reduction for Hematologic Toxicity on Day 1

ANC		Platelet Count	Gemcitabine/Cisplatin
≥1,000/mm^3	and	≥100,000/mm^3	Treat as scheduled
<1,000/mm^3	or/ and	<100,000/mm^3	Defer treatment by 1 week. Reduce dose by 1 level for next treatment.

The following dose modification rules will be used with respect to **hematologic toxicity on Day 8 of each treatment cycle** believed to be related to cisplatin or gemcitabine:

Table 7-4 Dose Reduction for Hematologic Toxicity on Day 8

ANC		Platelet Count	Gemcitabine/Cisplatin
≥1,000/mm^3	and	≥75,000/mm^3	Treat as scheduled
<1,000/mm^3	or/ and	<75,000/mm^3	Defer treatment 1 week. Reduce dose by 1 level for next treatment. If a second deferral is needed, treatment will be omitted

Note: Administration of granulocyte-colony stimulating factor (G-CSF) is allowed, but discontinuation is required at least 2 days prior to the next administration of chemotherapy. If symptoms do not resolve after 28 days of uninterrupted G-CSF, chemotherapy treatment should be stopped.

The following dose modification rules will be used with respect to **nonhematologic toxicity on Day 1 of each treatment cycle** believed to be related to cisplatin or gemcitabine.

Table 7-5 Dose Reduction for Nonhematologic Toxicity on Day 1

Nonhematologic Toxicity[1]	Gemcitabine/Cisplatin
Grade 1 or 2	Treat as scheduled
Grade 3 or 4	Defer treatment until resolves to ≤Grade 1. Reduce dose by 1 level for next treatment.

[1]Permissible exceptions to this rule are Grade 3 nausea, vomiting, hypertension, diarrhea, constipation, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care, and alopecia.

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Table 7-6 Dose Reduction for Nonhematologic Toxicity on Day 8

Nonhematologic Toxicity[1]	Gemcitabine/Cisplatin
Grade 1 or 2	Treat as scheduled
Grade 3 or 4	Defer treatment until resolves to ≤Grade 1. Reduce dose by 1 level for next treatment. If deferral is needed for more than 1 week, treatment will be omitted.

[1]Permissible exceptions to this rule are Grade 3 nausea, vomiting, hypertension, diarrhea, constipation, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care, and alopecia.

8 STUDY PROCEDURES

A schedule of study assessments is provided in Appendix A.

8.1 Restrictions during Study

Patients should be advised to adhere to restrictions as described in the package insert for cisplatin (Bristol-Myers Squibb Company, 2010), gemcitabine, (Lilly USA, LLC, 2018) and XERMELO (TerSera Therapeutics LLC, 2020).

8.2 Description of Study Assessments

8.2.1 Efficacy Assessments

8.2.1.1 Imaging Assessment

Each study site must have a designated radiologist or qualified individual who is responsible for the interpretation and evaluation of required images for this study according to RECIST v1.1 (Appendix J). If possible, the same radiologist/qualified individual should perform the evaluation for the entire duration of the study. All radiology evaluations will be performed initially by the local radiologist (or designee) with all images sent to a central reviewer.

Independent central radiology review includes radiology assessments by BICR and an Independent Adjudication Committee (IAC). All scans will be reviewed and adjudicated as set forth in the Independent Review Charter.

8.2.1.1.1 Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI)

Patients who have received previous treatment with chemotherapy in the adjuvant setting will be required to provide documentation of PD prior to study entry. This documentation requires least 2 evaluable CT or MRI studies performed ≥4 weeks apart and within 6 months prior to planned C1D1. For the purpose of this study, images submitted to BICR within 6 weeks prior to and including C1D1, i.e., which ever set was closest to C1D1 will be referred to as Baseline imaging. Copies of these images are to be sent to a central reviewer to use in the final analysis.

All patients should have at least 1 measurable lesion by CT or MRI as determined by RECIST v1.1. For the purposes of this study, CT refers to a contrast enhanced image by CT of the chest, abdomen, pelvis, and/or other areas of known disease. The preferred method of imaging for this study is CT with contrast; MRI of the abdomen and/or pelvis with noncontrast CT of the chest will be acceptable for patients with medical contraindications to either the procedure itself or contrast agent used (eg, allergy to the contrast agent). Suspected

or known central nervous system involvement should be followed with MRI unless contraindicated.

The same imaging technology and the same technique should be used to characterize each identified and reported lesion at Baseline and throughout the duration of the study. During the study, imaging studies will be performed as outlined in Appendix A.

8.2.1.1.1.1 Measurement Technique

All measurements should be taken and recorded in metric notation, using a ruler or calipers.

8.2.1.1.1.2 Tumor Response by Response Evaluation Criteria in Solid Tumors (RECIST)

Measurable disease lesions must be accurately measured in at least 1 dimension in accordance with RECIST v1.1 (Appendix J). Changes in tumor measurements must be confirmed by repeat assessments within 4-6 weeks after the criteria for response, or progression, are first met.

8.2.2 Clinical Laboratory Assessments

Clinical laboratory assessments will include, at a minimum, blood chemistry (complete metabolic profile [CMP], liver function tests [alkaline phosphatase (ALKP), ALT, AST, total bilirubin], lipid panel [high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides], coagulation parameters [PT, INR]), hematology (complete blood count [CBC] with differential, and platelet counts), and urinalysis.

Additional assessments such as serum and urine pregnancy tests will be performed on females of childbearing potential only. Urine pregnancy tests will be performed by the site staff and will not be sent to the central laboratory.

All other laboratory assessments will be performed by a central laboratory. **Note:** Central laboratory assessments for Day 8 are not required; sites may perform local laboratory assessments on Day 1 and/or Day 8 for patient management of chemotherapy infusion according to their practiced standard of care. In rare cases, laboratory results obtained from the local laboratory may be used to assess eligibility when the central laboratory lab result is unavailable. Authorization to use local laboratory results for determining eligibility must be obtained from the Sponsor prior to initiating study drug.

Out of range values should be assessed by the Investigator for clinical significance relevant to the patient population. For this protocol, assessments will be defined as not clinically significant (NCS) or clinically significant (CS). The incidence of clinically significant

laboratory values, as well as clinically significant shifts in laboratory values, should be reported as an AE in the eCRF (Section 9.1.1) and followed as described in Section 9.5; retests should be performed as frequently as clinically indicated.

8.2.3 Pharmacodynamic and Pharmacokinetic Assessments

8.2.3.1 [redacted]

Fasting (≥6 hours) blood samples for [redacted] in plasma will be collected at the study sites and analyzed by Frontage Laboratories, Inc. All sample processing information will be supplied by the laboratory in a separate document. Efforts should be made to schedule these visits in the morning, with instructions to the patient to arrive in a fasted state and not dose prior to the blood draw.

8.2.3.2 Other Tumor Biomarkers: Carbohydrate Antigen 19-9 (CA 19-9) and Carcinogenic Embryonic Antigen (CEA)

Blood samples will be collected for measurement of [redacted] throughout the duration of the study.

Note: [redacted] Patients should be advised to avoid multivitamins or dietary supplements containing biotin (vitamin B7), which is commonly found in hair, skin, and nail supplements and multivitamins, for 12 hours prior to sample collection.

8.2.3.3 Pharmacokinetic (PK) Assessments

Blood samples for the purposes of determining trough levels of XERMELO and LP-778902 concentrations in plasma will be collected for all patients as indicated in Appendix A. Efforts should be made to schedule these visits in the morning, with instructions to the patient to arrive in a fasted state and not dose prior to the blood draw.

A separate, optional substudy will be conducted to collect additional samples from a subset of patients over a 6-hour timeframe as indicated in Appendix B for the purposes of a population PK analysis.

Detailed procedures for the drawing, preparation, storage, and shipping of samples will be provided in a separate laboratory manual.

8.2.4 Safety Assessments

In addition to the clinical laboratory assessments described in (Section 8.2.2) and monitoring of AEs described in detail in Section 9.5, safety of patients will be monitored through vital

sign measurements (Section 8.2.4.1), PE findings (Section 8.2.4.2), and ECG findings (Section 8.2.4.3).

Findings outside of the normal range and/or expectation should be assessed by the Investigator for clinical significance relevant to the patient population. For this protocol, assessments will be defined as NCS or CS. Clinically significant changes compared with Baseline (C1D1) findings for these variables should be reported as AEs on the eCRF and followed as described in Section 9.5; additional testing and/or retests should be performed as frequently as clinically indicated.

8.2.4.1 Vital Sign Measurements

Measurement of vital signs will include assessment of blood pressure, respiratory rate, pulse rate, and temperature. Vital sign measurements should not be conducted within the 30 minutes immediately following any phlebotomy.

Efforts should be made to standardize blood pressure collection across all patients and visits. Patients should be seated for at least 5 minutes prior to collection. All measurements should be assessed on the same arm, using the same equipment, and by the same technician where possible.

Additional measurements may be obtained if clinically indicated.

8.2.4.2 Physical Examination (PE), Height, and Weight

A complete PE will be performed at specific time points as outlined in Appendix A. Physical examinations will include a minimum of a review of the patient's general appearance and mental status; visual assessment of the head, eyes, ears, nose, and throat (HEENT), back, extremities, musculoskeletal, and skin; palpitation of the abdomen and neck including thyroid, and auscultation of the heart and lungs.

Symptom-oriented PEs will be performed at all other time points and as clinically indicated.

In addition, body weight will be captured at each clinic visit. Efforts should be made to standardize weight collection across all patients and visits. Patients should be instructed to remove shoes and heavy clothing (eg, heavy coats, jackets) prior to measurement. For weight collection, an effort should be made to use the same scale throughout the study where possible. In instances where multiple scales may be used, efforts should be made to reset the scale to zero prior to collection of weight measurement.

Height (without shoes) will be measured once, during Screening. Body Mass Index (BMI) will be calculated by the eCRF once height and weight have been entered (see Appendix F for calculation details).

8.2.4.3 Electrocardiogram (ECG)

Electrocardiograms (12-lead ECGs) will be performed to monitor cardiac function. Tracings must include a documented assessment of clinical significance (eg, NCS or CS), as applicable and the assessment must be signed and dated by the Investigator (or designee).

8.2.4.4 Depression Detection

Patients will be evaluated prior to initiating treatment on Day 1, then periodically throughout the remaining duration of the Treatment Period as outlined in Appendix A. During the Baseline visit, the patient will first be asked to respond to the question "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" followed by "During the past month, have you often been bothered by little interest or pleasure in doing things?". A positive response prior to Day 1 dosing will be evaluated by the Investigator in order to assess if the response is clinically significant. Positive responses assessed as clinically significant will be captured on the medical history CRF page.

At all other timepoints, the patient will be asked to provide a response in relation to the last visit. "Since the last visit, have you often been bothered by feeling down, depressed, or hopeless?" followed by "Since the last visit, have you often been bothered by little interest or pleasure in doing things?". A positive response following Day 1 dosing will be evaluated by the Investigator to determine if the response is clinically significant. Positive responses assessed as clinically significant are to be reported as an AE and captured on the AE page, additional reporting requirements are discussed in Section 9.3.2.

The depression detection questions will automatically populate on the patient's electronic device for them to complete on the evening prior to each study visit. A positive response to any question will send an automatic email to the site alerting them of the response so follow-up with the patient can occur and clinical significance assessed.

8.3 Other Assessments

8.3.1 Performance Status Based on Eastern Cooperative Oncology Group (ECOG)

Performance status will be assessed throughout the duration of the study, the ECOG score will be recorded in the eCRF. Appendix G provides scoring criteria and a conversion table for Investigators using the Karnofsky Performance Scale (KPS) scoring system.

8.3.2 Health-related Quality of Life (HRQoL)

Health-related quality of life (HRQoL) will be evaluated using the [redacted] Module (Appendix I) at specific time points as outlined in Appendix A. These questionnaires will be completed by the patient at the clinic during the visit using the electronic device provided for the study; therefore, patients should be reminded to bring their electronic diaries with them to each study visit.

8.3.3 Characterization of the Tumor - Substudy

Baseline characterization of tumor tissue will be completed for a subset of patients in an optional substudy. Previously archived patient tumor biopsy samples will be requested, where available. These samples will be analyzed by IHC methods for 5-HT, TPH-1, and tumor fibrosis on patients who consent to participate. Additional markers may be added to this list if suggested by internal or external data. The purpose of these studies will be to further characterize the patient population.

Specific requirements for tissue preparation and submission will be supplied by the laboratory in a separate document.

8.4 Appropriateness of Assessments

The assessments used in this study conform to accepted clinical and laboratory assessments of patients with BTC in clinical trials and are typical of a Phase 2a study.

9 SAFETY REPORTING

It is the responsibility of the Investigator to document all AEs and special situations that occur during the study.

Adverse events will be collected at all study visits as outlined in Appendix A. Each AE should be recorded using the medical diagnosis; if a diagnosis is not established at the time of the reporting, a symptom or sign described by standard medical terminology may be used.

Adverse events should not be solicited with leading questions that suggest specific signs or symptoms. Rather, AEs should be solicited by asking the patient a nonleading question such as: "Do you feel different in any way since receiving the dose or since the last assessment?"

Adverse events that occur after the signing of informed consent and before the first dose of study drugs should be recorded as medical history unless the event is an SAE that could be associated with the trial procedures and could modify the conduct of the trial, or as otherwise specified.

9.1 Definitions and Special Considerations

9.1.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related.

An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring after a patient has provided informed consent, whether or not it is considered related to the study drugs.

This definition includes an exacerbation of preexisting medical conditions or events, historical conditions not present prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug-drug or drug-food interactions, medication errors, overdose (both intentional or unintentional), drug misuse/abuse, false positive laboratory test, or the significant worsening of the disease under investigation.

Anticipated day-to-day fluctuations of preexisting conditions that do not represent a clinically significant exacerbation or worsening need not be reported as AEs.

Treatment-emergent AEs are defined as any AEs reported after the first dose of study drugs and for 30 days following the last dose of study drugs.

Any treatment-emergent abnormal laboratory result should be reported as an AE if it meets 1 or more of the following conditions:

- Fulfills any of the criteria for an SAE (Section 9.1.2),
- Results in discontinuation of study treatment,
- Requires treatment, or
- Is considered by the Investigator to be clinically significant.

9.1.2 Serious Adverse Events

An SAE is defined as any AE that results in any of the following outcomes:

1. Death;
2. A life-threatening AE - defined as an event, in the view of the Investigator, the occurrence of which places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death;
3. Hospitalization or prolonging of an existing hospitalization;
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or,
5. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization is defined as any inpatient overnight stay in a hospital. This does not include an emergency room visit or admission to an outpatient facility.

A hospitalization in and of itself should not be reported as an SAE.

Hospitalizations for preplanned or elective surgery or routine clinical procedures without worsening of the underlying condition, or for administrative/social reasons (such as convenience, logistics) should not be reported as SAEs; however, if an elective procedure has to be performed sooner than planned due to a worsening of the underlying medical condition and the patient is hospitalized for the procedure, the worsening medical condition should be reported as an SAE.

Any laboratory abnormality fulfilling any of the criteria for an SAE should be reported as such.

9.1.3 Unexpected Adverse Events

An unexpected AE is an AE that is not listed in the Reference Safety Information (eg, the IB) or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to the AEs that are mentioned in the Reference Safety Information as occurring with the class of study drugs or as anticipated from the pharmacological properties of the study drugs but are not specifically mentioned as occurring with the study drugs.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents.

It the responsibility of the Sponsor to assess whether an AE is expected or unexpected.

9.2 Assessment of Adverse Events

The Investigator will evaluate all AEs with regards to the severity and relationship to each of the study drugs; XERMELO, cisplatin, and gemcitabine.

9.2.1 Severity

The Investigator will assess the severity of each AE using their clinical expertise and judgment using NCI CTCAE v5.0 criteria (Appendix H).

9.2.2 Causality

Causality assessment is a determination of whether there is a reasonable possibility that the study drug caused an AE. Factors that should be considered in causality assessment include, but are not limited to, temporal relationship, dechallenge/rechallenge information, association (or lack of association) with underlying disease or concomitant medication, biological plausibility, and previous observation or lack of with study drug or other medication(s) in the same class.

For each AE, the Investigator will assess the causal relationship between each of the study drugs and the AE using their clinical expertise and judgment according to the most appropriate description as follows:

Note: In cases of elevated LFT(s), it may not be possible to differentiate which drug is causing the AE. If, based on clinical judgement, an increase in LFT(s) is attributed to drug

treatment, causality could be assigned to each of the study drugs. Dose modification should be performed in accordance with Section 7.5.

- **Not related**: The AE does not follow a reasonable temporal relationship to administration of the study drug, or an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is more likely
- **Unlikely related:** The AE has an improbable temporal relationship to administration of the study drug, or an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is more likely
- **Possibly related**: The AE follows a reasonable temporal relationship to administration of the study drug (including the course after withdrawal of the drug), and an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is equally or less likely
- **Probably related**: The AE follows a reasonable temporal relationship to administration of the study drug (including the course after withdrawal of the drug), and an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is unlikely
- **Definitely related**: The AE follows a plausible temporal relationship to administration of the study drug (including the course after withdrawal of the drug) and alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) can be ruled out. Positive rechallenge (i.e., reappearance or worsening of the AE after study drug is reintroduced) or a response pattern known to be associated with administration of the study drug provides further evidence of a definitive causality assessment.

9.3 Special Situations

9.3.1 Pregnancy

Any patient who becomes pregnant during the study must be discontinued from the study immediately.

Any pregnancy during the study that occurs after administration of combination treatment, where the embryo or fetus may have been exposed to the study drugs (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth.

The pregnancy exposure should be reported on the Pregnancy Questionnaire and captured on the eCRF page for AEs. The pregnant woman (patient or partner) should be followed for

pregnancy outcome through delivery or termination of the pregnancy. In any pregnancy that progresses to term, the infant should be followed until 6 months after birth and any congenital abnormalities/birth defects in the infant should be reported as an SAE.

The outcome of a pregnancy, and the presence or absence of a congenital abnormality should be reported on the Pregnancy Outcome Form.

After the study period, pregnancies should be collected by requesting that study patients notify the Investigator if a female patient or a female partner of a male patient becomes pregnant within 30 days after last dose of XERMELO. These pregnancies should be reported and followed in the same manner as pregnancies occurring during the study.

9.3.2 Adverse Events of Special Interest (AESIs)

Based on the mechanism of action of telotristat etiprate, and observations in the clinical studies, events described in this section are considered AESIs. Monitoring of these AEs will be the responsibility of the Sponsor.

Additional information will be collected if clinically significant episodes of events described in this section occur.

9.3.2.1 Depression

Refer to the Section 8.2.4.4 for additional details regarding depression detection. Below is a list of terms that will be considered a depression-related AESI if deemed clinically significant by the Investigator:

- Adjustment disorder with depressed mood with or without mixed anxiety
- Agitated depression
- Anhedonia
- Antidepressant therapy
- Depressive symptom
- Decreased interest or depressed mood
- Feeling guilty or feelings of despair, worthlessness
- Helplessness
- Mixed anxiety and depressive disorder
- Assisted or completed suicide, including suicide attempt or threat
- Columbia suicide severity rating scale abnormal
- Depression suicidal

- Depression, including major, menopausal, perinatal
- Depression postoperative
- Dysphoria
- Electroconvulsive therapy
- Intentional overdose or self-injury
- Poisoning deliberate
- Self-injurious ideation
- Suicidal behavior or ideation

9.4 Reporting of Serious Adverse Events and Pregnancies

All SAEs, regardless of causal relationship to study drug, and pregnancies must be reported to the Sponsor within 24 hours of investigational site awareness of the event. Investigators should not wait for complete information on an event before notifying the Sponsor of an SAE. All SAEs, pregnancies, and other special situations should be recorded on the study participant's eCRF page for AEs.

Investigational site personnel must use the approved method of notification (eg, SAE Report form, Pregnancy Questionnaire form, eCRF page) provided by the Sponsor to report these events. Where applicable, information from relevant hospital records and autopsy reports should be obtained.

If paper report forms are used or to provide redacted supporting documents, they, should be sent to:

Safety Data Facsimile: CCI or

Email address (in case of fax failure): CCI

In case of failure of/lack of access to eCRF, email, or fax, the event can be reported to the TerSera Call Center CCI

If an SAE is reported via telephone, the telephone report should be followed by a written report using a reporting method described above (i.e., completion of eCRF or paper form).

For questions on safety reporting, please contact TerSera Pharmacovigilance at CCI CCI

For questions on study participant management related to AE, the Medical Monitor of the study should be contacted.

Additional information received after the initial SAE has been reported to the Sponsor should be reported as follow-up information following the same procedure and timeline as the initial SAE.

An SAE that occurs after completion of the study and, in the opinion of the Investigator is related to study drug, should be reported following the same procedure and timeline as an SAE that occurs during the study.

9.5 Follow-up of Adverse Events

All AEs should be followed until the event has resolved, the condition has stabilized, the patient is lost to follow-up, or at least 30 days following the last dose of any study drug (i.e., XERMELO, cisplatin, gemcitabine), whichever comes first. Final known outcome must be reported whenever possible.

Medically significant abnormal laboratory test results should be repeated and followed until the test results have returned to the normal range or Baseline value, and/or an adequate explanation of the abnormality is determined.

9.6 Safety Oversight

Safety review and oversight of this study will be the responsibility of the Sponsor according to the Sponsor's Standard Operating Procedures. Safety and tolerability will be reviewed based on data entered into the eCRFs, reported SAEs, and results of laboratory assessments on an approximate monthly basis. The clinical stopping rules described in Section 6.5 will be followed. An independent DSMB will not be utilized for this study.

10 STATISTICAL METHODOLOGY

10.1 Determination of Sample Size

The sample size was computed by satisfying design assumptions for the primary endpoint of the study; which is to assess the PFS rate at Month 6.

6-Month PFS rates of 70% and 55% are assumed for the XERMELO arm and historical control arms. Simon's 2-stage design (Simon, 1989) will be used to test these rates. The null hypothesis, that the true response rate is p0=0.55, will be tested against a 1-sided alternative. In the first stage, n1=20 patients will be accrued. If there are r1=11 or fewer responses in these n1=20 patients, the study will be stopped. Otherwise, 33 additional patients will be accrued for a total n=53. The null hypothesis will be rejected if r2= 33 + 1 or more responses are observed in 53 patients. This design yields a Type I error rate = 0.097 and statistical power = 0.802 when the true response rate is p1= 0.70.

The target sample size of 53 patients is expected to be accrued over a period of 18 months, with the last enrolled patient followed for 6 months after the start of receiving study treatment. Under an exponential sampling process, the median follow-up time for the time-to-event endpoints (e.g., PFS, OS) will be 15 months.

10.2 Analysis Populations

This is a single arm and open-label study. Safety data will be assessed periodically throughout the study in addition to the testing requirements of the Simon design. These safety-based interim analyses will not be used to assess efficacy; hence, there will be no inflation of the Type I error rate that would require an adjustment to the 53 patients sample size:

Per-protocol (PP): A PP population will consist of those patients that CCI CCI CCI CCI and have no major protocol violation(s) that would interfere with the collection or interpretation of the efficacy data. Determination of the PP dataset will be made before database lock.

Safety: The Safety population consists of all patients receiving any fraction of a dose of study drug.

PK: The PK population will be made up of all patients treated with at least 1 dose of study drug and who have adequate samples taken to reliably estimate the parameters of interest.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

The primary efficacy endpoint is to assess the PFS rate at Month 6, where patient progression is defined as the time from Baseline until the first determination of PD by central radiologic reading using RECIST v1.1 (Eisenhauer, 2009) or death from any cause.

Secondary efficacy endpoints include:

- OS
- OS rate at Months 6 and 12
- PFS rate at Month 12 median PFS
- DCR; CR + PR + SD at Months 6 and 12 and EOS
- ORR defined as CR + PR at Months 6 and 12 and EOS
- Local radiologist's assessment of PFS, ORR, and DCR

Exploratory efficacy endpoints include:

- Change from Baseline in plasma CCI CCI at Months 6 and 12 and EOS
- Change from Baseline in body weight at Months 6 and 12 and EOS
- Change from Baseline in serum albumin at Months 6 and 12 and EOS
- Subgroup analyses will be evaluated in:
  - Patients with changes in liver function tests
  - Patients with Biliary stents
  - Location of disease (intrahepatic, extrahepatic, or gallbladder)
- Efficacy will be evaluated by treatment cycles CCI CCI CCI CCI CCI of combination treatment)

Note: Unless otherwise indicated, all radiologic endpoints will be based on RECIST v1.1 as determined by BICR and compared to published historical data of cis/gem alone.

Exploratory efficacy endpoints include assessing the effect of XERMELO when used in combination with 1L therapy on the following endpoints:

- Changes in HRQoL as measured by CCI CCI items at Baseline, Months 6 and 12;
- Change from Baseline in CCI at Months 6 and 12 and EOS;

- Subgroup analysis of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment based on categorical group of Baseline and change from Baseline at Months 6 and 12 and EOS in:

  - serum albumin
  - correlation between Baseline neutrophil:lymphocyte ratio and OS

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, TEAEs by severity, TEAEs by relationship to each of the study drugs, TEAEs by study drugs exposure time, TEAEs leading to discontinuation from the study, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results including frequency of values meeting CTCAE Grades >1 for severity
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in weight
- Actual and change from Baseline in 12-lead ECG findings

10.3.3 Pharmacokinetic Endpoints

For patients with intensive PK assessments, the following PK parameters will be estimated, where possible, for XERMELO and its active metabolite, LP-778902, in plasma by non-compartmental methods:

C_{max}	maximum concentration in the sampled matrix (ng/mL), obtained directly from the observed concentration versus time data
C_{min}	minimum concentration in the sampled matrix (ng/mL), obtained directly from the observed concentration versus time data
t_{max}	time of maximum concentration (h), obtained directly from the observed concentration versus time data
$AUC_{(0-6)}$	area under the concentration-time curve in the sampled matrix from zero (predose) to 6 hours after dose administration.
$AUC_{(0-last)}$	area under the concentration-time curve in the sampled matrix from zero (predose) to time of last measurable concentration (ng·h/mL), calculated by linear up/log down trapezoidal summation.
Kel	apparent first-order terminal rate constant

t½	apparent terminal elimination half-life
Rac	accumulation ratio at steady state

PK structural models for telotristat (LP-778902) will be developed from already existing PK data in healthy subjects and patients. These models will be used, where possible, to develop a population PK analysis based on the data from this study. This analysis will include, where possible, an assessment of the effects of intrinsic and extrinsic factors on the PK of XERMELO.

10.3.4 Characterization of Tumor Substudy Endpoint

The endpoint of this substudy is to characterize the tumor tissue by IHC staining (i.e., 5-HT and TPH-1) at Baseline among patients who have consented to participate and for whom previously-banked tissue samples are available.

10.4 Statistical Methods

Demographic data, Baseline disease characteristics, prior and concomitant medications, treatment compliance, treatment exposure, AE, laboratory tests, vital signs, PE findings, 12-lead ECG findings, and final disposition will be summarized descriptively.

Continuous variables will be summarized descriptively by the number of patients with non-missing data, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized descriptively by their counts and associated percentages. All summaries will be reported by study time point, as applicable.

All data values will be provided in listings.

A more detailed description of the analysis and reporting of data will be provided in the Statistical Analysis Plan. An overview of the main analysis strategy is provided in the following sections.

10.4.1 Efficacy Analyses

All imaging will be assessed by local radiologist and the BICR. The BICR will supersede the local radiologist's assessment for the purpose of primary endpoint and all applicable key secondary objectives. A secondary analysis will be performed to further evaluate the primary and secondary efficacy endpoints using the local radiologist assessments.

A Simon's 2-stage design algorithm will be used to assess whether the study is successful at each stage of the analysis. In the Stage 1 Safety Population, if there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and

if 12 (60%) or more of the 20 patients enrolled who are deemed responders per the definition below after the 20th patient is censored, is alive and progression-free at the Month 6 assessment, or has discontinued for any reason, the study will be declared successful and enrollment will continue in Stage 2. Efficacy will also be assessed in the PP population and by treatment cycle.

Note: Patients are considered responders if they are alive and progression-free at the Month 6 assessment; otherwise, they are considered non-responders.

In Stage 2, an additional 33 patients will be enrolled. If 34 or more (>60%) of the 53 patients enrolled (Stage 1 + Stage 2) are deemed responders, the study will be considered successful.

The primary and secondary efficacy endpoints will be analyzed based on the Safety population. Additional analyses for the primary and secondary efficacy endpoints will be performed using the PP population.

For the primary endpoint, the Kaplan-Meier method (Kaplan, 1958) will also be used to estimate the survival function. The PFS rate at Month 6 and the corresponding 95% confidence interval (CI) will be presented. In addition, the median PFS value computed from this study will be compared with the historical/published median PFS time (published and clinically acceptable median PFS for cis/gem alone). Also, the PFS rate estimates and 95% CIs will be computed at Month 12. Patients without PD or death will be censored at the last confirmed radiographic assessment by the central reviewers prior to study completion or date of discontinuation from the study. The same methodology will be used to analyze the median OS and the OS rate at Months 6 and 12.

Subgroup analysis may be performed based on the primary tumor site, prior therapy(ies), performance status, major demographic and prognostic subgroups, extent of disease, and Baseline biomarker levels.

Radiographic assessments will incorporate standard and exploratory analyses. Additional secondary analyses will include assessment of ORR and DCR at Months 6 and 12 and EOS using RECIST v1.1. For binary endpoints estimated as binomial proportions, such as ORR and DCR, the frequency and proportion of patients assessed as responder and non-responder as an outcome will be presented at each assessed study time point.

Other efficacy endpoints will be summarized descriptively by study time point. Change from Baseline for CCI CCI CCI will be summarized descriptively and 1-sample t-tests may be performed to test for significance.

10.4.2 Safety Analyses

All safety summaries will be descriptive; no statistical significance tests will be performed on safety data.

Summaries will be prepared by study time point. All safety data will be listed by patient.

Treatment-emergent AE summaries will include the overall incidence (by System Organ Class [SOC] and Preferred Term [PT]), events by maximum severity, events by relationship to each study drug, events by length of exposure (at event onset) to each study drug, events leading to discontinuation from the study, and SAEs.

Vital signs, 12-lead ECG findings, PE findings, (including height and weight) and laboratory parameters (hematology, chemistry, and urinalysis) will be summarized descriptively at each time point. For quantitative variables, both actual and change from Baseline data will be summarized. In addition, shift table analysis will be applied to the laboratory data.

10.4.2.1 Adverse Events

All AEs will be coded and listed by SOC and PT based on the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be provided for TEAEs, drug-related AEs, SAEs, TEAEs leading to study discontinuation, TEAEs by drug relationship, TEAEs by severity, and TEAEs by length of exposure (at event onset) to the study drugs. Treatment-emergent AEs are those events not present at Day 1 but occurring after the first dose of study drug, or if existing on Day 1, increasing in severity after initiation of study drug. Summaries made by severity will select the event with the highest severity when multiple occurrences of the same event are reported for the same patient. In a similar manner, summaries prepared by drug relationship will select the event with the greatest degree of relationship when a patient reports multiple occurrences of the same event. On-study deaths will be reported for deaths occurring during study participation and the 30 days after stopping study drug. Also, deaths occurring outside the 30-day window, but secondary to an AE reported within the 30-day Follow-up Period, will be reported as well.

Listings will be provided for deaths, SAEs, AESIs, and discontinuations due to AEs. Additional summaries or listings of AEs may also be provided.

10.4.2.2 Clinical Laboratory Parameters

Laboratory results will be reported in conventional units and International System of Units (SI) units in all tables, figures, and listings. Laboratory results falling out of the normal range will be marked as high or low in the listings. Actual and changes from Baseline in clinical

laboratory results will be summarized by time point using descriptive statistics. Summaries of shifts from Baseline, based on CTCAE severity grades, will be provided.

10.4.2.3 Vital Sign Measurements

Actual and change from Baseline in vital signs results will be summarized by time point using descriptive statistics.

10.4.2.4 Electrocardiogram Findings

Clinically significant changes in ECGs compared to Baseline, as determined by the Investigator, will be summarized by time point using descriptive statistics. Actual and change from Baseline (predose values) to each time point in corrected QT (QTc) interval using Fridericia's formula (QTcF) and Bazett's formula (QTcB) will be summarized.

10.4.2.5 Physical Examination Findings, Height, and Weight

Physical examination findings will be listed. Weight will be analyzed as change from Baseline at all time points, as appropriate.

10.4.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

Actual and change from Baseline in ECOG will be summarized by time point using descriptive statistics.

10.4.3 Pharmacodynamic Analyses

Actual and change from Baseline in CCI CCI CCI will be summarized by time point using descriptive statistics.

10.4.4 Pharmacokinetic Analyses

For patients with intensive PK assessments, descriptive statistics will be used to summarize the plasma concentrations of XERMELO and LP-778902 at each time of collection. All PK parameters for XERMELO and LP-778902 will be listed and summarized using appropriate descriptive statistics.

PK data will be summarized by n, arithmetic and geometric mean, standard deviation, median, minimum, and maximum values at various time points. Regression models may be used to evaluate the type and magnitude of associations between trough concentration of XERMELO and LP-778902 at selected time points.

Based on intensive PK sampling from a subset of patients and sparse PK sampling (eg, trough concentrations) from the study population, Population PK analyses will explore the

effects of covariates including, but not limited to, age, sex, race, BMI on the systemic exposure to XERMELO and LP-778902. PK data from this study may be integrated with PK data from other clinical trials to further enhance the population PK analysis and/or support the development of an exposure-response model for safety and efficacy. Details of population PK analysis plan will be prepared in a separate document.

Results from the population (overall) PK analysis will be documented in a separate report.

10.4.5 Analysis of Health-related Quality of Life (HRQoL)

Actual and change from Baseline for QLQ-C30 and QLQ-BIL21 total and subscale scores will be summarized by time point using descriptive statistics.

10.4.6 Baseline Characteristics and Other Summaries

Demographic data, prior and concomitant medications, treatment compliance, and final disposition will be summarized descriptively.

10.4.7 Interim Analysis

Periodic reviews of study data will be conducted as described in Section 9.6 throughout the study for the purposes of safety monitoring but will not serve as a formal analysis of study data. A Stage 1 analysis in a total of 20 patients will be conducted, Stage 1 enrollment will include a Safety Run-in cohort. Safety, tolerability and efficacy data of the combination treatment from the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment will be evaluated. It is anticipated that a total of 20 patients will participate in Stage 1. If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug, and if 12 (60%) or more of the 20 patients enrolled who are deemed PFS responders in the Safety population, enrollment will continue to Stage 2. In addition, efficacy will be assessed in the safety population with aim Efficacy will also be assessed in the per-protocol population and by treatment cycle.

Three formal statistical interim analyses will be performed during this study as follows:

- Interim analysis 1: Conducted in Patients included in the Stage 1 analysis (first 20 patients enrolled) and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle.
- Interim analysis 2 added to (Stage 1+2) 6-month analysis: Conducted after all Patients (Stage 1 + Stage 2) complete the Month 6 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle.

- Interim Analysis 3 added to Stage (1+2) 12 month analysis: Conducted after all Patients (Stage 1 + Stage 2) complete the Month 12 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle.

These data will be used to help plan for future studies.

10.4.8 Protocol Deviations

Protocol deviations will be listed.

11 STUDY MANAGEMENT

The Investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, etc.

All data and corrections, if applicable, entered on to the eCRF must meet minimum requirements as specified in the case report form guidelines (CRFg). All eCRFs should be completed in their entirety and stored in accordance with International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance. The Investigator must sign the Investigator's statement in each patient's eCRF indicating that the data reported are accurate.

At the study site, clinical research associates may verify up to 100% of eCRFs in their entirety against source documentation as specified in the Clinical Monitoring Plan. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer-generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigator(s).

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, eCRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors.

11.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Study Manual requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Prospective requests to deviate from the protocol (i.e., waivers) will not be approved unless the approval is required to protect the health or welfare of participants enrolled in the study.

It is the responsibility of the Investigator and site staff to use continuous vigilance to identify and report deviations. In addition to notifying the Sponsor, protocol deviations are to be reported to the Institutional Review Board (IRB) as per applicable guidelines. The site study staff is responsible for knowing and adhering to IRB reporting requirements. Further details about the handling and reporting of protocol deviations will be included in a deviation plan.

Detailed procedures for the documentation, definition, and escalation of protocol deviations will be defined within a separate document.

11.3 Audits and Inspections

The Sponsor, regulatory authority, or IRB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, ICH GCP guidelines (E6), and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.4 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB approval prior to administration to patients. If any changes to the eCRF are required, the Sponsor will issue supplemental or revised eCRF pages.

11.5 Record Keeping

11.5.1 Drug Accountability

The Investigator must maintain accurate records of XERMELO receipt, dispensing information, and disposition. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.5.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information (PHI) in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

The Department of Health and Human Services updated a final rule to modify HIPAA. The new rule has been in effect since 26 Mar 2013, and strengthens the privacy and security protection for individual's health information; modifies the rule for Breach Notification for Unsecured PHI (Breach Notification Rule) under the HITECH Act to address public comment received on the interim final rule; modifies the HIPAA Privacy Rule to strengthen the privacy protections for genetic information by implementing section 105 of Title I of the Genetic Information Nondiscrimination Act of 2008 (GINA); and makes certain other modifications to the HIPAA Privacy, Security, Breach Notification, and Enforcement Rules (the HIPAA Rules) to improve their workability and effectiveness and to increase the flexibility for and decrease burden on the regulated entities.

The full text of the rule can be found at:

CCI CCI CCI

11.5.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.5.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.5.5 Retention of Study Documents

The new EU clinical trial regulation (Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 (Article 58) mandates a new minimum retention period for the trial master file of 25 years after the end of the clinical trial”. This establishes a more specific time period than with internationally accepted practice of ICH GCP.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12 ADMINISTRATIVE STRUCTURE OF THE STUDY

The study will be monitored by Sponsor personnel or the Sponsor's representative. The following functions for this study will be performed by organizations designated by the Sponsor: data management and statistical analysis, including pharmacodynamic analysis and reporting.

Specific functions designated by the Sponsor to another organization are to be defined via a formal transfer of obligations.

13 APPENDIX A – SCHEDULE OF EVENTS:

Procedure	Treatment Period[2,3,4] (1 cycle = 21 days, with Cis/Gem treatment on D1 & D8 and XERMELO treatment daily)																			
	Screening[1] (Up to 21 days)	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1	C19 D1	EOT [5,6]
Window (days)	NA	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4
Assess IE criteria	X	X																			
Medical history and demographics	X																				
Full physical exam[7]	X	X																			X
Symptom-oriented, brief physical exam[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																				
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[8]	X																				
Urine pregnancy test[8]		X																			X
Hematology[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Blood chemistry[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Serum CA 19-9[9,11]		X			X			X			X			X			X			X	X[10]
Serum CEA[9]		X			X			X			X			X			X			X	X[10]
Plasma 5-HIAA[9]		X			X			X			X			X			X			X	X[10]
PK trough sample[9,12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Urinalysis	X	X			X			X			X			X			X			X	X[10]
Tumor Assessment[13] (CT or MRI)	X[1]	X[1]			X			X			X			X			X			X	X[10]
ECG	X	X			X			X			X			X			X			X	X[10]

Procedure	Treatment Period[2,3,4] (1 cycle = 21 days, with Cis/Gem treatment on D1 & D8 and XERMELO treatment daily)																			
	Screening[1] (Up to 21 days)	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1	C19 D1	EOT [5,6]
Window (days)	NA	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4
ECOG Performance	X	X			X			X			X			X			X			X	X
Depression detection (ePRO)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-30 and QLQ-BIL21 (ePRO)		X																			X
Record concomitant medications[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and AESIs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Xermelo[4,15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[16]
Cis/Gem Infusion[17]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intensive PK substudy[18]		X			X			X			X			X			X			X	
Tumor characterization substudy[19]	X																				

1. The Screening Visit allows for up to 21 days prior to C1D1 if needed; however, if radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated at Day 1.
2. All assessments, including laboratory assessments, ECGs and questionnaires should be performed prior to initiating treatment regimen.
3. Treatment visit dates will be scheduled based on the date of enrollment.
4. All cycles are 21 days, with Cis/Gem treatment on D1 and D8 and XERMELO treatment daily. Patients are not required to complete a specific amount of cycles, patients may continue combination treatment for as many cycles possible until PD, unacceptable toxicity, or patient withdraws from treatment.
5. EOT procedures should be completed once the patient has confirmed PD, unacceptable toxicity, or withdraws from combination treatment. The patient will then begin the Post-treatment Follow-up Period (PTFP) where patients return to the site every 3 months to complete the required assessments until a new tumor directed therapy begins, the patient declines further treatment after progression, or withdraws from any further study visits. At that time, the EOS procedures should be completed and the patient should enter the Survival Follow-up Period (SFP) until the patient has completed a full 24 months of combination Post-treatment/Survival Follow-up. During SFP patients are to be contacted by phone every 3 months to obtain survival status; see Section 5.1.2.2 for details.
6. Procedures should not be repeated if end of treatment (EOT)/end of study (EOS) occurs during scheduled study visit; however, all EOT/EOS assessments should be completed; with those required by the scheduled visit to be recorded on the scheduled visit eCRF and additional assessments required by EOT/EOS recorded in the EOS eCRF.
7. A complete physical examination will include, at minimum, a review of the patient's general appearance, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, back, extremities,

skin and general neurological system. A symptom-related brief physical exam will only occur if the patient is experiencing symptoms or AEs. If a symptom-related brief physical exam is required, it should include a review of all body systems that relate to the symptoms and/or AE the patient is experiencing.

8. Females of childbearing potential only
9. Day 8 labs are optional (at the discretion of the Investigator) and will be analyzed by the local lab.
10. EOT assessments are not required if the last assessment occurred <3weeks prior; EOS assessments are not required if last assessment occurred ≤8weeks prior.
11. Patients should avoid multivitamins or dietary supplements containing biotin (vitamin B7) for 12 hours prior to sample collection.
12. PK trough samples are required to be drawn for ALL patients. Patients should be in a fasted state and should not have dosed prior to blood draw.
13. Tumor assessments are not required if progressive disease has been confirmed by CT/MRI at previous visit.
14. Prior medications taken within 30 days of screening will be recorded within the patient's medical history. Any medications that are ongoing at the time of screening should be recorded within the patient's concomitant medication page.
15. Xermelo will be dispensed on D1 of each cycle. The patient should be reminded to bring their bottles back on D8 of each cycle in order for dosing of Xermelo to be given with the chemotherapy infusion.
16. Xermelo can continue to be dispensed during the Post-treatment Follow-up Period, at the discretion of the Investigator, until the patient begins new tumor-directed therapy, declines further treatment after progression, or withdraws from any further study visits.
17. Cis/Gem are not being provided by TerSera. If cisplatin is stopped, gemcitabine may be continued alone at the Investigator's discretion.
18. Intensive PK is an optional substudy. These samples are only required for those patients who have consented to participate in this substudy and will be drawn on Day 1 and Day 8 of each cycle where collected; refer to Appendix B for additional details.
19. Archived tissue samples can be submitted at any time during the Treatment Period. Fresh biopsies will not be collected.
20. Total duration of the 2 combined Follow-up Periods should be no more than 24 Months.
21. Follow-up visits dates should be scheduled based on the EOT date.
22. Phone call to patient or caregiver, where appropriate, to obtain survival status.
23. Patients who enter PTFP and imaging assessments are not required, or who enter SFP without entering or completing PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. Reconsenting the patient may be required if previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

APPENDIX A – SCHEDULE OF EVENTS

Procedure	Follow-up Period[20,21]															
	Post-treatment Follow-up								Survival Follow-up							
	3 Month	6 Month	9 Month	12 Month	15 Month	18 Month	21 Month	24 Month / EOS[6]	3 Month	6 Month	9 Month	12 Month	15 Month	18 Month	21 Month	24 Month
Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Phone patient[22]									X	X	X	X	X	X	X	X
Full physical exam[7]								X								
Symptom-oriented brief physical exam[7]	X	X	X	X	X	X	X									
Weight								X								
Vital signs	X	X	X	X	X	X	X	X								
Urine pregnancy test[8]								X								
Hematology[9]	X	X	X	X	X	X	X	X[10]								
Blood chemistry[9]	X	X	X	X	X	X	X	X[10]								
Serum CA 19-9[9,11]	X	X	X	X	X	X	X	X[10]								
Serum CEA[9]	X	X	X	X	X	X	X	X[10]								
Plasma 5-HIAA[9]	X	X	X	X	X	X	X	X[10]								
PK trough sample[9,12]	X	X	X	X	X	X	X	X[10]								
Urinalysis								X[10]								
Tumor Assessment[13] (CT or MRI)	X[23]	X[23]	X	X	X	X	X[23]	X[10,23]								
ECG								X[10]								
ECOG Performance	X	X	X	X	X	X	X	X								
Depression detection (ePRO)								X								
EORTC QLQ-30 and QLQ-BIL21 (ePRO)		X						X								
Record concomitant medications[18]	X	X	X	X	X	X	X	X								
Record SAEs	X	X	X	X	X	X	X	X								
Record AEs and AESIs	X	X	X	X	X	X	X	X								
Dispense Xermelo[4,15]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]									

AE = adverse event; AESI = adverse event of special interest; CT = computed tomography; Cis = cisplatin; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; Gem = gemcitabine; IE = inclusion/exclusion; MRI = magnetic resonance imaging; SAE = serious adverse event; PK = pharmacokinetic

1. The Screening Visit allows for up to 21 days prior to C1D1 if needed; however, if radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated at Screening.
2. All assessments, including laboratory assessments, ECGs and questionnaires should be performed prior to initiating treatment regimen.
3. Treatment visit dates will be scheduled based on the date of enrollment.
4. All cycles are 21 days, with Cis/Gem treatment on D1 and D8 and XERMELO treatment daily. Patients are not required to complete a specific amount of cycles, patients may continue combination treatment for as many cycles possible until PD, unacceptable toxicity, or patient withdraws from treatment.
5. EOT procedures should be completed once the patient has confirmed PD, unacceptable toxicity, or withdraws from combination treatment. The patient will then begin the Post-treatment Follow-up Period (PTFP) where patients return to the site every 3 months to complete the required assessments until a new tumor directed therapy begins, the patient declines further treatment after progression, or withdraws from any further study visits. At that time, the EOS procedures should be completed and the patient should enter the Survival Follow-up Period (SFP) until the patient has completed a full 24 months of combination Post-treatment/Survival Follow-up. During SFP patients are to be contacted by phone every 3 months to obtain survival status; see Section 5.1.2.2 for details.
6. Procedures should not be repeated if end of treatment (EOT)/end of study (EOS) occurs during scheduled study visit; however, all EOT/EOS assessments should be completed; with those required by the scheduled visit to be recorded on the scheduled visit eCRF and additional assessments required by EOT/EOS recorded in the EOS eCRF.
7. A complete physical examination will include, at minimum, a review of the patient's general appearance, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, back, extremities, skin and general neurological system. A symptom-related brief physical exam will only occur if the patient is experiencing symptoms or AEs. If a symptom-related brief physical exam is required, it should include a review of all body systems that relate to the symptoms and/or AE the patient is experiencing.
8. Females of childbearing potential only
9. Day 8 labs are optional (at the discretion of the Investigator) and will be analyzed by the local lab.
10. EOT assessments are not required if the last assessment occurred <3weeks prior; EOS assessments are not required if last assessment occurred ≤8weeks prior.
11. Patients should avoid multivitamins or dietary supplements containing biotin (vitamin B7) for 12 hours prior to sample collection.
12. PK trough samples are required to be drawn for ALL patients. Patients should be in a fasted state and should not have dosed prior to blood draw.
13. Tumor assessments are not required if progressive disease has been confirmed by CT/MRI at previous visit.
14. Prior medications taken within 30 days of screening will be recorded within the patient's medical history. Any medications that are ongoing at the time of screening should be recorded within the patient's concomitant medication page.
15. Xermelo will be dispensed on D1 of each cycle. The patient should be reminded to bring their bottles back on D8 of each cycle in order for dosing of Xermelo to be given with the chemotherapy infusion.
16. Xermelo can continue to be dispensed during the Post-treatment Follow-up Period, at the discretion of the Investigator, until the patient begins new tumor-directed therapy, declines further treatment after progression, or withdraws from any further study visits.
17. Cis/Gem are not being provided by TerSera. If cisplatin is stopped, gemcitabine may be continued alone at the Investigator's discretion.
18. Intensive PK is an optional substudy. These samples are only required for those patients who have consented to participate in this substudy and will be drawn on Day 1 and Day 8 of each cycle where collected; refer to Appendix B for additional details.
19. Archived tissue samples can be submitted at any time during the Treatment Period. Fresh biopsies will not be collected.
20. Total duration of the 2 combined Follow-up Periods should be no more than 24 Months.
21. Follow-up visits dates should be scheduled based on the EOT date.
22. Phone call to patient or caregiver, where appropriate, to obtain survival status.
23. Patients who enter PTFP and imaging assessments are not required, or who enter SFP without entering or completing PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. Reconsenting the patient may be required if previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

14 APPENDIX B – INTENSIVE PK SUBSTUDY SCHEDULE

Schedule of Intensive PK Assessments[1]								
	Predose	**Morning Dose[2]**	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**6 hr**	**Midday Dose**
Intensive PK Assessments	X		X[4]	X[4]		X[4]	X[4]	
Time of Day (Example)	**Predose[3]**	**8:00**	**9:00**	**10:00**	**11:00**	**12:00**	**14:00**	**14:01**

[1]Patients who have consented to the intensive PK substudy should have PK samples collected at all time points shown above on Day 1 and Day 8 of all required cycles; see Appendix A.
[2]With food
[3]Fasted
[4]Samples should be collected within 15 minutes of scheduled collection time

15 APPENDIX C – ESTIMATED AMOUNT OF BLOOD TO BE COLLECTED FROM EACH PATIENT

Assessment		Sample volume (mL)	Number of samples*	Estimated total volume (mL)
Safety	Hematology	4	19	76
	Blood chemistry	6	19	114
	Serum hCG	2	1	2
Pharmacokinetic	XERMELO and LP-788902	4	*42*	*168*
CCI		4	*16*	*64*
CCI		4	*16*	*64*
CCI		4	*16*	*64*
			Total	*552*

* Maximum number of samples is indicated.

16 APPENDIX D – ETHICAL STANDARDS

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), ICH Guidance for Industry, E6 GCP: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are patient to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Patients
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current FDA Guideline for Institutional Review Boards and Clinical Investigators
- Current FDA Guideline for Good Clinical Practice

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human patients are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings;
- the potential benefits of the research justify the risks.

TerSera Therapeutics LLC is the Sponsor of the Investigational New Drug Application (IND). The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,

- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that FDA and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

17 APPENDIX E – INVESTIGATOR OBLIGATIONS

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the patient informed consent form will be approved by the IRB before enrollment of any patients. The opinion of the IRB will be dated and given in writing. A copy of the letter of approval from the IRB and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of XERMELO supplies to the Investigator.

The Investigator will ensure that the IRB will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to patients. The Investigator will also ensure that no changes will be made to the protocol without IRB approval.

As a part of the IRB requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of patient risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every patient prior to clinical trial participation. The rights, safety, and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators in the US must provide the Sponsor with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide the Sponsor with their own curriculum vitae and current curriculum vitae for each subinvestigator listed on the Form FDA 1572.

Protection of Human Patients (21 CFR Part 50)

Informed consent must be obtained from every patient before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB-approved consent form and signed by the patient or the patient's legally authorized representative. The Department of Health and Human Services suggests that when minors are

involved, a parent or guardian should sign the consent form. If the minor is an adolescent, their signature should also be included. Non-English-speaking patients must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the patient signing it. Another copy must be kept in the Investigator's files and made available to FDA representatives upon request. If, for any reason, patient risk is increased as the study progresses, a revised, IRB-approved consent form must be signed by the patient. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all patients.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB within 5 working days. In this situation, the Investigator may not administer any subsequent product to that patient until informed consent and IRB approval are obtained.

Informed Consent

Written informed consent must be obtained from each patient prior to entry in the study. One copy of the signed informed consent document will be given to the patient, and another will be retained by the Investigator. Additionally, the participant must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the participant is not legally competent to provide consent (i.e., mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research

- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA and representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the patient's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus, if the patient is or may become pregnant), which are currently unforeseeable
- Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs the patient may incur from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning patient consent.

Study Documentation

The protocol and informed consent form(s) for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB/Ethics Review Committee (ERC) prior to enrollment of participants in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval, which specifically identifies the study/protocol and a list of the committee members, must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for reevaluation and reapproval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the IB, drug accountability records, Sponsor/Investigator correspondence, IRB correspondence, protocol and amendments, information regarding monitoring activities, patient exclusion records, eCRFs, and data queries.

Confidentiality

The anonymity of participating patients must be maintained. Patients will be identified by an assigned patient number on eCRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the patient (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the FDA) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of XERMELO at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each patient, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that XERMELO is used only in accordance with the protocol.

18 APPENDIX F – CALCULATIONS

Cockcroft-Gault equation:

The equation for calculation of creatinine clearance, as an estimation of glomerular filtration rate, using the method of Cockcroft and Gault is:

$$\frac{[(140-\text{age}) \times \text{weight (in kg)}]}{[72 \times \text{serum creatinine (in mg/dL)}]}$$

If the patient is female, multiply the above by 0.85

For an online calculator, please use: http://www.nephron.com/cgi-bin/CGSI.cgi.

Source: Cockcroft D, Gault MD. Prediction of Creatinine Clearance from Serum Creatinine. Nephron. 1976;16:31-41.

Body Mass Index equation:

Measurement Units	Formula and Calculation
Kilograms and meters (or centimeters)	Formula: weight (kg) / [height (m)]^2 With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Since height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters. Example: Weight = 68 kg, Height = 165 cm (1.65 m) Calculation: 68 ÷ (1.65)^2 = 24.98
Pounds and inches	Formula: weight (lb) / [height (in)]^2 x 703 Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703. Example: Weight = 150 lbs, Height = 5'5" (65") Calculation: [150 ÷ (65)^2] x 703 = 24.96

For an online calculator, please use:

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From the Centers for Disease Control and Prevention site:

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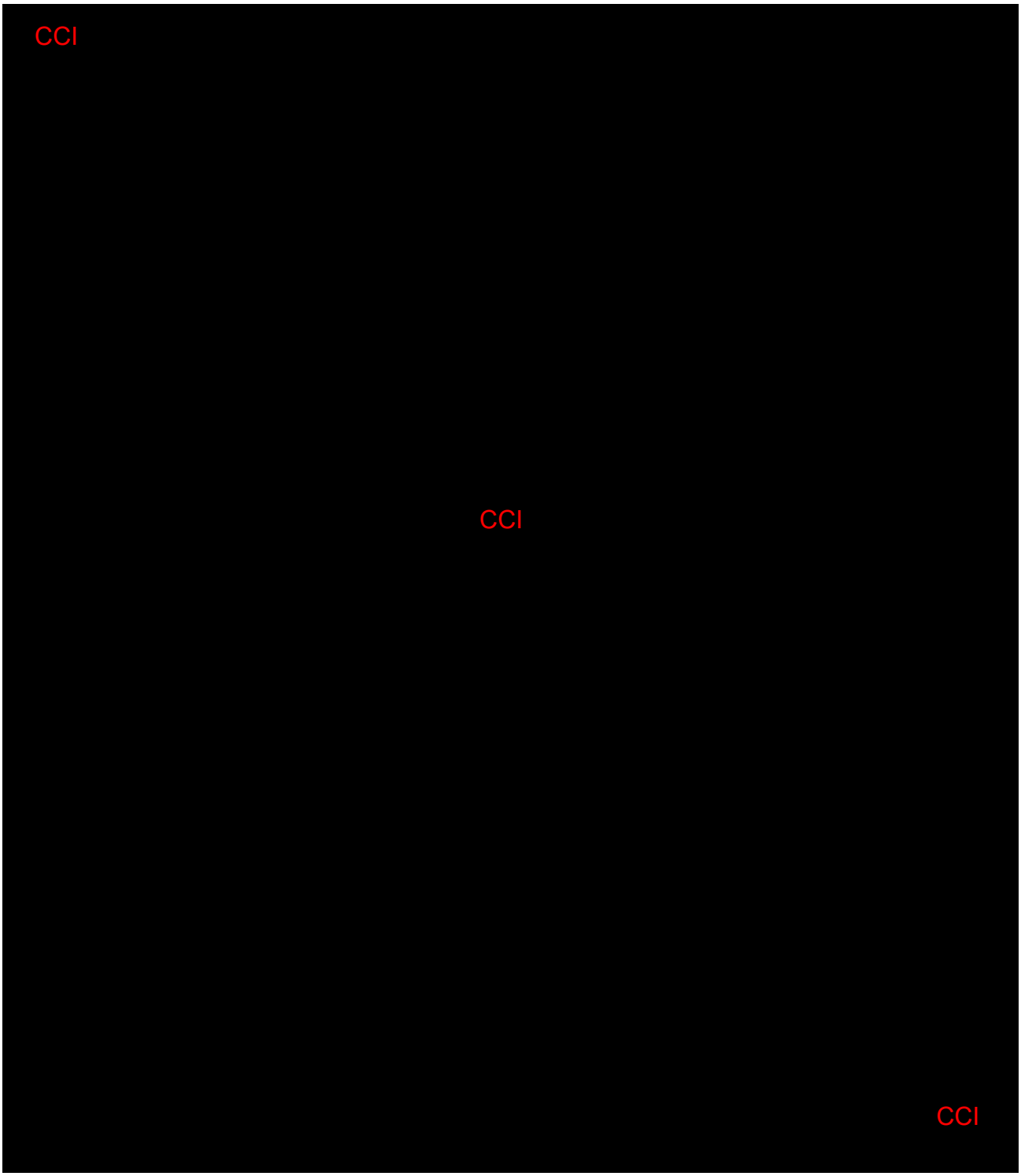

Reference:

National Cancer Institute – Cancer Therapy Evaluation Program. Clinical Data Update System (CDUS) Instructions and Guidelines version 3.0 Release 4. Capital Technology Information Services, Inc. 15 January 2008.

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20 APPENDIX H – NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V5.0

The NCI CTCAE v5.0 can be found at:

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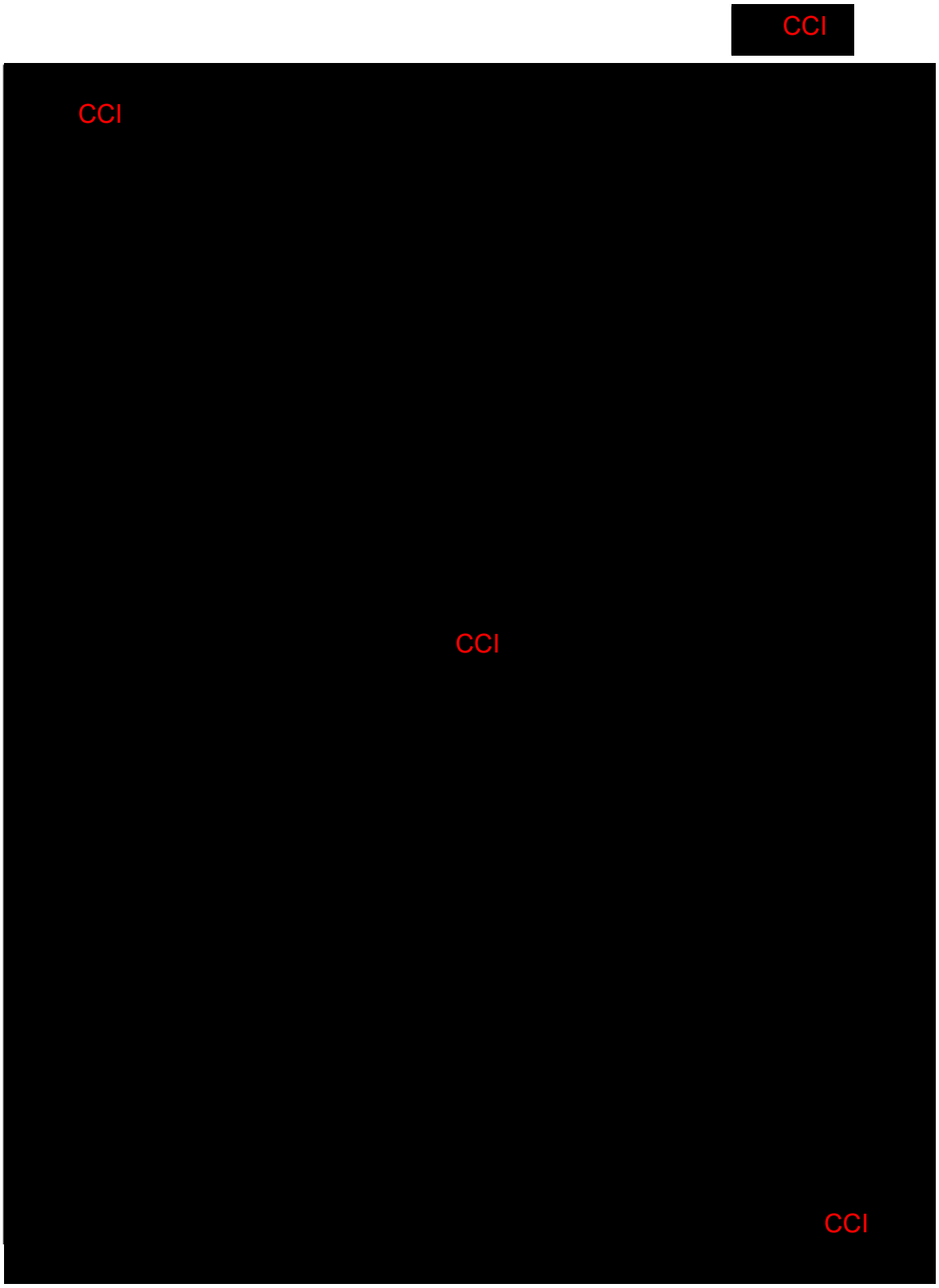
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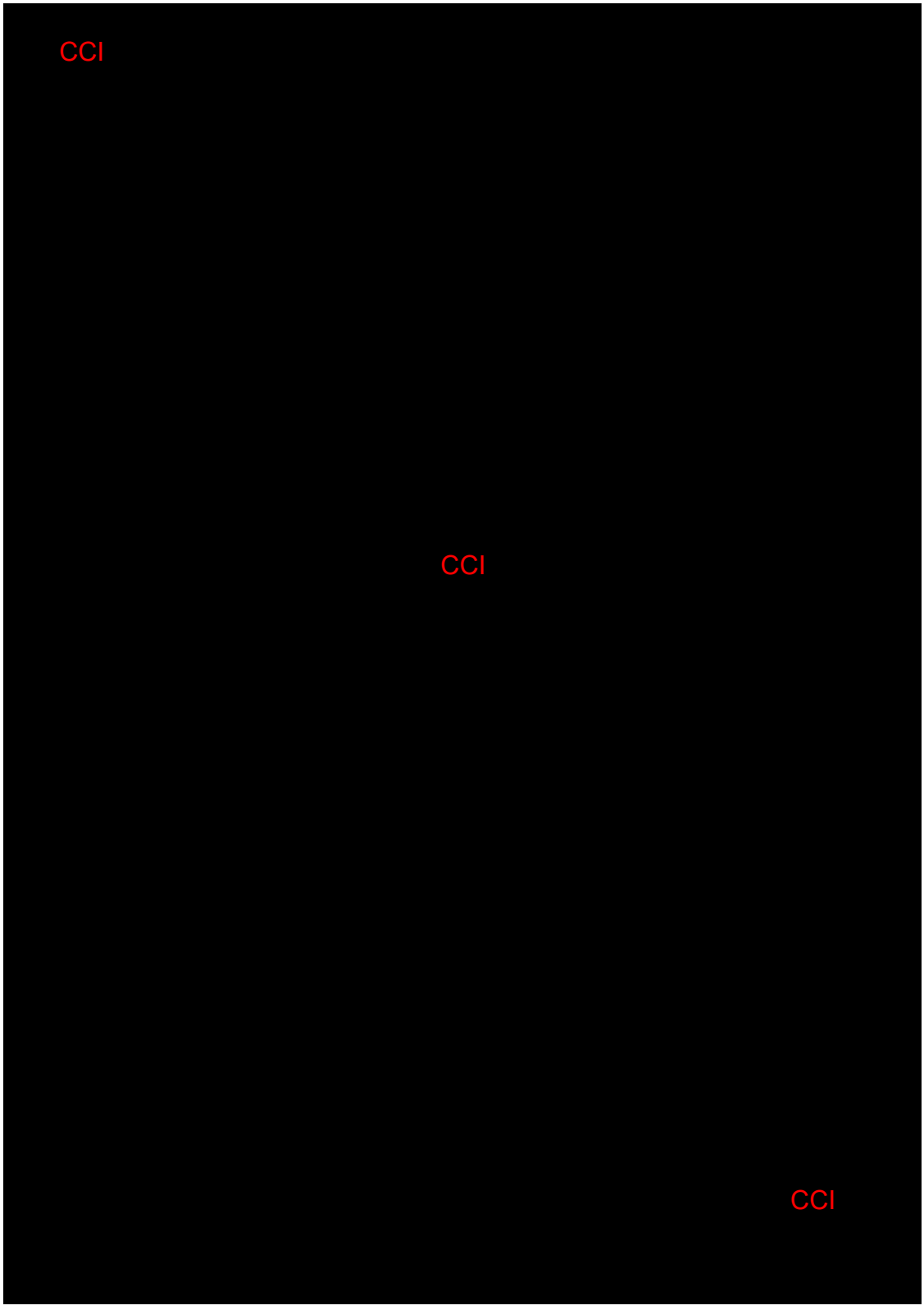
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22 APPENDIX J – RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

The RECIST Guidelines can be found at: CCI CCI

23 APPENDIX K - DETAILED SUMMARY OF PROTOCOL CHANGES

Section	Former Text	New Text (in Bold)	Rationale
Cover Page		Added Amendment 3 Date: 15 November 2020	
Cover Page	**Sponsor** Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160	**Sponsor** TerSera Therapeutics LLC 520 Lake Cook Road, Suite 500 Deerfield, IL 60015	
	CCI CCI CCI		
Investigator Signature Page		Added Amendment 3 Date: 15 November 2020	
Investigator Signature Page	**Sponsor** Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160	**Sponsor** TerSera Therapeutics LLC 520 Lake Cook Road, Suite 500 Deerfield, IL 60015	
	CCI CCI CCI		
Investigator Signature Page	CCI CCI CCI		

Section	Former Text	New Text (in Bold)	Rationale
Protocol Amendment Changes		Added: Protocol Amendment Summary Of Key Changes	
Synopsis-Primary Objective Section 4.1-Primary Objective	The primary objective of the study is to assess the safety and efficacy (progression-free survival rate at Month 6) of XERMELO in combination with cisplatin (cis) plus gemcitabine (gem)	The primary objective of the study is to assess the safety and efficacy (PFS rate at Month 6) in the Safety population receiving the combination of XERMELO plus 1L treatment with cis/gem combination chemotherapy. Efficacy (PFS rate at Month 6) will also be evaluated in the Per Protocol Population (PP) and by treatment cycle.	
Synopsis-Second Objectives Section 4.2-Secondary Objective Section 10.3-Study Endpoints	• PFS rate at Month 12 and median PFS	• PFS rate at Month 12 and median PFS **at Month 12**	
Synopsis-Exploratory Objectives Section 4.3-Exploratory Objectives Section 10.3-Study Endpoints	• Change from Baseline in CCI CCI CCI • Subgroup analyses of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment, based on categorical group of Baseline and change from Baseline	• Change from Baseline in CCI CCI **at Months 6 and 12 and EOS;** • Subgroup analyses of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment, based on categorical group of Baseline and change from Baseline **at Months 6 and 12 and EOS in:** Added the following new objectives: • **Subgroup analyses in:** ○ **Patients with changes in liver function tests**	

Section	Former Text	New Text (in Bold)	Rationale
		○ **Patients with Biliary stents** ○ **Location of disease (intrahepatic, extrahepatic, or gallbladder)** • **Efficacy analyses by treatment cycles (such as in patients who completed CCI CCI CCI with combination treatment)**	
Synopsis-Methodology	~~If 12 or more patients have survived and remain progression-free at Month 6, Stage 1 of the study will be considered successful and enrollment will continue in Stage 2.~~	Added: **Note: Efficacy (PFS rate at Month 6) will also be assessed in the Per Protocol population and by treatment cycle.** **Note: For statistical purposes and most analyses, Cycle 1 Day 1 is intended as Baseline, Cycle 10 Day 1 is intended as Month 6, and Cycle 19 Day 1 is intended as Month 12.** **If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug, and if efficacy in 12 (60%) or more of the 20 patients are deemed responders, in the Safety population, enrollment will continue to Stage 2. In addition, efficacy will be assessed in the Per-Protocol (PP) population and by treatment cycle.**	
Section 5.1.2.1-Treatment Period	From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 or more responses are observed (ie, patients are alive and progression-free at Month 6) the study will be declared successful	From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 **(>60%)** or more responses are observed **(i.e.,** patients are alive and progression-free at Month 6) **in the Safety population,** the study will be declared successful. **Efficacy will also be assessed in the PP population and by treatment cycle.**	

Section	Former Text	New Text (in Bold)	Rationale
Section 5.1.2.2-Follow-up Periods	**Note:** If a radiological assessment has not been performed within 6 weeks prior to Day 1, an assessment at Screening will also be required. All patients are expected to be followed for a total duration of 24 months after the Treatment Period unless they voluntarily withdraw consent from future study visits or assessments. Patients will complete scheduled study visits every 3 months for a total of 24 months or until the patient begins a new tumor-directed therapy, declines further treatment after progression, or withdraws consent from future study visits or assessments.	**Note: If a radiological assessment has performed within 6 weeks prior to Day 1, a Day 1 assessment will not be required.** All patients are expected to be followed for a total duration of 24 months after the Treatment Period unless they **prematurely discontinue or** voluntarily withdraw consent from future study visits or assessments. Patients will complete scheduled study visits every 3 months for a total of 24 months or until the patient begins a new tumor-directed therapy, **prematurely discontinues,** declines further treatment after progression, or withdraws consent from future study visits or assessments. Added: **Note: For those patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.** **Note: Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This**	

Section	Former Text	New Text (in Bold)	Rationale
		includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.	
Synopsis-Direction of Treatment		Added: **Note: Patients may continue to receive treatment for as many cycles possible, until progressive disease (PD) (up to 19 cycles during the Treatment Period), and during the Post Treatment Follow-up Period (up to an additional 24 months) at the discretion of the Investigator.**	
Synopsis-Interim Analysis		New Section: A formal statistical interim analysis will be performed on patients included in the Stage 1 analysis. The interim analysis results will include safety, efficacy (PF responder rates), and pharmacodynamic (biomarker) data. These data will be used to help plan for future studies. Interim Analysis will be conducted: • In addition to (Stage 1 + Stage 2) analysis, after all 53 patients complete Month 6 In addition to (Stage 1 + Stage 2) analysis after, all 53 patients complete Month 12	
Synopsis-Statistical Methods	CCI CCI CCI In Stage 1, if 12 or more of the 20 patients enrolled are deemed responders per the	**clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if 12 or more (≥60%)** of the 20	

Section	Former Text	New Text (in Bold)	Rationale
	definition below after the 20th patient is censored, is alive and progression-free at the Month 6 assessment, or has discontinued for any reason, the first stage of the study will be declared successful and enrollment will continue in Stage 2. In Stage 2, an additional 33 patients will be enrolled. If 34 or more of the 53 patients enrolled (Stage 1 + Stage 2) are deemed responders, the study will be considered successful.	patients enrolled are deemed responders per the definition below after the 20th patient is censored, is alive and progression-free at the Month 6 assessment, or has discontinued for any reason, the first stage of the study will be declared successful and enrollment will continue in Stage 2. **Efficacy will also be assessed in the PP populations and by treatment cycle.** In Stage 2, an additional 33 patients will be enrolled. If 34 **(>60%)** or more of the 53 patients enrolled (Stage 1 + Stage 2) are deemed responders, the study will be considered successful. **Efficacy will also be assessed in the PP populations and by treatment cycle.**	
Synopsis-PK Analysis Section 10.4.4-PK Analyses	PK data will be summarized by n, mean, standard deviation, median, minimum, and maximum values at various time points.	PK data will be summarized by n, **arithmetic and geometric mean,** standard deviation, median, minimum, and maximum values at various time points.	
Abbreviations	C1D1 Cycle 1, Day 1; Baseline	C1D1 Cycle 1, Day 1; Baseline **(Baseline value is defined as the last non-missing data on or before the first dose of the study drug, unless otherwise specified)** Added: **C10D1 Cycle 10, Day 1 is intended as Month 6** **C19D1 Cycle 19 Day 1 is intended as Month 12**	
Section 5.1.1-Screening	**Note**: If radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated during the Screening Period	**Note**: If radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated **at Day 1**.	

Section	Former Text	New Text (in Bold)	Rationale
Section 5.1.2.2-Follow-up Periods		Added: Reconsent In cases when a patient has prematurely discontinued from the study and/or withdrawn consent from conducting further study assessments, these patients may be asked to re-consent to provide permission for their local imaging and imaging reports to be submitted to BICR.	
Section 6.3.1.1-End-of-Treatment Procedures		Added: For those patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint.	
Section 6.3.1.2-End-of-Study Procedures	In addition, if a patient voluntarily ends participation in the study, it must be recorded on the eCRF the extent of withdrawal (eg, Does the patient agree to attend future study visits, allow contact by study personnel, and/or continued access to information about potential SAEs?). The date the patient discontinues participation and the primary reason for termination of participation (eg, AE, PD, protocol deviation, withdrawal of consent, lost to follow-up, death), must be recorded on the eCRF.	Added: Patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. In addition, if a patient voluntarily ends participation in the study at any time, **the primary reason for discontinuation (e.g., AE, PD, protocol deviation, withdrawal of consent, lost to follow-up, death)** must be recorded on the eCRF **and document whether** the patient **agrees** to attend future study visits, allow contact by study personnel, and/or continued access to information **and/or images** about **disease status** and potential SAEs. The date the patient discontinues participation and the primary reason for **discontinuation** of participation (eg, AE, PD,	

Section	Former Text	New Text (in Bold)	Rationale
	After the EOS visit occurs, patients who have not completed 24 months of follow-up will enter the SFP where all patients (or caregivers, where appropriate) will be contacted by phone every 3 months to obtain their survival status until death, withdrawal of consent, loss to follow-up, **or** for a total duration of 24 months after the last dose of chemotherapy (including the duration of the PTFP), whichever occurs first.	protocol deviation, withdrawal of consent, lost to follow-up, death), must be recorded on the eCRF. After the EOS visit occurs, patients who have not completed 24 months of follow-up will enter the SFP where all patients (or caregivers, where appropriate) will be contacted by phone every 3 months to obtain their survival status until death, **premature discontinuation**, withdrawal of consent, loss to follow-up, **or** for a total duration of 24 months after the last dose of chemotherapy (including the duration of the PTFP), whichever occurs first. Added: **Note: Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.**	
Section 7-Treatment	Lexicon	TerSera	
Section 7.3-Prohibited Medication or Concomitant Therapy	(Lexicon Pharmaceuticals, Inc., 2017),	(TerSera Therapeutics LLC. 2020)), Added: • Chronic treatment with corticosteroids, ≥5 mg/day of prednisone (or equivalent), or other immunosuppressive agent(s)	
Section 8-Study Procedures	(Lexicon Pharmaceuticals, Inc., 2017),	(TerSera Therapeutics LLC, 2020).	

Section	Former Text	New Text (in Bold)	Rationale
Section 8.2.1.1.1-CT/MRI	For the purpose of this study, C1D1 will be referred to as Baseline.	For the purpose of this study**, images submitted to BICR within 6 weeks prior to and including C1D1, i.e., which ever set was closest to** C1D1 will be referred to as Baseline **imaging.**	
Section 8.2.2-Clinical Laboratory Assessments		Added: **In rare cases, laboratory results obtained from the local laboratory may be used to assess eligibility when the central laboratory lab result is unavailable. Authorization to use local laboratory results for determining eligibility must be obtained from the Sponsor prior to initiating study drug.**	
Section 9.4-Reporting of SAEs and Pregnancies	If paper report forms are used, the form(s) should be sent to: Safety Data Facsimile: (832) 442-5462 or Email address (in case of fax failure): CCI CCI In case of failure of/lack of access to eCRF, email, or fax, the event should be reported using Safety Hotline: CCI If an SAE is reported via telephone, the telephone report should be followed by a written report using a reporting method described above (ie, completion of eCRF of paper form). For questions on safety reporting, the Safety Physician of the study should be contacted at: CCI Pharmacovigilance and Drug Safety Email: Phone: CCI	Added: **All SAEs, pregnancies, and other special situations should be recorded on the study participant's eCRF page for AEs.** Moved: Where applicable, information from relevant hospital records and autopsy reports should be obtained. If paper report forms are used or to provide redacted supporting documents, they, should be sent to: Safety Data Facsimile: CCI or Email address (in case of fax failure): CCI CCI In case of failure of/lack of access to eCRF, email, or fax, the event **can** be reported to the **TerSera Call Center** CCI If an SAE is reported via telephone, the telephone report should be followed by a written report	

Section	Former Text	New Text (in Bold)	Rationale
	For questions on study participant management related to AE, the Medical Monitor of the study should be contacted. ~~All SAEs, pregnancies, and other special situations should also be recorded on the study participant's eCRF page for AEs.~~	using a reporting method described above (**i.e.,** completion of eCRF **or** paper form). For questions on safety reporting, **please contact** [redacted]	
Section 10.4.1- Efficacy Analyses	A Simon's 2-stage design algorithm will be used to assess whether the study is successful at each stage of the analysis. In the Stage 1 Safety Population, if there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if 12 (60%) or more of the 20 patients enrolled who are deemed responders per the definition below after the 20th patient is censored, is alive and progression-free at the Month 6 assessment, or has discontinued for any reason, the study will be declared successful and enrollment will continue in Stage 2. Efficacy will also be assessed in the PP population and by treatment cycle. In Stage 2, an additional 33 patients will be enrolled. If 34 or more (>60%) of the 53 patients enrolled (Stage 1 + Stage 2) are deemed responders, the study will be considered successful.	A Simon's 2-stage design algorithm will be used to assess whether the study is successful at each stage of the analysis. In **the** Stage 1 **Safety Population**, if **there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if 12 (60%)** or more of the 20 patients enrolled **who** are deemed responders per the definition below after the **20th** patient is censored, is alive and progression-free at the Month 6 assessment, or has discontinued for any reason, the study will be declared successful and enrollment will continue in Stage 2. **Efficacy will also be assessed in the PP population and by treatment cycle**. In Stage 2, an additional 33 patients will be enrolled. If 34 or more **(>60%)** of the 53 patients enrolled (Stage 1 + Stage 2) are deemed responders, the study will be considered successful.	

Section	Former Text	New Text (in Bold)	Rationale
Section 10.4.7-Interim Analysis	Periodic reviews of study data will be conducted as described in Section 9.6 throughout the study for the purposes of safety monitoring but will not serve as a formal analysis of study data. ~~No formal interim analysis will be performed.~~	Periodic reviews of study data will be conducted as described in Section 9.6 throughout the study for the purposes of safety monitoring but will not serve as a formal analysis of study data: Added: **A Stage 1 analysis in a total of 20 patients will be conducted. Stage 1 enrollment will include a Safety Run-in cohort. Safety, tolerability and efficacy data of the combination treatment from the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment will be evaluated. It is anticipated that a total of 20 patients will participate in Stage 1. If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug, and if 12 (60%) or more of the 20 patients enrolled who are deemed PFS responders in the Safety population, enrollment will continue to Stage 2. In addition, efficacy will be assessed in the safety population with aim Efficacy will also be assessed in the per-protocol population and by treatment cycle.** **Three formal statistical interim analyses will be performed during this study as follows:** • **Interim analysis 1: Conducted in Patients included in the Stage 1 analysis (first 20 patients enrolled) and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle.** • **Interim analysis 2 added to (Stage 1+2) 6-month analysis: Conducted after all Patients (Stage 1 + Stage 2) complete the**	

Section	Former Text	New Text (in Bold)	Rationale
		Month 6 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle. • **Interim Analysis 3 added to Stage (1+2) 12 month analysis: Conducted after all Patients (Stage 1 + Stage 2) complete the Month 12 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle.** **These data will be used to help plan for future studies.**	
Appendix A-Schedule of Events	#1: The Screening Visit allows for up to 21 days prior to C1D1 if needed; however, if radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated at Screening #17: Lexicon ~~#22 Phone call to patient or caregiver, where appropriate, to obtain survival status.~~	Added footnotes to tumor assessment First table #1: The Screening Visit allows for up to 21 days prior to C1D1 if needed; however, if radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated at Day 1. #17:TerSera Added: #23 Patients who enter PTFP and imaging assessments are not required, or who enter SFP without entering or completing PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. Reconsenting the patient may be required if previously prematurely discontinued or withdrew consent from the Treatment Period of the study.	

Section	Former Text	New Text (in Bold)	Rationale
		Second Table Added: #22. Phone call to patient or caregiver, where appropriate, to obtain survival status. #23. Patients who enter PTFP and imaging assessments are not required, or who enter SFP without entering or completing PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. Reconsenting the patient may be required if previously prematurely discontinued or withdrew consent from the Treatment Period of the study.	
Appendix D-Ethical Standards	Lexicon Pharmaceuticals, Inc.	TerSera Therapeutics LLC	
Appendix K-Summary of Changes		New Section	

24 REFERENCES

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