ID: UMCC 2019.116	Gemcitabine and Cisplatin With or Without CPI-613 as First Line Therapy for Patients With Advanced Unresectable Biliary Tract Cancer (BilT-04)	NCT04203160

UMCC 2019.116
A Multi-Center Randomized Phase IB/II Study of Gemcitabine and Cisplatin With or Without CPI-613 as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer (BilT-04)

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Study Drug: CPI-613® (Devimistat)

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NOTE: To effectively manage restrictions put in place during public health or civil emergency or restrictions (i.e., COVID-19 pandemic), changes to protocol-required items are to be made to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens). These changes are listed in Appendix III of the protocol (Contingency Operations Plan)

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ABBREVIATIONS:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
BTC	Biliary Tract Cancer
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MSC	Multi-Site Coordinator
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
SAE	Serious Adverse Event
SD	Stable Disease
UaP	Unanticipated Problem
WBC	White Blood Cells

STUDY SCHEMA

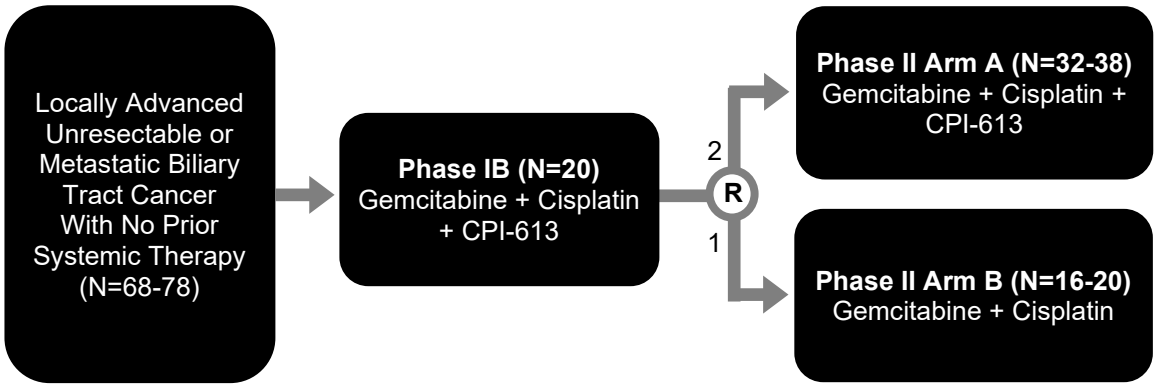

Figure 1. Study Schema

STUDY SYNOPSIS

Title	A Multi-Center Randomized Phase IB/II Study of Gemcitabine and Cisplatin With or Without CPI-613 as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer
Phase	Phase IB/II
Methodology	Phase IB – Single arm (TiTE-CRM) Phase II – Randomized 2:1, open-label
Study Duration	4 years
Study Center(s)	Multi-Center
Objectives	Primary objectives: 1. Phase IB – Determine the maximum tolerated dose/recommended phase 2 dose for gemcitabine and cisplatin with CPI-613 2. Phase II – Determine the overall response rate in patients with advanced BTC treated with gemcitabine and cisplatin with or without CPI-613. Secondary objectives: 1. Evaluate the median PFS and OS of patients with advanced BTC. 2. Evaluate the safety of CPI-613 in combination with gemcitabine and cisplatin in this patient population. Exploratory objectives: 1. To explore predictors of biomarker response and mechanisms of resistance based on the exploratory analysis of tissue obtained through serial biopsies and blood. a) Immunohistochemical staining for PDK, PDH, KGDH, SOD2 and CD79a b) Whole exome genomic and transcriptomic (RNAseq) analysis for tumor biology at baseline and progression. c) Blood collection, including serum, plasma and serum for future biomarker analysis, including ctDNA.
Number of Subjects	68-78

Eligibility Criteria	1. Patients must have a pathologically or cytologically confirmed carcinoma (except neuroendocrine) of the biliary tract (intra-hepatic, extra-hepatic (hilar, distal) or gallbladder) that is not eligible for curative resection, transplantation, or ablative therapies. Tumors of mixed cholangiocarcinoma/hepatocellular carcinoma histology are excluded. 2. Patients must not have received prior systemic treatment (chemotherapy or targeted therapy) for advanced BTC. Prior peri-operative chemotherapy is permitted provided it was completed > 6 months from enrollment. 3. Prior radiation, chemoembolization, radioembolization or other local ablative therapies or hepatic resection is permitted if completed ≥ 4 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity. Extrahepatic palliative radiation is permitted if completed ≥ 2 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity. 4. Patients must have radiographically measurable disease (as per RECISTv1.1) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site. 5. Must be ≥ 18 years of age 6. Must have an ECOG performance status of 0-1 7. Ability to understand and willingness to sign IRB-approved informed consent 8. Willing to provide archived tissue, if available, from a previous diagnostic biopsy or surgery 9. Must be able to tolerate CT and/or MRI with contrast 10. Must have adequate organ function obtained ≤2 weeks prior to enrollment (absolute neutrophil count $\geq$1500/mm^3, hemoglobin $\geq$9 g/dL, platelets $\geq$100,000/mm^3, serum creatinine $\leq$ 1.5 x upper limit normal (ULN), creatinine clearance ≥ 50 mL/min, albumin $\geq$3.0 g/dL, AST/ALT $\leq$3.0 x ULN ($\leq$5 x ULN if liver tumor or metastasis), total bilirubin $\leq$ 1.5 x upper limit normal, INR $\leq$ 1.5 upper limit normal) 11. Must not have prior history of brain metastasis (unless previously treated, asymptomatic and stable for at least 3 months), or organ transplantation. 12. Must not have undergone a major surgical procedure < 4 weeks prior to enrollment. 13. Must not have an active second malignancy other than in situ cancer or localized prostate cancer (Gleason score <8). Patients with a history of other malignancy are eligible provided primary treatment of that cancer was completed > 1 year prior to enrollment and the patient is free of clinical or radiologic evidence of recurrent or progressive malignancy. 14. Must have no ongoing active, uncontrolled infections (afebrile for > 48 hours off antibiotics). 15. Must not have a psychiatric illness, other significant medical illness, or social situation which, in the investigator's opinion, would limit compliance or ability to comply with study requirements. 16. Women must not be pregnant or breastfeeding since study drugs may harm the fetus or child. All females of childbearing potential (not surgically sterilized and between menarche and 1-year post menopause) must have a negative screening pregnancy test. 17. Women of child-bearing potential and men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation, and for 6 months (for men and women) following completion of study therapy. 18. Must not have active heart disease including symptomatic heart failure (NYHA class 3 or 4), unstable angina pectoris, uncontrolled cardiac arrhythmia or interstitial lung disease. 19. Prisoners or subjects who are involuntarily incarcerated, or compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious

	disease) illness would be excluded. 20. Must not have prolonged QTcF interval >480 msec 21. Patients with known hypersensitivity to cisplatin, gemcitabine or CPI-613, or its inactive components would be excluded.
Study Product(s), Dose, Route, Regimen	<u>Phase IB and Phase II Arm A (days 1, 8 Q21 days):</u> Gemcitabine 1000 mg/m^2 IV Cisplatin 25 mg/m^2 IV CPI-613 at dose level or RP2D IV <u>Phase II Arm B (days 1, 8 Q21 days):</u> Gemcitabine 1000 mg/m^2 IV Cisplatin 25 mg/m^2 IV
Duration of Administration	Patients may be treated on study for no longer than 2 years. Arm A: The patient may continue gemcitabine, cisplatin and CPI-613 in absence of disease progression or unacceptable toxicity. Arm B: The patient may continue gemcitabine and cisplatin in absence of disease progression or unacceptable toxicity.
Statistical Methodology	This protocol will enroll patients with locally advanced, unresectable or metastatic BTC to receive Gemcitabine, Cisplatin and CPI-613 in a limited Phase 1b study to confirm the safety profile of the combination therapy and the recommended Phase 2 dose (RP2D) using TiTE-CRM methodology. The primary endpoint for the phase IB portion is the occurrence/lack thereof of dose-limiting toxicity during the first 21-day cycle of combination therapy. After determining the combination RP2D, 48-58 additional evaluable patients will be enrolled in the phase 2 portion of the study and randomized 2:1 to treatment arms A (combination regimen at RP2D) and B (Gemcitabine and Cisplatin alone), respectively, using a Bayesian approach for the control arm. We will stratify the randomization by locally advanced versus metastatic disease. The primary endpoint for the phase 2 study is the ORR (PR+CR) per RECIST v1.1 criteria during active study treatment. Secondary endpoints include safety, PFS and OS. In practice, the 16-20 evaluable patients randomized to standard of care arm will suggest whether the historical ORR of 21% is reasonable for our current patient population. The ORR estimated and 95% confidence interval for the control group may suggest altering the historical null ORR value for comparison.

1.0 BACKGROUND AND RATIONALE

1.1 Biliary Tract Cancer - Disease Overview

Biliary tract cancer (BTC) develops as a result of malignant transformation of the biliary tract mucosa and is anatomically classified as intra-hepatic, extra-hepatic (hilar and distal) and gall bladder adenocarcinoma. BTC accounts for 10-15% of all primary liver cancer cases worldwide, and its incidence is rising (Shaib and El-Serag 2004). Advanced BTCs are aggressive tumors with median survival time from diagnosis of less than 12 months (Valle, Wasan et al. 2010), and five-year overall survival (OS) of ~5% despite therapy (Nathan, Pawlik et al. 2007). The options for systemic chemotherapy for patients with advanced BTC remains limited with only a few meaningful improvements made over the past few decades. Valle *et al* randomly assigned 410 patients with locally advanced or metastatic BTC to receive gemcitabine with or without cisplatin in the phase III ABC-02 trial (Valle, Wasan et al. 2010). Patients on the gemcitabine cisplatin arm demonstrated an improvement in OS (11.7 versus 8.1 months; hazard ratio (HR), 0.64; 95% CI, 0.52 to 0.80; $p<0.001$) as compared to the gemcitabine alone arm. The objective response rate was 26.1% in the cisplatin and gemcitabine combination arm. The following clinically relevant grade 3 and 4 adverse events were noted in the gemcitabine/cisplatin arm: neutropenia (25.3%), anemia (7.6%), thrombocytopenia (15.7%), abnormal liver function (16.7%), fatigue (18.7%), nausea (4%), vomiting (5.1%), impaired renal function (1.5%), infection (18.2%), deep vein thrombosis (2%), and thromboembolic event (3.5%). This result established the gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 combination as a standard first line regimen for patients with advanced BTC.

1.2 Introduction to CPI-613 and its Role in BTC

CPI-613 is a stable analog of normally transient, acylated catalytic intermediates of lipoic acid (lipoate), an essential co-factor for 2 enzyme complexes, pyruvate dehydrogenase (PDH) and a-ketoglutarate dehydrogenase (KGDH) central to the tricarboxylic acid (TCA) or Kreb's cycle (Zachar, Marecek et al. 2011). These lipoic intermediates are monitored by regulatory systems to control flux through these 2 enzymes. Regulatory systems controlling this flux are significantly modified during anabolic reprogramming in cancer making them more susceptible to CPI-613. Additionally, tumor cells take up CPI-613 preferentially, apparently through upregulated vitamin and fatty acid transporters which limits toxicity to normal cells (Stuart, Schauble et al. 2014). CPI-613 selectively inactivates these two enzymes, thereby collapsing mitochondrial metabolism of the tumor cells. This collapse of mitochondrial metabolism leads, in turn, to redundant activation of apoptotic and necrotic cell death pathways (Zachar, Marecek et al. 2011).

To date, 23 studies have been done with CPI-613 including 16 completed trials and 7 ongoing trials. Two of these trials are phase 3 trials in metastatic pancreatic adenocarcinoma (NCT03504423) and acute myeloid leukemia (NCT03504410). Over 800 subjects have received one or more doses of CPI-613 in these clinical studies.

1.3 Role of Chemotherapy in Conjunction with CPI-613

A total of 40 patients with advanced pancreatic cancer of which 14 patients received CPI-613 as a single agent on 3 trials (CPI-613-002, CL-CPI-613-023, CCCWFU57113), 6 patients received CPI-613 in combination with gemcitabine on the CL-CPI-613-004 trial, and 20 received CPI-613 in combination with modified FOLFIRINOX (mFOLFIRINOX) on the CCWFU57112 trial.

The phase 1 dose escalation CCWFU57112 trial of CPI-613 in combination with mFOLFIRINOX chemotherapy was conducted in patients with metastatic pancreatic adenocarcinoma with no prior treatment. A total of 20 patients, ages 48-72, were dosed with CPI-613 plus mFOLFIRINOX of which 18 were evaluable. The 2 patients who experienced DLTs were not evaluable as they did not have follow-up radiology

assessments per RECIST v1.1. Overall, 17% of patients achieved a complete response (CR), 44% achieved a partial response (PR), 17% achieved stable disease (SD), and 22% had progressive disease (PD). The overall response rate (ORR=CR+PR) was 61%. Median overall survival (OS) was 19.7 months, median progression free survival (PFS) 9.9 months, and duration of response (DOR) 12.6 months (Alistar, Morris et al. 2017). Based on these data, an international phase 3 clinical trial is being conducted in this patient population.

For the 18 patients given the maximum tolerated dose, the most common grade 3–4 non-hematological adverse events were hyperglycemia (ten [55%] patients), hypokalemia (six [33%]), peripheral sensory neuropathy (five [28%]), diarrhea (five [28%]), and abdominal pain (four [22%]). The most common grade 3–4 hematological adverse events were neutropenia (five [28%] of 18 patients), lymphopenia (five [28%]), anemia (four [22%], and thrombocytopenia in three [17%]). Sensory neuropathy (all grade 1–3) was recorded in 17 (94%) of the 18 patients and was managed with dose de-escalation or discontinuation per standard of care. No patients died while on active treatment; 11 study participants died, with cause of death as terminal pancreatic cancer (Alistar, Morris et al. 2017).

1.4 Rationale

Patients with advanced, unresectable or metastatic BTC have a poor prognosis despite systemic chemotherapy with gemcitabine and cisplatin. CPI-613 is an inhibitor of pyruvate dehydrogenase (PDH) and a-ketoglutarate dehydrogenase (KGDH) central to the Kreb's cycle. This selective inhibition leads to the collapse of mitochondrial metabolism and activation of apoptotic and necrotic cell death pathways. CPI-613 has shown significant efficacy (ORR 61%, median OS 19.7 months) compared to historical data (ORR 32%, median OS 11.1 months) when given in combination with mFOLFIRINOX in patients with metastatic pancreatic cancer (Conroy, Desseigne et al. 2011, Alistar, Morris et al. 2017).

Therefore, we hypothesize that CPI-613, a mitochondrial inhibitor, in combination with gemcitabine and cisplatin will improve the overall response, progression-free and overall survival in this population without increasing toxicity. These results are expected to have an important positive impact because they will provide a strong evidence-guided understanding of BTC microenvironment and identification of potential biomarkers of response (and resistance) to inform a phase III clinical trial in BTC.

1.5 Correlative Studies

We will study the BTC tumor microenvironment through the use of pre-treatment tissue (all sites) and post-treatment (optional for patients enrolled at all sites) tumor biopsies. In addition, blood will be collected as detailed in the schedule of events/study calendar. Identification of important biologic subsets of BTC patients that may have clinical efficacy from this drug combination will be the overarching goal of these translational studies along with developing biologic insights for future therapeutic development. Biologic markers and RNA expression will be examined in the context of tumor biology, and therapeutic efficacy.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Phase Ib: Determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) for gemcitabine and cisplatin with CPI-613

2.1.2 Phase II: Determine the overall response rate in patients with advanced BTC treated with gemcitabine and cisplatin with or without CPI-613.

2.2 Secondary Objectives

2.2.1 Evaluate the median PFS and OS of patients with advanced BTC.

2.2.2 Evaluate the safety of CPI-613 in combination with gemcitabine and cisplatin in this patient population.

2.3 Exploratory Objectives

2.3.1 To explore predictors of biomarker response and mechanisms of resistance based on the exploratory analysis of tumor tissue obtained through serial biopsies and blood.

a) Immunohistochemical staining for PDK, PDH, KGDH, SOD2 and CD79a
b) Whole exome genomic and transcriptomic (RNAseq) analysis for tumor biology at baseline and progression
c) Blood collection, including serum, plasma and serum for future biomarker analysis, including ctDNA.

2.4 Endpoints Assessment

2.4.1 Primary Endpoint Assessment: Overall response rate (ORR) will be determined as per the RECISTv1.1 criteria.

2.4.2 Secondary Endpoint Assessment: The progression-free survival (PFS) will be defined as time from date of treatment to date of radiological or clinical progression (leading to withdrawal from the study), or death from any cause, whichever comes first. Follow-up time will be censored at the date of last disease evaluation. Overall survival (OS) will be defined from the date of treatment to either date of death or censoring. Adverse events and reportable serious events are defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5.0).

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the eligibility criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Eligibility Criteria

3.1.1 Patients must have a pathologically or cytologically confirmed carcinoma (except neuroendocrine) of the biliary tract (intra-hepatic, extra-hepatic (hilar, distal) or gallbladder) that is not eligible for curative resection, transplantation, or ablative therapies. Tumors of mixed cholangiocarcinoma/hepatocellular carcinoma histology are excluded.

3.1.2 Patients may not have received prior systemic treatment (chemotherapy or targeted therapy) for advanced BTC. Prior peri-operative chemotherapy is permitted provided it was completed > 6 months from enrollment.

3.1.3 Patients may have received prior radiation, chemoembolization, radioembolization or other local ablative therapies or hepatic resection if completed ≥ 4 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity. Extrahepatic palliative radiation is permitted if completed ≥ 2 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity

3.1.4 Patients must have radiographically measurable disease (as per RECISTv1.1) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site.

3.1.5 Must be ≥ 18 years of age.

3.1.6 Must have an ECOG performance status of 0-1.

3.1.7 Ability to understand and willingness to sign IRB-approved informed consent.

3.1.8 Willing to provide archived tissue, if available, from a previous diagnostic biopsy or surgery.

3.1.9 Must be able to tolerate CT and/or MRI with contrast.

3.1.10 Adequate organ function obtained ≤ 2 weeks prior to enrollment:

absolute neutrophil count	≥ 1500/mm^3
hemoglobin	≥ 9 g/dL
platelets	≥ 100,000/mm^3
serum creatinine	≤ 1.5 x ULN
creatinine clearance	≥ 50 mL/min
albumin	≥ 3.0 g/dL
AST/ALT	≤ 3.0 x ULN (≤5 x ULN if liver tumor or metastasis)
total bilirubin	≤ 1.5 x ULN
INR	≤ 1.5 x ULN

3.1.11 Must not have prior history of brain metastasis (unless previously treated, asymptomatic and stable for at least 3 months), or organ transplantation.

3.1.12 Must not have undergone a major surgical procedure < 4 weeks prior to enrollment.

3.1.13 Must not have an active second malignancy other than in situ cancer or localized prostate cancer (Gleason score <8). Patients with a history of other malignancy are eligible provided primary treatment of that cancer was completed > 1 year prior to enrollment and the patient is free of clinical or radiologic evidence of recurrent or progressive malignancy.

3.1.14 Must have no ongoing active, uncontrolled infections (afebrile for > 48 hours off antibiotics)

3.1.15 Must not have a psychiatric illness, other significant medical illness, or social situation which, in the investigator's opinion, would limit compliance or ability to comply with study requirements.

3.1.16 Women must not be pregnant or breastfeeding since study drugs may harm the fetus or child. All females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a negative screening pregnancy test.

3.1.17 Women of child-bearing potential and men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation and for 6 months (for men and women) following completion of study therapy.

3.1.18 Must not have active heart disease including symptomatic heart failure (NYHA class 3 or 4), unstable angina pectoris, uncontrolled cardiac arrhythmia or interstitial lung disease.

3.1.19 Prisoners or subjects who are involuntarily incarcerated, or compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness would be excluded.

3.1.20 Must not have prolonged QTcF interval >480 msec

3.1.21 Patients with known hypersensitivity to cisplatin, gemcitabine or CPI-613, or its inactive components would be excluded.

4.0 SUBJECT SCREENING AND ENROLLMENT PROCEDURES

Patient enrollment and randomization for this trial will be centrally managed by the Oncology Clinical Trials Support Unit (i.e. the Coordinating Center) of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient enrollment request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator (MSC) of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the enrollment. Sites should inform the Multi-Site Coordinator of a potential enrollment by 5 p.m. on the day prior to enrollment. Same day enrollments cannot be guaranteed.

The registrar will send an email to the requesting site registrar to confirm patient enrollment and randomization and to provide the study identification number and randomization number assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 calendar days of enrollment otherwise the patient will be taken off study. Re-screening is allowed.

5.1.1 Phase IB

5.1.1.1 Dose Levels

Table 1. Phase IB Treatment Plan (Q21 days)			
Dose Level	**CPI-613**	**Gemcitabine**	**Cisplatin**
3	2,000 mg/m^2	1000 mg/m^2	25 mg/m^2
2	1,500 mg/m^2	1000 mg/m^2	25 mg/m^2
1*	1,000 mg/m^2	1000 mg/m^2	25 mg/m^2
-1	500 mg/m^2	800 mg/m^2	25 mg/m^2

**starting dose level*

The starting dose level of 1000 mg/m^2 is based on the use of 500 mg/m^2 dose in combination with FOLFIRINOX chemotherapy backbone for pancreatic cancer (NCT03699319), and use of 1500 mg/m^2 dose in combination with gemcitabine and nab-paclitaxel chemotherapy backbone for pancreatic cancer (NCT03435289).

5.1.1.2 Treatment Plan

Table 2. Phase IB – Regimen Description					
Agent	**Prophylaxis**	**Dose**	**Route[1]**	**Schedule[2]**	**Cycle Length**
CPI-613	Palonosetron 0.25 mg IV + dexamethasone 12 mg PO/IV + fosaprepitant 150 mg IV, OR per institutional policy	Per Dose Level	IV over 120 (range 110 – 150) minutes **before** gemcitabine[3]	Days 1 and 8	3 weeks (21 days)
Gemcitabine		Per Dose Level	IV over 25 – 40 minutes **after** CPI-613	Days 1 and 8	
Cisplatin		Per Dose Level	IV over 25 – 65 minutes **after** gemcitabine	Day 1 and 8	

[1]Infusion times may follow institutional policy for gemcitabine and cisplatin and/or be extended as needed for safety (e.g. infusion reaction occurs). These instances should be documented in the patient medical records.
[2]As per section 5.5, patients may not be treated on study for longer than 2 years.
[3] This rate is for all dose levels.

5.1.1.3 Dose Limiting Toxicities (DLTs)

A DLT will be any of the following occurring during the first 3 weeks of therapy, including cycle 2 day 1, attributed (possibly, probably, or definitely) to the drug combination following day 1 treatment and occurring in the 22-day interval as assessed using the NCI CTCAE v5.0.

a. Grade 4 or greater hematological toxicity with the exception of uncomplicated grade 4 leukopenia/ neutropenia lasting <7 days)
b. Grade 3 or higher thrombocytopenia with bleeding
c. Grade 3 or greater febrile neutropenia.
d. Grade 3 or greater non-hematological toxicity with the following exceptions:
    i. Grade 3 nausea, vomiting, or diarrhea < 72 hours with adequate antiemetic and other supportive care measures,
    ii. Grade 3 fatigue < 1 week,
    iii. Grade 3 or higher electrolyte abnormality that lasts <24 to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions,
    iv. Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
e. Any death not clearly due to the underlying disease or extraneous causes.
f. Toxicities meeting Hy's law criteria
g. Grade 2, treatment related non-hematological toxicity which prevents Cycle 1 day 8 or Cycle 2 day 1 dosing of one or more of the study agents.
h. Patients stopping treatment early due to or secondary to toxicity

With completion of cycle 1, and following DLT determination (**yes vs. no**) on cycle 2 day 1, cycle 2 may begin. All DLTs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center's DLT form as available in the study database

5.1.2 Phase II Arm A

Table 3. Phase II Arm A – Regimen Description

Agent	Prophylaxis	Dose	Route[1]	Schedule[2]	Cycle Length
CPI-613	Palonosetron 0.25 mg IV + dexamethasone 12 mg PO/IV + fosaprepitant 150 mg IV, OR per institutional policy	RP2D mg/m^2	IV over 120 (range 110 – 150) minutes **before** gemcitabine[3]	Days 1 and 8	3 weeks (21 days)
Gemcitabine		1000 mg/m^2 per commercial package insert	IV over 25 – 40 minutes **after** CPI-613	Days 1 and 8	
Cisplatin		25 mg/m^2 per commercial package insert	IV over 25 – 65 minutes **after** gemcitabine	Day 1 and 8	

[1] Infusion times may follow institutional policy for gemcitabine and cisplatin and/or be extended as needed for safety (e.g. infusion reaction occurs). These instances should be documented in the patient medical records.
[2] As per section 5.5, patients may not be treated on study for longer than 2 years.
[3] This rate is for all dose levels. RP2D for CPI-613 was determined to be 2000 mg/m^2.

5.1.3 Phase II Arm B

Table 4. Phase II Arm B – Regimen Description					
Agent	**Prophylaxis**	**Dose**	**Route[1]**	**Schedule[2]**	**Cycle Length**
Gemcitabine	Palonosetron 0.25 mg IV + dexamethasone 12 mg PO/IV + fosaprepitant 150 mg IV, OR per institutional policy	1000 mg/m^2 per commercial package insert	IV over 25 – 40 minutes **before** cisplatin	Days 1 and 8	3 weeks (21 days)
Cisplatin		25 mg/m^2 per commercial package insert	IV over 25 – 65 minutes **after** gemcitabine	Days 1 and 8	

[1] Infusion times may follow institutional policy and/or be extended as needed for safety (e.g. infusion reaction occurs). These instances should be documented in the patient medical records.
[2] As per section 5.5, patients may not be treated on study for longer than 2 years.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.2). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 5: Dose Modifications			
	Current Dose	**Percentage Decrease**	**Modified Dose**
Gemcitabine	1000 mg/m^2	20%	800 mg/m^2
	800 mg/m^2	20%	640 mg/m^2
	640 mg/m^2	100%	Discontinue
Cisplatin	25 mg/m^2	20%	20 mg/m^2
	20 mg/m^2	20%	16 mg/m^2
	16 mg/m^2	100%	Discontinue
CPI-613	2000 mg/m^2	25%	1500 mg/m^2
	1500 mg/m^2	33%	1000 mg/m^2
	1000 mg/m^2	50%	500 mg/m^2
	500 mg/m^2	100%	Discontinue

5.2.1 All dose reductions will be permanent unless otherwise noted or approved by the Sponsor-Investigator.

5.2.2 If more than one toxicity occurs requiring dose reduction, the dose administered should be based on the most severe toxicity.

5.2.3 Treatment delay of more than 28 days from last intended therapy will result in discontinuation from trial, unless otherwise agreed and documented between the treating investigator and the sponsor-investigator and the delay is not due to toxicity attributable to study treatment.

5.2.4 If one of the drugs is discontinued due to toxicity attributed to that agent, the patient will be allowed to continue a modified regimen with the remaining study arm agent/s. However, monotherapy with cisplatin is not permitted, though monotherapy with gemcitabine is allowed. Additionally, if both gemcitabine and cisplatin are held on day 1 or day 8, then also hold CPI-613. If both gemcitabine and cisplatin are discontinued, then CPI-613 should also be discontinued.

5.2.5 Investigators should consider dose re-calculation of gemcitabine, cisplatin, and/or CPI-613 with change in BSA as per standard of care/institutional guidelines. However, a change in BSA by 10% or more requires a dose re-calculation.

5.2.6 If a patient experiences neutropenic fever at any point in the treatment cycle, chemotherapy will be delayed until ANC $\geq$ 1,000 and antibiotic treatment of the event is completed. When treatment resumes, proceed with one dose level reduction as per Table 2 for one or more agents.

5.2.7 Doses will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of $\geq$ grade 3 neutropenia.

5.2.8 Laboratory abnormalities that are not clinically relevant (i.e., lymphopenia) do not require modification of dosing.

5.2.9 Missed Dose: If the regimen held or missed was to be given on Day 1 then that next cycle will not be considered to start until the day the first dose is actually administered. Held doses of either or all drugs on Day 8 will be considered omitted.

TABLE 6. Day 1 Dose Modifications for Hematologic Toxicity	
Hematologic Toxicity[1]	**Dose Adjustment**
ANC[1] ≥ 1000/mm^3 **AND** **Platelets ≥ 75,000/mm^3**	Treat as scheduled
ANC[1] < 1000/mm^3 **OR/AND** **Platelets < 75,000/mm^3**	Hold all protocol treatment up to a maximum of 28 days until ANC ≥ 1000/mm^3 AND platelets ≥ 75,000/mm^3 then resume at next lower dose level for *either OR both* gemcitabine and cisplatin as detailed in Table 5[2]. If not resolved, then discontinue all treatment.
*[1]Note: Growth factors may be added for low ANC BEFORE a dose reduction is instituted for subsequent cycles at the treating physician's discretion. Investigators **may consider** dose reduction for gemcitabine and/or cisplatin and/or CPI-613 for grade 3 or higher anemia.*	

Table 7: Day 8 Dose Modifications for Hematologic Toxicity			
Hematologic Toxicity	**Dose Adjustment for Gemcitabine**	**Dose Adjustment for Cisplatin**	**Dose Adjustment for CPI-613**
ANC[1] ≥1000/mm^3 **AND** **Platelets ≥ 75,000/mm^3**	No change in dose	No change in dose	No change in dose
ANC[1] 500-999/mm^3 **OR** **Platelets 50,000-74,999/mm^3**	Decrease Day 8 dose by 1 dose level for this cycle **[2]Consider** decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles	Decrease Day 8 dose by 1 dose level for this cycle **[2]Consider** decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles	**D**ecrease Day 8 dose by 1 dose level for this cycle **[2]Consider** decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles
ANC[1] <500/mm^3 **OR** **Platelets <50,000/mm^3**	Hold Day 8 treatment Decrease Day 1 & 8 by 1 dose level for subsequent cycles[1,2]	Hold Day 8 treatment Decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles[1,2]	Hold Day 8 treatment Decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles[1]
*[1]Note: Growth factors may be added for low ANC BEFORE a dose reduction is instituted for subsequent cycles at the treating physician's discretion. Investigators **may consider** dose reduction for gemcitabine and/or cisplatin and/or CPI-613 for grade 3 or higher anemia.* *[2]Note: Dose level reduction may be for one or more agents as per investigator discretion when toxicity is at least possible attributed to the agent*			

Table 8: Dose Modifications for Non-Hematologic Toxicity			
Non-Hematologic Toxicity	**Dose Adjustment for Gemcitabine**	**Dose Adjustment for Cisplatin**	**Dose Adjustment for CPI-613**
Alopecia, venous thromboembolism	No modification to doses		
Grade ≥3 Nausea and vomiting (ongoing after maximal anti-emetic therapy)	No change in dose	Consider dose reduction to next dose level or discontinuation of cisplatin	Hold CPI-613 until resolved to Grade 1 or baseline, and then consider dose reduction to next dose level.
Grade ≥3 Diarrhea (at least possibly attributed after negative infectious work-up AND maximal supportive therapy)	No change in dose	Consider dose reduction to next dose level	Hold CPI-613 until resolved to Grade 1 or baseline, and then consider dose reduction to next dose level.
Grade ≥2 Hyperbilirubinemia	Hold all protocol treatment up to a maximum of 28 days until toxicity resolves to Grade ≤ 1 or baseline, then may resume at same doses as before or next dose level for one or more agents. If not resolved, then discontinue all treatment. Doses will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of ≥grade 3 neutropenia		
Grade ≥3 possibly attributable to cytotoxic treatment	Hold all protocol treatment up to a maximum of 28 days until toxicity resolves to Grade ≤ 1 or baseline, then resume at next dose level for one or more agents.		
≥Grade 3 Peripheral neuropathy	No change in dose	Hold cisplatin up to a maximum of 28 days until toxicity resolves to Grade ≤ 2, then consider dose reduction to next dose level.	No change in dose
≥Grade 2 Creatinine increase (>1.5 x baseline or ULN whichever is higher)	No change in dose	Hold cisplatin, assess hydration and general medical status of the patient. Cisplatin may be resumed if creatinine improves to <1.5 x ULN or baseline with one dose level reduction.	Hold CPI-613, assess hydration and general medical status of the-patient. CPI-613 may be resumed if creatinine improves to <1.5 x ULN or baseline with one dose level reduction.

Note: Laboratory abnormalities that are not clinically relevant (i.e., lymphopenia) do not require modification of dosing. All dose adjustments for toxicity will be described in the clinical record.

5.3 Concomitant Medications/Treatments

The following concomitant medications or treatments are not permitted while the patient is currently receiving therapy on the protocol:

- Other investigational agents
- Concurrent radiation unless given for palliation during which study therapy must be held.

The following concomitant medications may require additional monitoring during cisplatin therapy:

- Plasma levels of anticonvulsant agents (valproic acid, phenytoin, and carbamazepine) may become sub-therapeutic and should be monitored.
- Concomitant use with aminoglycosides, tacrolimus, and amphotericin B increase risk of nephrotoxicity.
- Concomitant use with loop diuretics and aminoglycosides increase risk of ototoxicity.
- Concurrent use with lithium may result in reduced lithium plasma concentration.
- Concurrent use with warfarin may result in increased INR.
- Concurrent use with thioctic acid (alpha-lipoic acid) may result in decreased cisplatin effectiveness and should be avoided.

5.4 Other Modalities or Procedures

None

5.5 Duration of Therapy

Treatment may continue for a total of 2 years or until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 6 months after discontinuation of study treatment
- Patient who becomes pregnant or is breastfeeding
- Patient who cannot tolerate the minimum protocol-specified dose of study treatment
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Significant noncompliance with the protocol schedule in the opinion of the investigator
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.5 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.8. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-Up

After treatment discontinuation, follow-up for survival and initiation of any other anti-cancer therapies will be documented every 3 months via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment. Patients removed from treatment for unacceptable adverse events will also be followed more closely until resolution or stabilization of the adverse event.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

5.8.1 Patient withdraws consent (termination of treatment and follow-up);

5.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.8.3 Termination of the study by the Sponsor, the University of Michigan, or the FDA;

5.8.4 Patient completes protocol treatment and follow-up criteria;

5.9 Patient Replacement

Patients enrolled in the study will be considered non-evaluable under the following case scenarios and replaced by additional patients:

1. Patients who received no investigational therapy.
2. Patients who were discontinued or withdrew consent for study therapy prior to first response evaluation.
3. Patients meeting off study criteria 5.8.1 and 5.8.2.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

6.2 Time and Events Table/Schedule of Events/Study Calendar

Table 9. Study Calendar									
Procedures	**Screening[1]**	**Phase IB or II Arm A**			**Phase II Arm B**			**EOT Visit[8]**	**Follow-Up Q3 months +/- 1 week[9]**
		Cycle 1[13]	**Cycle X[13]**		**Cycle 1[13]**	**Cycle X[13]**			
		Day 1	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 8**		
Informed Consent	X								
History, Physical Examination	X	X	X		X	X		X	
Weight, BSA	X	X	X		X	X		X	
Vital Signs	X	X	X	X	X	X	X	X	
Performance Status	X	X	X		X	X		X	
Toxicity Evaluations		X	X	C1D8[12]	X	X		X	
Scans with Tumor Measurements	X		X[5]			X[5]			
CBC with differential	X	X	X	X	X	X	X		
CMP[2]	X	X	X	X	X	X	X		
HbA1c	X		X[11]			X[11]			
CA 19-9, CEA		X	X[10]		X	X[10]		X	
PT, PTT	X								
Pregnancy Test[3]	X								
Concomitant Medication Review	X	X	X		X	X			
ECG	X								
Research Blood[4]		X	X		X	X		X	
Tissue[6]	X							X	
Study Drug Administration[7]		X	X	X	X	X	X		
Survival Follow-up									X

1. All screening procedures to be completed within 2 weeks of enrollment, except imaging which should be ≤ 4 weeks. Protocol treatment is to begin ≤14 days of enrollment.
2. Comprehensive metabolic panel includes BUN/creatinine, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, albumin, AST, ALT, total bilirubin and total protein.

3. Required for females of childbearing potential. Serum or urine pregnancy test per site investigator discretion.
4. Cycle 1 Day 1 specimens will be collected prior to administration of initial dose, and Cycle X Day 1 specimens will be collected on Cycle 4 Day 1 prior to drug administration. Refer to the lab manual for sample collection and processing details.
5. MRI or CT (abdomen with or without pelvis) with contrast along with CT chest with or without contrast will be assessed every 8 ± 1 weeks starting from C1D1. Imaging assessment of scans at the site **should be completed by either a radiologist or an imaging core**, and not by the oncologist nor via abstraction of data from the subjective/clinical radiology report.
6. Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery. Procurement of tissue is mandatory for enrollment, however, all biopsies are optional. If tissue from initial biopsy is not available, a repeat biopsy is NOT required and patient will be eligible for enrollment. Refer to the lab manual for sample collection and processing details.
7. See Section 5.1 for details. Study drug administration with associated labs will have a window of ± 3 days.
8. End of treatment (EOT) visit should be completed within 30 days of last treatment. And if possible, end of treatment biopsy should be collected for patients enrolled on Phase IB or II Arm A only prior to start of subsequent therapy.
9. Patients will be followed every 3 months via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment.
10. Check CA 19-9 (preferred) and/or CEA every 6 +/- 1 weeks prior to infusion, if elevated at baseline. May be delayed if infusion is not scheduled within the window.
11. Check HbA1c every 12 +/ - 1 weeks prior to infusion. May be delayed if infusion is not scheduled within the window.
12. Mandatory for cycle 1 day 8 only; rest per institutional guidelines
13. A ± 1-day window will be allowed for all treatment visits and associated labs, unless otherwise specified. However, every effort must be made to follow the schedule outlined in the table above.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Objective response assessment will be determined by review of CT or MR scans of the chest, abdomen with or without pelvis using RECIST v1.1 every 8 weeks +/- 1 week while patients are on treatment (Eisenhauer, Therasse et al. 2009).

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for phase IB primary endpoint, MTD/RP2D. All patients that receive at least one dose of study therapy will be considered evaluable. Patients enrolled to therapy but that never receive study therapy will be replaced. See Section 5.9.

Evaluable for phase II primary endpoint, overall response rate. All enrolled patients who received at least 1 cycle(s) of therapy, and had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

7.1.2 Disease Parameters

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

- 10 mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measurable, if they have had subsequent progression by at least 5 mm.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using CT scan), are considered non-measurable disease. Bone lesions without measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

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

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

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

7.1.3 Guidelines for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR (taking as reference the baseline sum LD) nor sufficient increase to qualify for PD (taking as reference the smallest sum LD since the treatment started).

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes should be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression on non-target lesions in absence of stable target lesions is exceptional, *the opinion of the treating physician should prevail in such circumstances*.

7.1.4.3 Evaluation of Best Overall Response

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

Table 10. Response Evaluation as per RECISTv1.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response per RECISTv1.1	Confirmed Response for this Category Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	CR Non-CR/PD	No	PR	≥4 wks. confirmation
PR	CR Non-CR/PD	No		
SD	CR Non-CR/PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Any	PD	≥4 wks. confirmation
Any	PD*	Any		
Any	Any	Yes		

* Only in exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

NA=not applicable

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of adverse events (**http://ctep.cancer.gov/reporting/ctc.html**).

8.0 ADVERSE AND OTHER REPORTABLE EVENTS

8.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 30 days after the last dose of study treatment. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment or intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention. However, with regards to laboratory and vital sign abnormalities, only those which require protocol treatment to be modified or treatment to be rendered should be reported as AEs.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event. However, anticipated fluctuations of pre-existing conditions, including the disease under study, that don't represent a clinically significant exacerbation or worsening, need not be reported as AEs.

8.2 Definitions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

8.2.2 Serious Adverse Event

An adverse event is considered “serious” if, in the view of either the investigator or sponsor-investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- A life-threatening adverse event
  An adverse event is considered ‘life-threatening’ if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event: Any event 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 in this definition of “Serious Adverse Event”. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient’s medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.2.3 Expected Adverse Events

An adverse event (AE) is considered “expected” if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the CPI-613 Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.2.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, CPI-613 Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

RELATED

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.

UNRELATED

Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment/intervention.

8.4 Serious Adverse Event Reporting Guidelines

8.4.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center's SAE form as available in the study database. A copy of the SAE form as available in the study database should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only

in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

8.4.2 Reporting procedures to Cornerstone Pharmaceuticals

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 30 days following the last dose of the study treatment will be reported by the Coordinating Center to Cornerstone Pharmaceuticals. Any SAEs occurring after 30 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to Cornerstone Pharmaceuticals.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to SAEIntake@labcorp.com and safety@cornerstonepharma.com.

If only limited information is initially available or an ongoing SAE changes in its intensity or relationship to the study drug, or if new information becomes available, a follow-up report will be generated and sent to SAEIntake@labcorp.com and safety@cornerstonepharma.com.

Reporting procedures to FDA

In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A Form. The MICHR IND/IDE Assistance Program (MIAP) (University of Michigan) will assist the IND Sponsor in reporting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32. This reporting could include the initial report and follow-up reports when appropriate for the event. SAEs not meeting the expedited reporting requirements will be submitted to the FDA with the IND Annual Report.

8.5 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.6 Reporting of Pregnancy

Pregnancies that occur during study participation or within 6 months of last study dose should be reported to the Coordinating Center via e-mail at CTSU-Oncology-Multisite@med.umich.edu immediately upon site's knowledge of the event.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.8 Safety Report Reconciliation

The Sponsor will reconcile the clinical database SAE reports transmitted to Cornerstone Pharmaceuticals. Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. Cornerstone Pharmaceuticals will email, upon request from the Investigator, the GPV&E reconciliation report. The data elements listed on the GPV&E reconciliation report will be used for identification purposes. If the Investigator determines a report was not transmitted to Cornerstone Pharmaceuticals, the report should be sent immediately.

9.0 DRUG INFORMATION

9.1 Gemcitabine

9.1.1 Other Names

Gemzar®

9.1.2 Classification

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in-vivo* and *in vitro* tumors. Gemcitabine is approved for the treatment of patients with BTC and will be obtained commercially.

9.1.3 Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

9.1.4 Pharmacokinetics

1. Distribution: Gemcitabine plasma protein binding is negligible. The volume of distribution is increased with the infusion length. In a pharmacokinetics study of patients with various solid tumors, the volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions (70 to 285 minutes), the volume of distribution rose to 370 L/ m^2.

2. Metabolism: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. The gemcitabine di- and triphosphates do not appear to circulate in plasma in measurable amounts. Gemcitabine is metabolized by the liver to form the inactive uracil derivative, 2'-deoxy-2',2'-difluorouridine (dFdU). The inactive metabolite does not appear to accumulate with weekly dosing; however, it is excreted by the kidneys and may accumulate in patients with decreased renal function.

3. Elimination: Following a single 1,000 mg/m^2 over 30 min [14C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of the parent drug and the dFdU metabolite accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

   Clearance of gemcitabine is affected by age and gender and is lower in women and the elderly. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Studies showed that gemcitabine half-life for short infusions ranged from 42 to 94 minutes, for long infusions it varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The terminal phase half-life for the active metabolite, gemcitabine triphosphate, in mononuclear cells ranges from 1.7-19.4 hours.

9.1.5 Storage, Preparation and Stability

Refer to the current FDA-approved package insert for storage, stability and special handling information.

9.1.6 Dosing and Administration

See Section 5.1

9.1.7 Availability

Gemcitabine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

9.1.8 Handling and Disposal

Handling and disposal of gemcitabine should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of gemcitabine include laboratory coats and gloves.

9.1.9 Adverse Effects

1. Side Effects: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Adverse effects reported in >20% to 100% of subjects treated with gemcitabine include: myelosuppression including anemia, leukopenia, neutropenia, and thrombocytopenia, increased liver function tests (AST, ALT and/or alkaline phosphatase), proteinuria, hematuria, nausea, vomiting, low grade fever, flu-like symptoms, fatigue, rash and dyspnea. Adverse effects reported in 4% to 20% of subjects include: diarrhea, constipation, bleeding, infection, alopecia,

stomatitis, somnolence, paresthesia, blood or platelet transfusions, peripheral edema, infection, and injection site reaction. Adverse effects reported in 3% or less of subjects include: anaphylaxis, posterior reversible encephalopathy syndrome (PRES), arrhythmias, supraventricular arrhythmias, congestive heart failure, myocardial infarction, desquamation and bullous skin eruptions, gangrene, sepsis, cerebrovascular accident, hepatic failure, adult respiratory distress syndrome (ARDS), anaphylaxis, renal failure, pulmonary fibrosis, pulmonary edema, bronchospasm, and interstitial pneumonitis. Grade 3 and 4 adverse events in combination with cisplatin for BTC from the phase trial are as listed in Table 2 of the publication (Valle, Wasan et al. 2010).

2. Pregnancy and Lactation: Category D. Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

3. Drug Interactions: Per gemcitabine package insert, no formal drug interaction studies have been performed to date. When gemcitabine was administered with cisplatin there was minimal or no effect on the pharmacokinetics of the studied drugs.

9.2 Cisplatin

9.2.1 Other Names

CDDP, Platinol®, NSC-119875

9.2.2 Classification

Cisplatin is an alkylating agent, which inhibits DNA synthesis by producing cross-linking of parent DNA strands (cell-cycle phase-nonspecific). Cisplatin is approved for the treatment of patients with BTC and will be obtained commercially.

9.2.3 Mechanism of Action

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central platinum atom surrounded by two chloride atoms and two ammonia molecules in the cis position. It is water soluble and acts as a bifunctional alkylating agent with cell cycle nonspecific characteristics. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Although cisplatin seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents and that cisplatin does not exhibit cross-resistance with other alkylating agents or nitrosoureas.

9.2.4 Pharmacokinetics

1. Absorption: Following rapid IV injection of cisplatin over up to one hour, peak plasma drug and platinum concentrations occur immediately. When cisplatin is administered by IV infusion over 6 or 24 hours, plasma concentrations of

total platinum increase gradually during the infusion and peak immediately following the end of the infusion.

2. Distribution: Following intravenous dosing, cisplatin distributes rapidly into tissues, with highest concentrations in the liver, prostate and kidney. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90%. Cisplatin penetrates poorly into the CNS.

3. Metabolism: Cisplatin is non-enzymatically transformed to one or more metabolites that are extensively protein bound and have minimal cytotoxic activity. The non-protein bound (unchanged) fraction is cytotoxic.

4. Elimination: Urinary excretion is incomplete. Following bolus injection or infusion over a dose range of 40-140 mg/m2 varying in length from 1-24 hours, from 10 to about 40% of the administered platinum is excreted in the urine in 24 hours. Renal clearance of free platinum exceeds the glomerular filtration rate, indicating that cisplatin or other platinum containing molecules are actively secreted by the kidneys. Renal clearance of free platinum is nonlinear and variable, and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

9.2.5 Storage, Preparation and Stability

Refer to the current FDA-approved package insert for storage, stability and special handling information.

9.2.6 Dose and Administration

See Section 5.1

9.2.7 Availability

Cisplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

9.2.8 Handling and Disposal

Handling and disposal of cisplatin should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of gemcitabine include laboratory coats and gloves.

9.2.9 Adverse Effects

1. Side Effects: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Adverse effects reported in >20% to 100% of subjects treated with cisplatin include: nausea, vomiting, fatigue, myelosuppression with anemia, leucopenia, thrombocytopenia, nephrotoxicity (acute renal failure and chronic renal insufficiency), hyperglycemia, and alopecia. Adverse effects reported in 4% to 20% of subjects include: fever, stomatitis, electrolyte disorders such as hypocalcemia and hypomagnesemia, injection site reaction, increased liver function tests (AST, ALT and/or alkaline phosphatase), infection, headache, bleeding, hypotension, dysgeusia, diarrhea, hypersensitivity reaction, vestibular dysfunction, peripheral neuropathy, blurred vision or altered color

perception, and ototoxicity. Adverse effects reported in 3% or less of subjects include: rash, febrile neutropenia, sepsis, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome (PRES), muscle cramps, secondary malignancy and seizure. Other published literature suggests risk of thromboembolic events (Seng, Liu et al. 2012).

2. Pregnancy and Lactation: Category D. Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. This drug has been found to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, patients receiving cisplatin should not breast feed.

3. Drug Interactions: During cisplatin therapy, plasma levels of anticonvulsant agents (valproic acid, phenytoin, and carbamazepine) may become sub-therapeutic and should be monitored. Concomitant use with aminoglycosides, tacrolimus, and amphotericin B increase risk of nephrotoxicity. Concomitant use with loop diuretics and aminoglycosides increase risk of ototoxicity. Concurrent use with lithium may result in reduced lithium plasma concentration. Concurrent use with warfarin may result in increased INR. Concurrent use with thioctic acid may result in decreased cisplatin effectiveness and should be avoided.

9.3 CPI-613

9.3.1 Other Names

CPI-613® (devimistat) also known as 6,8-bis(benzylthio)-octanoic acid. It's chemical name is 6,8 bis(benzylsulfanyl) octanoic acid. It is a white to off white crystalline powder with slight sulphurous odor. Its empirical molecular formula is $C_{22}H_{28}S_2O_2$ and the molecular weight is 388.6.

9.3.2 Classification

CPI-613 is the first of a novel class of tumor-specific anti-mitochondrial metabolism inhibitors.

9.3.3 Mechanism of Action

CPI-613 is a stable analog of normally transient, acylated catalytic intermediates of lipoic acid (lipoate), an essential co-factor for 2 enzyme complexes, pyruvate dehydrogenase (PDH) and a-ketoglutarate dehydrogenase (KGDH) central to the tricarboxylic acid (TCA) or Kreb's cycle. These lipoic intermediates are monitored by regulatory systems to control flux through these 2 enzymes. Regulatory systems controlling this flux are significantly modified during anabolic reprogramming in cancer making them more susceptible to CPI-613. Additionally, tumor cells take up CPI-613 preferentially, apparently through upregulated vitamin and fatty acid transporters. CPI-613 selectively inactivates these two enzymes, thereby collapsing mitochondrial metabolism of the tumor cells. This collapse of mitochondrial metabolism leads, in turn, to redundant activation of apoptotic and necrotic cell death pathways.

9.3.4 Pharmacokinetics

1. Distribution: The elimination T1/2 from 0-8 hours post-administration of CPI-613 at 3000 mg/m^2 (the highest dose tested) was ~1 hr., Vd was ~5 L/kg, and CL was ~5 L/hr/kg. The results from 1st and 6th (last) dose of CPI-613 were similar, indicating that repeated dosing does not result in a change in the T1/2 and CL and Vd values and there was no evidence of accumulation on multiple dosing during the dosing interval. CPI-613 is rapidly and

extensively converted to its principal metabolite CPI-2850 which is produced predominantly in tumors by beta oxidation of the parent drug. This conversion has been observed in patients dosed with CPI-613 as a single agent and when dosed in combination with FOLFIRINOX. Both CPI-613 and CPI 2850 exhibit extensive and high affinity binding to serum albumin (greater than 99.7%).

2. Elimination: CPI-613 and its metabolites are eliminated from the body through the gut and urine. In a 26 patient phase I study, a relatively rapid decline in plasma levels occurred during the first 8-10 hours post-administration followed by low plasma CPI-613 values that persisted for several days. The concentration-time curves associated with all dose levels of CPI-613 were triphasic. The α-phase occurred during the first 6-8 hours post-administration and was associated with a relatively rapid decline in the mean plasma CPI-613 concentrations with a half-life of ~1.3 hrs. and mean residence time of ~1.8 hours. The β-phase occurred from 6-8 hours to 24 hours post-administration and was associated with a modest increase in the mean plasma CPI-613 values, from ~0.5 to 4 μM when averaged across all dose levels. The γ or final phase started from 24 hours until 72 hours post-administration and was associated with a very slow decline in mean plasma CPI-613 values, consistent with the high plasma protein binding properties of CPI-613. CPI-613 could not be detected in the plasma prior to administering the 1st dose, but the baseline plasma CPI-613 values associated with Dose 6 had an overall average value of ~3 μM. The amount of CPI-613 present in the plasma prior to the 6th dose was only ~10% of the Cmax value of ~45 μM induced by the MTD (2,940 mg/m2 given over 2 hours) of CPI-613. The small residual CPI-613 in the plasma did not have any significant drug accumulation effects, as reflected by the concentration-time curves associated with Dose 1 being comparable to that of the 6th (last) dose of Cycle 1.

9.3.5 Storage, Preparation and Stability

CPI-613 injection is a sterile, nonpyrogenic, clear, colorless to light yellow solution suitable for intravenous (IV) administration. CPI-613 injection is supplied in 10-mL USP type-I amber glass vial with 20 mm grey butyl stopper and royal blue flip off seal. Each mL contains: 50 mg of CPI-613 and 150 mg of Triethanolamine (TEA). CPI-613 injection is a concentrate and must be diluted with 5% dextrose (D5W) injection before use. CPI-613 injection is not compatible with saline solution.

CPI-613 injection must be stored in a refrigerator, 2°- 8°C (36° to 46°F) and protected from light. After dilution, the CPI-613 injection is chemically and physically stable for upto 24 hours at room temperature with normal light exposure. If CPI-613 injection is to be transferred from one storage area to another, or is to be prepared for dosing, care must be taken to maintain appropriate product temperature. CPI-613 injection slightly photosensitive when exposed to intense light. Therefore, after removal of CPI-613 drug product from the amber vials, CPI-613 injection should be administered to patients without unnecessary delay to minimize excessive exposure to light or covered to protect from light.

The contents of CPI-613 injection must be visually inspected prior to dilution to confirm that the contents are clear and colorless to light yellow. If not, it should not be used. CPI-613 injection must be diluted from 50 mg/mL to 12.5 mg/mL with 5% dextrose (D5W) prior to administration. The diluted drug product should be visually inspected for clarity. If haziness or precipitate is observed, do not use

the diluted drug product for dosing. After dilution with sterile D5W, the solution is clear and has a pH of 8.4 - 8.8. The diluted CPI-613 injection has been found to be stable for 24 hours with normal light exposure.

9.3.6 Dose and Administration

See Section 5.1 for dosage.

CPI-613 must be administered intravenously, via a central venous catheter that is free flowing and free of air in the dead space of the IV catheter, to minimize vascular irritation, inflammation and acute toxicity of CPI-613. Accidental co-administration of extra air in the dead space of IV catheters during administration of CPI-613 has demonstrated the potential to induce acute toxicity of CPI-613 according to animal studies. Also, accidental leakage of CPI-613 into the perivascular space during IV administration, which prolongs exposure of perivascular tissue to CPI-613, can induce significant local inflammation according to animal studies. To avoid local reactions at and around the site of administration, CPI-613 must be administered via a central venous catheter.

Diluted CPI-613 MUST be administered as by IV infusion and not as bolus via a central venous catheter over 2 hours via an infusion pump. This is to minimize potential acute toxicity of CPI-613.

The following precautions must be taken when administering CPI-613:
1. Confirmation of the placement of the IV line to ensure a lack of leakage of CPI-613 into the perivascular space to avoid local reactions at and around the site of administration
2. Confirmation that the IV line is free flowing
3. Confirmation that the IV line is free of dead air space
4. Dilute CPI-613® (devimistat) drug product with D5W (12.5 mg/mL) and infuse over 120 (110-150) minutes. Administer D5W concurrently at the rate of 125 mL/hr.
5. Administer CPI-613 by infusion, not as a bolus
6. After administration of CPI-613, flush the IV line with ~10 mL of D5W to remove residual CPI-613.

<u>Leaching of Diethylhexyl Phthalate (DEHP) by CPI-613</u>:
CPI-613 can cause leaching of DEHP from IV infusion sets and IV bags. Therefore, DEHP-containing IV infusion sets, IV bags or syringes SHOULD NOT be used in mixing or administration of CPI-613.

CPI-613 drug product is slightly photosensitive. Therefore, after removal of CPI-613 drug product from the amber vials, CPI-613 drug product *should be protected from excessive light before administration to patients.*

9.3.7 Availability

Cornerstone Pharmaceuticals will provide the study drug through a distribution depot.

9.3.8 Handling and Disposal

CPI-613 is an investigational drug and the toxicity in humans is not fully understood. All necessary precautions in handling potentially toxic chemicals must be strictly adhered to. Gloves and protective clothing must be worn when handling CPI-613. Avoid contact by all modes of exposure. If the solution contacts the skin, it must be washed immediately and thoroughly with soap and water. If the solution comes in contact with mucous membranes, the membranes

must be flushed thoroughly with water. Spills should be picked up with chemo spill kit. CPI-613 drug product is slightly photosensitive. Therefore, after removal of CPI-613 drug product from the amber vials, CPI-613 drug product should be protected from excessive light before administration to patients.

Each study site must ensure that the study drug is not used beyond expiration•

During the study, store the used CPI-613 vials (which must be separate from the unused CPI-613 vials) at controlled room temperature (20°C-25°C) in an access-limited area. Alternatively, destroy the used CPI-613 vials according to institutional guidelines and in compliance with applicable environmental guidelines or return the used and empty vials to depot. Drug destruction must be adequately documented. At the end of the study, deface the label (both used and unused vials) with a permanent marking pen. Destroy used CPI-613 vials according to institutional guidelines and in compliance with applicable environmental guidelines. Drug destruction must be adequately documented. All unused CPI-613 vials must be returned or destroyed according to institutional guidelines.

9.3.9 Adverse Effects

1. Adverse Effects: In a phase I open-label, single arm clinical trial of CPI-613 in patients with metastatic and locally advanced pancreatic adenocarcinoma and poor performance status (CCCWFU57113), 9 patients were dosed with CPI-613 alone. The safety of CPI-613 was evaluated in 6 patients. A total of 124 toxicities were reported of which 18 were considered Grade 3 or above (15%). In another phase 1 study of CPI-613 with modified FOLFIRINOX 20 patients were enrolled and included in the safety evaluation. A total of 674 treatment related and not related AEs were reported by the 20 patients, of which 114 were considered grade 3 or higher. For the 18 patients given the maximum tolerated dose, the most common non-hematological grade 3–4 adverse events were hypokalemia (n=6, 33%), diarrhea (n=5, 28%), abdominal pain (n=4, 22%), hyperglycemia (n=10, 55%), and peripheral sensory neuropathy (n=5, 28%) patients. The most common grade 3–4 hematological adverse events were neutropenia (n=5, 28%), lymphopenia (n=5, 28%), anemia (n=4, 22%), and thrombocytopenia (n=3, 17%). No patients died while on active treatment; 11 study participants died, with cause of death as terminal pancreatic cancer.

2. Pregnancy and Lactation: Category D. No data are available.

3. Drug Interactions: CPI-613 at levels of 30-50 μM have been found to inhibit a variety of liver S9 fraction enzymes including certain cytochrome P450 isozymes (NCL-044). Plasma levels of CPI-613 and its principal bioactive metabolite CPI 2850 have been observed to be 100 μM or substantially greater, even to > 300 μM. Thus, the potential exists for drug-drug interactions. At concentrations above 30 μM CPI-613 inhibits the activity of various cytochrome P450 isozymes responsible for oxidation and glucuronidation and other possible drug conjugation and transport phenomena. Based on data provided in the Investigator's Brochure (Edition 1.3), the drug-drug interactions potential between CPI-631 and co-medications (either substrates, inhibitors or inducers of CYP450 enzymes) are expected to be low.

10.0 CORRELATIVES/TRANSLATIONAL STUDIES

We will study the BTC tumor microenvironment through the use of pre-treatment tissue collection (at all sites) and post-treatment tissue collection (optional); refer to the lab manual for sample collection and processing details. Identification of important biologic subsets of BTC patients that may have clinical efficacy from CPI-613 will be the overarching goal of this translational science. Tissue (core biopsy, surgical excision) may be examined by whole exome analysis, RNA seq and histologically by immunohistochemistry (IHC). Biologic markers and RNA expression (using genomic analysis conducted on available/submitted tissue, as well as previously completed genomic analysis reports for enrolled patients from all sites, if available) will be examined in the context of patient efficacy.

10.1 Tissue Collection

Tissue will be collected at the time points specified in section 6.2 Study Calendar. Please refer to the lab manual for sample collection and processing details.

10.2 Blood Collection

Blood samples will be collected at the time points specified in section 6.2 Study Calendar. Please refer to the lab manual for sample collection and processing details.

10.3 Centralized Imaging

All CT scans will be coded using trial patient and site IDs and shipped or electronically uploaded for banking and exploratory endpoint assessment. Please see the lab manual for details regarding shipping address and/or information for electronic upload.

10.4 Specimen Banking

Patient samples collected for this study will be retained at University of Michigan. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This protocol will enroll patients with advanced, unresectable BTC to receive Gemcitabine, Cisplatin and CPI-613 in a limited Phase 1b study to confirm the safety profile of the combination therapy and the recommended Phase 2 dose (RP2D). The primary endpoint for the phase 1b portion is the occurrence/lack thereof of dose-limiting toxicity (defined in Section 5.1.1.3) during the first 21-day cycle of combination therapy. After determining the combination RP2D additional patients will be enrolled in the phase 2 portion of the study and randomized 2:1 to treatment arms A (combination regimen at RP2D) and B (Gemcitabine and Cisplatin alone), respectively. We will stratify the randomization by locally advanced versus metastatic disease. The primary endpoint for the phase 2 study is the ORR (PR+CR) per RECIST v1.1 criteria during active study treatment. Secondary endpoints include PFS and OS. The statistical comparison will not be between treatment groups; rather between the experimental treatment arm (A) and historical ORR levels. We will use the estimated ORR for the limited-sized control arm (B) to confirm the control arm has similar response rate as the historical ORR value.

11.2 Phase 1B

We will implement a limited phase 1b trial to assure that the dose levels suggested for this combination are safe. Because toxicity across the combined agents is expected to be mildly additive and not synergistic, and in light of the poor prognosis for these patients, we are willing to tolerate up to but not exceeding 35% DLT toxicity proportion during the first cycle (21-days) of therapy. To investigate this, we will enroll up to 20 patients with dose allocation using the Time-to-Event (TiTE) (Cheung and Chappell 2000) (O'Quigley, Pepe et al. 1990). This method assumes a model for the time to occurrence of toxic responses as a function of the dose. The time-to-event modification allows information from all patients treated (even those with only partial observation) to contribute information for calculating the dose-toxicity relationship. This method is flexible with regard to the number of patients treated at each dose level, patients may be continuously recruited without recruitment pauses subject to the trial's explicit accrual rules, given patients are assigned to a dose level deemed safe at the time of her/his enrollment. The dose toxicity relationship is estimated using all toxicity data observed when each new patient is scheduled to begin treatment. Population for estimation: Every patient enrolled and receiving at least one dose of CPI-613 will be considered evaluable for estimation of the probability of DLT. If a patient withdraws for any reason during the first cycle of therapy, not primarily or secondarily associated with toxicity, that patient's follow-up will be used in the ongoing estimation of the probability of toxicity; however, such a patient would be replaced when calculating the maximum trial size. Patients stopping treatment early due to or secondary to toxicity will be considered to have had a DLT event (as defined in section 5.1.1.3).

DLT target rate to determine MTD/RP2D. The highest probability of DLT at a dose level acceptable during the first cycle of therapy is 35%. The dose level with estimated probability closest to, but not exceeding the DLT target rate will be considered the RP2D.

Criterion for dose escalation. The dose level will be assigned to each new patient according to the estimates from the TiTE-CRM algorithm. Whenever a patient presents for enrollment on this trial, the probability of DLT will be estimated for each dose level, based upon the initial expectations and the incidence of DLT events in patients already treated on trial weighted by the percentage of the acute DLT observation period observed. The level that has an estimated toxicity closest to the target rate for DLT will be assigned, subject to the following:

The dose level cannot be escalated until at least 2 patients have been observed for the entire DLT observation period (22 days).
Patient 1 and 2 will be assigned to receive dose level 1.
Dose escalation is restricted to one dose level between consecutively treated patients.
Dose de-escalation is not restricted and may be reduced by more than one level between consecutively treated patients.
If at enrollment the TiTE-CRM algorithm estimates all dose levels (-1, 1, 2, and 3) to have probability of DLT above our target level (35%), the trial will close, declaring all available dose levels too toxic for treatment. The trial may seek to remain open after initiating a protocol amendment to alter dose levels to be less toxic.

Patients will be recruited and treated on this trial as naturally available. Accrual is estimated to be approximately 2 patients per month. The operating characteristics of this Phase 1B trial were evaluated through simulation using estimate for the true probability of DLT at each dose level under 3 scenarios (n=1,000 simulated trials per scenario). In the first scenario, the true probability of DLT at each dose level is as we had expected a posteriori; the second scenario we have moderately underestimated the true probabilities of DLT for higher dose levels; the third scenario the additive effect of CPI-613 upon the observed toxicity from the chemotherapy regimen is negligible and not dose dependent. The dose level nearest to but not exceeding our target rate is bolded for each scenario.

Table 11. Operating Characteristics of the Phase 1B Trial				
Dose Level	**Expected Probability of DLT**	**Simulation scenario #1**	**Simulation Scenario #2**	**Simulation Scenario #3**
-1	0.20	0.20	0.20	0.20
1	0.25	0.25	**0.30**	0.21
2	0.30	0.30	0.40	0.22
3	0.35	**0.35**	0.50	0**.23**

The figure below illustrates (top left) the mean number of patients per trial experiencing a DLT per dose level per simulated scenario; (top right) the mean number of patient per trial treated per dose level per simulated scenario; (bottom left) percent of simulated trials per simulated scenario that had 0-2, 3-5, 6-8, and 9-11 patients in total experiencing DLT events; (bottom right) the percent of simulated trials per simulated scenario that picked dose level -1, 1, 2, or 3 as the MTD or that declared all level too toxicity and stopped the trial early.

Reviewing the operating characteristics suggest that when the true probability of DLT is as expected (simulation scenario #1), the trial design will treat nearly 10 patients at the target level dose and selects that dose correctly as the MTD/RP2D dose in over 70% of simulated trials. Similarly, if toxicity is not increased by adding CPI-613 to standard of care chemotherapy (simulation scenario #3), the design treats nearly 12 patients at the target level dose and selects that dose as the MTD/RP2D in approximately 80% of simulated trials. In the event that we have underestimated toxicity a posteriori and the probability of DLT increases more sharply with increasing dose of CPI-613, the design will pick a dose at or below the target level in the majority of simulated trials more likely to pick lower dose levels or stop early.

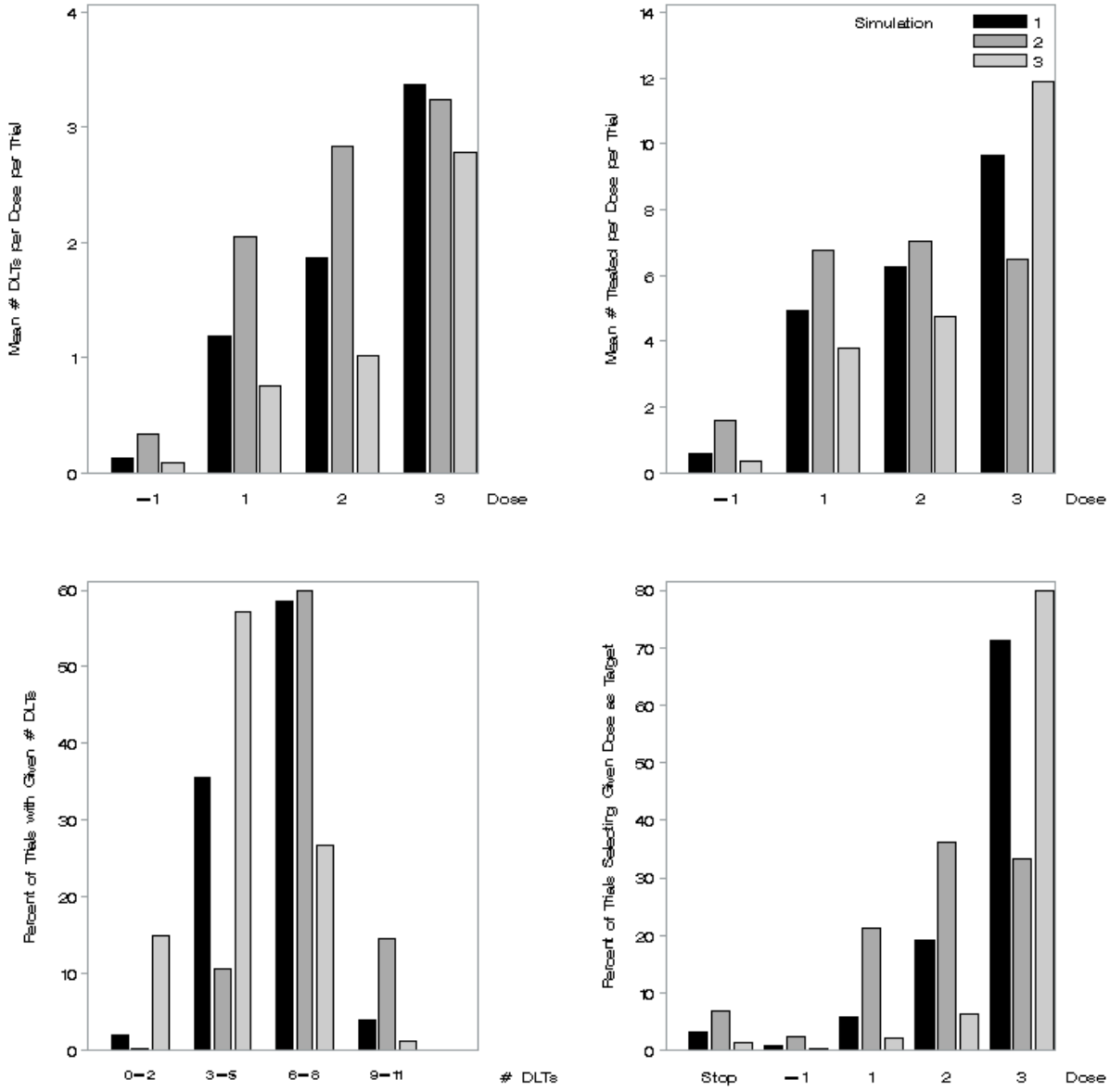

Figure 2. Simulated Scenario of Mean Number of Patients Experiencing a DLT per Dose Level

11.3 Phase 2

Upon completion of the 20 patient Phase 1b portion of the trial, an MTD/RP2D will have been determined or all dose levels for the combination deemed excessively toxic. After the MTD/RP2D is determined, additional patients will be enrolled and randomized in a 2 (Arm A: CPI-613+Gemcitabine+Cisplatin) to 1 (Arm B: Gemcitabine+Cisplatin) manner during the phase 2 portion of this trial to assess efficacy as measured by the ORR. Historical data at the time of trial inception suggested the ORR for Arm B in this patient population was approximately 25% (N=42/161) per phase 3 ABC-02 trial (Valle, Wasan et al. 2010). We suggested that the combination therapy at the MTD/RP2D would be successful by

increasing the ORR to 43%. Since the trial's inception, data from the phase 3 TOPAZ-1 trial treating similar patient population with either placebo or durvalumab in combination with gemcitabine plus cisplatin, has demonstrated a response rate of 18.7% (N=64) in 342 patients on the placebo (Gemcitabine + Cisplatin only) arm. As the placebo arm of TOPAZ-1 is consistent with this trial's Arm B we suggest a more accurate null hypothesis comparison for the ORR of Arm A (CPI-613+Gemcitabine+Cisplatin) would be to combine the ABC-02 and TOPAZ-1 data, suggesting a 21.1% ORR for the control group. With 50 patients receiving the combination therapy at the MTD/RP2D this trial will have >90% power to detect such a difference significantly using a two sided comparison to the point estimate 21.1%. With minimal acceptable power- 80% and using a two-sided comparison - we can detect a 38% alternative versus a 21.1% null value, with 5% type 1 error.

The operating characteristics presented above for the Phase 1B portion of the trial suggest that 10-12 patients will have been treated at the MTD/RP2D and those patients will be included in the Phase 2 efficacy assessment. Therefore, the Phase 2 portion of the trial will randomize approximately 48 to 58 patients in order to assure 50 patients in the CPI-613 treated group. Approximately 16 to 20 patients will be assigned to Arm B/standard of care regimen.

The comparison of interest will be between the observed ORR in those receiving combination therapy versus the historical estimate. Patients randomized to Arm B will help suggest whether the historical estimate for ORR is a reasonable null hypothesis for comparison. If the ORR estimated for the control group is higher than the historical value, it may suggest increasing the null hypothesis value for comparison. In order to operationalize this comparison, we will implement a Bayesian approach to estimate the probability of ORR (CR+PR) for the control patients. Given that the historical estimates published by Valle, et.al 2010 is ~25% for the 162 patients treated in that phase 3 trial and is ~19% for the 342 patient treated in the TOPAZ-1 chemotherapy only arm, we will formalize that probability using a beta distribution b (106,397), which is a unimodal distribution, with mean 0.21 with precision proportional to the sample size, 503. We will then collect binary outcome data for the control patients (yes/no ORR) which allows the posterior distribution (prior data + trial's experience for control patients) to be described also as a beta distribution. If after adding the trial's control data it is suggested that the probability that the ORR is greater than 21% is more than 0.7 (70%), we will increase the estimate for the null hypothesis in the primary outcome comparison to be the probability estimated from the mean of the posterior distribution. The following table lists the number of control patients with an overall response based upon the number of control patients treated (may range from 16 to 20) for biologically reasonable ORR rates above 21%.

Table 12. Operating Characteristics of the Control Arm in Phase 2

Number of Control Cases Randomized and Treated	Number of Control Cases with an OR	Null Hypothesis value for the Probability of ORR for control patients used to compare to experimental treatment
16	9	0.22031
16	10	0.22222
16	11	0.22414
17	9	0.21989
17	10	0.22180
17	11	0.22371
18	9	0.21947
18	10	0.22137
18	11	0.22328
18	12	0.22519
19	10	0.22095

19	11	0.22286
19	12	0.22476
19	13	0.22667
20	10	0.22053
20	11	0.22243
20	12	0.22433
20	13	0.22624

11.4 Data Analyses Plans

We will report the estimate probability of DLT with 95% Bayesian Credible Intervals for each dose level as estimated by the TiTE-CRM algorithm at the completion of the Phase 1. The probability of DLT will be updated using the experience of the Phase 2 patients at the MTD/RP2D as well.

We will record ORR as a yes/no outcome for each patient for the period of active study treatment and report the estimate and exact 95% binomial confidence intervals. Patients will be considered evaluable for ORR if the patient has at least the first scan, to be taken 8 weeks +/- 1 week following D1C1 or if the patient is taken off study treatment prior to first scan due to toxicity or clinical progression or by physician discretion secondary to toxicity or intolerability. If the patient is taken off treatment prior to first scan due for any other reason (patient revocation of consent, incarceration, pregnancy, etc.) then the patients will be replaced for assessment of the primary outcome. We will estimate PFS and OS using the product-limit method of Kaplan and Meier, for the response evaluable and total population (any patient receiving study therapy) Follow-up time will be defined as time from date of first study treatment until the date of radiological or clinical progression (leading to withdrawal from the study), or death from any cause, whichever comes first for PFS and for only death from any cause for OS. For patients without events, we will censor the follow-up time at the date of last disease evaluation at the time of analysis. We will report estimates for the median and 75th percentiles with 95% confidence intervals. We will summarize additional safety data (e.g., laboratory safety parameters, vital signs, concomitant medications and new physical examination findings) descriptively by reporting counts and percentages, with exact binomial confidence intervals where appropriate. ORR will be determined as per the RECISTv1.1 guidelines. We will report adverse events per the NCI CTCAE v5.0.

12.0 ADMINISTRATIVE PROCEDURES

12.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and be consistent with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives.

The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

12.2 Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the

MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of enrollment
    - Subject entry into the EDC
    - Subject Status
    - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. *[Information on dose limiting toxicity events must be entered within one business day.]* Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8.5 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

12.3 Record Retention

The Investigators must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, whichever is longer.

13.0 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor-Investigator (S-I)/Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Sponsor-Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined **[phase I: monthly / phase II: quarterly]** meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a **[phase I: monthly / phase II: quarterly]** basis for independent review.

14.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

15.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Rogel Cancer Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes [first treatment cycle/course]. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

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17.0 APPENDICES

Appendix I ECOG Performance Status
Appendix II Investigator's Statement
Appendix III Contingency Operations Plan

Appendix I ECOG Performance Status

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

Source: Eastern Cooperative Oncology Group

Appendix II Investigator's Statement

1. I have carefully read this protocol entitled "A Randomized Phase IB/II Study of Gemcitabine and Cisplatin With or Without CPI-613 as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer", **Version 4.1 dated 07/22/2022**, and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.

2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.

3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.

4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.

5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from University of Michigan unless this requirement is superseded by the FDA.

Site PI Name: _____

Site Name: _____

Signature of Site PI: _____

Date of Signature: _______________

Appendix III Contingency Operations Plan

In the event of a public health or civil emergency or restrictions, clinical changes may be necessary to effectively manage the study. Should such an instance occur, the following adjustments may be applied by participating sites as required to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens) and may be implemented without IRB acknowledgement/approval but are to be reported afterwards, as required.

1. **Infectious Diseases Testing:**
    a. Should testing be available/required for a public health or civil emergency, it is not currently being added to the protocol as part of the screening requirements, but may be done as part of the clinical assessment, as needed during the course of the event/restrictions.
    b. During the course of the study, Infectious Diseases tests/results will be recorded in the subject's source documents but will only be added as an Adverse/Serious Adverse Event in the eCRF should the test yield a positive result.
    c. The Sponsor-Investigator or designee is to be immediately informed in the event that a trial participant exhibits or reports symptoms consistent with the infectious diseases (whether or not confirmed by a positive test result). Depending on the investigational product being administered and the patient's clinical presentation, dosing may be withheld, until such time as symptoms resolve. This decision should be made by the site Principal Investigator, determining what is the best course of action for the patient, in consultation with the Sponsor-Investigator. In some cases, the site PI and/or Sponsor-Investigator may request a participant be retested before dosing of the investigational product is resumed.

2. **Study Visit Schedule:**
    a. For individual instances where assessments cannot be made and/or data are not able to be collected, the reasons for failing to obtain the data should be documented (e.g., identifying the specific limitation imposed by the event/restriction leading to the inability to perform the protocol-specified assessment) and recorded as a protocol deviation, as required.
    b. Ongoing participants who are unable or unwilling to attend protocol-specified trial visits and procedures, may continue in the trial if the site PI in consultation with the Sponsor-Investigator deems it appropriate and for as long as the patient continues to consent to participation and where patient safety can be monitored.
    c. Where participants cannot be seen at the site or by home visit, the use of telemedicine and adaptation of schedule of assessments can be implemented, where feasible to ensure patient safety.
    d. Adjustments to the protocol imaging visit window (8 ± 1 week) are permitted by the Sponsor-Investigator if on-schedule visits are not possible due to the national emergency/restrictions.

3. **Laboratory Assessments:**

    It may be possible that lab closure is required as a contingency measure during the course of a public health or civil emergency or restrictions. Should that occur:

    a. Correlative samples will not be collected unless the participating site lab facilities has appropriate storage capacity/capabilities to do so. If the participating site does not have lab storage capacity/capabilities, research bloods samples are not to be drawn. Operations will continue per usual once they are provided approval from the UM Coordinating Center that it is safe for labs to re-open
        i. Pre-Treatment and End of Treatment (EOT) biopsy samples will be obtained, if applicable/possible, and will be retained at site until further notification.
        ii. Cycle 1 Day 1, Cycle 4 Day 1 and End of Treatment blood samples will be obtained if possible and will be processed and shipped per the study lab manual. If the research

lab closes and is unavailable to accept samples, this will be communicated out to the study team.

b. Patients will be allowed to have safety labs (routine standard of care labs) drawn at a local lab and results will be reviewed by the study team.

4. **Study Medications:**

a. Adjustments for alternate drug administration will be permitted by the Supporters (Cornerstone Pharmaceuticals) and Sponsor-Investigator. Ongoing participants who are unable or unwilling to attend protocol-specified trial visits and procedures, may continue in the trial if the site PI in consultation with the Sponsor-Investigator deems it appropriate and for as long as the patient continues to consent to participation and where patient safety can be monitored.

b. The patient may remain on study without receiving drug for more than 28 days if the drug(s) are held due to the national emergency/restrictions.

c. If a patient does not receive investigational regimen consecutively for 4 weeks from last intended dose between consecutive CT scans due to the national emergency/restrictions, then the patient may continue on treatment despite progression on CT scan.