

Study Title:	A Phase II study of induction systemic mFOLFIRINOX followed by hepatic arterial infusion of Floxuridine and Dexamethasone given concurrently with systemic mFOLFIRI as a first-line therapy in patients with unresectable liver-dominant intrahepatic cholangiocarcinoma
Protocol Number:	16033
ClinicalTrials.gov ID	NCT04251715
Version Number:	4.5
Version Date:	15 August 2022
Replaces:	4.4
Principal Investigator:	Skye C. Mayo, M.D., M.P.H.
	Department of Surgery Division of Surgical Oncology Oregon Health & Science University 3181 SW Sam Jackson Park Road, Mackenzie Hall, Rm 3173 Portland, OR 97239 Phone: 503-494-5501 Email: mayos@ohsu.edu
<u>Statistician:</u>	Byung Park, Ph.D. Oregon Health & Science University, KR-BSR 3181 SW Sam Jackson Park Road Portland, Oregon 97239-3098 Phone: 503-418-0127 Email: parkb@ohsu.edu

SUMMARY OF CHANGES

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
5.	4.2	36	Addition of study exclusion criteria for participant with ICC containing known FGFR translocations.	This exclusion is added to avoid conflict in recruitment strategy for other ongoing trial(s) that target populations with FGFR gene mutations.
6.	5.1	43	Change in HAI pump make and model to SynchroMed II (Model 8637-20), manufactured by Medtronic Inc.	Johnson and Johnson, parent company to CODMAN®, announced that it is to discontinue manufacture of CODMAN® constant flow pump. The SynchroMed II pump requires similar surgical implantation and will provide equal or better delivery of floxuridine for HAI therapy. The SynchroMed II pump is programmable and is able to provide better control of pump flow rates (i.e., drug delivery).
7.	5.8	51	Removal of Glycerin	The use of programmable SynchroMed II pump does not require use of glycerin for pump maintenance
8.	6	55-62	Changed pump fill volume (20ml), and dosing of heparin and dexamethasone	The drug reservoir of the SynchroMed II Model 8637-20 is 20 ml. Dosages of heparin and dexamethasone have been revised accordingly

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
9.	6.1.3	57	Reduced starting dose of mFOLFIRI	Starting dose is reduced to decrease the potential for biliary sclerosis
10.	6.2.2	59	Floxuridine dose modification	Table 12 has been revised to provide more conservative management of floxuridine dosing for participants with elevated liver enzymes
11.	6.2.2.1	60	Restarting floxuridine after hold	Section revised to provide more conservative management of elevated liver enzymes and allows for continuous DEX throughout HAI pump treatment
12.	6.6	65	Added description of pump placement	The SynchroMed II HAI pump will be connect with a tapered silicone rubber catheter from a different manufacturer (Codman®)
13.	7.1.10	68	Addition of staging laparoscopy for disease assessment and collection of tumor biopsy	Laparoscopic staging is added at time of screening to assess the local stage of the disease and to evaluate the liver for metastases. This is procedure is being added because current imaging modalities (e.g., CT, MRI, PET) are relatively poor at determining the presence of peritoneal disease and limited in their ability to provide local staging.

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
				Baseline tumor biopsy will be collected at time of staging laparoscopy.
14.	Schema	8, 9	Added additional EOT biopsy	Revised to reflect protocol changes
15.	3.2.2	35	Added end time of PFS up to 1 year after completing study therapy	Revised for clarity
16.	4.2	38	Exclusion criteria #16, revised to state that allergies to contrast medium are permitted if they can be premedicated with steroids per institutional standards	Revised for clarity
17.	5	43-52	Timing of administering study agents revised to state per institutional standards	Revised for clarity
18.	6.1.2, 6.1.3	53	Added statement that choice of reservoir size for the SynchroMed II pump includes either 20 ml or 40 ml	Revised to reflect the two HAI pump models available and discretion of physician to decide which is better suited.
19.	6.2	56	Guidance on dosing delays added for start of HAI pump therapy	Guidelines added for clarity
20.	6.3.4	61-62	Conditions for pump removal revised	Revised for clarity
21.	7.1.10, 7.8	67, 75	Added optional EOT biopsy after completion of Treatment Period 2	An optional EOT biopsy has been added to gain better insight into the molecular underpinnings of the disease.

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
22.	8	77	Revised guidelines on when using RECIST	RECIST criteria will not be used after EOT, rather assessments will be reviewed by PI and a radiologist.
23.	9.5	88	SAE reporting requirements updated to 24 hrs from time of event	Updated according to institutional requirements.
24.	9.5	87	SAE reporting requirements updated to 24 hrs from sending finalized SAE to MedWatch	Corrected according to institutional requirements.
25.	6.1.1	53	Irinotecan starting dose reduced to 144 mg/m ² , and modified dose reduced to 108 mg/m ²	Revised to align with institutional standards
26.	7.2.2, 7.2.3, 7.8	67, 74	Timing and frequency of blood chemistry, and coagulation assessments revised	Revised to align with institutional standards
27.	7.3.2	68	b-values for DWI removed	DWI parameters under investigation as part of exploratory objective
28.	7.4.2.2, 7.8	70	Frequency of QOL assessment corrected	Corrected to align with study schema
29.	12.3.1	95	Duration of biospecimen storage revised from up to 15 years to indefinitely	Revised to align with BioLibrary repository
30.	12.5	96	Publication and data sharing revised	Revised to align with institutional policy

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
31.	4.3	39	Description of advertisement of trial added	Language added to align with institutional policy
32.	4.2	38	Revised exclusion criteria pertaining to history of prior malignancies	Criteria revised to reduce stringency for cancer unlikely to interfere with assessment of study intervention.”
33.	3.1	33	Post-operative day 3 updated to 4	Discrepancy – schedule of events footer H indicates no sooner than post-op day 4
34.	3.2.3	36	Updated 28 days prior to Treatment Period 1 to 30 days	Updated to match screening window
35.	6.1.1	53	Removal of row 4 containing 5FU Bolus in tables 6 and 7. Fluorouracil moved up.	No 5FU bolus in mFFX
36.	6.6	63	Removed “ Within 28 days prior to surgery, participants must undergo Hepatic CT angiogram to evaluate hepatic arterial anatomy in order to determine if HAI pump placement is technically feasible. “	Removed since this is done at prescreen 1
37.	7.1.10	66	Added language “ In the event that this evaluation is not able to be done in person, it is at the PI’s discretion if	To provide flexibility

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
			being done remotely is acceptable”	
38.	7.2.2	67	Added language: “At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable”	To provide flexibility
39.	7.2.2	67	Removal of magnesium from Bloody Chemistry	Magnesium not needed per SOC
40.	7.3.1	68	Updated from 28 days to 30 and added language “At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable”	To provide flexibility
41.	7.4.2	70	Added “at the end of treatment period 1 (Cycle 4 Day 1 of mFOLFIRINOX)” to provide clarity	To provide clarity
42.	7.4.2	70	Removal of Preop-HAI from Table 16 and added Cycle 4 mFOLFIRINOX	Reflect current practices
43.	7.5.2	73	Added last dose to clarify timing	To provide clarity

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
44.	7.8	76	Updated Schedule of Events Table to match current practices	Reflect current practices
45.	8.2	79	Added language "At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable" and matched screening timeline of 30 days	To provide flexibility
46.	7.11.1	69	Added Liver Tumor Board	To provide flexibility
47.	Synopsis, 6.1.3	10, 57	Revised 5-FU dosing to 1200 mg/m ²	Revised to align with institutional standards.
48.	7.4.5.2, 7.8	74, 78	Removed portal and hepatic vein blood collection during surgery	Peripheral blood collection alone is sufficient. Revised to reduce unnecessary risk to participant
49.	7.8	78	Cycle 2 Day 14 blood collection removed from schedule of events	This sample collection removed to align with standard of care procedures.
50.	Synopsis, 4.1	9, 39	Revised creatinine clearance eligibility criteria to: Serum creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance ≥ 40 mL/min ($\geq$	Revised creatinine clearance to align with standard of care

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
			0.675mL/sec) using the Cockcroft-Gault equation: Males: $(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine [mg/dL]} \times 72)$ Females: $[(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine [mg/dL]} \times 72)] \times 0.85$	
51.	7.6, 7.8	76, 78	EOT timing revised	Revised for clarification
52.	7.4.2.2, 7.8 and Table 16	72, 77-78	Updated protocol reflecting the addition of 2 QoL interviews and 1 QoL survey per study participant to be administered within 24 months of end of trial.	Updated to match additions
53.	9.5	89	Updated to remove interviews from AE review process	The purpose of the structured interviews and surveys is not to assess for any adverse events.
54.	List of Abbreviations	24	Change abbreviation for SAE to "Serious adverse event" instead of "Severe"	Revised for clarification
55.	7.4.2	72	Addition of language "The purpose of the structured interviews and surveys is not to assess for adverse	Revised for clarification

#	Section	Page(s)	Change	Justification
1.	Cover page, 4, 7	1, 38, 67	Names of clinical investigators have been removed	Several changes in co-investigators has prompted removal of this list from cover page. All researchers associated with this study are listed in institutional eIRB. Clinical investigator names have been replaced with appropriate medical role (i.e., surgical oncology or oncology)
2.	Cover page	1	Removed FDA IDE exempt status	This has been removed in lieu of study device changes
3.	1.5.1	31	Added risk language	Risk language pertaining to the splicing of the pump connector to catheter has been added
4.	3.1	33	Added Screening 1 language for clarity	Added Screening 1 language for clarity
			events.”	
56.	5.1	45	Revised language regarding warranty/ID card for HAI pump	Revised for flexibility

SYNOPSIS

Study Title	A Phase II study of induction systemic mFOLFIRINOX followed by hepatic arterial infusion of Floxuridine and Dexamethasone given concurrently with systemic mFOLFIRI as a first-line therapy in patients with unresectable liver-dominant intrahepatic cholangiocarcinoma
Protocol #	16033
Study Center	OHSU, single-site
Clinical Phase	Phase II - Combination
Investigation Components	FDA Approved Drug
Interventional Study Type	<i>Single-arm</i>
Précis	Delayed diagnosis of intrahepatic cholangiocarcinoma (ICC) renders the majority of patients (~70%) not suitable for hepatic resection. Moreover, failure to respond to current first-line therapies, gemcitabine and cisplatin, provides little treatment recourse. Regional therapy using a surgically implanted hepatic arterial infusion (HAI) pump allows for maximal liver-directed treatment of patients with unresectable ICC with agents that are processed in the liver, thereby limiting the toxic side effects seen with traditional chemotherapy. In this study, mFOLFIRINOX will be administered to participants with liver-dominant unresectable ICC as a means to select individuals that are most likely to benefit from a period of intensive liver-directed therapy using HAI to deliver floxuridine and dexamethasone (DEX). These participants will also concurrently receive a dose-modified systemic regimen of mFOLFIRI. The goal of using this treatment approach is to achieve better disease control and offer better quality of life than currently available therapies.
Primary Objectives	<ul style="list-style-type: none"> To evaluate the efficacy of systemic induction of mFOLFIRINOX, followed by HAI floxuridine-DEX administered concurrently with systemic mFOLFIRI. To assess safety of treatment with HAI floxuridine-DEX delivered concurrently with systemic mFOLFIRI.
Secondary Objectives	<ul style="list-style-type: none"> To evaluate response and survival following treatment.
Exploratory Objectives	<ul style="list-style-type: none"> To assess the radiographic response using diffusion-weighted MRI (DWI). Evaluate quality of life (QoL) pre-, during, and post-treatment. To explore potential biomarkers. Examine the differential expression pattern of RNA (microRNA and mRNA) in ICC. Characterize circulating hybrid cells (CHCs) pre-, during, and post-treatment.

Primary Endpoint	<ol style="list-style-type: none"> 1. Incidence of abnormal liver function, as defined by unacceptable elevation in liver enzymes (refer to Section 6.2, Table 12), or radiographic evidence of biliary sclerosis on CT/MRI (as measured following the completion of 2 cycles of HAI in Treatment Period 2). 2. To determine the disease control rate (DCR) from beginning of Treatment Period 2 to end of Treatment Period 2 (i.e., during the treatment with HAI Floxuridine + mFOLFIRI). [The DCR is defined as the percentage of patients who have achieved complete response (CR), partial response (PR), or stable disease (SD)].
Secondary Endpoints	<ol style="list-style-type: none"> 1.DCR from beginning of Treatment Period 1 to end of Treatment Period 2 (i.e., from the beginning of the entire treatment protocol until the end). 2.DCR from beginning of Treatment Period 1 to end of Treatment Period 1 (i.e., during the treatment with FOLFIRINOX alone). 3.Progression-free survival (PFS) from beginning of Treatment Period 1 to end of Treatment Period 1 (i.e., during the treatment with FOLFIRINOX alone). 4.PFS from beginning of Treatment Period 1 to end of Treatment Period 2 (i.e., from the beginning of the entire treatment protocol until the end). 5.PFS from beginning of Treatment Period 2 to end of Treatment Period 2 (i.e., during the treatment with HAI Floxuridine + mFOLFIRI). 6.Overall Response Rate (ORR) from beginning of Treatment Period 1 to end of Treatment Period 2 (i.e., from the beginning of the entire treatment protocol until the end). 7.Overall survival (OS) at the end of Treatment Period 1, at the end of Treatment Period 2, and at 1 year, and the whole study period. Overall Survival (OS) at 1 year. 8.Proportion of liver toxicity in participants receiving HAI Floxuridine + dexamethasone therapy. 9.Incidence of serious post-operative complications, which are defined as complications occurring within 9 weeks following surgery and $\geq$ Grade III per the Clavien-Dindo classification system (Appendix B)
Exploratory Endpoint	<ol style="list-style-type: none"> 1. DWI measure of tumor diffusion coefficients. 2. Quality-of-life evaluation (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire [EORTC QLQ]-MLC21; QoL-at the end of lifeQLQ-BIL21); SF36; Patient health questionnaire; Piper

	<p>Fatigue Scale; MOS Social Support Survey.</p> <p>3. Genomic alteration profiling.</p> <p>4. Gene and microRNA expression profiling.</p> <p>5. Determine changes in CHC frequency.</p>
Number of Participants	A maximum of 30 participants will be enrolled in this study. Six participants will be enrolled as part of the initial safety-run-in, after which an additional 24 participants will be enrolled.
Estimated Time to Complete Enrollment	24 months
Study Duration	Estimated time is 48 months from when the study opens to enrollment until completion of data collection for all participants.
Duration of Therapy	HAI treatment for patients with unresectable ICC is not intended to be curative, although we anticipate a few extraordinary responders who may be rendered resectable with this treatment regimen, but rather directed at control of disease progression. Patients who respond can continue treatment HAI/Sys treatment indefinitely as long as they are able to tolerate treatment.
Key Inclusion Criteria	<ul style="list-style-type: none"> • Liver-dominant ICC, must comprise <70% of the liver parenchyma, as defined by CT liver segmental volumetrics. • Disease must be considered technically unresectable or be multifocal in the liver at the time of preoperative evaluation • ECOG 0 or 1 status (Karnofsky $\geq$ 60) • WBC $\geq$ 3000 cells/mm³ • ANC $\geq$ 1500 cells/mm³ • Platelet count $\geq$ 100,000 / mm³ • INR $\leq$ 1.5 • Serum creatinine $\leq$ 1.5 x ULN OR creatinine clearance $\geq$ 40 ml/min (>0.675 ml/sec) using Cockcroft-Gault equation • Total bilirubin < 1.5 mg/dL • AST (SGOT)/ALT(SGPT) $\leq$ 2.5 x institutional ULN.
Key Exclusion Criteria	<ul style="list-style-type: none"> • Presence of extensive or multifocal metastatic extrahepatic or peritoneal disease. • Prior treatment with floxuridine, oxaliplatin, or irinotecan. • Prior external beam radiation therapy to the liver or hepatic arterial or venous delivery of internal radiation therapy such as Y-90. • Current biliary obstruction requiring placement of endoscopic or transhepatic stents for biliary decompression. • Pregnant or lactating women.

Investigational Components	<p><u>Treatment Period 1</u> is a systemic regimen of modified FOLFIRINOX (oxaliplatin 85 mg/m²; irinotecan 144 mg/m²; fluorouracil 2,400 mg/m²) for a total of 4 cycles (i.e., 8-weeks, with each cycle being 14 days). Dosages on Cycle 2, 3, and 4 will be reduced by 25%.</p> <p>Participants eligible for <u>Treatment Period 2</u> will undergo HAI pump placement, cholecystectomy and portal lymphadenectomy (via laparotomy). <u>Treatment Period 2</u> consists of 2 cycles, in which each cycle is 28 days. Each treatment cycle involves HAI delivery of floxuridine (0.12 mg/kg/day; adjusted for weight and flow rate) for 14 days followed by systemic mFOLFIRI (irinotecan 180 mg/m², folinic acid 400mg/m²; 5-FU 1200mg/m² + bolus 5-FU 400mg/m²) given on Day 15.</p>
Statistical Considerations	<p>An initial safety run-in will consist of the first 6 participants that completed mFOLFIRINOX (Treatment Period 1), undergo HAI placement, and receive HAI floxuridine-DEX (Treatment Period 2). This safety run-in period for the first 6 participants that enter Treatment Period 2 will monitor the incidence of abnormal liver function associated with HAI therapy. Specifically, the study will be stopped if, by the end of Treatment period 2, 2 of 6 (33.3%) participants experience an elevation in liver enzymes necessitating a complete dose-hold without the ability to restart HAI floxuridine-DEX, or show radiographic evidence suggestive of biliary sclerosis. If 1 or no toxicities are observed, then the study will proceed with the accrual of an additional 24 participants.</p> <p>This study is designed to accrue 21 patients for post-induction enrollment, including the 6 patients in the safety-run portion (i.e., 21 patients to complete Treatment period 1 and 2). Using a one-sided exact test with a targeted 0.05, accrual of 21 patients will result in a study with 80.2% power to detect a difference between a 60% and an 85% disease control rate at 6 months. An additional 9 individuals (for a total of 30 participants) will be enrolled to account for possible participant drop-out.</p> <p>Safety monitoring will be continuous throughout the trial, and the study will be stopped early should the incidence of this predefined toxicity exceed 33.3% at any time after the 6 patient safety-run-in.</p>

SCHEMATIC OF STUDY DESIGN

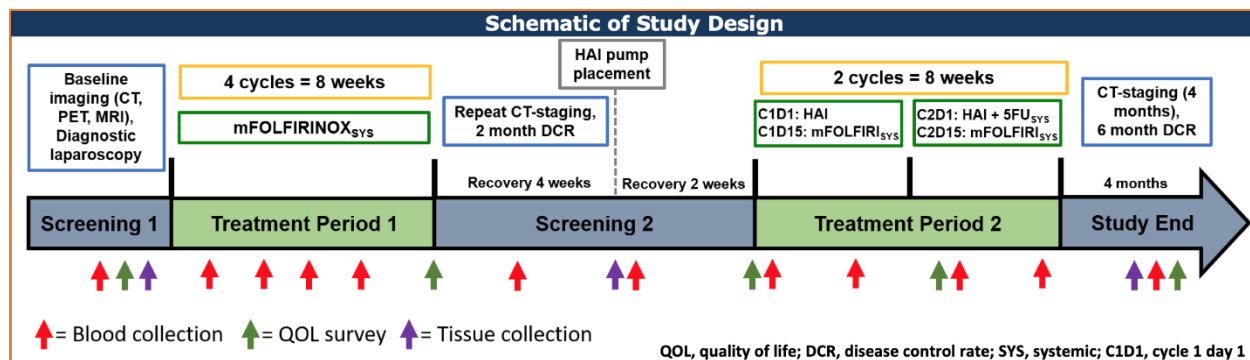


Figure 1. Overview of study design.

Screening 1 will evaluate participant eligibility, including CT imaging and staging laparoscopy to determine the presence of peritoneal disease and occult dissemination of ICC within the liver. Suspicious lesions will be biopsied for pathological assessment, and remaining excess tissue collected as part of the baseline biopsy. Following Screening 1, eligible participants enrolled in the study will receive a systemic regimen of modified FOLFIRINOX (mFOLFIRINOX_{SYS}) administered every 2-weeks for a total of 4 cycles (8 weeks; Treatment Period 1). Participants will undergo a second screening (Screening 2) and repeat imaging to assess disease response to treatment. Approximately 3-6 weeks after the last mFOLFIRINOX dose, (earlier or later time points at discretion and approval of PI), eligible participants will be taken to the operating room for a laparotomy with planned placement of a hepatic arterial infusion (HAI) pump, cholecystectomy and portal lymphadenectomy. Approximately 2-weeks after placement of HAI pump, participants will begin Treatment Period 2, in which HAI pump will deliver floxuridine and dexamethasone, and participants will receive separate systemic administration of mFOLFIRI (mFOLFIRI_{SYS}). Floxuridine and dexamethasone will be administered on day 1 of each cycle, in which the Floxuridine will be delivered via the HAI pump over 14 days. A fixed dose of mFOLFIRI will then be given on day 15 of the 4 week cycle. After completing 2 cycles, participants will undergo repeat MRI/CT imaging to assess disease response. Participants with controlled disease (as defined by RECIST criteria) may receive additional cycles of HAI-delivered floxuridine and dexamethasone, along with systemic administration of mFOLFIRI. Arrows indicated time points for blood and tissue collection, as well as intended quality of life (QoL) surveys.

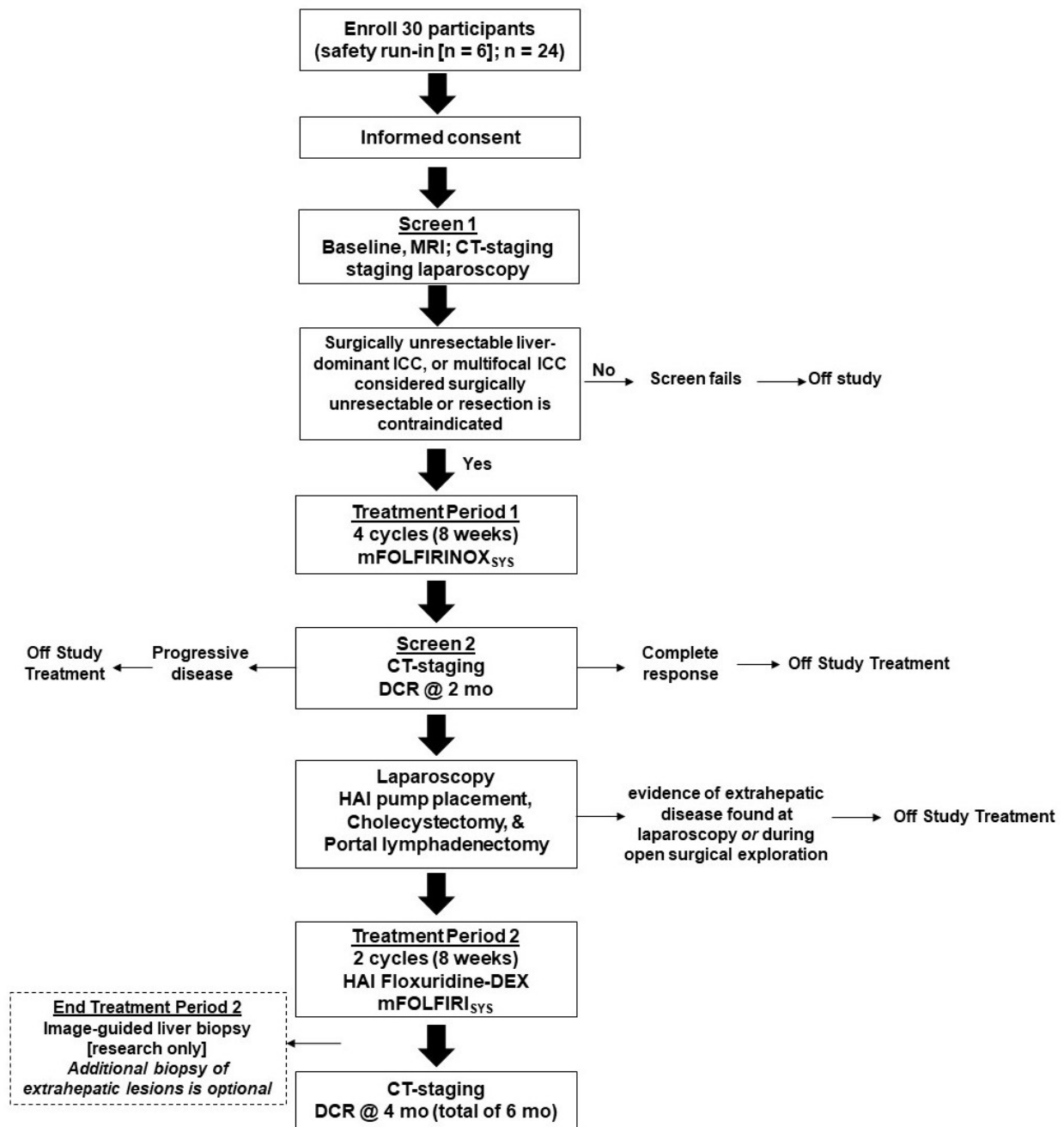


Figure 2. Study Flow

TABLE OF CONTENTS

SUMMARY OF CHANGES	2
SYNOPSIS	11
SCHEMATIC OF STUDY DESIGN	15
TABLE OF CONTENTS	ERROR! BOOKMARK NOT DEFINED.
LIST OF TABLES	25
LIST OF FIGURES	26
LIST OF ABBREVIATIONS	27
1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	29
1.1 Overview of Intrahepatic Cholangiocarcinoma	29
1.2 Systemic Therapy for Intrahepatic Cholangiocarcinoma	29
1.3 Hepatic Arterial Infusion	31
1.3.1 Other Liver Dominant Malignancies	33
1.3.2 Quality of Life	34
1.3.3 Safety of HAI Pump Therapy	35
1.4 Rationale	36
1.5 Potential Risks and Benefits	37
1.5.1 Known Potential Risks	37
1.5.2 Known Potential Benefits	37
2. OBJECTIVES	38
2.1 Primary Objectives	38
2.2 Secondary Objectives	38
2.3 Exploratory Objectives	38
2.3.1 Diffusion Weighted Magnetic Resonance Imaging (DWI)	38
2.3.2 Quality of Life Assessment (QoL)	38
2.3.3 Tumor Tissue Biomarker Assessment	38
2.3.4 microRNA (miR)	38
2.3.5 Circulating Hybrid Cells (CHC)	38
3. STUDY DESIGN AND ENDPOINTS	39
3.1 Description of the Study Design	39
3.2 Study Endpoints	40
3.2.1 Primary Endpoints	40

3.2.2 Secondary Endpoints	41
3.2.3 Exploratory Endpoints	41
4. STUDY ENROLLMENT AND WITHDRAWAL	43
4.1 Participant Inclusion Criteria	43
4.2 Participant Exclusion Criteria	44
4.2.1 Exclusion Criteria for Treatment Period 2	45
4.3 Strategies for Recruitment and Retention	45
4.3.1 Accrual Estimates	45
4.3.2 Inclusion of Children.....	47
4.4 Registration Procedures	47
4.4.1 Participant Registration	47
4.4.1.1 Local Registration	47
4.5 Participant Screening and Enrollment	47
4.6 Participant Withdrawal or Discontinuation	48
4.7 Criteria for Replacing Participants.....	48
4.8 Study Discontinuation	48
5. INVESTIGATIONAL PRODUCT	49
5.1 SynchroMed II Infusion System	49
5.2 Oxaliplatin.....	49
5.2.1 Acquisition.....	50
5.2.2 Formulation, Appearance, Packaging and Labeling	50
5.2.3 Product Storage and Stability	50
5.2.4 Compatibility	50
5.2.5 Handling.....	50
5.2.6 Preparation	50
5.2.7 Administration	50
5.2.8 Special Consideration for Administration.....	50
5.2.9 Accountability	51
5.2.10 Destruction and Return.....	51
5.3 Irinotecan.....	51
5.3.1 Acquisition.....	51
5.3.2 Formulation, Appearance, Packaging and Labeling	51
5.3.3 Product Storage and Stability	51
5.3.4 Compatibility	51
5.3.5 Handling.....	51

5.3.6 Preparation	52
5.3.7 Administration	52
5.3.8 Special Consideration for Administration	52
5.3.9 Accountability	52
5.3.10 Destruction and Return	52
5.4 Fluorouracil	52
5.4.1 Acquisition	52
5.4.2 Formulation	52
5.4.3 Storage and Stability	53
5.4.4 Compatibility	53
5.4.5 Handling	53
5.4.6 Preparation	53
5.4.7 Administration	53
5.4.8 Special Consideration for Administration	53
5.4.9 Accountability	53
5.4.10 Destruction and Return	53
5.5 Folinic Acid	53
5.5.1 Acquisition	53
5.5.2 Formulation	54
5.5.3 Storage and Stability	54
5.5.4 Compatibility	54
5.5.5 Handling	54
5.5.6 Preparation	54
5.5.7 Administration	54
5.5.8 Special Consideration for Administration	54
5.5.9 Accountability	54
5.5.10 Destruction and Return	54
5.6 Floxuridine	55
5.6.1 Acquisition	55
5.6.2 Formulation	55
5.6.3 Storage and Stability	55
5.6.4 Compatibility	55
5.6.5 Handling	55
5.6.6 Preparation	55
5.6.7 Administration	55
5.6.8 Special Consideration for Administration	56

5.6.9 Accountability	56
5.6.10 Destruction and Return	56
5.7 Dexamethasone	56
5.7.1 Acquisition	56
5.7.2 Formulation	56
5.7.3 Storage and Stability	56
5.7.4 Compatibility	56
5.7.5 Handling	57
5.7.6 Preparation	57
5.7.7 Administration	57
5.7.8 Special Consideration for Administration	57
5.7.9 Accountability	57
5.7.10 Destruction and Return	57
5.8 Heparin	57
5.8.1 Acquisition	57
5.8.2 Formulation	57
5.8.3 Storage and Stability	57
5.8.4 Compatibility	58
5.8.5 Preparation	58
5.8.6 Administration	58
5.8.7 Special Consideration for Administration	58
5.8.8 Accountability	58
5.8.9 Destruction and Return	58
6. TREATMENT PLAN	59
6.1 Dosage and Administration	59
6.1.1 mFOLFIRINOX	59
6.1.2 Floxuridine	59
6.1.2.1 Overweight dosing	60
6.1.2.2 Pump Flow Rate	60
6.1.3 mFOLFIRI	61
6.2 Dosing Delays and Modifications	61
6.2.1 Dose Modification – mFOLFIRINOX	62
6.2.2 Dose Modification – Floxuridine	63
6.2.2.1 Safety Run-in	63
6.2.2.2 Floxuridine – Restarting Treatment After Hold	64
6.2.3 Dose Modification – mFOLFIRI	64

6.3	Treatment Period and Maintenance	65
6.3.1	Treatment Period 1	65
6.3.2	Treatment Period 2	65
6.3.3	Pump Maintenance	66
6.3.4	Pump Removal.....	66
6.4	Concomitant Medication and Supportive Care Guidelines	67
6.4.1	Acute cholinergic syndrome	67
6.4.2	Dysarthria.....	67
6.4.3	Treatment of fever and neutropenia	67
6.4.4	Biliary Sclerosis.....	67
6.4.5	Social Services.....	67
6.5	Precautionary / Prohibited Medications, Treatments, and Procedures	68
6.5.1	Precautions regarding use of HAI pump	69
6.6	HAI Pump Placement and Operation	69
7.	STUDY PROCEDURES/EVALUATIONS AND SCHEDULE.....	71
7.1	Study Specific Procedures	71
7.1.1	Demographics and Medical history.....	71
7.1.2	Medication history	71
7.1.3	Physical examination.....	71
7.1.4	Vital Signs	71
7.1.5	Height and Weight.....	71
7.1.6	Performance Status.....	71
7.1.7	Electrocardiogram (ECG).....	72
7.1.8	Adverse Events	72
7.1.9	Counseling Evaluation.....	72
7.1.10	Staging Laparoscopy and Pre – and Post-treatment Biopsies	72
7.1.11	Multi-Disciplinary GASTROINTESTINAL ONCOLOGY Tumor Board or Liver Tumor Board.....	73
7.2	Laboratory Procedures and Evaluations	73
7.2.1	Hematology	73
7.2.2	Chemistry.....	73
7.2.3	Coagulation panel	73
7.2.4	Pregnancy test	73
7.3	Radiographic or other imaging assessments	74
7.3.1	Magnetic resonance Imaging (MRI) / Computed Tomography (CT) / Positron Emission Tomography (PET).....	74

7.3.2	Diffusion-weighted MRI (DWI)	74
7.3.3	CT Angiography	74
7.3.4	Single-Photon Emission CT / CT (SPECT/CT)	74
7.4	Biomarker, Correlative, and Special Studies	75
7.4.1	Radiographic Response Using DWI	75
7.4.2	Quality of Life	75
7.4.2.1	Outcome Measure	75
7.4.2.2	Method and Timing of Assessment	75
7.4.3	Tumor Tissue Biomarker Assessment (Knight Diagnostic Laboratory)	76
7.4.4	microRNA Profiling of ICC	76
7.4.4.1	Outcome Measure	77
7.4.4.2	Method of Assessment	77
7.4.4.3	Timing of Assessment	77
7.4.5	Circulating Hybrid Cells	77
7.4.5.1	Outcome Measure	78
7.4.5.2	Method of Assessment	78
7.4.5.3	Timing of Assessment	78
7.5	Screening Assessments	78
7.5.1	Pre-mFOLFIRINOX Treatment	79
7.5.2	Post-mFOLFIRINOX Treatment	79
7.5.3	Pre-Operative evaluation	79
7.5.4	Information to be Collected on Screening Failures	79
7.6	End of Treatment (EOT) Visit	80
7.7	Follow-up	80
7.8	Schedule of Events	81
8.	EFFICACY MEASURES	84
8.1	Definition of Efficacy Measures	84
8.1.1	Disease Parameters	84
8.2	Disease Evaluation	85
8.3	Efficacy Criteria for Tumor Response	85
8.3.1	Evaluation of Target Lesions	85
8.3.2	Evaluation of non-target lesions	86
8.3.3	Evaluation of Best Overall Response	86
8.3.4	Duration of Response	87
8.3.5	Progression-Free Survival	87
8.4	Response Review	88

9. SAFETY	89
9.1 Specification Of Safety Parameters	89
9.2 Definitions	89
9.2.1 Adverse Event (AE)	89
9.2.2 Serious Adverse Event (SAE)	89
9.2.3 Unanticipated Problems (UP)	90
9.2.4 Severity of Event	90
9.2.5 Assessment of Causality Relationship To Study Agent	91
9.3 Expectedness	91
9.4 Adverse Event List(s)	91
9.4.1 Adverse Event List for mFOLFIRINOX/mFOLFIRI	91
9.4.1.1 Irinotecan	91
9.4.1.2 Oxaliplatin	91
9.4.1.3 5-FU	91
9.4.2 Adverse Event list for Floxuridine - Dexamethasone	91
9.4.2.1 Floxuridine	91
9.4.2.2 Dexamethasone	92
9.4.2.3 Heparin	92
9.4.3 Adverse Event List for HAI Pump	92
9.4.3.1 Key safety concerns associated with HAI pump therapy	92
9.5 Adverse Event Assessment and Follow-Up	93
9.6 Reporting Procedures	94
9.6.1 OHSU IRB Reporting of Unanticipated Problems and Adverse Events	94
9.6.2 MedWatch Reporting	94
9.6.3 Reporting Of Pregnancy	94
9.7 Study Stopping Rules	95
10. STATISTICAL CONSIDERATIONS	96
10.1 Analysis Populations	96
10.2 Description of Statistical Methods	96
10.2.1 Analysis of Primary Endpoint	96
10.2.2 Analysis Of The Secondary Endpoints	96
10.2.3 Analysis Of The Exploratory Endpoints	97
10.2.3.1 DWI	97
10.2.3.2 microRNA	97
10.2.3.3 CHC	97
10.2.3.4 QoL	97
10.2.4 Stopping Rule	97

10.3	Sample Size, Power, Accrual Rate and Study Duration	98
10.3.1	Sample size and Power	98
10.4	Handling of Missing Data	98
11.	CLINICAL MONITORING	99
11.1	OHSU Knight Cancer Institute Data and Safety Monitoring Plan	99
11.2	Clinical Data and Safety Monitoring	99
11.3	Quality Assurance and Quality Control.....	100
12.	DATA HANDLING AND MANAGEMENT RESPONSIBILITIES	101
12.1	Source Data/Documents	101
12.2	Participant and Data Confidentiality	101
12.3	Data Collection and Storage	102
12.3.1	Future Use of Stored Specimens	103
12.4	Maintenance of Records	103
12.5	Publication and Data Sharing Policy	103
13.	ETHICS/PROTECTION OF HUMAN PARTICIPANTS	104
13.1	Ethical Standard	104
13.2	Institutional Review Board.....	104
13.3	Informed Consent	104
13.3.1	Consent Procedures and Documentation	104
13.4	Protocol Review	104
13.5	Changes to Protocol	105
14.	REFERENCES	106
	APPENDIX A: PERFORMANCE STATUS	110
	APPENDIX B: CLAVIEN DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS.....	111
	APPENDIX C: SPECT/CT IMAGING FOR HAI PUMP	112
	APPENDIX D: LIST OF COMMON AND SEVERE ADVERSE EVENTS.....	113

LIST OF TABLES

Table 1. Oxaliplatin- and fluorouracil-based combinations for treating ICC.....	30
Table 2. Selected Randomized Trials in Unresectable Metastases	31
Table 3. HAI floxuridine-DEX and systemic mFOLFIRI treatment regimen	39
Table 4. Population Demographics – Oregon (%)	46
Table 5. Projected Accrual for the Present Study	46
Table 6. Cycle 1 - mFOLFIRINOX Dosage.....	59
Table 7. mFOLFIRINOX Cycle 2, 3, and 4	59
Table 8. mFOLFIRI Dosage	61
Table 9. mFOLFIRINOX - Recommended Dose Modifications by Toxicity Grade	62
Table 10. mFOLFIRINOX - Recommended Dose Modifications for Hepatic Impairment	62
Table 11. mFOLFIRINOX - Recommended Dose Modifications for Renal Impairment.....	63
Table 12. Floxuridine - Recommended Dose Modification	63
Table 13. Floxuridine - Restarting Treatment After Hold.....	64
Table 14. mFOLFIRI – Recommended Dose Reduction for Hematologic Toxicities	65
Table 15. mFOLFIRI – Recommended Dose Reduction for Non-Hematologic Toxicities	65
Table 16. Method and Timing of QoL Assessments	76
Table 17. For Subjects with Measurable Disease (i.e., Target Disease).....	86
Table 18. For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)	87
Table 19. Key safety concerns associated with HAI pump therapy.....	92
Table 20. Pocock stopping boundary	98
Table 21. ECOG/ Karnofsky Performance Status.....	110
Table 22. Classification of Surgical Complications	111

LIST OF FIGURES

Figure 1. Overview of study design.	15
Figure 2. Study Flow	16
Figure 3. Outcomes of ICC and HCC patients receiving HAI floxuridine-DEX.	34
Figure 4. Assessment of survival following HAI and SYS versus SYS alone.	35
Figure 5. Splicing of SynchroMed II pump with tapered silicone catheter	70
Figure 6. Pocock Stopping Boundary	98

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	Blood urea nitrogen
CA19-9	Carbohydrate antigen 19-9
CBC	Complete blood cell (count)
CEA	Carcinoembryonic antigen
CHC	Circulating hybrid cell
CHF	Congestive heart failure
CR	Complete response
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CRLM	Colorectal liver metastases
CRQA	Knight Clinical Research Quality and Administration
CT	Computerized tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DEX	Dexamethasone
DFS	Disease-free survival
DLT	Dose limiting toxicity
DSS	Disease specific survival
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DWI	Diffusion weighted Magnetic Resonance Imaging
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
ETD	Early treatment discontinuation
FCBP	Female of childbearing potential
FFPE	Formaldehyde-fixed paraffin embedded
FDA	United States Food and Drug Administration
FGFR2	Fibroblast growth factor receptor type 2
FOLFIRINOX	Folinic acid (leucovorin); 5-fluorouracil; irinotecan; oxaliplatin
FOLFIRI	Folinic acid (leucovorin); 5-fluorouracil; irinotecan;
FOLFOX	Folinic acid (leucovorin); 5-fluorouracil; oxaliplatin
5FU	Fluorouracil, 5-fluorouracil
FUDR®	Floxuridine
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GTV	Gross Tumor Volume
HAI	Hepatic arterial infusion
HBsAg	Hepatitis B antigen
HBV	Hepatitis B virus

HCC	Hepatocellular carcinoma
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICC	Intrahepatic cholangiocarcinoma
uICC	Unresectable intrahepatic cholangiocarcinoma
ICJME	International Committee of Medical Journal Editors
ICH	International Conference on Harmonization
IDH	Isocitrate dehydrogenase
IND	Investigational new drug application
IP	Investigational product
IRB	Institutional Review Board
IV, iv	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
miRNA, miR	MicroRNA
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association
OHSU	Oregon Health and Science University
ORR	Overall response rate
OS	Overall survival
PD	Disease progression
PFS	Progression free survival
PHI	Personal health information
PI	Principal Investigator
PO	<i>Per os</i> (by mouth, orally)
PR	Partial response
QA	Quality assurance
QC	Quality control
QoL	Quality of Life
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RTOC	Radiation Therapy Oncology Group
SAE	Serious adverse events
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPECT	Single-photon emission computed tomography
Std Dev	Standard deviation
SYS, sys	Systemic
UP	Unanticipated problems
ULN	Upper limit of normal
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF INTRAHEPATIC CHOLANGIOCARCINOMA

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer in the United States, accounting for 10-20% of all primary liver cancers, with approximately 5,000 new cases diagnosed each year.^{1,2} ICC is pathologically distinct from hepatocellular carcinoma (HCC) and thus requires a unique clinical management strategy. There has been an increase in the reported annual incidence of ICC over the past 10 years. This is likely attributable to improved pathologic classification, coupled with the rising incidence of other risk factors including viral hepatitis and non-alcoholic fatty liver disease (e.g., steatohepatitis associated with a growing obese population).^{1,3} The overall survival (OS) for those diagnosed with ICC remains poor, with most patients succumbing to their disease in less than 12 months, even following the use of modern systemic regimens such as gemcitabine and cisplatin.⁴ While complete surgical resection remains the only potentially curative treatment for patients with resectable ICC, upwards of 70% of patients with newly diagnosed ICC are not candidates for hepatic resection due to the presence of advanced disease at diagnosis.⁵ Moreover, even after resection of ICC, 50–60% of patients develop recurrent disease in the liver, the peritoneum (20%), and portal lymph nodes (20–30%); and is reflective of the micro-metastatic hepatic disease burden present at diagnosis.⁶

1.2 SYSTEMIC THERAPY FOR INTRAHEPATIC CHOLANGIOCARCINOMA

The current standard-of-care in the treatment of patients with advanced, unresectable biliary tract cancer is systemic treatment with a first-line therapeutic combination of gemcitabine and cisplatin, which has shown superiority to gemcitabine alone.⁷ This practice is based upon the ABC-02 trial that included patients with a variety of advanced and metastatic biliary tract cancers (ICC, extrahepatic cholangiocarcinoma, gallbladder adenocarcinoma, etc.). In this trial, however, specific evaluation of tumor response by disease site revealed no significant difference in the 6-month disease control rate (DCR) for cholangiocarcinoma patients receiving either gemcitabine monotherapy or a combination of cisplatin and gemcitabine (69% vs. 79%, $p = 0.1$).⁷ A recent review of several other randomized and prospective, non-randomized trials of biliary tract cancer suggests that treatment with the combination of gemcitabine and cisplatin achieves an average DCR of 62% at 6 months.⁸

Treatment options following a failure to respond to a gemcitabine and cisplatin combination are even less certain, as no prospective trials have established an optimal second-line chemotherapeutic regimen. Among several second-line treatment options, oxaliplatin- and fluorouracil-based combinations have garnered increasing interest as potential strategies (Table 1).

Table 1. Oxaliplatin- and fluorouracil-based combinations for treating ICC.				
Trial (year)	Drugs	Dose	N	Median Overall Survival (mos)
He ⁹ (2014)	FOLFOX	oxaliplatin (85 mg/m ²) as a 2-hour i.v. infusion on day 1 and 2-hour i.v. infusion of leucovorin (200 mg/m ² /day) followed by a 5-fluorouracil i.v. bolus (400 mg/m ² /day) and 22-hour i.v. infusion of 5-fluorouracil (600 mg/m ² /day) for two consecutive days every 2 weeks.	37	14.1
Moretto ¹⁰ (2013)	FOLFIRI	irinotecan 180 mg/m ² , day 1; leucovorin 100 mg/m ² i.v., days 1 and 2; 5-fluorouracil 400 mg/m ² i.v. bolus, days 1 and 2; and 600 mg/m ² in 22 h i.v., continuous infusion days 1 and 2; every 14 days.	54	14.5
Guion-Dussere ¹¹ (2015)	FOLFIRI	Irinotecan (180 mg/m ² i.v. over 90 min) concurrently with folinic acid (400 mg/m ² i.v. over 120 min) followed by fluorouracil (400 mg/m ² i.v. bolus), then i.v. fluorouracil (2400 mg/m ² over 46 h), and bevacizumab (5 mg/kg) every 2 weeks.	13	20

In a phase II study of patients with advanced biliary tract cancer refractory to a gemcitabine and cisplatin regimen, the combination of Folinic Acid (leucovorin), Fluorouracil, and Oxaliplatin (FOLFOX) was evaluated for efficacy and safety. The FOLFOX regimen consisted of oxaliplatin (85 mg/m²) as a 2-hour i.v. infusion on day 1 and 2-hour i.v. infusion of leucovorin (200 mg/m²/day) followed by a 5-fluorouracil i.v. bolus (400 mg/m²/day) and 22-hour i.v. infusion of 5-fluorouracil (600 mg/m²/day) for two consecutive days every 2 weeks. The authors reported that the objective response rate was 22% among the 37 patients treated with FOLFOX. Disease control was achieved in 62.2% of the treated patients. Approximately 38% of patients experienced grade 3-4 toxicities, the most frequent of which were neutropenia and fatigue.⁹

Moretto et al¹⁰ evaluated a regimen of Folinic Acid (Leucovorin), fluorouracil, and irinotecan (FOLFIRI) as either a first or second-line treatment among 54 patients with pancreatic or biliary tract tumors. FOLFIRI treatment as a first-line approach was associated with a 25% response rate, and as a second-line therapy 43% of patients obtained a stable disease as best response. As a first-line and second-line therapy, the median progression-free survival rates were 3.1 months (95%CI, 1.9-4.4) and 3.5 months (95% CI, 2.6-4.4), respectively. Likewise, the median overall survival rates were 14.5 months (95% CI, 7.0-22.1) and 6.2 months (95% CI, 5.4-7.0), respectively, in the first-line and the second-line cohort of patients. The most frequent grade 3-4 adverse event were neutropenia, and grade 3 gastrointestinal toxicity was observed in only two cases.

Authors of a recent pilot study evaluated the combination of FOLFIRI and bevacizumab as a second-line therapy in 13 patient with metastatic ICC with gemcitabine and oxaliplatin refractory disease. Seven deaths occurred at the time of analysis. Progression free survival was 8 months (95%CI, 7 to 16), and median overall survival was 20 months (95%CI, 8 to 48). The response rate was 38.4% (95%CI, 12.5 to 89) and the disease control rate was 84.5% (95%CI, 42 to 100). No grade 4 toxic events were observed, but the authors noted four grade 3 hematological toxicities and one grade 3 digestive toxicity.¹¹

In the phase III PRODIGE trial, 342 patients with metastatic pancreatic cancer were randomly assigned to receive FOLFIRINOX or gemcitabine. The authors reported that the median overall

survival was 11 months for those receiving FOLFIRINOX as compared to 7 months in the gemcitabine group (HR for death, 0.57; 95% CI, 0.45 to 0.73; $P < 0.001$). Patients given FOLFIRINOX had a median progression-free survival of 6.4 months, whereas this was only 3.3 months for those receiving gemcitabine (HR for disease progression, 0.47; 95% CI, 0.37 to 0.59; $P < 0.001$). The objective response rate 3.3 times higher among those receiving FOLFIRINOX (32%) versus patients treated with gemcitabine (9.4%; $P < 0.001$). Compared to those treated with gemcitabine, patients in the FOLFIRINOX group reported a significantly lower degradation in the quality of life by 6 months, (31% vs. 66%, respectively; HR, 0.47; 95% CI, 0.30 to 0.70; $P < 0.001$).¹²

1.3 HEPATIC ARTERIAL INFUSION

Hepatic arterial infusion (HAI) originated in the early 1960s as a treatment approach for patients with gastrointestinal tumors metastatic to the liver.¹³ By taking advantage of first-pass liver metabolism, the underlying rationale for HAI is to expose the hepatic metastases to high chemotherapy concentrations and minimize systemic toxicity. This is achieved by infusion of drug into the hepatic artery, which provides a majority of tumor blood supply. This is in contrast to the hepatic portal vein, which mostly supplies blood to normal liver cells. Since its inception, HAI has been used to deliver a variety of agents such as: 5-fluorouracil (5-FU), mitomycin, cisplatin, doxorubicin, and 5-fluoro-2'-deoxyuridine (floxuridine). Of these chemotherapeutic agents, floxuridine (a.k.a., FUDR) is the most frequently studied; largely because it is associated with high hepatic extraction (94-99%) followed by rapid clearance. Notably, tumor levels of floxuridine are 15-times greater when infused via the hepatic artery as opposed to the portal vein.¹³

Initial phase II trials first reported survival benefit in patients with unresectable colorectal liver metastases (CRLM) that used an implantable pump for HAI of floxuridine (HAI floxuridine). Radiographic response rates were reported as high as 88%, and the 1-year survival rate and median survival were superior compared to historic controls (82% vs 36% and 26 months vs 8 months, respectively ($P < .0001$)).¹⁴

Other randomized trials have shown significant improvements in response, time to hepatic progression, or overall survival following HAI floxuridine, as compared to systemic chemotherapy (Table 2).^{15,16}

Table 2. Selected Randomized Trials in Unresectable Metastases					
Trial	Drug	N	HAI Dose	IV Dose	Median OS (months)
Colorectal cancer liver metastases (CRLM)					
Kemeny ¹⁶	HAI floxuridine vs IV floxuridine	99	0.3 mg/kg/d for 14 days/28 days	0.125 mg/kg/d (14 days every mo)	17 vs 12
Chang ¹⁵	HAI floxuridine vs IV floxuridine	64	0.3 mg/kg/d for 14 days/28 days	0.125 mg/kg/d (14 days q 28 days)	17 vs 12
Hohn ¹⁷	HAI floxuridine vs IV floxuridine	143	0.2-0.3 mg/kg/d for 14 days/28 days	0.075 mg/kg/d (14 days q 28 days) 0.025 increase/cycle	16.5 vs 5.8
Safi ¹⁸	HAI floxuridine vs HAI & IV floxuridine	44	0.2 mg/kg/d for 14 days/28 days	0.3 mg/kg/d for 14 days/28 days	NS
Wagman ¹⁹	HAI floxuridine vs IV 5FU	41	0.1-0.5 mg/kg/d for 14 days/28	10-50 mg/kg weekly	13.8 vs 1.6

Table 2. Selected Randomized Trials in Unresectable Metastases					
Trial	Drug	N	HAI Dose	IV Dose	Median OS (months)
			days		
Martin ²⁰	HAI floxuridine vs IV 5FU/LV	74	0.3 mg/kg/d for 14 days/28 days	500 mg/m ² /d (5 days q 35 days)	12.6 vs 0.5
Rougier ²¹	HAI floxuridine vs IV 5FU vs Observation	163	0.3 mg/kg/d for 14 days/28 days	500 mg/m ² /d (5 days q 4 weeks)	15 vs 11*
Allen-Mersh ²²	HAI floxuridine vs Observation	100	0.2 mg/kg/d for 14 days/28 days		
Lorenz ²³	HAI floxuridine vs HAI 5FU/LV vs IV 5FU/LV	168	0.2 mg/kg/d for 14 days/28 days	800-1000 mg/m ² /d + 200 mg/m ² /d (5 days q 28 days)**	12.7 vs 18.7 vs 17.6
Kerr ²⁴	HAI 5FU/LV vs IV 5FU/LV	290	bolus 200 + 400 mg/m ² and 22-h infusion 1600 mg/m ² , days 1 and 2 (every 14 days)	bolus 200 + 400 mg/m ² and 22-hr infusion 600 mg/m ² days 1 and 2 (q 14 days)	14.7 vs 14.8
ICC and HCC					
Jarnagin ²⁵	HAI floxuridine	34	0.16 mg/kg floxuridine + 25 mg DEX for 14 days / 4-week cycle		
	ICC	26			PR = 14 (53.8%) SD = 11 (42.3%) PD = 1 (3.8%)
	HCC	8			PR = 2 (25%) SD = 3 (37.5%) PD = 3 (37.5%)
Konstantinidis ²⁶	HAI floxuridine + SYS ^a vs. SYS ^a	236	0.16 mg/kg floxuridine + 25 mg DEX for 14 days / 4-week cycle		30.8 vs 18.4 months [†]
<p>* Statistically significant</p> <p>** Same dose was given as HAI</p> <p>MOS = Median Overall Survival, HAI = hepatic artery infusion, IV = intravenous, 5-FU = 5-fluorouracil, LV = leucovorin, DEX = dexamethasone, NS = not significant, SYS = systemic chemotherapy.</p> <p>^aA variety of SYS regimens were used: gemcitabine monotherapy; gemcitabine and cisplatin; gemcitabine, cisplatin, and sorafenib; gemcitabine, cisplatin, and irinotecan; gemcitabine and oxaliplatin; gemcitabine and capecitabine; gemcitabine and erlotinib; gemcitabine and irinotecan; gemcitabine, carboplatin, and taxol; 5-fluoruracil; 5-fluoruracil and irinotecan; 5-fluoruracil and oxaliplatin; and other SYS agents (GX-8951S, platinum-based regimens, and taxol-based regimens).</p> <p>[†]Overall survival (OS) for the combined group was longer than overall survival for the patients who received SYS alone (P < 0.001).</p> <p>Adapted from Homsí and Garret²⁷</p>					

Authors of a 5-year retrospective review examined 125 patients that underwent hepatic resection followed by adjuvant HAI-delivered floxuridine-dexamethasone (DEX) in combination

with systemic FOLFOX or FOLFIRI. Using multivariate analysis, the authors observed that HAI-floxuridine was independently associated with improved liver recurrence-free survival (HR, 0.34; $P \leq 0.01$), overall recurrence-free survival (HR, 0.65; $P = 0.01$), as well as disease-specific survival (HR, 0.39; $P = 0.01$).²⁸

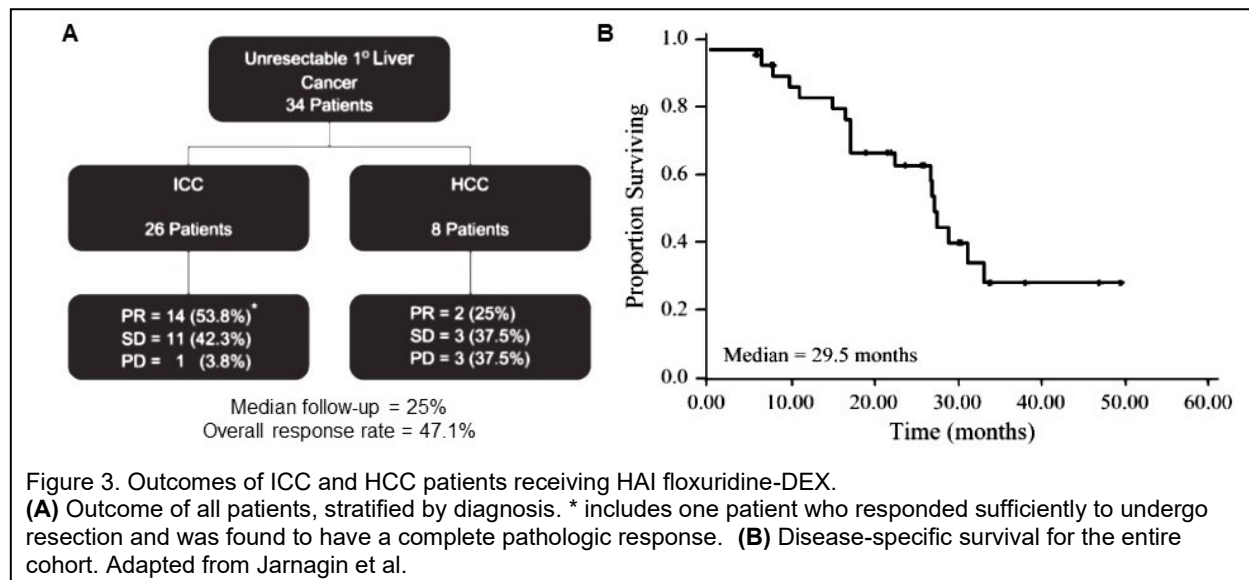
Kemeny et al²⁹ investigated the treatment outcomes in CRLM patients that had undergone hepatic resection. A total of 156 patients were randomly assigned to receive either HAI floxuridine-DEX along with i.v. 5-FU/leucovorin, or i.v. 5-FU/leucovorin alone. Of those receiving HAI and systemic therapy, the median overall survival was 72 months, but was only 59 months for patients receiving 5-FU/leucovorin alone. Hepatic recurrence free survival was notably higher among those receiving HAI chemotherapy and systemic therapy versus those treated with systemic therapy alone (90% vs. 60%, respectively; $P < 0.001$); however, disease free survival at 2 years was not significant between treatment groups (57% vs 42%; $P = 0.07$). In both treatment groups, a total of 6 patients required biliary stents (4 were alive at time of reporting, 2 died of progressive liver disease). In the remaining participants, serum total bilirubin levels returned to normal when the hepatic arterial infusion was discontinued. Although toxicity was greater in the combined group and resulted in therapy dose reductions, the overall number of deaths during treatment was not different between treatment groups. It is important to note that this trial completed accrual prior to the advent of either oxaliplatin- or irinotecan-based systemic regimens, which is not the standard of care for patients with advanced colorectal cancer.

In an updated study, Kemeny et al³⁰ sought to determine the rate at which CRLM patients could convert to a resectable disease following HAI floxuridine-DEX with systemic oxaliplatin and irinotecan. Among the 49 patients evaluated, those that received HAI floxuridine-DEX with systemic irinotecan and oxaliplatin, achieved a response rate of 92%, with 47% of patients demonstrating a conversion to resection. Whereas the median survival from the start of HAI therapy was 50.8 for chemotherapy-naïve patients, those that had been previously treated had a median survival of 35 months.

Cercek et al³¹ evaluated the role of HAI therapy in CRLM patients with metastatic colorectal cancer that were refractory to oxaliplatin, irinotecan, and fluorouracil-based treatments. Among 110 patients, 57 were characterized as CRLM only, and 53 were found to have low volume extrahepatic disease (LME). The authors observed that patients with only CRLM had a response rate of 33% and a median survival of 20 months. Although LME patients had a response rate of 36% following HAI therapy, the median survival among this patient cohort was only 11.4 months. These findings suggest that a regional directed approach is useful in treating liver dominant disease that is otherwise refractory to standard lines of cytotoxic chemotherapy.

1.3.1 OTHER LIVER DOMINANT MALIGNANCIES

The interest in HAI therapy has now expanded to treating other liver-dominant cancer types including ICC and HCC, where liver-dominant disease is characterized by the majority of disease confined to the hepatic parenchyma, with very limited extrahepatic disease. While there are only a small number of published studies, their initial results demonstrate that use of HAI therapy for treating other liver-dominant cancer is both safe and feasible.

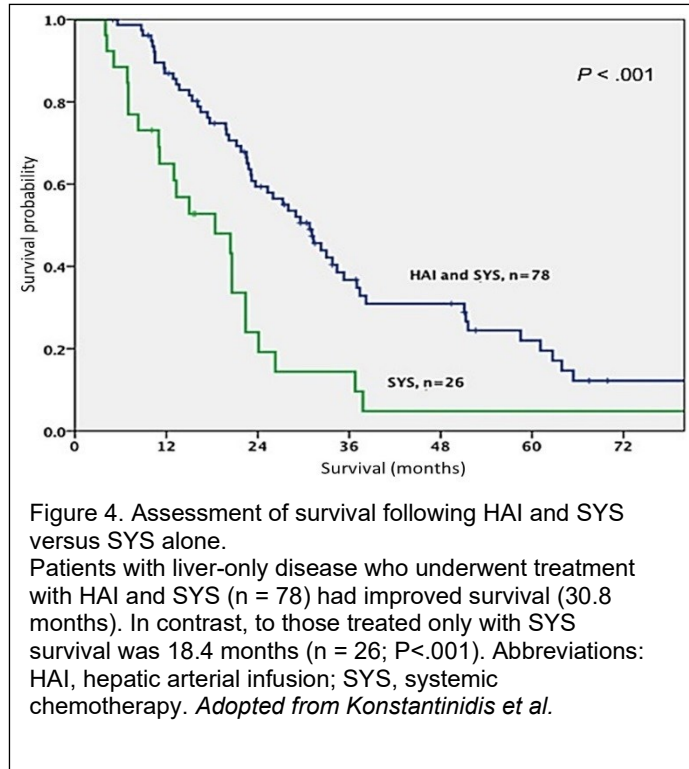


Jarnagin et al²⁵ reported on the efficacy of HAI delivery of floxuridine and DEX to treat patients with unresectable ICC (n = 26) or HCC (n = 8) (Figure 2A). The authors observed an overall response rate of 47% among all patients, with a time to progression and response duration were 7.4 and 11.9 months, respectively. Median survival was 29.5 months (Figure 2B). A partial response was seen in 14 patients with ICC (54%), of which, one patient responded sufficiently enough to undergo resection and was found to have a complete pathologic response. Patients with HCC had a partial response rate of only 25% (Figure 2A). Thirty-three of 34 patients developed disease progression at a median follow-up of 25 months, of which 73% (24 of 33 patients) received additional HAI treatment after removal from the study. Among these, 14 received HAI floxuridine in conjunction with systemic therapy (gemcitabine/ oxaliplatin, or irinotecan). The OS at 2 years was 67%. The authors noted 5 chemotherapy-related complications, including: three patients with elevated serum bilirubin (grade 4 in two and grade 3 in one), one patient with grade 3 abdominal pain, and one patient with grade 3 diarrhea. Eight (24%) of 34 patients incurred post-operative complications that were related to pump placement. One patient was removed from the study after two cycles with disease progression and liver failure due to exacerbation of chronic hepatitis B infection.

Konstantindis et al²⁶ at Memorial Sloan Kettering Cancer Center in New York (MSKCC) reported on their experience in n=104 patients with liver-only disease treated with HAI of floxuridine-DEX combined with various systemic regimens, including fluorouracil and irinotecan. The authors report an improved OS for the combined HAI + SYS group compared to patients who receive SYS alone (30.8 vs. 18.4 months, $P<0.001$) (Figure 4). Additionally, this survival difference was maintained when the analysis included patients with disease metastatic to portal lymph nodes.

1.3.2 QUALITY OF LIFE

Aside from the OS impact, controlling a patient's hepatic disease burden has important potential quality-of-life (QoL) benefits. In 2006, Kemeny et al³² reported on the multi-institutional CALGB



9481 prospective trial involving n=135 patients with CRLM randomized to either HAI floxuridine-DEX or systemic treatment with 5-FU/LV. The investigators demonstrated that, OS was significantly longer for HAI therapy versus systemic treatment (median OS, 24.4 v 20 months; $P=0.0034$), as were response rates (47% and 24%; $P=0.012$). Moreover, QoL measurements showed that physical functioning at the 3- and 6-month follow-up was significantly better among those in the HAI group compared to those receiving systemic therapy³². This study provided evidence that in patients with unresectable CRLM, HAI therapy provided superior survival with improved physical functioning when compared to systemic treatment alone. Importantly, this trial accrued prior to the development of oxaliplatin- and irinotecan-based systemic regimens for metastatic colorectal cancer, which is

the current first- and second-line treatments used in the United States in the current era. In addition, numerous subsequent studies have demonstrated the improved efficacy of co-administration of HAI treatment with systemic therapy. However, the concurrent administration of HAI therapy + modern systemic treatment has not been evaluated in a prospective, randomized QoL study for patients with any metastatic or primary liver cancer.

Allen-Mersh et al²² compared QoL and survival in CRLM patients that either received HAI floxuridine or conventional symptom palliation. In addition to a significant increase in overall survival for those receiving HAI floxuridine compared to conventional therapy (median survival of 405 vs 226 days, respectively), the authors observed significant QoL improvements associated with HAI therapy. This included significant prolongations in normal-quality survival for physical symptoms, as well as anxiety and depression.

1.3.3 SAFETY OF HAI PUMP THERAPY

HAI of floxuridine is safe, but not without potential complications. Particularly, biliary sclerosis is one of the most feared treatment-related complications associated with HAI floxuridine therapy. However, this complication occurs relatively infrequently and with minimal patient or treatment impact with modern dosing and reductions.³³

For patients that underwent HAI with floxuridine and dexamethasone (with or without bevacizumab) in advanced ICC, Konstantinidis et al³⁴ reported that postoperative complications related to pump placement occurred in six (14 %) patients (3 in each treatment arm). The authors noted that Grade 3/4 toxicity occurred in ten (23%) of patients that were mostly biliary toxicity-related. Notably, the excessive toxicity associated with the addition of bevacizumab to floxuridine led to early termination of this trial. As a result, bevacizumab is no longer given along with HAI floxuridine centers offering this treatment.

In a trial related to the bevacizumab study, D'Angelica et al³⁵ reported on 49 patients with unresectable CRLM that received HAI therapy. The overall grade 3/4 toxicity rate was 41% (20/49), with the first 24 patients receiving floxuridine and bevacizumab experiencing an unexpectedly high rate of biliary toxicity, in which 3 patients required biliary stents. Once bevacizumab was removed from the trial, the remaining 25 patients enrolled in the study had a 28% rate of grade 3/4 toxicity, and a significantly better biliary toxicity profile, with only 1 (4%) patient requiring a biliary stent. Seven patients (14%) experienced a grade 1 or 2 complication associated with pump placement.

Jarnagin et al²⁵ evaluated the safety and efficacy of 34 participants with unresectable ICC or HCC that were treated with HAI floxuridine. Patients in this study received a median of 7 treatment cycles, during which time floxuridine dose reductions, typically for serum liver enzyme elevations, was 62.5% lower (0%–98%) than the starting dose. Five patients (14.7%) in this study experienced grade 3 or 4 toxicity, 3 of which had elevations of serum bilirubin (grade 4 in two and grade 3 in one), all of which resolved with dose modification; there were no biliary strictures. The other 2 grade 3 complications (migraine headache and diarrhea) were attributable to diuretic therapy and a preexisting condition, respectively.

At OHSU, our experience with HAI floxuridine therapy currently extends to 14 HAI pumps that have been surgically placed (10 for unresectable CRLM and 4 as adjuvant therapy for high-risk CRLM). Of these, there has been only 1 case (7.1%) of biliary sclerosis that resulted in a 3 week delay to patient treatment. Once symptoms resolved HAI floxuridine treatment was resumed. In another patient, there was a single case of extrahepatic perfusion that was immediately recognized and corrected with IR angioembolization allowing the patient to quickly resume both HAI and systemic treatment.

1.4 RATIONALE

This is a Phase II, single-arm, open label study to assess the safety, toxicity, and tolerability of using systemic induction of mFOLFIRINOX, followed by systemic administration of mFOLFIRI in combination with HAI floxuridine-DEX, as a first-line treatment for liver-dominant, technically unresectable ICC.

Regional therapy using a surgically implanted HAI pump allows for maximal liver-directed treatment of patients with unresectable ICC with agents that are processed in the liver, thereby limiting the toxic side effects seen with traditional chemotherapy. Since the chemotherapy delivered via HAI is processed in the liver, much higher doses can be delivered than could ever be tolerated if given systemically by traditional means. With a greater than 95% first-pass metabolism, floxuridine epitomizes the ideal agent for delivery via HAI. Notably, treatment of ICC patients, and those with other liver-dominant cancers, appears to work best in combination with systemic therapy.²⁶

Results from the PRODIGE trial demonstrated that progression-free survival is nearly twice the amount with FOLFIRINOX compared to first-line gemcitabine and cisplatin (6.4 months vs. 3.3 months, respectively) for patients with pancreatic cancer, and is a preferred treatment for this disease.¹² Encouraged by these findings, the National Comprehensive Cancer Network (NCCN) guidelines provide a category 2a recommendations for the use of platinum-based and fluoropyrimidine-based chemotherapeutic regimens to treat patients with unresectable ICC.³⁶ Similar NCCN category 2b recommendations support the used of HAI therapy for treating unresectable ICC.

There is a dearth of prospective information to suggest what treatment approach is most effective to treating unresectable ICC. Given the rarity of this disease and limited prospective data, then it is reasonable to consider that the combination of FOLFOX, FOLFIRI, or FOLFIRINOX provide a viable chemotherapeutic option for the systemic treatment of patients with ICC. Notably, this treatment approach has been adopted by numerous NCCN-designated Comprehensive Cancer Centers, including the Knight Cancer Institute at OHSU.

In this study, mFOLFIRINOX will be administered upfront as a maximal induction treatment to participants with liver-dominant, unresectable, ICC. Exposure to this regimen will enable selection of individuals that are most likely to benefit from a period of intensive liver-directed therapy using HAI to deliver floxuridine and DEX, as well as provide justification for a concurrent dose-modified systemic regimen of mFOLFIRI. A fundamental goal of this study is to provide prospective data regarding DCR and PFS among disease patient that are treated with FOLFIRINOX and HAI therapies.

1.5 POTENTIAL RISKS AND BENEFITS

1.5.1 KNOWN POTENTIAL RISKS

The potential risk associated with treatment are detailed in Section 9. Additional details regarding specific risks for those participating in this clinical trial including treatment and surgical risks may be found in the informed consent documents.

This study will utilize the SynchroMed II HAI pump to administered floxuridine. This FDA-approved HAI pump will be spliced to a tapered catheter that is in turn inserted into the hepatic artery. This splicing of the pump connector to catheter has the potential for catheter malfunction including obstruction and disconnection. If the catheter were to become obstructed at the splice site, the HAI pump would alarm indicating an obstruction. In such events, the connection can be respliced with a minor procedure. A disconnection at the splicing point could result in the floxuridine/dexamethasone being infused at a slow rate intra-peritoneally. To prevent disconnection, the splicing connection is tested numerous times in the operating room. In addition, the participant will undergo a nuclear medicine HAI pump study in which there is testing of the device under direct imaging to specifically evaluate for extra-hepatic perfusion (which includes evaluation of the spliced area [refer to Section 7.3]).

1.5.2 KNOWN POTENTIAL BENEFITS

Given the lack of treatment options for treating metastatic liver ICC, the current study may provide access to a new treatment approach not previously available. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

1. Assess the toxicity, safety and tolerability of HAI floxuridine therapy.
2. Evaluate the efficacy of systemic induction of mFOLFIRINOX, followed by HAI of floxuridine-DEX administered concurrently with systemic mFOLFIRI

2.2 SECONDARY OBJECTIVES

1. To evaluate tumor response to treatment and participant survival.
2. Assess rate of post-operative complications
3. Evaluate serious post-operative complications following surgical placement of the HAI pump.

2.3 EXPLORATORY OBJECTIVES

2.3.1 DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING (DWI)

To assess the radiographic response using DWI as part of an MRI examination. In this objective, DWI will be investigated as a potential imaging biomarker and will measure restricted diffusion as a means to predict treatment response.

2.3.2 QUALITY OF LIFE ASSESSMENT (QoL)

Determine whether, compared to historical controls, induction mFOLFIRINOX combined with integrated HAI of floxuridine-DEX and systemic mFOLFIRI treatment will improve patient QoL including fatigue and depression.

2.3.3 TUMOR TISSUE BIOMARKER ASSESSMENT

Investigate molecular signature associated with ICC.

2.3.4 MICRORNA (miR)

Generate a differential expression pattern of RNAs (miR and mRNA) in patients with ICC derived from tumor samples compared to adjacent normal liver samples as well as lymphatic tissue, blood and bile).

2.3.5 CIRCULATING HYBRID CELLS (CHC)

Characterize the changes in the population of CHCs pre-, during, and post-treatment.

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Please refer to Section 10, STATISTICAL CONSIDERATIONS for additional information regarding statistical methods used in this study.

This is a Phase II, single-arm, open label study to assess the safety, toxicity, tolerability, and efficacy of using systemic induction of mFOLFIRINOX, followed by systemic administration of mFOLFIRI in conjunction with HAI of floxuridine and DEX, as a first-line treatment of liver-dominant, unresectable ICC. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

In Screening 1, participants will be evaluated for study eligibility by CT imaging and staging laparoscopy to determine the presence of peritoneal disease and occult dissemination of ICC within the liver. Suspicious lesions will be biopsied for pathological assessment, and remaining excess tissue collected as part of the baseline biopsy. Eligible trial participants will then proceed on with the treatment portions of the study.

This study consists of a two-part treatment plan in which eligible participants will first receive a systemic regimen of mFOLFIRINOX with 25% dose reduction of oxaliplatin, irinotecan, and fluorouracil administered every 2-weeks for 4 cycles (8 weeks) (Treatment Period 1). After completing mFOLFIRINOX induction, participants' disease will be reevaluated by MRI/CT imaging. In this second screening process (i.e., Screening 2), only those that achieve disease control based on RECIST criteria (v1.1) will be eligible HAI therapy (Treatment Period 2). Participants with development of new or progressive extrahepatic disease will be taken off study directed treatment. Likewise, participants with a complete radiographic response will also be taken off-study directed treatment for consideration of further systemic mFOLFIRINOX per standard of care. Participants eligible for Treatment Period 2 will be taken to the operating room for a diagnostic laparoscopy to further evaluate for peritoneal disease and if negative will immediately undergo an exploratory laparotomy with planned placement of an HAI pump, cholecystectomy and portal lymphadenectomy. After the operation has concluded, SPECT/CT imaging of the HAI pump (no sooner than post-operative day 4) will be used to confirm acceptable hepatic perfusion without evidence of extrahepatic perfusion. Treatment Period 2 will begin approximately 14 days after their operation. During this time, participants will begin the first 4-week cycle of HAI floxuridine-DEX. Provided that no dose holds due to predefined toxicity are required, the floxuridine dosages will be adjusted for changes in weight and pump flow rate specific for the participant and implanted device as per our established practice at OHSU. This will be followed up with systemic administration of fixed-dose mFOLFIRI.

Starting on Day 1 of each cycle, HAI floxuridine-DEX will be infused over a 14 (+7) day period. Participants will then receive mFOLFIRI on Day 15 of each cycle (Table 3). After completing two cycles of HAI floxuridine-DEX and systemic mFOLFIRI, participants will undergo repeat imaging to restage disease.

Table 3. HAI floxuridine-DEX and systemic mFOLFIRI treatment regimen			
Cycle 1		Cycle 2	
Day 1	Day 15	Day 1	Day15
HAI floxuridine-DEX	HAI heparin-saline	HAI floxuridine-DEX	HAI heparin-saline

No systemic FOLFIRI	systemic FOLFIRI	Systemic 5-FU	systemic FOLFIRI
---------------------	------------------	---------------	------------------

MRI examinations of the abdomen and pelvis are obtained at baseline following operation, prior to treatment initiation, and 4 weeks after initiation of HAI floxuridine-DEX. Subsequently, the participant may undergo MR imaging at months 3, 6, and 9 months thereafter to assess tumor response according to RECIST criteria (v1.1). A CT of chest, abdomen, and pelvis with oral and IV contrast will also be obtained as part of routine clinical care. Patients will remain on study treatment as long as they show continued response as defined in Section 8, and do not experience significant toxicity as defined in Section 9, SAFETY.

This Phase II study consists of an initial 6 person safety run-in phase, in which the incidence of abnormal liver function associated with HAI therapy in Treatment Period 2 will be monitored. Specifically, the study will be stopped if, at by the end of treatment period 2, 2 of 6 (33.3%) participants experience an elevation in liver enzymes that necessitates a dose-hold of HAI floxuridine-DEX that cannot be restarted per the established OHSU HAI protocol (refer to Section 6.2.2, Table 12 Table 13), or show radiographic evidence of biliary sclerosis on CT/MRI. If fewer than 2 toxicities are observed, then enrollment of an additional 24 participants will proceed as described. Safety monitoring will be continuous throughout the trial, and the study will be stopped early should the incidence of this predefined toxicity exceeds 33.3% at any time after the initial 6 participants.

The phase II objective is to evaluate the efficacy of the treatment regimen as measured by the DCR from the start to end of the combination HAI floxuridine-DEX and mFOLFIRI treatment (approximately 2 months). Additional analysis will evaluate the DCR for the entire therapeutic course including from the start of mFOLFIRINOX to end of combination HAI-Dex and mFOLFIRI (approximately 6 months). The DCR determined in this study will be compared to the historical DCR of 60% at 6 months for ICC patients treated with the current first-line combination of gemcitabine and cisplatin. Separating the DCR in this fashion allows for an evaluation of the DCR attained with mFOLFIRINOX independent from the DCR achieved with the HAI floxuridine-DEX and mFOLFIRI regimen.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINTS

Objective	Endpoint
1. Assess the toxicity, safety and tolerability of HAI floxuridine therapy.	1. Incidence of abnormal liver function, as defined by unacceptable elevation in liver enzymes (refer to Section 6.2, Table 12), or radiographic evidence of biliary sclerosis on CT/MRI (as measured following the completion of 2 cycles of HAI in Treatment Period 2).[post-induction population will be used]
2. To evaluate the efficacy of systemic induction of mFOLFIRINOX, followed by HAI floxuridine-DEX administered concurrently with systemic mFOLFIRI.	2. To determine the disease control rate (DCR) from beginning of Treatment Period 2 to end of Treatment Period 2 during treatment with HAI + SYS. The DCR is defined as the percentage of

	patients who have achieved complete response (CR), partial response (PR), or stable disease (SD).
--	---

3.2.2 SECONDARY ENDPOINTS

Objective	Endpoint
To evaluate tumor response to treatment and participant survival.	1. DCR from beginning of Treatment Period 1 to end of Treatment Period 2 (i.e., from the beginning of the entire treatment protocol until the end of study treatment).
	2. DCR from beginning of Treatment Period 1 to end of Treatment Period 1 (i.e., during the treatment with FOLFIRINOX alone).
	3. PFS from beginning of Treatment Period 1 to end of Treatment Period 1 (i.e., during the treatment with FOLFIRINOX alone).
	4. PFS from beginning of Treatment Period 1 to end of Treatment Period 2 (i.e., from the beginning of the entire treatment protocol until the end of study treatment).
	5. PFS from beginning of Treatment Period 2 to up to 1-year after the end of Treatment Period 2 (i.e., during the treatment with HAI Floxuridine + mFOLFIRI).
	6. ORR from beginning of Treatment Period 1 to end of Treatment Period 2 (i.e., from the beginning of the entire treatment protocol until the end of study treatment).
	7. OS at the end of Treatment Period 1, at the end of Treatment Period 2, and at 1 year, and the whole study period.
	8. Proportion of liver toxicity in participants receiving HAI Floxuridine + dexamethasone therapy.
Determine rate of serious post-operative complications.	9. Incidence of serious post-operative complications, which are defined as complications occurring within 9 weeks following surgery and $\geq$ Grade III per the Clavien-Dindo classification system (Appendix B). ³⁷

3.2.3 EXPLORATORY ENDPOINTS

Objective	Endpoint	Start	End
1. To assess the radiographic response using diffusion-weighted MRI (DWI).	1. DWI measure of tumor diffusion coefficients.	≤ 30 days prior to Treatment Period 1	14 ± 5 days following end Treatment Period 2
2. Evaluate QoL pre-, during, and post-treatment.	2. QoL measures		
3. Explore potential biomarkers.	3. Genomic alteration profiling. Gene expression profiling.		
4. Examine differential miR expression pattern.	4. miR expression profiling		
5. Characterize CHCs pre- and post-treatment	5. Determine changes in CHC frequency.		

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age $\geq$ 18 years
2. Histologically confirmed intrahepatic cholangiocarcinoma (ICC; also variously reported as peripheral cholangiocarcinoma, cholangiolar carcinoma or cholangiocellular carcinoma) with confirmation of the pathologic diagnosis at OHSU.
3. Surgically unresectable liver-dominant ICC, or multifocal ICC considered surgically unresectable or resection is contraindicated ³⁸.
 - a. For liver-dominant ICC, disease must comprise $<70\%$ of the liver parenchyma, as defined by CT liver segmental volumetrics (see Section 9.4.1).
4. Limited extrahepatic disease.
 - a. Clinical or radiographic evidence of metastatic disease to regional lymph nodes and limited extrahepatic disease to the lungs is permitted at the discretion of the PI.
5. Radiographically measurable hepatic disease per RECIST v1.1 criteria.
6. Disease must be considered technically unresectable at the time of preoperative evaluation or radiographically multifocal as determined by hepatobiliary surgical oncologists
7. Participants should be treatment naïve. Those previously treated with systemic chemotherapy (e.g., gemcitabine, cisplatin, or other investigational agents) may be eligible at the discretion of the PI.
8. Participants with an ECOG 0 or 1 status (Karnofsky $\geq$ 60), and can be considered candidates for general anesthesia, abdominal exploration and hepatic artery pump placement.
9. Participants with treated chronic hepatitis (e.g., treated HBV, treated HCV) are eligible, but must be Child-Pugh class A.
10. WBC $\geq$ 3000 cells/mm³
11. ANC $\geq$ 1500 cells/mm³
12. Platelet count $\geq$ 100,000 / mm³
13. INR $\leq$ 1.5
14. Serum creatinine $\leq$ 1.5 x ULN OR creatinine clearance $\geq$ 40 ml/min (>0.675 ml/sec) using Cockcroft-Gault equation:
 - Males: $(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine [mg/dL]} \times 72)$
 - Females: $[(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine [mg/dL]} \times 72)] \times 0.85$
15. Total bilirubin $<$ 1.5 mg/dL
16. AST (SGOT)/ALT(SGPT) $\leq$ 2.5 x institutional upper limit of normal.
17. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

18. Participants must be able to read, understand, and sign informed consent.
19. Participants must be willing and able to fully comply with required post-operative visits associated with HAI chemotherapy.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Presence of extensive or multifocal metastatic extrahepatic or peritoneal disease. Clinical or radiographic evidence of metastatic disease to regional lymph nodes will be allowed, as will limited pulmonary disease at the discretion of the OHSU PI.
2. Prior treatment with floxuridine, oxaliplatin, or irinotecan.
3. Prior treatment with hepatic arterial infusion therapy.
4. Known to have experienced an allergic reaction or other signs of intolerance to implanted devices.
5. Body size that is insufficient to accommodate the physical size of the pump.
6. Diagnosis of sclerosing cholangitis.
7. Diagnosis of hepatic encephalopathy.
8. Clinical evidence of portal hypertension (ascites, gastroesophageal varices, or portal vein thrombosis) or hepatic venous wedge pressures > 8mmHg if available.
9. History of multiple abdominal operations that would preclude HAI pump placement.
10. Active infection.
11. Current biliary obstruction requiring placement of endoscopic or transhepatic stents for biliary decompression.
12. Presence of aberrant or replaced hepatic arterial anatomy not amenable to placement of a hepatic arterial infusion pump catheter as judged by the operating surgeon.
13. History of peripheral neuropathy > Grade 1.
14. Allergies to iodine contrast medium, that cannot be premedicated with steroids per institutional radiology guidelines (e.g., dexamethasone).
15. Uncontrolled severe coagulation disorders (INR > 1.5 in patients not on warfarin therapy).
16. Pregnant or lactating women.
17. History of malignancy other than cholangiocarcinoma within 5 years prior to screening, with the exception of:
 - a. Malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, melanoma in situ, localized prostate cancer, ductal carcinoma in situ, or
 - b. Stage I uterine cancer or a malignancy whose natural history or treatment has, in the opinion of the principal investigator, the potential to interfere with the safety or efficacy assessment of the intervention under investigation.
18. Life expectancy ≤ 12 weeks.

19. Inability to comply with study and/or follow-up procedures.
20. Emotional or psychiatric problems that would preclude successful participation in the hepatic arterial infusion program as judged by the one of the study investigators, and further corroborated by the mandatory interview and assessment with medical oncology social worker.

4.2.1 EXCLUSION CRITERIA FOR TREATMENT PERIOD 2

1. Participants with radiographic evidence of extrahepatic disease.
2. Evidence of extrahepatic disease found at laparoscopy during open surgical exploration for HAI pump implantation. Participants with extrahepatic disease found at time of laparoscopy or laparotomy will not undergo surgical placement of HAI pump.

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential research participants will be recruited from OHSU. Participants will be identified by a member of the patient's treatment team, the PI, research team, or medical and surgical oncology clinics part of OHSU. As a member of the treatment team, the Investigator will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential participants contacted by their treating physician will be referred to the Investigator or research staff of the study. Every effort will be made to include women and minorities. This study may also use IRB-approved recruitment materials (e.g., flyers, websites, social media) and word of mouth to create further awareness; thus, potential participants may also contact the study team regarding possible inclusion in this study.

The Investigator may also screen the medical records of potential participants with whom the Investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential participants regarding the possibility of enrolling in the study.

During the initial conversations, the Investigator and/or research staff may ask the potential participant to provide certain health information necessary to the recruitment and enrollment process. The Investigator/research staff may also review portions of the potential participants' medical records in order to further assess eligibility. If the participant is ineligible for the research study, research staff will destroy all information collected on that individual, except for any information that must be maintained for screening log purposes.

The consenting professional will explain in detail the study and review the informed consent with the participant. Participants will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits they may incur. Participants will be required to read, agree to, and sign an IRB-approved Informed Consent form prior to registration on this trial.

4.3.1 ACCRUAL ESTIMATES

This OHSU Knight Cancer Institute study will not focus on any particular gender, racial or ethnic subset. No individual will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon (Table 4 and Table 5).

Table 4. Population Demographics – Oregon (%)			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	6.4	6.3	12.7
Not Hispanic or Latino	38.7	37.9	87.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native	0.9	0.9	1.8
Asian	2.2	2.2	4.4
Black or African American	1.1	1.0	2.1
Native Hawaiian or other Pacific Islander	0.2	0.2	0.4
White	44.2	43.4	87.6
More than one race	1.9	1.8	3.7
Racial Category: Total of all subjects*			100*
TOTALS	50.5	49.5	100*
Source: Adapted from U.S. Census Bureau, 2016			
*Totals may not equal 100 due to rounding			

Table 5. Projected Accrual for the Present Study				
Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	2	2	-	4
Not Hispanic or Latino	13	13	-	26
Unknown	-	-	-	-
Ethnic Category: Total of all participants*	15	15	-	30*
Racial Category				
American Indian or Alaskan Native	0-1	0-1	-	1
Asian	1	1	-	1
Black or African American	0-1	0-1	-	1
Native Hawaiian or other Pacific Islander	0	0	-	0
White	13	13	-	26
More than one race	1	1	-	1
Racial Category: Total of all participants*	15	15	-	30*
Source: Adapted from U.S. Census Bureau, 2016.				
*Totals may not equal 100 due to rounding.				

This study will recruit 30 participants in order to obtain 21 evaluable participants. Based on the current volume of patients with ICC (>20 patients/year) plus additional referrals of patients specifically for this trial, we anticipate to complete trial accrual in ≤ 2 years.

4.3.2 INCLUSION OF CHILDREN

This protocol does not include children (<18-years-old) as the number of children with ICC is limited.

4.4 REGISTRATION PROCEDURES

4.4.1 PARTICIPANT REGISTRATION

4.4.1.1 Local Registration

This is a Phase II trial, and there is no randomization for treatment. Participants will be identified for eligibility through oncology or surgical referrals to outpatient or inpatient services. Eligibility criteria (Section 4.1 and 4.2) will be confirmed by the enrolling physician and study staff.

Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (eCRIS). At a minimum, registration of OHSU participants will include:

- A completed Eligibility Checklist signed by the investigator.
- Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization.

4.5 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study signed informed consent will be obtained from the participant or the participant's legally acceptable representative. The Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

This study consists of a two-part screening process. The first screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 1 of the study; where Day 1 of the clinical trial will be when participants receive mFOLFIRINOX (Treatment Period 1). Initial screening and baseline evaluations will be performed during the screening phase (i.e., up to 1 day before receiving mFOLFIRINOX treatment). All eligible participants enrolled in this study will undergo this initial screen to stage disease prior to beginning systemic treatment with mFOLFIRINOX. Participants will undergo a second screening to restage disease and determine eligibility to proceed with surgical placement of the HAI pump. The second screening will begin upon completion of systemic mFOLFIRINOX induction, and end after 4 (+2) weeks. Participants with development of new or progressive extrahepatic disease will be taken off study treatment and offered an alternative 2nd line therapy. Likewise, participants with a complete radiographic response will also be taken off study treatment for consideration of further systemic mFOLFIRINOX. Participants eligible to proceed with study will undergo a laparotomy for HAI pump placement, cholecystectomy, and portal lymphadenectomy. Eligible participants will subsequently receive floxuridine-DEX in conjunction with systemic mFOLFIRI.

Total accrual of all participants is anticipated to take a total of 24 months (or 2 years).

4.6 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. If a participant no longer wants to receive treatment, but is willing to come for follow-up appointments, the participant's request should be honored, if possible. No further participant contact should be made if the participant withdraws consent for participation in the study; however, participants who choose to keep their HAI pump may be contacted for appropriate maintenance of the device in accordance with institutional standards.

Information about the reason(s) for discontinuation and collection of any new or ongoing adverse events (AEs) should be collected at the time the participant withdraws consent.

The following are examples demonstrating why a participant's treatment might be discontinued:

- Participant withdraws informed consent.
- Disease progression.
- Participant has unacceptable AEs or failure to tolerate the study treatment.
- Any other medically appropriate reason or significant protocol violation, in the opinion of the investigator.

4.7 CRITERIA FOR REPLACING PARTICIPANTS

Criteria for replacing participants who have discontinued include the following:

- Participants who discontinue treatment ≤ 2 weeks from start of mFOLFIRINOX treatment (i.e., Treatment Period 1), for reasons other than disease progression or study drug related toxicity, will be replaced.

4.8 STUDY DISCONTINUATION

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Where necessary, written notification, documenting the reason for study suspension or termination, will be provided by the investigator-sponsor to regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

5. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 9.4, Adverse Event List(s).

5.1 SYNCHROMED II INFUSION SYSTEM

The SynchroMed II Infusion System® (Models 8637-20 and -40) is an implantable, and programmable infusion pump manufactured by Medtronic Inc. The pump is indicated to provide continuous infusion of drugs or fluids, among which, floxuridine (FUDR) or methotrexate, are indicated for the treatment of primary or metastatic cancer. Bacteriostatic water or preservative-free sterile saline, USP, can be used to flush the pump reservoir. Saline or heparinized saline may be used during an interruption in chemotherapy to maintain pump and catheter patency.

Made from titanium, the device is completely implantable beneath the skin. The circular pump has a small rubber center (termed, “septum”) that is used to fill the drug chamber with medication, and the medication is subsequently delivered from the drug chamber through a catheter access port into the implanted catheter. The SynchroMed II is powered by a lithium battery, and contains a microprocessors that controls the rate of drug delivery. The flow rate accuracy of the pump is within $\pm 14.5\%$ of the programmed flow rate at 0.048 to 24 mL/day, 37°C, 50% reservoir volume, and 300 meters above sea level.

The pump has a built in elective replacement indicator (ERI) that displays messages on the programmer signifying the the pump nears the end of its service life (EOS). Device longevity is between 5 to 7 years, depending on programming. The pump can operate for 90 days from time of ERI activation to EOS at rates up to 1.5 mL/day.

The pump comes with a patient identification card and a manufacturer warranty card. At the time of implantation, the warranty card may be photographed and scanned into the electronic medical record by the OR staff and operating surgeon for future reference. Additionally, the patient and family may be given a HAI pump patient instruction and information booklet, and may also be given a patient identification card with the HAI pump serial number.

The pump can be replaced (as needed) with a new pump without the need for laparotomy by dividing the catheter and placement of a new pump using a splicing kit from the manufacturer in the case of a primary pump malfunction (rare occurrence).

The pump should be (re)filled only by qualified medical personnel, knowledgeable in the servicing of implantable devices and catheters, and trained specifically to refill the pump. Likewise, pump should only be programmed by qualified medical personnel with knowledge of using the clinician programmer. The OHSU inpatient, radiology, and outpatient nursing staff have been educated and completed an in-service evaluation on using this new device. Of note, this same pump and model are implanted frequently by the OHSU Department of Neurosurgery for management in patients with chronic pain so there is existing institutional expertise.

All agents that are administered into the pump must be preservative free.

5.2 OXALIPLATIN

Oxaliplatin, also known as 1-OHP; L-OHP; oxalatoplatin; oxaliplatinum, or Eloxatin® (Sanofi Aventis).

Oxaliplatin is a platinum alkylating agent, containing platinum complexed to oxalate and diaminocyclohexane complex. Platinum complexes are formed intracellularly and inhibit DNA synthesis through covalent binding of DNA molecules to form intra- and inter-strand DNA cross-links. Oxaliplatin-induced cytotoxicity is cell-cycle nonspecific, and considered a radiation-sensitizing agent. Please refer to package insert for additional details.

5.2.1 ACQUISITION

Oxaliplatin will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.2.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Oxaliplatin is provided as a sterile, preservative-free lyophilized powder.

5.2.3 PRODUCT STORAGE AND STABILITY

After final dilution, the Oxaliplatin shelf life is 6 hours at room temperature [20° to 25°C] or up to 24 hours under refrigeration [2° to 8°C]. Unopened vials should be stored at 15-30°C, and protected from light.

5.2.4 COMPATIBILITY

Compatible with D5W (D5W-Dextrose 5%).

Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication. Oxaliplatin should always be administered before fluorouracil.

5.2.5 HANDLING

Care should be exercised in the handling and preparation of infusion solutions prepared from Oxaliplatin Injection. The use of gloves is recommended. If a solution of oxaliplatin contacts the skin, wash the skin immediately and thoroughly with soap and water. If oxaliplatin contacts the mucous membranes, flush thoroughly with water.

5.2.6 PREPARATION

Oxaliplatin reconstituted in water or 5% Dextrose.

5.2.7 ADMINISTRATION

Oxaliplatin is delivered by IV infusion per institutional standards.

5.2.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia. Oxaliplatin may be administered at the same time as leucovorin.

5.2.9 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.2.10 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of oxaliplatin should be destroyed according to institutional policies.

5.3 IRINOTECAN

Also known as camptothecin-11; CPT-11; U-101440E, or Camptosar® (Pfizer).

Irinotecan is a semi-synthetic derivative of camptothecin, an alkaloid extract from *Camptotheca acuminata*. Camptothecin and its analogue belong to the class of topoisomerase I inhibitors. Irinotecan is metabolized to its active form, SN38, in the presence of hepatic or gastrointestinal carboxylesterase. Irinotecan and its active metabolite, SN-38, bind to the topoisomerase DNA complex, preventing re-ligation of the single-strand breaks in the DNA molecule. The drug and its active metabolite exert their cytotoxic effects during the S-phase of cell cycle. Please see package insert for additional details.

5.3.1 ACQUISITION

Irinotecan will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.3.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Irinotecan is provided as a sterile, IV solution (20 mg/ml).

5.3.3 PRODUCT STORAGE AND STABILITY

Solution is stable at room temperature and ambient fluorescent light for up to 24 hours. Solution diluted in D5W is stable for 48 hours when refrigerated and protected from light; use within 24 hours. Do not refrigerate solutions diluted with NS. Use within 4 hours if solution is kept at room temperature. Do not freeze reconstituted or diluted solutions. Use solution immediately after reconstitution if possible. Complete infusion within 12 hours (if kept at room temperature) or 24 hours (if kept refrigerated) if reconstitution and dilution are performed under strict aseptic conditions.

5.3.4 COMPATIBILITY

Compatible with D5W (D5W-Dextrose 5%).

5.3.5 HANDLING

Care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan. The use of double gloves and gown is recommended. If a solution of irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water.

5.3.6 PREPARATION

Irinotecan is supplied as a sterile, pale yellow, clear, aqueous solution, and can be reconstituted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL.

5.3.7 ADMINISTRATION

Irinotecan is delivered by IV infusion per institutional standards.

5.3.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Contraindicated in patients with a known hypersensitivity to the drug or its excipients.

5.3.9 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.3.10 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of irinotecan should be destroyed according to institutional policies.

5.4 FLUOROURACIL

Fluorouracil (5-fluorouracil; 5-FU; Adrucil™; Carac™; Efudex™, Efudix™) is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase). Please refer to package insert for additional detail.

5.4.1 ACQUISITION

5-FU will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.4.2 FORMULATION

5-FU is provided as a sterile, non-pyrogenic injectable solution for intravenous administration (50 mg/ml vial).

5.4.3 STORAGE AND STABILITY

5-FU is stored at room temperature 15° to 30°C and protected from light. 5-FU IV admixtures (50 to 1000 mL NS or D5W) or (undiluted solutions in syringes) are stable for 72 hours at room temperature.

5.4.4 COMPATIBILITY

Broad compatibility. Please refer to package insert.

5.4.5 HANDLING

Appropriate care should be exercised in the handling and preparation of 5-FU infusion solutions.

5.4.6 PREPARATION

5-FU is supplied ready for injection.

5.4.7 ADMINISTRATION

5-FU is delivered by IV infusion per institutional standards.

5.4.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Injection should be administered only intravenously, using care to avoid extravasation.

5.4.9 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.4.10 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of 5-FU should be destroyed according to institutional policies.

5.5 FOLINIC ACID

Also known as calcium folinate, citrovorum factor, Leucovorin® (Pfizer).

Folinic acid is a reduced form of folic acid. As part of the FOLFIRI regimen, folinic acid is used to enhance the activity of 5-FU by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of thymidylate. Please refer to package insert for additional details.

5.5.1 ACQUISITION

Folinic acid will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.5.2 FORMULATION

Folinic acid is supplied as lyophilized powder for injection in 50 mg, 100 mg, and 200 mg vials.

5.5.3 STORAGE AND STABILITY

Folinic acid injection, powder, lyophilized, for solution: Store vials at 20° to 25°C (68° to 77° F). Protect from light.

Folinic acid solution for injection: Store in refrigerator 2° to 8°C (36° to 46°F). Protect from light.

5.5.4 COMPATIBILITY

Can be diluted in D5W, lactated ringers, water (sterile or bacteriostatic).

5.5.5 HANDLING

No special handling required under conditions of normal product use. Follow institutional and manufacturer guidelines.

5.5.6 PREPARATION

Each 50, 100, and 200 mg vial of folinic acid for injection when reconstituted with 5, 10, and 20 mL, respectively, of sterile diluent yields a leucovorin concentration of 10 mg/mL. Folinic acid for Injection contains no preservative, inactive ingredient is Sodium Chloride, USP, added to adjust tonicity. Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, use immediately and discard any unused portion.

5.5.7 ADMINISTRATION

Administer immediately if reconstituted with sterile water for injection. Administer IV at maximum rate of 160 mg/min.

5.5.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Do not administer the injectable product intrathecally. Do not mix with 5-FU in the same infusion as a precipitate may form.

5.5.9 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.5.10 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of folinic acid should be destroyed according to

institutional policies.

5.6 FLOXURIDINE

Floxuridine (5 Fluoro 2-deoxyuridine; FUDR[®]) is the deoxyribonucleoside derivative of 5-fluorouracil, a pyrimidine antimetabolite. Rapid intra-arterial injection of floxuridine is quickly catabolized to 5-fluorouracil, and produces the same toxic and antimetabolic effects as 5-FU. The primary effect is to interfere with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibit the formation of ribonucleic acid (RNA). In contrast, when floxuridine is given by continuous intra-arterial infusion its direct anabolism to floxuridine monophosphate is enhanced, and results in increased inhibition of DNA synthesis.

5.6.1 ACQUISITION

FUDR is a commercially available product from Fresenius Kabi USA, LLC. Floxuridine will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.6.2 FORMULATION

Floxuridine is distributed as a vial of 500mg sterile, nonpyrogenic, lyophilized powder for reconstitution. Floxuridine is a white to off-white odorless solid which is freely soluble in water.

5.6.3 STORAGE AND STABILITY

The sterile powder should be stored at room temperature (20° to 25°C).

5.6.4 COMPATIBILITY

Can be diluted in D5W or 0.9% sodium chloride.

5.6.5 HANDLING

No special handling required under conditions of normal product use. Follow institutional and manufacturer guidelines.

5.6.6 PREPARATION

Each vial is reconstituted with 5 mL of preservative free sterile water for injection to make a clear odorless aqueous solution. An appropriate amount of reconstituted solution is then diluted with 0.9% preservative free sodium chloride to a quantity sufficient 30 mL of solution for intra-arterial infusion.

Floxuridine dose will be prepared according to weight-adjusted calculation described in Section 6.2.2.

Floxuridine will be prepared with dexamethasone (25mg), heparin (50,000 units), and *q.s.* 0.9% sodium chloride for a total volume of 30 mL.

5.6.7 ADMINISTRATION

Floxuridine is for intraarterial use only. Floxuridine will be delivered by hepatic arterial infusion

using the SychroMed II pump.

5.6.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Floxuridine is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections.

The pump should be refilled only by qualified medical personnel, knowledgeable in the servicing of implantable devices and catheters, and trained specifically to refill the pump.

5.6.9 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.6.10 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of folinic acid should be destroyed according to institutional policies.

5.7 DEXAMETHASONE

Dexamethasone sodium phosphate (dexamethasone acetate; DEX; Decadron®, Dexasone®, Diodex®, Hexadrol®, Maxidex®) is an adrenocortical steroid anti-inflammatory. In HAI treatment it can be added to either doses of heparinized saline or FUDR as an agent to prevent liver damage.

5.7.1 ACQUISITION

Dexamethasone sodium phosphate, injection is a commercially available product from West-Ward Pharmaceuticals. Dexamethasone will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.7.2 FORMULATION

Dexamethasone sodium phosphate, injection is distributed as a 10 mg per 1 mL solution. Each vial contains a colorless odorless aqueous solution.

5.7.3 STORAGE AND STABILITY

Store at controlled room temperature, between 20 and 25°C (68 and 77°F), with excursions permitted between 15 and 30°C (59 and 86°F). Do not freeze or heat sterilize; protect from light

5.7.4 COMPATIBILITY

Dexamethasone is practically insoluble in water and sparingly soluble in alcohol. Dexamethasone can be administered directly from vial, or it can be added to Sodium Chloride Injection or Dextrose Injection. Refer to package insert for additional details regarding

compatibility.

5.7.5 HANDLING

Appropriate care should be exercised in the handling and preparation of dexamethasone solutions. Sterile precautions should be observed when mixed with an infusion solution.

5.7.6 PREPARATION

Dexamethasone will be prepared with heparin (50,000 units) and 0.9% sodium chloride (q.s.) for a total volume of 30 ml.

5.7.7 ADMINISTRATION

Dexamethasone will be administered be delivered by hepatic arterial infusion using the SychroMed II pump.

5.7.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

The SychroMed II pump should be refilled only by qualified medical personnel, knowledgeable in the servicing of implantable devices and catheters, and trained specifically to refill the pump.

5.7.9 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.7.10 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of dexamethasone should be destroyed according to institutional policies.

5.8 HEPARIN

Heparinized saline is used to keep the HAI pump line patent during non-treatment weeks.

5.8.1 ACQUISITION

Heparin is a commercially available solution from Fresenius Kabi USA, LLC. Heparin will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

5.8.2 FORMULATION

Preservative free heparin is distributed as a 5,000 units per 0.5 mL vial of odorless, colorless to slightly yellow aqueous solution.

5.8.3 STORAGE AND STABILITY

Heparin is to be stored at room temperature.

5.8.4 COMPATIBILITY

0.9% normal saline, or D5W.

5.8.5 PREPARATION

Heparin should be diluted in 0.9% preservative free sodium chloride to the required concentration.

5.8.6 ADMINISTRATION

Heparin is administered via direct injection into HAI pump reservoir using the SychroMed II Refill Kit per manufacturer instructions.

5.8.7 SPECIAL CONSIDERATION FOR ADMINISTRATION

The SychroMed II pump should be refilled only by qualified medical personnel, knowledgeable in the servicing of implantable devices and catheters, and trained specifically to refill the pump

5.8.8 ACCOUNTABILITY

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

5.8.9 DESTRUCTION AND RETURN

At the end of each treatment, unused supplies of heparin should be destroyed according to institutional policies.

6. TREATMENT PLAN

6.1 DOSAGE AND ADMINISTRATION

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks associated with modified (m) FOLFIRINOX, mFOLFIRI and HAI floxuridine-DEX are described in Section 9. Appropriate dose modifications for mFOLFIRINOX/mFOLFIRI and HAI floxuridine-DEX are described in Section 6.2. No therapy other than those described herein may be administered with the intent to treat the participant's malignancy.

6.1.1 mFOLFIRINOX

After completing staging and evaluation to determine trial eligibility, mFOLFIRINOX regimen (Treatment Period 1) will be administered to participants on Day 1 of Cycle 1 (Table 6). This dose regimen follows current OHSU institutional guidelines. As the pre-operative chemotherapy, participants will continue to receive this regimen for a total of 4 cycles (i.e., 8-weeks). Administration of mFOLFIRINOX will occur as a 14-day treatment cycle. The dose of oxaliplatin, folinic acid, irinotecan, and 5-fluorouracil administered on subsequent Cycles 2, 3, and 4 will be reduced by 25% (Table 7).

Table 6. Cycle 1 - mFOLFIRINOX Dosage			
	Drug Regimen	Starting Dose	Route
1	Oxaliplatin	85 mg/m ²	<i>i.v.</i> over 2 hours
2	Folinic acid	400 mg/m ²	<i>i.v.</i> over 2 hours
3	Irinotecan*	144 mg/m ²	<i>i.v.</i> over 90 minutes
4	Fluorouracil**	2,400 mg/m ²	<i>i.v.</i> continuous infusion over 46 hours
* To be administered after oxaliplatin. Irinotecan is given concurrently with folinic acid.			
** To be administered after irinotecan.			
† May be omitted if there is concern over toxicity.			

Table 7. mFOLFIRINOX Cycle 2, 3, and 4			
	Drug Regimen	25% Dose Reduction	
1	Oxaliplatin*	63.8 mg/m ²	<i>i.v.</i> over 2 hours
2	Folinic acid	300 mg/m ²	<i>i.v.</i> over 2 hours
3	Irinotecan**	108 mg/m ²	<i>i.v.</i> over 90 minutes
4	Fluorouracil***	1800 mg/m ²	<i>i.v.</i> continuous infusion over 46 hours
* To be administered <i>per</i> institutional standards			
** To be administered <i>per</i> institutional standards after oxaliplatin. Irinotecan is given concurrently with folinic acid.			
*** To be administered <i>i.v.</i> as a continuous infusion <i>per</i> institutional standards after irinotecan.			
† May be omitted if there is concern over toxicity.			

6.1.2 FLOXURIDINE

Toxicity-related dose modification for floxuridine are described in Section 6.2.2.

The SynchroMed II pump is available in two size of reservoir; 20 ml or 40 ml. The choice of the pump reservoir will be at the discretion of the treating surgeon in consultation with the PI. Dosing of floxuridine and DEX should remain at 20 ml regardless of reservoir size (i.e., 20 or 40 ml). Heparin and saline dosing may be adjusted according to reservoir size as clinically appropriate. Participants will receive floxuridine-DEX (with heparin and saline) on Day 1 of each 4-week treatment cycle. The pump will be emptied and filled with heparin and normal saline on Day 15 of each cycle. The minimum fill volume of normal saline is 20 mL. Provided no dose

modification due to toxicity is required, the floxuridine dosages given below (adjusted for changes in weight and pump flow rate) will be repeated on Day 1 of Cycle 2 and all subsequent cycles. The administration of floxuridine is consistent with current institutional guidelines for HAI floxuridine therapy of patients with CRLM.

The floxuridine dosing formula is:

$$\frac{\left(\frac{0.12 \text{ mg}}{\text{kg}}\right) \times \text{patient weight (kg)} \times 20 \text{ mL} \times (0.9)}{\text{pump flow rate} \frac{\text{mL}}{\text{day}}} = 2.16 \text{ mg/kg}$$

The floxuridine will initially be administered at 50% of the established dose, and thereafter subsequent dose increases at the discretion of investigator are permitted as follows:

HAI-Floxuridine Dose levels	Floxuridine Dose
Dose level 1 [Starting dose]	50% of 0.9(0.12 mg/kg/day) * 20 mL = 1.08 mg/kg
Dose level 2*	75% of 0.9(0.12 mg/kg/day) * 20 mL = 1.62 mg/kg
Dose level 3	0.9(0.12 mg/kg/day) * 20 mL = 2.16 mg/kg

DEX will be administered at a dose of 1mg/day (20 mL)/pump flow rate.

6.1.2.1 Weight dosing

The following parameters should be used to floxuridine dosing:

- Greater than (>) 25% above ideal body weight (IBW) - use adjusted body weight with 50% cofactor
- Less than or equal to (≤) 25% above IBW - use actual body weight

The adjusted body weight described in this treatment plan is set for 50%; if the participant meets criteria for adjusted body weight, then this adjusted weight should apply to the whole treatment plan.

For weight changes:

1. If greater than 5% weight gain, then no dose adjustments are warranted
2. If greater than 5% weight loss, then treatment plan should be updated accordingly.

6.1.2.2 Pump Flow Rate

The first total dose of floxuridine will be determined using a programmed flow of 1.0 mL/day. The pump will be filled with either floxuridine, DEX, or heparinized preservative free saline (25,000 units heparin in 20 mL). The PI is to be notified if a significant (> 20%) discrepancy is observed between the programmed flow rate and the calculated flow rate observed with each HAI pump fill.

To recalculate flow rate, the amount of any residual infusate removed from the pump at the end of the 14-day infusion is subtracted from the total pump volume. This result is divided by the number of days in the infusion period (typically 14 days).

Example: If the HAI pump is filled with 20.0 mL infusate on Day 1, and upon emptying the pump

reservoir on Day 15, the volume obtained yielded 12 ml residual, then

$$\text{Recalculated flow rate (over the 14-day period): } \frac{20 \text{ ml} - 12 \text{ ml}}{14 \text{ days}} = \frac{8 \text{ ml}}{14 \text{ days}} = \frac{0.6 \text{ ml}}{\text{day}}$$

If no dose modification due to toxicity is required, the dosages given above (adjusted for changes in weight and pump flow rate) will be repeated on Day 1 of Cycle 2 and all subsequent cycles.

6.1.3 mFOLFIRI

At the end of a 6-week recovery period after treatment with mFOLFIRINOX, and as part of Treatment Period 2, eligible participants will receive mFOLFIRI on Day 15 of each 4-week treatment cycle (i.e., every 2-weeks, or q2wk). Participants will receive the maximally allowed systemic dose (see Table 8 for initial starting dose) and continue to receive this dose provided no toxicities are observed. This dose regimen follows OHSU institutional guidelines. Participants that experience grade 3 or 4 toxicity may continue mFOLFIRI treatment at a lower dosage level once toxicities have fully resolved (see Table 14 and Table 15).

Table 8. mFOLFIRI Dosage			
	Drug Regimen	Starting Dose	Route
1	Irinotecan	150 mg/m ²	IV over ~30 minutes to 1 hour
2	Folinic acid	400 mg/m ²	IV. over ~30 minutes to 1 hour
4	5-FU	1200 mg/m ²	IV. continuous infusion over ~46 hours

Starting on Day 1 of Cycle 2, participants will receive systemic 5-FU (1200mg/m² IV; ~46 hour continuous infusion) independent of the mFOLFIRI regimen given on Day 15 of each cycle (Table 8).

6.2 DOSING DELAYS AND MODIFICATIONS

In general, participants should start HAI pump therapy within 6 weeks after surgical placement of the HAI pump. If the delay to start HAI pump therapy is ≥6 weeks, then participants should undergo disease restaging with CT imaging (per institutional standards). Provided that results of imaging do not show presence of extrahepatic disease, participants may remain eligible to remain on study and should be planned to initiate their HAI pump therapy within 1 week (± 5 days). If after 6 weeks, participants are unable to start (for any reason) they will discontinue protocol-directed therapy and proceed to follow-up.

Participants must meet all hematologic and blood chemistry criteria outlined in Section 4.0 before beginning the first cycle of therapy. For subsequent cycles, patients must meet the following criteria:

WBC	> 2.5 K/uL
ANC	≥ 1.0 K/uL
Platelet count	> 75 K/uL
Creatinine	< 1.8 mg/dL
Bilirubin	< 1.5 mg/dL

If counts are outside these levels on the date of schedule treatment, then therapy will be delayed one week.

6.2.1 DOSE MODIFICATION – mFOLFIRINOX

Eligible participants entering Treatment Period 1 will receive systemic mFOLFIRINOX as described in Section 6.1.1. Dose modifications, per treating oncologist, will follow institutional standard of care. General guidelines are referenced in Table 9.

Table 9. mFOLFIRINOX - Recommended Dose Modifications by Toxicity Grade				
Toxicity	Occurrence	Irinotecan ^{a,b}	Oxaliplatin ^{a,b}	5-FU ^{a,b}
<ul style="list-style-type: none"> • Febrile neutropenia, OR, • Grade 4 ANC > 7 d, OR, • Delay 1-2 weeks for ≥ Grade 1 ANC 	1st	decrease 1 dose level	No change	Discontinue
	2nd	As above	decrease 1 dose level	
<ul style="list-style-type: none"> • Thrombocytopenic bleeding, OR, • ≥ grade 3 platelets, OR, • Delay 1-2 weeks for grade 2 platelets 	1st	No change	decrease 1 dose level	decrease 1 dose level
	2nd	decrease 1 dose level	As above	decrease 1 dose level if ≥ grade 3 platelets
<ul style="list-style-type: none"> • Diarrhea ≥ grade 3, OR • Diarrhea with fever or ≥ Grade 3 ANC 	1st	decrease 1 dose level	No change	Discontinue
	2nd	As above	decrease 1 dose level	As above & decrease 1 dose level
Grade 3 or 4 mucositis or hand-foot syndrome	-	No change	No change	decrease 1 dose level
Grade 2 persistent neurotoxicity	-	No change	decrease 1 dose level	No change
Grade 2 other non-hematological	-	Consider decrease	Consider decrease	Consider decrease
Grade 3 neurotoxicity (recovers prior to next cycle)	-	No change	decrease 1 dose level	No change
Grade 3 other non-hematological	-	decrease 1 dose level	decrease 1 dose level	decrease 1 dose level
Pneumonitis	Any	Discontinue	Discontinue	Discontinue
<ul style="list-style-type: none"> • Grade 3 persistent neurotoxicity, OR • Grade 4 neurotoxicity 	Any	Discontinue	Discontinue	Discontinue
<ul style="list-style-type: none"> • Grade 4 other non-hematological, OR, • RPLS, OR • Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia 	Any	Discontinue	Discontinue	Discontinue
Pharyngolaryngeal dysesthesia	-	-	↑ infusion to 6 hr	-
^a Do not treat until ANC ≥ 1.5 x 10 ⁹ /L, platelets ≥ 75 x 10 ⁹ /L, diarrhea resolved to baseline and other toxicity ≤ grade 2. Do not re-escalate dose if reduced for toxicity. ^b Discontinue the regimen if toxicity recurs after 2 dose reductions or if cycle delayed for > 2 weeks. RPLS, reversible posterior leukoencephalopathy syndrome				

Table 10. mFOLFIRINOX - Recommended Dose Modifications for Hepatic Impairment				
Transaminases	Bilirubin	Irinotecan	Oxaliplatin	5FU
	1-1.5x ULN or Gilbert's	Consider decrease	No change	No change

Table 10. mFOLFIRINOX - Recommended Dose Modifications for Hepatic Impairment				
Transaminases	Bilirubin	Irinotecan	Oxaliplatin	5FU
> 5 X ULN	>1.5-4x ULN	Omit	No change	No change
	> 4x ULN	Omit		Omit
ULN, upper limit of normal range				

Table 11. mFOLFIRINOX - Recommended Dose Modifications for Renal Impairment			
Creatinine Clearance	Oxaliplatin	Irinotecan	5FU
>60 mL/min	No change	No change	No change
>30-60 mL/min	Caution	No change	No change
10-30 mL/min	Discontinue	Caution	Consider dose reduction
< 10 mL/min	Discontinue	Caution	Consider dose reduction

6.2.2 DOSE MODIFICATION – FLOXURIDINE

Floxuridine dose reductions will be performed according to the standard and established OHSU HAI protocol (Table 12). To determine if a floxuridine dose modification is necessary, participant's reference laboratory values (defined as the laboratory values obtained on the first day of participant's first post-operative floxuridine dose) will be compared to the either the value obtained on the day pump was emptied (e.g. day 14) or the value obtained on the day of planned pump filling (e.g. day 28), whichever is higher.

Table 12. Floxuridine - Recommended Dose Modification		
	Reference Value [†]	% Floxuridine dose ^{**}
SGOT*	2 to < 3 x reference value	80%
	3 to < 4 x reference value	50%
	≥4 x reference value	Hold
ALK PHOS*	1.2 to < 1.5 x reference value	50%
	≥1.5 reference value	Hold
TOT BILI*	1.2 to < 1.5 x reference value	50%
	≥ 1.5 x reference value	Hold
If SGOT ≥ 4x reference value, alkaline phosphatase ≥ 1.5x reference value, total bilirubin ≥ 1.5x reference value, then treatment will be held and will not be reinstituted until values resolve to more normal levels, as indicated in section 6.2.2.2, "Floxuridine – Restarting Treatment After Hold".		
* Determined at pump emptying and day of planned retreatment.		
** Percentages listed under "floxuridine dose" refer to percentage of last dose of floxuridine administered.		
† Reference value (RV) is defined as the laboratory values obtained on the first day of the participant's first post-operative dose.		

6.2.2.1 Safety Run-in

An initial 6 participants enrolled in this study will be evaluated for abnormal liver function associated with HAI floxuridine-DEX. Participants that proceed to Treatment Period 2 and initiate HAI floxuridine-DEX treatment will be placed on a treatment hold if they have unacceptable elevations in the liver enzymes: SGOT, ALK PHOS, or TOT BILI (as defined in Table 12). The study will be stopped early if, after reaching the end of two cycles (i.e., 8 weeks from initiating HAI floxuridine-DEX), 2 of 6 participants are still on treatment hold because of an abnormal liver function and cannot be restarted per Table 13, or show radiographic evidence suggestive of biliary sclerosis. Monitoring of participants for elevation of liver enzymes will occur continuously throughout Treatment Period 2. If the incidence of abnormal liver function exceeds 33% among all participants receiving HAI floxuridine-DEX, the study will be stopped.

6.2.2.2 Floxuridine – Restarting Treatment After Hold

If participant develops a TOT BILI ≥ 3.0 mg/dl, the pump should be emptied and replaced every 14 days with 20 mL saline containing: DEX (1 mg/ml) and heparin (25,000 units in 20 ml). Once there is no longer evidence of toxicity and/or liver enzymes (SGOT, ALK PHOS, or TOT BILI) resolve to the upper limit of their reference values, then DEX dose may be tapered in increments of 5 mg every 14 days (i.e., reduced in 0.25 mg/ml increments). Tapering should continue unless liver enzymes increase. At the discretion of the investigators, participants may continue to receive DEX (≤ 1 mg/ml) as part of all subsequent HAI floxuridine treatments. For participants restarting HAI pump treatment, floxuridine should be restarted using 25% of the last floxuridine dose given (with DEX, heparin and saline) in the pump for 7 days. The HAI pump should then be emptied after 7 days, and patients given a 3-week rest period. This treatment and treatment schedule should continue as long as TOT BILI remains ≤ 1.5 mg/dl and liver enzyme values do not increase.

Epigastric pain unresponsive to oral proton pump inhibitor use is suggestive of gastroduodenal irritation or ulcer. Severe pain should prompt workup with an upper gastrointestinal endoscopy. Serum amylase and lipase will be checked along with the routine blood screen in patients with abdominal pain. If an ulcer or gastroduodenitis is documented, therapy should be held for one month to allow healing. If abdominal pain is severe, the pump should be emptied of floxuridine until results of workup are available.

If participants have delays in floxuridine treatment, the cycle numbering will proceed as:
2 systemic treatments = 1 cycle

Table 13. Floxuridine - Restarting Treatment After Hold		
Reason for treatment delay	Chemotherapy resumed when value returns to:	% floxuridine dose
SGOT elevation	4 x RV	25% of last dose
AlkPhos elevation	1.7 x RV	25% of last dose
TOT BILI	1.7 x RV	25% of last dose

If participants return for floxuridine and the liver function tests (SGOT, Alk Phos, TOT BILI) are too elevated (as described in Table 12), then participants will wait one week. If markers of liver function are still elevated, participants will start the next cycle with systemic and not with floxuridine. During that cycle, if the liver function tests have sufficiently decreased, then participants will be able to receive floxuridine again at a lower dose (Table 13). In that case, the participant can receive floxuridine, then 2-weeks later receive systemic mFOLFIRI once afterwards, and then move onto the next cycle.

6.2.3 DOSE MODIFICATION – mFOLFIRI

If participants have delays in treatments due to hospitalization or other reasons, they should proceed with treatment at the discretion of the treating physician.

Participants that experience grade 3 or 4 toxicity may continue treatment at a lower dosage level once toxicities have fully resolved (see Table 14 and Table 15). Toxicity should resolve within 2-weeks. If the Investigator feels the participants cannot tolerate systemic therapy, treatment can be held for 1-week. If the participant has elevated liver function tests, systemic therapy can be held and dexamethasone can be placed in the pump with heparin saline.

Guidelines for re-starting medication are listed in Table 14 and Table 15.

For total bilirubin >1 but ≤1.5, then Irinotecan should be dosed at 150mg/m².

Table 14. mFOLFIRI – Recommended Dose Reduction for Hematologic Toxicities				
Grade	Toxicity	Irinotecan	5FU Infusion	Folinic Acid
3	Neutropenia	20% decrease	20% decrease	20% decrease
4	Neutropenia	30% decrease	30% decrease	30% decrease
3	Febrile neutropenia ^a	20% decrease	20% decrease	20% decrease
4	Febrile neutropenia ^a	30% decrease	30% decrease	30% decrease
3	Thrombocytopenia	20% decrease	20% decrease	20% decrease
4	Thrombocytopenia	30% decrease	30% decrease	30% decrease
^a Febrile Neutropenia = ANC < 1.0 x 10 ⁹ /L with fever ≥ 38.5°C				

Table 15. mFOLFIRI – Recommended Dose Reduction for Non-Hematologic Toxicities				
Grade	Toxicity	Irinotecan	5FU Infusion	Folinic Acid
3	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	20% decrease	20% decrease	20% decrease
3	Diarrhea despite premedication with an effective antidiarrheal therapy	20% decrease	20% decrease	20% decrease
4	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	30% decrease	30% decrease	30% decrease
4	Diarrhea despite premedication with an effective antidiarrheal therapy	30% decrease	30% decrease	30% decrease
3	Stomatitis	No dose reduction	20% decrease	20% decrease
4	Stomatitis	No dose reduction	30% decrease	30% decrease
≥ 2	Cardiac toxicity	No dose reduction	Stop treatment	Stop treatment
3 or 4	Hand/Foot Skin reaction	No dose reduction	20% decrease	20% decrease

6.3 TREATMENT PERIOD AND MAINTENANCE

6.3.1 TREATMENT PERIOD 1

Participants will receive mFOLFIRINOX for 4 cycles (8 weeks), after which they will undergo restaging using MRI/CT imaging to assess disease response. Participants with development of new or progressive extrahepatic disease will be taken off study treatment. Likewise, participants with a complete radiographic response will also be taken off-study treatment for consideration of further systemic mFOLFIRINOX.

6.3.2 TREATMENT PERIOD 2

Participants that proceed to the next stage of treatment, will receive 2 cycles (8 weeks) of HAI floxuridine-DEX and concurrent systemic administration of mFOLFIRI. After two treatment cycles, participants are considered off-protocol directed therapy and will undergo MRI/CT imaging to assess disease response. In an effort to control disease, participants may receive additional cycles of HAI floxuridine-DEX and systemic mFOLFIRI. Additional cycles of HAI floxuridine-DEX and systemic mFOLFIRI may be administered at the discretion of the PI in consultation with the participants.

While the primary goal of this treatment approach is to achieve disease control, upwards of 10% of patients may be converted to resection following treatment with HAI floxuridine-DEX and systemic mFOLFIRI. If participants are converted they may be offered hepatic resection with curative intent, and continue to receive HAI floxuridine-DEX and systemic mFOLFIRI treatment.

6.3.3 PUMP MAINTENANCE

Participants are at increased risk of catheter thrombosis if the pump reservoir is allowed to completely empty, and must therefore be compliant with all their postoperative scheduled visit as described in Section 7.8, Schedule of Events. To avoid the HAI pump running empty, the reservoir should be filled with Heparinized saline (25,000 units total dose), to make a total reservoir volume of 20 mL. Heparin saline may be adjusted to fill 40 ml reservoir size, but not to exceed a maximum of 50,000 units. During treatment, participants are to return every 2-weeks to refill the pump with heparinized saline and/or floxuridine-DEX.

Following completion of this study, the participant will be required to return every 2-4 weeks at which point the pump will be filled with heparinized saline (25,000 units total dose), to make a total reservoir volume of 20 mL. Heparin saline may be adjusted to fill 40 ml reservoir size, but not to exceed a maximum of 50,000 units. The pump should be programmed to 1.0 mL/day to extend the minimum rate mode. Pump maintenance should only be discontinued if the pump is removed, or participant death, whichever comes first. Any travel away from resources necessary to manage the pump is undesirable, but should a participant elect to travel, the pump should not contain chemotherapy and be as full as possible (i.e. 20 ml or 40 ml) with heparinized saline before departure.

The HAI pump requires routine maintenance, and participants will receive care from adult oncology nursing staff who have been specifically trained in the care of patients with HAI pumps, and how to fill the HAI pumps prior to discharge. Following surgical placement of HAI pump, when the participant is ready to be discharged, oncology nursing staff will access the HAI pump with the refill needle and removes all of the heparinized saline from the chamber. The volume extracted will be recorded and used to calculate the flow rate. The HAI pump is then immediately refilled with 20 mL of 25,000 units of preservative-free heparinized saline per protocol. Heparin saline may be adjusted to fill 40 ml reservoir size, but not to exceed a maximum of 50,000 units. Depending on the schedule of events, participants will have the HAI pump filled either with floxuridine-DEX or heparinized saline every 14 days from the day of discharge, using a pre-programmed flow rate of 1.0 (± 0.5) ml/day. Participants will also have will also have their first post-operative follow-up in the outpatient infusion unit, where they will be assessed by both surgical oncology and medical oncology physicians.

6.3.4 PUMP REMOVAL

Removal of the HAI pump will be performed as an outpatient procedure. Reasons for pump removal include:

- Primary pump malfunction
- Pump pocket hematoma or infection
- Removed at the request of the participant or provider.
- Unless alternative arrangements can be made, participants that no longer want to undergo scheduled pump maintenance may be asked to have the pump removed.

In the case that pump is removed, the catheter will be tied off, cut and left in the abdomen, while the pump is removed. Prior to the consenting pump removal, the participant will be informed that once the pump is removed, it is highly unlikely that it can technically be replaced. Participants that have the pump removed may be offered to continue with the systemic mFOLFIRI treatment, if within Treatment Period 2. All participants that discontinue HAI pump treatment for any reason other than completion of planned protocol therapy will be considered off-protocol directed therapy, but may remain on-study for follow-up. In such cases, participants will have their disease managed in accordance with institutional standards.

6.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants undergoing treatment for ICC.

Medications required to treat AEs, manage post-surgical care and cancer symptoms, as well as concurrent diseases and supportive care agents are allowed in general. These may include, but not limited to: pain medications, anti-emetics (e.g., ondansetron), and anti-diarrheals (e.g., loperamide). These medication may be administered prior to chemotherapy and/or to be taken as part of a take-home regimen. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered during the study must be listed on the case report form (CRF).

6.4.1 ACUTE CHOLINERGIC SYNDROME

Irinotecan is associated with acute cholinergic syndrome (e.g., early diarrhea), and may be treated with atropine sulfate (250 µg s.c.), unless clinically contraindicated. Atropine may be administered prior to irinotecan, if indicated.

6.4.2 DYSARTHRIA

Dysarthria (marble mouth) associated with irinotecan may be treated with diphenhydramine (50 mg IV) as needed, until symptoms resolve. Diphenhydramine premedication may be given before initiating subsequent cycles of irinotecan.

6.4.3 TREATMENT OF FEVER AND NEUTROPENIA

Neutropenic fever (defined as ANC < 0.5/mm³ or 1.0/mm³ and known to be falling, and temperature ≥ 38.0°C) will be treated per institution guidelines.

6.4.4 BILIARY SCLEROSIS

Participants will receive ursodiol (300 mg, PO, bid) if they experience abnormal elevations in liver function enzymes that requires a subsequent 25% dose reduction of floxuridine or hold of their HAI treatment (refer to Section 6.2.2). Participants requiring ursodiol will continue to receive ursodiol for entire duration of HAI treatment once started.

6.4.5 SOCIAL SERVICES

OHSU oncology social workers will be available to provide counseling about the psychological and social issues related to HAI treatment. These social workers will aid the participant and family adjust to the planned treatment regimen (e.g., arranging transportation). Refer to Section 7.1.9, Counseling Evaluation for additional details.

6.5 PRECAUTIONARY / PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

No other concomitant therapies or investigational therapies are allowed during the study. Use of alternative medications (herbal or botanical for anticancer purposes) is not permitted during the study.

To prevent unwanted hepatic or gastro-intestinal toxicities while on study, participants are not permitted, unless at the discretion of the investigator, new over-the-counter drugs, as well as herbal and dietary supplements.

Drug	Precautionary / Prohibited Medications
Irinotecan	<ul style="list-style-type: none"> Irinotecan is a major substrate of cytochrome P450 CYP2B6 and CYP3A4. Risk of drug interactions causing decreased concentrations of irinotecan with CYP3A inducers. Risk of drug interactions causing increased concentrations of irinotecan with CYP3A inhibitors. <ul style="list-style-type: none"> Avoid concomitant use of CYP3A4-inducing (e.g., rifampicin, carbamazepine, Phenobarbital, phenytoin) or inhibiting (e.g., ketoconazole, clarithromycin, indinavir, nefazodone, atazanavir, gemfibrozil) drugs. Participants should also be counselled on the consumption of grapefruit, starfruit, Seville oranges juices or products. Concomitant use of St John's Wort is contraindicated. Prochlorperazine anti-emetic should be avoided on the same day as irinotecan treatment due to an increased risk of akathisia. Prochlorperazine may be taken as part of take-home regimen.
Oxaliplatin	<ul style="list-style-type: none"> May increase the effects of warfarin and other anticoagulants. Nephrotoxic agents may increase toxicity. Cold temperatures or cold objects can precipitate or exacerbate symptoms of acute peripheral neuropathy. <ul style="list-style-type: none"> Concomitant use of ice for mucositis prophylaxis during infusion should be avoided as cold temperature can exacerbate acute neurological symptoms. QT prolongation and ventricular arrhythmias (including fatal Torsade de Pointes) – avoid drugs known to prolong the QT interval (e.g., Class Ia and III anti-arrhythmics).
5-FU	<ul style="list-style-type: none"> Initiation of 5-FU treatment regime in patients stabilized on warfarin therapy is associated with marked elevations of prothrombin time and INR. Concurrent administration of 5-FU and phenytoin may result in increased serum levels of phenytoin. May increase the effects of warfarin and other anticoagulants. 5-FU should be administered in conjunction with medications that may affect dihydroprimidine dehydrogenase activity.

6.5.1 PRECAUTIONS REGARDING USE OF HAI PUMP

The HAI pump is to be used, operated, and refilled according to manufacturer instructions.

Additional precautions include:

- Use 22-gauge non-coring needle (for filling the pump), and 24-gauge non-coring needle (for flushing the catheter access port).
- Never aspirating fluid from the pump port or catheter, as aspiration will result blood collecting and occluding within the pump or catheter.
- Participants should receive precaution over the following activities:
 - Activities involving exposure to high altitudes – Participants should avoid any prolonged engaging in activities (e.g., airline flights, hiking, or skiing in the mountains) at altitudes greater than 2,438 meters (8,000 feet) as these expose them to lower air pressure conditions that may cause an increase in the flow rate of the pump. Participants should inform study team of any high-altitude activity so that the infusion rate can be adjusted to offset potentially higher flow rates.
 - Activities involving exposure to high temperatures - Participants should avoid using hot tubs, hot showers, steam rooms, saunas, or tanning beds where the temperature is greater than 39°C (102°F) as this increased temperature can increase the flow rate of the pump

6.6 HAI PUMP PLACEMENT AND OPERATION

The technical details of HAI pump placement have been previously described.³⁹ Participants must first be evaluated by a hepatobiliary surgical oncologist who has been trained with documented experience of placing hepatic arterial infusion pumps (Drs. Mayo, Eil, Rocha or other surgical oncologist approved by the PI at OHSU/Knight). Eligible participants will first complete a pre-surgical evaluation by a physician in OHSU's preoperative medical clearance clinic.

Following completion of the pre-surgical evaluation, with a target operative date of 3-6 weeks (earlier or later time points at discretion and approval of PI) all eligible participants will undergo exploratory (staging) laparoscopy to examine for radiographically occult extrahepatic disease, which would otherwise preclude them from HAI pump placement and subsequent treatment. Open surgical exploration with HAI pump implantation will continue if there is no evidence of extrahepatic disease found at laparoscopy.

In brief, an open operation through a midline incision will be performed. The hepatic artery tree will be fully skeletonized and the gastroduodenal artery will be identified. As part of the surgical procedure, a small portion of liver and tumor will be biopsied for further evaluation. A portal lymphadenectomy will be performed to collect suspicious appearing lymph nodes in the region of the *porta hepatis* for further evaluation. A cholecystectomy will also be performed to limit the risk of acute cholecystitis related to the infusion of chemotherapy.

The SynchroMed II is attached with a silicone rubber catheter intended for long term delivery of medications to various body sites. All study participants that undergo surgical placement of the SynchroMed II pump will have the connector device spliced with a tapered rubber catheter (Codman®) placed before the HAI therapy can begin. During the surgical procedure, the Medtronic pump is connected to the Medtronic connector (Figure 5A). The Medtronic connector will be cut (Figure 5B) before the metal flange at the end of the connector so that the catheter can then be connected to the cut end of the tapered silicone catheter connector (Figure 5C).

Silk ties are used on both ends of the Catheter to ensure that the fit to the connection is secure (Figure 5D).

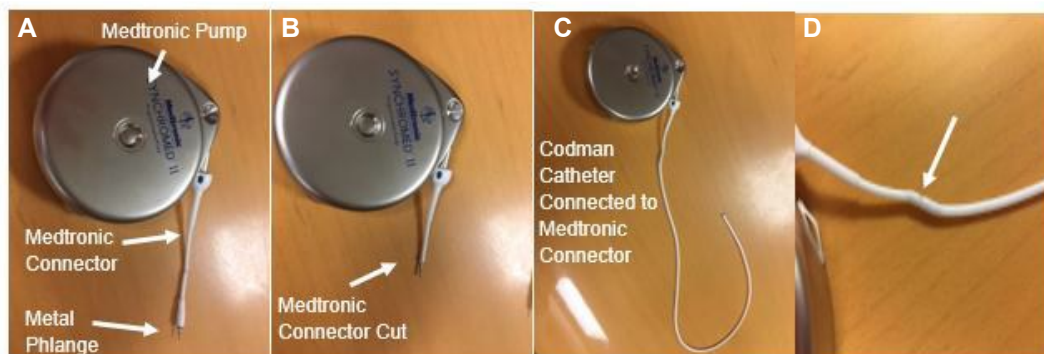


Figure 5. Splicing of SynchroMed II pump with tapered silicone catheter

Once the HAI pump is fully primed and warm, it will then be secured to the abdominal wall. Briefly, the pump will be placed into a subcutaneous pocket created in either the left or right lower quadrant of the abdominal wall. The pump catheter is then passed through the abdominal wall, trimmed, and then inserted countercurrent into the gastroduodenal artery via an arteriotomy until the distal tip is placed exactly at the origin of the gastroduodenal artery. On rare occasions at the discretion of the operating surgeon, the HAI catheter may be placed into a different artery than the GDA. A small volume (~5 ml) of methylene blue will be injected into the side bolus pump channel to assess the catheter function and identify any areas of extrahepatic perfusion, as well as evaluate uniformity of intrahepatic perfusion. If further investigation of extrahepatic perfusion is needed, the HAI pump will be injected with fluorescein and assessed with a ultraviolet light Wood's lamp. Once satisfactory hepatic perfusion and no extrahepatic perfusion is determined, the midline incision and the pump pocket will then be closed.

Post-operative care will follow institutional guidelines. Approximately 3-4 days after pump placement, the participant will undergo single-photon emission computed tomography/computed tomography (SPECT/CT) to further evaluate hepatic perfusion of the HAI pump (see Section 7.3.4 for additional details).

7. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

7.1 STUDY SPECIFIC PROCEDURES

7.1.1 DEMOGRAPHICS AND MEDICAL HISTORY

Demographic data and a complete medical history will be collected at visits prior to starting study treatment. Changes in medical history in between visits should be documented at each study visit. The date of birth, race, ethnicity, and sex of the subject are to be recorded during screening.

7.1.2 MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history.

7.1.3 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. The physical exam at baseline should include a complete physical exam per institutional standards. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings.

As part of screening/baseline visit, physical examination is to be conducted within 14 days prior to first dose of mFOLFIRINOX.

7.1.4 VITAL SIGNS

Vitals to be collected include BP, HR, temperature, and oxygen saturation by pulse oximetry. As part of screening/baseline visit, vitals should be obtained within 14 days prior to first dose of mFOLFIRINOX. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF page.

7.1.5 HEIGHT AND WEIGHT

Height is only required as part of screening.

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

7.1.6 PERFORMANCE STATUS

Performance status (ECOG preferred) will be determined for all participants at screening and at select times during treatment as per assessment schedule in Section 7.8. See Appendix A for additional details regarding performance status scale.

7.1.7 ELECTROCARDIOGRAM (ECG)

A standard 12-lead ECG will be performed as per the assessment schedule in Section 7.8.

7.1.8 ADVERSE EVENTS

Toxicities and adverse experiences will be assessed at each visit using the [CTCAE v5.0](#). Safety will be monitored by assessing physical examination, vital signs, body weight, performance status, as well as hematology, and chemistry as indicated in the schedule of events.

7.1.9 COUNSELING EVALUATION

A licensed medical oncology social worker, formally trained in the assessment of candidacy in HAI program established by Dr. Mayo, will perform an in-person evaluation during Screen 1. The evaluation consists of an interview to assess multiple psychosocial areas including social support infrastructure, economic stability, as well as drug and alcohol use. During this time, the medical oncology social worker will explain the limitations once the HAI pump is placed, and discuss the participant's ability to travel to OHSU at least every 2 weeks for the duration of the study. Additional counseling services will be available, as needed, to participants throughout the duration of the study. In the event that this evaluation is not able to be done in person, it is at the PI's discretion if being done remotely is acceptable.

7.1.10 STAGING LAPAROSCOPY AND PRE – AND POST-TREATMENT BIOPSIES

Pretreatment tumor biopsies are required for individual participation in the study. The baseline biopsy may be a fresh or archival specimen. Fresh biopsies are preferred; however formalin-fixed paraffin-embedded (FFPE) tissue is acceptable at baseline (i.e., before the start of Treatment Period 1), as long as there is adequate sample available. As part of Screen 1, participants will undergo a staging laparoscopy to determine the presence of peritoneal disease and occult dissemination of ICC within the liver. The procedure will be performed by a qualified surgeon in accordance with institutional standards. The procedure consists of laparoscopic inspection of the peritoneum (including the falciform ligament, liver and diaphragm, porta, and lesser omentum). Suspicious lesions will be biopsied for pathological assessment, and remaining excess tissue collected as part of the baseline biopsy. **The initial staging laparoscopy should be performed within 30 days prior to start of planned treatment (Screen 1).** A second staging laparoscopy will occur in Screen 2 prior to HAI pump placement (refer to Section 6.6 and 7.5.3). At the completion of Treatment Period 2, participants will be asked to undergo an optional end of treatment biopsy. This end of treatment biopsy will be performed according to institutional guidelines and may be excisional, incisional or core needle (e.g., FNA or brush biopsy, or laparoscopy). The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. This end of treatment biopsy is optional and participant's refusal will not impact their eligibility to remain on study.

If a participant is scheduled to have a tumor biopsy (i.e., via staging laparoscopy) for the purposes of this study and it is subsequently determined that tissue cannot safely be obtained, then the participant may still enroll in the study, after consultation with the Investigator.

7.1.11 MULTI-DISCIPLINARY GASTROINTESTINAL ONCOLOGY TUMOR BOARD OR LIVER TUMOR BOARD

The participant's medical history will be presented at the Multi-Disciplinary GI Tumor Board or Liver Tumor Board; an evaluation conference comprised of hepatobiliary surgical oncologists, medical oncologists, hepatobiliary radiologists, radiation oncology, and surgical pathology. In this conference, the prospective participant's imaging and pathology will be reviewed to see if the group is in agreement that they satisfy all inclusion and exclusion criteria. In addition, all interval imaging will be reviewed during the study to assess for disease-control rate and treatment continuation. Tumor boards may be conducting virtually using an institutionally-approved method of virtual communication (e.g., phone, web-based meeting). Attendance of the PI at these tumor board meetings is not compulsory.

7.2 LABORATORY PROCEDURES AND EVALUATIONS

7.2.1 HEMATOLOGY

Hematologic profiling will be collected per institutional standards, and should include evaluation of hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.

7.2.2 CHEMISTRY

Blood chemistry will be collected per institutional standards and should include the following: albumin (screening only), BUN, creatinine, Bili, SGOT, SGPT, Alk Phos, serum electrolytes, and calcium.

CEA, AFP, and CA19-9 are to be performed at screening. Thereafter, only those markers considered to have clinically abnormal levels should be followed, and only as clinically indicated.

LDH and serum bile acids should only be assessed on Cycle 1, Day 1, of each treatment period (i.e. treatment period 1 and 2). Additional assessments only as clinically indicated.

Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA) to be evaluated only as part of the initial screen. At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable

7.2.3 COAGULATION PANEL

Repeat INR, prothrombin time, and PTT during screening is not required if obtained prior to port placement. Thereafter only as clinically indicated.

7.2.4 PREGNANCY TEST

A serum or urine pregnancy test is required for all female subjects during screening for women of childbearing potential. If the urine pregnancy test is positive, serum pregnancy tests must be performed per institutional standards. For all women of childbearing potential, a urine sample will be obtained within 72 hours of initiating mFOLFIRINOX treatment, as well as prior to beginning the integrated HAI floxuridine-DEX and mFOLFIRI regimen.

7.3 RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS

7.3.1 MAGNETIC RESONANCE IMAGING (MRI) / COMPUTED TOMOGRAPHY (CT) / POSITRON EMISSION TOMOGRAPHY (PET)

Preoperative imaging is required to assess disease status, as well as evaluate the extent of intra-hepatic disease, and confirm the absence of extra-hepatic metastatic disease.

CT imaging of the chest, abdomen, pelvis and all known sites of disease within 30 days prior to first dose. At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable CT volumetry correlated with body surface area (BSA) will be used to determine segmental liver volumetrics according to established methods.^{40,41}

MRI may be obtained instead of CT if patient's disease is not visible on CT. Refer to SynchronMed II technical report regarding safety information for MRI procedures (i.e., imaging, angiography, functional imaging). The SynchronMed II pump is compatible with MRI, provided the following conditions are use:

- 1.5-Tesla (T) and 3T horizontal closed bore
- Maximum spatial gradient of 19T/m (1900 gauss/cm)
- Maximum gradient slew rate: 200 T/m/s
- Maximum RF field intensity: First level controlled operating mode defined in IEC 60601-2-33.

Refer to SynchronMed manual for additional information regarding patient positioning and procedures during MRI examinations.

Fluorodeoxyglucose (¹⁸F)-PET may be used selectively, at the discretion of the treating physician, for the detection of extrahepatic metastases.

7.3.2 DIFFUSION-WEIGHTED MRI (DWI)

An MRI of the liver to include DWI will be performed as per the assessment schedule in Section 7.8. The MRI sequences will include a coronal T2-weighted sequence, axial fat-saturated T2-weighted sequence, axial in- and out-of-phase T1-weighted sequence, pre- and dynamic post-contrast fat-saturated T1-weighted sequences, and DWI.. An apparent diffusion coefficient (ADC) map based on these values will be created to assess for true diffusion restriction.

7.3.3 CT ANGIOGRAPHY

An established HAI protocol using CT angiogram will assess hepatic arterial anatomy for any anomalies, which may preclude participants from the HAI portion of the study. CTA should be conducted during initial screening.

7.3.4 SINGLE-PHOTON EMISSION CT / CT (SPECT/CT)

Combined SPECT/CT imaging, using ^{99m}Tc-labeled macroaggregated albumin (^{99m}TcMAA), will be conducted to evaluate hepatic perfusion and assess for any evidence of extrahepatic perfusion. SPECT/CT imaging will take place 3-4 days after surgical placement of the pump in the Nuclear Medicine suite at OHSU. Administration of ^{99m}TcMAA will be performed by interventional radiology according to institutional standards. In general, with the participant in the supine position, the port of the HAI pump will be slowly injected with 4 mCi of ^{99m}TcMAA in

10 ml of saline at a rate of 5 mL/min. Technical details of SPECT/CT are provided in Appendix C.

7.4 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

7.4.1 RADIOGRAPHIC RESPONSE USING DWI

There has been increased interest in quantifying the radiographic response of primary liver and other cancers using DWI during MRI evaluations and correlating these findings with observed clinical responses seen in patients.⁴²⁻⁴⁴ DWI depicts the random Brownian motion of water molecules, specifically protons within water molecules. The degree of motion is determined by the surrounding environment. Protons that diffuse freely, such as fluid in simple cysts, result in little to no signal intensity in DWI. Protons that cannot move freely, such as fluid within intact cells, contribute an increased signal intensity in DWI.⁴⁵ In the case of ICC, the higher cell density within the lesion results in a higher concentration of cell membranes which restricts the free diffusion of water. This restricted diffusion translates to a higher signal intensity in ICC relative to liver parenchyma. As an indirect measure of tumor hypercellularity, DWI provides higher sensitivity and positive predictive value for the detection of ICC.

In this study, DWI is used as an investigative approach to measure tumor diffusion coefficients before initiating treatment and again on follow-up MRI scans during treatment. Participants will undergo DWI prior to mFOLFIRINOX, after mFOLFIRINOX as part of restaging, and then again following combined treatment with HAI floxuridine-DEX and mFOLFIRI. The results from these imaging studies will help quantify an objective response for mFOLFIRINOX alone versus HAI floxuridine-DEX plus mFOLFIRI, and will provide support for including DWI as an integral staging component for a potential future trials for patients with liver-dominant unresectable ICC treated with a systemic and HAI regimen.

7.4.2 QUALITY OF LIFE

For patients with unresectable, liver-dominant ICC, their only treatment option is chemotherapy for the duration of their life with very few patients ever having enough response to go on to a potentially curative operation. The treatment to control their disease will have a substantial impact on their remaining quality of life (QoL). Regional therapy using HAI allows for liver-directed treatment of liver-dominant ICC with agents that are processed in the liver. This limits the toxic side effects often seen with traditional chemotherapy. In-depth data on patient QoL are essential to understanding the impact of HAI treatment as patients' progress through the treatment of their disease. In this trial, QoL care metrics, including questionnaire and interview data on participants' unique perspectives, will be assessed. We hypothesize that integrated HAI floxuridine-DEX and systemic mFOLFIRI treatment will improve patient QoL by giving patients time off of systemic therapy and the associated side effects while their liver disease is still being maximally treated with HAI therapy.

7.4.2.1 Outcome Measure

Examine QoL including fatigue, depression, and social support as perceived by participants with unresectable ICC liver metastases undergoing integrated HAI floxuridine-DEX and systemic mFOLFIRI treatment.

7.4.2.2 Method and Timing of Assessment

Study participants will be asked to complete a series of 6 questionnaires and interviews, both of which will be conducted at 5 different time points during the trial (Table 16). From the End of Study up to 24 months post study, study participants will be asked to complete 2 additional interviews and 1 questionnaire based on changes in their treatments and/or disease process. The purpose of completing the questionnaires and interviews is to obtain a rich and in-depth description of patients' experiences of QoL including fatigue, depression, and social support. It will take 10-20 minutes to complete the questionnaires and 30-40 minutes to complete the interviews. The reliable and valid questionnaires were selected based on our clinical knowledge and experience with this patient population. Completion of QoL questionnaires and interviews will take place at baseline, at the end of treatment period 1 (on or around Cycle 4 Day 1 of mFOLFIRINOX), and prior to each HAI treatment cycle (on or around the Day 15 visits for systemic therapy), at the end of study, and again from the End of Study up to 24 months post study. Interviews will be audio-recorded to obtain an accurate account of their view and conducted in-person in a clinic room. If a patient is unable to meet in-person, a telephone interview or WebEx session will be scheduled at the patient's convenience. Telephone interviews will be audio-recorded; WebEx sessions will be audio- and video recorded. Interviews may also be conducted in-person at patient's home or other private place convenient for them. These in-person interviews will also be audio-recorded. The purpose of the structured interviews and surveys is not to assess for adverse events.

Table 16. Method and Timing of QoL Assessments								
	Measurement	Reliability	Baseline	Cycle 4 mFOLFIRINOX	Cycle 1 Day 15	Cycle 2 Day 15	End of Study	Post Study
QoL	SF-36 ^{46,47}	$\alpha = 0.73 - 0.96$	X	X	X	X	X	X
QoL	EORTC QLQ-LMC21 ⁴⁸	$\alpha = 0.69 - 0.93$	X	X	X	X	X	X
QoL	Quality of Life at the End of Life ^{49,50}	$\alpha = 0.68 - 0.87$	X	X			X	X
Depression	Patient Health Questionnaire ⁵¹	$\alpha = 0.89$	X	X			X	X
Fatigue	Piper Fatigue Scale Revised ⁵²	$\alpha = 0.97$	X	X	X	X	X	X
Social Support	MOS Social Support Survey ⁵³	$\alpha = 0.91$	X				X	X

7.4.3 TUMOR TISSUE BIOMARKER ASSESSMENT (KNIGHT DIAGNOSTIC LABORATORY)

Tumor biopsy samples will be used to identify mutations associated with ICC. Tumor biopsy sample will also be used to investigate molecular signatures associated with response or resistance to treatment. Samples will be processed and analyzed within the OHSU's [Knight Diagnostic Laboratory](#). Deoxyribonucleic acid prepared from tissue samples may also be included in the analysis. Deoxyribonucleic acid analysis may include somatic mutation analysis, T-cell and B-cell receptor diversity, and epigenetic analysis. Ribonucleic analysis may include expression analysis by RNAseq and changes in the expression profile will be assessed. Other assays relevant to the study objectives may be performed based on emerging data.

7.4.4 microRNA PROFILING OF ICC

There is no sensitive method to detect ICC in people that are at highest risk. This exploratory study aims to develop a novel fluid biopsy based on microRNA (miR) and mRNA signatures in patients who are newly diagnosed with ICC by collecting blood, bile, and tissue samples taken throughout the participants' course of treatment. In addition to advancing our knowledge of the basic tumor biology of ICC, we anticipate that results from these studies will inform our ability to develop both a screening modality that can be used for early detection, provide an assessment of treatment response, and ultimately detect the earliest evidence of recurrence in order to improve patient outcome and quality of life.

7.4.4.1 Outcome Measure

Generate a differential expression pattern of RNAs (miR and mRNA) in patients with ICC derived from tumor samples compared to adjacent normal liver samples as well as lymphatic tissue, blood and bile.

7.4.4.2 Method of Assessment

Blood and tissue collection times are detailed in the Schedule of events. RNA will be extracted, using the miRneasy kit (Qiagen), according to manufacturer's protocol, which is established in the Anand Lab.⁵⁴ We will use a Universal spike-in controls (from Exiqon) for normalization of the samples. RNA quality (RIN scores) will be evaluated using standard protocols on an Agilent Bioanalyzer (OHSU Genomics core). We will use a NanoString miR panel for miR analysis and NanoString cancer pathways panel for mRNA analysis. We chose this approach since this platform is compatible with low yields and moderate quality (RIN) scores of RNA. In addition, the signature we utilize is directly translatable without cross platform validation since a number of clinical labs utilize the NanoString platform. Following signal quantification, data will be preprocessed and normalized using the n-Count analysis system (NanoString Technologies, Seattle). A random forest classifier will be used on these data to generate signatures that will distinguish tumor from normal tissue, as well as identify which subsets of tumor RNAs are detectable in blood. We will report on the model's performance criteria important for tumor discrimination.

7.4.4.3 Timing of Assessment

The collection of blood, bile, and tissue is detailed in schedule of events.

7.4.5 CIRCULATING HYBRID CELLS

The Wong research group has recently discovered that macrophages (MΦs) fuse with cancer cells to form a hybrid cancer cell that retains genotypes and phenotypes of both the parental cancer cell and MΦs. The resulting tumor cell hybrid displays hallmarks of metastatic cancer cells but appears to have greater "stem cell"-like behavior. Interestingly, these cells represent a unique population of circulating tumor cells (CTCs) that we call circulating hybrid cells (CHCs) that exist in blood as a log-fold higher than conventionally isolated CTCs in late stage disease. Based upon this novel biologic finding in combination with HAI treatment of patients with ICC, we hypothesize that CHC frequency will reflect the tumor response to therapeutic delivery and risk for both intrahepatic recurrence and development/progression of extrahepatic disease with greater sensitivity than monitoring of conventional CTCs or other serum tumor biomarkers (e.g., CA19-9). Successful completion of this work will establish the foundation to develop a novel liquid biopsy to inform patient treatment in the metastatic setting.

7.4.5.1 Outcome Measure

1. To investigate the utility of newly discovered CHCs as a biomarker for early detection of extrahepatic disease and disease progression in patients with uICC.
2. To develop a sensitivity and specificity model using this cellular biomarker in combination with high level analyses of tumor stage specific transcriptome expression at single cell resolution.
3. Establish sensitivity and specificity of CHC biomarkers in patient samples.
4. Determine how CHC are temporally altered with treatment.

7.4.5.2 Method of Assessment

Outcome Measure #1: The first goal of this study is to investigate the utility of the newly discovered CHC as biomarkers for detection of extrahepatic disease progression in patients with uICC.

We will be analyzing CHCs from patient blood samples to correlate frequency with stage and progression. Genomic analyses will be conducted using RNA-seq on batched and single cells to determine the depth of heterogeneity among CHC and identify novel stage-specific or MΦ-specific expression to increase CHC biomarker specificity.

Outcome Measure #2: The second goal of this study is to establish sensitivity and specificity of CHC biomarkers in patient samples.

As noted above we will be obtaining several unique blood samples from the start of patient enrollment in this trial. In addition to the initial treatment naïve samples and samples during mFOLFIRINOX induction, we will also obtain samples proximate to the HAI pump operation prior from the peripheral blood,. These samples will represent a spectrum of disease. RNA sequencing will be performed to enhance stage-specific classifications to refine biomarker sensitivity. In the cases where RNA sequencing is not feasible, isolated CHCs will be subjected to gene expression of a panel of genes identified from mouse studies along with previously reported stage specific candidate genes.

Outcome Measure #3 and #4: The third goal of the study is to establish sensitivity and specificity of CHC biomarkers in patient samples and the fourth goal is to determine how CHC are temporally altered with treatment; in particular we will assess the impact on the CHC population with mFOLFIRINOX induction as compared to treatment with HAI floxuridine-DEX + systemic mFOLFIRI.

To address these questions, CHCs will be isolated from human patients will be longitudinally evaluated throughout the duration of their treatment plan. Treatment naïve specimens will be evaluated by single cell RNA-seq and compared to downstream specimens to provide insight to patient response (either recurrence or resistance to treatment). These studies will establish efficacy of CHC biomarkers in monitoring response to therapeutic treatment.

7.4.5.3 Timing of Assessment

As detailed in the schedule of events.

7.5 **SCREENING ASSESSMENTS**

Toxicities which occur prior to administration of mFOLFIRINOX will not be subject to analysis. The screening periods includes baseline tumor assessment before mFOLFIRINOX administration (Screen 1), and again after systemic induction of mFOLFIRINOX (Screen 2).

Consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period. Informed consent should be obtained within 30 days before the first dose of mFOLFIRINOX.

7.5.1 PRE-mFOLFIRINOX TREATMENT

Participants will undergo screening evaluations to determine study eligibility. All qualifying screening and eligibility assessments must be performed within 30 days before the first dose of mFOLFIRINOX. At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable. Tests used for baseline disease assessments must be performed within specified time frame of the initial dose of study treatment. This includes CT angiogram to assess for hepatic arterial anatomy, and staging laparoscopy. Participants found to have metastatic extrahepatic or peritoneal disease (e.g., determined by imaging or staging laparoscopy) will be considered screen failures and removed from study. Those not eligible for continued study participations will be offered alternative cancer-directed therapy per institutional guidelines. Formal screening by an oncology social worker will assess capacity to participate in study (see Section 7.1.9, Counseling Evaluation). Refer to schedule of events for additional details.

7.5.2 POST-mFOLFIRINOX TREATMENT

Within 4 weeks after last dose systemic induction of mFOLFIRINOX, participants will undergo repeat imaging to restage disease and assess eligibility for HAI pump placement and subsequent treatment.

7.5.3 PRE-OPERATIVE EVALUATION

Pre-operative evaluation of participant prior to surgery is required as part of standard of care. The participant will be evaluated by a clinician in OHSU's preoperative medical clearance clinic. All participants will have a baseline evaluation of hematology and biochemistry (including testing for hepatitis B and C).

Participants eligible for Treatment Period 2 that are will be taken to the operating room for a diagnostic (staging) laparoscopy to further evaluate for peritoneal disease. If a laparoscopic staging is not feasible due to anticipated scarring from prior abdominal operations, the study PI will document this as not safely feasible and will proceed with exploratory laparotomy. If the laparoscopy is negative, the participant will immediately undergo an exploratory laparotomy with planned placement of an HAI pump, cholecystectomy and portal lymphadenectomy. If there is evidence of extrahepatic disease found at laparoscopy or laparotomy, surgical placement of HAI pump will not occur.

7.5.4 INFORMATION TO BE COLLECTED ON SCREENING FAILURES

A participant who signed an informed consent form but failed to be started on treatment for any reason will be considered a screen failure. Those found not to be eligible after signing the main study consent will be considered screening failures, and data will be handled in the same

manner. The demographic information and informed consent should be recorded. No other data will be entered into the clinical database for individuals who are screen failures.

7.6 END OF TREATMENT (EOT) VISIT

The End of Treatment Visit will occur approximately 1 to 2 weeks after completing Treatment Period 2 (Cycle 2 Day 15 visit). EOT visit assessments completed outside this timeframe are permitted (per PI discretion). Participants that undergo mFOLFIRINOX treatment (Treatment Period 1), but are not eligible for Treatment Period 2 (i.e., not eligible to undergo HAI pump placement and receive subsequent HAI floxuridine-DEX and mFOLFIRI treatment) may be evaluated at the EOT visit. Aspects of this evaluation, as described in the schedule of events, will take place ~4 months following the end of Treatment Period 1.

7.7 FOLLOW-UP

Following completion of study treatment, participants will be required to return every 2-8 weeks to fill pump with heparinized saline, depending on reservoir size of HAI pump (i.e., 20 ml or 40 ml). Participants will be followed for up to 1-year after discontinuing protocol-directed therapy, or until death, whichever occurs first. At a minimum, participants will be followed-up for disease status, and survival. This information may be updated periodically via electronic health records, or follow-up contact may be made with the participant (e.g., by phone) or their treating physician to that end.

7.8 SCHEDULE OF EVENTS

Procedure	Screening Period	TREATMENT PERIOD 1 [†] mFOLFIRINOX Induction								TREATMENT PERIOD 2 [‡] HAI floxuridine-DEX + SYS mFOLFIRI						EOT**	Post Treatment***	
	Screen 1 ^A	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Screen 2 ^M	HAI ^G	Cycle 1		Cycle 2			1	2
Day of Cycle (± 10 days)		1	14	1	14	1	14	1	14			1	15	1	15			
mFOLFIRINOX		X		X ^B		X ^B		X ^B										
HAI floxuridine-DEX												X		X				
HAI heparinized saline													X		X	X ^L		
mFOLFIRI													X		X			
5-FU														X				
Maintenance*																X		
Demographics/Medical History	X									X								
Medication History	X									X								
Physical Exam	X									X						X		
Vitals	X									X								
Performance Status	X									X		X		X		X		
Height ^C & Weight	X	X		X		X		X		X		X	X	X	X			
ECG	X									X								
Hematology	X	X		X		X		X		X	X	X		X				
Chemistry	X	X		X		X		X		X		X		X				
CEA, AFP, CA19-9	X	**Monitor only marker considered abnormal at baseline. Monitor as clinically indicated**																
Coagulation	X	**only as clinically indicated**																
LDH/serum bile acids		X								X		X						
Pregnancy ^D	X	X		X		X		X		X		X						
Mediport placement ^E	X																	
Counseling ^F	X																	
RECIST										X						X		
Adverse Event		Continuous assessment																

Procedure	Screening Period	TREATMENT PERIOD 1† mFOLFIRINOX Induction								TREATMENT PERIOD 2‡ HAI floxuridine-DEX + SYS mFOLFIRI						EOT**	Post Treatment***	
	Screen 1 ^A	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Screen 2 ^M	HAI ^G	Cycle 1		Cycle 2			1	2
Day of Cycle (± 10 days)		1	14	1	14	1	14	1	14			1	15	1	15			
CT/MRI/PET ^N	X									X						X		
DWI	X									X						X		
CT angiography	X ^A																	
SPECT/CT											X ^H							
Staging Laparoscopy	X										X							
Tissue Biopsy	X ^O															X ^{optional}		
Surgical tissue collection											X ^K							
CHC		X				X			X		X ^I	X ^J			X ^J	X ^J		
KDL ^P	X																	
microRNA									X		X ^I				X ^J	X ^J		
QoL	X							X					X		X	X	X	

Where possible, it is preferable that the timing of all scheduled visits is consistent with planned standard of care visits. Planned assessments may be adjusted to occur as much as 10 days before or 10 days after the scheduled date. Study assessments conducted as part of a participant's standard of care are acceptable.

[†] Treatment cycle is 2 weeks.

[‡] Treatment cycle is 4 weeks.

* The pump requires a heparin saline refill every 2-8 weeks , depending on reservoir size.

** The End of Treatment Visit will occur approximately 1-2 weeks after completing Treatment Period 2 (Cycle 2, Day 15). EOT visit assessments completed outside this timeframe are permitted (per PI discretion).

*** The Post Treatment Visits will occur after End of Treatment up to 24 months post study.

^A Screening procedures to occur within 30 days prior to treatment start.

^B mFOLFIRINOX administered at a 25% dose reduction from starting dose.

^C Height only required at screening assessment.

^D Within 72 hours prior to treatment start.

^E Mediport placement is at the discretion of investigator, and is to be installed any time prior to enrollment.

^F Additional counseling services will be available, as needed, to participants throughout the duration of the study.

^G HAI pump placement and associated surgical procedures are to occur 3-6 weeks after last mFOLFIRINOX dose. Participants are required to undergo evaluation for preoperative medical clearance by a medical physician in OHSU's preoperative medical clearance clinic. At this time, all patients will have baseline screening of the following: comprehensive metabolic panel, hematology, chemistry (including ldh, ca19-9, and serum bile acids), coagulation panel, as well as evaluation of hepatitis B and C..(earlier or later time points at discretion and approval of PI)

Procedure	Screening Period	TREATMENT PERIOD 1 [†] mFOLFIRINOX Induction								TREATMENT PERIOD 2 [‡] HAI floxuridine-DEX + SYS mFOLFIRI								EOT**	Post Treatment***	
	Screen 1 ^A	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Screen 2 ^M	HAI ^G	Cycle 1		Cycle 2		1	2			
Day of Cycle (± 10 days)		1	14	1	14	1	14	1	14			1	15	1	15					

^H To occur no sooner than post-operative day 4.

^IPeripheral blood at time of surgery will be collected.

^J Repeat blood collections will occur just prior to, and after, administration of floxuridine-Dex or mFOLFIRI.

^K Tissue will be collected at the time of pump placement.

^L Following completion of this study, participant will be required to return every 6 weeks to fill pump with heparinized glycerol.

^M Secondary screening to determine eligibility for HAI pump placement. CT/MRI imaging will be reviewed by medical oncology board. Secondary screening will occur within 4 weeks after the last treatment with mFOLFIRINOX.

^N CT scan is the default imaging approach. MRI and/or PET may, at the discretion of the investigator, be used to image disease.

^O Tissue biopsy will be collected as part of a staging laparoscopy (per institutional standards). Pretreatment biopsy may be fresh or archival FFPE. An optional end of treatment biopsy will be requested for each participant.

^P Knight Diagnostic Laboratory (KDL) genetic screening.

^Q QoL assessments to be conducted prior to surgery (e.g., during pre-surgical consultation).

8. EFFICACY MEASURES

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).⁵⁵ Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

For the purposes of this study, participants will undergo a CT chest/abdomen/pelvis (or MRI), approximately every 8 weeks (± 2 weeks) while on study. Determination of progression will be made according to the RECIST v1.1. Assessments conducted after the EOT (i.e., end of Treatment Period 2) will be conducted without RECIST, but rather jointly assessed by the PI and the treating radiologist.

8.1 DEFINITION OF EFFICACY MEASURES

8.1.1 DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs but, in addition, should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as **non-target lesions** and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.2 DISEASE EVALUATION

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment. At the discretion of the PI, screening procedures that fall outside the 30 day window are acceptable

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

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Use of MRI is also acceptable.

FDG-PET: Use of FDG-PET scanning to complement CT scanning may be utilized in the assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Cytology, Histology: Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases.

Tumor markers: Tumor markers alone cannot be used to assess response. This data will be collected, but will not be used the purpose of response evaluation.

8.3 EFFICACY CRITERIA FOR TUMOR RESPONSE

8.3.1 EVALUATION OF TARGET LESIONS

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.3.2 EVALUATION OF NON-TARGET LESIONS

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the principal investigator.

8.3.3 EVALUATION OF BEST OVERALL RESPONSE

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

Table 17. For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

Table 18. For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<p>* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</p>		

8.3.4 DURATION OF RESPONSE

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

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

8.3.5 PROGRESSION-FREE SURVIVAL

PFS is defined as the duration of time from start of treatment to time of progression or death,

whichever occurs first. In this study, evaluation of PFS will include from start of treatment with mFOLFIRINOX, and repeat evaluation from start of HAI floxuridine-DEX and mFOLFIRI combination.

8.4 **RESPONSE REVIEW**

Response assessment will be determined by the investigator.

9. SAFETY

9.1 SPECIFICATION OF SAFETY PARAMETERS

The principal investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse event (AE) reports and the results of safety evaluations at specified time points as described in Section 10.5, Schedule of Events. Any clinically significant abnormalities persisting at the end of treatment visit will be followed by the investigator until resolution or death, whichever comes first.

All AEs, complaints, or symptoms that occur from the time informed consent is signed are to be recorded on the appropriate case report form (events ongoing prior to consent are considered medical history unless they worsen during study). Documentation must be supported by an entry in the participant's source medical records. Laboratory abnormalities requiring treatment or considered by the Investigator to be clinically relevant should be reported in the case report form as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product. After discontinuing study treatment, the reporting of all AEs is to continue for 100 days from the last dose of HAI floxuridine-DEX, or until the participant receives alternative therapy for their cancer. Any SAE that occurs after treatment with alternative therapy will be reported only if the investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the current version of the NCI Common Terminology Criteria for Adverse Events ([CTCAE v5.0](#)).

All toxicities, with the exception of hepatic enzyme toxicities and skin or nail related toxicities, will be rated per [CTCAE v5.0](#). The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting.

9.2 DEFINITIONS

9.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). This includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

9.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

9.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. 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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

9.2.4 SEVERITY OF EVENT

The investigator will grade the severity of each AE using, when applicable, the current version of the [CTCAE v5.0](#). In the event of an AE for which no grading scale exists, the investigator will classify the AE as defined below:

- **Mild** (grade 1) – An event that is usually transient in nature and generally not interfering with normal activities
- **Moderate** (grade 2) – An event that is sufficiently discomforting to interfere with normal activities
- **Severe** (grade 3) – An event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity
- **Life-threatening/debilitating** (grade 4) – An event that puts the participant at immediate or potential risk of death, requires hospitalization, or which drastically impacts a participant's well-being
- **Fatal** (grade 5)

9.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definite* – The AE is clearly related to the study treatment.
- *Probable* – The AE is likely related to the study treatment.
- *Possible* – The AE may be related to the study treatment.
- *Unlikely* – The AE is doubtfully related to the study treatment.
- *Unrelated* – The AE is clearly NOT related to the study treatment.

9.3 EXPECTEDNESS

The investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.4 ADVERSE EVENT LIST(S)

9.4.1 ADVERSE EVENT LIST FOR mFOLFIRINOX/mFOLFIRI

Detailed information about the risks and expected AEs of floxuridine, and the drug agents comprising mFOLFIRINOX/mFOLFIRI regimens, may be found in the manufacturer's package insert for each respective component.

9.4.1.1 Irinotecan

Acute cholinergic syndrome, diarrhea (early and late onset), respiratory disorders (i.e., severe pulmonary toxicity). Refer to Appendix D for additional AEs.

9.4.1.2 Oxaliplatin

Anaphylaxis (associated with platinum hypersensitivity), laryngopharyngeal dysesthesia, gastrointestinal complications, venous occlusive disease, hemolytic uremic syndrome (HUS). Refer to Appendix D for additional AEs.

9.4.1.3 5-FU

Cardiotoxicity (myocardial ischemia and angina), dihydropyrimidine dehydrogenase (DPD) deficiency, Palmar Plantar Erythrodysesthesia (PPE). Refer to Appendix D for additional AEs.

9.4.2 ADVERSE EVENT LIST FOR FLOXURIDINE - DEXAMETHASONE

9.4.2.1 Floxuridine

The most common AEs are nausea, vomiting, diarrhea, enteritis, stomatitis and localized erythema. Risk of myocardial infarction is associated with floxuridine.

Several other AEs associated with floxuridine include:

gastrointestinal complications:	duodenal ulcer, duodenitis, gastritis, bleeding,
---------------------------------	--

	gastroenteritis, glossitis, pharyngitis, anorexia, cramps, abdominal pain; possible intra- and extrahepatic biliary sclerosis, as well as acalculous cholecystitis
dermatologic complications:	alopecia, dermatitis, nonspecific skin toxicity, rash

9.4.2.2 Dexamethasone

AEs associated with DEX are sodium retention, fluid retention, hypertension, development of cushingoid state, secondary adrenocortical and pituitary hypo-responsiveness, decreased carbohydrate tolerance, manifestations of latent diabetes.

9.4.2.3 Heparin

Common	
Hematologic:	Thrombocytopenia (up to 30%)
Hepatic:	Increased liver aminotransferase level
Serious	
Hematologic:	Hemorrhage (5% to 10%), Heparin-induced thrombocytopenia (1% to 10%), Heparin-induced thrombocytopenia with thrombosis (less than 1%)
Immunologic:	Hypersensitivity reaction
Neurologic:	Non-traumatic spinal subdural hematoma

9.4.3 ADVERSE EVENT LIST FOR HAI PUMP

Complications associated with the use of the implantable pump have been reported in the range of 12% to 41% of patients ⁵⁶. AEs associated with implantation of HAI pump include: catheter thrombosis, bolus path occlusion, vessel thrombosis, pump dislodgement, seroma, or recurrent hematoma, infection, extravasation, catheter shear, dislodgement or leakage, and migration. In the event that the pump is unusable, participants will receive standard systemic therapy (e.g., mFOLFIRINOX). Refer to SynchroMed manual for additional risks associated with HAI pump placement.

Here at OHSU, technical complications associated with using HAI for treating CRLM patient is 8% at 1 year (n=13 patients). One of 13 patients had extrahepatic perfusion that was immediately identified, and successfully salvaged with angioembolization of an aberrant hepatic artery (OHSU interventional radiology). The patient was immediately restarted on HAI + systemic.

9.4.3.1 Key safety concerns associated with HAI pump therapy

Abnormal liver function associated with HAI floxuridine (Section 6.2.2.1 and 10.2.4) will be continuously assessed throughout the study, and used as the guidelines for assessing unwanted toxicities that will trigger the stopping rules. Additional safety concerns associated with HAI pump therapy are described in Table 19.

Table 19. Key safety concerns associated with HAI pump therapy.		
Key safety concern:	Threshold for action:	Management:
Seroma formation	Typically be managed expectantly	Needle aspiration in the outpatient setting under local anesthesia.

Table 19. Key safety concerns associated with HAI pump therapy.		
Key safety concern:	Threshold for action:	Management:
Hematoma formation	Size of the collection should be quantified using radiographic imaging	Pump pocket hematomas that occur early in the perioperative setting should be taken back to the operating room for evacuation of the clot and identification of the bleeding source.
Cellulitis		<ul style="list-style-type: none"> • Treated with antibiotics, oral or intravenous, depending on the severity of the cellulitis and the patient's clinical condition. • If infected fluid collection within the pump pocket is suspected, attempts at pump salvage should be reserved for those without evidence of systemic infection. <ul style="list-style-type: none"> ○ Pump may be removed from the pocket in the operating room. Pump pocket is debrided before pump is secured back in place.
Wound dehiscence		If integrity of pump is compromised, then device needs to be removed.
Primary pump malfunction with high pump flows	Increased rate of pump perfusion	This exceedingly rare occurrence is often detected during the heparinized saline fills before the HAI chemotherapy is instilled. It manifests as a higher than typical calculated HAI flow rate. It requires replacement of the HAI pump with splicing of a new HAI pump to the existing catheter.
Clot or fibrin formation at the tip of the catheter	Decrease in the infusion rate	Installation of enough volume of fibrinolytic agent to fill the catheter via the access port or using the bolus needles

9.5 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for AEs) or 30 days (for SAEs) after the last day of treatment period 2. During this time, all SAEs must be reported to local IRB within 24 hours of sending finalized SAE to MedWatch. Any SAE occurring after treatment with alternative therapy will be reported only if the investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the [CTCAE v5.0](#).

9.6 REPORTING PROCEDURES

9.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the [OHSU IRB web site](#).

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. Events that meet the criteria for OHSU Reportable New Information (RNI) must be reported to the IRB within 5 days of learning of the event. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

9.6.2 MEDWATCH REPORTING

The Investigator is required to report AEs to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500, the MedWatch Voluntary Reporting form (available [here](#)), or completed [online](#). A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

9.6.3 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy and follow-up should be recorded by the Investigator. Any SAE experienced during pregnancy must be reported.

If while on study treatment a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

9.7 STUDY STOPPING RULES

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to HAI pump and systemic mFOLFIRI.
- As described in Section 3.1
- As indicated by statistical stopping rules in Section 10.2.4.

10. STATISTICAL CONSIDERATIONS

Please refer to Section 3.1, for a detailed description of study design and endpoints.

10.1 ANALYSIS POPULATIONS

The intent to treat (ITT) analysis population will include all participants who consent and receive at least one treatment. Per protocol population includes participants who receive at least one cycle of study therapy. Post-induction population (PIP) will include only participants entering Treatment Period 2. Post-induction population will be used for primary safety and efficacy endpoint, while ITT population will be used for secondary safety analysis and per protocol population will be used for analyzing secondary efficacy endpoints.

10.2 DESCRIPTION OF STATISTICAL METHODS

10.2.1 ANALYSIS OF PRIMARY ENDPOINT

1. Incidence of abnormal liver function, as defined by unacceptable elevation in liver enzymes (refer to Section 6.2, Table 12), or radiographic evidence of biliary sclerosis on CT/MRI (as measured following the completion of 2 cycles of HAI in Treatment Period 2).
2. To determine the disease control rate (DCR) from beginning of Treatment Period 2 to end of Treatment Period 2. [The DCR is defined as the percentage of patients who have achieved complete response (CR), partial response (PR), or stable disease (SD).]

10.2.2 ANALYSIS OF THE SECONDARY ENDPOINTS

1. DCR from beginning of Treatment Period 1 to end of Treatment Period 2. All participants that enter Treatment Period 1, and receive at least 1 cycle of treatment will be considered evaluable.
2. DCR from beginning of Treatment Period 1 to end of Treatment Period 1. All participants that enter Treatment Period 1, and receive at least 1 cycle of treatment will be considered evaluable.
3. PFS from beginning of Treatment Period 1 to end of Treatment Period 1. All participants that enter Treatment Period 1, and receive at least 1 cycle of treatment will be considered evaluable.
4. PFS from beginning of Treatment Period 1 to end of Treatment Period 2. All participants that enter Treatment Period 1, and receive at least 1 cycle of treatment will be considered evaluable.
5. PFS from beginning of Treatment Period 2 to up 1 year after the end of Treatment Period 2. All participants that enter Treatment Period 2, and receive at least 1 cycle of treatment will be considered evaluable.
6. ORR from beginning of Treatment Period 1 to end of Treatment Period 2.
7. OS at the end of Treatment Period 1, at the end of Treatment Period 2, at the end of 1 year, and whole study period.
8. Proportion of liver toxicity in participants receiving HAI Floxuridine-DEX therapy

9. Incidence of serious post-operative complications, which are defined as complications occurring within 9 weeks following surgery and $\geq$ Grade III per the Clavien-Dindo classification system (Appendix B).

The Kaplan-Meier method will be used to obtain estimates for overall survival and progression-free survival.

Serious post-operative complications are defined as complications occurring within 9 weeks following surgery and $\geq$ Grade III per the Clavien-Dindo classification system (Appendix B).³⁷ This rate, along with exact two-sided 95% confidence intervals, will be reported for the study.

Safety data will be analyzed and reported for all patients with post-induction enrollment. Laboratory values will be summarized both by actual result and by toxicity grade. The maximum grade for each type of toxicity will be recorded and reported for each patient, and frequency tables will be reviewed to determine toxicity patterns.

10.2.3 ANALYSIS OF THE EXPLORATORY ENDPOINTS

10.2.3.1 DWI

The b -values of 0, 50, and 600 s/mm² will be obtained, and an ADC map based on these values will be created to assess for true diffusion restriction.

10.2.3.2 microRNA

A random forest classifier will be used on these data to generate signatures that will distinguish tumor from normal tissue, as well as identify which subsets of tumor RNAs are detectable in blood.

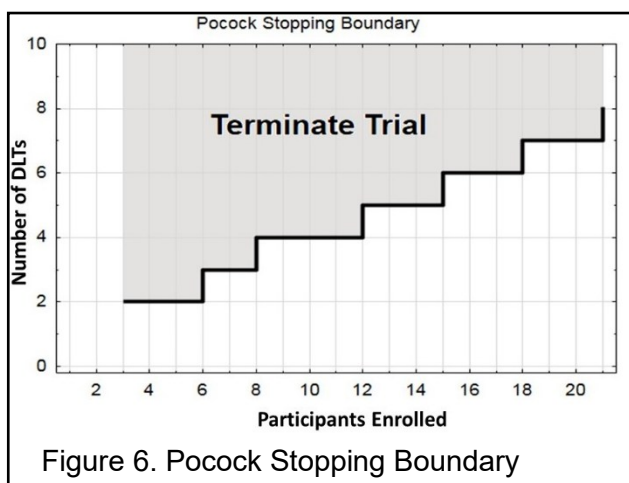
10.2.3.3 CHC

A linear regression model will be used to establish sensitivity and specificity of CHC biomarkers in patient samples.

10.2.3.4 QoL

Statistical analyses will be conducted according to the design of each QoL assessment. Qualitative conventional content analysis will be used to investigate participants' perceptions and experiences of QoL as captured during interviews. The software program QSR NVivo 11 will be used to organize the data.

10.2.4 STOPPING RULE



The safety monitoring associated with HAI floxuridine therapy in Treatment Period 2 will be continuous throughout the trial, and the study will be stopped early should the incidence of post-induction dose (i.e., Treatment Period 2) limiting toxicities (DLT) exceeds targeted unacceptable toxicity at any point during the trial. The DLT is defined as unacceptable elevations in the liver enzymes: SGOT, ALK PHOS, or TOT BILI (as described in Table 12). The Pocock stopping boundary was used for continuous safety monitoring and stopping rule (Figure 6).⁵⁷ The Pocock boundary was constructed with underlining assumption of a true toxicity of 0.2 and unacceptable toxicity of 0.3 with significance

level of 0.05. The trial will be terminated if the number of toxicities exceeds the boundary ($> k$) shown in Table 20. For example, the trial will be terminated if more than 3 out of 7 patients experienced DLT.

Table 20. Pocock stopping boundary

Number of Patients (N)																				
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Number of Patients experienced DLT (K)																				
-	-	2	2	2	3	3	4	4	4	4	5	5	5	6	6	6	7	7	7	8

10.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

10.3.1 SAMPLE SIZE AND POWER

A total of 30 participants will be recruited in order to accrue at least 21 participants for post-induction enrollment under the assumption that 70% of participants will be eligible for the post-induction (Treatment Period 2). Using a one-sided exact test with a targeted significance level of 0.05, accrual of 21 patients will result in a study with 80.2% power to detect a difference between a 60% and 85% DCR at 6 months. The actual significance level of the study will be 0.037.

10.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

11. CLINICAL MONITORING

11.1 OHSU KNIGHT CANCER INSTITUTE DATA AND SAFETY MONITORING PLAN

This study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial subjects, the accuracy and integrity of the data and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The Knight DSMC will review and monitor study progress, toxicity, safety and other data from this study. Information that raises any questions about participant safety or protocol performance will be addressed by the investigator, statistician and study team. Should any major concerns arise, the Knight DSMC may recommend corrective action and determine whether or not to suspend the study.

The Knight DSMC will review each protocol every 6 months, but may occur more often, if required, to review toxicity and accrual data (please refer to Knight DSMP for additional details on audit frequency). The Knight DSMC will review accrual, toxicity, response and reporting information. Information to be provided to the DSMC may include: participant accrual; treatment regimen information; AEs and SAEs reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.2 CLINICAL DATA AND SAFETY MONITORING

The OHSU investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all participating sites, and final analysis of study data.

If monitoring is required, per the Knight DSMP, then monitoring visits will be performed during the study to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements. In this cases, details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate TSMP.

If monitoring is required, per the Knight DSMP, then the Investigator agrees that the monitor will be permitted to conduct monitoring visits at appropriate intervals. The Investigator agrees to provide all relevant information and documentation as requested by the monitor, including access to all original study documents and source data, including access to electronic medical records and/or source documents if necessary. The monitor will conduct source data review and verification as outlined in the TSMP, and following each visit will generate a report

summarizing the visit findings.

In the absence of a formal monitoring plan, the investigator may work with his/her study team to conduct and document internal monitoring of the study to verify protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time investigator noncompliance is discovered at OHSU, the investigator shall promptly either secure compliance or halt the study until compliance is secured, or terminate the study.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

11.3 QUALITY ASSURANCE AND QUALITY CONTROL

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

Quality assurance (QA) auditing activities will occur as detailed in the Knight DSMP. All discrepancies, queries, deviations, observations, and findings will be compiled into a final audit report along with a Corrective and Preventative Action Plan.

The Sponsor-investigator, or designee, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

12. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

12.1 SOURCE DATA/DOCUMENTS

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

12.2 PARTICIPANT AND DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Authorized representatives of the sponsor, representatives of the IRB, may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files and printed copies of de-identified interview transcripts for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per [OHSU's Information Security Directives](#). Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per [OHSU's Information Security Directives](#). At the end of the study, all study databases will be de-identified and archived within the Knight Cancer Institute.

12.3 DATA COLLECTION AND STORAGE

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the [OHSU's Information Security Directives](#) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples, questionnaires, interview audio- and video-recordings, and printed copies of interview transcripts..

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Patient experiences and perceptions of QoL will be captured in interviews conducted in-person, over the telephone, or over a WebEx session. Interviews conducted in-person or over the phone will be audio-recorded. Interviews conducted over a WebEx session will be video-recorded. WebEx video-recordings will be transferred from WebEx into Echo360 to generate an audio file for download. Each video-recording will be deleted once the audio-recording has been downloaded. All audio-recordings will be reduced to writings (i.e. transcripts), and used to conduct qualitative analysis. Electronic data obtained from completed interviews, audio- and video-recordings, and interview transcripts will be stored on secure OHSU computers and restricted drives. Printed copies of interview transcripts will be stored in locking file cabinets in a secure location (office 234 in the School of Nursing). Data will be transported in locking bags from meeting with participants to the locking file cabinets where they will be stored.

Audio recordings of interviews conducted in-person, over the telephone, or during a WebEx meeting will be transcribed by Westside Secretarial Services (WSS), a HIPAA certified transcription service. Transcription is necessary to reduce the interview to a writing (i.e. transcripts) in order to memorialize what was said during the interview for qualitative data

analysis. Digital audio recordings of interviews and electronic transcription files will be transferred between research team and WSS electronically via a secure username and password protected ShareSync folder that is limited only to study investigators, staff, and WSS employees with authorization to access the data. The ShareSync folder is located on a secure WSS secure server. Any PHI and names of persons and places mentioned during interviews will be deleted and changed to pseudonyms in the transcripts. To further preserve confidentiality, patients will be prohibited from independently recording WebEx session interviews.

As specified in the EDC, data from certain correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 11.3, Quality Assurance and Quality Control.

12.3.1 FUTURE USE OF STORED SPECIMENS

Each participant who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will be used to identify any participant specific samples. Blood and tissue samples collected for the purposes of this protocol will be stored until they can be analyzed and will then be destroyed unless the participant consents to participation in the KCI [BioLibrary](#) or Laboratories of Dr. Sudarshan Anand or Dr. Melissa Wong (co-PIs). If the participant agrees, any remaining samples (tumor) may be stored indefinitely in the KCI [BioLibrary](#) or laboratories of Drs. Anand or Wong and further analyzed to address scientific questions and/or development of biological tests related to cancer.

12.4 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

12.5 PUBLICATION AND DATA SHARING POLICY

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment. Results information will be submitted no later than 1 year after the study's Primary Completion Date, as described in 42 CFR 11.44(a) of the final rule.

13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312 (for IND studies), 21 CFR 812 (for IDE studies), and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of [21 CFR Part 50](#). If a participant's signature cannot be obtained, and for all participants under the age of 18, the Investigator must ensure that the informed consent is signed by the participant's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

13.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

13.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and FDA if under an IND/IDE) within 5 business days after the implementation.

14. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
2. Ghouri Y, Mian I, Blechacz B. Cancer review: Cholangiocarcinoma. *Journal of Carcinogenesis*. 2015;14(1):1-1.
3. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol*. 2004;40(3):472-477.
4. Valle JW, Furuse J, Jitlal M, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol*. 2014;25(2):391-398.
5. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg*. 2008;248(1):84-96.
6. Doussot A, Gonen M, Wiggers JK, et al. Recurrence Patterns and Disease-Free Survival after Resection of Intrahepatic Cholangiocarcinoma: Preoperative and Postoperative Prognostic Models. *J Am Coll Surg*. 2016.
7. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281.
8. Park JO, Oh D-Y, Hsu C, et al. Gemcitabine Plus Cisplatin for Advanced Biliary Tract Cancer: A Systematic Review. *Cancer Research and Treatment : Official Journal of Korean Cancer Association*. 2015;47(3):343-361.
9. He S, Shen J, Sun X, Liu L, Dong J. A phase II FOLFOX-4 regimen as second-line treatment in advanced biliary tract cancer refractory to gemcitabine/cisplatin. *Journal of Chemotherapy*. 2014;26(4):243-247.
10. Moretto R, Raimondo L, De Stefano A, et al. FOLFIRI in patients with locally advanced or metastatic pancreatic or biliary tract carcinoma: a monoinstitutional experience. *Anticancer Drugs*. 2013;24(9):980-985.
11. Guion-Dusserre JF, Lorgis V, Vincent J, Bengrine L, Ghiringhelli F. FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma. *World J Gastroenterol*. 2015;21(7):2096-2101.
12. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.
13. Lewis HL, Bloomston M. Hepatic Artery Infusional Chemotherapy. *Surgical Clinics of North America*. 2016;96(2):341-355.
14. Balch CM, Urist MM, Soong SJ, McGregor M. A prospective phase II clinical trial of continuous FUDR regional chemotherapy for colorectal metastases to the liver using a totally implantable drug infusion pump. *Ann Surg*. 1983;198(5):567-573.
15. Chang AE, Schneider PD, Sugarbaker PH, Simpson C, Culhane M, Steinberg SM. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg*. 1987;206(6):685-693.
16. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. *Ann Intern Med*. 1987;107(4):459-465.
17. Hohn DC, Stagg RJ, Friedman MA, et al. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol*. 1989;7(11):1646-1654.
18. Safi F, Bittner R, Roscher R, Schuhmacher K, Gaus W, Beger GH. Regional

- chemotherapy for hepatic metastases of colorectal carcinoma (continuous intraarterial versus continuous intraarterial/intravenous therapy). Results of a controlled clinical trial. *Cancer*. 1989;64(2):379-387.
19. Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. *J Clin Oncol*. 1990;8(11):1885-1893.
20. Martin JK, Jr., O'Connell MJ, Wieand HS, et al. Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. *Arch Surg*. 1990;125(8):1022-1027.
21. Rougier P, Laplanche A, Huguier M, et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol*. 1992;10(7):1112-1118.
22. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet*. 1994;344(8932):1255-1260.
23. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol*. 2000;18(2):243-254.
24. Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. *Lancet*. 2003;361(9355):368-373.
25. Jarnagin WR, Schwartz LH, Gultekin DH, et al. Regional chemotherapy for unresectable primary liver cancer: results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. *Ann Oncol*. 2009;20(9):1589-1595.
26. Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer*. 2016;122(5):758-765.
27. Homsí J, Garrett CR. Hepatic arterial infusion of chemotherapy for hepatic metastases from colorectal cancer. *Cancer Control*. 2006;13(1):42-47.
28. House MG, Kemeny NE, Gonen M, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. *Ann Surg*. 2011;254(6):851-856.
29. Kemeny NE, Ron IG. Hepatic arterial chemotherapy in metastatic colorectal patients. *Semin Oncol*. 1999;26(5):524-535.
30. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol*. 2009;27(21):3465-3471.
31. Cercek A, Boucher TM, Gluskin JS, et al. Response rates of hepatic arterial infusion pump therapy in patients with metastatic colorectal cancer liver metastases refractory to all standard chemotherapies. *J Surg Oncol*. 2016;114(6):655-663.
32. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol*. 2006;24(9):1395-1403.
33. Ito K, Ito H, Kemeny NE, et al. Biliary sclerosis after hepatic arterial infusion pump chemotherapy for patients with colorectal cancer liver metastasis: incidence, clinical features, and risk factors. *Ann Surg Oncol*. 2012;19(5):1609-1617.

34. Konstantinidis IT, Do RK, Gultekin DH, et al. Regional chemotherapy for unresectable intrahepatic cholangiocarcinoma: a potential role for dynamic magnetic resonance imaging as an imaging biomarker and a survival update from two prospective clinical trials. *Ann Surg Oncol*. 2014;21(8):2675-2683.
35. D'Angelica M I, Correa-Gallego C, Paty PB, et al. Phase II Trial of Hepatic Artery Infusional and Systemic Chemotherapy for Patients With Unresectable Hepatic Metastases From Colorectal Cancer: Conversion to Resection and Long-term Outcomes. *Ann Surg*. 2014.
36. NCCN. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Hepatobiliary Cancers. (Version 1.2010). © 2010. 2017; www.NCCN.org. Accessed April 8, 2010.
37. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.
38. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol*. 2011;29(23):3140-3145.
39. Kemeny MM. The surgical aspects of the totally implantable hepatic artery infusion pump. *Arch Surg*. 2001;136(3):348-352.
40. Ribero D, Chun YS, Vauthey JN. Standardized liver volumetry for portal vein embolization. *Semin Intervent Radiol*. 2008;25(2):104-109.
41. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery*. 2000;127(5):512-519.
42. Dzik-Jurasz A, Domenig C, George M, et al. Diffusion MRI for prediction of response of rectal cancer to chemoradiation. *Lancet*. 2002;360(9329):307-308.
43. Galons JP, Altbach MI, Paine-Murrieta GD, Taylor CW, Gillies RJ. Early increases in breast tumor xenograft water mobility in response to paclitaxel therapy detected by non-invasive diffusion magnetic resonance imaging. *Neoplasia*. 1999;1(2):113-117.
44. Vandecaveye V, De Keyser F, Verslype C, et al. Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. *Eur Radiol*. 2009;19(10):2456-2466.
45. Moore WA, Khatri G, Madhuranthakam AJ, Sims RD, Pedrosa I. Added value of diffusion-weighted acquisitions in MRI of the abdomen and pelvis. *AJR Am J Roentgenol*. 2014;202(5):995-1006.
46. Aaronson NK, Acquadro C, Alonso J, et al. International Quality of Life Assessment (IQOLA) Project. *Qual Life Res*. 1992;1(5):349-351.
47. Garratt AM, Ruta DA, Abdalla MI, Russell IT. SF 36 health survey questionnaire: II. Responsiveness to changes in health status in four common clinical conditions. *Qual Health Care*. 1994;3(4):186-192.
48. Blazeby JM, Fayers P, Conroy T, et al. Validation of the European Organization for Research and Treatment of Cancer QLQ-LMC21 questionnaire for assessment of patient-reported outcomes during treatment of colorectal liver metastases. *Br J Surg*. 2009;96(3):291-298.
49. Steinhäuser KE, Bosworth HB, Clipp EC, et al. Initial assessment of a new instrument to measure quality of life at the end of life. *J Palliat Med*. 2002;5(6):829-841.
50. Steinhäuser KE, Clipp EC, Bosworth HB, et al. Measuring quality of life at the end of life: validation of the QUAL-E. *Palliat Support Care*. 2004;2(1):3-14.
51. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity

- measure. *J Gen Intern Med*. 2001;16(9):606-613.
52. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum*. 1998;25(4):677-684.
53. Blumenthal JA, Burg MM, Barefoot J, Williams RB, Haney T, Zimet G. Social support, type A behavior, and coronary artery disease. *Psychosom Med*. 1987;49(4):331-340.
54. Wilson R, Espinosa-Diez C, Kanner N, et al. MicroRNA regulation of endothelial TREX1 reprograms the tumour microenvironment. *Nat Commun*. 2016;7:13597.
55. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
56. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg*. 2005;201(1):57-65.
57. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64(2):191-199.

APPENDIX A: PERFORMANCE STATUS

Table 21. ECOG/ Karnofsky Performance Status			
Grade	ECOG Status	%	Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

ECOG = Eastern Cooperative Oncology Group.

APPENDIX B: CLAVIEN DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS

Table 22. Classification of Surgical Complications	
Grade	Definition
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also needed.
Grade III	Requiring surgical, endoscopic, or radiological intervention.
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complications (including CNS complications)* requiring IC/ICU management.
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVa	Multi-organ dysfunction.
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.
*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, immediate care; ICU, intensive care unit. Adapted from ³⁷	

APPENDIX C: SPECT/CT IMAGING FOR HAI PUMP

Technique:

1. Dynamic portion:

- a. Position patient with the dome of liver at the top of the FOV.
- b. Start the camera immediately before injecting the dose.
- c. See technical information below:

Dynamic Acquisition:

Time/Frame: 5 sec/frame
Duration: 2 minutes
Collimator: LEHR or VXGP
Matrix: 128 x 128
Zoom: 1.0

2. Static images:

- a. Anterior/Posterior Lungs
 - i. See technical information below.
- b. Anterior/Posterior Liver
 - i. Dome of liver at the top of the FOV
 - ii. See technical information below.
- c. Liver SPECT/CT
 - i. Dome of liver at the top of the FOV, entire liver must be included in FOV.
 - ii. See technical information below.

Static Acquisition

Time: 180 sec
Collimator: LEHR or VXGP
Matrix: 512 x 512
Zoom: Zoom as necessary

SPECT/CT Acquisition Technical Information:			
Philips XCT SPECT		Philips XCT CT	
Time/Angle:	30 sec	kV:	120
Collimator:	LEHR	mA:	20
Zoom:	1.46 x (40.9) cm	X-Ray Segments:	3
Matrix:	128 x 128	Slice Thickness:	1mm
# of Angles:	64	Matrix:	512 x 512
Rotations:	1	Low Pass Filter:	Soft Tissue
Sat Behavior:	Continue	FOV:	Liver centered
SPECT mode:	Step	Recon Type:	Std. + Iterative
Orbit type:	Non-Circular auto		
Philips Precedence SPECT		Philips Precedence CT	
Time/Angle:	15 sec	kV:	120
Collimator:	VXGP	mA/slice:	80
Zoom:	1.46 x (40.9) cm	CT Rotation:	Continuous
Matrix:	128 x 128	Resolution:	Standard
# of Angles:	128	Slice Thickness:	5mm x 5mm
Rotations:	1	Low Pass Filter:	Standard (B)
Sat Behavior:	Continue	FOV:	Liver centered
SPECT mode:	Step	Recon Type:	Std. + Iterative
Orbit type:	Non-Circular	Matrix:	512

APPENDIX D: LIST OF COMMON AND SEVERE ADVERSE EVENTS

Irinotecan – Common AEs	
System	AE (grade, frequency (%))
Dermatologic	<ul style="list-style-type: none"> Alopecia (43.1% to 60%)
Endocrine metabolic	<ul style="list-style-type: none"> Weight decreased (30%)
Gastrointestinal	<ul style="list-style-type: none"> Abdominal pain (all grade, 17.2% to 67.7%; grade 3 and 4, 2.1% to 14%), Constipation (all grade, 30% to 43.9%; grade 3 and 4, 0.4% to 10%), Diarrhea, All grade (early-onset, 43% to 51%; late-onset, 72.4% to 88%), Loss of appetite (all grade, 34.2% to 55%; grade 3 and 4, 2.1% to 7.2%), Nausea (all grade, 66.9% to 86%; grade 3 and 4, 2.1% to 17%), Vomiting (all grade, 44.8% to 67%; grade 3 and 4, 3.5% to 14%)
Hematologic	<ul style="list-style-type: none"> Anemia (all grade, 60% to 97.2%), Drug-induced eosinophilia, leukopenia (all grade 63% to 96.9%), Neutropenia (all grade 54% to 96.9%), Thrombocytopenia (all grade, 32.6% to 96%)
Hepatic	<ul style="list-style-type: none"> Increased bilirubin level (19.1% to 87.6%)
Neurologic	<ul style="list-style-type: none"> Asthenia (all grade, 57.9% to 76%; grade 3 and 4, 9% to 19.5%), Dizziness (15% to 23.1%), Parasympathomimetic adverse reaction (28.3%)
Respiratory	<ul style="list-style-type: none"> Cough (17% to 26.7%), Dyspnea (9.7% to 27.6%)
Irinotecan – Serious AEs	
Cardiovascular	<ul style="list-style-type: none"> Disorder of cardiovascular system
Gastrointestinal	<ul style="list-style-type: none"> Diarrhea, Grade 3 and 4 (4.9% to 31%), Gastrointestinal perforation
Hematologic	<ul style="list-style-type: none"> Anemia (grade 3 and 4, 2.1% to 8.4%), Febrile neutropenia (adults, 2% to 7.1%), Hemorrhage (1% to 5%), Infectious disease, Neutropenic (1% to 2.2%), Leukopenia (grade 3 and 4, 17.4% to 37.8%), Neutropenia (grade 3 or 4, adults, 26% to 53.8%), Thrombocytopenia (grade 3 and 4, up to 4%), Thromboembolic disorder (5.4% to 11.7%)
Immunologic	Hypersensitivity reaction
Respiratory	Interstitial lung disease

Oxaliplatin – Common AEs	
System	AE (grade, frequency (%))
Gastrointestinal	<ul style="list-style-type: none"> Abdominal pain (Monotherapy, 31%; combination therapy, up to 39%), Constipation (Combination therapy, up to 32%), Diarrhea (Monotherapy, 46%; combination therapy, up to 76%), Loss of appetite (Monotherapy, 20%; combination therapy, up to 35%), Nausea (Monotherapy, 64%; combination therapy, 64% to 83%), Stomatitis (Monotherapy, 14%; combination therapy, up to 42%), Vomiting (Monotherapy, 37%; combination therapy, 40% to 64%)

Hematologic	<ul style="list-style-type: none"> Anemia (all grades, monotherapy, 64%; combination therapy, 25% to 81%), Granulocytopenic disorder (grade 3 and 4 (39% to 45%), Leukopenia, (all grades, monotherapy, 13%; combination therapy, up to 85%), Neutropenia, (all grades, Monotherapy, 7%; combination therapy, 71% to 81%), Thrombocytopenia (all grades onotherapy, 30%; combination therapy, 44% to 77%)
Hepatic	<ul style="list-style-type: none"> Abnormal alkaline phosphatase (Combination therapy, 14% to 16%), ALT/SGPT level abnormal (Monotherapy, 36%; combination therapy, 5% to 31%), AST/SGOT level abnormal (Monotherapy, 54%; combination therapy, 11% to 47%)
Musculoskeletal	<ul style="list-style-type: none"> Backache (Monotherapy, 11%; combination therapy, 19%)
Neurologic	<ul style="list-style-type: none"> Paresthesia (62% to 77%)
Respiratory	<ul style="list-style-type: none"> Cough (Monotherapy, 11%; combination therapy, up to 35%)
Other	<ul style="list-style-type: none"> Fatigue (Monotherapy, 61%; combination therapy, up to 70%), Fever (Monotherapy, 25%; combination therapy, 29%)
Oxaliplatin – Serious AEs	
Cardiovascular	<ul style="list-style-type: none"> Edema (Monotherapy, 5%; combination therapy, up to 15%), Prolonged QT interval, Torsades de pointes
Endocrine	<ul style="list-style-type: none"> Metabolic acidosis
Gastrointestinal	<ul style="list-style-type: none"> Bowel obstruction, Colitis (including clostridium difficile) diarrhea, acute pancreatitis
Hematologic	<ul style="list-style-type: none"> Anemia (grade 3 or 4, Monotherapy, 1%; combination therapy, 1% to 3%), Febrile neutropenia (Combination therapy, up to 12%), Hemolytic anemia, Immuno-allergic, Leukopenia, (grade 3 or 4, Combination therapy, 13% to 24%), Neutropenia (grade 3 or 4, Combination therapy, 36% to 53%), Thrombocytopenia (grade 3 or 4, Monotherapy, 3%; combination therapy, 2% to 5%), Thrombocytopenia, Immuno-allergic
Hepatic	<ul style="list-style-type: none"> Increased liver function test (Combination therapy, 57%), Veno-occlusive disease of the liver
Immunologic	<ul style="list-style-type: none"> Anaphylaxis, hypersensitivity reaction (Monotherapy, grade 3 or 4, 1% to 3%; combination therapy, all grades, 6% to 12%), Infusion reaction
Musculoskeletal	<ul style="list-style-type: none"> Rhabdomyolysis
Neurologic	<ul style="list-style-type: none"> Dysesthesia, Pharyngolaryngeal (1% to 38%),

	<ul style="list-style-type: none"> Neuropathy, Acute or persistent (Overall neuropathy, 69% to 92%; acute neuropathy, 56%; persistent neuropathy, 21% to 60%), Posterior reversible encephalopathy syndrome (less than 0.1%)
Ophthalmic	<ul style="list-style-type: none"> Transient visual loss
Otic	<ul style="list-style-type: none"> Hearing loss
Renal	<ul style="list-style-type: none"> Hemolytic uremic syndrome, Interstitial nephritis, acute
Respiratory	<ul style="list-style-type: none"> Dyspnea (Monotherapy, 13%; combination therapy, up to 20%), Pneumonitis (Severe), Pulmonary fibrosis (Less than 1%)
Other	<ul style="list-style-type: none"> Angioedema, Sepsis

5-FU – Common AEs	
Dermatologic	Allergic contact dermatitis, Crust on skin, Hand-foot syndrome due to cytotoxic therapy, Pruritus, Scar, Sensation of burning of skin, Sore skin, Ulcer of skin or mucosa
Gastrointestinal	Diarrhea, Inflammatory disease of mucous membrane
Hematologic	Leukocytosis
5-FU – Serious AEs	
Cardiovascular	Angina pectoris, Cardiotoxicity, Nonspecific ST-T abnormality on electrocardiogram
Gastrointestinal	Gastrointestinal ulcer
Hematologic	Myelosuppression, Anemia, leukopenia, thrombocytopenia
Neurologic	Hyperammonemic encephalopathy, Neurotoxicity