# A Phase II Trial of Systemic Chemotherapy (Gemcitabine and Cisplatin) in Combination with Conventional Transarterial Chemoembolization (cTACE) in Patients with Advanced Intra-Hepatic Cholangiocarcinoma (ICC)

**ClinicalTrials.gov#: NCT02994251**

**Version Date: 7/19/2018**

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**HIC Protocol #: 1603017367**

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**Protocol Revision Record**

Original Version: March 7, 2016

Protocol Amendment #1: April 27, 2017

Protocol Amendment #2: July 19, 2018

# Table of Contents

**Investigator Agreement Page**

Study Title: A Phase II Trial of Systemic Chemotherapy (Gemcitabine and Cisplatin) in Combination with Conventional Transarterial Chemoembolization (cTACE) in Patients with Advanced Intra-Hepatic Cholangiocarcinoma (ICC)

I confirm agreement to conduct the study in compliance with the protocol and all applicable regulations.

Investigator Name: _____

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## Schema/Synopsis

**Name of Sponsor:**

Todd Schlachter, MD (Investigator Initiated)

**Title of Study:**

A Phase II Trial of Systemic Chemotherapy (Gemcitabine and Cisplatin) in Combination with Conventional Transarterial Chemoembolization (cTACE) in Patients with Advanced Intra-Hepatic Cholangiocarcinoma (ICC)

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| **Anticipated Study Period (years):** | **Phase of Development:** |
|---|---|
| June 2016 – Dec 2019 (3.5 years) | Phase II |

**Abstract:**

Cholangiocarcinoma is a primary cancer of the bile ducts arising from malignant transformation of cholangiocytes, the epithelial cells that line the biliary apparatus. The disease is relatively uncommon, with an annual incidence of 5,000 new cases in the United States, but incidence rates are rising particularly in industrialized countries. The cause is not completely clear, but studies have shown an increasing prevalence of associated risk factors with chronic hepatic damage including alcoholic liver cirrhosis, non-alcoholic steatohepatitis, HCV infection, and diabetes.

Intrahepatic cholangiocarcinoma frequently presents as a mass lesion in the absence of jaundice or other constitutional symptoms, and treatment can revolve around resection, radiation, systemic chemotherapy, or intra-arterial directed therapies among others. However, the majority of patients are not eligible for curative treatments due to extent of disease. Patients who are not eligible for curative treatments for unresectable ICC may still benefit from locoregional therapy. Transarterial chemoembolization is already the most widely performed procedure for patients with unresectable hepatocellular carcinoma, and involves the periodic injection of a chemotherapeutic agent, mixed with an embolic material, into selected branches of the hepatic arteries feeding a liver tumor thus combining chemotherapy administration with intra-tumor ischemia.

Gemcitabine and platinum-based systemic chemotherapy regimens have been explored with encouraging results, but benefits for a combined approach in treating ICC have been found not only in combination with conventional TACE (Lipiodol-based transarterial chemoembolization), but also DEB-TACE (drug-eluting bead TACE) and radioembolization. These studies provide the foundation for the proposed protocol, demonstrating that TACE is a feasible, safe, and efficacious option for the treatment of advanced ICC.

**Hypothesis:**

We hypothesize that the addition of conventional TACE (cTACE) to standard chemotherapy will result in an improvement in PFS in patients with advanced, unresectable ICC, including patients with extra-hepatic disease.

**Advances in knowledge:**

Results of the study will be used to develop guidelines for the integration of TACE with standard chemotherapy in clinical practice for the treatment of patients with intrahepatic cholangiocarcinoma.

**Primary objective:**

- Evaluate the 12-month progression-free survival (PFS) rate in adult patients with intrahepatic cholangiocarcinoma after treatment with gemcitabine and cisplatin in combination with conventional TACE. Radiographic assessment of disease burden will be evaluated by mRECIST and qEASL using MRI taken after every 2 cycles of systemic chemotherapy.

**Secondary objectives:**

- Evaluation of overall survival (OS) of adult patients with advanced ICC treated with gemcitabine/cisplatin in combination with conventional TACE.
- Evaluation of the overall time to progression (TTP) and time to untreatable progression (TTUP) in liver lesions in adult patients with ICC treated with gemcitabine/cisplatin in combination with cTACE.
- Evaluation of toxicities of the gemcitabine and cisplatin regimen in combination with cTACE therapy in adult patients with advanced ICC. Toxicities to be assessed using CTCAE v5.0.
- Evaluate whether early changes in dynamic contrast-enhanced MRI (DCE-MRI) will correlate with long term PFS or OS, specifically as they relate to lesions targeted with cTACE therapy. Tumor response to be assessed by mRECIST and 3D volumetric assessments including qEASL and vRECIST.

**Study Design:**

The study will be a single-center, single-arm, Phase II study of gemcitabine and cisplatin in combination with conventional trans-arterial chemoembolization therapy in adult patients with advanced ICC. 25 patients will be enrolled over the course of 2 years, with an additional 1.5 years for patient follow-up.

**Treatment Synopsis:**

Eligible patients enrolled on study will receive a chemotherapy regimen of gemcitabine and cisplatin administered intravenously on Days 1 and 8 of a 21-day cycle. After every 2 cycles of systemic chemotherapy, patients will receive contrast-enhanced MRI to assess liver disease; conventional TACE will be performed as indicated based on this assessment. Patients will receive a maximum of 8 cycles of the gemcitabine/cisplatin combination. Up to 3 TACE treatments may be delivered in this same time frame, with the first TACE taking place after 2 cycles of systemic chemotherapy. Following the treatment period, patients will continue clinical follow-up at 3 month intervals until study exit at 18 months post the start of treatment.

**Diagnosis:**

Patients must have advanced, unresectable intrahepatic cholangiocarcinoma (ICC) defined as biopsy-confirmed adenocarcinoma in the liver, with an immunohistochemical profile consistent with a pancreatico-biliary primary, not involving the common bile duct or bifurcation, and not amenable to surgical resection. Patients must be eligible for the systemic gemcitabine and cisplatin regimen as well as fit the requirements for conventional transarterial chemoembolization. Patients are allowed up to 2 cycles of gemcitabine/cisplatin therapy performed as standard of care prior to enrollment on protocol. Disease must be liver-dominant with no other active malignancy within 2 years. Patients must have an ECOG performance status of 0-1 at study entry and a Child-Pugh class of A to B7 without significant liver decompensation.

**Inclusion Criteria:**

1. Patient is at least 18 years of age.
2. Patient has advanced, unresectable intrahepatic cholangiocarcinoma (ICC). Advanced, unresectable ICC is defined as biopsy-confirmed adenocarcinoma in the liver, with an immunohistochemical profile consistent with a pancreatico-biliary primary, not involving the common bile duct or bifurcation, and not amenable to surgical resection.
3. Eligible for conventional TACE as defined by local treatment guidelines.
4. Child-Pugh class of A to B7.
5. Adequate end-organ and bone marrow function as manifested as:
    - Hemoglobin ≥ 9 g/dL
    - Absolute neutrophil count ≥ 1500/$mm^3$
    - Creatinine ≤ 2.0 g/dL
    - AST and ALT ≤ 5 x ULN
    - Albumin ≥ 2.4 mg/dL
    - Total bilirubin ≤ 2.5 mg/dL
    - Platelets ≥ 100,000/$mm^3$
    - For TACE procedures, subjects are allowed to have platelets ≥ 75,000/$mm^3$.
6. Disease is liver-dominant with >70% of measurable disease burden within the hepatic parenchyma.
7. ECOG performance status of 0-1.
8. No other active malignancy within 2 years.
9. Women of child-bearing potential and men must agree to use adequate contraception prior to

study entry and for the duration of the study.
10. Ability to understand and willingness to sign a written informed consent document.

**Exclusion Criteria:**

1. Greater than 2 cycles of prior gemcitabine and/or cisplatin therapy for advanced ICC.
2. History of allergic reactions attributed to compounds of similar chemical or biological composition to gemcitabine, cisplatin, doxorubicin, or mitomycin-C.
3. Active treatment with CYP3A4 strong inhibitors or inducers.
4. Recent surgical procedure within 21 days of study enrollment precluding TACE or systemic therapy.
5. Severe and/or uncontrolled co-morbid medical conditions including, but not limited to, active infection, viral hepatitis, congestive heart failure, cardiac arrhythmia, unstable angina pectoris, and psychiatric illness or social circumstance that would limit compliance with study requirements.
6. Pregnancy during study duration.
7. Active immunosuppressive medications.
8. Presence of grade 2 or higher hepatic encephalopathy.
9. Complete occlusion of the entire portal venous system. Partial or branch portal vein occlusion allowed if without reversal of flow.
10. Radiotherapy within 21 days from treatment with study interventions or medications.
11. Current, recent (within 4 weeks of first infusion of this study), or planned participation in additional experimental drug.
12. Unstable angina.
13. New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix C).
14. History of myocardial infarction or CVA within 6 months prior to study enrollment.
15. Clinically significant peripheral vascular disease.
16. Inability to comply with study and/or follow-up procedures.
17. Life expectancy of less than 12 weeks.

**Statistical Considerations:**

The primary endpoint of this phase II study is the 12-month progression-free survival (PFS) in adult patients with ICC after treatment with gemcitabine and cisplatin in combination with conventional transarterial therapy. The currently used drug regimen in this patient population is expected to have a 12-month PFS rate of 20%. Alternatively, the experimental treatment will be considered worthy of further study if the PFS at 12 months is 40% or better.

Secondary endpoints include OS, TTP, TTUP, and toxicities. Correlations between early changes in DCE-MRI with long-term PFS or OS will be examined, specifically as related to lesions treated with cTACE therapy. This will include mRECIST, qEASL, and 3D volumetric assessments of tumor response on imaging.

## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| 5-FU | 5-Fluorouracil |
| ADL | Activities of Daily Living |
| AE/SAE | Adverse Event/Serious Adverse Event |
| AJCC | American Joint Committee on Cancer |
| ALKP | Alkaline phosphatase |
| ALT | Alanine transaminase |
| ANC | Absolute neutrophil count |
| APHI | Acute progressive hepatic insufficiency |
| AST | Aspartate transaminase |
| BTC | Biliary tract cancer |
| BUN | Blood urea nitrogen |
| CA 19-9 | Cancer antigen 19-9 |
| CBC | Complete blood count |
| CEA | Carcinoembryonic antigen |
| CMP | Complete metabolic panel |
| CR | Complete response |
| CRF | Case report form |
| CT scan | Computerized tomography scan |
| cTACE | Conventional transarterial chemoembolization |
| CVA | Cerebrovascular accident |
| DCE-MRI | Dynamic contrast-enhanced magnetic resonance imaging |
| DEBTACE | Drug-eluting bead transarterial chemoembolization |
| DSMB | Data Safety Monitoring Board |
| DSMC | Data Safety Monitoring Committee |
| EASL | European Association for the Study of the Liver |
| ECC | Extrahepatic cholangiocarcinoma |
| ECOG-PS | Eastern Cooperative Oncology Group – Performance Status |
| FDA | Food and Drug Administration |
| H&P | History and physical |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C Virus |
| HIC | Human Investigation Committee (Yale IRB) |
| HRPP | Human Research Protection Program |
| IAT | Intra-arterial therapy |
| ICC | Intrahepatic cholangiocarcinoma |
| ICH GCP | International Conference on Harmonization: Good Clinical Practice |
| IR | Interventional radiology |
| IRB | Institutional review board |
| mRECIST | Modified RECIST |
| NCI CTCAE | National Cancer Institute: Common Terminology Criteria for Adverse Events |
| NYHA | New York Heart Association |

| | |
|---|---|
| OS | Overall survival |
| PD | Protocol deviation |
| PD (tumor response) | Progressive disease |
| PFS | Progression-free survival |
| PHI | Protected health information |
| PI | Principal investigator |
| PR | Partial response |
| PRC | Protocol Review Committee |
| PT/INR | Prothrombin time/International normalized ratio |
| PVA particles | Polyvinyl alcohol particles |
| qEASL | Quantitative EASL |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SD | Stable disease |
| TACE | Transarterial chemoembolization |
| TAE | Transarterial embolization |
| TTP | Time to progression |
| TTUP | Time to untreatable progression |
| UICC | Union for International Cancer Control |
| ULN | Upper limit of normal |
| UPIRSOs | Unanticipated Problems Involving Risks to Subjects and Others |
| WBC | White blood count |
| Y-90 | Yttrium-90 |
| YCC | Yale Cancer Center |

# 1. Introduction: Background Information and Scientific Rationale

## 1.1. Study Disease: Intrahepatic Cholangiocarcinoma

Cholangiocarcinoma is a primary cancer of the bile ducts arising from malignant transformation of cholangiocytes, the epithelial cells that line the biliary apparatus. Cholangiocarcinoma are encountered in three anatomic regions along the biliary tract: as intrahepatic (ICC), hilar/perilhilar (Klatskin) which occur at the bifurcation of the left and right hepatic ducts, and as distal extrahepatic. The disease is relatively uncommon, with an annual incidence of 5,000 new cases in the United States. Worldwide, it accounts for 3% of all gastrointestinal cancers (1). Specifically regarding ICC, incidence data from the American Cancer Society are somewhat difficult to interpret as both ICC and primary hepatocellular carcinoma (HCC) are classified within one group, with about 33,190 cases diagnosed and 23,000 cancer-related deaths in 2014 (2). Registry data suggests that about 10-15% of these cases are truly ICC. Incidence rates of ICC are rising, particularly in industrialized countries, and though the cause is not completely clear (3) studies have shown an increasing prevalence of associated risk factors with chronic hepatic damage including alcoholic liver cirrhosis, non-alcoholic steatohepatitis, HCV infection, and diabetes (4).

Cholangiocarcinoma of the proximal or distal bile duct often presents with features of biliary obstruction. In contrast, ICC occurs within the hepatic parenchyma where it frequently presents as a mass lesion in the absence of jaundice or other constitutional symptoms. As such, it was traditionally staged according to HCC criteria; but with recent developments necessitating the distinction between HCC and ICC, the 7$^{th}$ edition of the AJCC/UICC staging manual reflects new guidelines for staging intrahepatic bile duct cancers. One of the new updates is eliminating tumor size as a prognostic factor. T-classification is instead based on number of lesions, vascular invasion, intrahepatic metastasis, and invasion into adjacent structures which were better discriminatory predictors of survival (5). On imaging, ICC typically appears hypointense on T1-weighted MRI and hyperintense on T2-weighted images. Dynamic CT scanning can help differentiate between intrahepatic cholangiocarcinoma and hepatocellular carcinoma: up to 81% of ICC are characterized by progressive contrast uptake from arterial to venous, and HCC is characterized by rapid enhancement during the arterial phase and washout in venous or delayed phases (6). Radiological assessments of ICC are often insufficient for diagnosis other than in non-cirrhotic patients who will undergo surgical resection; pathological diagnosis is required in most cases.

Curative options such as hepatic resection exist for cholangiocarcinoma patients, but unfortunately most present with unresectable disease with a survival rate of less than 12 months following diagnosis (7). ICC in particular is generally associated with lower resectability and curability when compared to other hepatobiliary malignancies (8). Liver transplantation for cholangiocarcinoma has historically been controversial by being associated with disease recurrence and poor survival rates, but may be improved with careful patient selection (9).

For patients not eligible for resection or transplant, therapeutic options include external beam radiation therapy, locoregional procedures (transarterial chemoembolization or TACE, radioembolization, ablation), molecular targeting, and chemotherapy among others. Due to the small number of patients

and the heterogeneous patient population in biliary tract cancers as compared with other more common malignancies, randomized phase III studies examining systemic chemotherapy and other treatments have been a challenge to conduct. However, based on current experience from phase II studies, systemic chemotherapy has improved from traditional fluoropyrimidine-based regimens that have response rates of only 10% to 30% to gemcitabine-based combination regimens with response rates in the range of 22% to 50% (10). Molecularly targeted agents that inhibit angiogenesis and epidermal growth factor receptor pathways have recently started to enter clinical trials for unresectable ICC, but none have shown to improve patient survival as of yet. Most clinical practitioners based their treatment paradigms on the ABC-02 trial completed in 2009 which confirmed the combination of gemcitabine and cisplatin as the standard first line therapy for cases of advanced biliary tract cancers (11). This combination therapy yielded a median progression-free survival of 8.0 months but did not stratify the patients based on intrahepatic cholangiocarcinoma vs extrahepatic cholangiocarcinoma due to small numbers in each group.

Despite the observation that growth in the primary tumor is the first site of disease progression in 70% of ICC cases, there is no approved liver-directed therapy for this disease. Therefore, we hypothesize that the addition of conventional transarterial chemoembolization to standard chemotherapy will result in an improvement in PFS in patients with advanced, unresectable ICC, including patients with extra-hepatic disease.

### 1.2. Chemotherapy: Gemcitabine and Cisplatin for Cholangiocarcinoma

Patients with advanced ICC are under-represented in clinical trials, and have traditionally been assimilated in studies of biliary tract cancers with extra-hepatic cholangiocarcinoma (ECC) and gallbladder cancer due to small patient population. As a result, conducting trials to develop an effective chemotherapy regimen presented many challenging obstacles that needed to be overcome. The first trial to demonstrate increased overall survival and quality of life using systemic chemotherapy over best supportive care in patients with advanced pancreatic and biliary cancer utilized a combination of 5-fluorouracil plus leucovorin and etoposide therapy (12). Another trial looked at a combination of 5-FU, mitomycin-C, and doxorubicin in 17 patients and found 31% of the patients had measurable tumor response (13). In another trial comprised of two consecutive studies, both gemcitabine therapy and a combination of 5-FU, leucovorin, and mitomycin-C were found to be feasible, although the studies lacked patients with impaired liver function (14).

Since then, several studies have looked at treatment regimens for biliary tract and gallbladder cancer. In a multicenter phase II study in the treatment of BTC examining single-agent gemcitabine or in combination with levofolinic acid and IV 5-FU, Gebbia noted that single-agent gemcitabine is active against advanced, unresectable BTC with a partial response recorded in 4 cases (22%) with a median duration of 4.5 months. Stable disease was seen in 5 cases (28%) and toxicities were mild with no severe grade 4 toxicities (15). Gemcitabine was also used in a phase II study as part of a regimen in combination with cisplatin for patients with gallbladder cancer: median overall survival was 20 weeks with 1-year survival rate of 18.6% (16). 4 (13.3%) of the patients were complete responders with

disappearance of all disease, 7 (23.3%) partial responders, and 7 (23.3%) patients had stable disease. The authors concluded that the gemcitabine and cisplatin combination was well tolerated and active in this disease profile. A study looking at chemotherapy in comparison with best supportive cancer in gall bladder cancer concluded not only the efficacy of chemotherapy in improving overall survival and progression-free survival over best supportive care, but the superiority of the gemcitabine and oxaliplatin combination over fluorouracil and folinic acid (17). By RECIST criteria, the disease response rate was 30.7% (7.7% complete response and 23.1% partial response) in the gemcitabine/oxaliplatin arm.

Gemcitabine's efficacy in the treatment of advanced BTC along with its favorable toxicity profile has been exemplified in numerous other clinical trials. A review of gemcitabine regimens as a single agent and in combination with other chemotherapeutic drugs noted remarkable tolerance for gemcitabine, with less than 5% of patients experiencing grade 4 hematological toxicities (18). In Japan where one of the prominent treatments is with S-1 (tegafur/gimeracil/oteracil), a multi-center retrospective analysis of chemotherapy for unresectable biliary tract cancer concluded that gemcitabine was the most effective treatment studied with a reduction in mortality of 50% (19). Chemotherapy regimens examined in this study were 5-FU based regimens; S-1 alone; gemcitabine alone; 5-FU, doxorubicin, and mitomycin-C; and cisplatin-based regimens. Cisplatin was also found to reduce mortality by 40% albeit with more toxicities, and future studies examining a combination of gemcitabine and cisplatin were recommended. With its unique mechanism of action and low toxicity profile, gemcitabine is seen to be safe to combine with other drugs (20).

While gemcitabine is grounded as a treatment option for advanced BTC, the role and identity of a combinatory chemotherapeutic drug is more debatable. The EORTC trial (21) was the first randomized study to evaluate a combination chemotherapy regimen with platinum-based compounds for the treatment of BTC. The trial compared high-dose 5-FU vs 5-FU, folinic acid, and cisplatin and found an improved response rate in the combination therapy. On the 5-FU arm, no patients expressed a complete response and 7% a partial response; the combination arm had an improved objective response rate (4% for complete response and 15% for partial response), as well as an increase in overall median survival (8.0 months compared to 5.0 months on the high-dose 5-FU arm). A Phase III study comparing 5-FU, etoposide, leucovorin vs epirubicin, cisplatin, 5-FU as first-line therapy for patients with advanced BTC failed to enroll enough subjects to detect a significant difference between the two regimens. However, the patients on the epirubicin/cisplatin/5-FU regimen produced similar response rate, symptom resolution, and failure-free survival as the other arm but with significantly less acute toxicity (22). The combination of gemcitabine and docetaxel was examined in another study that reported an overall median survival rate of 11 months for patients with gallbladder, biliary, or cholangiocarcinomas (23).

Of the various combinations of gemcitabine, platinum-based compounds showed the most promise with improved response rate over gemcitabine monotherapy and increased progression free survival over 5-FU and other therapies (24-26). Oxaliplatin and cisplatin are the most commonly seen additions: gemcitabine/oxaliplatin chemotherapy is frequently used due to easier administration of oxaliplatin, but gemcitabine/cisplatin may have a short survival advantage (27). Part of this may be due to a synergistic

interaction between cisplatin and gemcitabine related to reduced DNA repair, as the combination did not cause any additive DNA damage than gemcitabine alone (28). This leads to a synergistic or additive effect found both in vitro and in vivo; but is time-dependent and thus dependent on the scheduling of both drugs (29).

Numerous Phase II trials have been conducted investigating the efficacy, safety, dosage and administration of the gemcitabine and cisplatin combination treating patients with biliary tract cancer: generally, results have been improved tumor response and overall survival compared to other treatment options with low to moderate toxicities (30-37). The studies that have established the gemcitabine and cisplatin treatment for cholangiocarcinomas were the Phase II ABC-01 and subsequent Phase III ABC-02 trials performed in the UK (10, 38). These two studies examined the gemcitabine and cisplatin combination against gemcitabine monotherapy and found that the combination lead to significantly improved progression-free survival of 8.0 months compared to 5.0 months on monotherapy, and overall median survival of 11.7 months to 8.1 months. Tumor control (complete response plus partial response plus stable disease) was achieved in 131 (81.4%) of patients in the combination therapy and 102 (71.8%) on monotherapy. The effectiveness of gemcitabine and cisplatin over gemcitabine alone were also supported by the BT22 Phase II study in Japan (39). Disease control rate was 68.3% for the combination and 50.0% for monotherapy. Median survival and progression-free survival were both superior on the combination arm, at 11.2 months and 5.8 months respectively compared to 7.7 months and 3.7 months on the monotherapy arm. With both ABC-01/ABC-02 and BT22 trials showing superior outcomes with combination therapies despite different risk factors for BTC in Western and East Asian populations, gemcitabine/cisplatin became an accepted standard of treatment for cholangiocarcinoma (40).

### 1.3. Transarterial Chemoembolization for Intrahepatic Cholangiocarcinoma

Patients who are not eligible for curative treatments for unresectable intrahepatic cholangiocarcinoma may still benefit from locoregional therapy. Transarterial chemoembolization is already the most widely performed procedure for patients with unresectable hepatocellular carcinoma, and involves the periodic injection of a chemotherapeutic agent, mixed with an embolic material, into selected branches of the hepatic arteries feeding a liver tumor thus combining chemotherapy administration with intra-tumor ischemia. The rationale for conventional TACE is that the infusion of drugs such as doxorubicin, mitomycin-C, and cisplatin suspended in an oily medium followed by embolization of the blood vessel with embolic agents will reduce arterial blood supply to the tumor allowing greater delivery of the chemotherapy and thus causing necrosis of the tumor. In HCC, TACE has been shown to deliver up to 400 times the intra-hepatic concentration of chemotherapy in comparison to intravenous administration depending on the chemotherapeutic agent (41). As such, tissue levels of chemotherapy within the tumor were found to be 40 times of that found in surrounding normal hepatic tissue. Embolization of a branch of the hepatic artery after the administration of chemotherapy results in the detection of the chemotherapeutic agent within the tumor of upwards of several months post administration (42-44).

Early studies suggested prolonged survival in patients treated with arterial chemotherapy infusion therapy. One study examined arterial chemoinfusion in the context of 3 different chemotherapy regimens: 8 patients with 5-FU, Adriamycin or epirubicin, mitomycin C, and/or cisplatin; 1 patient with 5-FU; 2 patients with 5-FU and cisplatin (45). A greater than 50% decrease in tumor size was seen in 5 (45.5%) out of 11 patients, with 2 (18.2%) patients exhibiting a minor response of 25-50% tumor decrease in size, 2 patients with stable disease, and 2 patients that had progressed. Mean survival period was 26.0 months.

With the effectiveness of TACE in improving survival for patients with unresectable HCC (46, 47) along with previous studies showing potential for intra-arterial treatment of cholangiocarcinoma, Burger, et al, examined 17 patients with unresectable cholangiocarcinoma that were treated with TACE (48). 15 of the 17 patients were treated with conventional TACE consisting of a mixture of cisplatin, doxorubicin, and mitomycin-C emulsified in Lipiodol before embolization with polyvinyl alcohol or Embosphere particles. One of the remaining 2 patients received two cisplatin hepatic arterial infusions before starting on the standard cTACE therapy, and the last received a mixture of cisplatin and Lipiodol for the first procedure before the standard therapy. Estimated median survival was 23 months from date of diagnosis, and 7 of 9 patients still alive had evidence of significant tumor necrosis without progression on MR imaging. Tumor response by RECIST criteria was not very demonstrated, although this may be due to RECIST criteria being based on tumor size, whereas TACE does not usually result in tumor size reduction (49). Nevertheless, 79% of the patients showed significant tumor necrosis, and the procedure was well-tolerated by the patients with 9 (53%) experiencing no side effects, and 5 (29%) experienced common transient post-embolization symptoms that quickly resolved. Another study demonstrating promise of TACE in ICC patients was conducted by Kiefer et al, which presented elevated survival outcomes (50). 62 patients were treated on study with a chemoembolization mixture of Lipiodol, mitomycin-C, doxorubicin, and cisplatinum followed by PVA particles: 37 with pathologically proven cholangiocarcinoma and 25 with poorly differentiated adenocarcinoma of unknown primary but likely to be cholangiocarcinoma. By RECIST criteria, 5 (11%) exhibited partial response, 29 (64%) stable disease, and 11 (24%) with progression of disease. Median survival was found to be 20 months from time of diagnosis; 1-year survival was 75%, 2-year survival 39%, and 3-year survival 17%.

A multivariate analysis evaluating the clinical efficacy of chemoembolization or arterial chemoinfusion for unresectable ICC looked at 49 patients and found tumor vascularity to be the only significant factor associated with success after TACE for ICC out of tumor size and treatment group (51). For survival, tumor size, vascularity, and Child-Pugh class were found to be independent factors. The authors also noted that a large percentage of their patients demonstrated hypervascularity on angiography in the area of the disease similar to other studies (49, 52), concluding that TACE could be effective palliative treatment for these cases. When compared to supportive therapy for unresectable ICC, TACE was found to result in significantly greater survival benefits with a median survival of 12.2 months compared to 3.3 months when treated with symptomatic relief (53). Within the subgroup of patients who received TACE therapy, survival rates were significantly higher in those that showed objective tumor response to TACE (median survival of 22 months) compared to those who showed no response to TACE (median of 10.9 months).

Gemcitabine-based regimens for conventional TACE were explored in a single-institute study performed by Gusani, et al (54). 42 patients with unresectable cholangiocarcinoma were treated: 18 received gemcitabine only; 2 with gemcitabine followed by cisplatin; 4 with gemcitabine followed by oxaliplatin; 14 with gemcitabine and cisplatin in combination; and 4 with gemcitabine and cisplatin, followed by oxaliplatin. Based on RECIST criteria, 20 patients were found to have stable disease, 15 patients had progressive disease, and 7 patients were not evaluable. Median overall survival from the date of first TACE was 9.1 months; however, there was significant variation by response to TACE and by regimen. For patients who had stable disease, the median survival was 13.1 months post-TACE in contrast to patients who had progressive disease with a median survival of 6.9 months. By TACE regimen, there was a statistically significant increase in survival for patients receiving gemcitabine-cisplatin combination (13.8 months) to those receiving gemcitabine alone (6.3 months).

Another trial with varying TACE-regimens in the context of intrahepatic cholangiocarcinoma examined retrospectively a total of 115 patients with unresectable ICC (55): 24 patients were treated with mitomycin-C only; 8 with gemcitabine-only; 54 with gemcitabine-mitomycin-C; and 29 with gemcitabine, mitomycin-C, and cisplatin. Median and mean survival times from start of TACE treatment were 13 and 20.8 months respectively: 1-year survival rate was 52%, 2-year 29%, and 3-year 10%. By RECIST criteria, 8.7% (10/115) patients achieved partial response, 57.4% stable disease, and 33.9% progressive disease.

Our group has published a retrospective analysis of almost 200 patients with intrahepatic cholangiocarcinoma who underwent some form of intra-arterial therapy at one of five participating academic institutions (56). This analysis covered a 20 year period up to 2012, and comprised patients with a median age of 61 years, about half of whom had a solitary lesion in the liver with a median tumor size of 8.1 cm. Most of these patients were treated with conventional TACE (64.7%), with smaller numbers receiving Y-90 radioembolization (23.2%), drug-eluting bead (DEB-TACE 5.6%), or bland embolization (TAE 6.6%). Two-thirds of these patients underwent at least two separate IAT sessions, with younger patients, and those with multifocal or bulkier tumors more likely to receive multiple sessions. Treatments were generally associated with a low morbidity, and only 30% of patients developed a post-procedure complication. 8% of patients developed a more significant complication, requiring extensive medical or surgical intervention. Encouraging tumor responses were observed in this patient population, with 25% exhibiting a partial or complete response, and 60% exhibiting stable disease per mRECIST criteria. Responses did correlate well with overall survival in this retrospective study, and the median OS for the cohort was 13.2 months, with a 1-year survival of 54%. Those patients achieving a complete or partial response to initial therapy had a median OS of 32.4 months.

### 1.4. Combination of TACE and Systemic Chemotherapy for Intrahepatic Cholangiocarcinoma

There have been few studies that sought to combine both systemic chemotherapy and trans-arterial therapies in the treatment of ICC. For hepatocellular carcinoma, Jang, et al conducted a retrospective, 2 arm study of 52 patients with unresectable HCC: one arm was treated with transarterial infusion of

cisplatin and epirubicin, systemic infusion of 5-FU, and additional percutaneous ethanol injection; the other received transarterial infusion with doxorubicin followed by embolization with Gelfoam (57). Objective tumor response was increased in the combination arm (53.3%) compared to the monotherapy arm (22.7%), although no complete responses were observed on either arm. Overall survival was also elevated on the combination arm, with survival rates for 6, 12, 18, and 24 months at 90%, 57%, 27%, and 17% respectively; for the doxorubicin group, they were 73%, 37%, 7%, and 0%. As such, the combination therapy appeared to be feasible and possibly confer a survival benefit, although it should be noted that the patients in this study were in a more advanced stage with regards to tumor burden, and a high proportion of the patients had portal vein thrombosis.

In 2005, Kirchhoff, et al, conducted a prospective single arm study of 8 patients with nonresectable cholangiocarcinoma with gemcitabine and conventional TACE (58). Both systemic and locoregional therapies were well-tolerated, with nausea and vomiting were the most common toxicities experienced by patients; no severe toxicities were reported. In terms of imaging response, 5 patients had stable disease and 3 patients had progressive disease. The median time to tumor progression was 7 months (range 3-18), and overall survival was 12 months. The authors conclude that in patients with ICC, regional chemoembolization in addition to a systemic gemcitabine regimen is well-tolerated, and may enhance the palliative effect of systemic therapy alone.

A retrospective study conducted by Li, et al, examined 66 patients with unilateral, advanced Wilms tumors divided into 3 treatment arms: pre-operative systemic therapy, pre-operative conventional TACE, and the combination of pre-operative cTACE and systemic chemotherapy (59). Patients treated with the combination therapy demonstrated a significant improvement in response over the systemic therapy alone, with 72.0% being good responders (at least 40% reduction in tumor volume) compared to only 35% in the systemic arm. The 2-year relapse-free survival rates were found to be 65.0% in the systemic arm, 80.9% in the TACE arm, and 100.0% in the combination group.

Generally, response rates and survival for ICC appear to be higher for intra-arterial and TACE therapies than those with systemic chemotherapy regimens (60). Benefits for a combined approach in treating liver lesions have been found not only in cTACE combinations, but also studies that utilized DEBTACE or radioembolization (61-67). Our experiences with ICC and past studies provide the foundation for the proposed protocol, demonstrating that IAT is a feasible, safe, and efficacious option for the treatment of advanced ICC, and opening the possibility of improved survival over that seen with systemic therapy alone.

## 2. Study Objectives

### 2.1. Primary Objectives/Endpoints

The primary objective of this study is to evaluate the 12-month progression-free survival (PFS) rate in adult patients with intrahepatic cholangiocarcinoma (ICC) after treatment with gemcitabine and cisplatin in combination with conventional TACE. This is the percentage of patients alive and free of

progression at 12-months from enrollment on study. Radiographic assessment of disease burden will be evaluated by mRECIST and qEASL using an MRI scan obtained at the IR clinic visit.

### 2.2. Secondary Objectives/Endpoints

Secondary objectives include:

- Evaluation of overall survival (OS) of adult patients with advanced ICC treated with gemcitabine and cisplatin in combination with conventional TACE. Overall survival is the time from enrollment on study until death of the patient from any cause.
- Evaluate the overall time to progression (TTP) and time to untreatable progression (TTUP) in liver lesions in adult patients with ICC treated with gemcitabine and cisplatin in combination with conventional TACE. Overall TTP is the time from enrollment on study until radiographic evidence of overall disease progression. TTUP in liver lesions is measured from the time of initiation on cTACE therapy until radiographic evidence of disease progression in targeted lesions. Radiographic assessment will be evaluated by mRECIST using MRI every 2 cycles after intra-arterial therapy.
- To evaluate the toxicities of the gemcitabine and cisplatin regimen in combination with cTACE therapy in adult patients with advanced ICC. Safety will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Incidence of adverse events, serious adverse events, changes in baseline vital signs, ECOG performance status, and laboratory data (hematologic, liver and kidney function) will be assessed.
- Evaluate whether early changes in dynamic contrast-enhanced MRI (DCE-MRI) will correlate with long term PFS or OS, specifically as they relate to lesions targeted with cTACE therapy. Pre- and post-treatment images will be analyzed for 3D volumetric functional analysis in arterial and venous phases with tumor assessments by mRECIST, qEASL, and 3D volumetric response criteria.

## 3. Study Enrollment and Withdrawal

### 3.1. Subject Selection

Patients must have advanced, unresectable intrahepatic cholangiocarcinoma (ICC) defined as biopsy-confirmed adenocarcinoma in the liver, with an immunohistochemical profile consistent with a pancreatico-biliary primary, not involving the common bile duct or bifurcation, and not amenable to surgical resection. Patients must be eligible for the systemic gemcitabine and cisplatin regimen as well as fit the requirements for conventional transarterial chemoembolization. Patients are allowed up to 2 cycles of gemcitabine/cisplatin therapy performed as standard of care prior to enrollment on protocol. Disease must be liver-dominant with no other active malignancy within 2 years. Patients must have an ECOG performance status of 0-1 (Appendix A) at study entry and a Child-Pugh class of A to B7 without significant liver decompensation (Appendix B).

Patients who drop out or have incomplete follow-up will be treated as a treatment failure. There will not be replacement patients.

### 3.2. Subject Inclusion Criteria

In order to be eligible to participate in this study, the prospective participant must meet all of the following inclusion criteria:

1. Patient is at least 18 years of age.
2. Patient has advanced, unresectable intrahepatic cholangiocarcinoma (ICC). Advanced, unresectable ICC is defined as biopsy-confirmed adenocarcinoma in the liver, with an immunohistochemical profile consistent with a pancreatico-biliary primary, not involving the common bile duct or bifurcation, and not amenable to surgical resection.
3. Eligible for conventional TACE as defined by local treatment guidelines.
4. Child-Pugh class of A to B7.
5. Adequate end-organ and bone marrow function as manifested as:
    - Hemoglobin ≥ 9 g/dL
    - Absolute neutrophil count ≥ 1500/$mm^3$
    - Creatinine ≤ 2.0 g/dL
    - AST and ALT ≤ 5 x ULN
    - Albumin ≥ 2.4 mg/dL
    - Total bilirubin ≤ 2.5 mg/dL
    - Platelets ≥ 100,000/$mm^3$
    - For TACE procedures, subjects are allowed to have platelets ≥ 75,000/$mm^3$.
6. Disease is liver-dominant with >70% of measurable disease burden within the hepatic parenchyma.
7. ECOG performance status of 0-1.
8. No other active malignancy within 2 years.
9. Women of child-bearing potential and men must agree to use adequate contraception prior to study entry and for the duration of the study.
10. Ability to understand and willingness to sign a written informed consent document.

### 3.3. Subject Exclusion Criteria

Subjects must not have any of the following exclusion criteria in order to participate in this study:

1. Greater than 2 cycles of prior gemcitabine and/or cisplatin therapy for advanced ICC.
2. History of allergic reactions attributed to compounds of similar chemical or biological composition to gemcitabine, cisplatin, doxorubicin, or mitomycin-C.
3. Active treatment with CYP3A4 strong inhibitors or inducers.

4. Recent surgical procedure within 21 days of study enrollment precluding TACE or systemic therapy.
5. Severe and/or uncontrolled co-morbid medical conditions including, but not limited to, active infection, viral hepatitis, congestive heart failure, cardiac arrhythmia, unstable angina pectoris, and psychiatric illness or social circumstance that would limit compliance with study requirements.
6. Pregnancy during study duration.
7. Active immunosuppressive medications.
8. Presence of grade 2 or higher hepatic encephalopathy.
9. Complete occlusion of the entire portal venous system. Partial or branch portal vein occlusion allowed if without reversal of flow.
10. Radiotherapy within 21 days from treatment with study interventions or medications.
11. Current, recent (within 4 weeks of first infusion of this study), or planned participation in additional experimental drug.
12. Unstable angina.
13. New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix C).
14. History of myocardial infarction or CVA within 6 months prior to study enrollment.
15. Clinically significant peripheral vascular disease.
16. Inability to comply with study and/or follow-up procedures.
17. Life expectancy of less than 12 weeks.

### 3.4. Subject Registration Process

All patients would be seen for an initial clinic visit, where a clinician would present all appropriate treatment options. If the patient expresses an interest in this study, a member of the study team designated to consent patients would discuss the protocol in greater detail explaining the risks and benefits of the study, and obtain informed consent form the patient or a legally acceptable representative. Imaging, laboratory results, and medical history will be used as part of the screening process to determine the patient's eligibility for the study.

Patients consented for the study will be registered with OnCore, Yale's Clinical Trials Management System, and be assigned a study identifier and counted for the final data analysis. Patients' progress while on the study will be managed via OnCore.

### 3.5. Subject Withdrawal

A study participant may be removed from the study for any of the following reasons:

- At the request of the patient or a representative, i.e., withdrawal of consent
- Unmanageable toxicities related to the study drugs

- Significant extrahepatic disease progression
- Substantial non-compliance with the requirements of the study
- Reached Time to Untreatable Progression (TTUP) where TTUP is defined as disease progression beyond the scope of further intra-arterial therapy, which includes: overt extra-hepatic progression to the extent that extrahepatic disease is greater than 30% of the global tumor burden, development of clinically significant ascites, markedly abnormal liver function tests, complete absence of portal venous blood flow, and deteriorated performance status (greater than ECOG 2)
- Concomitant illness that prevents further participation
- Use of illicit drugs or other substances that may, in the opinion of the investigator, contribute to toxicity

### 3.6. Premature Termination or Suspension of Study

The investigator has the right to close the study, at any time, although this should occur only after consultation between involved parties. The Institutional Review Board (IRB) and associated Ethics Committees must be informed. Events that may trigger a premature termination of a study include, but are not limited to: new toxicity finding, results of any interim analysis, completed accrual and follow-up of patients, non-compliance with the protocol, change in development plans for the study drug, slow recruitment, or poor quality data.

## 4. Study Design/Investigational Plan

### 4.1. Overview

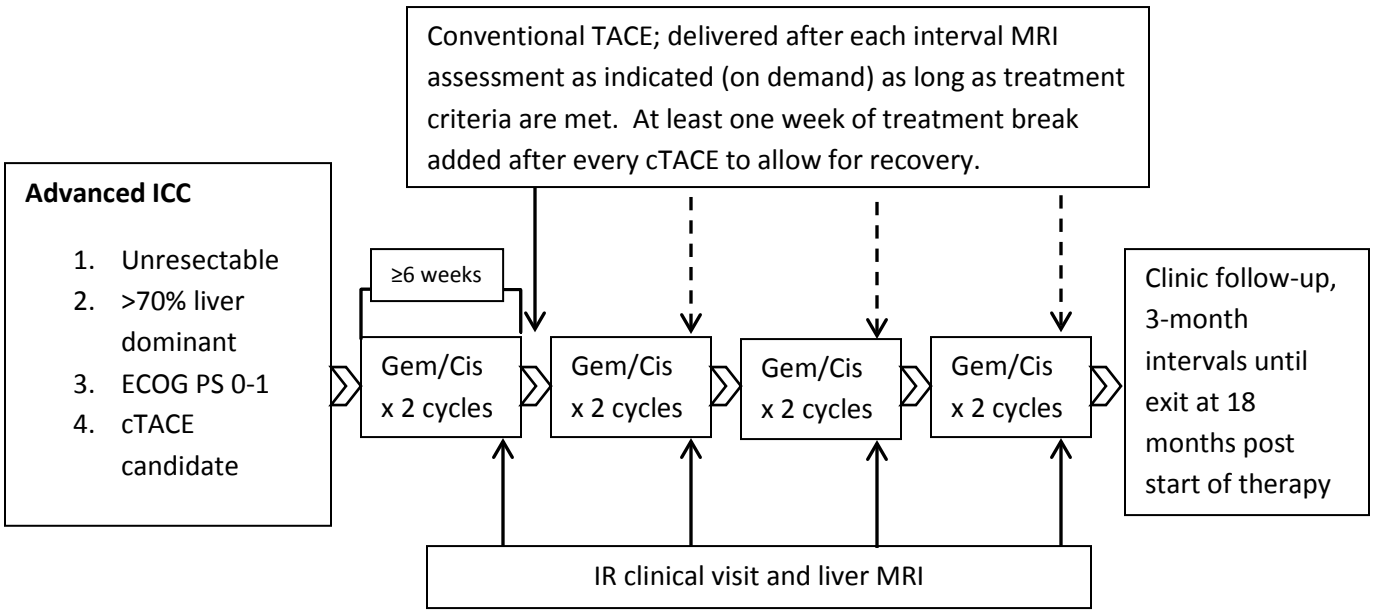
The study will be a single-center, single-arm, Phase II study of gemcitabine and cisplatin in combination with conventional trans-arterial chemoembolization therapy in adult patients with advanced ICC. 25 patients will be enrolled over the course of 2 years, with an additional 1.5 years for patient follow-up.

Eligible patients enrolled on study will receive a chemotherapy regimen of gemcitabine and cisplatin administered intravenously on Days 1 and 8 of a 21-day cycle. After every 2 cycles of systemic chemotherapy, patients will receive contrast-enhanced MRI to assess liver disease; conventional TACE will be performed as indicated based on this assessment. Patients will receive up to a maximum of 8 cycles of the gemcitabine/cisplatin combination on study protocol. Patients are allowed up to 2 cycles of gemcitabine/cisplatin therapy performed as standard of care prior to enrollment on protocol. Up to 3 TACE treatments may be delivered in the initial six months. Following the treatment cycle, patients will continue clinical follow-up at 3 month intervals until study exit at 18 months post the start of treatment.

We hypothesize that the addition of conventional TACE therapy to standard chemotherapy will result in an improvement in PFS for patients with advanced unresectable ICC, even those patients with extrahepatic disease.

### 4.2. Study Schedule

**Schema: Treatment Overview**



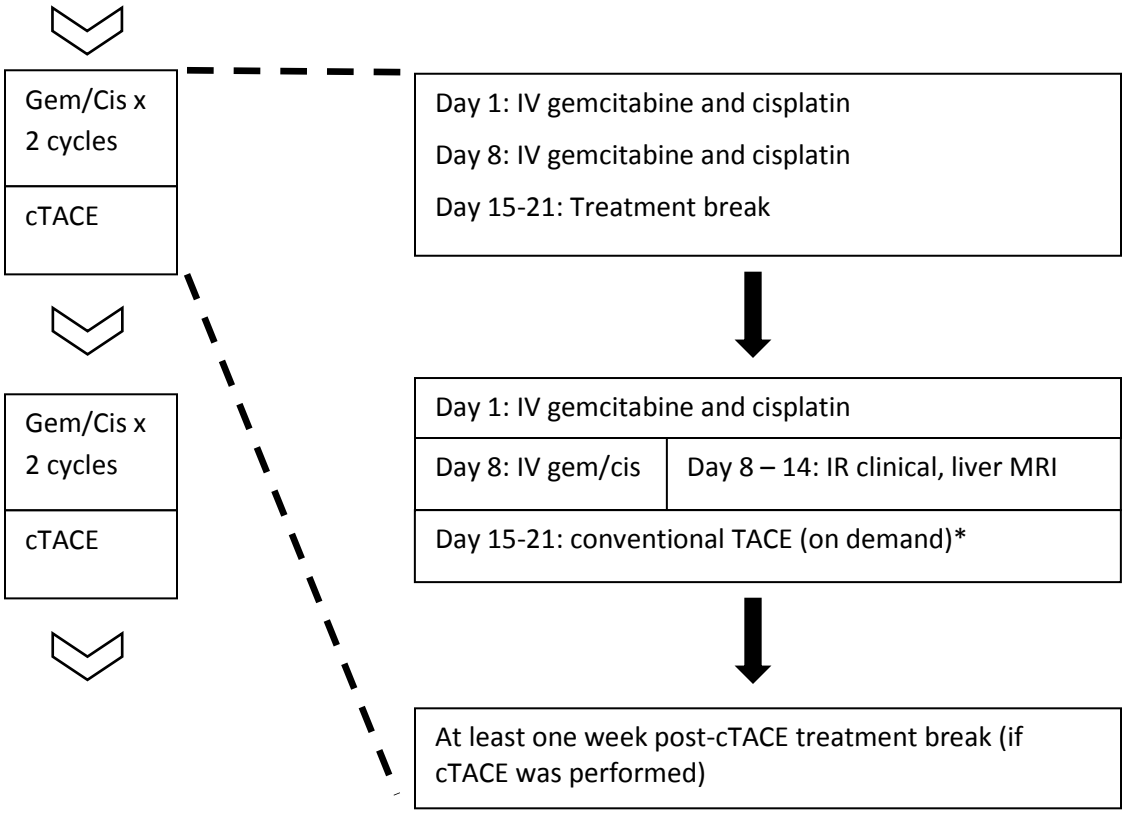

Maximum of 8 cycles of gemcitabine/cisplatin (24 weeks of systemic therapy) on study protocol

Maximum of 3 cTACE treatments delivered (at each 6-weekly assessment). The first cTACE treatment is required; additional cTACE treatments will be delivered as indicated.

Dose delay, reduction decision for systemic therapy and cTACE made independently based on schedule of clinical and laboratory assessments

Maximum of 4 week delay in any scheduled therapy (systemic or cTACE)

**Schema: Gemcitabine/cisplatin x 2 cycles, clinic, and cTACE**




*cTACE treatment (or systemic therapy) may be delayed without a protocol deviation for a maximum of 4 weeks to allow for recovery from toxicities and adverse events.

Initial doses: 1000 mg/m$^2$ of gemcitabine, 25 mg/m$^2$ cisplatin on Day 1 and 8 of each cycle.

Instructions for dose reductions noted in Section 4.3.3

Labs drawn as standard on day of IV chemotherapy prior to administration to confirm patient is eligible for treatment.

## 4.3. Systemic Treatment Cycles: Combination of Cisplatin and Gemcitabine

### 4.3.1. Treatment Schedule and Dosage

Intravenous chemotherapy will be delivered on Days 1 and 8 of a 21-day cycle. The initial doses administered for gemcitabine/cisplatin-naïve patients will be 1000 mg/$m^2$ of gemcitabine and 25 mg/$m^2$ cisplatin intravenously. Enrolled participants that had prior or current gemcitabine/cisplatin therapy may continue at an adjusted dose. Dosages may be modified or delayed due to toxicities; see Sections 4.3.2 and 4.3.3 for instructions. There is a systemic treatment break on Week 3 of every systemic chemotherapy cycle.

There will be a maximum delay of 4 weeks in any scheduled therapy: patients who exceed that will be exited from the study. Patients will receive a maximum of 8 cycles of systemic chemotherapy for a total of 24 weeks of systemic therapy.

After every two cycles of systemic treatment, patients will be assessed with MR imaging to see if TACE treatment is necessary. If TACE is necessary, the patient will proceed into the TACE treatment phase including a treatment break of at least 1 week after TACE to allow the patient to recover. If TACE is not deemed necessary, the next cycles of gemcitabine/cisplatin will proceed without interruption. All patients will receive the first cTACE on study.

Chemotherapy infusion will take place on an outpatient basis in accordance with standard institutional practices. An example is as follows: patients will be pre-hydrated prior to treatment with 1 liter of 0.9% saline, 20 mEq potassium chloride, and 2g magnesium sulfate administered over 2 hours. Patients will then be premedicated prior to starting therapy in accordance with standard clinical practice and the gemcitabine and cisplatin package insert. Gemcitabine in 250-500 mL of 0.9% saline is administered over 30 min followed by cisplatin in 250-500 mL of 0.9% saline over 30 min-1 hour with hydration as required.

### 4.3.2. Criteria for a Patient Starting the Next Systemic Treatment Cycle

A new cycle of gemcitabine/cisplatin may be initiated for patients meeting the following criteria:

- ANC ≥ 1000/$mm^3$ (Grade 2 or lower)
- Platelet count ≥ 75 x $10^9$/L (Grade 1 or lower)
- Liver associated enzymes/function (e.g. AST, ALT, ALKP, bili: Grade 2 or lower)
- Any other drug-related AEs that may have occurred resolved to baseline or Grade 1 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. The maximum treatment delay is 4 weeks prior to necessitating withdrawal from the systemic portion of the study. The patient may continue on protocol without systemic therapy under the discretion of the investigator.

Patients for whom the investigator decides it is in their best interest to stop both TACE and systemic therapies are exited from the study and their treatment procedures discontinued.

### 4.3.3. Dose Modifications and Treatment Changes

Adjustments to the dosage of either systemic agent will be carried out independent of the plan for intra-arterial therapy. Doses may be modified separately based on individual toxicities. If both systemic agents are permanently stopped due to toxicity during the planned 8 cycles of therapy, treatment can continue on protocol using TACE alone at the discretion of the treating physician. Dose modifications will follow pre-defined dose levels:

**Gemcitabine**

- Dose level 1: 1000 mg/$m^2$
- Dose level 2: 750 mg/$m^2$
- Dose level 3: 500 mg/$m^2$
- Dose level 4: Discontinue

**Cisplatin**

- Dose level 1: 25 mg/$m^2$
- Dose level 2: 20 mg/$m^2$
- Dose level 3: 15 mg/$m^2$
- Dose level 4: Discontinue

Doses of both gemcitabine and cisplatin can be modified as per patient tolerance, according to the guidelines below:

- Dose re-escalation is not permitted. If a dose reduction has been instituted during the prior cycle, then that most recently delivered dose will become the starting dose for the subsequent cycle.
- Doses omitted during cycles will not be made up
- The maximum dose delay in systemic therapy is 4 weeks.
- If more than 2 dose reductions are required in either agent, then the drug should be permanently discontinued.
- If the dose of either or both drugs was omitted from Day 8 of the previous cycle, then the starting dose for this cycle will be a reduction of one dose level for gemcitabine and/or cisplatin (whichever is applicable) compared with most recently delivered dose.

Suggested dosing modifications for gemcitabine and cisplatin based upon observed nonhematological and hematological toxicities are outline in the tables below. Toxicities are graded according to CTCAE v5.0.

**Table 1: Suggested Dose Modifications for Non-hematological Toxicities**

| 1. Toxicity | Grade | Management/Next Dose Gemcitabine | Management/Next Dose Cisplatin |
|---|---|---|---|
| **Peripheral neuropathy** | **Grade 1-2, tolerable** | No change in dose | No change in dose |
| | **Grade 2, intolerable** | No change in dose | Hold until ≤ tolerable G2. Resume at dose reduction. |
| | **Grade 3-4** | No change in dose | Hold until ≤ G2. Resume at dose reduction. |
| **Elevated creatinine** | **≤ 0.4 above baseline** | No change in dose | No change in dose |
| | **0.5-1.0 above baseline** | No change in dose | Hold until ≤ 0.4 above baseline. Resume at same dose, increase pre and post cisplatin hydration. |
| | **≥ 1.1 above baseline** | No change in dose | Hold until ≤ 0.4 above baseline. Resume at dose reduction. |
| **Other non-hematologic toxicities*** | **≤ Grade 1** | No change in dose | No change in dose |
| | **Tolerable Grade 2** | No change in dose | No change in dose |
| | **Grade 3 or 4** | Hold until ≤ tolerable G2. Resume at dose reduction. | Hold until ≤ tolerable G2. Resume at dose reduction. |

* Asymptomatic non-hematological laboratory abnormalities will not be cause for dose reduction, but will be corrected as per standard clinical practice.

**Table 2: Suggested Dose Modifications for Hematologic Toxicities**

| Toxicity | Grade/Laboratory Value | Management/Next Dose Gemcitabine | Management/Next Dose Cisplatin |
|---|---|---|---|
| **Neutropenia*** | **Day 8 of a cycle: < 900/mcL** | Hold until ≥ 900, resume at reduced dose, if indicated | Hold until ≥ 900, resume at reduced dose, if indicated |
| **Thrombocytopenia**** | **Day 8 of a cycle: < 70 x $10^9$/L** | Hold until ≥ 70, resume at reduced dose, if indicated | Hold until ≥ 70, no change in dose, if indicated |

* Use of growth factors is permitted
** A platelet goal of 50K should be considered for those on anticoagulation

For patients who are noted to have new onset Grade 3 or higher increases in AST, ALT, and/or bilirubin, an evaluation for obstruction and cholangitis will be performed; the presence of either obstruction or cholangitis will necessitate withholding of treatment until resolution to baseline. To administer Day 8 chemotherapy, these liver associated biochemical abnormalities must resolve to ≤ Grade 2 or baseline.

Supportive care use of transfusion for symptomatic anemia or hemoglobin < 8 g/dL and colony-stimulating factors (CSFs) for neutropenia is encouraged per established guidelines.

### 4.4. IR Clinical Visit

Clinical follow-up with Interventional Radiology will take place on Week 2 of every second cycle of systemic chemotherapy. New MRI of the liver will be obtained and assessed at this time point to determine whether further conventional TACE treatment is warranted. Labs and toxicities will also be assessed and recorded.

### 4.5. Conventional TACE with Doxorubicin/Mitomycin-C

#### 4.5.1. Treatment Phase – Conventional TACE with Doxorubicin/Mitomycin-C

If conventional TACE is warranted based on MRI assessment and the patient meets all the eligibility criteria for TACE therapy, then cTACE will be scheduled to take place during Week 3 of that cycle. Patients will always receive the first cTACE for study; follow-up cTACE will occur on demand. Laboratory and imaging results should have been completed on the previous clinical visit, but if any procedures need to be repeated they can be repeated up until the day of the TACE. Patients are allowed a maximum of 3 treatments during the treatment phase. Conventional TACE treatments will be performed according to standard of care hospital protocol as detailed in the next section.

Patients who do not meet the criteria for TACE therapy at the time of treatment may be eligible to receive transfusions pre-treatment to meet the requirements for TACE. If this is the case, new labs will be drawn to ensure patients meet the criteria for TACE before treatment. If the patient is ineligible for TACE due to toxicities, therapy can be delayed a maximum of 4 weeks at which point the patient will exit the study.

If patients discontinue all systemic therapy due to toxicities, they may remain on study and receive cTACE under the discretion of the principal investigator.

Patients may continue to receive cTACE if needed after the completion of the treatment phase and during the follow-up phase; if this occurs and the patient receives additional cTACE treatment prior to the 1 year time point, then their data will be omitted from the PFS analysis.

### 4.5.2. Conventional TACE Overview

To perform the conventional TACE, the common femoral artery is accessed using Seldinger technique. A 5-French vascular sheath is then placed into the artery over a glide wire. Under fluoroscopic guidance, a visceral-shape catheter is used to perform diagnostic visceral arteriogram (celiac and SMA) to depict arterial flow to the tumor, hepatic arterial anatomy, and portal vein blood flow. The diagnostic catheter or a microcatheter is advanced into the target hepatic artery branch, depending on tumor location. Angiography is performed to confirm safety of the location to delivery of the chemoembolic emulsion, which is injected under fluoroscopy, followed by injection of 1% lidocaine and 100-300 micron embospheres.

The amount of chemoembolization material administered is titrated to the area being treated, i.e., a smaller area (lesion) may be adequately treated with a portion of the prepared chemoembolization material. The chemoembolization material consists of 10cc of chemotherapy (with 50 mg doxorubicin and 10 mg mitomycin-C) mixed 1:1 with Lipiodol (approximately 10cc) giving a total of approximately 20cc. After the chemotherapy is administered, approximately 10cc of 1% lidocaine and 1-2 vials of embospheres measuring 100-300 microns are injected. The amount of 1% lidocaine and embospheres is also titrated to each clinical situation.

Intra-arterial chemotherapy materials include:

- 10 cc of chemotherapy (50mg doxorubicin and 10mg of mitomycin-C) mixed 1:1 with Lipiodol (approximately 10cc) giving a total of approximately 20cc
- 10 cc of 1% lidocaine
- 1-2 vials of embospheres measuring 100-300 microns to achieve angiographic end-point of 2-5 heart beats to clear the contrast column

Following the chemoembolization procedure, the patient is admitted for observation, pain control, and hydration, and is discharged home once stable. The day after the TACE procedure, a non-contrast CT scan is performed to document the deposition of the Lipiodol in the targeted areas.

Follow-up MR imaging will be performed approximately 6 weeks following the cTACE procedure and assessed at the IR clinical visit.

## 4.6. Treatment Delays

Gemcitabine/cisplatin therapy and TACE therapy may be delayed up to a maximum of 4 weeks for toxicities to allow sufficient time for patient recovery. Patients who do not recover from toxicity will be discontinued from the study.

Missed chemotherapy doses will not be made up.

Treatment may be delayed for no more than 7 days to account for holidays, weekends, scheduling conflicts, inclement weather, or other justifiable events and will not be considered a protocol violation.

### 4.7. Concomitant Medications, Therapies, and Supportive Care

No other chemotherapy, immunotherapy, hormone therapy, or any other type of therapy (including herbal or natural supplements) for treatment of ICC or experimental drugs will be permitted while the patients are on study. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form.

Necessary supportive measures for optimal medical care will be given throughout the study, including IV antibiotics to treat infections, growth factor support, and blood components, etc. Additional care, including palliative radiotherapy (excluding target lesions and lesions representing progressive disease) may be administered as indicated by the treating physician and patient's medical need.

## 5. Clinical and Study Procedures

### 5.1. Screening/Baseline Evaluations

Assessments completed in the initial clinic visits (pre-consent), as part of standard of care, may be used as part of the study screening assessment. Laboratory tests, MRI, and H&P should be performed within 30 days of treatment. If clinically indicated, laboratory tests will be repeated within 1 week of treatment.

- Detailed medical history including previous cancer history and cancer treatment. Any additional relevant medication taken one year prior to study start will also be recorded.
- History and physical exam (including vital signs, ECOG-PS assessment, height, weight) within 30 days of study enrollment.
- Chemistry panel: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (total and direct), alkaline phosphatase (AP), total protein, albumin, calcium, phosphate, glucose, creatinine, blood urea nitrogen (BUN).
- Electrolyte panel: sodium, potassium, chloride.
- Complete blood count: hemoglobin, hematocrit, platelet count, white blood cell count (WBC). WBC should include differential neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.
- Prothrombin time and INR.
- Tumor marker (CA 19-9, CEA, etc)
- Serum or urine pregnancy test for women of childbearing potential (must be negative).

- Contrast enhanced MRI of the liver within 30 days of treatment. A CT may be used if a MRI would be improbable to obtain.
- CT of the chest without contrast.

Eligible patients that have completed their screening procedures will be enrolled on study and start treatment on Cycle 1 Day 1.

### 5.2. Treatment Phase – Systemic Chemotherapy Cycles

Subjects will complete 8 cycles (each cycle consisting of 21 days) of a systemic chemotherapy regimen of gemcitabine and cisplatin on this study for a total of 24 weeks of systemic therapy. Study drugs will be administered on Day 1 and Day 8 of every cycle. Starting doses are 1000 mg/m$^2$ of gemcitabine intravenously Day 1 and Day 8, along with 25 mg/m$^2$ intravenously Day 1 and Day 8. Doses may be reduced or skipped due to toxicities but re-escalation is not permitted. Doses omitted during a treatment cycle will not be made up; the maximum dose delay in systemic therapy is 4 weeks. If more than 2 dose reductions are required, then the drug should be discontinued.

Patients will need to have new CMP (comprehensive metabolic panel) and CBC (complete blood count with differentials) labs drawn prior to administration of chemotherapy on Day 1 and Day 8. Exceptions may be made if recent and relevant labs were drawn (for screening or clinical assessment).

### 5.3. Treatment Phase – IR Clinical Visits and TACE Interventions

During each second cycle of systemic treatment, patients will return for clinical follow-up on Days 8-14. Clinical follow-up will include: H&P, laboratory tests (CMP, CBC, PT/INR, tumor markers), and contrast-enhanced MR imaging (CT if MRI is not possible).

If conventional TACE is warranted based on MRI assessment, it will be scheduled for the next week (Days 15-21 of a cycle). At least a one-week rest period following the TACE will be allotted to allow the patient to recover with extensions up to 4 weeks if toxicities are unresolved; afterwards, the patient will restart the gemcitabine/cisplatin cycles. Otherwise, if the patient does not require TACE treatment, the regular schedule of gemcitabine/cisplatin will apply.

### 5.4. Study Follow-up Phase

After completion of the treatment phase, patients will enter the follow-up phase. Follow-up clinical assessments occur every 3 months at a minimum, although they may occur more frequently if warranted or if the patient undergoes further TACE procedures. Clinical assessments will include H&P, laboratory tests (CMP, CBC, PT/INR, tumor markers), and contrast-enhanced MR imaging.

Patients will be followed for approximately 1 year after the treatment phase, for a total of 18 months on study.

### 5.5. Final Study Visit

Patients that have completed their follow-up phase will exit the trial after their final clinical follow-up. The final study visit will include the standard assessments performed at each clinical visit. Patients will continue to be followed off-protocol by the clinical team to ensure any toxicities or adverse events are followed and resolved.

## 6. Study Evaluations

### 6.1. Tumor Response (mRECIST, qEASL, vRECIST Criteria)

Patients with measurable disease will be evaluated prior to starting treatment, and at regular intervals afterwards to occur about week 2 of every 2$^{nd}$ cycle of systemic gemcitabine/cisplatin therapy. Lesions and tumor response as analyzed from contrast-enhanced MR imaging will be determined utilizing mRECIST (modified Response Evaluation Criteria in Solid Tumors) and qEASL (quantitative or volumetric European Association for the Study of the Liver) criteria. The details for each guideline are listed below. Tumor response is defined as complete response and partial response.

The RECIST criteria were designed primarily for the evaluation of cytotoxic agents with the only criterion for tumor response being shrinkage in size. However, RECIST assessments alone can be misleading when applied to other anti-cancer therapies, such as molecular-targeted therapies and chemoembolization which could induce tumor necrosis but with no change in total size. The modified RECIST criteria as utilized in this trial include changes in size of tumor necrosis as a factor of response. With the mRECIST criteria, viable tumor is defined as uptake of contrast agent in the arterial phase of dynamic CT or MRI.

To select a target lesion using mRECIST, a lesion should meet all of the following criteria at baseline:

- The target lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

The mRECIST criteria for tumor response are:

- Complete response – disappearance of any intratumoral arterial enhancement in all target lesions.

- Partial response – at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as a reference the baseline sum of the diameters of target lesions.
- Stable disease – Any cases that do not qualify for complete response, partial response or progressive disease.
- Progressive disease – An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

In contrast to the RECIST criteria, the EASL criteria evaluate response to treatment based on changes in tumor enhancement. However, there are some limitations in its application to hepatic tumors treated with TACE therapy, which result in inhomogeneous tumor necrosis. Furthermore, RECIST, mRECIST, and EASL are applied to one representative axial slice of the tumor, and a different slice selection could lead to different response assessments. For EASL, assessments of percent enhancement of tumoral area are made based on visual approximation and grouped into brackets, but the assessment could be inaccurate if the enhancement percentage is within the boundary thresholds between two brackets. The criteria also do not take into account the entire tumor volume.

As a result, quantitative EASL assessments will be performed to account for entire tumor volume, and to determine percentage enhancement throughout (68-71). Semi-automatic three-dimensional volumetric segmentation will be performed using software by an experienced interventional radiologist utilizing the contrast-enhanced MRI obtained for the study as source data. Comparisons can then be performed on a voxel by voxel basis, giving a 3D volumetric assessment of tumor enhancement based on total tumoral volume rather than a 2D assessment of tumoral area.

The qEASL criteria for tumor response are:

- Complete response – disappearance of any intratumoral arterial enhancement in all target lesions.
- Partial response – at least a 65% decrease in the sum of enhancing tissue volume of the lesions.
- Stable disease – Any cases that do not qualify for complete response, partial response, or progressive disease.
- Progressive disease – An increase of at least 73% in the sum of enhancing tissue volume of the lesions.

### 6.2. Toxicities, Survival, Time to Progression, and Time to Untreatable Progression

Toxicities will be assessed and reported based on the NIH Common Terminology Criteria for Adverse Events (CTCAE) v5.0. These would include laboratory data for hematologic, liver, and kidney function, post embolization syndrome, incidences of adverse events and serious adverse events, and clinical observations.

Overall survival will be measured from enrollment on study until death of the patient from any cause.

Time to progression (TTP) will be measured from enrollment on study until radiographic evidence of overall disease progression.

Time to untreatable progression (TTUP) in liver lesions will be measured from time of initiation of cTACE therapy until radiographic evidence of disease progression in targeted lesions.

# 7. Safety Profiles of Study Interventions

## 7.1. Gemcitabine

### 7.1.1. Gemcitabine Description

Gemcitabine hydrochloride (Gemzar®) is a nucleoside analog of deoxycitidine. Its full chemical name is 2'-deoxy-2',2'-difluorocytidine monohydrochloride. It is a white to off-white or translucent solid with empirical formula $C_9H_{11}F_2N_3O_4$ • HCl and molecular mass of 299.66 g/mol. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemzar is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. The lyophilized compound should be stored at controlled room temperature, 59° to 96°F (15° to 30°C).

To make a solution containing 38 mg/mL final concentration, add 5 mL normal saline (0.9% sodium chloride) to the 200mg vial or 25 mL normal saline to the 1,000 mg vial. Normal saline is the only diluent approved. Do not use other diluents.

Handling precautions: gemcitabine is a toxic material which could cause skin and eye irritation. Ingestion or inhalation exposure of sufficient quantities could result in decreased white and red blood cells, hypospermatogenesis, gastrointestinal disturbances, and other signs of toxicity. Laboratory animal studies indicate that compounds in this therapeutic class may be reproductive toxins and may induce fetal malformations. Contact or inhalation should be avoided.

Gemcitabine is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

### 7.1.2. Gemcitabine Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and inhibits the progression of cells through the G1/S-phase boundary. It is metabolized by nucleoside kinases to a diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The diphosphate inhibits ribonucleotide reductase, an enzyme responsible for

catalyzing the generation of deoxynucleoside triphosphates for DNA synthesis including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA, which results in only one additional nucleotide being added to the growing DNA strands eventually leading to initiation of apoptosis.

### 7.1.3. Pharmacology of Gemcitabine

The pharmacokinetics of gemcitabine were examined in 353 patients with solid tumors. PK parameters were derived from patients treated with varying durations of therapy, given weekly with periodic rest weeks, and using both short and long infusions. The volume of distribution was increased with infusion length; from 50 L/$m^2$ in infusions lasting <70 min to 370 L/$m^2$ in longer infusions. Gemcitabine pharmacokinetics are linear and described by a 2-compartment model. Analyses of combined single and multiple dose studies showed that the volume of distribution was significantly influenced by duration of infusion and gender.

Gemcitabine is metabolized intracellularly to form active gemcitabine diphosphate and triphosphates. Additional metabolites have not been identified in either plasma or urine. The gemcitabine di- and tri-phosphates do not appear to circulate in plasma in measurable amounts. The compound is metabolized principally by the liver to form an inactive uridine derivative (dFdU or 2'-deoxy-2',2'-difluorouridine). The plasma protein binding of gemcitabine is negligible.

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

Half-life ranged from 11 to 26 minutes for patients receiving single dose infusions (1000 mg/$m^2$ to 2500 mg/$m^2$ and 3600 mg/$m^2$. The increase in half-life may relate to the appearance of a possible third exponential phase (representing a deep compartment) that is not observed following the shorter infusions. Clearance obtained for female patients was 46.2 L/hr/$m^2$ and for males was 66.8L/hr/$m^2$. These moderate to high gemcitabine values suggest that the molecule is metabolized by various tissues, including the liver. The renal clearance for gemcitabine is less than 10% of the systemic clearance.

Maximum dFdU plasma concentrations were achieved from 0 to 30 minutes after the discontinuation of gemcitabine infusions, ranging from 0.4 to 4.75 hours. The apparent formation of dFdU (determined from the fraction of the gemcitabine dose excreted as dFdU) ranged from 91.2% to 98.2% of gemcitabine clearance in a single-dose study. Based on the imputed formation rate of dFdU, the mean dFdU volume of distribution at steady-state was 150.4 L/$m^2$, indicating that dFdU was extensively distributed into tissues. The metabolite was excreted in urine without undergoing further biotransformation. The mean apparent clearance of dFdU was 2.5L/hr/$m^2$.

### 7.1.4. Toxicology of Gemcitabine

Dose limiting toxicity is bone marrow suppression with mild to moderate granulocytopenia, anemia, and thrombocytopenia. There has been no evidence of cumulative white blood cell or platelet toxicity.

Gastrointestinal toxicities include nausea, vomiting, and diarrhea. Gemcitabine should be used with caution in patients with impaired liver function since abnormalities of liver transaminase enzymes have been reported.

Mild proteinuria and hematuria have been reported but were not clinically significant and usually not associated with any change in serum creatinine or BUN. A few cases of renal failure of uncertain etiology have been reported. While on study, one patient who received prior mitomycin developed hemolytic uremic syndrome requiring dialysis. The relationship of this event to gemcitabine is not known. Gemcitabine should be used with caution in patients with impaired renal function.

Toxicities associated with allergic reaction include rash, pruritus, desquamation, vesiculation, ulceration, and dyspnea. Bronchospasm has been reported in less than 1% of patients. 20% of patients have also experienced flu-like symptoms such as fever, headache, back pain, chills, myalgia, asthenia, anorexia, cough, rhinitis, malaise, sweating, and insomnia.

Other toxicities include edema or peripheral edema in 30% of patients, alopecia, somnolence, constipation, and oral toxicity (soreness and erythema). Pulmonary edema has been a rare occurrence (less than 1%). A few cases of hypotension have been reported, as well as myocardial infarction, congestive heart failure, and arrhythmia. However, there is no clear evidence that gemcitabine causes cardiac toxicity.

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

## 7.2. Description of Cisplatin

### 7.2.1. Cisplatin Description

Cisplatin is a platinum-based, alkylating-like agent. Its full chemical name is (*SP*-4-2)-diamminedichloroplatinum(II) with empirical formula of $H_6Cl_2N_2Pt$ and molecular mass of 300.01 g/mol. Cisplatin is a yellow to orange crystalline powder that is soluble in water or saline at 1 mg/mL and in

dimethylformamide at 24 mg/mL. Intact vials of cisplatin are stored at room temperature; solutions diluted with sodium chloride or dextrose are stable up to 72 hours at room temperature. Due to the risk of precipitation, cisplatin solutions should not be refrigerated.

The desired dose of cisplatin is diluted with 250-1000 mL of saline and/or dextrose solution. Varying concentrations of 0.225-5% sodium chloride and 5% dextrose may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

Cisplatin is usually administered as an intravenous infusion over 30 minutes to 24 hours; multiday continuous infusions are occasionally used. The drug may also be administered intra-arterially, intraperitoneally, and intravesicularly. Pre-treatment hydration is recommended prior to cisplatin administration, with between 1 and 2 liters of fluid, and adequate post-hydration to maintain urine output of 100 cc/hr thereby avoiding renal precipitation.

Caution should be exercised in handling the powder and preparing the solution of cisplatin. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing cisplatin for injection. Skin reactions associated with accidental exposure may occur. If cisplatin powder or solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

### 7.2.2. Cisplatin Mechanism of Action

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; a chloride ligand of cisplatin is displaced allowing the platinum atom to bind to a DNA base. This denatures the double helix and disrupts DNA function, ultimately leading to cell apoptosis if not fixed by DNA repair enzymes. The *cis*-isomer of cisplatin is 14 times more cytotoxic than the *trans*-isomer; although both forms cross-link DNA and bind to nucleotide bases, the *cis*- isomer is less easily recognized by cellular repair mechanisms and thus less likely to be fixed. Cisplatin can also bind two adjacent guanine bases on the same strand of DNA producing intrastrand cross-linking and breakage.

### 7.2.3. Pharmacology of Cisplatin

Cisplatin distributes rapidly into tissues, and requires no metabolic steps for activation. Rather, the chlorine atoms are more subject to displacement by nucleophiles. The ratios of cisplatin to total free platinum in the plasma vary between patients and range from 0.5 to 1.1 after a dose of 100 mg/m$^2$. Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding, but the platinum atom binds to several plasma proteins with greater than 90% protein binding in circulation. The platinum-albumin molecule complex dissociate slowly and are eliminated with a minimum half-life of 5 days. Metabolism is non-enzymatic,

with inactivation by sulfhydryl groups in both cells and in the bloodstream. Cisplatin covalently binds to glutathione and thiosulfate.

High concentrations of platinum are achieved in kidneys, liver, prostate; somewhat lower in bladder, muscle, testicle, pancreas, and spleen; lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissue for as long as 180 days after last administration.

The half-life of cisplatin ranges from 14 to 49 minutes for initial elimination, with beta- and gamma-elimination occurring in 0.7-4.6 hours and 24-127 hours respectively. After a 7 hour infusion of 100 $mg/m^2$, the total body clearances and volumes of distribution at steady-state for cisplatin are about 15 to 16 $L/h/m^2$ and 11 to 12 $L/m^2$. The renal clearance of free platinum also exceeds the glomerular filtration rate indicating that cisplatin is actively secretly by the kidneys. Excretion is almost entirely renal, with minimal excretion noted in feces.

### 7.2.4. Toxicology of Cisplatin

Dose-related, cumulative renal tubular injury can occur with administration of cisplatin, a risk that is usually minimized with adequate hydration and diuresis. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.

Dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus occurs in about 30% of patients. Paresthesias, decreased vibratory, position, and touch sensations are less common particularly at cumulative doses < 400 $mg/m^2$.

Mild leukopenia and thrombocytopenia occur in 25-30% of patients, but are rarely dose-limiting. Anemia is more uncommon. A potentially fatal hemolytic uremic syndrome has been reported.

Severe, dose-limiting nausea and vomiting may occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea, a delayed (72-96 hour) reaction, requiring additional therapy may occur. Anorexia and taste changes may also occur.

Allergic reactions are reported in up to 20% of patients. Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.

Other toxicities including electrolyte wasting (magnesium, potassium, and sodium), papilledema, optic neuritis, retrobulbar neuritis have been reported.

Prior to administration of cisplatin, assessments of labs (complete blood count, platelet count, BUN, creatinine), urine output (100-150 mL/hr for at least 4-6 hours), and for signs of ototoxicity or neurotoxicity should be made. Supportive medications to be administered include antiemetics (5HT3 antagonists and dexamethasone combinations can usually be once daily), hydration (diuretics), and observe for signs of allergic reaction.

Cisplatin administration is incompatible with amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, and thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. Cisplatin has also been reported to be found in human milk. Patients receiving cisplatin should be apprised of the potential hazard to the fetus, and should avoid becoming pregnant or breast-feeding while receiving the drug.

### 7.3. Doxorubicin Profile

**Other Names:** Adriamycin, Rubex, Adriamycin RDF, Adriamycin PFS, hydroxydaunorubicin, ADR.

**Mechanism of Action:** Doxorubicin is an anthracycline antibiotic that intercalates between adjoining nucleotide pairs in the DNA helix, causing inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin is also an inhibitor of topoisomerase II.

**Storage and Stability:** Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

**Availability:** Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/mL solution for injection in 10, 20, 50, and 200 mg vials.

**Preparation:** 50 mg doxorubicin is reconstituted with mitomycin-C in sterile contrast and water to give a final drug concentration of 5 mg/mL doxorubicin in a total volume of 10 mL.

**Administration:** The chemotherapy solution of doxorubicin and mitomycin-C is emulsified with 10 mL of Lipiodol. The chemotherapy-Lipiodol mixture is administered into the target vessel with embolic agents to follow. The amount of the mixture administered is titrated to the area being treated.

**Incompatibilities:** Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

**Side Effects:**

Hematologic: Leukopenia (Dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.

Dermatologic: Alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.

Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis.

Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with doses greater than 550 mg/$m^2$, mediastinal irradiation, pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.

Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity; secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an alkylating agent, especially if one or both are given at higher than standard doses.)

Local effects: Vesicant if extravasated; flush along vein, facial flush.

### 7.4. Mitomycin-C Profile

**Other Names:** Mutamycin, mitomycin

**Mechanism of Action:** Mitomycin is an antitumor antibiotic that is cell cycle non-specific. It appears to be most active in the late G1 and early S phase of the cell cycle. The mechanism of action is similar to alkylating agents, causing cross-linking of DNA and possible inhibition of RNA and protein synthesis.

**Storage and Stability:** Unreconstituted vials are stored at room temperature. At a concentration of 0.5 mg/mL the drug is chemically stable for at least 7 days at room temperature and 14 days when refrigerated and protected from light.

**Availability:** Commercially available in 5, 20, and 40 mg vials.

**Preparation:** 10 mg mitomycin-C is reconstituted with doxorubicin in sterile contrast and water to give a final drug concentration of 1 mg/mL doxorubicin for a total volume of 10 mL.

**Administration:** The chemotherapy solution of doxorubicin and mitomycin-C is emulsified with 10 mL of Lipiodol. The chemotherapy-Lipiodol mixture is administered into the target vessel with embolic agents to follow. The amount of the mixture administered is titrated to the area being treated.

**Incompatibilities:** Undergoes rapid decompensation at acidic and basic pH.

**Compatibilities:** Dilute solutions (20-40 mg/mL) are chemically stable at room temperature in normal saline for 12 hours, in 5% dextrose for 3 hours, and in sodium lactate 1/6 M for 24 hours. Mitomycin 5-15 mg is compatible with heparin (1000-10,000 units) in 30 mL normal saline for 48 hours at room temperature. The pH of maximal stability is 6-10.

**Side Effects:**

Hematologic: Leukopenia, thrombocytopenia: late, cumulative and dose-limiting; anemia; hemolytic uremic syndrome (renal failure, profound thrombocytopenia, pulmonary edema, and hypotension) rarely.

Dermatologic: Stomatitis, alopecia, dermatitis, pruritus; tissue necrosis, ulceration, and cellulitis if extravasation occurs; skin erythema and ulceration weeks to months after administration and distant from the site of injection.

Gastrointestinal: Nausea, vomiting, anorexia.

Hepatic: Veno-occlusive disease of the liver, manifested as abdominal pain, hepatomegaly and liver failure, in patients receiving mitomycin and autologous bone marrow transplantation.

Neurologic: Paraesthesias.

Pulmonary: Interstitial pneumonitis (infrequent but severe); acute bronchospasm.

Renal: Nephrotoxicity, increasing in frequency when doses exceed 50 mg/$m^2$, manifested as increased serum creatinine and BUN.

Other: Fatigue, pain on injection, phlebitis, fever, lethargy, weakness, blurred vision; secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an anthracycline, especially if one or both drugs are given at higher than standard doses); secondary tumors (rare).

### 7.5. Medical Risks or Expected Adverse Events Associated with TACE

Overall, the rate of complications of chemoembolization is approximately 20-25%. Serious complications are estimated to be approximately 5-7%.

The following are recognized complications of chemoembolization in the liver:

- 30 day mortality (usually from liver failure or infection) occurs in approximately 4% of cases. The risk of post procedure mortality increases with the number of treatments and the treatment of patients with portal vein thrombosis, non-selective embolization and severe liver impairment.
- Post-embolization syndrome, a constellation of flu-like symptoms, is seen in almost 100% of the patients who undergo solid organ arterial embolization. The symptoms include nausea, vomiting, fever, leukocytosis, pain, and adynamic ileus. The severity of the pain usually peaks around 12 to 24 hours post procedure and may last up to 3 to 5 days. The pain is generally managed according to standard hospital practice.
- Acute Progressive Hepatic Insufficiency (APHI) occurs in approximately 2-13% of cases. APHI is defined as a new onset of ascites, encephalopathy, and increased serum bilirubin (> 2 mg/dL) or doubling of the bilirubin or greater than 3 second increase in PTT after TACE from pre-TACE levels. Most insufficiency returns to baseline within 1 week. It is also common for liver enzymes to demonstrate a transient rise peaking at 24-36 hours and returning to baseline after 5-7 days.

- Non-target embolization to the gut
- Liver abscess
- Cholecystitis, gall bladder perforation
- Periprocedural cardiac events
- Renal insufficiency
- Pulmonary embolism
- Gastrointestinal bleeding
- Bile duct injury
- Acute pancreatitis
- Peptic ulcer

# 8. Adverse Events

## 8.1. Adverse Event Definitions

### 8.1.1. Unanticipated Problems

As defined by Yale policy, adverse events and unanticipated problems are stated as follows:

**Unanticipated Problem Involving Risks to Subjects or Others:**

An Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOs) comprises any incident, experience, or outcome that meets all 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device/drug effects*. ***Please note*** that adverse events (as defined below) are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

**Unanticipated Adverse Device/Drug Effect:**

Any serious adverse effect on health or safety, or any life-threatening problem or death caused by (or associated with) a device or drug, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; any other

unanticipated, serious problem associated with a device or drug that relates to the rights, safety, or welfare of subjects.

### 8.1.2. Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence or worsening of a pre-existing medical condition in a patient and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding, for example), symptom, or disease temporally associated with the treatment. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

### 8.1.3. Serious Adverse Events

A Serious Adverse Event (SAE) is an untoward medical occurrence that at any dose produces any of the following outcomes:

- Results in death;
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below for exceptions);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

NOTE:

The following hospitalizations are not considered SAEs:

- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy);

- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases;

Admission encounter for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

### 8.2. Adverse Event Capture

Adverse Events are collected at baseline, and at clinical follow-ups for each cycle. AEs are documented for each patient on the case report form (CRF), and are transcribed to a study-specific electronic log which is reviewed regularly by the PI and is available for the IRB and monitoring committees for review.

Study deviations (protocol deviations: PDs) are collected and reported in the same way as the AEs are managed. PDs are collected throughout the study duration, documented on CRFs, and transcribed to a study-specific electronic log reviewed by the PI and available for the IRB and monitoring committees. Both AEs and PDs are submitted during continuing reviews.

### 8.3. Characteristics of an Adverse Event

#### 8.3.1. Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

- 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 likely not to be related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

For purposes of reporting, AEs attributed as “unlikely” or “unrelated” will not be subject to expedited reporting.

#### 8.3.2. Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

#### 8.3.3. Severity of Event

CTCAE term (AE description) and grade: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized to grade severity of the AE and for all AE reporting. The criteria are as follows:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death

### 8.4. Reporting Procedures

#### 8.4.1. Events Requiring Prompt Reporting to IRB

UPIRSOs that may require a temporary or permanent interrupt of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the PI. The Cancer Center Protocol Review Committee (PRC), Yale Cancer Center Data and Safety Monitoring Committee (DSMC), study sponsor, funding and regulatory agencies will be informed of serious adverse events within 5 days of the event becoming known to the Principal Investigator.

The following events may represent UPIRSOs that should be promptly reported:

- Adverse device effects that are unanticipated;
- Adverse events or injuries that are serious, unexpected, *and* related;
- Breaches of confidentiality involving risks;
- Data and Safety Monitoring Board (DSMB) reports, interim analysis, or other oversight committee/monitoring reports altering the risk/benefit profile by identification of increased risks;
- Revisions to safety information, such as Investigational New Drug (IND) Safety Reports and MedWatch Reports, that meet the definition of a UPIRSO;
- New information indicating an unexpected increase in risks or decrease in potential benefits (e.g., literature/scientific reports or other published findings);

- Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur;
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject;
- Other problem or finding (e.g. loss of study data or forms) that an investigator or research staff member believes could influence the safe conduct of the research.

### 8.4.2. Events Not Requiring Prompt Reporting to IRB

Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") are described in the informed consent form and do not require prompt reporting to the IRB. The following are examples of events that do not require prompt reporting:

- Adverse device effects that are non-serious, anticipated, *or* unrelated;
- Adverse events or injuries that are non-serious, expected, *or* unrelated;
- Deaths not attributed to the research (e.g., from "natural causes", accidents, or underlying disease when the Principal Investigator has ruled out any connection between the study procedures and the subject's death);
- DSMB reports, interim analyses; or other reports, findings, or new information not altering the risk/benefit profile;
- Protocol deviations or violations unlikely to recur or not involving risks to subjects;
- Subject complaints that were resolved or complaints not involving risks;
- Problems or findings not involving risk (unless the PI believes the information could affect subjects' willingness to continue in the research).

All related internal and external events involving risks but not meeting the *prompt* reporting requirements will be reported to the IRB in summary form at the time of continuing review.

### 8.4.3. Reporting of SAEs and AEs to Guerbet as Lipiodol Provider

SAE submissions to Guerbet are made at: Guerbet LLC, phone: 1-877-729-6679 or at Pharmacovigilance.headquarters@guerbet-group.com.

## 9. Study Oversight and Monitoring

**Personnel Responsible for the Safety Review and its Frequency:**

This study is expected to be of moderate risk, and as such, will follow the guidelines for a greater than minimal risk DSMP. The principal investigator is responsible for monitoring the data, assuring protocol

compliance, and conducting the safety reviews. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. An internal monitoring plan will be established with the YCC to facilitate this process, and the study will be reviewed every 6 months at minimum.

The principal investigator, the Institutional Review Board (IRB), Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

**Risks Associated With the Current Study:**

The proposed study is not assessed as high risk due to the established safety and validity of each treatment regimen, conventional TACE and systemic chemotherapy of gemcitabine and cisplatin for intrahepatic cholangiocarcinoma as established in the medical literature. The risks of the combination therapy are not expected to exceed any risk for each individual treatment alone.

Although the assessment of the proposed study is one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

**Attribution of Adverse Events:**

To assess relationship of an event to study intervention, the following guidelines are used:

- 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 likely not to be related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

For purposes of reporting, AEs attributed as “unlikely” or “unrelated” will not be subject to expedited reporting.

**Plan for Grading Adverse Events:**

CTCAE term (AE description) and grade: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized to grade severity of the AE and for all AE reporting. The criteria are as follows:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death.

**Plan for Determining Seriousness of Adverse Events:**

The criteria for a serious adverse event are as noted in Section 8.1.3 above. It is important to note that an adverse event may be graded as severe by the grading criteria but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its seriousness to determine whether reporting to the IRB is necessary.

**Plan for Reporting UPIRSOs (Including Adverse Events) to the IRB:**

As noted in Sections 8.1.1 and 8.4.1.

**Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies:**

For the current study, the following individuals, funding, and/or regulatory agencies will be notified: all co-investigators listed on the protocol; Yale Cancer Center Data and Safety Monitoring Committee (DSMC); funding company Guerbet.

The principal investigator, Todd Schlachter, MD, will conduct a review of all adverse events upon completion of every study subject. The PI will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

# 10. Statistical Considerations

## 10.1. General Overview

The primary endpoint of this phase II study is the 12-month progression-free survival (PFS) in adult patients with ICC after treatment with gemcitabine and cisplatin in combination with conventional transarterial therapy. The currently used drug regimen in this patient population is expected to have a 12-month PFS rate of 20%. Alternatively, the experimental treatment will be considered worthy of further study if the PFS at 12 months is 40% or better. We plan to enroll 25 patients over 2 years, with 1.5 years of follow-up for a total duration of 3.5 years.

### 10.2. Trial Design

The 25 patients will be enrolled in a non-randomized, single arm, single cohort with no planned stopping rule for lack of efficacy. The primary endpoint is 12-month PFS. The length of follow-up required to assess this endpoint made a Simon two-stage design less ideal, and no early termination is planned in this study for efficacy or futility reason. The primary endpoint will be analyzed as a binomial distribution with a sample size of 25 and probability of success equal to 0.2 under the null hypothesis. If nine or more patients are progression-free at 12 months then the trial rejects the null hypothesis with significance 0.047. If the underlying rate is 45% then this criteria has power 87%. If the underlying rate is 40% then the power is 73%.

### 10.3. Analysis of Primary Endpoints

The primary endpoint is the 12-month progression free survival rate. Radiographic assessment of disease burden will be evaluated by mRECIST and qEASL after every 2 cycles of systemic chemotherapy. Descriptive statistics will be used to present the statistical results of this phase II trial. 12-month progression free survival rate will be calculated with an exact 95% confidence interval.

### 10.4. Analysis of Secondary Endpoints

Secondary endpoints include overall survival, time to progression, time to untreatable disease progression, time to toxicity. All of these endpoints will be examined with a product limit (Kaplan-Meier) estimate of the time to event data including censoring. Rates and duration of toxicities will be listed by frequency and duration. We will evaluate whether early changes in DCE-MRI will correlate with long term PFS or OS, specifically as they relate to lesions targeted with cTACE therapy. This will include mRECIST, qEASL and 3D volumetric assessments of tumor response on imaging. We have not powered for any of these secondary endpoints and will not correct for multiplicity of statistical tests.

### 10.5. Safety and Toxicity Analysis

Safety analysis, which include tabulated summaries of adverse events, changes in lab results and vital signs, will be performed on patients who receive at least one treatment cycle.

Adverse event data will be listed and tabulated by cohort and severity level. Furthermore, adverse events will be classified based on the likelihood they are treatment-related. Adverse events which lead to treatment withdrawal and all serious adverse events will be summarized separately.

## 11. Ethics/Protections of Human Subjects

### 11.1. Ethical Standard

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice (ICH GCP), and applicable local regulatory requirements and laws.

### 11.2. Institutional Review Board

It is the responsibility of the investigator/sponsor to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All IRB correspondence should be retained in the Investigator File.

### 11.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any reports, publications, or in any other disclosures, except where required by laws.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form must be used in this study, and any changes made during the course of the study must be prospectively approved by the IRB before implementation.

The investigator must ensure that each subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

### 11.4. Inclusion of Women and Minorities

All patients, regardless of sex and ethnicity, presenting for cTACE for intrahepatic cholangiocarcinoma will be reviewed for study eligibility. For participants who are not fluent in spoken or written English, interpreter services will be available both during the informed consent process and during the subject's participation as needed. A translated short form consent will be provided.

Women that are breastfeeding or pregnant will not be eligible to join the study due to the possible toxic effects that the chemotherapy regimen may have on a fetus or an infant.

## 12. Data Handling and Record Keeping

### 12.1. Data Capture Methods: Case Report Forms

As used in this protocol, the term case report form (CRF) refers to a paper form. A CRF is required and should be completed for each included subject.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms.

All CRFs must be signed by the investigator to verify the data contained on the CRFs is accurate. Any corrections to entries made in the CRFs and source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Usually, source documents are the hospital's or the physician's subject medical chart. In these instances the data collected on the CRFs must match the data in the corresponding charts. A CRF, or part of the CRF, may also serve as a source document.

Electronic master logs of all adverse events and protocol deviations will also be recorded and kept in an encrypted database with access only available to study team members. An individual physical paper CRF will also be kept with the patient's research binder.

### 12.2. Study Records Retention

To enable inspections and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (i.e. information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the IRB's policies or the FDA's regulations, whichever is longer but for a minimum of 5 years.

If the investigator is unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the study records must be transferred to a designee acceptable to the investigator such as another investigator or another institution.

## 13. Protocol Deviations and Noncompliance

### 13.1. Definitions of Noncompliance and Protocol Deviations

As outlined in Yale policy, noncompliance is defined as any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with either the research plan as approved by a designated IRB, or federal regulations or institutional policies governing human subject research. Noncompliance may range from minor to serious, be unintentional or willful, and may occur once or several times. Noncompliance includes failure to have protocols reviewed by IRB as required, protocol deviations in protocols approved by the IRB, including deviations made in the interest of a single participant such as changing a participant's scheduled study visits. Noncompliance may result from the action of the investigator, research personnel, or a participant, and may or may not impact the rights and welfare of research participants or others or the integrity of the study. Complaints or reports of noncompliance from someone other than the Principal Investigator or study team personnel are handled as allegations of noncompliance until such time that the report is validated or found to be invalidated or dismissed.

Minor Noncompliance: Any behavior, action, or omission in the conduct or oversight of research involving human participants that deviates from the approved research plan, federal regulations, or institutional policies but, because of its nature, the research project, or subject population, **does or does not:**

1. Harm or pose an increased risk of substantive harm to a research participant;
2. Result in a detrimental change to a participant's clinical or emotional condition or status;
3. Have a substantive effect on the value of the data collected; and
4. Result from willful or known misconduct on the part of the investigators or study staff.

Examples of minor noncompliance may include, but are not limited to, the following:

- Changing study personnel without notifying the IRB;
- Shortening the duration between planned study visits;
- Implementing minor wording changes in study questionnaires without first obtaining IRB approval;
- Routine lab missed at scheduled visit and re-drawn later.

Serious Noncompliance: Any behavior, action, or omission in the conduct or oversight of human research that, in the judgment of a convened IRB, has been determined to:

1. Adversely affect the rights and welfare of participants;
2. Harm or pose an increased risk of substantive harm to a research participant;
3. Result in a detrimental change to a participant's clinical or emotional condition or status;
4. Compromise the integrity or validity of the research; or
5. Result from willful or knowing misconduct on the part of the investigators or study staff.

Examples of serious noncompliance may include, but are not limited to, the following:

- Conducting non-exempt research that requires direct interaction or intervention with human participants without first obtaining IRB approval;

- Enrolling participants who fail to meet the inclusion or exclusion criteria in a protocol that involves greater than minimal risk and that in the opinion of the IRB Chair, designee, or convened IRB, places the participants at greater risk;
- Failing to submit a continuing review application to the IRB before study expiration for an ongoing study;
- Failing to obtain and/or document a participant's informed consent provided the IRB has not granted a waiver of consent;
- Failing to retain copies of signed informed consent forms;
- Performing a study procedure not approved by the IRB; or failing to perform a required study visit or procedure that, in either case, may affect subject safety or data integrity;
- Failing to follow the safety monitoring plan;
- Enrolling study subjects after the IRB-approval of a study has expired; or
- Failing to report serious adverse events and/or unanticipated problems to the IRB in accordance with IRB policy.

Continuing Noncompliance: A pattern of noncompliance that in the judgment of a convened IRB:

1. Indicates a lack of understanding or disregard for the regulations or institutional requirements that protect the rights and welfare of the participants;
2. Compromises the scientific integrity of a study such that important conclusions can no longer be reached;
3. Suggests a likelihood that noncompliance will continue without intervention; or
4. Involves frequent instances of minor noncompliance, for example, repetitive protocol deviations.

Examples of continuing noncompliance may include, but are not limited to, the following:

- Repeated failure to respond to requests from the IRB to resolve an episode of noncompliance or a pattern of minor noncompliance, such as repetitive protocol deviations; or
- Consistently late submissions of continuing review applications or other items that require prompt reporting to the IRB

Protocol Deviation: Any alternation/modification to an IRB-approved protocol made without prior IRB approval.

**Note:** Whether a protocol deviation qualifies as minor or serious noncompliance depends heavily on the specific facts of the situation. The examples of minor or serious noncompliance provided above are not intended to be an exhaustive list. The key to whether a protocol deviation will qualify as "minor" or "serious' depends upon whether, under the specific circumstances, it may adversely affect the rights and welfare of participants, harm or pose an increased risk of substantive harm to a research participant, have a substantive effect on the value of the data collected, or result from willful or knowing misconduct on the part of the investigators or study staff.

Deviations from the study design and/or procedures that are due to a study participant's non-adherence do not need to be reported to the IRB (e.g., study participant did not return for a scheduled study visit or participant refused to have blood drawn) unless they impact the participant's safety or well-being, or if a pattern of protocol deviations indicate a need for changes in the protocol and/or informed consent documents.

### 13.2. Reporting of Noncompliance and Protocol Deviations

Serious and/or continuing noncompliance will be reported to the IRB office within 5 working days of becoming aware of the incident/issue. Reports will be submitted using HIC Form 700 FR1 (Notification of Deviation from a Protocol/Noncompliance Report Form) to the Human Research Protection Program (HRPP) Compliance Manager.

Minor noncompliance will be summarized for the IRB at the time of continuing review.

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## 15. Appendices

### Appendix A – ECOG Performance Status

| GRADE | 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 |
| 5 | Death |

**ECOG Performance Status**: describes a patient's functional level in terms of self-care and physical activity.

## Appendix B – Child-Pugh Classification

| Parameter | Points Assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin, mg/dL | ≤ 2 | 2-3 | > 3 |
| Albumin, G/dL | > 3.5 | 2.8-3.5 | < 2.8 |
| Prothrombin Time | | | |
| Seconds over control | 1-3 | 4-6 | > 6 |
| INR | < 1.7 | 1.8-2.3 | > 2.3 |
| Encephalopathy | None | Grade 1-2 | Grade 3-4 |

**Child-Pugh Classification of Liver Disease Severity:** Modified Child-Pugh classification of liver disease severity according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time (seconds over control **or** INR), and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one-year and two-year percent survival; grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C – 45 and 35 percent, respectively.

## Appendix C – New York Heart Association Classification

| Class | Description |
|---|---|
| I | Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain. |
| II | Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain. |
| III | Subjects with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or angina pain. |
| IV | Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

## Appendix D – Tables for Dose Modifications

**Table 1: Suggested Dose Modifications for Non-hematological Toxicities**

| 1. Toxicity | Grade | Management/Next Dose Gemcitabine | Management/Next Dose Cisplatin |
|---|---|---|---|
| **Peripheral neuropathy** | **Grade 1-2, tolerable** | No change in dose | No change in dose |
| | **Grade 2, intolerable** | No change in dose | Hold until ≤ tolerable G2. Resume at dose reduction. |
| | **Grade 3-4** | No change in dose | Hold until ≤ G2. Resume at dose reduction. |
| **Elevated creatinine** | **≤ 0.4 above baseline** | No change in dose | No change in dose |
| | **0.5-1.0 above baseline** | No change in dose | Hold until ≤ 0.4 above baseline. Resume at same dose, increase pre and post cisplatin hydration. |
| | **≥ 1.1 above baseline** | No change in dose | Hold until ≤ 0.4 above baseline. Resume at dose reduction. |
| **Other non-hematologic toxicities*** | **≤ Grade 1** | No change in dose | No change in dose |
| | **Tolerable Grade 2** | No change in dose | No change in dose |
| | **Grade 3 or 4** | Hold until ≤ tolerable G2. Resume at dose reduction. | Hold until ≤ tolerable G2. Resume at dose reduction. |

* Asymptomatic non-hematological laboratory abnormalities will not be cause for dose reduction, but will be corrected as per standard clinical practice.

**Table 2: Suggested Dose Modifications for Hematologic Toxicities**

| Toxicity | Grade/Laboratory Value | Management/Next Dose Gemcitabine | Management/Next Dose Cisplatin |
|---|---|---|---|
| **Neutropenia*** | **Day 8 of a cycle: < 900/mcL** | Hold until ≥ 900, resume at reduced dose, if indicated | Hold until ≥ 900, resume at reduced dose, if indicated |
| **Thrombocytopenia**** | **Day 8 of a cycle: < 70 x $10^9$/L** | Hold until ≥ 70, resume at reduced dose, if indicated | Hold until ≥ 70, resume at reduced dose, if indicated |

* Use of growth factors is permitted
** A platelet goal of 50K should be considered for those on anticoagulation

For patients who are noted to have new onset Grade 3 or higher increases in AST, ALT, and/or bilirubin, an evaluation for obstruction and cholangitis will be performed; the presence of either obstruction or cholangitis will necessitate withholding of treatment until resolution to baseline. To administer Day 8 chemotherapy, these liver associated biochemical abnormalities must resolve to ≤ Grade 2 or baseline.

Supportive care use of transfusion for symptomatic anemia or hemoglobin < 8 g/dL and colony-stimulating factors (CSFs) for neutropenia is encouraged per established guidelines.

## Appendix E – Study Calendar

| | Screening Phase | Treatment Phase | | | | | | | Follow-up Phase |
|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1, 3, 5, 7 | | | Cycle 2, 4, 6, 8 | | | | |
| | Day -30 to 0 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 8-14 | Day 15-21 | Q3 mo post treatment |
| Inf. Consent | X | | | | | | | | |
| I/E Criteria | X | | | | | | | | |
| Medical History, H&P | X | | | | | | X | | X |
| ECOG-PS | X | | | | | | X | | X |
| CMP labs | X | X | X | | X | X | X* | | X |
| CBC w/ diff | X | X | X | | X | X | X* | | X |
| PT/INR | X | | | | | | X* | | X |
| Tumor marker: CEA, CA 19-9, etc | X | | | | | | X | | X |
| Serum/urine pregnancy | X* | | | | | | | | |
| MRI liver with contrast | X | | | | | | X | | X |
| CT chest w/o contrast | X | | | | | | | | |
| cTACE procedure | | | | | | | | X* | |
| Gemcitabine, Cisplatin | | X | X | | X | X | | | |
| AE Assessment | X | X | X | | X | X | X | | X |
| Concomitant Medications | X | X | X | | X | X | X | | X |

* if required. First cTACE is mandatory for continued enrollment.