Abbreviated Title: HAIP for Colorectal Cancer

NIH Protocol #: 18C0024

Version Date: 06/17/2025

NCT Number: NCT03366155

Title: A Single-Arm Phase II Study of Hepatic Artery Infusion Pump Chemotherapy with Floxuridine and Dexamethasone in Combination with Systemic Chemotherapy for Patients with Colorectal Cancer Metastatic to the Liver

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Device Name:	Medtronic SynchroMed II Pump	Codman 3000 Constant Flow Pump Catheter	Floxuridine (FUDR)	Dexamethasone
IDE Number:	G180291			
Sponsor:	Center for Cancer Research, NCI			
Manufacturers:	Medtronic	Intera Oncology, Inc.	Generic	Generic
Supplier:	CC Pharmacy	CC Pharmacy	CC Pharmacy	CC Pharmacy

Commercial Device: None

Commercial Agents: 5FU, leucovorin, Irinotecan, Oxaliplatin, Cetuximab, Panitumumab

PRÉCIS

Background:

- Nearly 60% of patients with colorectal cancers will develop liver metastases over the course of their disease.
- Of patients with metastatic colorectal cancer, the liver will be the sole site of recurrence or the survival-limiting site of disease for 20%.
- Liver directed therapy, which has taken many forms over the last several decades, is a potential means to prolong survival for properly selected patients and delay progression at that site.
- Hepatic artery infusion of floxuridine (FUDR) via an implantable hepatic artery infusion pump (HAIP) induces objective clinical response rates of nearly 50% in heavily pre-treated patients with metastatic colorectal cancer to the liver.
- The identification of patients likely to respond to HAIP and those likely to suffer pump-related adverse events is currently unknown and has limited the wide-spread adoption of this otherwise well-tolerated intervention.

Objective:

- To assess the safety of hepatic artery infusion therapy using the Medtronic pump with the Codman catheter.
- To determine the response rate in patients with unresectable metastatic colorectal cancer treated with HAIP chemotherapy as measured by RECIST.

Eligibility:

- Histologically or cytologically confirmed colorectal adenocarcinoma metastatic to the liver.
- Patients with liver metastases not amenable to resection to No Evidence of Disease (NED) in one stage.
- Patients must have received systemic chemotherapy.
- Age ≥ 18 years.

Design:

- Single arm, Phase II study of HAIP chemotherapy.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To assess the safety of the HAIP chemotherapy using the Medtronic pump with the Codman catheter in patients with unresectable metastatic colorectal cancer.
- To determine the response rate in patients with unresectable metastatic colorectal cancer treated with HAIP chemotherapy as measured by RECIST.

1.1.2 Secondary Objectives

- To determine the hepatic progression-free survival.
- To determine the extra-hepatic progression-free survival.
- To determine overall survival (OS).

1.1.3 Exploratory Objectives

- To determine outcome predictors for response and biliary toxicity.
- To evaluate the chemotherapeutic and immunotherapeutic agent effects in tumors from patients with unresectable metastatic colorectal cancer undergoing HAIP chemotherapy using a novel *ex vivo* platform, the SMART System.

1.2 BACKGROUND AND RATIONALE

1.2.1 Standard Treatment of Colorectal Carcinoma

There are approximately 150,000 new cases of colorectal carcinoma diagnosed annually in the United States [1]. Synchronous or metachronous hepatic metastases as the sole or dominant site of life-limiting progressive disease will afflict approximately 20% of all patients with colorectal cancer [2]. In patients with resectable hepatic metastases, 5-year overall survival ranges from 20 - 35%, suggesting that if liver metastases can be effectively controlled, a long-term survival benefit may result [3]. For patients with unresectable colorectal cancer with metastases confined to the liver, regional treatment of metastatic disease has been a topic of considerable interest given the underwhelming response rates to systemic chemotherapy alone [2]. Modern combination chemotherapy for unresectable Colorectal Liver Metastases (CRLM) rarely results in 5-year survival and is associated with a median survival of roughly 20 months [3]. Irinotecan alone, Irinotecan/Cetuximab, and Oxaliplatin/5-Fluorouracil(5FU)/Leucovorin(LV) will produce responses ranging from 9% to 22% in patients whose tumors have progressed on first-line chemotherapy. However, the median survival time for these patients after second-line therapy is 12 months or less [4, 5]. Local ablative therapies including microwave and radiofrequency ablation have been shown to effectively control metastatic deposits in the liver but based on current technological limitations it is difficult to treat patients with lesions greater than 5 cm or who have more than 3 or 4 metastatic deposits in the liver. Impairment of liver function by tumors contributes significantly to morbidity and mortality in patients with advanced colorectal cancer, while metastases to other organs tend to develop more slowly.

1.2.2 Regional Chemotherapy and Hepatic Artery Infusion (HAI)

Many patients have liver-only disease at the time of progression on first-line therapy, prioritizing the rationale for regional chemotherapy. Many regional chemotherapeutic interventions have been attempted over the last several decades to control hepatic disease. Of the available liver-directed regional therapy options, the hepatic artery infusion pump (HAIP) has been utilized primarily at Memorial Sloan Kettering Cancer Center (MSKCC), and has the most robust toxicity and efficacy data obtained through several prospective trials [6-10]. The advantage of HAI regional therapy is the ability to administer high doses of chemotherapy locally. For a drug such as Floxuridine (FUDR), which has a liver extraction rate of 94%, the local delivery via hepatic artery infusion (HAI) greatly exceeds what could otherwise be delivered by systemic infusion. In a Cancer and Leukemia Group B trial comparing HAI FUDR/LV/Dexamethasone (Dex) with systemic 5FU/LV, the response rate (48% v 25%, respectively) and median survival time (24 v 20 months, respectively; P .0013) was higher in the HAI group. Although time to hepatic progression was better in the HAI arm compared with the systemic arm (9.8 v 7.3 months, respectively; P .034), the time to extrahepatic progression was better in the systemic arm (7.7 v 14.8 months, respectively; P .029) [10]. Data from this trial lead us to several conclusions. First, FUDR delivery via HAI is more effective in controlling hepatic disease than systemic 5FU alone. Second, patients with metastatic colorectal cancer, even those with ostensibly liver-confined disease, have micro metastases in multiple organs. Finally, an optimal approach to patients with liver dominant metastatic colorectal cancer is liver control with FUDR delivered via HAI in combination with systemic chemotherapy. Fortunately, systemic toxicity from HAI FUDR is extremely rare, allowing full doses of systemic chemotherapy to be administered concurrently. Indeed, combining HAI with systemic chemotherapy results in improved efficacy relative to either approach alone.

In a Phase I study of 36 patients with liver-only metastases to examine toxicity of combination HAI with modern systemic agents, the response rate was high compared with other second-line therapies [8]. The partial response rates were 90% and 87% with the HAI plus Oxaliplatin/Irinotecan and HAI plus Oxaliplatin /5FU/LV combinations, respectively. More than 50% of patients showed a greater than 75% reduction in their tumor, and seven patients were able to undergo liver resection, two of whom had complete pathologic response. Combination therapy with HAI FUDR and Dex plus systemic Oxaliplatin/Irinotecan or Oxaliplatin /5FU/LV was safe and well tolerated. Importantly the combination of HAI and systemic Oxaliplatin did not impact the dose of Oxaliplatin or irinotecan that could be administered. In a separate Phase 1 study using HAI Floxuridine and Dexamethasone plus systemic chemotherapy with Oxaliplatin/Irinotecan, forty-nine patients with unresectable liver metastases (53% previously treated with chemotherapy) were evaluated [9]. Ninety-two percent of the 49 patients had complete (8%) or partial (84%) response, and 23 (47%) of the 49 patients were able to undergo resection in a group of patients with extensive disease (73% with > five liver lesions, 98% with bilobar disease, 86% with ≥ six segments involved). For chemotherapy-naïve and previously treated patients, the median survival from the start of HAI therapy was 50.8 and 35 months, respectively. Interestingly, variables reflecting extensive anatomic disease, such as number of lesions or number of vessels involved, were not significantly associated with the probability of resection.

In a prospective Phase-II trial designed to evaluate the rate of conversion to resection in 49 patients, HAI and systemic chemotherapy was used in patients with unresectable colorectal liver metastases [11]. The trial was powered to detect an increase in conversion to resection from 15 to 30%, which represents approximately a doubling of the conversion rate reported with systemic chemotherapy.

Combination HAI and systemic therapy resulted in very high response rates in both previously treated (72%) and chemotherapy-naïve patients (82%); overall 8% CR (4 patients). The primary endpoint of the study (conversion to resection) was achieved with 47% of patients undergoing complete resection. Among the whole cohort, overall survival was 38 months, and one and 3-year survival rates were 92% and 55%, respectively. These results are encouraging, especially considering the high rate of previously treated patients, the large bulk of disease, oncologic adverse features that most patients exhibited. Careful data review suggests responders derive survival benefit whereas non-responders derive little benefit while being exposed to potential toxicity. Toxicity from HAI, which is largely related to biliary injury, can lead to early cessation of treatment, ineligibility for other investigational studies, and biliary strictures requiring complex interventions such as stenting to maintain bile flow (rare) [12].

As mentioned above, regional therapy for single site metastases can be undertaken with modalities other than the HAIP. Today, the most common alternative modality, as endorsed by the National Comprehensive Cancer Network (NCCN), is radioembolization. Although this is an interventional radiology and can be ordered by any treating physician, the procedures are invasive and associated with significant complications[13]. From the available literature, we have constructed the following **Table 1** regarding the efficacy and complications of both HAIP and radioembolization for chemo-refractory metastatic colorectal cancer.

Table 1: Outcomes of HAI vs. Radioembolization

	HAIP[11, 14, 15]	Radioembolization[13, 15-17]
Required Procedures	1	2
COMPLICATIONS		
Pump Infection	2.5%	0%
Thrombosis	6%	1%
Radiation Gastritis/Ulcer	0%	5-10%
Biliary Injury Requiring Stents	5%	5-8%
Hepatic Insufficiency/Failure	<1%	4%
Radiation Pneumonitis	0%	20%
Diarrhea	20%	37%
EFFICACY		
Partial Response Rate	76%	10%
Conversion to Resection	47%	<1%

1.2.3 Optimization of HAIP

Patients with colorectal cancer metastatic to the liver, who have not responded or have stopped responding to conventional first-line chemotherapy, may benefit from regional chemotherapy if the disease remains largely confined to the liver and this site of disease will be survival-limiting. Despite the impressive efficacy, the use of the HAIP (**Figure 1**) has not become ubiquitous in the management of patients with metastatic colorectal cancer (CRC), and is rarely used outside of

select centers. Although efficacy has been documented at numerous institutions (**Table 2**), HAIP has not been adopted as standard of care primarily due to the expertise required to place the pump, and the biliary toxicity observed (personal communication with Dr. Kemeny) when FUDR titration and administration has been the responsibility of inexperienced personnel, as well as the strong financial incentive of oncologists to use new systemic chemotherapeutic agents.

Table 2: Randomized clinical trials documenting the RR of HAIP FUDR in metastatic CRC

Trial Reference	Publication Year	# of Patients	Response Rates
Chang et al.	1987	32	62%
Kemeny et al.	1987	48	53%
Hohn et al.	1989	75	42%
Martin et al.	1990	39	48%
Wagman et al.	1990	100	55%
Rougier	1992	81	41%
Lorenz & Muller	2000	53	43%
Kemeny	2006	68	47%

With appropriate expertise, the HAIP can be placed with minimal risk to the patients. Please see **Table 3** for perioperative complications observed in 544 patients treated consecutively at MSKCC.

In this protocol, we aim to establish the use of the HAI FUDR in the management of patients with liver-dominant colorectal metastases at the clinical center. Our team has a combined six years of experience in placing HAI pumps and we will manage the FUDR chemotherapy including all titrations.

Table 3: Perioperative complications observed in 544 consecutive patients undergoing HAIP placement [14]

Type of Complication	Percentage of Patients	Percent Salvaged
Pump Malfunction	1%	100%
Pump Pocket		
Infection	0.7%	50%
Hematoma	0.2%	100%
Migration	0.2%	100%
Arterial		
Hemorrhage	0.2%	100%
Thrombosis	2.3%	31%

Extra-hepatic Perfusion	1.6%	100%
Incomplete Perfusion	1.6%	75%

We aim to advance the field of regional therapy by identifying tumor and liver characteristics of patients associated with various outcomes such that patients enrolled in future studies can be better selected based upon a more clearly delineated risk/benefit ratio. It is particularly important to note that no study has compared HAIP with radioembolization in a prospective fashion. As we establish the clinical center as a viable (and attractive) option for patients with metastatic colorectal cancer, we will gain the expertise to compare these two modalities in a randomized fashion. We will gain experience with radioembolization at this institution through referral of patients to interventional radiology (IR physicians are AIs on this study), who are not candidates for HAIP secondary to arterial anatomy.

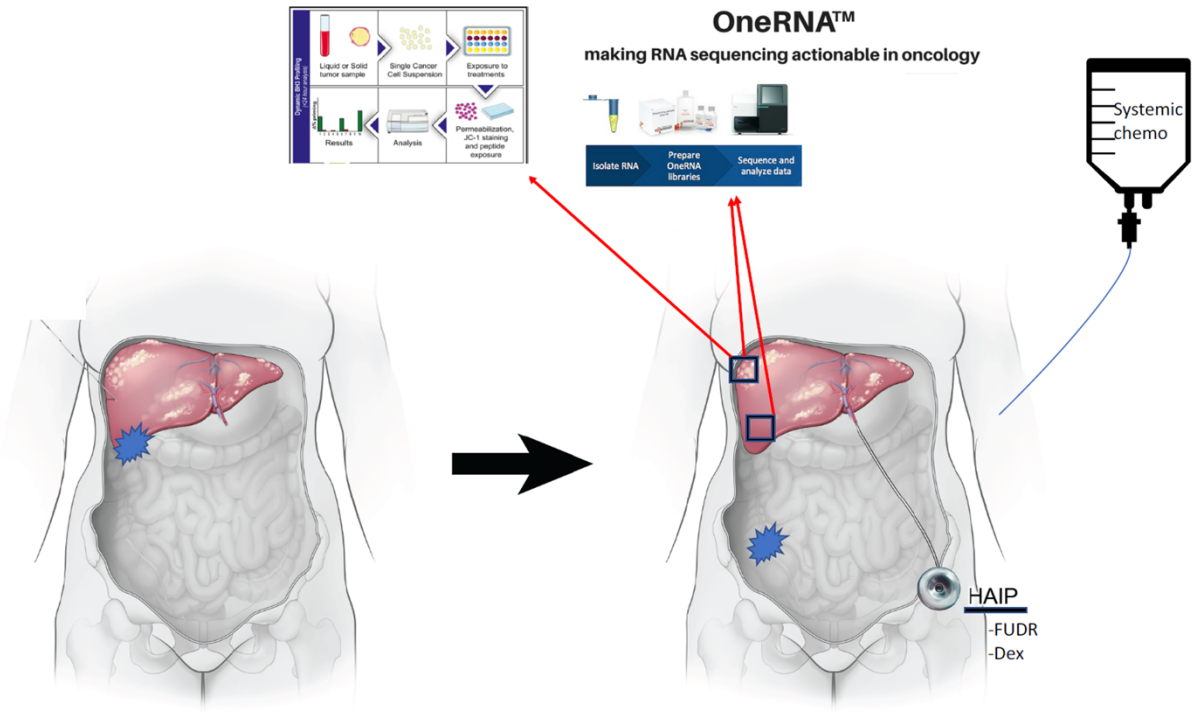


Figure 1: Treatment Schema. Eligible patients will undergo a limited laparotomy for placement of the HAIP catheter into the gastroduodenal artery such that FUDR can be directly infused into the hepatic artery. The HAIP itself will sit in a subcutaneous location superior to the anterior superior iliac spine and inferior to the costal margin such that it is palpable and easily accessible. During the laparotomy, tumor and normal liver will be removed for research purposes. The HAIP will be filled every two weeks with heparinized saline or drug.

1.2.4 HAI Pump

The manufacturer of the commercially available C3000 Codman Pump has announced that it will terminate production in 2018. The design of the pump contains many unique and individual components, and several suppliers of those components have ceased operations, thus limiting the availability of critical parts that enable the pump to be manufactured to the approved specifications.

Medtronic Pump has been approved by U.S. Food and Drug Administration (FDA) to deliver drugs via intravenous infusion or injection to spinal canal, so that it reaches the cerebrospinal fluid (see Section **14.2.1**).

Codman catheter has been approved by FDA as a component of another Codman hepatic pump, developed to connect pump and hepatic artery (see Section **14.2.2**).

The use of the Medtronic Pump with a Codman Catheter has previously been successfully employed at MSKCC in clinical studies evaluating the effectiveness of HAI chemotherapy in colon and colorectal patients (personal communication with Dr. Kemeny). In the MSKCC studies, at least ten (10) subjects have successfully received pump implantation surgery with the Medtronic pump and straight Codman catheter. None of the 10 patients underwent surgical or pump complications such as infection or disconnection (as of September 2018). Based on this preliminary data, it has been determined that an identical approach to the one that was adopted at MSKCC will be used for this study. Specifically, the Medtronic pump will be connected to a short Medtronic connector catheter and then to the Codman catheter via a metal phalange.

All patients will undergo surgery to have the Medtronic pump and Codman catheter placed appropriately before HAI therapy can begin. During the surgical procedure, the Medtronic pump is connected to the Medtronic connector as seen in **Figure 2**. The Medtronic connector will be cut (**Figure 3**) before the metal phalange at the end of the connector so the Codman catheter can then be connected to the cut end of the Medtronic connector (**Figure 4**). Silk ties will be used on both ends of the catheter to ensure the fit to the connection is secure (**Figure 5**).

Figure 2: Medtronic Pump connected to the connector catheter.

Figure 3: Medtronic connector catheter is cut and a metal phalange is inserted into the connector to allow for connection to the Codman Catheter.

Figure 4: The Codman catheter is now connected to the Medtronic pump using the metal phalange.

Figure 5: Silk ties will then be tied down onto both the Medtronic connector catheter (red arrow) and Codman catheter (blue arrow) over the metal phalange to ensure stability of the connection. Of note, this connection will sit in the pump pocket atop the patient's fascia and underneath subcutaneous fat.

1.2.5 Tumor and Liver Profiling

As with any therapy, patient selection is crucial to maximize benefits to those patients with disease susceptible to the therapy while withholding treatment from those unlikely to benefit or likely to suffer toxicity. At present, there is no push to stratify FUDR HAI therapy based upon tumor and liver profiles.

We seek delineate a transcriptomic biomarker signature of response, as well as of toxicity, which we envision can be used in subsequent studies to triage therapy. These are important questions not being pursued elsewhere and will be essential in order to provide patients with a personalized best care option. As data mounts suggesting an aggressive approach to control of the metastatic disease results in improved survival, triaging patients to the most beneficial form of local/regional therapy will become paramount. Some patients will progress while others have stable disease. Baseline tumor expression profiling will allow us to assign associations with outcome for all patients. The group of patients that respond initially and then progress can serve as their own control (assuming the patient is agreeable to a biopsy at the time progression is documented) and will provide value information regarding potential causality for treatment refractoriness such that additional treatments can be designed to circumvent.

1.2.6 Liver Microenvironment Studies

Tumor and normal liver will be submitted to Dr. Hernandez's laboratory. Tumor cells will be immediately labelled using fluorescent protein tags and subsequently injected into a small portal venule of the resected piece (2x2 cm) of normal liver. Labelled tumor cells can then be tracked over time with the use of the lab's multi-photon imaging system. We will use the Miltenyi kit for tumor cell dispersal, which promises to protect the vast majority of cell surface markers. We think

this will minimally affect the cell's ability to traffic. After labelling with any number of tracking dyes (e.g., Dapi), cells will be injected into a small piece of liver followed by sectioning into 250 uM slices using a vibratome. Thin sections can be kept alive for 72 hours using various established techniques.

For the colonization studies, we will utilize previously labelled human pancreatic and colorectal cell lines and pieces of human liver from patients undergoing HAIP. Prior data has demonstrated viability of liver section (up to 250 uM for 3 days). We will be able to determine the impact of various gene manipulations on the cells ability to grow in human liver. Our data also indicates that collagen crosslinking is one of the crucial early steps in colonization. We have obtained simtuzumab, a monoclonal antibody to LOXL2 (Gilead), and will test its impact upon colonization capacity and its ability to halt tumor-derived ECM manipulations. The changes in the ECM will be evaluated using second generation harmonic imaging with the 2-photon microscope.

A major goal of Dr. Hernandez's lab is to understand the how tumor cells adapt to and co-opt the liver microenvironment for eventual metastatic outgrowth. With tumor cells labelled and observable throughout week-long time courses, many downstream applications will be possible, including (but not limited to) interrogation of the tumor cells at various time-points and at various stages of the metastatic cascade, with and without forced over-expression of various genes of interest.

1.2.7 *Ex Vivo* Hepatic Perfusion Model

Patients who have a complete or partial response to the HAIP therapy and can then be rendered NED, will undergo a second operation and partial hepatectomy. The resected tissue from this second operation will be utilized for the *ex vivo* perfusion model.

This study is an important step toward our goal of implementing an ideal tumor model system. The ability to recapitulate the complexities of solid human tumors for the purposes of drug development and testing has been, and remains, a major obstacle in the progress of cancer care. Despite great efforts expended on pre-clinical optimization using existing validation models, most drugs simply fail to demonstrate efficacy when subjected to Phase III clinical trial scrutiny.

Our interpretation is that the currently available model systems lack the appropriate clinical predictive power. The reasons for the inadequacies of these model systems, which are largely based upon cell lines, mouse models or patient-derived xenografts, are myriad but are almost certainly related to the absence of the human stromal component and its intricate relationship with tumor cells. Indeed, modeling the multi-faceted interactions between human cancer cells and the multitude of various stromal components, including activated fibroblasts, immune cell infiltrate and the abnormal vasculature is, at present, an impossibility. The advent of a model system capable of accurately reproducing human tumors ex vivo carries broad implications across many fields of investigational medicine and brings with it the potential to fundamentally alter the translational research landscape.

Moreover, if it were possible to represent a given patient's tumor in that model system, the benefits of personalized medicine could leap from generating lists of potentially useful drugs to designation of efficacious agents.

We intend to satisfy all the requirements of an ideal tumor model system by utilizing resected segments of tumor-containing liver and repurposing the Liver-Assist perfusion device for prolonged *ex vivo* animation via native blood vessel perfusion. This is entirely novel and has not

been attempted elsewhere in the world. Moreover, the expertise required to accomplish this make it unlikely to be successful anywhere other than the clinical center. Patients with colorectal liver metastasis are an ideal starting point because this is the most common metastatic disease treated by the practicing HPB Oncologic surgeon, and consistency when implanting the new model system will be paramount. Moreover, we estimate that approximately 45% of patients enrolled may become eligible for a second stage procedure in order to render the patient No Evidence of Disease (NED). This resection offers patients that best opportunity for long term survival and ample liver/tumor to develop our model system **Figure 6**.

We will start the model with optimization of perfusion conditions for maintenance of both tumor and normal liver with serial evaluation to include the following:

1) Ultrasonographic evaluation to document preservation of tumor echogenic properties.

2) Core needle biopsy to document histopathologic preservation of the microscopic architecture and cellular viability. Sufficient tissue will be obtained for any necessary staining

3) Transcriptomic profiling will be undertaken using snap-frozen biopsies. Samples from a given tumor will be run together to minimize variability. Standard HiSeq RNA platform with a read depth of 30-40 million will be employed.

4) Metabolomic profiling will be undertaken using snap-frozen biopsies. Samples from a given tumor will be run together to minimize variability.

We anticipate patterns will emerge among tumors such that likely drug combinations can be estimated for use in our ex-vivo model. Importantly, our model system finally represents avenue to utilize drugs in the HAIP other than FUDR, thereby moving HAIP-directed chemotherapy forward for the first time.

For patients that experience a significant response and conversion to resectable disease, we will utilize those segments of resected tumor bearing liver on our ex-vivo machine. This will allow us to utilize various agents in combination or with the use of the HAIP, which will be incorporated into the arterial line of the perfusion circuit. This novel model system will enable us to evaluate drug delivery, cell-based therapies, etc. given the unlimited use of repeat biopsies. The perfusate is also the ideal medium for biomarker discovery, which can be related to actual changes demonstrable in the tumor.

On this protocol we are not going to make any clinical decisions based on correlative studies.

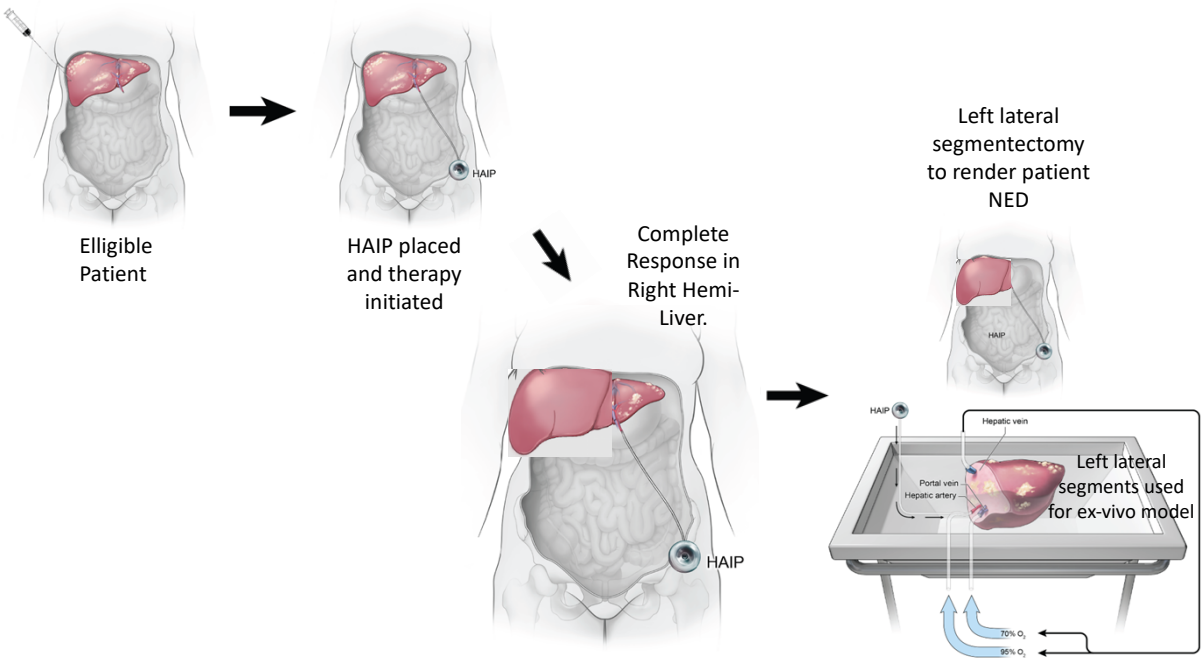


Figure 6: Schema example showing utilization of resected segments of tumor-bearing liver to develop our model of prolonged ex-vivo animation. In future studies this model will enable us to directly test novel drug combinations, delivery vehicles such as nano-technology, etc, both systemically and via the HAIP.

1.2.8 Simulated Metastasis Assay with Relevant Tissue (SMART) Chamber

Correlative studies in proteogenomic characterization of primary and metastatic cancers and *ex vivo* tumor tissue modeling of peritoneal metastasis utilizing the SMART Chamber have been added to this study. In conjunction with ongoing laboratory work, segments of the peritoneum are removed from patients with peritoneal carcinomatosis at the time of operation. This peritoneal tissue is utilized in the SMART Chamber system to imitate conditions of metastasis within the abdominal cavity. This *ex vivo* tissue model system allows for observation of peritoneal metastasis, real-time cellular imaging, and manipulation of tumor-environment interactions.

1.2.9 The SMART System

The SMART System is an important step toward our goal of realizing personalized translational cancer care. The ability to recapitulate the complexities of solid human tumors for the purposes of drug development and testing has been, and remains, a major obstacle in the progress of cancer therapy. Despite great efforts expended on pre-clinical optimization using existing validation models, most drugs simply fail to demonstrate efficacy when subjected to Phase III clinical trial scrutiny. Our interpretation is that the currently available model systems lack the appropriate clinical predictive power. The reasons for the inadequacies of these model systems, which are largely based upon cell lines, mouse models or patient-derived xenografts, are myriad but are almost certainly related to the absence of the human stromal component and its intricate relationship with tumor cells.

There has been a sizable expansion of oncologic pharmaceuticals that have targeted and/or immunomodulatory effects. However, the predictive accuracy of drug testing is predicated on models that accurately represent the architectural/cellular organization of the tumor and faithfully

reflect the *in vivo* biology. We have satisfied many of the requirements of an ideal tumor model utilizing resected mesothelial metastases to create the SMART (**S**ustained **M**icroenvironment for **A**nalysis of **R**esected **T**issue) System. Multiple solid tumors commonly manifest with metastatic disease to the mesothelial surface (peritoneum, pleura, liver capsule) and some are candidates for metastasectomy. During these operations, resected tumor-bearing mesothelial tissue is affixed to a specialized platform and perfused in a sterile, oxygenated circuit at 37^0C to maintain normal physiologic parameters (**Figure 7**). Circulating oxygenated perfusate within the system is comprised of human plasma (from the patient), DMEM media, antibiotics, insulin (slow infusion).

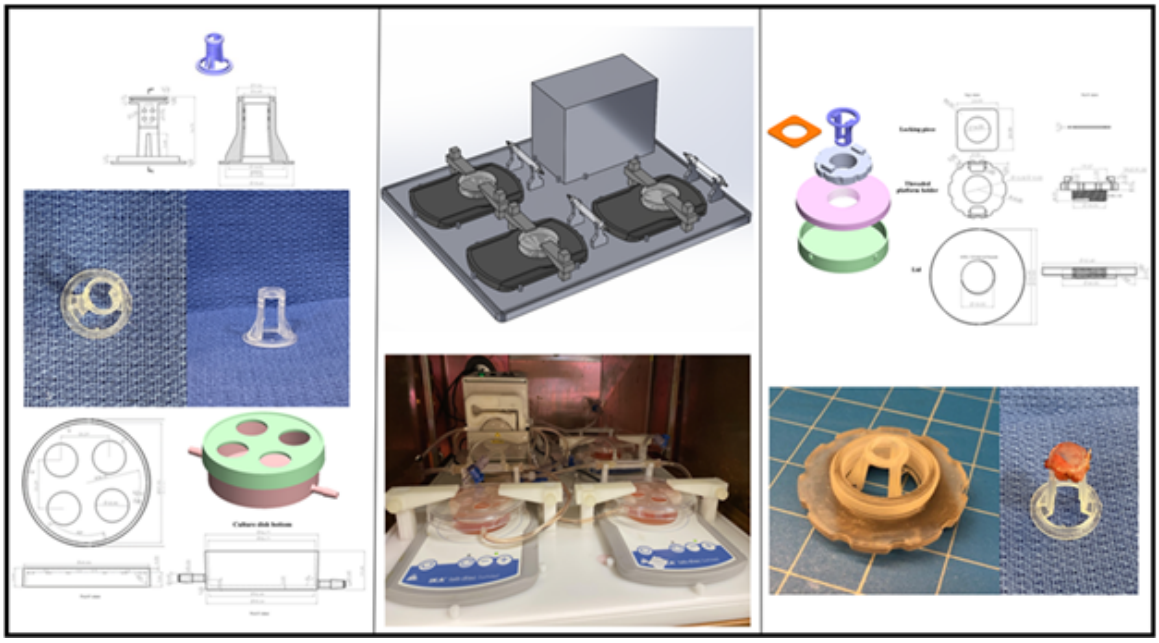


Figure 7: The SMART System Consisting of SMART Platform

The SMART platform (Top Left) is designed to mount the human mesothelial tissue containing tumor and be suspended in the reservoir of perfusate (Bottom Left), the SMART chamber. The chambers suspend maximum of 4 SMART platforms and placed on stir plate in the incubator (Middle). The SMART system boasts a physiologic oxygenated perfusion circuit that is suitable to keep tissue viable for up to four days. The Right Panel demonstrates the customized holder for each SMART platform that is imaged using complex imaging techniques.

We have evaluated gastric adenocarcinoma, pancreatic adenocarcinoma, gastrointestinal stromal tumor, and breast adenocarcinoma in the SMART system and documented *ex vivo* viability at 4 days with expected immune cell populations, intact architecture, and expected mitotic activity (**Figure 8A**). RNA sequencing was performed as well to compare transcriptomics between Day 0 and Day 4. Genes associated with hypoxia, oncogenes/tumor suppressor, cancer stem cells, metabolism, and epithelial-mesenchymal transition were isolated from the sequencing data and demonstrated conservation of transcriptomics (**Figure 8B**). These results ultimately demonstrate that tumor nodules in their native, functional microenvironment can be preserved *ex vivo* for 4 days with fidelity.

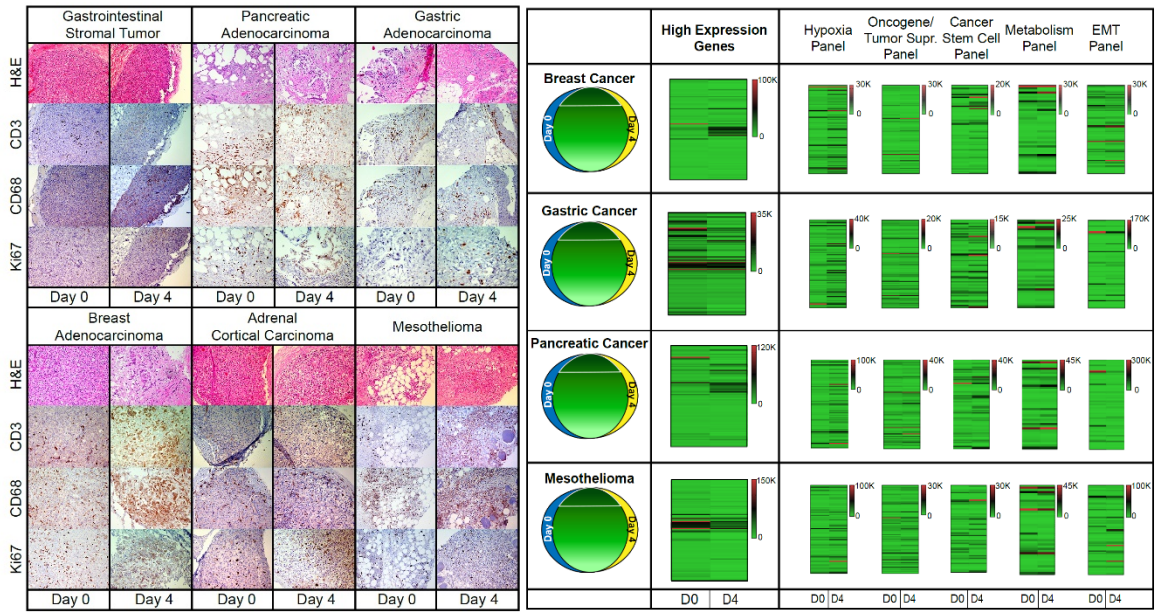


Figure 8: Ex Vivo Normal and Tumor Preservation in the SMART System

A (Left): Demonstration of various histologies on H&E, CD3, CD68 and Ki67 stains on Day 0 and Day 4.
B (Right): Conservation of transcriptomics in hypoxic panel, oncogene/tumor suppressor, cancer stem cell, metabolism and EMT panels over breast, gastric, pancreatic and mesothelioma histology.

Due to the translucent nature of the mesothelial tissue, the system is readily amenable to dynamic interrogation with confocal, two photon and light sheet microscopy. This avenue of investigation is supported by a research collaborative agreement (RCA) with BioLegend and our affiliation with CAT-I to develop fluorescently labelled Fab fragment for live cell labelling. For example, with the increasing use of checkpoint inhibitors like Pembrolizumab in solid tumors, we decided to evaluate the drug in the SMART system using tumor from a patient with gastric adenocarcinoma and a patient with colorectal adenocarcinoma. We demonstrated immune cell engagement with tumors cells for both gastric and colorectal adenocarcinoma, and captured tumor cell lysis with the latter (**Figure 9**). Such responses at the cellular level are key to understanding why some cells respond to the immune system while others are ostensibly resistant.

As the only currently known platform that has an intact, immunocompetent tumor microenvironment, the SMART System allows for the analysis of agents utilizing real controls to increase current understandings of the tumor microenvironment. Analyses can be readily imaged (taking video up to an hour) to obtain tangible visualizations of the tested agent effects (see **Figure 9**).

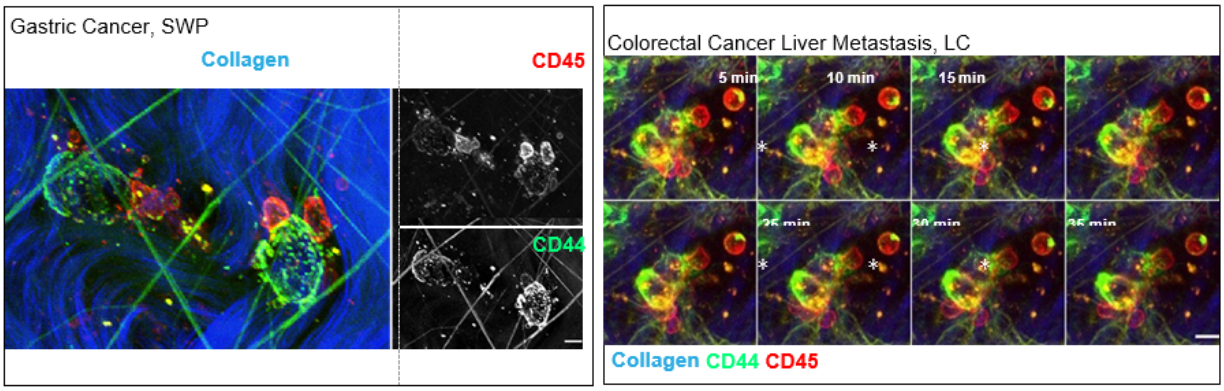


Figure 9: SMART Platforms are Valuable Tools for Drug Evaluations Such as Pembrolizumab

Left: SMART platforms with peritoneum from a patient with gastric cancer incubated with immune checkpoint inhibitor Pembrolizumab for 2 days followed by Alexa488CD44/ Alexa594CD45 antibodies. Maximum projections of 2-photon images illustrate the intimate contact between CD45-positive cells and the cancer cells.
Right: Timeseries montage taken from liver capsule tissue mounted on SMART platforms from a colorectal cancer patient with liver metastases incubated with 5 g/mL pembrolizumab for 4 hours. CD45-positive cells bound to CD44-positive cancer cell undergoing apoptosis.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed diagnosis of colorectal adenocarcinoma.

2.1.1.2 Patients must have measurable liver metastatic disease, defined in Section **6.3.2**.

2.1.1.3 Patients must have progressed on, been intolerant of or have residual disease after oxaliplatin- or irinotecan-containing, fluorouracil-based, chemotherapeutic regimen.

2.1.1.4 Age ≥ 18 years.

2.1.1.5 ECOG performance status ≤ 1 (see **Appendix A**).

2.1.1.6 Patients must have adequate organ and marrow function as defined below:

- leukocytes > 3,000/mcL
- absolute neutrophil count > 1,500/mcL
- platelets > 90,000/mcL
- total bilirubin < 1.5 X institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) < 2.5 X institutional upper limit of normal
- creatinine within normal institutional limits OR eGFR within normal as predicted by the CKD-EPI equation > 60 mL/min/1.73 m2.

2.1.1.7 The hepatic artery infusion pump chemotherapy has potential teratogenic and/or abortifacient effects. For this reason, 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, for the duration of study participation and after completion of study treatment: 3 months after the last study drug for men; 6 months after the last study drug for women. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.8 Arterial anatomy on CT angiogram amenable to placement of the HAIP.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.10 HIV-positive patients may be considered for this study only after consultation with an HIV trained physician.

2.1.1.11 Patients must agree to co-enroll on the Surgical Oncology Program's tissue collection protocol 13C0176, "Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or Surgical Resection of Solid Tumors"

2.1.2 Exclusion Criteria

2.1.2.1 Patients with liver metastases amenable to resection to No Evidence of Disease (NED) in one stage.

2.1.2.2 Patients who are receiving any other investigational agents.

2.1.2.3 Patients with incontrovertible radiographic evidence of disease outside of the colon/rectum (primary) and liver given unlikelihood of benefit from liver-directed therapy.

Note: The exception to this exclusion is patients with fewer than five lung lesions greater than 1 cm that have not increased in size by more than 10% over a 4-month period of time and are amenable to resection should subsequent problematic growth occur. Lesions less than 1 cm are indeterminant as far as etiology is concerned and will be ignored. Patients with liver metastases and oligometastatic lung lesions (we define oligometastatic as less than 5 amenable to thoracoscopic removal) are still likely to benefit from liver directed therapy.

2.1.2.4 Patients who have undergone extra-hepatic metastasectomy and have a documented disease-free interval less than or equal to 4 months.

2.1.2.5 MSI-high patients who need to be treated with check-point inhibitors.

2.1.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. This also includes any condition, including the presence of laboratory abnormalities, which in the opinion of the Principal Investigator places the

subject at unacceptable risk if they were to participate in the study or confounds the ability to interpret data from the study.

2.1.2.7 Active concurrent malignancies within the last five years other than colorectal primary except basal cell skin carcinoma and thyroid carcinoma.

2.1.2.8 Prior radiation to liver.

2.1.2.9 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects of the HAIP chemotherapy. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with HAIP, breast-feeding should be discontinued if the mother is treated. These potential risks may also apply to other agents used in this study. Lactating women must not breastfeed during study treatment and until at least 7 days after the final dose of study drug(s).

2.1.2.10 Patients with active Hepatitis B or C infection because of the potential for increased liver toxicity given the damaging effects of the virus.

2.1.2.11 History of allergic reactions attributed to compounds of similar chemical composition to FUDR or heparin.

2.1.3 Recruitment Strategies

This study may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. Participants will be recruited from the current patient population at NIH, and local community physicians.

2.2 SCREENING EVALUATION

2.2.1 Screening Activities Performed Prior to Obtaining Informed Consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these screening activities has been requested in Section **12.6.2**.

2.2.2 Screening Activities Performed After a Consent for Screening Has Been Signed

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent (if determined to be applicable per PI discretion). Studies should be done within 6 weeks prior to enrollment unless otherwise noted below.

- History and Physical Examination:
    - Complete medical history and physical examination (including height, weight, vital signs, EKG and ECOG performance status).

  - Consultation with NIAID physician in HIV positive subjects.

- Laboratory Evaluation:
  - Hematological profile: CBC with differential and platelet count.
  - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin (including direct and indirect), calcium, phosphorus, albumin, magnesium.
  - HIV, Hepatitis B and C serology and/or viral load.
  - PT/PTT/INR
  - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy), performed within 7 days prior to enrollment.
- CT of chest, abdomen and pelvis.
- CT Angiogram (abdomen), performed at any time prior to enrollment.
- Tumor measurement(s).
- Histologic confirmation (at any time point prior to enrollment). If there is no available tumor sample, a biopsy will be performed to confirm the diagnosis. Note: Histologic confirmation performed at outside facilities or on another NIH protocol are acceptable per PI discretion.
- MSI status (at any time prior to enrollment).
- Co-enroll on protocol 13C0176 (at any time prior to enrollment).

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2: CCR Participant Registration & Status Updates found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

2.3.2 Treatment Assignment Procedures (For Registration Purposes Only):

Cohorts

Number	Name	Description
1	Cohort 1	Subjects with colorectal cancer metastatic to the liver.

Arms

Number	Name	Description
1	Arm 1	HAIP chemotherapy + Systemic chemotherapy

Arm Assignment

Subjects in Cohort 1 with be directly assigned to Arm 1.

2.4 BASELINE EVALUATION

Tests listed below that were performed within the appropriate timeframe at screening need not be repeated.

Within 3 weeks prior to pump placement unless otherwise indicated:

- Complete physical examination (including weight, vital signs, EKG and ECOG performance status).
- Laboratory Evaluation:
  - Hematological profile: CBC with differential and platelet count.
  - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin (including direct and indirect), calcium, phosphorus, albumin, magnesium.
  - PT/PTT/INR
  - CEA
  - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy), performed within 3 days prior to pump placement.
- CT of chest, abdomen and pelvis

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a single arm Phase 2 trial designed to determine the safety and efficacy of hepatic artery infusion pump (HAIP) chemotherapy in patients with colorectal cancer and unresectable hepatic metastases.

Patients will be seen and evaluated at the clinical center with advanced CT imaging. Eligible candidates will be taken to the OR at the CC and have the HAI pump and catheter placed. During this operation, core biopsies of tumor and normal liver will be taken for profiling. Patients will be discharged from the hospital after having their pump filled with heparinized saline. Patients will be seen at the clinical center every two weeks thereafter.

HAIP FUDR and Dexamethasone chemotherapy will be initiated in cycles within four weeks of HAIP placement.

All patients will have 14 days of treatment with FUDR and Dexamethasone in 25,000 units Heparin/Saline (Heparin + 0.9% Sodium Chloride) delivered by HAIP, on Days 1-14 of every cycle. On Days 15-28 of every cycle Heparin/Saline will be delivered by HAIP.

On Cycle 1 Day 15 (+3 days) patents will receive standard of care chemotherapy delivered intravenously.

Beginning from Cycle 2 patents will receive standard of care chemotherapy on Day 1 (+3 days) and Day 15 (+3 days) of every cycle delivered intravenously.

Depending on patent medical history and previous treatments, the PI will decide what standard of care regimen to use for each subject. Based upon toxicity, systemic agents may change during treatment at the discretion of the PI.

Cycle (28 days)			
Day 1*	Days 1-14	Day 15	Days 15-28
Standard of care chemotherapy based on combination of drugs: Oxaliplatin 5FU Leucovorin Irinotecan Cetuximab Panitumumab	HAI (FUDR/Dex in 25,000 units Heparin/Saline)	Standard of care chemotherapy based on combination of drugs: Oxaliplatin 5FU Leucovorin Irinotecan Cetuximab Panitumumab	HAI (Heparin/ Saline)

* Starting Cycle 2

Treatment will be continued until patient meets off treatment criteria.

If a patient experiences a response to therapy such that a subsequent operation would render the patient NED, this operation will be performed, and the patient will be taken off protocol therapy.

The resected tissue that will render the patient NED will be used for our ex-vivo perfusion model.

3.1.1 Re-Treatment

If patient progresses after NED operation and HAIP is still in place, patient can be re-treated once with HAIP therapy and systemic chemotherapy. Before re-treatment all baseline evaluations should be repeated, see Section **3.6**.

3.2 PROTOCOL STOPPING RULES

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for grading systemic toxicity. For safety reasons, the protocol will be temporarily halted until an amendment will be sent to FDA for review and IRB for approval for either of the following events attributable to treatment regimen occurring within 30 days of study devices installation:

- One occurrence of Grade 5 toxicity.
- Two occurrences of Grade 4 toxicity.

Leakage from the catheter connection or loss of integrity of the pump/catheters from a single patient will be considered unacceptable and will result in an immediate suspension of enrollment of the trial pending FDA notification and a full investigation of the event. The treatment will be stopped in the patient in whom the event occurred and decisions about the continued treatment in other patients will be based on FDA response.

3.3 SURGICAL PUMP PLACEMENT AND REMOVAL

The HAIP with catheter will be installed surgically in the Clinical Center operating room under the direction of the Principal Investigator or designated Associate Investigators, who have extensive experience in complex hepatobiliary surgery including placement of the HAIP. Adequate pump placement, integrity of the catheters, and perfusion of the liver will be verified in the operating room using methylene blue. Additionally, a radiographic/nuclear medicine pump study will be obtained through the catheter access port prior to the start of treatment as a double check of catheter integrity so as to ensure no leakage or extra-hepatic perfusion. As indicated, the pump may be removed surgically in the Clinical Center under the direction of the Principal Investigator or designated Associate Investigator.

3.4 DRUG ADMINISTRATION

Chemotherapy will be administered on a 4-week (28 days) cycle basis.

3.4.1 HAIP

Pump therapy with FUDR and Dexamethasone in 25,000 units Heparin/Saline will be started on Day 1 of each cycle. The pump will be filled with 20 mL of mixture of FUDR, Dexamethasone and Heparin/Saline which will continuously perfuse the liver for 14 days. On Day 15 of each cycle, the pump will be emptied and filled with Heparin/Saline.

Hepatic pump will be filled at the bedside on Days 1 and 15 of every cycle. Patents do not need to go to the OR for this procedure.

For the first cycle, doses of FUDR and Dexamethasone in 25,000 units Heparin/Saline will be calculated based on the predetermined flow rate provided by the pump manufacturer. Thereafter, doses will be adjusted based on actual observed flow rate (refer to Section **3.5.1**, **FUDR Dose Modifications**).

3.4.1.1 FUDR, Dexamethasone and Heparin/Saline Dose Calculation

- **FUDR:**

$$\frac{\textbf{0.12 mg/kg x kg [patient weight] x 20 mL [pump volume] x 0.9}}{\textbf{1 ml/day [pump flow rate]}}$$

- **Dexamethasone:** flat dose of 20 mg

  [+]**Note:** If a patient develops elevated laboratory values that can be ameliorated by Dexamethasone (such as elevated alkaline phosphatase or total bilirubin), Dexamethasone in a Heparin/Saline solution may be added to the pump at any time at the discretion of the investigator as clinically indicated. The patient's treatment and treatment schedule will continue as indicated within the protocol.

- **Heparin/Saline:** 25,000 units as part of treatment with FUDR and Dexamethasone
- **Overweight Patients:** The dose of FUDR used for overweight patients (25% above Ideal Weight) is an average of Ideal Body Weight and Real Weight. The calculation for Ideal Weight (kg), is as follows:

  Males: 50 kg + (2.3 x height in inches above 5 ft)
  (i.e.: for a patient who is 5'10", use 10),
  Females: 45.5 kg + (2.3 x height in inches above 5 ft)

  Example: Male who is 100 kg and 5'10"
  Ideal Body Weight is: 50 + (2.3 x 10) = 73 kg
  Therefore, the Ideal Average Weight to use is: 100 + 73 = 173 ÷ 2 = 86.5 kg

Table 4: Medtronic Pump Dose Calculation For 20 mL Mixture of FUDR, Dexamethasone and Heparin/Saline

FUDR*	Dexamethasone+	Heparin/Saline
$\frac{0.12 \text{ mg/kg x kg [patient weight] x 20 mL [pump volume] x 0}}{1 \text{ ml/day [pump flow rate]}}$	20 mg	25,000 units
Note: Medtronic Pump volume is 20 mL. * The dose of FUDR used for overweight patients (25% above Ideal Weight) is an average of Ideal Body Weight and Real Weight (refer to calculation for Ideal Weight in **3.4.1.1**). ** Doses will be adjusted after Cycle 1 based on actual observed flow rate (refer to Section **3.5.1**, **FUDR Dose Modifications**). + If a patient develops elevated laboratory values that can be ameliorated by Dexamethasone (such as elevated alkaline phosphatase or total bilirubin) refer to the note for Dexamethasone in **3.4.1.1**.		

3.4.1.2 Heparin/Saline

- **Heparin/Saline:** 25,000 units total dose, the quantity sufficient to make total reservoir volume of 20 mL (Days 15-28 of every cycle only).

3.4.2 Systemic Chemotherapy

Systemic chemotherapy will be administered IV on Day 1 (starting with Cycle 2) and Day 15 of each cycle.

For standard chemotherapy drugs details including formulation, preparation, administration, toxicity and storage information, please, see package inserts for Oxaliplatin, Leucovorin, 5-Fluorouracil (5-FU), Irinotecan, Cetuximab and Panitumumab.

In general, the treatment will be delivered as below (starting with Section **3.4.2.1**):

Note: Patients who are unable get standard systemic chemotherapy in the NIH Clinical Center on Days 1 or 15 may have the option, if felt to be a medically appropriate alternative, for the standard systemic chemotherapy on this protocol to be administered by IV by the patient's home oncologist

on Day 1 (+3 days) and Day 15 (+3 days) of each cycle, starting with C1D15; **all medications provided through the pump will only be given at the NIH - there will be no exceptions**). The outside provider will be trained by the PI on the protocol and will agree to administer the standard of care chemotherapy, send administration records and report adverse events; this agreement will be recorded in the patient's medical record. The patient will be only receiving standard systemic chemotherapy from the outside provider and the timepoints for the systemic chemotherapy will be as indicated in the protocol. Patient notes will be faxed from the outside provider to the NIH study team within 72 business hours. The PI will remain responsible for study activities and the assessment of adverse events. Any urgent clinical changes will be reported by the outside provider via telephone to the PI, and the PI will report the event per protocol guidelines. No outside laboratories will be used. An in-person visit, either locally or at NIH, may be reconsidered at any time if felt to be medically necessary.

Patients who receive the standard systemic chemotherapy by an external provider (as indicated above) will still be seen in the NIH Clinical Center to have labs drawn and HAIP pump filled as indicated within the protocol (see Section **3.6**, **Study Calendar**).

3.4.2.1 Oxaliplatin, Leucovorin and 5-Fluorouracil (5-FU)

Starting on Day 15 (+3 days) of Cycle 1, Oxaliplatin (85 mg/m^2) and Leucovorin (400 mg/m^2) will be administered concurrently via a Y-Line over a 120-minute infusion. The patient then receives a 46-hour infusion of 5FU (2000 mg/m^2). The 5FU will be administered via an ambulatory device through the day hospital at CCR. Specifically, two back-to-back 23-hour infusions will occur. Barring the occurrence of an event requiring dose modification (Section **3.5**), patient will receive the same doses of Oxaliplatin, Leucovorin, and 5FU again on Days 1 (+3 days) and 15 (+3 days) of each subsequent cycle.

3.4.2.2 Irinotecan, Leucovorin and 5-Fluorouracil (5-FU)

Starting on Day 15 (+3 days) of Cycle 1, Irinotecan (150 mg/m2) and Leucovorin (400 mg/m^2) will be administered concurrently via a Y-Line over a 30-minute infusion. The patient then receives a 46-hour infusion of 5FU (2000 mg/m^2). The 5FU will be administered via an ambulatory device through the day hospital at CCR. Specifically, two back-to-back 23-hour infusions will occur. Barring the occurrence of an event requiring dose modification (Section **3.5**), patient will receive the same doses of Irinotecan, Leucovorin, and 5FU again on Days 1 (+3 days) and 15 (+3 days) of each subsequent cycle.

3.4.2.3 Cetuximab

Starting on Day 15 (+3 days) of Cycle 1, Cetuximab (500 mg/m^2 infusion over 120 minutes for the initial dose and then 60 minutes for subsequent doses) will be used as single drug or in combination with Irinotecan, Leucovorin, Oxaliplatin or 5-Fluorouracil (5-FU). Barring the occurrence of an event requiring dose modification (Section **3.5**), patient will receive the same doses of Cetuximab again on Days 1 (+3 days) and 15 (+3 days) of each subsequent cycle.

3.4.2.4 Panitumumab

Starting on Day 15 (+3 days) of Cycle 1, Panitumumab (6 mg/kg infusion over 60 minutes) may be used as single drug or in combination with Irinotecan, Leucovorin, Oxaliplatin or 5-Fluorouracil (5-FU). Barring the occurrence of an event requiring dose modification (Section **3.5**), patient will receive the same doses of panitumumab again on Days 1 (+3 days) and 15 (+3 days) of each subsequent cycle.

Note: Panitumumab may be used per Principal Investigator digression in cases where the Investigator deems that, in the best clinical judgement of the Investigator, Panitumumab would be more clinically efficient than Cetuximab.

3.5 DOSE MODIFICATIONS

3.5.1 FUDR Dose Modifications

"Reference value" is defined as the value obtained on the first day of the most recent FUDR dose or the upper limit of normal for SGOT, Alk. Phos. or Total Bili (whichever is higher).

To determine if a FUDR dose modification is necessary, compare reference value to the either the value obtained on the day pump was emptied or the value obtained on the day of planned pump filling, whichever is higher.

Percentages listed under "FUDR Dose" refer to percentage of last dose of FUDR administered.

3.5.1.1 FUDR DOSE MODIFICATION SCHEMA:

	Reference Value	% FUDR dose
SGOT *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 2 x reference value	100%
	2 to < 3 x reference value	80%
	3 to < 4 x reference value	50%
	≥ 4 x reference value	Hold
ALK PHOS *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 1.2 x reference value	100%
	1.2 to < 1.5 x reference value	50%
	≥ 1.5 x reference value	Hold
TOT BILI *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 1.2 x reference value	100%
	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 come down to more normal levels, as indicated in Section **3.5.1.2** "Recommencing FUDR Treatment After Hold".

***If patient's Alkaline Phosphatase or T Bili shows a continual rise from Day 1 of treatment,**

then the Day 1 value will be used as the reference value for that patient when determining whether to hold treatment, and time of re-treatment after hold.

3.5.1.2 RECOMMENDING TREATMENT AFTER HOLD

REASON FOR TREATMENT DELAY	**Chemotherapy resumed when value has returned to:**	**% FUDR dose**
SGOT elevation	3X reference value	25% of last dose
Alk Phos elevation	1.2X reference value	25% of last dose
Tot Bili elevation	1.2X reference value	25% of last dose

If patient develops a total bilirubin > 3.0 mg/dl, the pump should be emptied and Dexamethasone 25 mg plus Heparin 25,000 u and Saline (0.9% Sodium Chloride) 20 mL placed in the pump q 14 days. Once there is no longer evidence of toxicity, Dex dose should be tapered in increments of 5 mg every 14 days. Tapering will continue unless enzymes increase. FUDR should be permanently discontinued unless there is evidence of disease progression (increasing CEA, worsening CT scan, worsening clinical status) AND bilirubin has returned to < 1.5 mg/dl. In this case, FUDR can be restarted as follows: Use 25% of the last FUDR dose given with Dex, heparin and 0.9% Sodium Chloride in the pump for 7 days. Pump should be emptied after 7 days, and patients given a 3-week rest period. This treatment and treatment schedule should continue as long as bilirubin remains < 1.5 mg/dl and liver enzyme values do not increase.

Epigastric pain unresponsive to oral PPI use is suggestive of gastroduodenal irritation or ulcer. Severe pain should prompt workup with an upper gastrointestinal endoscopy. Serum amylase should be checked along with the routine blood (screening profile, creatinine, and CBC) 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 FUDR until results of workup are available.

3.5.2 Oxaliplatin/5FU

Guidelines for re-starting medication are listed in table below.

Note: Oxaliplatin/5FU dose adjustments will be made with consideration of the suggested guidelines below but will ultimately be made using the best clinical judgement of the investigator.

Patients who experience Grade 3 or 4 toxicity may, at the discretion of the investigator, continue treatment at a lower dosage level once toxicities have resolved to Grade 0 or 1.

3.5.2.1 Oxaliplatin + 5FU/Dose Reduction for Hematologic Toxicities (mg/m^2/day)

Grade	Toxicity	5FU infusion	Oxaliplatin
3	Neutropenia	20% reduction	20% reduction
4	Neutropenia	30% decrease	30% decrease

3	Febrile Neutropenia [a]	20% decrease	20% decrease
3	Thrombocytopenia	20% decrease	20% decrease
4	Febrile Neutropenia	40% decrease	20% decrease
4	Thrombocytopenia	40% decrease	20% decrease

[a]Febrile Neutropenia = ANC < 1.0 x 10^9/L with fever > 38.5° C

3.5.2.2 Oxaliplatin + 5FU/LV Dose Reductions for Non-Hematologic Toxicities (mg/m^2/day)

Grade	Toxicity	5FU Infusion	Oxaliplatin
3	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	20% decrease	20% decrease
4	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	40% decrease	20% decrease
3	Diarrhea despite premedication with an effective antiemetic therapy	20% decrease	20% decrease
4	Diarrhea despite premedication with an effective antiemetic therapy	40% decrease	20% decrease
3	Stomatitis	20% decrease	No Dose reduction
4	Stomatitis	30% decrease	20% decrease
≥2	Cardiac Toxicity	Stop	No Dose reduction
3 or 4	Hand/Foot Skin Reaction	20% decrease	No Dose reduction

3.5.2.3 Oxaliplatin Dose Modifications for Neurosensory Toxicity

	< 7 days	Persistent Between Cycles
Dysesthesias with cold	No change	No change
Paresthesias	No change	Decrease 25%
Paresthesias with functional Impairment	n/a	Stop

Note: If pseudo laryngopharyngeal dysesthesia occurs, the next dose of Oxaliplatin should be administered as a three-hour infusion. Subsequent Oxaliplatin infusions should be administered as three-hour infusions, or shorter as tolerated.

3.5.3 Irinotecan/5FU Dose Modifications for Hematologic Toxicity and Diarrhea

Note: Irinotecan/5FU Dose Modifications will be made with consideration of the suggested guidelines below but will ultimately be made using the best clinical judgement of the investigator.

Grade	Toxicity	Irinotecan	5FU
3	Neutropenia, thrombocytopenia, diarrhea	20% decrease	20% decrease
4	Neutropenia, thrombocytopenia, diarrhea	40% decrease	40% decrease

3.5.4 Cetuximab Dose Modifications

Infusion-Related Adverse Events: following cetuximab label instructions, medications such as corticosteroids and antihistamines may be administered at the discretion of the Investigator to treat an existing infusion reaction, or as premedication for a patient who has previously experienced an infusion reaction. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 + 15 minutes.

For subjects who experience toxicities while on study, one or more doses of cetuximab may need to be withheld, reduced, or delayed. Dose escalations above 500 mg/m^2 starting dose are not allowed. Cetuximab dose reductions are listed in **Table 5**.

Symptomatic skin- or nail-related toxicity felt to be intolerable by the subject can have a reduction in dose according to **Table 5**.

Table 5: Cetuximab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/m^2	500	400	300

3.5.4.1 Criteria for Withholding a Dose of Cetuximab

Skin- or nail-related toxicities:

- Skin or nail infection requiring IV antibiotic or IV antifungal treatment.
- Any skin- or nail-related serious adverse event.

Non-skin- or nail-related toxicities:

- Any Grade 3 or 4 toxicity with the following exceptions:
  - Cetuximab will only be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement.
  - Cetuximab will only be withheld for Grade 3 or 4 nausea, diarrhea, or vomiting that persists despite maximum supportive care.
  - Cetuximab will only be withheld for Grade ≥ 3 anemia or Grade 4 thrombocytopenia that cannot be managed by transfusion(s) or cytokine therapy.

3.5.4.2 Criteria for Re-Treatment with Cetuximab

Skin- or nail-related toxicities:

- Cetuximab administration may recommence once:
  - The adverse event has improved to ≤ Grade 2 or returned to baseline, or;
  - The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,
  - Systemic steroids are no longer required, or
  - IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:

- Cetuximab administration may recommence once the adverse event has improved to ≤ Grade 1 or returned to baseline.

3.5.4.3 Cetuximab Dose Modification Schedule

- Subjects should be assessed for toxicity before each dose. Dose modification should be performed according to the schedule described below.

- Subjects who develop a toxicity that does not meet the criteria for withholding a dose of cetuximab should continue to receive cetuximab and their symptoms should be treated.
- Cetuximab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with cetuximab.

For subjects who experience a toxicity that meets the criteria for withholding a dose of cetuximab:

- Subjects receiving either 100% or 80% of the starting dose of cetuximab are allowed to have up to 2 subsequent doses withheld for toxicity. However, a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent dose is due.
- Subjects treated at the 100% dose level whose toxicity resolves after 1 dose of cetuximab is withheld should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, subjects treated at the 100% dose or 80% dose should be re-started at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of cetuximab.
- Subjects treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of cetuximab are withheld should be re-started at the 80% dose level.
- Subjects treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of cetuximab should be re-started at the 60% dose level.
- Subjects who experience toxicity at the 60% dose level will not be re-treated with cetuximab.

Subjects who miss more than 2 consecutive scheduled doses due to toxicity or are unable to receive a dose of cetuximab within 6 weeks of having received their previous dose of cetuximab due to toxicity will be considered unable to tolerate cetuximab and will not be retreated with cetuximab.

3.5.4.4 Discontinuation of Cetuximab

Cetuximab will be administered until subjects develop disease progression or are unable to tolerate cetuximab.

3.5.4.5 Guidelines for Diarrhea Management

- Symptoms of diarrhea and/or abdominal cramping may occur at any time and should be managed according to standard institutional practice.
- Subjects should also be instructed to notify the investigator or nurse for the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline) within 24 hours. Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.
- Changes in electrolytes, even without BUN/urea and/or creatinine elevation, may reflect early physiologic consequences of treatment-induced gastrointestinal toxicity. Subjects with clinically significant electrolyte changes should be evaluated for dehydration and receive aggressive fluid and electrolyte replacement, if indicated.

3.5.4.6 Electrolyte Management

- Subjects should be evaluated and managed as per local medical practice. If hypomagnesemia is present, replacement should be managed with either oral or parental replacement, or both, according to institutional practice and to the degree of hypomagnesemia present. It is recommended that subject's serum magnesium level should be maintained within the normal range during study treatment.

It is important to assess and manage serum potassium and calcium (adjusted for albumin) in subjects who have concomitant hypomagnesemia. Subject's serum potassium and calcium parameters are recommended to be maintained, as per local medical practice, within the normal ranges during study treatment.

3.5.5 Panitumumab Dose Modifications

Infusion-Related Adverse Events: following Panitumumab label instructions, if a patient experiences an infusion-associated adverse event, premedication will be given for the next infusion; however, the infusion time may not be decreased. Premedication with an antihistamine and with acetaminophen (for example, 25-50 mg diphenhydramine PO and/or 500-1000 mg acetaminophen PO or IV equivalent) approximately 60 to 120 minutes prior to panitumumab and at the discretion of the Investigator. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 + 15 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 + 10 minutes.

For subjects who experience toxicities while on study, one or more doses of panitumumab may need to be withheld, reduced, or delayed. On resolution of toxicity, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed. Dose escalations above 6 mg/kg starting dose are not allowed. Panitumumab dose reductions are listed in **Table 6**.

Symptomatic skin- or nail-related toxicity felt to be intolerable by the subject can have a reduction in dose according to **Table 6**.

Table 6: Panitumumab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	6	4.8	3.6

3.5.5.1 Criteria for Withholding a Dose of Panitumumab

Skin- or nail-related toxicities:

- Skin or nail infection requiring IV antibiotic or IV antifungal treatment.
- Any skin- or nail-related serious adverse event.

Non-skin- or nail-related toxicities:

- Any Grade 3 or 4 toxicity with the following exceptions:
    - Panitumumab will only be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement.
    - Panitumumab will only be withheld for Grade 3 or 4 nausea, diarrhea, or vomiting that persists despite maximum supportive care.
    - Panitumumab will only be withheld for Grade ≥ 3 anemia or Grade 4 thrombocytopenia that cannot be managed by transfusion(s) or cytokine therapy.

3.5.5.2 Criteria for Re-Treatment with Panitumumab

Skin- or nail-related toxicities:

- Panitumumab administration may recommence once:
    - The adverse event has improved to ≤ Grade 2 or returned to baseline, or;
    - The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,
    - Systemic steroids are no longer required, or
    - IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:

- Panitumumab administration may recommence once the adverse event has improved to ≤ Grade 1 or returned to baseline.

3.5.5.3 Panitumumab Dose Modification Schedule

- Subjects should be assessed for toxicity before each dose. Dose modification should be performed according to the schedule described below.
- Subjects who develop a toxicity that does not meet the criteria for withholding a dose of Panitumumab should continue to receive Panitumumab and their symptoms should be treated.
- Panitumumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with Panitumumab.

For subjects who experience a toxicity that meets the criteria for withholding a dose of Panitumumab:

- Subjects receiving either 100% or 80% of the starting dose of Panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However, a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent dose is due.
- Subjects treated at the 100% dose level whose toxicity resolves after 1 dose of Panitumumab is withheld should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, subjects treated at the 100% dose or 80% dose should be re-started at the

80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of Panitumumab.

- Subjects treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of Panitumumab are withheld should be re-started at the 80% dose level.
- Subjects treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of Panitumumab should be re-started at the 60% dose level.
- Subjects who experience toxicity at the 60% dose level will not be re-treated with Panitumumab.
- It is recommended that panitumumab doses will be escalated in subjects whose toxicity resolves to the degree that meets the criteria for re-starting a dose of panitumumab. Dose escalations are recommended but not required. Dose escalations should occur in the following manner:
- Subjects treated at the 80% dose level whose toxicity does not recur should receive the 100% dose level at the next dose unless a previous attempt to re-escalate to the 100% dose level was not tolerated (re-initiation of the 80% dose is allowed as an alternative to dose escalation).
- Subjects treated at the 60% dose level whose toxicity does not recur should receive the 80% dose at the next dose unless a previous attempt to re-escalate to the 80% dose level was not tolerated (re-initiation of the 60% dose is allowed as an alternative to dose escalation).

Subjects who miss more than 2 consecutive scheduled doses due to toxicity or are unable to receive a dose of Panitumumab within 6 weeks of having received their previous dose of Panitumumab due to toxicity will be considered unable to tolerate Panitumumab and will not be retreated with Panitumumab.

3.5.5.4 Discontinuation of Panitumumab

Panitumumab will be administered until subjects develop disease progression or are unable to tolerate cetuximab.

3.5.5.5 Guidelines for Diarrhea Management

- Symptoms of diarrhea and/or abdominal cramping may occur at any time and should be managed according to standard institutional practice.
- Subjects should also be instructed to notify the investigator or nurse for the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline) within 24 hours. Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.
- Changes in electrolytes, even without BUN/urea and/or creatinine elevation, may reflect early physiologic consequences of treatment-induced gastrointestinal toxicity. Subjects with clinically significant electrolyte changes should be evaluated for dehydration and receive aggressive fluid and electrolyte replacement, if indicated.

3.5.5.6 Electrolyte Management

- Subjects should be evaluated and managed as per local medical practice. If

hypomagnesemia is present, replacement should be managed with either oral or parental replacement, or both, according to institutional practice and to the degree of hypomagnesemia present. It is recommended that subject's serum magnesium level should be maintained within the normal range during study treatment.

It is important to assess and manage serum potassium and calcium (adjusted for albumin) in subjects who have concomitant hypomagnesemia. Subject's serum potassium and calcium parameters are recommended to be maintained, as per local medical practice, within the normal ranges during study treatment.

3.6 STUDY CALENDAR

	Screening	Baseline[1]	Pump Placement	Cycles (28 days)[3]				EOT[6]	F Up[8]
				1	2-14	15	16-28		
HAI (FUDR + Dex + Heparin/Saline)				X	X				
HAI (Heparin/Saline)						X	X		
Standard Systemic Chemotherapy, **3.4.2**				X[10]		X			
Confirmation of Pathology	X								
Consultation with NIAID physician in HIV positive subjects	X								
NIH Advance Directives Form [2]		X							
Medical history	X								
Height	X								
Physical exam, weight, vital signs, ECOG[11]	X	X		X					
EKG[11]	X	X							
Concurrent Medications[11]		X		X		X			
AEs[12]		X	X	X		X		X	
CT C/A/P [4, 11]	X	X		X					
CT Angiogram (abdomen)	X								
Tumor measurement(s) [4, 11]	X	X		X					

	Screening	Baseline[1]	Pump Placement	Cycles (28 days)[3]				EOT[6]	F Up[8]
				1	2-14	15	16-28		
General labs [5, 11]	X	X		X		X		X	
PTT, PT, IN[11]	X	X		X					
CEA [7, 11]		X		X					
HIV, Hepatitis B and C serology and/or viral load	X								
Tumor and normal liver biopsy for research [9]			X					X	
Urine or serum HCG [11]	X	X		X		X			
Phone call, e-mail or other NIH approved remote platforms									X
MSI status	X								

[1] Does not need to be repeated on Baseline if test was performed on Screening at defined timeline.

[2] As indicated in Section **12.3**, all subjects will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended but is not required.

[3] One cycle is 28 (+/- 2 days) days. Tests can be done within 48 hours before Day 1 of every cycle.

[4] CT of chest/abdomen/pelvis and tumor measurements at screening/baseline and to be repeated on every 12 weeks (+/- 1 week) after start of chemotherapy.

[5] Labs: CBC with differential and platelet count, electrolytes, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin (including direct and indirect), calcium, phosphorus, albumin, magnesium. Note: Labs may be done within 48 hours before standard systemic chemotherapy, to be completed at the NIH Clinical Center.

[6] End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone/videocall or other NIH approved remote platform (used in compliance with policy, including HRPP Policy 303) for symptoms.

[7]At the time of CT evaluation, baseline and every 12 weeks (+/- 1 week) after start of chemotherapy.

[8] After removal from study therapy, patients will be followed every six months by phone call, e-mail or videocall/other NIH approved remote platform (used in compliance with policy, including HRPP Policy 303) for survival, performance status and new cancer treatments. If patient is re-treated per Section **3.1.1**, on therapy assessments will be resumed per study calendar until patient once again meets off therapy criteria, at which point follow-up will resume.

[9] The first optional tumor biopsy will be done during surgery to install the pump, if the risk of an adverse event (e.g., bleeding) is felt to be negligibly low by the surgeon performing the pump installation. Additional optional biopsy may be performed at the time of progression if considered safe by PI.

[10] Starting Cycle 2.

[11] Should be repeated before re-treatment.

[12] For AEs collection, please, see Section **6.1**.

3.7 SURGICAL GUIDELINES

3.7.1 Preoperative Patient Management

Patients will receive standard preoperative care as appropriate to the planned surgical intervention and the patient's underlying health status. This will include:

- Clear liquid diet the evening prior to operation, without additional bowel preparation.
- Hibiclens shower the night before operation.
- Preoperative IV antibiotics administered within 2 hours prior to operation start.
- Sequential compression devices will be placed on the lower extremities prior to induction of general anesthesia.
- Subcutaneous heparin administration for venous thromboembolism prophylaxis just prior to operation start.

3.7.2 Patient Management in the Operating Room

3.7.2.1 At Operation

- Patients will undergo an upper midline incision with right sub-costal extension. A thorough examination of the abdomen will ensue to rule-out occult metastatic disease on the peritoneal surfaces, or unrecognized suspicious lymphadenopathy. The porta hepatis will be dissected to identify the relevant arterial anatomy. The hepatic and gastroduodenal arteries will be dissected fully. The hepatic artery infusion pump catheter will be placed into the gastroduodenal artery and the vessel will be ligated distally. Adequate hepatic perfusion will be determined with infusion of methylene blue dye. The pump catheter will be placed in a subcutaneous position, atop the fascia in the LLQ between the ASIS and the costal margin.
- Multiple core needle biopsies of tumor(s) and normal liver will take place. Total amount of tumor and liver tissue removed for research purposes will not exceed 200 grams and 50 grams, respectively.
- At the initial operation, a minimal wedge resection/ablation of tumor(s) no greater than one fourth of one segment will be undertaken if the wedge resection/ablation will result in a future remnant liver that is disease-free and viable. If the patient were to experience a partial or complete response to HAIP therapy, then a subsequent second operation would be undertaken to render the patient NED. For example, a minimal wedge resection or ablation of the left hemi liver will be undertaken at initial operation and placement of HAIP. If the patient were then to have a complete or partial response, then a subsequent right hepatectomy would be undertaken to render patient NED. The wedge resection or ablation will not exceed an amount of tissue that would leave a future remnant liver unviable.
- Regarding patients with primary colorectal cancers that have not yet been removed: Partial colectomy may be combined with HAIP placement at the discretion of the surgeon. For example, a patient with a large bulky primary tumor likely to encounter difficulty with bowel continuity should undergo a concomitant resection.
- All surgical procedures will be done according to the standard of care for hepatobiliary and colorectal resections.

3.7.2.1.1 Lymph Node Dissection

- Portal lymph nodes may be removed at the time of pump placement to facilitate placement, but no formal lymphadenectomy will take place as part of this protocol.
- If the patient's primary tumor is removed during the HAIP placement, the standard lymphadenectomy will be performed.

3.7.3 Postoperative Care

3.7.3.1 Patient Monitoring

- The patients will be monitored on the surgical ward per routine care.
- Patients will receive routine post-operative care; early ambulation will be encouraged.
- Laboratory evaluations will include:
  - CBC, platelets, acute care, mineral and hepatic panel on post-operative Days 1 through 3, and then as clinically indicated until discharge.
  - Patients will be transfused as appropriate to maintain a hemoglobin greater than or equal to 8 g/dL.

3.7.4 Discharge

- Total hospitalization may be approximately 4-7 days.
- Patients who are discharged within this time frame should be able to tolerate an oral diet with or without dietary supplements.
- Patients may require evaluation by their referring physician following discharge; any clinically indicated laboratory testing obtained locally will be faxed to the Research Nurse.

3.7.5 Post-Discharge/Follow-Up

Patients will return to the NIH CC every two weeks from the date of operation. At these time points, patients will undergo refilling of the HAIP with heparinized 0.9% Sodium Chloride or medication. Standard of care will be provided as clinically indicated. Other tests possible at these time points include:

- Physical examination including ECOG
- HAIP pump study if indicated
- General labs as listed in Section **3.7.3.1**

3.7.5.1 Follow Up Visits After Removal from Study Therapy

After removal from study therapy, patients will be followed by phone call, or e-mail or videocall/other NIH approved remote platform (used in compliance with policy, including HRPP Policy 303) for survival, performance status and new cancer treatments (refer to Section **3.6**, **Study Calendar** for details).

3.8 COST AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.8.2 Compensation

Participants will not be compensated on this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.9.1 Criteria for Removal from Protocol Therapy

Please note that re-treatment is allowed on this protocol and subjects may subsequently resume treatment after being taken off protocol therapy if meeting the criteria addressed in Section **3.1.1**. Off treatment criteria are identical for each HAIP

- Intrahepatic progressive disease
- Resection to NED after response to treatment.
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined by persistent bilirubin elevation above 3 or development of a biliary stricture.
- Principal investigator discretion
- Pump failure or infection requiring pump removal
- Positive pregnancy test

3.9.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Death
- Principal investigator discretion
- Pump failure or infection requiring pump removal
- Screen failure
- Lost to follow up
- PI decision to end the study

3.9.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 3 business days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls/video calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

During the post-operative period, patients will receive all standard of care supportive measures, including possible nasogastric tube drainage and bowel rest for ileus, pulmonary toilet teaching and incentive spirometry to prevent atelectasis, transfusions, and antibiotics as indicated per NIH CC pharmacy guidelines.

5 CORRELATIVE STUDIES

5.1 BIOSPECIMEN COLLECTION

5.1.1 Biospecimen Sharing on Protocol

Identifiable data or specimens, collected as part of a different NIH protocol, may be obtained, or shared for research in this protocol – specifically:

- We may *review the participant's NIH medical records* to obtain results of procedures conducted under another protocol in order to minimize repeating procedures/tests or meet the research objectives on this protocol.
- We may *obtain existing identifiable research data and/or tissue, and blood specimens collected under 13C0176* (NIH protocol titled "Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or Surgical Resection of Solid Tumors") for co-enrolled participants to minimize repeating procedures/tests or meet the research objectives.

Identifiable data or specimens may be shared with another NIH protocol for analysis and then may receive research results that can be linked to participants who are co-enrolled on both protocols – specifically:

- We may *share identifiable research data and/or specimens with 13C0176* (NIH protocol titled "Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or

Surgical Resection of Solid Tumors"), in order to minimize repeating procedures/tests or meet the research objectives *if participants are co-enrolled (only)*.

5.2 SAMPLE ANALYSIS

Note: The location of specimen processing or analysis may be adjusted with the permission of the PI or laboratory investigator. Platforms and procedures may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses.

5.2.1 Tumor and Tissue Collection

Tumor and normal liver samples will be collected during surgery to install the pump, if the risk of an adverse event (e.g., bleeding) is felt to be negligibly low by the surgeon performing the pump installation. Total amount of tumor and liver tissue removed for research purposes will not exceed 200 grams and 50 grams, respectively.

Additional optional biopsy may be performed at the time of progression if considered safe by PI.

Tumor and normal tissue will be used for liver microenvironment studies.

Part of the sample will be immediately used in the Dr. Hernandez lab and the rest will be sent for barcoding and initial storage to Biospecimen Processing Core (BPC).

For patients that respond and convert to resectable disease, the resected segments of liver will be utilized for a novel, first ever human tumor model. In this model, selected drug combinations in conjunction with novel delivery methods will be utilized to push the frontiers of personalized medicine. See Section **5.2.3**.

On this protocol we are not planning to do any clinical decision making based on the results of correlative studies.

5.2.2 Liver Microenvironment Studies

Tumor and normal liver removed during the procedure will be analyzed in Dr. Hernandez's laboratory as indicated in Section **1.2.6** for an increased understanding of how tumor cells adapt to and co-opt the liver microenvironment for eventual metastatic outgrowth.

5.2.3 Proteogenomic Characterization of Primary and Metastatic Cancers

Tumor tissue obtained from metastatic colorectal cancers collected during study procedures (refer to Section **3.6**) will undergo in-depth genomic characterization (as outlined in Section **1.2.8**) in Dr. Hernandez's laboratory to support the study of the underpinnings of cancer initiation and metastasis.

Tumor-bearing mesothelial tissue from solid tumors with metastatic disease to the mesothelial surface collected during study procedures (refer to Section **3.6**) will be sent to Dr. Hernandez's laboratory for *ex vivo* analysis utilizing the SMART (Sample Microenvironment of Resected Metastatic Tumor) Chamber (Section **1.2.8**), and resected mesothelial metastases will undergo *ex vivo* SMART System modeling (as outlined in Section **1.2.9**) in the laboratory to support the identification of underpinnings of interventional chemotherapeutic and immunomodulatory agent effects.

5.3 STORAGE, USE, AND SHARING OF SPECIMENS AND DATA (INCLUDING FOR SECONDARY RESEARCH)

5.3.1 Sample Tracking and Processing

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

Tissue samples will be sent to Biospecimen Processing Core (BPC) for barcoding and initial storage until they are distributed to Dr. Hernandez lab for sample analysis as described in the protocol.

5.3.1.1 Biospecimen Processing Core (BPC)

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.3.2 Sample Storage and Disposition

Barcoded samples are stored in barcoded boxes according to stability requirements. Access to stored clinical samples is restricted. Unless other permission obtained, samples are only to be used for research purposes associated with this trial (as per the IRB-approved protocol) by investigators named on the protocol. It is the responsibility of the Principal Investigator to ensure that samples are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of a sample tracking database (e.g., Labmatrix). It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, to correlate results with sample characteristics.

5.3.3 Protocol Completion/Secondary Use/Sample Destruction

Any specimens remaining at the completion of the protocol will be transferred to the participant co-enrolled protocol 13C0176 and stored indefinitely per the conditions described in the 13C0176 protocol. Participants will be co-enrolled on protocol 13C0176. Thus, all tissue will be stored, tracked and disposed after transfer as specified in protocol 13C0176. The 18C0024 study will remain open so long as sample or data analysis continues. All samples and data from consenting participants will be stored in identifiable format until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the participant, if so requested. The participant's samples and data will be excluded from future distributions, but those which already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

With the permission of the participant, specimens and data collected on this study, identifiable through a code available to the study team, will be stored indefinitely and used for secondary research, including genetic research. Furthermore, the data and/or specimens, may be shared with other investigators in identifiable or coded (code key not available to recipient) format for secondary research. Any investigator conducting secondary research in human subjects will seek either additional regulatory approval or exemption for research as appropriate.

Data will also be shared in public database per the study's data sharing plan in compliance with NIH policies.

In addition, specimens/data may be anonymized and further research, including genetic research, conducted at the site or other institutions without participant consent. Participants will be informed that the possibility for this type of research exists.

5.3.4 Certificate of Confidentiality

A Certificate of Confidentiality will be obtained for the study as described in Section **12.4.8**.

5.3.5 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory.

5.3.6 Genetic Counseling

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the time of operation through 30 days after the last dose of study therapy. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Grade 1 AEs will not be collected.

Only those medications that the patient is taking at baseline on a routine basis or medications that cause an AE will be captured. (Thus, one-time medications, PRN medications, and medications given to treat adverse events will not be captured.)

All deaths will be collected.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in a NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center).
- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov, dbGaP.
- BTRIS (automatic for activities in the Clinical Center).
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.

- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

This study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

The intended RNA evaluation was removed in the 03/23/2022 amendment/version prior to any analyses; therefore, large scale genomic data were not, and will not, be generated on this study.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 12 weeks (not less than 4) weeks following initial documentation of objective response.

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) [18]. 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. CT or MRI will be used for response criteria.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of the placement of the HAIP.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 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) as:

- By chest x-ray: >20 mm;
- By CT scan:
  - Scan slice thickness 5 mm or under as >10 mm with CT scan
  - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: >10 mm.

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. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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 5 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.

6.3.3 Methods for Evaluation of Measurable Disease

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 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during 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.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers

(e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [18], [19], [20]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [21].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in 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.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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.

6.3.4 Response Criteria

6.3.4.1 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 of 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 of diameters while on study.

6.3.4.2 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 patient 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 review panel (or Principal Investigator).

6.3.4.3 Evaluation of Best Overall Response

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

For Patients 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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

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

For Patients 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

* '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

6.3.5 Duration of Response

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

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.

6.3.6 Progression-Free Survival

Intrahepatic PFS is defined as the duration of time from date of operation to the date of first observation of progressive disease within the liver or death, whichever comes first.

Extrahepatic PFS is defined as the duration of time from date of operation to the date of first observation of progressive disease outside of the liver or death, whichever comes first.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802: Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section 7.2.1 will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Investigator Agreement as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

UADEs will be:

1. Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Investigator Agreement as the site principal investigator or sub-investigator.
2. Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
3. Followed through resolution by a licensed study physician listed on the Investigator Agreement as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **6.1**. All unanticipated adverse device events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in Section **8.4**.

8.3 REPORTING OF UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

Any AE that meets protocol-defined criteria of an unanticipated adverse device effect that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. (OSRO has confirmed that the CCR SAE report form can be used for UADEs as the criteria for reporting unanticipated device events is almost identical.) Any exceptions to the expedited reporting requirements are found in Section **8.4**.

All UADE reporting must include the elements described in Section **8.2**.

UADE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator.

CCR SAE report form and instructions can be found at: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI.

Following the assessment of the UADE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As overall survival which includes death due to disease progression is part of the study objectives, and captured as an endpoint in this study, death due to disease progression will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship

between the study device and the event, report the event in an expedited manner according to Section **8.3**.

In addition, we request a waiver for expected events related to the following commercially approved products:

> Commercial Agents: Floxuridine, Dexamethasone, 5FU, leucovorin, Irinotecan, Oxaliplatin, Cetuximab, Panitumumab

The PI will submit a summary table of all Grade 3-5 events, whether or not considered related to the product, every 6 months. The report shall include the number of patients treated in the timeframe, the number of events per AE term per grade which occurred in the 6-month timeframe and in total since the start of the study, attribution, and type/category of serious.

Reports will be submitted to the Center for Cancer Research (CCR) at OSROSafety@mail.nih.gov.

The Sponsor might request case summaries for those events if, upon review, the Sponsor determines that an aggregate safety report is required.

8.5 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI.

8.5.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **7.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.5.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of chemotherapy.

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IDE

Following notification from the investigator, CCR, the IDE sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators

to whom the sponsor is providing study product under its IDEs or under any investigator's IDE) in an IDE safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 812.150(b).

All serious events will be reported to the FDA at least annually in a summary format.

8.7 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING PLAN

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary Efficacy Endpoint

The primary endpoints of this trial are to determine the clinical response rate in patients with metastatic colorectal cancer treated with HAIP chemotherapy as measured by RECIST; and, to assess the safety of the HAIP chemotherapy administered using the Medtronic pump with the Codman catheter in patients with unresectable metastatic colorectal cancer.

10.1.2 Secondary Endpoints

Hepatic progression free survival (HPFS), the extra-hepatic progression free survival (EHPFS) and the overall survival (OS).

10.2 SAMPLE SIZE DETERMINATION

Data from several published trials in the second line setting in patients with metastatic colorectal cancer who were given chemotherapy through conventional means demonstrated overall response rates of 15-20%. In order to establish improved efficacy of chemotherapy using a pump compared to conventionally administered chemotherapy, the primary objective would be to determine if using the proposed pump-based chemotherapy would rule out a 20% response rate and result in a response rate consistent with 40%. As such, this trial will be conducted using a Simon optimal two-stage Phase II trial design (Simon R, Controlled Clinical Trials 10:1-10, 1989) in order to rule out an unacceptably low PR+CR rate of 20% (p0=0.20) in favor of an improved response rate of 40% (p1=0.40). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), the first stage will enroll 17 evaluable patients, and if 0 to 3 of the 17 have a clinical response, then no further patients will be accrued in this trial. If 4 or more of the first 17 patients have a response, then accrual would continue until a total of 37 evaluable patients have been treated. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 4 to 10 patients with a response out of 37 patients, this would be an uninterestingly low response rate. If there were 11 or more of 37 (29.7%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (20% response rate), the probability of early termination is 54.9%.

With no more than 37 evaluable participants needed, as well as planning for a small number of inevaluable participants (2), we intend to initiate intervention in up to 39 (37+2=39) participants. It is expected that approximately 10-12 patients per year may enroll onto this trial. Thus, it is expected that 3 to 3.5 years may be required in order to enroll up to 37 evaluable patients. Note:

To additionally allow for 1 screen failure, a total of 40 (37+2+1=40) participants will be set for the purposes of the NIH accrual ceiling.

10.3 POPULATIONS FOR ANALYSIS

Modified intention to treat: only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Response fractions, and time to event endpoints will be reported along with appropriate confidence intervals.

10.4.2 Analysis of the Primary Endpoints

To assess efficacy: the fraction of patients who experience a PR or CR using the study treatment will be determined by dividing the number of responders by the total evaluable patients. The fraction will be reported along with 80% and 95% two-sided confidence intervals.

To assess safety: the type, grade and frequency of toxicities will be reported.

10.4.3 Analysis of the Secondary Efficacy Endpoints

Hepatic progression-free survival (HPFS) will be determined using the Kaplan-Meier method, evaluating those who develop hepatic progression as failures, and censoring those who do not.

Extra-hepatic progression-free survival (EHPFS) will be determined using the Kaplan-Meier method, evaluating those who develop progression outside the liver as failures, and censoring those who do not.

Overall survival (OS) will be determined using the Kaplan-Meier method.

Each of these will be calculated starting from the date the patient enrolled onto the trial. Appropriate confidence intervals will be reported for each of these measures.

10.4.4 Safety Analyses

Because biliary toxicity is a potential concern with use of the hepatic artery infusion pump, the trial will monitor for presence of this toxicity on an ongoing basis. If within the first 5 patients, there is a single case of Grade 3 or 4 biliary toxicity, or if at any time after 5 patients have been treated, the cumulative fraction with Grade 3 or 4 biliary toxicity is 20% or greater, then the trial will suspend accrual and will only reopen following review of the safety data and amendment to modify the treatment appropriately.

10.4.5 Baseline Descriptive Statistics

Demographic and baseline clinical characteristics of all patients will be reported.

10.4.6 Planned Interim Analyses

As indicated above, in this Simon two-stage design, after 17 patients have been enrolled, an analysis of the response rate will be undertaken to determine if there are sufficient responses to proceed to the second stage.

10.4.7 Exploratory Analyses

Factors associated with biliary toxicity may be explored by comparing the factors to those with and without biliary toxicity using an appropriate two-group test such as a Wilcoxon rank sum test for continuous parameters and Fisher's exact test for dichotomous parameters. Other techniques may be used as appropriate.

Ex vivo analysis of peritoneal tumor tissue with resected mesothelial metastases will be performed utilizing the SMART System to support the identification of underpinnings of interventional chemotherapeutic and immunomodulatory agent effects in subjects with unresectable metastatic colorectal cancer undergoing HAIP chemotherapy.

11 COLLABORATIVE AGREEMENTS

There are no CRADAs, CTAs or CDAs assigned to this protocol.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale for Subject Selection

Patients with a diagnosis of colorectal cancer with predominantly hepatic metastases will be eligible for this study. Eligibility assessment will be made solely on the patient's medical status. Recruitment of patients on this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted. The investigational nature and objectives of this trial, the procedure and the treatments involved, the attendant risks and discomforts, potential benefits and potential alternative therapies will be carefully explained to the subjects in the clinic setting and in the hospital prior to treatment and prior to obtaining a signed informed consent.

12.2 Participation of Children

Children are excluded from this study because no dosing or adverse event data are currently available on the use of hepatic artery infusion pump chemotherapy in patients <18 years of age. Since the efficacy of this experimental procedure is unknown, it does not seem reasonable to expose children to this risk without further evidence of benefit. Should results of this study indicate efficacy in treating colorectal cancer, which is not responsive to other standard forms of therapy, future research can be conducted in the pediatric population to evaluate potential benefit in that patient population.

12.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **12.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can

make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see Section **12.6.1** for consent procedure.

12.4 Evaluation of Benefits and Risks/Discomforts

The potential benefit to patients undergoing this therapy would be palliation in terms of preventing or delaying intra-abdominal tumor progression and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise. In addition, significant tumor response may extend progression free and overall survival.

The risks for this protocol include the risks associated with any abdominal surgery. This includes postoperative bleeding, intra-abdominal infection, wound healing complications including fascial dehiscence, enterocutaneous fistulas, anesthetic mishap and perioperative death. Additionally, the use of HAIP chemotherapy is associated with biliary injury that may result in biliary stricture requiring stent placement. In addition, the toxicities of chemotherapy place the patients under risk. A combination of surgery and chemotherapy may decrease healing at a time when healing of abdominal wounds and bowel anastomosis is essential for recovery. All attempts will be made to avoid unnecessary enterotomies or a bowel resection where feasible. In the case of intra-abdominal catastrophe after surgery, patients may require reoperation. It is also conceivable that the HAIP my flip or twist after placement requiring a return trip to the operating room for fixation. As with any metal implant future imaging (MRI) can be obscured by the pump.

12.4.1 Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop. No more than about 34 mL will be collected at a timepoint. No more than about 148 mL of blood will be collected over a single 8-week period.

12.4.2 General Anesthesia

Risks of general anesthesia include temporary confusion and memory loss, although this is more common in the elderly, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, sore throat due to the breathing tube.

12.4.3 Tissue Collection Risks

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, MD. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

12.4.3.1 Biopsy

Biopsy side effects may include a mild burning sensation when the numbing medicine is injected into the skin, small amounts of bleeding at the biopsy site, and rarely, a small infection at the site. Biopsy sites usually heal very well and with very little scarring.

12.4.3.2 Conscious Sedation

The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.4.4 Echocardiogram

This test is safe and side effects are unlikely, but may include brief light headedness or slight soreness of the chest.

12.4.5 Scans and Contrast

The most common discomfort is the length of time a patient must lay still during a scan. Patients may also become uncomfortable with the closed space of the machines.

There is a small risk of reaction in scans involving contrast. Common reactions include pain in the vein where the contrast was given, a metallic or bitter taste in the mouth, headache, nausea and a warm or flushing feeling that lasts from 1-3 minutes. In very rare cases, severe reactions that affect breathing, heart rhythm or blood pressure have occurred.

An IV line may need to be inserted for administration of the contrast agent or anesthetic, which may cause pain at the site where the IV is placed and there is a small risk of bruising or infection.

12.4.6 Risks of Exposure to Ionizing Radiation

This research study involves radiation from the following sources:

- 2 CT guided optional biopsies
- 6 CT C/A/P scans
- 1 CT whole body angiogram
- 1 one-time radiopharmaceutical injection administered through the newly implanted pump with immediate image acquisition* to check pump perfusion to the liver (Section **3.7**).

Subjects will be exposed to approximately 9.46 rem. This amount of radiation is above the guideline of 5 rem per year, and will expose the subject to the roughly the same amount of radiation as 31.5 years of background radiation.

*Note: All participants are required to get a nuclear perfusion study before starting hepatic artery infusion pump therapy under sterile conditions in the NIH Nuclear Medicine department. Once access is established, 5 mCi of 99mTc-MAA is administered by through the pump via the access port bypassing the pump mechanism. Immediately following this injection, anterior and posterior planar images of the upper abdomen are acquired. The time between the radiopharmaceutical injection and image acquisition is minimized to avoid breakdown of 99mTc-MAA and accumulation of free pertechnetate. After planar imaging, SPECT/CT is performed to evaluate for extrahepatic tracer distribution in the abdomen. SPECT/CT is preferred over SPECT alone, as the addition of CT enables more precise anatomic localization. A normal hepatic pump scintigraphic study shows radiotracer uptake in only the liver and is pre-requisite to instituting therapy. Dosimetry average total = 3mSv (0.3 rem).

12.4.7 Non-Physical Risks of Genetic Research

12.4.7.1 Risk of Receiving Unwanted Information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

12.4.7.2 Risk Related to Possibility that Information May be Released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

12.4.7.3 Risk to Family or Relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems.

12.4.8 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to prevent forced disclosure of personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality

12.5 RISKS/BENEFITS ANALYSIS FOR ALL PARTICIPANTS

The potential benefit is great for patients if a regional response is obtained. Therefore, although this protocol involves greater than minimal risk, it presents the prospect of direct benefit to individual subjects. For those patients that do experience a response, data strongly suggests the impartment of a survival advantage. The major risk with HAIP chemotherapy is biliary toxicity, which will limit the ability to undergo further treatment and, may irreparably damage the biliary ductal system necessitating repeat stenting procedures. Fortunately, this is uncommon, although is it at present an unpredictable event in determining which patients will be affected.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with

the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (Non-Electronic) Signature on Electronic Document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in Section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

12.6.2 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in Section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, funding agencies, the Investigational New Drug (IND) sponsor and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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 that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and

procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). 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.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies 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.

The study participant's contact information will be securely stored at the 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 the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, 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 the clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

14.1 PHARMACEUTICAL INFORMATION

14.1.1 Oxaliplatin

Oxaliplatin will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.1.1 Toxicity

The most common side effects of oxaliplatin include:

- neutropenia, anemia, thrombocytopenia, hypertension, diarrhea, nausea, vomiting, constipation, oral mucositis, abdominal pain, anorexia, fatigue, injection site reactions, alopecia and dehydration

Potentially serious toxicities include:

- Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to oxaliplatin has been observed in 2-3% of colon cancer patients. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy or desensitization protocol for continuation of therapy.

- Peripheral sensory neuropathy (acute ≤ 14 days and persistent > 14 days) was reported in adjuvant patients treated with ELOXATIN as part of FOLFOX with a frequency of 92% (all grades) and 13% (Grade 3). At the 28-day follow-up after the last treatment cycle, 60% of all patients had any grade (Grade 1=40%, Grade 2=16%, Grade 3=5%) peripheral sensory neuropathy decreasing to 39% at 6-month follow-up (Grade 1=31%, Grade 2=7%, Grade 3=1%) and 21% at 18 months of follow-up (Grade 1=17%, Grade 2=3%, Grade 3=1%).

Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82% (all grades) and 19% (Grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (Grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) has been observed in clinical trials (< 0.1%) and postmarketing experience. Signs and symptoms of RPLS could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension. Diagnosis of RPLS is based upon confirmation by brain imaging.

- Pulmonary Toxicity. oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and < 1% (Grade 3) with no Grade 4 events in the oxaliplatin plus infusional 5-fluorouracil/leucovorin arm compared to 4.5% (any grade) and no Grade 3 and 0.1% Grade 4 events in the infusional 5- fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the oxaliplatin combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (Grade 3 and 4) in the oxaliplatin plus 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (Grade 3 and 4) in the irinotecan plus 5-fluorouracil/leucovorin arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, ELOXATIN should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

- Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the oxaliplatin combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases

14.1.1.2 Formulation

Powder

ELOXATIN is supplied in single-use vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient.

Solution

ELOXATIN is supplied in single-use vials containing 50 mg, 100 mg or 200 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml. Water for Injection, USP is present as an inactive ingredient.

14.1.1.3 Preparation

Powder

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

ELOXATIN is not light sensitive.

Solution

Do not freeze and protect from light the concentrated solution.

A final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.

The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

After final dilution, protection from light is not required.

ELOXATIN 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.

14.1.1.4 General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with oxaliplatin should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

14.1.1.5 Stability and Storage

Powder for solution for infusion:

Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Concentrate for solution for infusion:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze and protect from light (keep in original outer carton).

14.1.1.6 Administration Procedures

Please see Section **3.4.2.1** and package insert.

14.1.1.7 Incompatibilities

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m2 oxaliplatin and 5-fluorouracil/leucovorin has been observed in patients treated every 2 weeks. Increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m2 oxaliplatin dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds; although, this has not been specifically studied.

14.1.2 5-FLUOROURACIL (5-FU)

14.1.2.1 Source

5-FU will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.2.2 Toxicity

5-FU should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function.

Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of 5-fluorouracil.

The administration of 5-fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Although pyridoxine has been reported to ameliorate the palmar-plantar erythrodysesthesia syndrome, its safety and effectiveness has not been established.

Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy.

Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of

treatment, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range.

Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. It is generally reversible and usually responsive to symptomatic treatment.

Other adverse reactions are:

- Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia.
- Cardiovascular: myocardial ischemia, angina.
- Gastrointestinal: gastrointestinal ulceration and bleeding.
- Allergic Reactions: anaphylaxis and generalized allergic reactions.
- Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.
- Dermatologic: dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation; palmar-planter erythrodysesthesia syndrome, as manifested by tingling of the hands and feet followed by pain, erythema and swelling.
- Ophthalmic: lacrimal duct stenosis, visual changes, lacrimation, photophobia.
- Psychiatric: disorientation, confusion, euphoria.
- Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails)

14.1.2.3 Formulation and Preparation

Formulation

ADRUCIL (fluorouracil injection, USP) an antineoplastic antimetabolite, is a sterile, nonpyrogenic injectable solution for intravenous administration. Each 10 mL contains 500 mg fluorouracil; pH is adjusted to approximately 9.2 with sodium hydroxide.

For intravenous use. ADRUCIL Injection (fluorouracil injection, USP) is available at a concentration of 50mg/mL.

The 50 mL and 100 mL pharmacy bulk packages are packaged 5 vials per shelf pack.

Preparation

No dilution is required.

14.1.2.4 Stability and Storage

Store at room temperature 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until time of use.

14.1.2.5 Administration Procedures

Please see Section **3.5.2** and package insert.

14.1.2.6 Incompatibilities

Leucovorin calcium may enhance the toxicity of fluorouracil.

14.1.3 LEUCOVORIN

14.1.3.1 Source

Leucovorin will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.3.2 Toxicity

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin per se.

Table 7 below summarizes significant adverse events occurring in 316 patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for advanced colorectal carcinoma. These data are taken from the Mayo/NCCTG large multicenter prospective trial evaluating the efficacy and safety of the combination regimen.

Table 7: Percentage of Patients Treated with Leucovorin/Fluorouracil for Advanced Colorectal Carcinoma Reporting Adverse Experiences or Hospitalized for Toxicity

Toxicity	(High LV) /5-FU (N=155)		(Low LV) /5-FU (N=161)		5-FU Alone (N=70)	
	Any (%)	Grade 3+ (%)	Any (%)	Grade 3+ (%)	Any (%)	Grade 3+ (%)
Leukopenia	69	14	83	23	93	48
Thrombocytopenia	8	2	8	1	18	3
Infection	8	1	3	1	7	2
Nausea	74	10	80	9	60	6
Vomiting	46	8	44	9	40	7
Diarrhea	66	18	67	14	43	11
Stomatitis	75	27	84	29	59	16
Constipation	3	0	4	0	1	-
Lethargy/Malaise/Fatigue	13	3	12	2	6	3
Alopecia	42	5	43	6	37	7
Dermatitis	21	2	25	1	13	-

Toxicity	**(High LV) /5-FU (N=155)**		**(Low LV) /5-FU (N=161)**		**5-FU Alone (N=70)**	
	Any (%)	**Grade 3+ (%)**	**Any (%)**	**Grade 3+ (%)**	**Any (%)**	**Grade 3+ (%)**
Anorexia	14	1	22	4	14	-
Hospitalization for Toxicity	5%		15%		7%	
High LV = Leucovorin 200 mg/m2, Low LV = Leucovorin 20 mg/m2 Any = percentage of patients reporting toxicity of any severity Grade 3+ = percentage of patients reporting toxicity of Grade 3 or higher						

14.1.3.3 Formulation

Leucovorin Calcium Injection USP is a sterile, preservative-free solution indicated for intramuscular (IM) or intravenous (IV) administration in a 50 mL single-dose vial. Each mL contains leucovorin calcium equivalent to 10 mg Leucovorin, USP; 8 mg sodium chloride; sodium hydroxide and/or hydrochloric acid for pH adjustment pH 7.8 (6.5 to 8.5).

There is 0.004 mEq of calcium per mg of leucovorin. Solution contains no bacteriostat or antimicrobial agents.

Leucovorin Calcium for Injection is a sterile product indicated for intramuscular (IM) or intravenous (IV) administration and is supplied in 50 mg, 100 mg, 200 mg, and 350 mg vials.

Each 50 mg vial of Leucovorin Calcium for Injection, when reconstituted with 5 mL of sterile diluent, contains leucovorin (as the calcium salt) 10 mg/mL.

Each 100 mg vial of Leucovorin Calcium for Injection, when reconstituted with 10 mL of sterile diluent, contains leucovorin (as the calcium salt) 10 mg/mL.

Each 200 mg vial of Leucovorin Calcium for Injection, when reconstituted with 20 mL of sterile diluent, contains leucovorin (as the calcium salt) 10 mg/mL.

Each 350 mg vial of Leucovorin Calcium for Injection, when reconstituted with 17.5 mL of sterile diluent, contains leucovorin (as the calcium salt) 20 mg/mL.

In each dosage form, one milligram of leucovorin calcium contains 0.002 mmol of leucovorin and 0.002 mmol of calcium.

14.1.3.4 Preparation

These lyophilized products contain no preservative. The inactive ingredient is Sodium Chloride, USP, added to adjust tonicity.

Because of the benzyl alcohol contained in certain diluents used for reconstituting Leucovorin Calcium for Injection, when doses greater than 10 mg/m2 (as in this study) are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP, and used immediately.

14.1.3.5 Stability and Storage

Store at 20°C to 25°C (68° to 77° F). Protect from light. Retain in carton until time of use.

Reconstituted form should be used immediately.

14.1.3.6 Administration Procedures

Please see Section **3.4.2** and package insert.

14.1.3.7 Incompatibilities

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible pediatric patients.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of 5-fluorouracil

14.1.4 Floxuridine

14.1.4.1 Source

Floxuridine will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.4.2 Toxicity

The more common adverse reactions to the drug are nausea, vomiting, diarrhea, enteritis, stomatitis and localized erythema. The more common laboratory abnormalities are anemia, leukopenia, thrombocytopenia and elevations of alkaline phosphatase, serum transaminase, serum bilirubin and lactic dehydrogenase.

Other adverse reactions are:

Gastrointestinal: duodenal ulcer, duodenitis, gastritis, bleeding, gastroenteritis, glossitis, pharyngitis, anorexia, cramps, abdominal pain; possible intra- and extrahepatic biliary sclerosis, as well as acalculous cholecystitis.

Dermatologic: alopecia, dermatitis, nonspecific skin toxicity, rash.

Cardiovascular: myocardial ischemia.

Miscellaneous Clinical Reactions: fever, lethargy, malaise, weakness.

Laboratory Abnormalities: BSP, prothrombin, total proteins, sedimentation rate and thrombocytopenia.

Procedural Complications of Regional Arterial Infusion: arterial aneurysm; arterial ischemia; arterial thrombosis; embolism; fibromyositis; thrombophlebitis; hepatic necrosis; abscesses; infection at catheter site; bleeding at catheter site; catheter blocked, displaced or leaking.

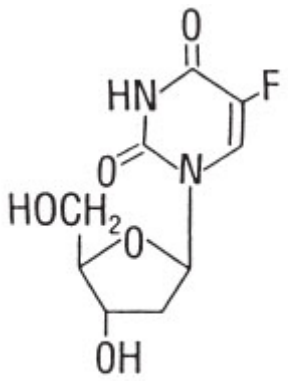
The following adverse reactions have not been reported with floxuridine but have been noted following the administration of 5-fluorouracil. While the possibility of these occurring following floxuridine therapy is remote because of its regional administration, one should be alert for these

reactions following the administration of floxuridine because of the pharmacological similarity of these two drugs: pancytopenia, agranulocytosis, myocardial ischemia, angina, anaphylaxis, generalized allergic reactions, acute cerebellar syndrome, nystagmus, headache, dry skin, fissuring, photosensitivity, pruritic maculopapular rash, increased pigmentation of the skin, vein pigmentation, lacrimal duct stenosis, visual changes, lacrimation, photophobia, disorientation, confusion, euphoria, epistaxis and nail changes, including loss of nails.

14.1.4.3 Formulation and Preparation

Floxuridine is a fluorinated pyrimidine. Chemically, floxuridine is 2'-deoxy-5-fluorouridine. It is a white to off-white odorless solid which is freely soluble in water. The 2% aqueous solution has a pH of between 4.0 and 5.5.

The structural formula is:



$C_9H_{11}FN_2O_5$ M.W. 246.19

Floxuridine for Injection, USP, an antineoplastic antimetabolite, is available as a sterile, nonpyrogenic, lyophilized powder for reconstitution. Each vial contains 500 mg of floxuridine.

14.1.4.4 Stability and Storage

The sterile powder should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Reconstituted vials should be stored under refrigeration 2° to 8°C (36° to 46°F) for not more than 2 weeks.

14.1.4.5 Administration Procedures

Please see Section **3.4.1** and package insert.

14.1.5 Irinotecan

14.1.5.1 Source

Irinotecan will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.5.2 Toxicity

Likely	**Less Likely**	**Rare but Serious**

• Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light.
• Nausea
• Vomiting
• Loss of appetite
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells can make it easier to get infections
• Fever
• A feeling of weakness and tiredness
• Hair loss
• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
• An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions.
• Inflammation and/or sores in the mouth, throat and/or esophagus
• Infections
	• Fewer red blood cells and platelets in the blood.
	  ○ A low number of red blood cells can make you feel tired and weak
	  ○ A low number of platelets causes you to bruise and bleed more easily
	• Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body
	• Constipation
	• Pain at the injection site
	• A slow heart beat
	• Low blood pressure
	• Shortness of breath with cough
	• Headache
	• Acid or an upset stomach (heartburn)
	• Confusion or sleepiness
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening
		• Inflammation of the lungs which could lead to chest pain and shortness of breath and which may be life-threatening
		• Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain
		• Blood clots which may be in rare cases life-threatening
		• A stoppage (or blockage) of the intestine which may require treatment

14.1.5.3 Formulation

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

CHEMICAL NAME: (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate

Molecular Weight: 586.678 g/mol

Molecular Formula: C33H38N4O6

14.1.5.4 Stability and Storage

Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40 mg (2 mL), 100 mg (5 mL), 300 mg (15 mL), and 500 mg (25 mL).

Store at controlled room temperature 15°-30°C (59°-86°F) and protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

14.1.5.5 Administration Procedures

Injection must be diluted prior to infusion. Irinotecan should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration within the range of 0.12 to 2.8 mg/mL.

14.1.6 Cetuximab

14.1.6.1 Source

Cetuximab will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.6.2 Toxicity

Dermatologic and Soft Tissue Toxicity

Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving cetuximab therapy.

Electrolyte Depletion/Monitoring

The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab.

Infusion Reactions

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone in Study 1.

Pulmonary Fibrosis/Interstitial Lung Disease (ILD)

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion reactions [See Boxed Warning, Warnings and Precautions (5.1).]
- Cardiopulmonary arrest [See Boxed Warning, Warnings and Precautions (5.2).]
- Pulmonary toxicity [See Warnings and Precautions (5.3).]
- Dermatologic toxicity [See Warnings and Precautions (5.4).]
- Hypomagnesemia and Electrolyte Abnormalities

The most common adverse reactions in cetuximab clinical trials (incidence >25%) include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most serious adverse reactions with Erbitux are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus

14.1.6.3 Formulation and Preparation

Cetuximab is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives.

14.1.6.4 Stability and Storage

Store vials under refrigeration at 20 C to 80 C (360 F to 460 F). Do not freeze. Increased particulate formation may occur at temperatures at or below 0 C.

14.1.6.5 Administration Procedures

Please see package insert.

14.1.7 Panitumumab

14.1.7.1 Source

Panitumumab will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.7.2 Toxicity

Dermatologic and Soft Tissue Toxicity

In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC Grade 3 and higher) in 15% of patients with mCRC receiving Vectibix. The clinical manifestations

included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with Vectibix. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Vectibix. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g.,Stevens-Johnson syndrome or toxic epidermal necrolysis).

Electrolyte Depletion/Monitoring

Progressively decreasing serum magnesium levels leading to severe (Grade 3-4) hypomagnesemia occurred in up to 7% (in Study 2) of patients across clinical trials.

Infusion Reactions

In Study 1, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions (NCI-CTC Grade 3-4).

Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix administration. Fatal infusion reactions occurred in postmarketing experience.

Acute Renal Failure in Combination with Chemotherapy

Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix in combination with chemotherapy.

Pulmonary Fibrosis/Interstitial Lung Disease (ILD)

Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated with Vectibix. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix.

Photosensitivity

Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix.

Ocular Toxicities

Serious cases of keratitis and ulcerative keratitis, known risk factors for corneal perforation, as well as corneal perforation have occurred with Vectibix use. Monitor patients for evidence of keratitis, ulcerative keratitis, and corneal perforation. Interrupt or discontinue Vectibix use for acute or worsening keratitis, ulcerative keratitis, or corneal perforation.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Dermatologic and Soft Tissue Toxicity
- Increased Tumor Progression, Increased Mortality, or Lack of Benefit in KRAS-Mutant mCRC
- Electrolyte Depletion/Monitoring

- Infusion Reactions
- Acute Renal Failure in Combination with Chemotherapy
- Pulmonary Fibrosis/Interstitial Lung Disease (ILD)
- Photosensitivity
- Ocular Toxicities
- Increased Mortality and Toxicity with Vectibix in combination with Bevacizumab and Chemotherapy

14.1.7.3 Formulation and Preparation

Vectibix (panitumumab) is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab has an approximate molecular weight of 147 kDa. Panitumumab is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Vectibix is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion, which may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates. Each single-use 5 mL vial contains 100 mg of panitumumab, 29 mg sodium chloride, 34 mg sodium acetate, and Water for Injection, USP. Each single-use 10 mL vial contains 200 mg of panitumumab, 58 mg sodium chloride, 68 mg sodium acetate, and Water for Injection, USP. Each single-use 20 mL vial contains 400 mg of panitumumab, 117 mg sodium chloride, 136 mg sodium acetate, and Water for Injection, USP.

14.1.7.4 Stability and Storage

Store vials in the original carton under refrigeration at 2^0 to 8^0C (36^0 to 46^0F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since Vectibix does not contain preservatives, any unused portion remaining in the vial must be discarded.

14.1.7.5 Administration Procedures

Refer to Section **3.4.2.4**. For additional information, please see package insert.

14.1.8 Dexamethasone

14.1.8.1 Source

Dexamethasone will be supplied by the local pharmacy using supply purchased from commercial sources.

14.1.8.2 Toxicity

Common:

Cardiovascular: Hypertension

Dermatologic: Atrophic condition of skin, Finding of skin healing, Impaired

Endocrine metabolic: Cushing's syndrome, Decreased body growth

Gastrointestinal: Disorders of gastrointestinal tract

Immunologic: At risk for infection

Musculoskeletal: Osteoporosis

Ophthalmic: Cataract (5%), Raised intraocular pressure (25%)

Psychiatric: Depression, Euphoria

Respiratory: Pulmonary tuberculosis

Serious:

Endocrine metabolic: Hyperglycemia, Primary adrenocortical insufficiency

Ophthalmic: Conjunctival hemorrhage (22%), Glaucoma, Vitreous detachment (2%)

14.1.8.3 Formulation and Preparation

Oral Tablet (Scored): 4 mg

Injection, solution, as sodium phosphate: 4 mg/mL (1 mL, 5 mL, 30 mL);

14.1.8.4 Administration Procedures

IV: Administer intravenously over 10 minutes.

14.1.8.5 Incompatibilities

Contraindicated: Praziquantel (theoretical), Rotavirus Vaccine, Live (established)

Major: Aldesleukin (theoretical), Bupropion (theoretical), Darunavir (theoretical), Dasatinib (theoretical), Etravirine (theoretical), Fosamprenavir (theoretical), Imatinib (theoretical), Ixabepilone (theoretical), Lapatinib (theoretical), Nilotinib (theoretical), Quetiapine (probable), Romidepsin (theoretical), Sunitinib (theoretical), Temsirolimus (theoretical), Thalidomide (probable)

14.2 DEVICE INFORMATION

14.2.1 Medtronic SynchroMed II Pump

This pump is a programmable drug delivery system that stores and delivers infusion treatment. This device is implanted under the skin and is indicated for chronic intravascular infusion of floxuridine (FUDR) or doxorubicin hydrochloride (Adriamycin) and, when required bacteriostatic water, physiological saline and/or heparin.

14.2.1.1 Indications

- Chronic infusion of Lioresal Intrathecal (baclofen injection) for the management of severe spasticity of spinal or cerebral origin.
- Chronic intrathecal or epidural infusion of sterile, preservative-free morphine sulfate for chronic, intractable pain of malignant and/or non-malignant origin.
- Chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain.
- Chronic intravascular infusion of chemotherapy for the treatment of cancer.
- Chronic intravascular infusion of Floxuridine (FUDR) or methotrexate for the treatment of primary or metastatic cancer.

14.2.1.2 Specifications

SynchroMed II Drug Infusion Pump:

Model	8637-20 (20 mL reservoir)	8637-40 (40 mL reservoir)
Battery Life	4 to 7 years	4 to 7 years
Weight (empty/full)	165/185 g (5.8/6.5 oz)	175/215 g (6.2/7.6 oz)
Thickness	19.5 mm (0.78 in)	26 mm (1.0 in)
Minimum flow rate	0.048 mL/day	0.048 mL/day

Sutureless pump connector revision kit:

Model 8578, Length= 7.6 cm. Volume= 0.0022 mL/cm.

14.2.1.3 Safety Features

The pump includes a smart software that helps guide the clinician through programming the system via informational and warning screens. The pump has critical alarms that are triggered if the reservoir is empty, the pump is at the end of service, the motor stalls or if the pump has a critical memory error.

14.2.1.4 Source

Medtronic SynchroMed II Pump will be purchased from Medtronic.

14.2.1.5 Risks

- arterial aneurysm (weakness in the walls of the artery)
- arterial ischemia (death of portions of the artery)
- arterial clotting or bleeding
- pseudoaneurysm
- infection at pump site
- pump blocked, displaced or leaking
- abnormal narrowing of the bile duct
- bile duct injury
- pocket seroma at the implant site
- pump inversion or position change
- allergic reaction or immune system response to the implanted materials
- component failure (a part of the pump may stop working, including potential for drug overdose, loss of ability to program the pump, or loss and/or change in participant therapy)
- dislodgement or disconnection from catheter that may expose the subject to tissue damage, serious injury, or death due to perforation of vital organs and/or major blood vessels, or loss and/or change in participant therapy

14.2.2 Codman 3000 Infusion Pump Catheter

Originally approved as a component of the Codman 3000 Infusion Pump (P890055), the Codman 3000 Infusion Pump Catheter is designed to be connected to the Codman 3000 Implantable Pump. The pump catheter is made of medical-grade silicone elastomer impregnated with a radiopaque material. The catheter has a length of 30 inches; the inner diameter is 0.025 inches; the outer diameter is 0.090 inches. The catheter will be supplied with a connector. The straight catheter connector ends are designed to be connected into the pump catheter and silicone extension tubing from the drug delivery system.

14.2.2.1 Specifications

IP-38000 Codman 3000 series straight silicone rubber catheter (radiopaque) with connector.

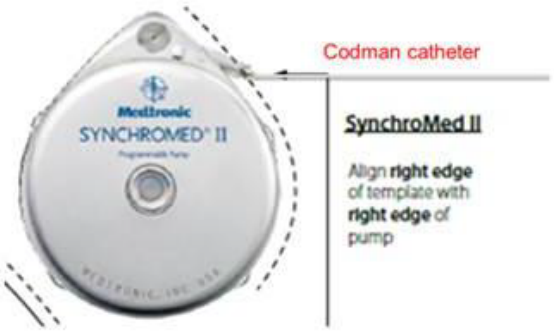
Length= 51.7 cm. Volume= 0.003 mL/cm.

14.2.2.2 Source

The Codman 3000 Infusion Pump Catheter will be purchased from Intera Oncology, Inc.

14.2.3 Pump and Catheter Connection/Combination

The Medtronic pump catheter will be sharply cut, and the metal Codman connector will be used to splice the Codman catheter to the Medtronic catheter. This connector and splicing technique has been used extensively (> 20 years) at MSKCC with the previous Medtronic pumps. Two ties will be used to ensure the splicing technique is durable (see below).



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16 APPENDICES

16.1 APPENDIX A – PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

16.2 APPENDIX B – PATIENT CONTACT SHEET

Note: The full, printable patient contact sheet is located on the next page.

NATIONAL CANCER INSTITUTE
Center for Cancer Research

Important Phone Numbers: Chain of command
Emergency: call the NIH page operator, 301-496-1211 and ask to have the Surgical Oncology Fellow paged.
Nurse Practitioner: Cathleen Hannah, 240-858-7006, **cathleen.hannah@nih.gov**
Physician Assistant: Stacy Joyce, 240-858-3868, **stacy.joyce@nih.gov**
Doctor: Dr. Jonathan Hernandez, 240-760-6072, **jonathan.hernandez@nih.gov**
Research Nurse: Kate Smith, 240-858-3531, **kathleen.smith3@nih.gov**
Patient Care Coordinator: Rosie Melendez, 240-910-1398, **rosie.melendez@nih.gov**

Call the office if you have:

- A fever of 100.4 ^{0}F (38.0 ^{0}C) or higher, shaking, or chills. Use an oral thermometer to take your temperature.
- Any other possible signs of infection, such as sore throat, cough, cold, flu, burning with urination, or rash.
- Pump malfunction (Implanted Medtronic Pump) – call the team first (numbers above) if unavailable call the Medtronic number listed on the back of your ID card.
- Pump malfunction (Chemotherapy pump) – call the team first (numbers above) if unavailable call 3 SES Day Hospital (Mon-Fri 8:00 AM – 8:00 PM, Sat-Sun 8:00 AM – 6:30 PM) at 301-451-1152. If the Day Hospital is closed, please call 3 SEN at 301-451-1101.
- Any signs of bleeding.
- New swelling of your arms or legs.
- Mouth sores or pain in your mouth that make it hard to swallow food or liquids.
- Nausea or vomiting that does not get better with medication.
- 3 or more watery bowel movements a day, not controlled by anti-diarrheal medicine.
- No bowel movement in 2 days.
- Any new pain, increasing pain, or chest pain.
- Any other concerns you might have.

Caring for yourself:

- Please discuss with us in advance if you need a dental cleaning or dental work.
- Do not use rectal suppositories, rectal thermometers, and enemas unless directed.
- When in the sun, wear SPF 30 or higher on all exposed skin surfaces and reapply frequently.
- Use birth control while on chemotherapy to avoid pregnancy. If you have questions, ask your MD/RN.
- Please try not to make any other appointments on the day of your treatment. We care for many patients and sometimes have emergencies, so although we make every effort to be on time, we may be delayed.

Medications:

- Keep a list of all medication you are taking, even over-the-counter medications. Please tell us of any changes. You will need to update your medication list at each visit.
- Do not take aspirin or medications that have aspirin in them unless specifically prescribed by your doctor.
- Do not take vitamins or herbs without talking with your doctor. You may take a regular daily multivitamin.
- Please do not wait until your medications has run out to request a refill. Your prescriptions can be refilled and you can pick them up the Outpatient Pharmacy located on the 1st floor. 1-888-465-8208

Forms:

- Please allow 5-10 business days for completion of any disability, medical leave, and health insurance forms or letters from the doctor.

16.3 APPENDIX C – PATIENT & CAREGIVER EDUCATION: YOUR IMPLANTED LIVER INFUSION PUMP

Note: The full, printable patient & caregiver education pamphlet is located on the next 4 pages.

PATIENT & CAREGIVER EDUCATION:

ABOUT YOUR IMPLANTED LIVER INFUSION PUMP:

This information describes your implanted liver infusion pump (Medtronic Synchromed II Programmable Pump®), including how it is placed, how it works, and how it is refilled.

You will get your medication through the pump that is implanted in your abdomen with the catheter inserted into your hepatic artery. This is to make sure that the medication flows directly to your liver. The pump is a small disc-shaped device that is made of titanium metal. It is about 3 inches in diameter, about 1 inch thick, and weighs about 0.40 lbs.

You will have a surgery to implant the pump in your abdomen. It will be connected by a catheter (small, flexible tube) to your hepatic artery. This is the main blood vessel that goes into your liver.

Your doctor/ nurse will give you more information about your surgery and tell you how to prepare.

HOW YOUR PUMP IS IMPLANTED:

Your doctor will give you general anesthesia (medication to make you sleep). Once you are asleep, your doctor will make a pocket in your lower abdomen between the skin and muscle. He will place the pump in this pocket. Your doctor will attach the catheter on the pump to your hepatic artery. (see Figure 1: Placement of pump below).

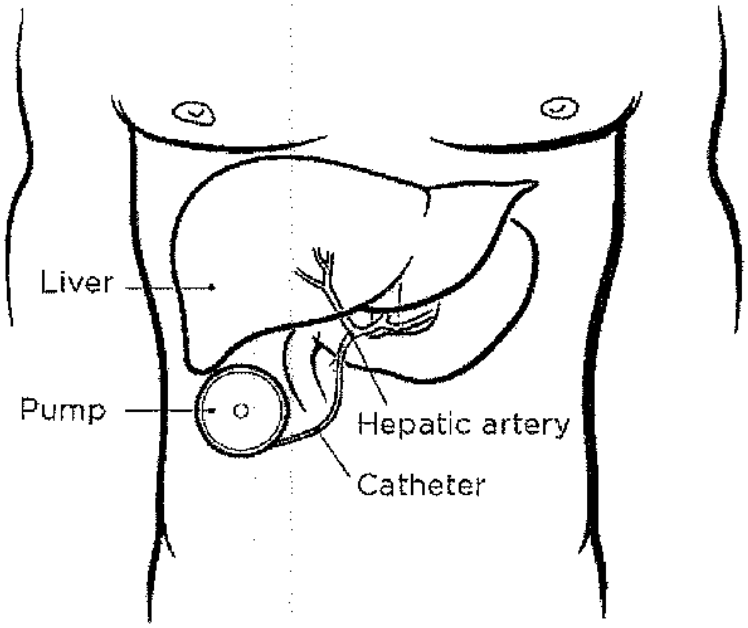


Figure 1: Placement of pump

Your surgery will take 90 minutes to 2 hours. You will then stay in the hospital for 4 or 5 days. Your doctor or nurse practitioner will give you an identification card that says you have an implanted device. **You must always carry this card while you have your pump.**

HOW YOUR PUMP WORKS:

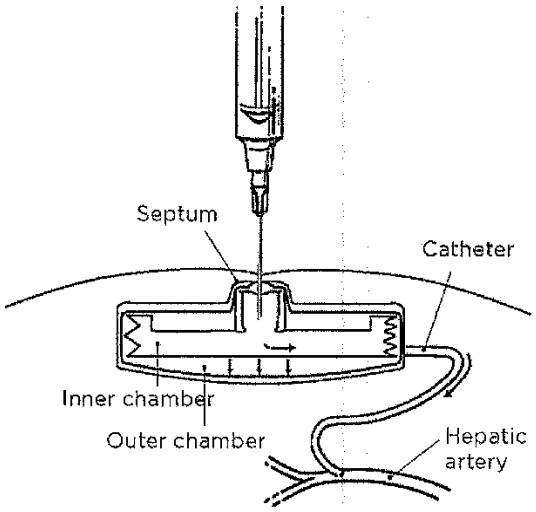


Figure 2: Parts of the pump

HOW MEDICATION IS GIVEN THROUGH YOUR PUMP:

Before you begin using your pump, you will have a procedure called a flow scan to make sure your pump is working properly. The test will be done in Nuclear Medicine located in the Radiology department on the 1st floor.

After your flow scan, your MD/NP will fill your pump with medication through a raised area in the center called the septum (see Figure 2: Parts of the pump above). You will be given information about the medication and possible side effects.

Medication can be given by the pump in 2 ways. With both methods, the medication goes straight into the catheter and into your hepatic artery. Most often, the medication is given at a constant rate all day. The other way is with a single, fast injection called a bolus. With the bolus method, the medication is not stored in the inner chamber of the pump.

Your pump will only hold enough medication for 14 days. It must be refilled on the 14th day. When you are not receiving medication, your pump will be filled with glycerol. It is a thick solution that lets you go 6 weeks between pump refills.

Some people may develop stomach ulcers during treatment with the pump. You will be given antiulcer medication during treatment to help prevent this.

HOW IS YOUR PUMP IS REFILLED:

The MD/NP will clean your skin at the pump site and insert a needle into the septum. You may experience discomfort from the prick of the needle.

If any medication is still in your pump, it will be removed with a syringe and measured (see Figure 3: Taking medication out of the pump below). You will not experience any discomfort while the medication is being taken out of the pump.

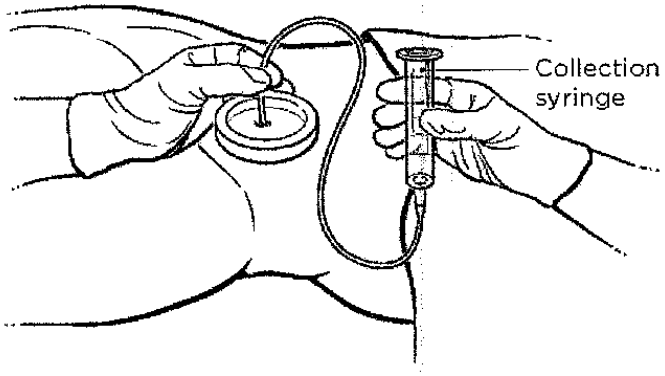


Figure 3: Taking medication out of the pump.

The MD/NP will make sure that the catheter is not blocked. He or she will refill your pump with medication through a syringe that is inserted into the inner chamber (see Figure 4: Refilling the pump with medication below). You will not experience any discomfort while the medication is being refilled.

The procedure to refill your pump will take 10 to 15 minutes.

It is very important that you keep all your refill appointments. Your pump can run dry if it is not refilled regularly. If that happens, it could become clotted and damaged. Call if you cannot keep a refill appointment. Tell your team if you will be out of town at any point while you have your pump.

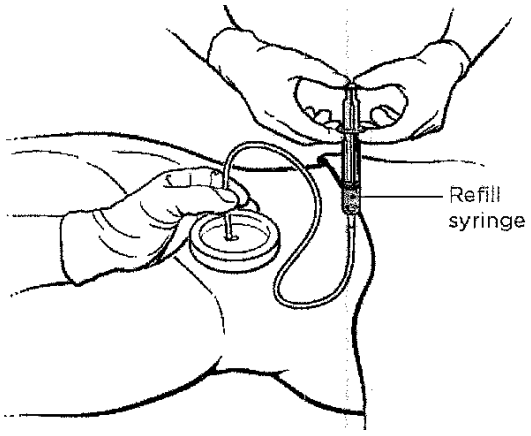


Figure 4: Refilling the pump with medication.

ACTIVITIY:

After you recover from your surgery, you can resume most of your usual activities. However, follow the guidelines:

- Avoid rough physical activity such as contact sports, that can cause injury to your pump site.
- Avoid deep sea or scuba diving. You can swim or snorkel.
- Avoid lifting heavy objects after surgery, until you have been cleared by the doctor.
- Avoid activities that can raise your body temperature because this can make your medication flow faster. Do not:
    - Place heating pads, electric blankets, or hot water bottles directly on your pump site.
    - Take hot baths or showers
    - Go in a sauna or hot tub
    - Overexpose yourself to the sun. if you are planning to be outdoors, make sure you are broad-spectrum sunscreen with an SPF of at least 30.

CALL YOUR DOCTOR OR NURSE IF YOU:

- Have a temperature of 100.4 ^{0}F (38 ^{0}C) or higher.
- Have any signs of infection at your pump site, such as tenderness, drainage, or redness,
- Have swelling over our pump site.
- Cannot keep a scheduled refill appointment.
- Have any unexplained or unusual reactions.
- Have any questions or concerns.

If you have any question or concerns, talk with a member of your team. If you are unable to reach a member of the team, please call the NIH operater at 301-496-1211 and ask for the Surgical Oncology Branch Fellow to be paged.

16.4 APPENDIX D – PATIENT TRAVEL LETTER

Note: The full, printable patient travel letter is located on the next page.

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

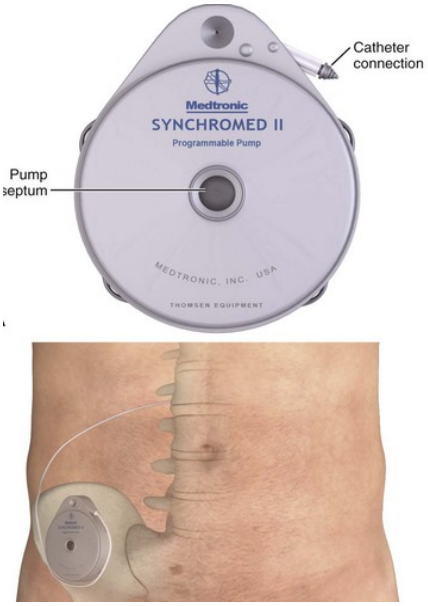
Surgical Oncology Program

To whom it may concern,

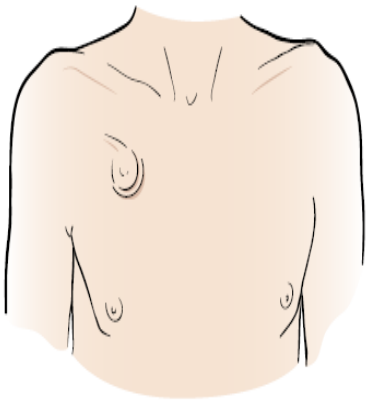
[*Name of patient and DOB*] has an implanted liver infusion pump (Medtronic Synchromed II Programmable Pump®) located in his/her abdomen – under the skin. The pump is a small disc-shaped device that is made of titanium metal. It is about 3 inches in diameter, about 1 inch thick, and weighs about 0.40 lbs. The pump is used to deliver medication to the liver. The pump may be located on the right or left side of the abdomen.

The pump can safely go through the airport metal detector. Be aware the pump may set off the metal detector. It is recommended when approaching theft detectors and security screening devices (such as those found in airports, libraries, and department stores) that the patient not linger near or lean on the security screening device.

In addition to having an implanted liver perfusion pump, the patient may also have a mediport (an implanted port most commonly found in the chest). Most implanted ports in the chest will be the size of a quarter- either circular, oval or triangular. This device allows the healthcare team to give the patient necessary medication intravenously.



Medtronic Synchromed II Programmable Pump



Mediport

Sincerely,

Jonathan Hernandez, MD
Surgical Oncology Program
Center for Cancer Research, National Cancer Institute
National Institutes of Health

16.5 APPENDIX E – FUDR (FLOXURIDINE) – INTRAHEPATIC DRUG FACT SHEET

FUDR (floxuridine) – Intrahepatic

FUDR interferes with an enzyme cancer cells need to live and grow.

HOW IS IT GIVEN?

Slow continuous infusion in to the hepatic (liver) artery via the implanted liver infusion pump.

YOU MAY EXPERIENCE SOME OF THE FOLLOWING SIDE EFFECTS: (usually not before 7 days)

- Heartburn and upset stomach
- Irritation of the liver cells, resulting in generalized body itching, yellow skin or eyes
- Mild nausea and vomiting
- Diarrhea

CALL YOUR DOCTOR IF YOU HAVE:

- Signs or symptoms of hepatitis which include:
  - Yellow skin or eyes (jaundice)
  - Generalized body itching
  - Liver pain
  - Dark / tea-colored urine
  - Light tan stools
- Excessive diarrhea lasting longer than 24 hours
- Abdominal pain, heartburn, or upset stomach
- Any unexpected or unexplained problems
- Any questions/ concerns

SPECIAL POINTS:

- Take your anti-ulcer medications as prescribed.
- Do not take aspirin or products containing aspirin unless instructed by MD.
- It is important to have all blood tests done as ordered on the date ordered.
- Chemotherapy should not remain in the pump for longer than the prescribed amount of time.
- FUDR is given once every 4 weeks, and must be taken out of the pump after 14 days.
- Do NOT consume alcohol.

The information on this sheet is selective and does not cover all possible side effects; others may occur. Please report any problems to your doctor.