Comprehensive Cancer Center of Wake Forest University
A Pilot Study: Open-Label Clinical Trial of CPI-613 in Patients with Advanced Bile Duct Cancers
CCCWFU # 59212

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Investigational Drug: CPI-613

IND Number: 117,500

Drug Sponsor: Cornerstone Pharmaceuticals, Inc.

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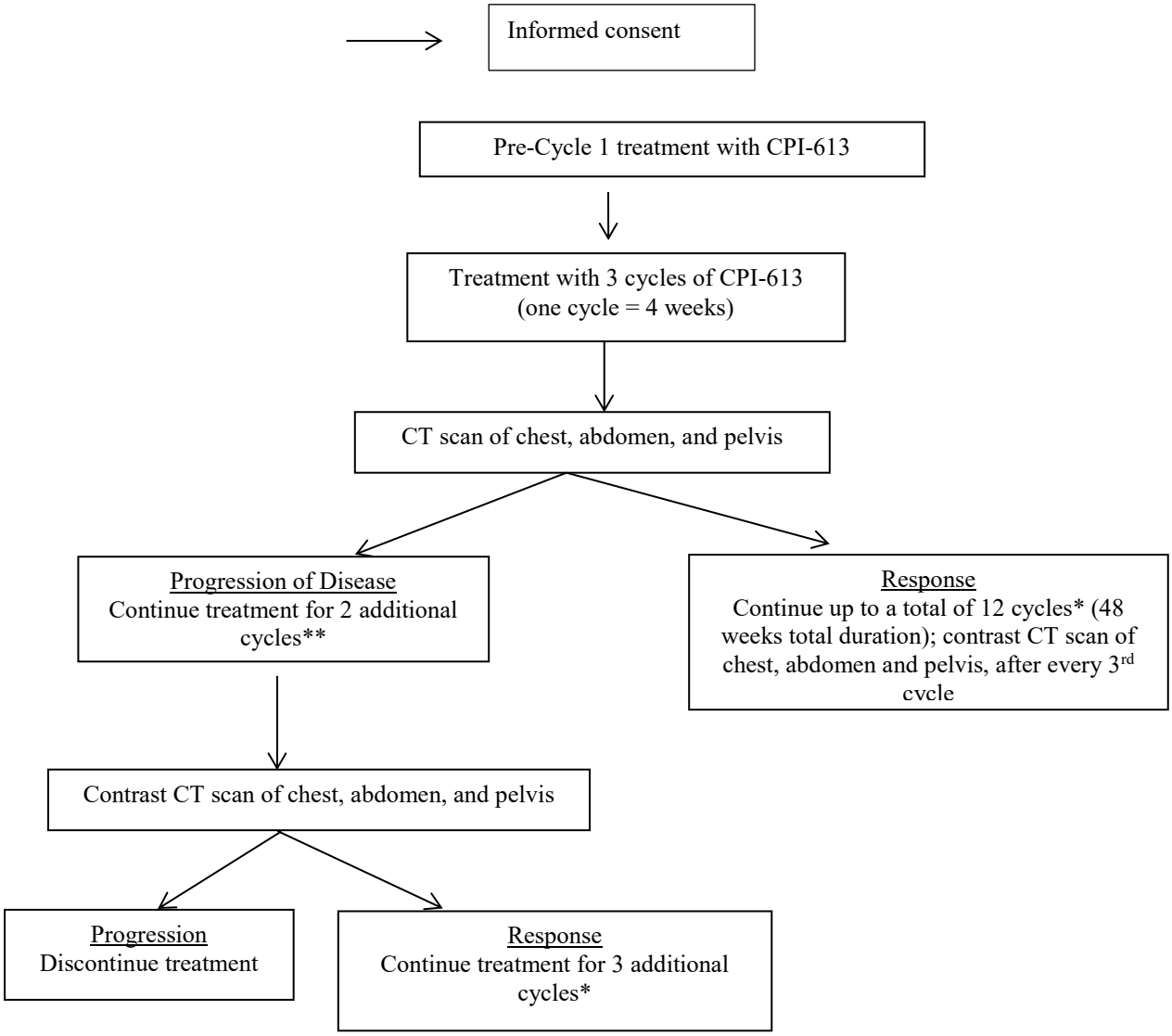
Proprietary and Confidential

SCHEMA

Patients with histologically and cytologically proven bile duct cancer



Primary Objective

To evaluate the safety and anti-cancer activities (assessed based on Response Rate) of CPI-613 in patients with advanced unresectable bile duct cancer who have failed available therapies.

Secondary Outcome measures

- Progression-free survival
- Overall Survival

Design

Open-label single arm

* Maximum number of cycles allowed is 12, unless the investigator considers additional treatment can provide clinical benefit

** Two additional cycles will not be given if the patient no longer meets eligibility criteria, has worsening of biliary function, or has symptomatic progression.

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1. BACKGROUND AND STUDY OBJECTIVES

Biliary duct carcinoma is a rare but highly fatal malignancy. Estimated incidence of bile duct and gallbladder cancer approached 10,000 cases in 2009, with nearly 3,400 estimated deaths according to the American Cancer Society.

Cholangiocarcinoma is an epithelial cancer of the biliary duct system that may originate in the liver and extrahepatic bile ducts, which may terminate at the ampulla of Vater. Based on anatomical location, cholangiocarcinoma can be divided into 3 categories: (1) intrahepatic (20-25%), occurring in the bile ducts residing within the liver; (2) extrahepatic or perihilar (also known as Klatskin tumour, 50%), occurring at the confluence of the right and left hepatic ducts; and (3) distal extrahepatic bile duct (20-25%), occurring beyond the liver. More than 90% of cholangiocarcinoma are adenocarcinomas, with different histological variants including adenocarcinoma, papillary adenocarcinoma, intestinal-type adenocarcinoma, and mucinous adenocarcinoma.

Conventional chemotherapy and radiation therapy have not been shown to be effective in prolonging long-term survival. Although photodynamic therapy has been reported to be effective as a palliative treatment, it is not curative. Radical surgery is the only potentially curative treatment modality. However, in most cases, the tumors are well advanced at the time of diagnosis, which results in limited treatment options. The impact of chemotherapy on survival remains controversial. The overall survival for patients with cholangiocarcinoma is ~6 months.

Gemcitabine, with or without cisplatin, is the first line chemotherapy. However, the outcomes of this therapy are limited. After gemcitabine/cisplatin therapy, there is essentially no known effective chemotherapy. The poor response of cholangiocarcinoma to current therapy highlights the need for a safe and effective therapy.

CPI-613 is a novel anti-cancer agent (Zachar et al. 2011). CPI-613 selectively targets the altered form of mitochondrial energy metabolism in tumor cells, causing changes in mitochondrial enzyme activities and redox status which leads to apoptosis, necrosis and autophagy of tumor cells (Zachar et al. 2011). The activities of CPI-613 involve the catalytic and regulatory functions of the altered form of the pyruvate dehydrogenase complex (PDC) and the α-ketoglutarate dehydrogenase complex (KGDHC) found in tumor cells (Zachar et al. 2011). CPI-613 is also well-tolerated at doses up to 3,000 mg/m^2, according to Phase 1 trials in patients with solid tumors and hematologic malignancies. Although it has not been investigated in patients with cholangiocarcinoma, CPI-613 has exhibited anti-cancer activities against a variety of advanced cancers including different types of solid tumors (Lee et al. 2011 & 2012; Senzer et al. 2012) and hematologic malignancies (Pardee et al, 2011a and b, & 2012). Therefore, the anti-cancer activities and safety of CPI-613 against advanced bile duct cancers are investigated in this study. Interestingly, after the first two cycles of treatment, the radiologic response by CAT scan or PET scan did not correlate well with the clinical response for various tumor types, and patients had increased survival despite pseudo-progression on their initial scan. One of the reasons is that CPI-613 seems to be producing an inflammatory and necrotic local effect that can

be read as pseudo-progression on a standard CT. For this reason, we will allow patients to continue for an additional two cycles even if the first treatment scan shows progression of disease by RECIST criteria. After 2 additional cycles, we expect to understand if the patient responded to therapy or not as the inflammatory/necrotic effect should have subsided. Allowing 2 additional treatment cycles with Disease Progression according to RECIST cannot take place if any of the following conditions occur:

- the patient no longer meets eligibility criteria set at the start of the protocol (see Section 3.)
- worsening of biliary function when compared to baseline
- the patient has symptomatic progression

2. STUDY DESIGN

2.1 Study Objective

The objective of this study is to evaluate the safety and efficacy of CPI-613 in patients with advanced unresectable bile duct cancers who have failed available therapies.

2.2 Outcome Measures

The primary outcome measures are safety and anti-cancer activities (assessed based on Response Rate [RR]).

The secondary outcome measures are:

- Progression-Free-Survival (PFS).
- Overall Survival (OS).

2.3 Open-Label Single-Arm Study Design

This is an open-label study, and investigators and subjects are not blinded to the treatment. Also, the assignment of patients will not be randomized, since there is only a single arm in this study.

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria before enrollment:

A. Histologically and cytologically proven bile duct cancer of any type (including intrahepatic cholangiocarcinomas, extrahepatic primary cholangiocarcinomas, hilar cholangiocarcinomas, cholangiocarcinomas located in the gall bladder or hepatic capsule effraction, and carcinoma of the Ampulla of Vater, etc.) that is not amenable

to surgery, radiation, or combined modality therapy with curative intent, and has failed or is not eligible for available chemotherapies such as gemcitabine with or without platinum.

B. Local, locally-advanced, or metastatic disease documented as having shown progression on a scan (e.g., CT, MRI).
C. Measurable tumor according to RECIST 1.1 criteria with at least one unidimensionally measurable target lesion.
D. No evidence of biliary duct obstruction, unless obstruction is controlled by local treatment or, in whom the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to below 1.5x Upper Level of Normal (ULN).
E. No acute toxic effects from previous treatment superior to grade 1 at the start of the study.
F. Eastern Cooperative Oncology Group (ECOG) performance status being 0-2.
G. Expected survival >3 months.
H. Male and female patients18 years of age and older.
I. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation.
J. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.
K. Laboratory values ≤2 weeks must be:
    - Adequate hematologic (granulocyte count ≥1500/mm^3; white blood cell [WBC] ≥3500 cells/mm^3 or ≥3.5 bil/L; platelet count ≥100,000 cells/mm^3 or ≥100 bil/L; absolute neutrophil count [ANC] ≥1500 cells/mm^3 or ≥1.5 bil/L; and hemoglobin ≥9 g/dL or ≥90 g/L).
    - Adequate hepatic function (aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present), bilirubin ≤1.5x UNL).
    - Adequate renal function (serum creatinine ≤2.0 mg/dL or 177 μmol/L).
    - Adequate coagulation ("International Normalized Ratio or INR must be ≤1.5" unless on therapeutic blood thinners)
L. No evidence of active infection and no serious infection within the past month.
M. Mentally competent, ability to understand and willingness to sign the informed consent form.

3.2 Exclusion Criteria

Patients with the following characteristics are excluded:

A. Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 2 weeks prior to initiation of CPI-613 treatment.
B. Serious medical illness that would potentially increase patients' risk for toxicity.
C. Any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease).
D. Pregnant women, or women of child-bearing potential not using reliable means of contraception (because the teratogenic potential of CPI-613 is unknown).
E. Lactating females.
F. Fertile men unwilling to practice contraceptive methods during the study period.
G. Life expectancy less than 3 months.
H. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.
I. Unwilling or unable to follow protocol requirements.
J. Dyspnea with moderate exertion.
K. Patients with clinically significant pleural or pericardial effusions.
L. Active heart disease including but not limited to symptomatic congestive heart failure, symptomatic coronary artery disease, symptomatic angina pectoris, symptomatic myocardial infarction, or symptomatic congestive heart failure. Also patients with a history of myocardial infarction that is <1 year prior to registration, or patients with previous congestive heart failure (<1 year prior to registration) requiring pharmacologic support or with Left Ventricular Ejection Fraction <50%).
M. A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)
N. Evidence of active infection, or serious infection within the past month.
O. Patients with known HIV infection.
P. Patients with baseline troponin levels greater than the institutional limit of normal.
Q. Patients who have received cancer immunotherapy of any type within the past 2 weeks prior to initiation of CPI-613 treatment.
R. Requirement for immediate palliative treatment of any kind including surgery.
S. Patients that have received a chemotherapy regimen with stem cell support in the previous 6 months.
T. Prior illicit drug addiction.
U. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of the patient.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for participation in this trial.

4.0 REGISTRATION PROCEDURES

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control

trial, **must** be registered with the CCCWFU Protocol Registrar or entered into the Oncology Research Information System (ORIS) Screening Log within 24 hours of informed consent.

Patients **must** be registered prior to the initiation of treatment.

In order to ensure prompt registration of your patient, please:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the WFUHS registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

Contact Information:

Protocol Registrar PHONE (336) 713-6767
Protocol Registrar FAX (336) 713-6772
Protocol Registrar E-MAIL (registra@wakehealth.edu)
*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Please fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 STUDY PROCEDURES

Table 5-1 (below) provides an overview of the study procedures for the pre-study screen and pre-cycle 1 treatment period. The specifics are described in subsequent sections.

Table 5-1: Study Procedures for Pre-Study Screen and Pre-Cycle 1 Treatment Period

Assessments	Pre-Study Screen[8]	Pre-Cycle 1 treatment (Given Only Once for Each Patient)	
		Days 1-5	Days 6-7
CPI-613[1]		√	
Medical history	√		
Pregnancy test for women of child-bearing potential	√		
Evaluation of symptoms and vital signs	√[3]	√[4]	
ECOG performance status and survival	√		
Clinical chemistry, hematology and coagulation[2]	√	√[5]	
Cardiac: Troponin I	√	√[5]	
Cardiac: ECG	√	√[5]	
CT w/ contrast (chest/abdomen/pelvis)	√		
CA-19-9	√		
Plasma CPI-613 concentrations, possibly metabolite concentrations, and possibly other analyses[6]		√[7]	
Optional blood and serum samples[9]	√		
Adverse event evaluation		√	√

ECOG = Eastern Cooperative Oncology Group; hr = hour; min = minute.

[1] CPI-613 is given as a 2-hr IV infusion via a central venous catheter.

[2] Specific chemistries are listed in section 5.2.2. Renal function will be assessed utilizing the Cockcroft-Gault formula. Coagulation (PT/PTT) will only be assessed at screening.

[3] Other than evaluation of symptoms and vital signs, height and weight, physical exam, and medications are also determined during pre-study medical screening.

[4] Perform on Days 1 and 4 only.

[5] Perform on Days 1 and 5 only.

[6] Obtained according to the following schedule: pre-dose (~5 min before dosing), and at 0.5, 1, 1.5, 2, and 4 hrs post-dose of CPI-613.

[7] Day 1 only

[8] Pre-study screening tests, which are also enrollment evaluations, must be performed according the following time frames:
Within 4 weeks: tumor assessment (CT w/ contrast), CA-19-9
Within 2 weeks: medical history, physical exam, vital signs, height, weight, ECG, ECOG, evaluation of symptoms and medications, clinical chemistry, hematology, coagulation, and troponin
Within 1 week: pregnancy test for women of child-bearing potential, pre-study labs and ECG obtained before enrollment may be used for Day 1

[9] Optional blood and serum samples are for possible testing of biomarkers, predictors of biological responses, toxicity, genotype vs. drug response relationship, etc.

Table 5-2 (below) provides an overview of the study procedures for all treatment cycles and the follow-up period. The specifics are described in subsequent sections.

Table 5-2: Study Procedures for All Treatment Cycles and Follow-Up Period

Assessments	Cycles 1 and 2 (Each cycle is 4 weeks)							Cycles 3 through 12 (Each cycle is 4 weeks)							Follow-Up
	Week 1		Week 2		Week 3		Week 4	Week 1		Week 2		Week 3		Week 4	Every 2 months until death
	D1	D4	D1	D4	D1	D4	D3,4,or 5	D1	D4	D1	D4	D1	D4	D3, 4, or 5	
CPI-613[1]	√	√	√	√	√	√		√	√	√	√	√	√		
Evaluation of symptoms and vital signs	√[2]		√[2]		√[2]			√[2]		√[2]		√[2]			
ECOG performance status and survival	√[2]		√[2]		√[2]			√[2]		√[2]		√[2]			
Clinical chemistry, hematology [2,3,9]	√[2]	√	√	√	√	√		√[2]							
Cardiac: Troponin I and ECG[9]	√[2]							√[2]							
CT w/ contrast (chest/abdomen/pelvis)														√[4]	
CA-19-9														√[4]	
Plasma CPI-613 concentrations, possibly metabolite concentrations, and possibly other analyses [6]	√[8]														
Optional blood and serum samples[10]														√[4]	
Phone contact															√[7]

ECOG = Eastern Cooperative Oncology Group; hr = hour; min = minute; D1 = day 1; D4 = day 4.

[1] CPI-613 is given as a 2-hr IV infusion via a central venous catheter. Treatment with CPI-613 may be adjusted +/- 1 day.

[2] These tests are performed with results available for review within 24 hrs before administration of the anti-tumor agents.

[3] Specific chemistries are listed in section 5.2.2. Renal function will be assessed utilizing the Cockcroft-Gault formula.

[4] Performed at the following time points: during week 4 (preferably Wednesday or later) of cycle 3 for all patients. For patients without progression, perform during week 4 of cycles 6, 9, and 12. In patients where progression was detected from the cycle 3 scan, perform during week 4 of cycle 5. If patient remains on study after cycle 5, perform every 3 months thereafter.

[6] Plasma samples will be obtained pre-dose (~5 min before dosing), and at 0.5, 1, 1.5, 2, and 4 hrs post-dose of CPI-613.

[7] Survival and post-study cancer treatment will be monitored bimonthly via telephone contact after the patients are taken off the trial.

[8] Cycle 1 only

[9] Within 1 week: pre-study labs and ECG obtained before enrollment may be used for Day 1

[10] Optional blood and serum samples are for possible testing of biomarkers, predictors of biological responses, toxicity, genotype vs. drug response relationship, etc.

5.1 Pre-Study Screening Tests and Safety Assessment

5.1.1 Pre-Study Screening Tests

Pre-study screening tests, which are also enrollment evaluations, must be performed according the following time frames:

Within 4 weeks: tumor assessments based on contrast CT of chest, abdomen, and pelvis, and optional blood and serum samples.

Within 2 weeks: medical history, physical exam, vital signs, height, weight, ECG, ECOG, evaluation of symptoms and medications, clinical chemistry, hematology, coagulation, and troponin I.

Within 1 week: pregnancy test for women of child-bearing potential.

5.1.2 Safety Assessment

The safety of CPI-613 will be assessed from the first dose to 1 month after last dose of CPI-613. The assessment will be based on:

- evaluation of symptoms
- vital signs
- ECOG performance status and survival
- clinical chemistry
- renal function
- hematology
- coagulation
- cardiac safety assessments via troponin I and ECG

The specifics of the safety tests are described in Section 5.2. All safety assessment tests are performed during screening (performed within 2 weeks prior to treatment with CPI-613 during Pre-Cycle 1), on Day 5 during Pre-Cycle 1, and prior to each treatment cycle with results available for review within 24 hrs before administration the anti-tumor agents. Chemistries, hematology, and renal function will also be performed on Days 1 and 4 of each treatment week during the first 2 cycles. ECOG performance status and survival will be assessed on Day 1 of each treatment week.

5.1.3 Tumor Assessment

Tumor response to treatment will assessed at baseline, and initially after the time frame encompassing the pre-cycle 1 treatment and the first three cycles using

contrast CT of the chest, abdomen and pelvis as well as serum levels of tumor marker CA-19-9 and performance status. Should the principal investigator determine that tumor progression has occurred the patient will be removed from the study. Should the principal investigator determine that the patient has stable disease or has had a favorable response, those patients will continue treatment with CPI-613 for an additional three cycles (approximately three months). At that time, patients will then undergo re-imaging contrast CT, CA-19-9 and performance status.

According to the Response Evaluation Criteria in Solid Tumors (RECIST), the efficacy of treatment for solid tumors is determined by the tumor size. RECIST criteria are the golden standard to evaluate the tumor. In this study RECIST criteria will be used to evaluate response. However, there is a *pseudoprogression* phenomenon described with the use of CPI-613 in Phase I solid tumor studies (Lee et al. 2012).

It is felt that if CPI-613-induces necrosis of the tumor lesion there may be some radiographic evidence for increasing size. CPI-613 induces tumor necrosis due to its mechanism of action – selectively targeting the altered form of mitochondrial energy metabolism in tumor cells, causing changes in mitochondrial enzyme activities and redox status, which leads to apoptosis, necrosis, and autophagy of tumor cells (2,3,7,17,18).

For the purposes of this study, pseudoprogression will be defined and considered in patients who meet RECIST criteria of progression. It will be the treating physician's discretion to continue treatment in this situation if the patient is deemed to be getting clinical palliative benefit. In these patients, the study drug can be given for another two cycles prior to making definitive determination of progression or response.

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Assessment of tumor response will be the responsibility of the principal investigator and should be based on radiologic findings (i.e., contrast CT of the chest, abdomen, and pelvis, and MRI of the abdomen), CA-19-9 and performance status.

OS will be monitored bimonthly via telephone contact after treatment termination. (**Note:** During the bimonthly post-study telephone contact, information related to cancer treatment received after the study will also be collected). OS and PFS will be calculated from the first day of treatment. The duration of OS will be measured until the date of death or censored at follow-up. The duration of response (evaluated by PFS) will be measured from the date a first objective response is documented until the first sign of progression assessed by MRI and CT.

****NOTE:** Tumor necrosis alone should not be criteria for determining

progression.

Safety and RR of CPI-613 are the primary endpoints, whereas PFS and OS are secondary endpoints.

Pseudoprogression will be ruled out by allowing patients to receive the study drug for another 2 cycles after the first response assessment before making definitive assessment of progression or response. However, patients will not be allowed to continue treatment with CPI-613 at the time of "pseudo-progression" if any of the following criteria are met:

a. The patient does not meet eligibility criteria set at the start of the protocol.
b. Biliary function worsens.
c. The patient has symptomatic progression.

OS will be determined from the first dose of CPI-613 to death, assessed up to 3 years after the first dose of CPI-613. Post-study survival, medical and cancer treatment information will be collected bimonthly via telephone contact after treatment termination.

RR is defined as % of patients who experienced a Complete Response (CR) or Partial Response (PR). CR and PR are based on Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1 Eisenhauer et al. 2009). The best response recorded from the start of the treatment until Disease Progression (DP) will be considered.

PFS will be determined from the first dose of CPI-613 to DP or death due to any cause, assessed up to 3 years after the first dose of CPI-613.

5.2 Specifics of Tests Performed During the Study

Described below are the specifics of the tests performed in this study.

5.2.1 ECOG Performance Status

The ECOG Performance Status scales (Oken et al 1982) will be used to assess how a patient's disease is progressing and assess how the disease affects the daily living abilities of the patient. These scales are listed in Table 5.2.1-1 (below). The higher the ECOG score, the worse the prognosis.

Table 5.2.1-1: Scales Used in ECOG Performance Status

Grade	ECOG
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
5	Dead

5.2.2 Clinical Chemistry, Hematology and Coagulation

Clinical chemistry assessed includes:

glucose	BUN
creatinine	AST/serum glutamic-oxaloacetic transaminase (SGOT)
total protein	ALT/serum glutamic-pyruvic transaminase (SGPT)
albumin	alkaline phosphatase (ALP)
Na^+	total bilirubin
K^+	
Cl^-	
Mg	
Ca^{+2}	
PO_4	
CO_2	

Hematology includes:

complete blood count	hemoglobin
differential count	hematocrit
platelet count	

Coagulation includes:

Prothrombin time	Partial thromboplastin time

Cardiac assessment includes:

Troponin I
ECG

5.2.3 Analyses of Plasma CPI-613 Concentrations, Possibly Metabolite Concentrations, and Possibly Other Analyses

Plasma samples for the determination of CPI-613 concentrations, possibly metabolite concentrations and possibly other analyses will be obtained before and at various times after dosing of CPI-613 on Day 1 of Pre-Cycle 1 & Day 1 of Cycle 1 at the following time points: ~5 min before dosing, and at 0.5, 1, 1.5, 2, and 4 hrs post-dose of CPI-613.

Blood (4 mL for each sample) should be obtained from a peripheral vein, and not from a central venous catheter. The blood samples should be collected in 4-mL lavender top collection tubes containing K2-EDTA anticoagulant. The procedures for obtaining plasma samples are described in subsequent sections.

The specific procedures for collecting the blood samples are:
Sample Collection:

1. Collect 4 mL of blood into K2-EDTA plasma tubes.
2. Blood samples should be processed within 30 minutes of collection and kept on ice or in an ice block until processing.
3. Turn the filled tube upside down and then return it to the upright position. Do this 8-10 times. Do not shake or vortex the tube. You can also place the tubes on a mechanical shaker for 10 minutes to ensure full mixing.
4. The samples are then immediately centrifuged (< 1300x g for 10 minutes). There should be ~2 mL of plasma from each 4 mL blood sample.
5. The plasma fraction should then be transferred in approximately equal fractions using a disposable pipette to two 1.8-mL Nunc cryovial (provided by Cornerstone) and immediately frozen. The total time from collection to freezing should not exceed 60 minutes. The recommended temperature for sample storage is -80°C (or lower).

Sample Tube Labeling

Each sample vial should be marked with a unique identifier, to be provided by Cornerstone. The unique identifier include the date and time of collection, dose, and subject number. A separate document (the "PK Sample Collection Log") should then identify the number as it pertains to dosage, date, time of collection, etc.

Sample Tube Shipment

When all samples from each patient have been collected, they should be shipped to Cornerstone Pharmaceuticals, Inc., to the attention of Asela Boteju.

Sample vials should be kept frozen during shipment through the use of dry ice. Boxes should contain 30-40% of the box volume in dry ice, or enough to keep the samples frozen for at least three days. Dry ice pellets, as opposed to a single slab of dry ice, are preferred and should surround the sample.

Samples should be shipped via priority overnight courier Monday, Tuesday or Wednesday to ensure arrival before the end of the business week. Do not ship during a holiday week or when severe weather is expected that may delay the shipment either at the final destination or transfer points.

Ensure that the total package weight does not exceed 27.2 kg (60 pounds). Notify the contract lab via email on the morning of the shipment day. The contract labs and the email addresses are:

Lab: Cornerstone Pharmaceuticals, Inc.
Email Address: Asela@cornerstonepharma.com

Documentation Accompanying Shipment

Each shipment should contain the following information on a document separate from the sample vials (the PK Sample Collection Log). The document should be placed in an envelope taped to the outside of the Styrofoam container but inside the outer cardboard box.

Also, send an email to give Asela Botejuat Cornerstone Pharmaceuticals, Inc. notice that the shipment is coming. The email should provide the protocol number, number of insulated boxes being shipped, a scan of the PK Sample Collection Logs of the patient samples being shipped, the name of the express courier including the tracking number and the method of shipment (preferably FedEx Priority Overnight), and expected date and time of arrival, plus the contact information of the person at Wake Forest University Health Sciences who is responsible for the shipment.

Shipment Address

Samples should be shipped to:

Asela BotejuCornerstone Pharmaceuticals, Inc.
1 Duncan Drive
Cranbury, NJ 08512-3629
Office Tel: 609-409-7050 ext. 212
Mobile Tel: (609) 423-9804Fax: (609) 409-6035
Email: Asela@cornerstonepharma.com

CPI-613 and Metabolite Assays

Plasma concentrations of CPI-613 and possibly metabolites will be assayed

using the validated Liquid Chromatography (LC)-Mass Spectroscopy/Mass Spectroscopy (LC/MS/MS) method (Cornerstone Study# VLD-002). Individual and mean plasma concentrations of CPI-613 and possibly metabolites for each patient will be tabulated at each time point and presented graphically. The following parameters will be estimated in all patients (as appropriate) from individual plasma concentration vs. time data:

- the maximum observed concentration (C_{max})
- area under the curve from time zero until the last measurable concentration (AUC_{0-t}, calculated by the linear trapezoidal rule and extrapolated to infinity by acceptable methods)
- area under the curve from time zero to infinity ($AUC_{0-infinity}$)
- K_{el} (estimated by linear regression of the terminal elimination phase)
- $t_{1/2}$
- Cl
- V_d
- C_{end}

5.2.4 Optional Sampling and "Banking" of Blood and SerumSamples

Optional blood and serum samples (10 mL and 8.5 mL, respectively) will be obtained and "banked" for possible testing of biomarkers, predictors of biological responses, toxicity, relationship between genotype and drug responses, etc. These samples will be obtained prior to treatment initiation (within 4 weeks prior to 1st dose), as well as prior to each restaging scan.

Whole Blood Samples

- Samples (10 mL each) will be collected into a green top sodium heparin Vacutainer® tube.
- Invert the tube a minimum of 10 times to mix the anticoagulant (sodium heparin) completely, then place sample on crushed ice.
- Label sample and store at refrigerated temperature (2-8°C).
- Samples will be shipped on cold pack to the address shown at the bottom of this section within 24-48 hours.

Serum Samples

- Collect blood (8.5 mL each) in serum separator tube (10.0mL, with Polymer gel/Silica activator).
- Gently invert the tube 8-10 times, and let tube sit in an upright position for at least 15-30 minutes at room temperature to allow the blood to clot.
- Within 2 hours from time of collection while at room temperature, spin the tubes at 1000x g using a standard room temperature centrifuge for 10-15

minutes.

- After centrifugation, pipette 1.0 mL aliquots of plasma into each of the 1.8 mL-size polypropylene screw-capped cryovials. Expect to collect between 3-5 cryovials each containing 1.0 mL aliquots of plasma.
- Label the aliquots.
- Quickly freeze the aliquots by placing them either on dry ice or in a –70°C freezer. Store the samples at –70°C or colder until shipment.
- Samples will be shipped on dry ice to the address shown at the bottom of this section

Shipment of Optional Samples

All optional samples and specimens should be shipped to:

Asela BotejuCornerstone Pharmaceuticals, Inc.
1 Duncan Drive
Cranbury, NJ 08512
Tel: (609) 409-7050 ext.215
Fax: (609) 409-6035
Email: Asela@cornerstonepharma.com

6.0 TREATMENT WITH CPI-613

CPI-613 will be administered to patients as shown in Table 6-1 (below). Briefly, a treatment cycle is 4 weeks, with CPI-613 given on Days 1 and 4 of the first 3 weeks. CPI-613 will also be given for 5 consecutive days a week before the start of Cycle 1, and this Pre-Cycle 1 treatment will only be given once in each patient. During Pre-Cycle 1 and each treatment cycle, patients will be treated with CPI-613 at the same dose, unless dose modification is warranted (see Section 6.2).

Table 6-1: Administration of CPI-613 in Patients with Advanced Cholangiocarcinoma

Treatment Cycle			Administration of CPI-613
	Week	**Day**	
Pre-Cycle 1 (1 week)	1	1	2-hr IV infusion via a central venous catheter
		2	2-hr IV infusion via a central venous catheter
		3	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
		5	2-hr IV infusion via a central venous catheter
Cycle 1 (4 weeks)	1	1	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
	2	1	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
	3	1	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
	4		
Cycle 2 (4 weeks)	1	1	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
	2	1	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
	3	1	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
	4		
Etc. up to a total of 12 cycles[a]			

hr = hour; IV = intravenous; min = minutes.
[a] Additional cycles can be given if the investigator considers it beneficial to do so.

6.1 Dose Levels, Dose Escalation, Sample Size and Justification of the Dose

6.1.1 Dose Levels, Dose Escalation and Sample Size

The dose levels to be used in assessing the safety and anti-cancer activities of CPI-613 in 10 patients with advanced bile duct cancers will be determined from a dose-escalation scheme using cohorts of patients with advanced bile duct cancers, as described below. The dose-escalation scheme is based on the number of patients exhibiting dose-limiting toxicity (DLT), and DLT is defined as toxicity of Grade 3 or higher attributed as probably or definitely related to CPI-613. The DLT determining period for all cohorts in the dose-escalation scheme is through the first cycle.

Cohort 1: The first 3 patients will not be treated with the 5 daily doses of CPI-613 during the pre-Cycle 1 week, and will only be treated with 3-weeks-on-1-week-off treatment cycles (see Table 6-1). The dose of CPI-613 will be 2,300 mg/m^2 (which is approximately three-quarters of the target dose). If none of these 3 patients develop a dose-limiting toxicity (DLT) through Cycle 1, the dose for the 3-weeks-on-1-week-off treatment cycles will be 3,000 mg/m^2 in all subsequent patients in this trial. However, if a DLT is observed in a patient (whether it is the 1st, 2nd or 3rd of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the dose for the 3-weeks-on-1-week-off treatment cycles will be 3,000 mg/m^2 in all subsequent patients in this trial. However, once DLT is observed in 2 patients, no additional patients will be treated at 2,300 mg/m^2 for the 3-weeks-on-1-week-off treatment cycles from that point on, even though the total number of patients in this cohort is as few as 2. The dose level of 2,300 mg/m^2, which induces a DLT in 2 or more patients, is considered to be above the maximum tolerated dose (MTD) for the 3-weeks-on-1-week-off treatment cycles. In this case, all subsequent patients in this trial will be treated at 1,700 mg/m^2 for the 3-weeks-on-1-week-off treatment cycles.

Cohort 2: In another 3 patients, the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. These patients will also be treated with the 5 daily doses of CPI-613 during the pre-Cycle 1 week. The dose of CPI-613 for the pre-Cycle 1 week will be 1,200 mg/m^2/day, which has previously been established to be the weekly MTD (see Section 6.1.2). If none of these 3 patients develop a DLT, the study can move onto Cohort 3.

However, if a DLT is observed in a patient (whether it is the 1st, 2nd or 3rd of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Sub-Cohort 2 (see below). However, if a DLT is observed in 2 patients, no additional patients will be treated at 1,200 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this cohort is as few as 2. The dose level of 1,200 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 600 mg/m^2/day (or 3,000 mg/m^2/week, equivalent to the MTD when given as a single dose).

Sub-Cohort 2: Sub-Cohort 2 is activated only if 1 out of 6 patients exhibits DLT in Cohort 2. There are 3 patients in this sub-cohort, the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. These patients will also be treated with the 5 daily doses of CPI-613

during the pre-Cycle 1 week. The dose of CPI-613 for the pre-Cycle 1 week will be 1,700 mg/m^2/day. If none of these 3 patients develop a DLT, the study can move onto Cohort 3. However, if a DLT is observed in a patient (whether it is the first, second or third of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Cohort 3. However, if a DLT is observed in 2 patients, no additional patients will be treated at 1,700 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this sub-cohort is as few as 2. The dose level of 1,700 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 600 mg/m^2/day (or 3,000 mg/m^2/week, equivalent to the MTD when given as a single dose).

Cohort 3: This cohort will be performed only if DLT is observed in Cohort 2, or DLT is observed in 1 or less patients in Sub-Cohort 2. There are 3 patients in this cohort, and the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. The dose for the 5 daily IV infusions during the pre-Cycle 1 week will be 2,300 mg/m^2/day. If none of these 3 patients develop a DLT, the study can move onto Cohort 4. However, if a DLT is observed in a patient (whether it is the 1st, 2nd or 3rd of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Cohort 4. However, if a DLT is observed in 2 patients, no additional patients will be treated at 2,300 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this sub-cohort is as few as 2. The dose level of 2,300 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 1,700 mg/m^2/day.

Cohort 4: This cohort will be performed only if DLT is observed in 1 or less patients in Cohort 3. There are 3 patients in this cohort, and the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. The dose for the 5 daily IV infusions during the pre-Cycle 1 week will be 3,000 mg/m^2/day. If none of these 3 patients develop a DLT, the study can move onto Cohort 5. However, if a DLT is observed in a patient (whether it is the first, second or third of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Cohort 5. However, if a DLT is observed in 2 patients, no additional patients will be treated at 3,000 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this cohort is as few as 2. The dose level of 3,000

mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 2,300 mg/m^2/day

Cohort 5: This cohort is performed once the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles has been determined from Cohort 1, and once the dose of CPI-613 for the pre-Cycle 1 week has been determined from Cohort 2-4. There are 10 patients in this cohort. These patients will be treated with CPI-613 for 5 days during the pre-Cycle 1 week at doses as determined from Cohorts 2-4, and the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1.

6.1.2 Justification of the Dose

Based on Phase I trials in patients with solid tumors and hematologic malignancies, 3,000 mg/m^2 is the MTD, when CPI-613 is given as a single agent infused over 2 hours on Days 1 and 4 for 3 weeks of a 4-week treatment cycle. CPI-613 did not induce any significant adverse effects at or below MTD. Additionally, CPI-613 at or below 3,000 mg exhibits anti-tumor activities in patients with various types of solid and hematologic malignancies (Pardee et al, 2011a and b, & 2012; Lee et al. 2011 & 2012; Senzer et al 2012). Because of the safety and efficacy against other cancers, 3,000 mg/m^2 is the target dose for this pilot study.

In this study, patients will be treated with CPI-613 for 5 consecutive days during pre-Cycle 1, prior to being treated with CPI-613 given 2x weekly for 3 weeks. A sub-MTD (2,300 mg/m^2, approx. three-quarters of the MTD) will be used in the first 3 patients (in Cohort 1) who will be treated with the 4-week treatment cycles and without treatment during the pre-Cycle 1 week to ensure safety, before initiating the dose escalation procedure to determine the MTD. The maximum plasma concentration (C_{max}) of CPI-613 associated with the dose level of 2,300 mg/m^2 is ~90 μM, which is significantly lower than the C_{max} of ~200 μM associated with 3,000 mg/m^2. Therefore, 2,300 mg/m^2 is expected to be a safe starting dose.

After determining the dose to be used in 3-weeks-on-1-week-off cycles, the safety of the dailyx5 treatment with CPI-613 during pre-Cycle 1 will be evaluated in a dose-escalated manner in Cohorts 2-4.

6.2 Dosing Delay and Dose Modification of CPI-613 in the Event of Adverse Events

For adverse events unrelated to serum creatinine elevation or reduction in renal function but are possibly related to CPI-613, the occurrence of Grade 1 toxicity does not generally require dose modification for subsequent doses for that patient. However, if Grade 2 toxicity (other than alopecia and nausea) probably related to CPI-613 develops, treatment is to be withheld and can resume only after the Grade 2 toxicity has been reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 25% of the dose at which such Grade 2 toxicity occurs. Grade 2 alopecia and nausea do not require withholding treatment or dose reduction. If Grade 3 or 4 toxicity probably related to CPI-613 develops, dosing of CPI-613 of that patient will be withheld and the patient shall be monitored for recovery from, and reversibility of, such Grade 3 or 4 toxicity. To resume treatment with CPI-613 for a patient who has had CPI-613-related Grade 3 or 4 toxicity, the Grade 3 or 4 toxicity must be reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced to 50% of the dose at which such Grade 3 or 4 toxicity occurs.

For adverse events related to creatinine elevation or reduction in renal function that are possibly related to CPI-613, dosing of the patient will be withheld even if the severity level is Grade 2 or above. Treatment can resume only after the toxicity has been reduced to Grade 1. The dose level for subsequent doses for that patient will be reduced by 15% if the severity level is of Grade 1, by 25% for Grade 2 toxicity, and by 50% for Grade 3 or 4 toxicity.

Furthermore, if the toxicity possibly related to CPI-613 is acute renal failure and the severity level is Grade 3 or 4, further patient enrollment will be temporarily suspended in order to enable assessment of the following aspects of the trial and implementation of corrective measures or protocol amendment, and if necessary:

- compliance of the study sites and investigators to the study protocol
- evaluation of the appropriateness of the procedures for monitoring renal function

6.3 Duration of Treatment for Each Patient at Each Cohort

Twelve cycles of treatment is recommended for patients who have a response, unless or until:

- Patients exhibit progression of disease together with worsening of biliary function, no longer meeting eligibility criteria, or exhibiting symptomatic progression; or patients exhibit progression of disease which was confirmed after 1 additional treatment cycles
- Unacceptable toxicity from CPI-613
- Patient withdrawal of consent

- Investigator's discretion to withdraw patients from the study because continued participation in the study is not in the patient's best interest.
- Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
- General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
- Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
- Termination of the clinical trial by the sponsor

When terminating treatment during this trial, the investigator should make every effort to contact the patient and to perform a final evaluation. Also, the reason(s) for withdrawal from the study must be recorded.

All patients will be followed until death.

Additional treatment cycles beyond the recommended 12 cycles can be given if the investigator considers it beneficial to do so.

7.0 STUDY DRUG - CPI-613

7.1 Description of CPI-613 Drug Product

CPI-613 is provided in 10-mL amber glass vials. Each vial contains 10 mL of CPI-613 at a concentration 50 mg/mL, equivalent to 500 mg of CPI-613. The drug product of CPI-613 is a clear and colorless solution that is free of any particulate matter.

7.2 Handling of CPI-613

CPI-613 is an investigational drug and its 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 absorbent material and the area must be washed at least 3 times with ethyl alcohol followed by water.

CPI-613 drug product is slightly photosensitive (Study# PHO-001). 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.

7.3 Storage of CPI-613

CPI-613 should be stored under refrigeration, at 2˚-8˚C (36˚-46˚F), except when being prepared for administration.

7.4 Intravenous (IV) Infusion Sets, Syringes and IV Bags to be Used for Administration of CPI-613

CPI-613 must be administered IV by infusion, via an IV catheter with D5W running at a rate of about 125-150 mL/hr. To avoid local reactions at and around the site of administration, CPI-613 should be administered via a central venous catheter. Subsequent sections describe the appropriate types of IV catheters, IV bags, syringes and clinical solutions that can be used in mixing and administering CPI-613 to patients.

Leaching of Diethylhexyl Phthalate (DEHP): CPI-613 can cause leaching of DEHP from IV infusion sets and IV bags (Study COM-003). Therefore, DEHP-containing IV infusion sets, IV bags or syringes should not be used in mixing or administration of CPI-613. Examples of the IV sets, IV bags and syringes that do not contains DEHP and therefore can be used in the administration of CPI-613 are:

Extension Set for Syringe Pump Use: All extension sets from MED-RX do not contain DEHP.

Syringes: Kendall Monoject syringes, all mono-ject syringes are DEHP free.

IV Infusion Sets: A compatibility study has been conducted showing that CPI-613 is compatible with 4 commonly used IV infusion sets (Study# COM-001). Therefore, these 4 types of IV infusion sets, and IV infusion sets that are made with the same materials, can be used to administer CPI-613. These IV infusion sets are:

- PVC material - ADDitIV® Primary IV Set with Universal Spike, Backcheck Valve, 2 Injection Sites, DEHP-Free and Latex-Free, 15 drops/mL, REF V14453, B Braun Medical Inc.
- Latex material - Interlink® System Secondary Medication Set, 10 drops/mL, 2C7451, Baxter Healthcare Corporation
- PVC material - Surshield™ Safety Winged Infusion Set, 0.19 mL Volume, Latex-Free, DEHP-Free, SV*S25BLS, Terumo Medical Products Hangzhou Co. Ltd.
- Polyethylene material - Interlink® System Paclitaxel Set by Baxter HealthCare, Non DEHP-free: Polyethylene tubing with a 0.22 microfilter Item # 2C7558 10 drops/mL

Syringes: Compatibility studies (Studies# COM-001 and COM-002) have shown that CPI-613 drug product (50 mg/mL), and drug product diluted with D5W to various concentrations (1.6-25 mg/mL) are compatible with various types of syringes, as listed below. Therefore, any of these types of syringes, and syringes that are made with the

same materials, can be used to administer CPI-613. Also, glass syringes can also be used, since glass (such as glass containers) is compatible with CPI-613 drug product.

- Norm-Ject, polyethlyene barrel, polyethylene plunger, latex free (Henke Sass Wolf GMBH) syringes
- Becton Dickinson syringes
- Terumo syringes
- Monoject syringes
- Glass syringes

7.5 Reconstitution and Administration of CPI-613

CPI-613 must be diluted from 50 mg/mL to 12.5 mg/mL with 5% Dextrose Water or D5W (i.e., 1 portion of CPI-613 diluted with 3 portions of D5W) prior to administration. The diluted drug product should be visually inspected for clarity. If haziness, precipitate or coloration (other than colorless) 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 drug product has been found to be stable for 24 hrs at room temperature and refrigeration temperature (Studies STA-010).

CPI-613 must be administered IV, via an IV 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 (Study NCL-049). 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 (Study NCL-049). 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 (Studies NCL-027 and NCL-030). To avoid local reactions at and around the site of administration, CPI-613 must be administered via a central venous catheter.

CPI-613 must not be administered as a bolus, but by infusion, at a rate of ~0.5 mL/min, via a central venous catheter with D5W running at a rate of about 125-150 mL/hr. This is to minimize potential acute toxicity of CPI-613, according to animal studies (Study NCL-049).

The following precautions must be taken when administering CPI-613:

A. Confirmation of the placement of the IV line to ensure a lack of leakage of CPI-613 into the perivascular space.
B. Confirmation that the IV line is free flowing.
C. Confirmation that the IV line is free of dead air space.
D. Dilute CPI-613 drug product with D5W, as instructed in the study protocol.
E. Administer CPI-613 by infusion, not as a bolus.
F. After administration of CPI-613, flush the IV line with ~10 mL of D5W to remove

residual CPI-613.

G. To avoid local reactions at and around the site of administration, CPI-613 should be administered via a central venous catheter.

7.6 Request for CPI-613

CPI-613 must be requested from Cornerstone by the Principal Investigator (or authorized designees). CPI-613 may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in this clinical study. Cornerstone policy requires that CPI-613 be shipped directly to the institution where the patient is to be treated. Cornerstone does not permit the transfer of CPI-613 between institutions (unless with prior written approval from Cornerstone). Requests must be submitted to Cornerstone by fax or email to the following address:

Ms. Claudia Maturo
Department of Regulatory and Clinical Affairs
Cornerstone Pharmaceuticals, Inc.
25 Health Sciences Drive
Stony Brook, NY 11790
Telephone: 631-444-6868
Telefax: 631-444-6895
Email: claudia@cornerstonepharma.com

The following information must be provided in the request of CPI-613 from Cornerstone:

- Names of the principal investigator and the requestor (if different)
- Name of the study site
- Name of the pharmacist responsible for receiving and storing CPI-613
- Name of the person and address where CPI-613 is to be shipped to
- Amount (# vials) requested
- Date of request
- Date shipment expected
- Study Protocol (title and protocol#) for which the requested CPI-613 is to be used

7.7 Procurement of Investigational Drug

Relevant regulations require investigators to establish a record of the receipt, use and disposition of all investigational products. Investigators may delegate responsibility of drug ordering, storage, accountability and preparation to their designees.

The investigator, or the designee, will be responsible for dispensing and accounting of CPI-613 provided by Cornerstone and for exercising accepted medical and pharmacy practices.

Records of inventory, dispensation and disposition (vials received, source and dates) must be maintained. In addition, all doses dispensed should be accounted for by recording the date, study number and name, patient identification, patient initials, patient medical record number and balance forward. These records must be maintained and kept at the study site, and will be reviewed by Cornerstone, or its designee, during periodic monitoring visits.

7.8 Disposal of CPI-613

The following procedures are to be taken in disposal of CPI-613:

- During the study, store the used CPI-613 vials (which must be separate from the unused CPI-613 vials) at room temperature in an access-limited area. Alternatively, destroy the used CPI-613 vials according to institutional policy after documentation of the number of used CPI-613 vials and remaining volume in each used vial.
- At the end of the study, deface the label (both used and unused vials) with a permanent marking pen.
- For used CPI-613 vials (if not already destroyed according to institutional policy), after documentation of the number of used CPI-613 units and remaining volume in each container, the used containers should be destroyed at the site according to the institutional procedures for destroying toxic chemicals. A certificate documenting the destruction of used vials must be kept on file.
- All unused CPI-613 vials must be destroyed according to the policy of the institution. The destruction of CPI-613, and the quantity destroyed, must be documented. A copy of the Certificate of Destruction should be sent to:

Ms. Claudia Maturo
Department of Regulatory and Clinical Affairs
Cornerstone Pharmaceuticals, Inc.
25 Health Sciences Drive
Stony Brook, NY 11790
Telephone: 631-444-6868
Telefax: 631-444-6895
Email: claudia@cornerstonepharma.com

7.9 Calculation of the Amount of CPI-613 for Each Patient

The amount of CPI-613 at each dose level is based on the BSA of the patient. The BSA values will be calculated based on the height and body weight taken during screening and this BSA value is used throughout the study. This is unless there is a >10% change in the body weight from baseline during the study. At that point, BSA should be revised based on the new body weight and height. The new BSA values will be used from that point on

for the remainder of the study, unless there is another >10% change in body weight which will require another revision of the BSA.

7.10 Concomitant Medications and Prophylactic Treatment

Patients cannot receive any standard or investigational treatment (except CPI-613) for their cancer, or any other investigational drugs for any indications, while on this study. All otherwise permitted concomitant medications (including trade and generic names, dosage and dosing schedule) must be recorded.

Prophylactic treatment for drug-related symptoms is not planned, or it will interfere with the assessment of the toxicity of the investigational product. However, following the evaluation of the causal relationship of the symptom(s) to the study drug and the information has been documented, the investigator may prescribe supportive treatment. Supportive treatment may include anti-emetic, anti-diarrhea, anti-pyretic, anti-allergic, anti-hypertensive medications, analgesics, antibiotics, allopurinol, and others such as blood products and bone marrow growth factors. Patients may use erythropoietin for chronic anemia. Also, the hemoglobin should be maintained ≥9 g/dL or ≥90 g/L during the course of the study. The treating physician may utilize erythropoietic factors, or blood or platelet transfusions at their discretion.

8.0 ADVERSE EVENTS LIST AND REPORTING REQUIREMENTS

8.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE 4.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:
  - 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.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

List of Adverse Events to be Reported:

*Abdominal pain
Alkaline phosphatase
ALT (SGPT)
Anorexia
AST (SGOT)
Bilirubin (hyperbilirubinemia)
Calcium (hypercalcemia, hypocalcemia)
*Creatinine
*Diarrhea
Flushing
Hemoglobin (anemia)
*Injection site Reaction
Leukocytes
Lymphopenia
*Nausea
Neutrophils (neutropenia)
Platelets (thrombocytopenia)
Potassium
Sodium
*Vomiting

All grade 3, 4, 5 adverse events should be reported on flowsheets and in ORIS regardless of whether they are on this list.
Asterisk (*) denotes expected Adverse Events.

All Serious Adverse Events (SAEs) which are Possibly, Probably or Definitively Related to CPI-613, and Unexpected are required to be reported to Cornerstone Pharmaceuticals via the provided SAE Reporting Form within 7 days. All completed forms must be sent to Claudia Moore at Cornerstone. Cornerstone will submit any applicable SAEs to the FDA.

SAE reports must be submitted to Cornerstone by fax or email to the following address:

Department of Regulatory and Clinical Affairs
Cornerstone Pharmaceuticals, Inc.
25 Health Sciences Drive
Stony Brook, NY 11790
Telephone: 631-444-6868
Telefax: 631-794-2319 Email: claudiamoore2001@yahoo.com

8.2 STRC SAE Reporting Requirements

The Safety and Toxicity Review Committee (STRC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix B. STRC

currently requires that all unexpected grade 4 and all grade 5 SAE's on these trials be reported to them for review. This procedure is a part of the CCCWFU Data Safety Monitoring Plan that our institution has on file at the NCI. All CRM staff members assisting a PI in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC committee as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.3 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the

safety, rights or welfare of research subjects.

9.0 STATISTICAL CONSIDERATIONS

This is a pilot study with the primary goal to be able to determine initial estimates of RR, and secondary goals to determine PFS and OS. Data from this trial will also provide additional data concerning the safety profile of the CPI-613 therapy. Since there is some uncertainty about what dose to examine for the 10 patients in this pilot study we propose the following pre-defined dose escalation scheme in order to determine the appropriate dose to provide to 10 patients with advanced bile duct cancers. This scheme has been discussed/proposed by the FDA and it is very specific and is described below. The dose-escalation scheme is based on the number of patients exhibiting dose-limiting toxicity (DLT), and DLT is defined as toxicity of Grade 3 or higher. The DLT determining period for all cohorts in the dose-escalation scheme is through the first cycle. Note – this section is redundant with section 6.1 but is included for completeness.

Cohort 1: The first 3 patients will not be treated with the 5 daily doses of CPI-613 during the pre-Cycle 1 week, and will only be treated with 3-weeks-on-1-week-off treatment cycles (see Table 6-1). The dose of CPI-613 will be 2,300 mg/m^2 (which is approximately three-quarters of the target dose). If none of these 3 patients develop a dose-limiting toxicity (DLT) through Cycle 1, the dose for the 3-weeks-on-1-week-off treatment cycles will be 3,000 mg/m^2 in all subsequent patients in this trial. However, if a DLT is observed in a patient (whether it is the 1st, 2nd or 3rd of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the dose for the 3-weeks-on-1-week-off treatment cycles will be 3,000 mg/m^2 in all subsequent patients in this trial. However, once DLT is observed in 2 patients, no additional patients will be treated at 2,300 mg/m^2 for the 3-weeks-on-1-week-off treatment cycles from that point on, even though the total number of patients in this cohort is as few as 2. The dose level of 2,300 mg/m^2, which induces a DLT in 2 or more patients, is considered to be above the maximum tolerated dose (MTD) for the 3-weeks-on-1-week-off treatment cycles. In this case, all subsequent patients in this trial will be treated at 1,700 mg/m^2 for the 3-weeks-on-1-week-off treatment cycles.

Cohort 2: In another 3 patients, the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. These patients will also be treated with the 5 daily doses of CPI-613 during the pre-Cycle 1 week. The dose of CPI-613 for the pre-Cycle 1 week will be 1,200 mg/m^2/day, which has previously been established to be the weekly MTD (see Section 6.1.2). If none of these 3 patients develop a DLT, the study can move onto Cohort 3.

However, if a DLT is observed in a patient (whether it is the 1st, 2nd or 3rd of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Sub-Cohort 2 (see below). However, if a DLT is observed in 2 patients, no additional patients will be treated at 1,200 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this cohort is as few as 2. The dose level of 1,200 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the

pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 600 mg/m^2/day (or 3,000 mg/m^2/week, equivalent to the MTD when given as a single dose).

Sub-Cohort 2: Sub-Cohort 2 is activated only if 1 out of 6 patients exhibits DLT in Cohort 2. There are 3 patients in this sub-cohort, the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. These patients will also be treated with the 5 daily doses of CPI-613 during the pre-Cycle 1 week. The dose of CPI-613 for the pre-Cycle 1 week will be 1,700 mg/m^2/day. If none of these 3 patients develop a DLT, the study can move onto Cohort 3. However, if a DLT is observed in a patient (whether it is the first, second or third of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Cohort 3. However, if a DLT is observed in 2 patients, no additional patients will be treated at 1,700 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this sub-cohort is as few as 2. The dose level of 1,700 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 600 mg/m^2/day (or 3,000 mg/m^2/week, equivalent to the MTD when given as a single dose).

Cohort 3: This cohort will be performed only if DLT is observed in Cohort 2, or DLT is observed in 1 or less patients in Sub-Cohort 2. There are 3 patients in this cohort, and the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. The dose for the 5 daily IV infusions during the pre-Cycle 1 week will be 2,300 mg/m^2/day. If none of these 3 patients develop a DLT, the study can move onto Cohort 4. However, if a DLT is observed in a patient (whether it is the 1st, 2nd or 3rd of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Cohort 4. However, if a DLT is observed in 2 patients, no additional patients will be treated at 2,300 mg/m^2/day during the pre-Cycle 1 week even though the total number of patients at this sub-cohort is as few as 2. The dose level of 2,300 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 1,700 mg/m^2/day.

Cohort 4: This cohort will be performed only if DLT is observed in 1 or less patients in Cohort 3. There are 3 patients in this cohort, and the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1. The dose for the 5 daily IV infusions during the pre-Cycle 1 week will be 3,000 mg/m^2/day. If none of these 3 patients develop a DLT, the study can move onto Cohort 5. However, if a DLT is observed in a patient (whether it is the first, second or third of the 3 intended patients), the number of patients in this cohort will be expanded to a maximum of 6 patients. If no DLT is observed in another patient out of a maximum of 6 patients, the study will move onto Cohort 5. However, if a DLT is observed in 2 patients, no additional patients will be treated at 3,000 mg/m^2/day during the pre-Cycle 1 week

even though the total number of patients at this cohort is as few as 2. The dose level of 3,000 mg/m^2/day during the pre-Cycle 1 week, which induces a DLT in 2 or more patients, is considered to be above the MTD for the pre-Cycle 1 week. In this case, the dose of CPI-613 for the pre-Cycle 1 week in subsequent patients in this trial will be 2,300 mg/m^2/day

Cohort 5: This cohort is performed once the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles has been determined from Cohort 1, and once the dose of CPI-613 for the pre-Cycle 1 week has been determined from Cohort 2-4. There are 10 patients in this cohort. These patients will be treated with CPI-613 for 5 days during the pre-Cycle 1 week at doses as determined from Cohorts 2-4, and the dose of CPI-613 for the 3-weeks-on-1-week-off treatment cycles will be as determined from Cohort 1.

As can be seen by the above scheme there are several possible scenarios that could occur in order to determine the dose for the 10 patients to be evaluated in the pilot trial. Once the above procedure is completed we will then enroll 10 patients at the determined dose.

Accrual Rate

We anticipate accruing one patient per month for this protocol. Since the dose escalation procedure described above may involve a variable number of patients (at least 6 but possibly more) we cannot be certain the entire length of accrual for this protocol. However, we do anticipate that the total number of patients in this protocol will be between 16-40 (with 16-22 being the most likely range). Thus, we anticipate that we will reach the target sample size of 10 patients treated at MTD within two years. A minimum of 16 patients to a maximum of 40 patients will be accrued to the study, with the first 6-30 being evaluated for toxicity in a dose-escalated manner for determining the MTD, and the remaining 10 used in the analytic sample.

Proposed Analyses

The analyses for this protocol will be primarily descriptive. With a sample size of 10 treated at MTD, we do not expect to see statistically significant effects for the outcomes of interest, however this data will provide useful preliminary data on the overall safety and efficacy of CPI-613 and provide useful data to predict the variability and likely effect sizes for these outcomes.

For the time-to-event outcomes we will estimate survival curves for OS and PFS using Kaplan-Meier techniques. In addition, we will estimate the 6 month and 1-year OS and PFS rates for these participants. For response rate we will present the proportion of patients who are CR, PR, SD or PD. In addition, we will estimate the proportion of responders as the percent of patients who are CR or PR. For this rate we will also include a 95% confidence interval.

We will also examine toxicities for these 10 patients by looking at each toxicity identified earlier in the protocol by grade.

Sample Size Considerations

Since this is a pilot study we do not anticipate having statistical power to detect specific effects, however with this sample size we will be able to estimate the response rate using a 2-sided 95% confidence interval with an interval that will extend no more than 0.31 from the observed

response rate.

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APPENDIX A – REGISTRATION GUIDELINES AND FORMS

The following guidelines have been developed in order to ensure timely registration of your patient.

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into ORIS Screening Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

In order to ensure prompt registration of your patient, please:

1. Complete the Eligibility Checklist (attached)
2. Complete the Protocol Registration Form (attached)
3. Alert the WFUHS registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:

   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.
4. Please fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

CCCWFU # 59212 **Eligibility Checklist**

Yes	No	N/A	Inclusion Criteria (All responses must be **YES** in order to enter study)	**Eligibility Confirmation (registrar)**
☐	☐	☐	1. Does the patient have histologically and cytologically proven cholangiocarcinoma of any type (including intrahepatic chlangiocarcinoma, extrahepatic primary cholangiocarcinoma, hilar cholangiocarcinomas, cholangiocarcinomas located in the gall bladder or hepatic capsule effraction, and carcinoma of the Ampulla of Vater, etc.) that is not amenable to surgery, radiation, or combined modality therapy with curative intent, and has failed or is not eligible for available chemotherapies such as gemcitabine with or without platinum?	
☐	☐	☐	2. Does the patient have local, locally-advanced, or metastatic disease documented as having shown progression on a scan (e.g., CT, MRI)?	
☐	☐	☐	3. Does the patient have measurable tumor according to RECIST 1.1 criteria with at least one unidimensionally measurable target lesion?	
☐	☐	☐	4. Does the patient have no evidence of biliary duct obstruction, unless obstruction is controlled by local treatment or, in whom the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to below 1.5x Upper Level of Normal (ULN)?	
☐	☐	☐	5. Is the patient free from acute toxic effects from previous treatment superior to grade 1 at the start of the study?	
☐	☐	☐	6. Does the patient have an ECOG performance status of 0 to 2?	
☐	☐	☐	7. Is the patient's expected survival greater than 3 months?	
☐	☐	☐	8. Is the patient a male or female age 18 years and older?	
☐	☐	☐	9. If the patient is a woman of child-bearing potential (i.e., pre-menopausal or not surgically sterile), does she agree to use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and agree to have a negative serum or urine pregnancy test within 1 week prior to treatment initiation?	
☐	☐	☐	10. If the patient is a fertile man, does he agree to practice effective contraceptive methods during the study, unless documentation of infertility exists?	

CCCWFU # 59212 **Eligibility Checklist**

☐	☐	☐	11. Does the patient have documentation (≤2 weeks) of the following laboratory values?: • Adequate hematologic (granulocyte count ≥1500/mm^3; white blood cell [WBC] ≥3500 cells/mm^3 or ≥3.5 bil/L; platelet count ≥100,000 cells/mm^3 or ≥100 bil/L; absolute neutrophil count [ANC] ≥1500 cells/mm^3 or ≥1.5 bil/L; and hemoglobin ≥9 g/dL or ≥90 g/L). • Adequate hepatic function (aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present), bilirubin ≤1.5x UNL). • Adequate renal function (serum creatinine ≤2.0 mg/dL or 177 µmol/L). • Adequate coagulation ("International Normalized Ratio or INR must be ≤1.5" unless on therapeutic blood thinners)	
☐	☐	☐	12. Is the patient free from evidence of active infection and no serious infection within the past month?	
☐	☐	☐	13. Is the patient mentally competent, able to understand and willing to sign the informed consent document?	
Yes	**No**	**N/A**	Exclusion Criteria (All responses must be **NO** in order to enter study)	
☐	☐	☐	1. Is the patient receiving any other standard or investigational treatment for their cancer, or have they received any other investigational agent for any indication within the past 2 weeks prior to initiation of CPI-613 treatment?	
☐	☐	☐	2. Does the patient have a serious medical illness that would potentially increase his or her risk for toxicity?	
☐	☐	☐	3. Does the patient have any active uncontrolled bleeding, or a bleeding diathesis (e.g., active peptic ulcer disease)?	
☐	☐	☐	4. Is the patient a pregnant woman, or a woman of child-bearing potential who is not using reliable means of contraception?	
☐	☐	☐	5. Is the patient a lactating female?	
☐	☐	☐	6. Is the patient a fertile man who is unwilling to practice contraceptive methods during the study period?	
☐	☐	☐	7. Is the patient's life expectancy less than 3 months?	
☐	☐	☐	8. Does the patient have any condition or abnormality which may, in the opinion of the investigator, compromise his or her safety?	
☐	☐	☐	9. Is the patient unwilling or unable to follow protocol requirements?	
☐	☐	☐	10. Does the patient experience dyspnea with moderate exertion?	
☐	☐	☐	11. Does the patient have clinically significant pleural or pericardial effusions?	

CCCWFU # 59212 **Eligibility Checklist**

☐	☐	☐	12. Does the patient have active heart disease including but not limited to symptomatic congestive heart failure, symptomatic coronary artery disease, symptomatic angina pectoris, symptomatic myocardial infarction, or symptomatic congestive heart failure?	
☐	☐	☐	13. Does the patient have a history of myocardial infarction that is <1 year prior to registration, or previous congestive heart failure (<1 year prior to registration) requiring pharmacologic support or with Left Ventricular Ejection Fraction <50%)?	
☐	☐	☐	14. Does the patient have a history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)?	
☐	☐	☐	15. Does the patient have evidence of active infection, or serious infection within the past month?	
☐	☐	☐	16. Does the patient have known HIV infection?	
☐	☐	☐	17. Does the patient have baseline troponin levels greater than the institutional limit of normal?	
☐	☐	☐	18. Will the patient have received cancer immunotherapy of any type within the past 2 weeks prior to initiation of CPI-613 treatment?	
☐	☐	☐	19. Does the patient require immediate palliative treatment of any kind, including surgery?	
☐	☐	☐	20. Has the patient received a chemotherapy regimen with stem cell support in the previous 6 months?	
☐	☐	☐	21. Does the patient have a history of prior illicit drug addiction?	
☐	☐	☐	22. Does the patient have any condition or abnormality which may, in the opinion of the investigator, compromise his or her safety?	

Signature: _____ Date: _____

Please send source documentation with Eligibility Form.

CCCWFU # 59212 **Protocol Registration Form**

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____
MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___
SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic
Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PAIFIC ISLANDER ☐ NATIVE AMERICAN
Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)
Surface Area: ___ ___.___m^2
Zip Code: ___ ___ ___ ___ ___
Primary Diagnosis: _____
Date of Diagnosis: ___ ___ /___ ___/___ ___
Performance Status : _____
Stage of Disease: _____

CURRENT DISEASE STATUS AT REGISTRATION: _____

Prior Therapies/ Protocol # if applicable	Start / End Date of Prior Therapy	Best Response (PROG, TE, STAB, ,NE, CR, PR, NE)	Date of Best Response	Date of Relapse	Duration of Best Response (in Months)
#1 _____	_____/_____	_____	_____	_____	_____
#2 _____	_____/_____	_____	_____	_____	_____
#3 _____	_____/_____	_____	_____	_____	_____
#4 _____	_____/_____	_____	_____	_____	_____

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___
MD Name (last) : _____
Date protocol treatment started: ___ ___ / ___ ___ / ___ ___
Informed written consent: ☐ YES ☐ NO
(consent must be signed prior to registration)
Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

CCCWFU # 59212 Eligibility Source Documentation Checklist
(to be submitted with Protocol Registration Form)

	Source Documents Needed	✓ or N/A
1	Pathology report confirming histologically and cytologically proven cholangiocarcinoma of any type	
2	Lab report documenting all initial required lab values	
3	Radiologic documentation that patient has local, locally-advanced, or metastatic disease that has shown progression	
4	Documentation of measurable tumor according to RECIST 1.1 criteria with at least one unidimensionally measurable target lesion	
5	Documentation that the patient is free of evidence of biliary duct obstruction (unless obstruction is controlled by local treatment) OR documentation that patinent's biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent bilirubin to below 1.5x ULN	
6	Documentation that the patient is free from acute toxic effects from previous treatment superior to grade 1	
7	Documentation of ECOG performance status of 0, 1 or 2	
8	Documentation of expected survival > 3 months	
9	Most recent H&P documenting patient is 18 – 80 years of age	
10	For female patients of childbearing potential, documentation that patient agrees to use accepted contraceptive methods during the study and to have a negative serum or urine pregnancy test within 1 week prior to initiation of treatment	
11	For male patients, documentation of infertility OR for fertile men, documentation that patient agrees to practice effective contraceptive methods during the study	
12	Lab report performed (≤ 2 weeks) documenting the following values: • Granulocyte count ≥1500/mm^3 • White blood cell ≥3500 cells/mm^3 or ≥3.5 bil/L • Platelet count ≥100,000 cells/mm^3 or ≥100 bil/L • Absolute neutrophil count ≥1500 cells/mm^3 or ≥1.5 bil/L • Hemoglobin ≥9 g/dL or ≥90 g/L • Aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL] • Alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present) • Bilirubin ≤1.5x UNL • Serum creatinine ≤2.0 mg/dL or 177 µmol/L • International Normalized Ratio or INR must be ≤1.5 unless on therapeutic blood thinners	
13	Documentation that the patient is free from evidence of active infection and has had no serious infection within the past month	
14	Documentation that the patient is mentally competent	
15	Copy of signed consent form	
16	Documentation that the patient is not currently receiving any other standard or	

	Source Documents Needed	✓ or N/A
	investigational treatment for their cancer, and has not received any other investigational agent for any indication within the past 2 weeks prior to initiation of treatment with CPI-613	
17	Documentation that the patient does not have a serious medical illness, condition, or abnormality that would potentially increase his or her risk for toxicity or compromise his or her safety	
18	Documentation that the patient does not have evidence of active uncontrolled bleeding or a bleeding diathesis	
19	Documentation that the patient is not pregnant, lactating, or (if a woman of childbearing potential) using a reliable means of contraception	
20	Documentation that the patient is not unwilling or unable to follow protocol requirements	
21	Documentation that the patient does not experience dyspnea with moderate exertion	
22	Documentation that the patient does not have clinically significant pleural or pericardial effusions	
23	Documentation that the patient does not have active heart disease including but not limited to: symptomatic congestive heart failure, symptomatic coronary artery disease, symptomatic angina pectoris, symptomatic myocardial infarction, or symptomatic congestive heart failure	
24	Documentation that the patient does not have a history of myocardial infarction that is <1 year prior to registration, or previous congestive heart failure (<1 year prior to registration) requiring pharmacologic support or with Left Ventricular Ejection Fraction <50%)	
25	Documentation that the patient does not have a history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)	
26	Documentation that the patient's albumin is <2.5 g/dL or <25 g/L	
27	Documentation that the patient does not have known HIV infection	
28	Documentation that the patient does not have baseline troponin levels greater than the institutional limit of normal	
29	Documentation that the patient has not received cancer immunotherapy of any type within the past 2 weeks prior to initiation of treatment with CPI-613	
30	Documentation that the patient does not require immediate palliative treatment of any kind, including surgery	
31	Documentation that the patient has not received a chemotherapy regimen with stem cell support in the previous 6 months	
32	Documentation that the patient does not have a history of prior illicit drug addiction	

APPENDIX B STRC SAE REPORTING GUIDELINES

Mandatory Safety and Toxicity Review Committee (STRC; Previously CROC) Serious Adverse Event (SAE) Notification Procedure

Mandatory STRC SAE Reporting Requirements – Revised 6/05/2012

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on CCCWFU Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI summary IV reporting guidelines, **CCCWFU Institutional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to them for review. All Clinical Research Management (CRM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone, followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO EVERYONE WORKING WITH CANCER CENTER INSTITUTIONAL PROTOCOLS.

What is considered an SAE under this mandatory procedure?

Any **unexpected grade 4** event not including routinely experienced events per protocol (e.g. myelosuppression) and **all grade 5 events** (death during protocol intervention) should be reported. The patient is considered "on-treatment" as defined in the protocol, which can extend days/weeks/months past the last date of actual protocol intervention.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx.

   This will ensure that all persons that the event applies to will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate persons on the STRC has been contacted.

4. Follow up with/update the clinical member of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the electronic STRC form:

1. ORIS Patient ID (PID)
2. Name of STRC Clinician notified/Date/Time/Comments.
3. Grade of event.
4. Is this related to protocol intervention or treatment?
5. Is suspension of the protocol needed?
6. Is any change to consent or protocol needed?
7. Was the nature or severity of the event unexpected?
8. Date of the event.
9. Brief description of the event using approved CTC version terminology.
10. Date of last study dose before event.
11. Relevant tests/labs.
12. **Most importantly make sure that the Investigator assigns attribution to the reported event (grade) using the appropriate CTCAE version for the protocol.**

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD – Director-at-Large, CCCWFU; Chair, PRC; Section Head, Hematology/Oncology

Glenn Lesser, MD – Hematology Oncology

Kathryn Greven, MD – Vice Chair – Radiation Oncology

Marissa Howard-McNatt, MD – General Surgery

Definition of Unavailable: As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting your STRC notification form. The important criteria is that have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made further communication directly with the investigator may be warranted. STRC reserves the right to agree with the investigator's assessment if STRC does not agree with the investigator STRC reserves the right to suspend the trial pending further investigation.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

APPENDIX C – CCCWFU ADVERSE EVENT LOG

Adverse Event Description	Cycle of Toxicity Onset	Start Date	Stop Date	AE Type	Grade (1-5) per CTC v. 4.0	Attribution	Dose Limiting Toxicity	Serious	Action Taken
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _______ ☐N/A
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _______ ☐N/A
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _______ ☐N/A
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _______ ☐N/A

Appendix D – Efficacy Assessment Form

ORIS PID: _____ **Date Completed:** ____ / ____ / ____

Visit Type: ☐ Pre-Study ☐ Cycle 1 Visit ☐ Cycle 2 Visit ☐ Cycle 3 Visit ☐ Cycle 4 Visit
☐ Cycle 5 Visit ☐ Cycle 6 Visit ☐ Cycle 7 Visit ☐ Cycle 8 Visit ☐ Cycle 9 Visit
☐ Cycle 10 Visit ☐ Cycle 11 Visit ☐ Cycle 12 Visit

☐ Other (Specify: _____)

ECOG Performance Status (Date Performed: ____ / ____ / ____):

☐ 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.

Date of CT (Chest/abdomen/pelvis): ____ / ____ / ____

CT (Chest/abdomen/pelvis) Result:

☐ Stable disease

☐ Mixed response

☐ Pseudo-progression (for 1st CT only)

☐ Partial response

☐ Progression of disease

Were new lesions identified on CT (Chest/abdomen/pelvis)? ☐ Yes ☐ No

Were the new lesions confirmed by biopsy? ☐ Yes ☐ No ☐ NA

Has this subject progressed? (As determined by the Principal Investigator) ☐ Yes ☐ No

Was tissue obtained for research purposes? ☐ Yes ☐ No

COMMENTS: _____
_____
_____

Appendix E – Withdrawal of Participation Form

ORIS PID _____ **Date Completed** ____ / ____ / ____

Name of person completing form _____

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Was the subject withdrawn from the study? Yes ☐ No ☐

Reasons for withdrawal: (*Check all that apply and provide additional information*)

☐ Patient exhibited progression of disease

- ☐ Patient exhibited progression of disease together with worsening of biliary function
- ☐ Exhibiting symptomatic progression
- ☐ Patient exhibit progression of disease which was confirmed after 2 additional treatment cycles

☐ Unacceptable toxicity from CPI-613

☐ Patient withdrawal of consent

- ☐ For just the primary intervention (CPI-613 administration only)
- ☐ For all components of the research study (including follow up in the medical record)

☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest

☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible

☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment

☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits

☐Termination of the clinical trial by the clinical sponsor

COMMENTS: _____
_____
_____

Appendix F - Post Study Bimonthly Telephone Follow Up Form

ORIS PID _____ **Date of Bimonthly Telephone Call** ____ / ____ / ____

Name of person completing form _____

What was the result of the telephone call?

☐ Call was unanswered

☐ Spoke directly with the subject

☐ Spoke to a family member

☐ Left a message

Comments:

_____

_____

Is this subject still living? Yes ☐ No ☐ Unknown ☐

If the subject has expired, list date of death: ____ / ____ / ____

Is the subject currently receiving or has received since coming off the 59212 study systemic chemotherapeutic cancer treatment? Yes ☐ No ☐

Type of cancer treatment being received (including the dose, dosing schedule and duration, if applicable and if known):

_____

Is the subject receiving radiation for cancer treatment? Yes ☐ No ☐

Type of radiation treatment being received:

_____

ECOG Performance Status:

☐ 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.

COMMENTS: _____

_____

_____