Abbreviated Title: IP and IV Paclitaxel for GC
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Title: A Phase II Study of Intraperitoneal and Intravenous Paclitaxel Chemotherapy with Oral Capecitabine for Gastric Adenocarcinoma with Peritoneal Carcinomatosis

NCI Principal Investigator: Jeremy L. Davis, MD
Surgical Oncology Program (SOP), CCR, NCI, NIH
Building 10, Room 4-3760
10 Center Drive
Bethesda, MD 20892
Phone: 240-858-3731
E-mail: jeremy.davis@nih.gov

Investigational Agents: None

Commercial Agents: Paclitaxel (Taxol®), Capecitabine (Xeloda®)

Commercial Device: BardPort Titanium Implanted Port with Peritoneal Catheter

PRÉCIS

Background:

- An estimated 28,000 cases of gastric adenocarcinoma are diagnosed annually in the U.S.
- Peritoneal metastasis is a common finding at diagnosis, making curative surgical resection possible in an estimated 25% of patients.
- Systemic chemotherapy is the recommended treatment for patients with metastatic gastric cancer to the peritoneal cavity, however selective use of cytoreductive surgery and intraperitoneal chemotherapy has been associated with improved overall survival.
- Multiple chemotherapeutic agents and delivery systems have been described for intraperitoneal therapy, but no standard regimen exists.

Objective:

- Determine the progression free survival (PFS) in patients with peritoneal metastases from gastric cancer after repeated intraperitoneal chemotherapeutic infusion (IPC) and systemic paclitaxel administration with concomitant capecitabine therapy.

Eligibility:

- Histologically confirmed adenocarcinoma of the stomach.
- Radiographic evidence of peritoneal carcinomatosis and/or sub-radiographic evidence of peritoneal carcinomatosis found at staging laparoscopy.
- Medically fit for systemic chemotherapy and intraperitoneal chemotherapy.
- Men and women age $\geq$ 18 years.

Design:

- Phase II, nonrandomized, open label study.
- Patients will enroll in two cohorts: those with prior systemic chemotherapy and those who are treatment naïve.
- Patients will undergo staging laparoscopy and placement of peritoneal access port.
- Intraperitoneal paclitaxel (60 mg/m^2 weekly), intravenous paclitaxel (80 mg/m^2 weekly), and capecitabine (825 mg/m^2 twice daily for 14 days of each cycle) for 12 weeks.
- Treatment response will be assessed with imaging and laparoscopy.
- It is expected that 16-20 patients per year for total 4 years will be enrolled. The accrual ceiling is set at 74 patients.

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on 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

- Determine the progression free survival (PFS) in patients with peritoneal metastases from gastric cancer after repeated intraperitoneal chemotherapeutic infusion (IPC) and systemic paclitaxel administration with concomitant capecitabine therapy.

1.1.2 Secondary Objectives

- Determine intra-peritoneal progression free survival (iPFS).
- Determine distant (extra-peritoneal) disease free survival.
- Determine the frequency of objective histopathologic response to therapy.
- Describe the morbidity of this treatment strategy.
- Determine overall survival.

1.1.3 Exploratory Objectives

- Evaluate the impact of repeated intraperitoneal chemotherapeutic infusion (IPC) and systemic paclitaxel administration with concomitant capecitabine therapy on circulating tumor cells and immune subsets.
- Determine the pharmacokinetics of repeated intraperitoneal chemotherapeutic infusion (IPC) and systemic paclitaxel administration with concomitant capecitabine therapy in patients with peritoneal metastases from gastric cancer.
- Evaluate the genomic DNA and genotype in patients with peritoneal metastases from gastric cancer in order to determine the most relevant drug metabolizing enzymes and transporters (DMET) through pharmacogenetic analyses.
- Define the risk of developing peritoneal metastasis in gastric cancer, and other associated cancers, through genotype/phenotype correlations.

- Determine the molecular changes and mechanisms of tumor initiation, invasion and metastasis in gastric cancers with peritoneal metastasis.
- Evaluate chemotherapeutic and immunotherapeutic agent effects of systemic paclitaxel administration with concomitant capecitabine therapy in patients with peritoneal metastases from gastric cancer using a novel ex-vivo platform, the SMART System.

1.2 BACKGROUND AND RATIONALE

1.2.1 Study Disease

Worldwide, gastric cancer remains a global health concern given the nearly 1 million new diagnoses made annually. Of those diagnosed, three quarters of patients will die of their disease making gastric cancer the third most common cause of cancer-related death.[1] Survival at 5-years remains a dismal 33%, with a median survival of approximately 12 months for patients with stage IV disease.[2, 3] While systemic chemotherapy can extend survival for patients, only surgical resection offers the chance for cure. Unfortunately, only 25% of newly diagnosed patients with gastric cancer are eligible for resection due to metastatic disease at presentation.[4]

A major barrier to successful surgery in gastric cancer is its propensity for peritoneal metastasis. Metastases range from microscopic (i.e., positive cytology) to overt tumor nodules and omental caking. Moreover, diagnosis of peritoneal carcinomatosis is challenging as non-invasive modes of identification are insensitive. As such, laparoscopic staging is recommended for newly diagnosed patients without radiographic evidence of metastases. In addition to visual inspection at laparoscopy, in nearly 20% of cases, peritoneal washings with cytopathologic examination will identify microscopic peritoneal disease.[5] Thus, the addition of staging laparoscopy and peritoneal cytology can prevent non-curative laparotomy in 23-31% of patients considered surgically resectable due to no radiographic evidence of metastasis.[6, 7]

To address the unique problem of peritoneal metastasis, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been evaluated in several studies attempting to establish this technique as a treatment strategy for gastric cancer. Unfortunately, the lack of standardization across studies and the failure to reproduce positive results have left the purported benefit of CRS/HIPEC in question.[8] In studies where a survival advantage has been shown, it was primarily in patients with low disease burden and when complete resection could be achieved.[9] For patients in whom complete macroscopic resection cannot be achieved, systemic chemotherapy remains first-line therapy. Our branch has an open treatment protocol (17C0070; HIPEC for Gastric Cancer) for patients with gastric cancer and limited peritoneal carcinomatosis. Patients with low peritoneal cancer index (PCI $\leq$ 10) who have received a minimum of 3 months of systemic chemotherapy are eligible for treatment with gastrectomy, cytoreduction and HIPEC. As of August 15, 2018, twelve patients have been enrolled and treated. The median PCI at time of study enrollment was 5. Although this low PCI portends a better prognosis, the median time to progression in the 5 of 12 patients with adequate follow-up is 6 months. While this study is ongoing, it highlights the severity of the disease and the urgent need for better therapy. Moreover, less than 50% of patients screened with laparoscopy for that trial (17C0070) have proven eligible based on a PCI greater than 10.

Metastatic gastric cancer is commonly treated systemically with a fluoropyrimidine and platinum chemotherapeutic agents. This combination therapy has a modest median survival benefit of 1.6 months compared to single agent therapy.[4] In patients with good performance status and limited

comorbidities, triple drug regimens that include a taxane have been shown to increase time to progression and overall survival.[10] The first successful targeted therapy of gastric cancer with trastuzumab for HER2-positive tumors conveyed a mere 2.7 month median overall survival advantage in the 20% of patients in which HER2 was overexpressed.[11] [12] Beyond first-line therapy, most second-line options are limited.[13] Although immune checkpoint inhibitors (e.g. anti-PD-L1) show great promise, few patients with peritoneal metastasis are eligible for immunotherapy. Based on the Keynote-059 study of pembrolizumab in patients with advanced gastric cancer, an impressive median overall survival of 20.7 months was demonstrated in patients with PD-L1-positive tumors. The most likely tumors to either express PD-L1 and/or respond to immune checkpoint inhibitors are EBV+ or microsatellite unstable (MSI-hi) tumors. Based on TCGA data in gastric adenocarcinoma, EBV+ and MSI gastric cancers are molecularly distinct from the so-called Genomically Stable (GS) molecular sub-type. Peritoneal metastasis is most likely to occur in the diffuse histologic subtype of gastric cancer, which makes up 70% of the GS molecular sub-group in the TCGA data set. In our own prospective analysis of patients with metastatic gastric adenocarcinoma (17C0044; Molecular Profiling of Gastric Tumors) we have re-capitulated the TCGA findings by showing that gastric adenocarcinomas of the diffuse histologic subtype do not demonstrate PD-L1 positivity or microsatellite instability (MSI-hi, by immunohistochemical analysis) (data not shown).

1.2.2 Rationale for Regional Therapy in Gastric Cancer

With the limited efficacy of systemic chemotherapy and the inconsistent results of cytoreductive surgery, patients with peritoneal carcinomatosis have limited viable treatment options. One potential treatment strategy is normothermic intraperitoneal chemotherapy (without cytoreductive surgery). Intraperitoneal (IP) drug delivery is an effective treatment strategy in certain solid tumors prone to peritoneal carcinomatosis. The rationale for regional chemotherapy to the peritoneal surfaces is to maximize drug delivery to affected sites of disease while increasing the therapeutic window by limiting systemic toxicity. Work performed at NCI and elsewhere has established the pharmacokinetic rationale for IP drug delivery.[14-16] Subsequent clinical studies have established IP chemotherapy as the optimal treatment for patients with ovarian carcinomatosis, primary peritoneal mesothelioma and appendiceal mucinous neoplasms.[17-19]

For intraperitoneal chemotherapy administration, taxanes are ideal agents given their high molecular weight and hydrophobic properties that allow for prolonged intraperitoneal retention.[20] Taxanes are a class of cytotoxic chemotherapeutic agents that induce excessive polymerization of tubulin resulting in dysfunctional microtubules, which leads to mitotic arrest and subsequent cell death.[21] In a review of intraperitoneal pharmacokinetics by Markman, paclitaxel was found to have the highest peak intraperitoneal concentration compared to other commonly used intraperitoneal agents.[22] When compared to cisplatin, the most common chemotherapeutic used for HIPEC, the peak concentration of paclitaxel was 50 times higher.[22] This high intraperitoneal concentration is believed to lead to its direct cytotoxic effects. While concentrations can remain elevated as long as 72 hours after infusion[23], morphologic signs of cellular distress are noted just 6 hours after infusion.[24] Another challenge of intraperitoneal drug delivery is the complex network of microvasculature that supplies tumors. It is hypothesized that increased blood supply enhances metabolic features of these cells and leads to increased proliferation and further metastatic spread.[25] This vast microvascular network is also hypothesized to contribute to the ineffectiveness of intravenous chemotherapeutics. The purported mechanism for systemic therapy resistance is leakage of chemotherapeutic agents from the

vasculature of the tumor into the free peritoneal space.[25] *In vitro* experiments using human gastric cancer nodules have demonstrated that intraperitoneal paclitaxel was found to result in injury or collapse of tumor micro vessels. This angiogenic inhibition results in a layer of hypoxic cell death surrounding a far less metabolically active central tumor.[25] We hypothesize that the coadministration of systemic chemotherapy can have an additive effect given the microvascular destruction and decreased likelihood of intraperitoneal leakage.

Depth of tumor penetration by taxanes after a single dose is limited. The two most commonly used taxanes, paclitaxel and docetaxel, have been directly compared *in vitro*. In a study by Kyle et al, paclitaxel tumor invasion was found to be twice that of docetaxel but the majority of drug accumulated in the first 100 µm of tumor.[26] In order to augment the limited penetration of a single dose, the utilization of peritoneal catheters has been employed for repeated dosing. In early Phase I studies, the pharmacokinetic analysis and safety profile of paclitaxel has been established. Kodera et al, established a recommended dose of 60 mg/m^2 with minimal toxicity when intraperitoneal paclitaxel was given as a single agent. At this dose level, drug half-life ranged from 17.4-65.3 hours.[27] Although peak intraperitoneal concentration was 7000 times higher than that of the plasma[28], some systemic absorption was expected. Another Phase I study of combined intravenous and intraperitoneal paclitaxel established a recommended dose of 20 mg/m^2.[29] Despite a one-third dose reduction of the intraperitoneal paclitaxel, the authors were able to demonstrate consistently high peak peritoneal concentration at both 48 and 72 hours after administration.[29]

Clinical studies using intraperitoneal taxanes have shown good patient tolerance and limited systemic adverse events, even with concomitant intravenous administration (**Table 1**).[23, 27-31] In Phase I studies, anemia was the most common toxicity although the majority of these were Grade 2.[29] In that same Phase I study, of the six patients that received 20 mg/m^2, no Grade 5 toxicity was seen and leukopenia and neutropenia were the only Grade 3 or 4 toxicities.[29] In a subsequent Phase II study of 40 patients receiving both intraperitoneal and intravenous paclitaxel, the rate of Grade 3 and 4 adverse events were 40% and 15% respectively.[23] The most common adverse events were neutropenia (38%), leukopenia (18%) and anemia (10%).[23] Notably no patients experienced adverse effects related to intraperitoneal infusion such as abdominal pain or cramping.[23]

Table 1: Summary of Previous Intraperitoneal and Intravenous Paclitaxel Administration in Gastric Cancer

Author	Trial Design	Intervention	Recommended Dose	Accrual	Toxicity	Treatment Response	Survival
Ishigami, H. et al (2009)	Phase 1	PAX (IP/IV) S-1 (PO)	PAX IV 50mg/m^2 PAX IP 20mg/m^2 S-1 PO 80mg/m^2/day	n = 9 patients	Dose level 1 - n= 4 grade 3/4 (leukopenia/neutropenia) Dose level 2 - n = 4 grade 3 (leukopenia/neutropenia/diarrhea)	6/7 patients converted to negative cytology	N/A
Kurita, N. et al (2011)	Phase 1	PAX (IP) S-1 (PO) Gastrectomy	PAX IP 40mg/m^2 S-1 PO 80mg-100mg/day	n = 18 patients	Dose level 2 - n=1 grade 3 (leukopenia) Dose level 5 - n=2 grade 3 (leukopenia)	2/18 patients converted to negative cytology, 2/18 PR, 15/18 SD	Median OS 11mo
Ishigami, H. et al (2009)	Phase II	PAX (IV/IP) S-1 (PO)	PAX IV 50mg/m^2 PAX IP 20mg/m^2 S-1 PO 80mg/m^2	n = 40 patients	Grade 3/4 - leukopenia (18%), neutropenia (38%), anemia (10%), Anorexia (5%), N/V (8%), diarrhea (3%)	24/40 patients converted to negative cytology, 10/40 PR, 6/40 SD	1-yr OS 78%, Median OS 22.5mo
Imano, M et al (2012)	Phase II	PAX (IP) One Dose PAX (IV) S-1 (PO)	PAX IV 80mg/m^2 PAX IP 80mg/m^2 S-1 PO 80mg/m^2/day	n = 35 patients	Grade 3/4 - anemia (5.7%), leukopenia (8.6%), neutropenia (22.8%), ALT elevation (5.7%)	15/22 reduction in gastric wall thickening 1/8 Target Lesion CR 1/7 Target Lesion PR	1yr OS 68.6%, Median OS 21.3mo
Yamaguchi, H et al (2013)	Phase II	PAX (IP/IV) S-1 (PO)	PAX IV 50mg/m^2 PAX IP 20mg/m^2 S-1 PO 80mg/m^2	n = 35 patients	Grade 3/4 - neutropenia (34%), leukopenia (23%), anemia (9%)	5/7 Target Lesion OR 28/35 converted to negative cytology	1yr OS 77.1%, 2yr OS 44.8%, Media OS 17.6mo

Intraperitoneal administration of paclitaxel has shown promising results in Phase I and II studies. When repeated intraperitoneal paclitaxel infusion was added to approved systemic chemotherapy regimens, tumor response rates greater than 50% were observed with associated median survival times of 22.6 and 17.6 months.[23, 31] Specifically, a Phase II study by Yamaguchi and colleagues evaluated IP paclitaxel combined with IV paclitaxel and oral S-1 chemotherapy in patients with macroscopic peritoneal metastases in patients with gastric cancer.[31] S-1 is a combination of three compounds (tegafur, gimeracil, oteracil potassium) developed as a replacement for infusional 5-FU therapy. In that study, 35 patients were enrolled and evaluated for survival endpoints. The 1-year survival was 77%, which compared favorably to approximately 50% 1-year survival in historical controls treated with systemic therapy alone. Moreover, in patients with measurable intraperitoneal disease, the objective response rate was 71% and positive peritoneal cytology resolved to negative in 97% (28 of 29) of patients. Although Yamaguchi et al. demonstrated safety and efficacy of IP and IV paclitaxel along with S-1, this oral 5-FU prodrug is not available in the United States. S-1 is combined with cisplatin and is standard systemic therapy for advanced gastric cancer in Japan. Similarly, 5-FU is combined with multiple cytotoxic chemotherapy agents for treatment of patients with gastric adenocarcinoma in the U.S. and other European nations.

Importantly, investigators have observed that patients whose tumors do not respond to intraperitoneal chemotherapy do not appear to benefit from cytoreductive surgery. Therefore, we propose using IP paclitaxel to aid in the identification of patients who may benefit from this treatment strategy of regional and systemic therapy.

1.2.3 Drivers of Peritoneal Metastasis in Gastric Cancer

Gastric adenocarcinoma is a heterogeneous disease with various environmental and genetic predisposing factors. Comprehensive molecular analyses published in recent years have provided additional insight into distinct sub-classifications of gastric cancer based on unique molecular alterations.[32, 33] These studies have revealed novel correlations of molecular subtypes with distinct tumor phenotypes and clinical outcomes.[33] Peritoneal carcinomatosis is a particularly morbid and common feature of gastric adenocarcinomas. The association between diffuse-type tumor histology and increased rates of carcinomatosis is well-documented.[34] Somatic gene alterations that impair E-cadherin protein expression are also a recurring feature of sporadic diffuse-type gastric cancers.[35] Germline mutation in CDH1, the gene that encodes the cell-cell adhesion protein E-cadherin, results in a heritable form of diffuse-type gastric cancer that may aid our understanding of sporadic disease.[36] Even though disruption of cell-cell adhesion is cited as an initiating event in this histologic subtype, true drivers of tumor invasion and peritoneal metastasis have not been characterized.[37, 38] Better understanding of molecular alterations associated with unique patterns of metastasis may uncover key drivers of distinct malignant phenotypes.[39]

Translational and basic science research efforts have been established in our branch to investigate drivers of peritoneal metastasis in gastric adenocarcinoma. Clinical protocols incorporating both sporadic and hereditary diffuse gastric cancers (HDGC) are being conducted in parallel to strengthen the search for key drivers of peritoneal metastasis. Patients who undergo risk-reducing total gastrectomy for HDGC and those enrolled on the gastrectomy and HIPEC trial are providing a unique opportunity for in-depth analysis of molecular changes associated with gastric cancer initiation, invasion and metastasis.

The current protocol is designed to address the challenges outlined above by evaluating a strategy for treating gastric cancers with peritoneal metastasis. Our aim is to investigate the use of intraperitoneal paclitaxel chemotherapy as an adjunct to systemic therapy for gastric cancer with peritoneal carcinomatosis. We hypothesize that the combination of systemic and regional therapy will result in disease control and improved intraperitoneal progression free survival. If so, this strategy could serve as a platform for adding novel anti-cancer agents for the treatment of this deadly disease.

1.2.4 Simulated Metastasis Assay with Relevant Tissue (SMART) Chamber

In the Surgical Oncology Program laboratory of Dr. Jonathan Hernandez, a novel tumor modeling system is being developed, referred to as the 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 will be added to this study, utilizing the SMART Chamber. 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.

1.2.5 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**ample **M**icroenvironment of **R**esected **M**etastatic **T**umor) 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 1**). Circulating oxygenated perfusate within the system is comprised of human plasma (from the patient), DMEM media, antibiotics, insulin (slow infusion).

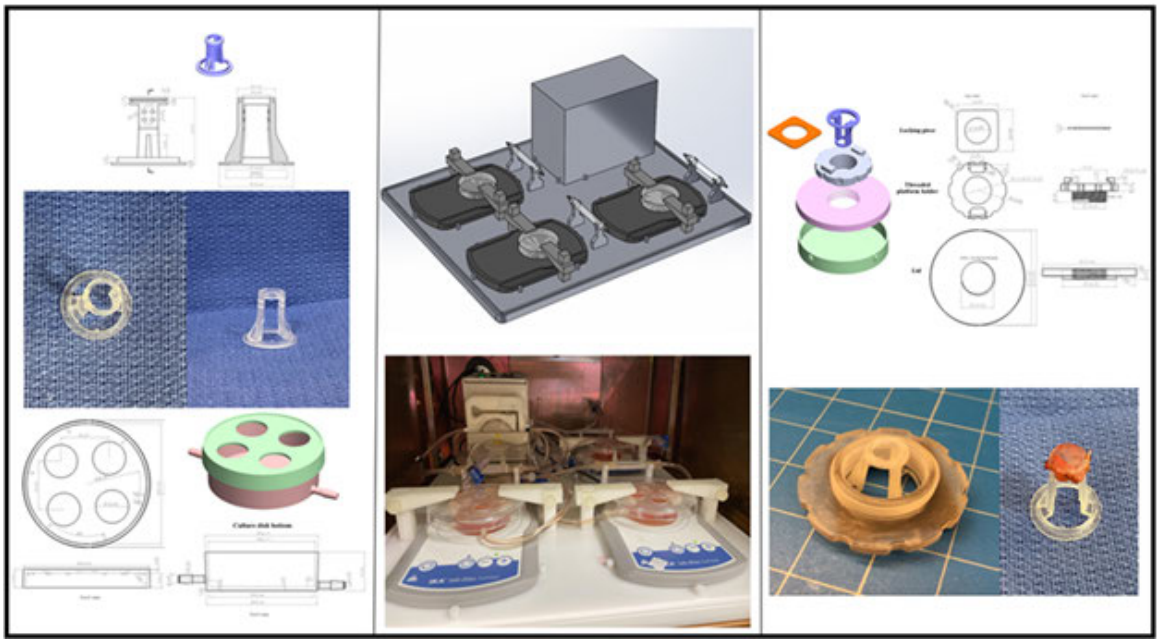


Figure 1: The SMART System Consisting of SMART Platform.

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 2A**). 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 2B**). These results ultimately demonstrate that tumor nodules in their native, functional microenvironment can be preserved *ex vivo* for 4 days with fidelity.

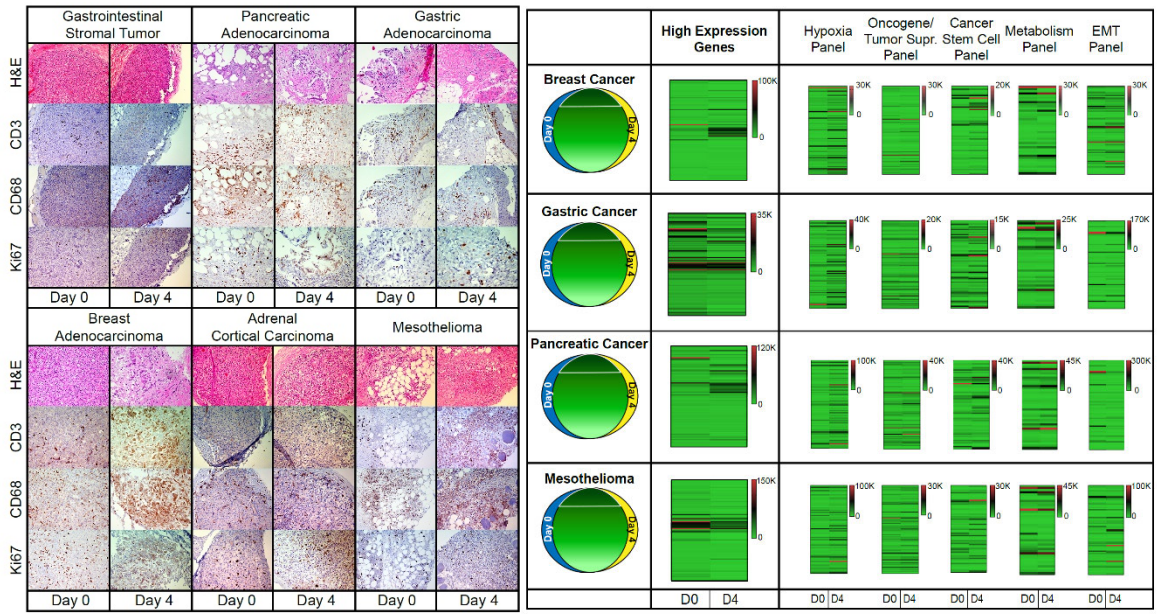


Figure 2: Ex Vivo Normal and Tumor Preservation in the SMART System.

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 3**). Such responses at the cellular level are key to understanding why some cells respond to the immune system while others are ostensibly resistant.

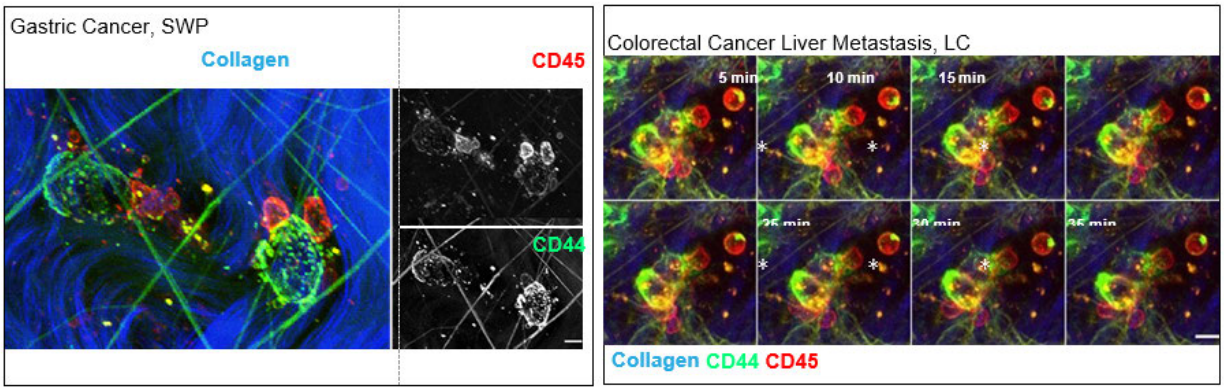


Figure 3: SMART Platforms are Valuable Tools for Drug Evaluations Such as Pembrolizumab.

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.

1.2.6 Rationale for Intraperitoneal Paclitaxel Dose Increase

The primary objective of this study (19C0129) is to determine the progression free survival (PFS) in patients with peritoneal metastases from gastric cancer after repeated intraperitoneal (IP) infusion and systemic paclitaxel administration with concomitant capecitabine therapy. The first patient treated on study was on 07/14/2020. Since that time 4 patients have received IP and IV paclitaxel on study. Based on an IP paclitaxel dose of 20 mg/m^2, the average dose administered to our patients is 34.5 mg (range 31-38.4 mg). We selected this IP paclitaxel dose based on existing clinical trial data in patients with gastric cancer suggesting both safety and potential efficacy for treating carcinomatosis. We have observed no treatment-related deaths and no toxicity attributed directly to the IP paclitaxel dosing. Of the 4 patients, as of 03/09/2021, three patients are now off-treatment and one is currently undergoing a second course of therapy without any serious adverse events.

Objective responses have been mixed with 2 patients exhibiting stable disease after 2 courses of treatment; 1 patient experienced rapid progression of disease during the first course of treatment; and 1 patient has stable disease after 1 course of treatment. One of the patients with stable disease after 2 courses of treatment was subsequently enrolled and successfully treated on our Phase II study of gastrectomy and hyperthermic intraperitoneal chemotherapy (17C0070).

Because an IP paclitaxel dose of 20 mg/m^2 appears both safe and tolerable in our current study we wish to increase the IP dose of paclitaxel to 60 mg/m^2 (see Section **3.2.2**). The aim of this dose modification is to increase the likelihood of objective intraperitoneal tumor response to therapy.

The data supporting the use of 60 mg/m^2 dosing of IP paclitaxel comes from both the gastric cancer and ovarian cancer literature. The seminal study by Armstrong et al. [18] utilized both IP cisplatin (100 mg/m^2) and paclitaxel (60 mg/m^2) added to intravenous paclitaxel for treatment of patients with stage III ovarian carcinoma. Notably, the most common reason for discontinuation of IP chemotherapy was catheter-related complications. Although direct comparison of that study to 19C0129 cannot be made, the fact that 60 mg/m^2 of IP paclitaxel combined with IP cisplatin was safe, tolerable, and effective in the context of concomitant intravenous paclitaxel suggests that an IP paclitaxel dose of 60 mg/m^2 would be safe and tolerable in our gastric cancer patients, also.

One could argue whether we should use an even higher dose of IP paclitaxel to achieve greater objective tumor response in our study. To that point, early studies in ovarian cancer showed a maximum tolerated dose (MTD) for IP paclitaxel given every 4 weeks was 150 mg/m^2 [40]. That dose level has been associated with chemical peritonitis [41]. However, subsequent studies in ovarian cancer patients using 75 mg/m^2 showed safety and minimal toxicity, which was most often attributed to abdominal discomfort and nausea [42]. Similarly, a study by Imano et al. [28] in patients with advanced gastric cancer used an 80 mg/m^2 dose of IP paclitaxel that was well-tolerated when combined with intravenous paclitaxel and oral S-1.

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 gastric adenocarcinoma, including Siewert III gastroesophageal junction adenocarcinoma, confirmed by the NCI Laboratory of Pathology, and have provided a block or unstained slides of primary or metastatic tumor tissue or newly obtained fresh biopsy of a tumor lesion in case archival tissue sample is not available.

2.1.1.2 Patients may be treatment naïve or have received systemic chemotherapy prior to enrollment:

- Trastuzumab allowed as prior treatment for HER2/neu over-expressing cancers as clinically indicated.
- Last dose of chemotherapy at least 2 weeks prior to enrollment with recovery to Grade 1 from chemotherapy-related toxicities.

2.1.1.3 Radiographic evidence of peritoneal carcinomatosis and/or sub-radiographic evidence of peritoneal carcinomatosis found at staging laparoscopy.

2.1.1.4 Age ≥18 years. Children under the age of 18 will not participate in this study as gastric cancer is rare in this population.

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

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

– hemoglobin	≥ 8.0 g/dL
– absolute neutrophil count	≥ 1,000/mcL
– platelets	≥ 100,000/mcL
– total bilirubin	≤ 1.5 X institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional upper limit of normal
– creatinine	< 1.5 mg/dl OR
– creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

2.1.1.7 Physiologically able to undergo laparoscopy and systemic chemotherapy.

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

2.1.1.9 Previous exploratory laparotomy or laparoscopy with tissue biopsy or peritoneal lavage is permitted.

2.1.1.10 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study treatment. 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.

2.1.1.11 Patients must be co-enrolled in protocol 13C0176 (NCT01915225) and 17C0044 (NCT03027427) for sample collection.

2.1.1.12 HIV-positive patients may be considered for this study only after consultation with a NIAID physician.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents.

2.1.2.2 Previous cytoreductive surgery or intraperitoneal chemotherapy.

2.1.2.3 Disseminated extra-peritoneal or solid organ metastases:

- Excludes greater omentum and ovarian metastases.
- Radiographic signs or clinical symptoms consistent with malignant bowel obstruction.

2.1.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Paclitaxel or Capecitabine or other agents used in study.

2.1.2.5 Previous treatment with paclitaxel or nab-paclitaxel resulting in progression of disease.

2.1.2.6 Existing peripheral neuropathy, Grade 3 or greater.

2.1.2.7 Past medical history of dihydropyrimidine dehydrogenase deficiency.

2.1.2.8 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.

2.1.2.9 Pregnant women are excluded because paclitaxel and capecitabine can cause fetal harm when administered to pregnant women. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with paclitaxel and capecitabine, breastfeeding should be discontinued if the mother is treated with paclitaxel and capecitabine.

2.1.3 Recruitment Strategies

Both men and women from all races and ethnic groups are eligible for this trial.

This protocol 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 as well as referrals at NIH.

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:

- Communications with prospective subjects, via email or phone conversations

- 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

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

The following screening activities will be performed only after the subject has signed the study consent OR the consent for study 17C0044 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility per PI discretion, once a patient has signed the consent.

Unless otherwise indicated evaluations may be performed at any time prior to enrollment.

- Cytologic or Histopathologic Confirmation of the Disease (at Any Time Point Prior to Initiation of Study Therapy)

  A block or unstained slides of primary or metastatic tumor tissue will be required from each participant to confirm diagnosis with analysis being performed by the Laboratory of Pathology, NIH. In cases where archival tissue sample is not available, a fresh biopsy will be done.

- History and Physical Evaluation
  - Complete history and physical examination (including vital signs, height and weight as well as ECOG assessment, EKG and review of systemic treatment records).
  - Dietary assessment by a Registered Dietitian.
  - Concurrent medication reconciliation.
  - Consultation with NIAID physician in HIV positive subjects.

- Laboratory Evaluation, within 8 weeks prior to initiation of study therapy
  - General Labs:
    - CBC with differential
    - Acute care panel: Sodium (Na), Potassium (K), Chloride (Cl), total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN)
    - Mineral panel: Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Albumin
    - Hepatic panel: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin
    - Total Protein, total CK
    - PT/PTT & INR
  - HIV test, Hepatitis B surface antigen and Hepatitis C antibody.
  - Nutrition Labs: C-reactive protein, Hg A1c, Ferritin, Prealbumin, Thiamine, Iron and transferrin panel, Vitamin B12, Methylmalonic acid, Zinc, 25-hydroxy Vitamin D, folate, lipid panel (Cholesterol (total), LDL, HDL and Triglycerides).

- Urinalysis.
- Tumor markers: CEA, CA 19-9, CA 15-3, CA 125, CA 27-29.
- β- HCG test (serum) for women of child-bearing potential (within 3 days from study enrollment).

- CT Scan with or without PET (with or without standard oral/IV contrast), within 4 weeks prior to initiation of study therapy

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://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

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 or entered in the study. 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

Cohorts

Number	Name	Description
1	Cohort A	Patients with confirmed diagnosis of gastric adenocarcinoma or gastroesophageal junction (Siewert I-III) adenocarcinoma who have received prior systemic chemotherapy.
2	Cohort B	Patients with confirmed diagnosis of gastric adenocarcinoma or gastroesophageal junction (Siewert I-III) adenocarcinoma who are treatment naïve.

Arms

Number	Name	Description
1	Arm 1	IP and IV paclitaxel administration with concomitant oral capecitabine.

Arm Assignment

Patients in Cohort A and B will be directly assigned to Arm 1.

2.4 BASELINE EVALUATION

Tests done at screening do not need to be repeated on baseline (C1D1) if performed within 4 weeks prior to initiation of study therapy except:

- Physical exam (including vital signs and ECOG assessment)
- Laboratory Evaluations
    - CBC with differential
    - Chem 20 equivalent
    - Serum pregnancy test (repeat if > 3 days) for women of child-bearing potential.

Please refer to Section **2.2** for screening evaluation details.

Patients will also undergo:

- Initial laparoscopy.
- CT Scan with or without PET (with or without standard oral/IV contrast)
- Evaluation of extent of peritoneal carcinomatosis by method of peritoneal cancer index (PCI).
- Placement of peritoneal chemo-infusion port.
- Endoscopy with biopsy (esophagogastroduodenoscopy, EGD) if indicated.
- Research Correlatives:
    - Blood, peritoneal ascites (or peritoneal washing) and tissue sample collection as indicated in Section **5**.
    - QOL Questionnaire (see Section **3.6.6**).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a Phase II trial designed to determine the efficacy of intraperitoneal paclitaxel in combination with intravenous paclitaxel and oral capecitabine in patients with gastric cancer and intraperitoneal metastasis.

After placing the peritoneal chemo infusion port Days 1 to 3, as dictated by clinical status, patients will begin intraperitoneal paclitaxel and intravenous paclitaxel (Day 1) followed by oral capecitabine on the evening of Day 1 to the morning of Day 15, followed by a 7-day treatment free interval, in each 3-week cycle. One course will comprise 3 treatment cycles (3 weeks each; total 9 weeks). There will be a total of two courses for patients with an objective response or stable disease.

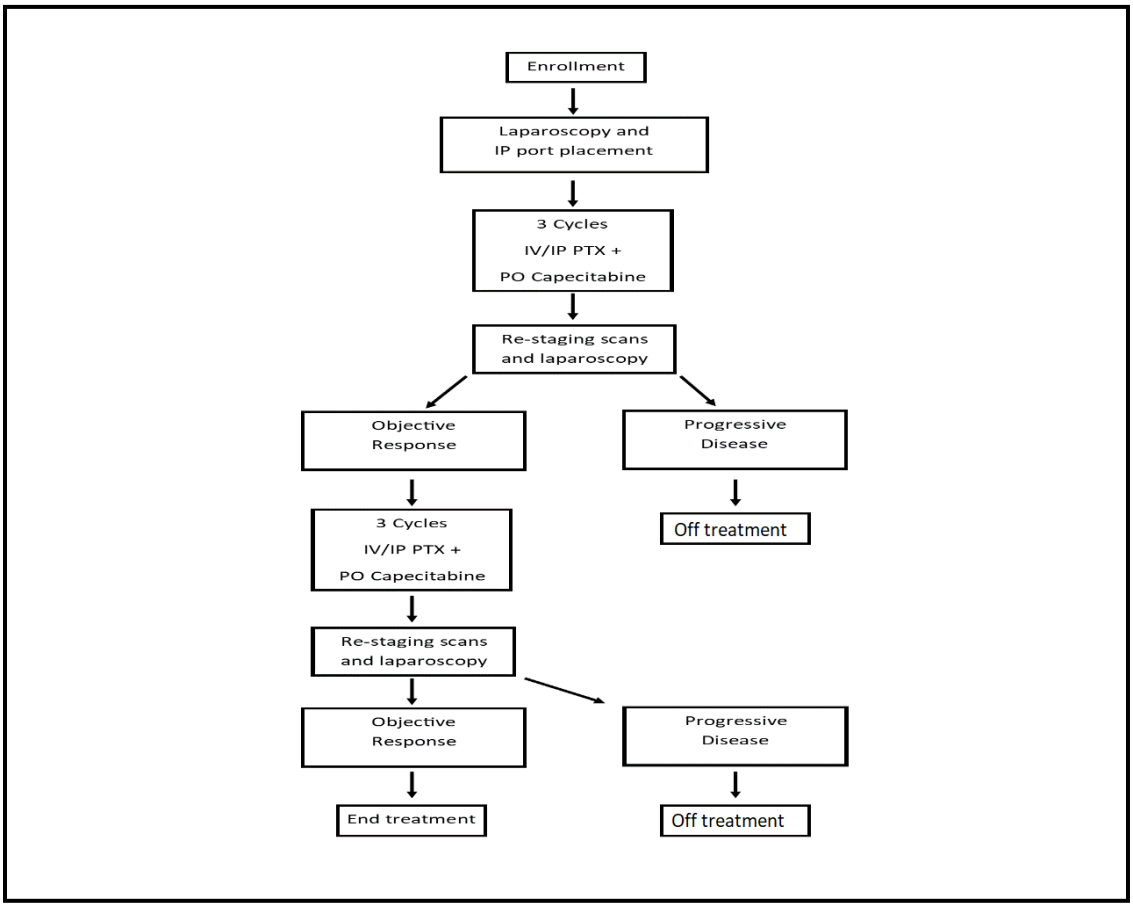
Treatment evaluation will take place after 3 cycles of treatment are completed (+/- 7 days) with repeat staging studies and laparoscopy to assess for treatment response. Patients with progressive disease will be taken off study treatment and will be followed for survival. Patients with an objective response or stable disease will continue to a second course of treatment. After a second course of treatment (+\- 7 days), patients will have repeat staging studies and laparoscopy to assess for treatment response. Patients with objective response will receive no further study-related treatment after the second course but will remain on study for determination of secondary endpoints.

In cases when a patient has an exceptional response to this treatment strategy, two treatment options will be discussed in a multi-disciplinary gastrointestinal malignancy meeting and discussed with the patient. First, continued treatment with IP and IV paclitaxel with oral capecitabine may be considered. The rationale is that the intervention is potentially effective and that stopping the therapy may not be desirable. These patients who choose continued treatment will not be evaluated for primary endpoint analysis.

Second, and in the setting of exceptional response with residual peritoneal disease (PCI $\leq$ 10), cytoreductive surgery with hyperthermic intraperitoneal chemotherapy may be considered an alternate treatment option. This surgery would be done off protocol under a generic standard of care protocol within CCR. Patients would stay on this study to be followed for survival.

Lastly, patients may elect to stop therapy per protocol and initiate observation without active treatment.

The IP port and catheter will be removed at the time of study completion, or earlier if needed (such as surgical extraction due to port complications or patient withdrawal from the study) except in circumstances of death, lost to follow-up, and in cases in which patients may not be able to return to NIH if they progress on study (and consequently the port and catheter may remain in place).



3.1.1 Chemotherapy Schema

Study Course														
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Week 1	*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 3	✓													
Week 4	*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 6	✓													
Week 7	*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 8	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 9	✓	× (Within Day 1 to Day 7)												
IP/IV Paclitaxel * PO Capecitabine ✓ Treatment Evaluation ×														

3.2 DRUG ADMINISTRATION

3.2.1 Intraperitoneal Paclitaxel

Intraperitoneal chemotherapy will be delivered via an implantable subcutaneous-peritoneal port. Body surface area will be calculated at each cycle for each patient.

Patients who are concurrently receiving or requiring any of the agents listed below, which may increase the risk for paclitaxel/capecitabine related toxicities, will have all medications reconciled by a NIH Clinical Center clinical pharmacist.

The following drugs will be discontinued one week prior to administration of paclitaxel:

- Nonsteroidal anti-inflammatory medications
- Aspirin
- Conivaptan
- Cyclosporine
- Disulfiram
- Eliglustat
- Epirubicin
- Febuxostat
- Idelaslisib
- Mitotane
- Nilotinib
- Penicillamine
- Tolvaptan

- Vemurafenib
- Clozapine
- Echinacea

The following drugs may be held, or doses modified, during therapy as indicated by the clinical pharmacist:

- Metronidazole
- Gemfibrozil
- Filgrastim G-CSF
- Platelet inhibitors

3.2.2 Intraperitoneal and Intravenous Paclitaxel Administration

Intraperitoneal paclitaxel (60 mg/m^2) will be diluted in 500 mL of 0.9% NS and warmed to 37^{0}C. The solution will then be infused as rapidly as tolerated once per 3-week cycle on Day 1. The patient will then be instructed to adjust position every 15 minutes for 2 hours.

Intravenous paclitaxel (80 mg/m^2) will be administered concomitantly over 3 hours (+ 1 hour)* diluted in 100 to 250 mL of 0.9% NS once per 3-week cycle on Day 1. Standard intravenous hypersensitivity prophylaxis (dexamethasone 20 mg, diphenhydramine 50 mg and ranitidine 50 mg) will be given at least 30 minutes prior to intravenous paclitaxel. ***Note:** Refer to Section **3.3.1** for dose delays/dose modification guidelines in the event of an adverse event.

IP and IV paclitaxel will be given at the same time. We will ask the Pharmacy to add a brightly colored label that says "**NOT for IV use**" to the IP chemo bag so that Paclitaxel IP and IV doses do not get reversed.

3.2.3 Capecitabine Administration

Patients will receive a 14-day supply of oral capecitabine (825 mg/m^2) to be taken twice a day starting the evening of Day 1 of each cycle. Capecitabine will continue for 28 doses until the morning of Day 15, followed by a 7-day rest period during each 3-week cycle. Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal.

3.2.3.1 CCR Self – Administered Study Drugs Policy Regarding Capecitabine

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice. All oral study drugs will be recorded in the patient diary found in **Appendix C**. This will be used as a memory aide for subjects. The clinical research team will maintain the primary source record. Subjects should be asked to bring the diary as well as unused study agent and empty containers with them to each study visit. If a subject goes off study while at home, the research nurse will ensure and document the return of the unused oral investigational agents from the participant. Unused investigational study agents will be disposed and destroyed per CC Pharmacy SOPs.

3.3 Dose Modifications

Toxicity will be evaluated before each treatment cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

3.3.1 General Guidance for Dose Modification

To Begin the Next Treatment Cycle

- Patients must have platelet count > 100,000/mcL, absolute neutrophil count > 1,000/mcL
- Non-hematologic toxicity covered to < Grade 2 (or tolerable Grade 2 or baseline)

In the event of an adverse event at least possibly related to the investigational agent, the dose of the investigational agent should be adjusted according to the guidelines shown in the dose delays/dose modifications tables shown below (**Table 2** and **Table 3**). If an adverse event is not recovered in such tables, doses may be held at the discretion of the investigator for the subject's safety.

Table 2:

Hematologic Events	Treament Modification
Neutrapenia	
Grade 3	
Associated with fever (>38°C)	First occurrence: Paclitaxel reduction by 25%, Capecitabine continued
	Second occurrence: Paclitaxel discontinued, capecitabine continued
Grade 4	
> 5 Days or associated fever	First occurrence: Paclitaxel reduction by 25%, Capecitabine continued
	Second occurrence: Paclitaxel discontinued, capecitabine continued
Thrombocytopenia	
Grade 4	25% dose reduction after recovery

Table 3:

NCI-CTCE Grade	Treatment Modification
Grade 1 - Mild	
Mild transient reaction; infusion interruption not indicated: intervention not indicated	Treatment continued at the same dose.

Grade 2 - Moderate	
Therapy or infusion interruption indicated but responds promptly to symptomatic treatment	First occurrence: Treatment delay until toxicity has resolved to < Grade 2.
	Second occurrence: Treatment delay until toxicity has resolved to < Grade 2; dose reduction of all agents by 25%.
	Third occurrence: Treatment delay until toxicity has resolved to < Grade 2; dose reduction of all agents by 50%.
	Fourth occurrence: Treatment discontinued.
Grade 3 or Grade 4 - Severe or life threatening	
Grade 3: Prolonged; recurrence of symptoms following initial improvement. hospitalization indicated for clinical sequelae	First occurrence: Treatment delay until toxicity has resolved to < Grade 2; dose reduction of all agents by 25%.
	Second occurrence: Treatment delay until toxicity has resolved to < Grade 2; dose reduction of all agents by 50%.
	Third occurrence: Treatment discontinued.
Grade 4: Life-threatening consequences; urgent intervention indicated	Treatment discontinued.

Note: Subjects will be removed from the study treatment if they fail to recover to CTCAE Grade 0-1, tolerable Grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities), or baseline from a treatment-related adverse event within 42 days.

3.3.2 Treatment Delays and Modification for Administrative Needs

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, and government holidays, etc. Delays of up to 1 week will not be considered protocol deviations and will not be separately reported. A patient that interrupts therapy for more than 3 weeks will be taken off treatment.

3.3.3 Treatment Delays and Modifications for Medical Needs

Patients experiencing complications of their disease or other medical illness not attributable to disease progression, or protocol therapy may also require brief interruptions and delays that will not be considered protocol deviations and will not be separately reported. A patient that interrupts therapy for more than 3 weeks will be taken off treatment.

3.4 SUBCUTANEOUS INFUSION PORT COMPLICATIONS

Patients experiencing complications associated with or related to implanted infusion port including, but not limited to: malfunction, non-function, erosion, infection, leak, or severe pain may require medical treatment (antibiotics, pain medications, etc.) and/or surgical extraction. Surgical re-implantation of a port may be delayed until the cause of removal has been fully addressed. Delays due to port problems may require brief interruptions in treatment. Delays that last ≥ 5 days will be reported as Protocol Deviations. A patient that interrupts therapy for more than 4 weeks (30 days) will be taken off study treatment.

3.5 STUDY CALENDAR

Procedure	Screening	Baseline[1]	Treatment[10] (Course 1)									End Course 1[10]	Safety Visit (30 Days After Last Study Intervention)	Post-Discharge Visits/ Follow-Up (Every 3 Months)[4]	Semi-Annual Follow-Up (Semi-Annually for Years 3-5)[4]	Long-Term Follow-Up (Semi-Annually or Annually after Year 5)[4]
			Cycle 1 (Weeks 1-3)			Cycle 2 (Weeks 4-6)			Cycle 3 (Weeks 7-9)							
			1	2	3	4	5	6	7	8	9[9]					
Confirmation of Pathology	X															
Relevant History and Physical Exam	X	X										X		X	X	X
Height	X															
ECOG Performance Status	X	X	X			X			X			X	X			
Vital Signs and Weight	X	X										X				
Laboratory Tests																
Labs (as listed in Section 2.2 and 2.4)	X	X										X		X	X	X
HepB, HepC Testing	X															
Pregnancy Test (Serum)	X															
EKG	X															
Treatment																
Paclitaxel (IP and IV)[6]			X			X			X							
Capecitabine (PO)[7]			X	X		X	X		X	X						

Procedure	Screening	Baseline[1]	Treatment[10] (Course 1)									End Course 1[10]	Safety Visit (30 Days After	Post-Discharge Visits/	Semi-Annual Follow-	Long-Term Follow-Up (Semi-
Scans and Others																
Staging Laparoscopy and Port Placement		X										X				
CT C/A/P or PET-CT[2]	X	X										X		X	X	X
Concurrent Medications	X	X	X			X			X			X	X			
Dietary Assessment	X											X		X	X	X
Peritoneal Biopsy[8]		X										X				
Endoscopy with Biopsy; EGD[3]	X	X														
QOL Questionnaire (refer to Section 3.6.6)		X										X		X	X	
HIV Testing and Consultation with NIAID Physician in HIV Positive Subjects[3]	X															
NIH Advanced Directives Form[5]	X															
Correlative Studies (Refer to Section 5)																
Research Blood[11]		X			X			X				X				

1 Does not need to be repeated on baseline if test was performed on screening (per Section 2.4).

2 CT and PET may be combined or substituted for one another during post-op discharge visits/follow-up (see Section **3.6.5**).
3 If clinically indicated.
4 Post-Discharge/Follow-Up for patients with an objective response or stable disease will return to the NIH for follow up as indicated in Section **3.6.5.1**; patients with no objective response will be followed for survival as indicated in Section **3.6.5.2**.
5 As indicated in Section **9.3**, all subjects will be offered the opportunity to complete an NIH advanced directive form. This should be done preferably at baseline but can be done at any time during the study as long as the subject's capacity to do so is retained. The completion of the form is strongly recommended but is not required.
6 Please refer to Section **3.2.2** for details**.**
7 Please refer to Section **3.2.3** for details.
8 Mandatory Biopsy will be done at baseline, at end of treatment Course 1, and end of treatment Course 2 (if given in case of stable disease or objective response). Leftover biopsy tissue may be used for research purposes (refer to Section **5**); peritoneal ascites or peritoneal washings may be collected during the procedure for research into circulating tumor cell and immune subsets analyses (**5.2.1**).
9 Patients will be re-evaluated for response after the first course of treatment at the 9th week, and after the second course if both courses given (refer to Section **6.3**).
10 There will be a total of two courses of treatment for patients with an objective response or stable disease. Note: If given, Course 2 will continue treatment and assessment as indicated for Course 1; CT/PET and laparoscopy will be performed after the completion of each course treatment for evaluation of response.
11 Research blood to be collected within 7 days prior to laparoscopic staging at baseline and as indicated Section **5**.

3.6 SURGICAL GUIDELINES

3.6.1 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:

- Hibiclens shower the night before operation.
- Preoperative IV antibiotic administered within 2 hours prior to the start of the operation.
- Sequential compression devices will be placed on the lower extremities prior to the induction of general anesthesia.
- Subcutaneous heparin administration for venous thromboembolism prophylaxis prior to the induction of general anesthesia.

3.6.2 Patient Management in the Operating Room

3.6.2.1 Staging Laparoscopy and Port Placement

- Staging laparoscopy will be performed to calculate PCI (**Appendix B**).
- Intraperitoneal ports will be placed over the abdominal wall fascia on the side most convenient to the patient.
- Prior to skin closure the port will be flushed with 10 mL of heparinized saline (100 USP/mL) to ensure patency.

3.6.2.2 Re-Staging Laparoscopy

- After first course of treatment patients will undergo re-staging laparoscopy.
- PCI will be calculated, and representative biopsies will be taken to assess response.

3.6.3 Postoperative Care Staging Laparoscopy and Port Placement

3.6.3.1 Patient Monitoring Staging Laparoscopy and Port Placement

Patients will receive standard post-operative care as appropriate to the planned surgical intervention and the patient's underlying health status.

3.6.4 Discharge

Patients will be discharged (as clinically indicated) according to standard discharge criteria.

- Total hospitalization may be approximately 3-4 days.
- Patients may first be eligible for discharge the day following IP paclitaxel administration to ensure tolerance of both chemotherapeutics.
- Patients may require evaluation by their referring physician following discharge; any clinically indicated laboratory testing obtained locally will be faxed to the Research Nurse.

3.6.5 Post-Discharge/Follow-Up

3.6.5.1 Patients with Objective Response or Stable Disease

Patients with an objective response or stable disease will return to the NIH at 1, 3, 6, 9, 12, 15, 18, 21 and 24 months from the date of completion of treatment. After 24 months, the patients will return every 6 months for Years 3-5, and every 6 months thereafter. Follow up visits may vary +/-

2 weeks for the first 2 years, and +/- 4 weeks thereafter. Follow up visits at NIH will include scans for radiological assessment and patient completion of the QOL questionnaire (only first 5 years).

If patients are not able to come to NIH after 5 years, they will be followed by phone, videocall or other NIH approved remote platform contact (used in compliance with policy, including HRPP Policy 303) every 6 months for survival, performance status, new cancer treatment.

Patients with an objective response or stable disease who are unable to come to NIH for follow up visits within the first 5 years may have the option of having follow up done with a local physician at the recommended interval, per discretion of the PI. The healthcare team will follow up by phone or secure videocall/other NIH approved remote platform (used in compliance with policy, including HRPP Policy 303), to include at least a verbal report from the patient regarding disease status. Medical records from visits done with the home physician may be faxed or securely sent to the study team per CC policy and procedures. Evaluation may include radiological assessment for potential correlative studies (as indicated in Section **3.5**). Patients may also complete the research questionnaire electronically or by phone/videocall as applicable.

Note: There will be no requirement for follow up visits, tests or procedures for patients with objective response or stable disease who have come off-treatment (e.g., they have elected for a different line of therapy elsewhere, etc.) and decide not to return to NIH or have local physician follow up visits (as indicated above) before 5 years from the date of completion of treatment. These patients will be followed from receipt of patient decision not to return to NIH or have local physician follow up visits onward by phone, videocall or other NIH approved remote platform contact (used in compliance with policy, including HRPP Policy 303) for survival, performance status, and new cancer treatment every 6 months for 5 years or until patient death, whichever comes first.

Additionally, clinically indicated imaging studies and laboratory assessments may be performed locally; symptom assessments may be performed remotely by phone/videocall.

3.6.5.2 Patients with No Objective Response

Patients with no objective response will be taken off study treatment and will be followed for survival over the phone, videocall or other NIH approved remote platform (used in compliance with policy, including HRPP Policy 303) annually.

3.6.6 Measurement of Health Related Quality of Life for Research

For patients fluent in English, Quality of Life questionnaires (QOL) will be completed at the pre-treatment evaluation prior to intervention, at the end of each course, and at each post-treatment clinical visit (every 3 months +/- 2 weeks) for 5 years.

Patients will be informed of the details of the QOL part of this study and reassured that their decision to participate will not have an effect on the application of the treatment intervention. Once enrolled, the patient has the right at any time to elect not to continue completing the questionnaires.

In the event a patient goes off-study prior to completion of the follow up time points, the data gathered from their completed QOL questionnaires will be included in the final analysis.

We will use tools specifically developed for assessment of QOL in gastric cancer patients: FACT-Ga. Measures will be initially administered by an Associate Investigator Research Nurse or designee. The Research Nurse or designee will assess the patient's ability to read, and if the patient is unable to read, it will not be administered. The Research Nurse or designee will administer the

questionnaires providing a firm surface at a table or clipboard and pencil. QOL data will be collected in stored in Labmatrix. If it becomes available, electronic versions of QOL questionnaires will be developed with the assistance of Jason Levine, MD, and will be offered to patients via secure, web-based application. The patients will be directed to complete the questionnaires using the following instructions:

> *We would like to better understand how you and other persons in this study feel, how well you are able to do your usual activities, and how you rate your health while you are participating in this research study. To help us better understand these things about you and other persons participating in this study, please complete these two questionnaires about your quality of life. Both questionnaires should not take longer than 15 minutes to complete.*
>
> *The questionnaires are simple to fill out. Be sure to read the instructions on the top each questionnaire. Remember, this is not a test and there are no right or wrong answers. Choose the response that best represents the way you feel. I will quickly review the questionnaires when you are done to make sure that all the items have been completed. Please answer all the items with the response that is most applicable.*
>
> *You should answer these questions by yourself. Your husband/wife or other family members or friends should NOT assist you in completing the questionnaires. Please fill out the questionnaires now. Return the questionnaires to me when you have completed them. We will be asking you to complete these again during some of your follow up visits. If you have any questions, please ask.*

The Research Nurse or designee will request that the patient complete the questionnaires prior to seeing the physician, as the interaction between the patient and physician may influence the patient's answers to the questionnaires.

Once the patient has completed the questionnaires, the Research Nurse or designee, will review them for completeness and thank the patient for their cooperation. Subsequent measurements will be administered by the Associate Investigator Research Nurse, or designee, when the patient returns for follow-up visits as specified in Section **3.6.5**.

3.7 COST AND COMPENSATION

3.7.1 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 performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 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.

3.8 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.

Note: As overall survival is a study objective, patients may be removed from treatment but remain on-study for long-term follow-up (Section **3.6.5**).

3.8.1 Criteria for Removal from Protocol Therapy

- Completion of protocol therapy
- Progression of disease
- Participant requests to be withdrawn from active therapy
- Investigator discretion
- Enrollment on another study (**Note:** Patient may remain on-study but off therapy for survival endpoint data, to include enrollment onto another treatment protocol.)
- Positive pregnancy test
- Patient does not follow protocol-related instructions given by the study team
- Malfunction of IP port which cannot be salvaged

3.8.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Investigator discretion
- Death
- PI decision to end the study
- Lost to follow up
- Screen failure

3.8.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 4 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 team will attempt to contact the participant and reschedule the missed visit within 3 weeks 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 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.

5 CORRELATIVE STUDIES

5.1 BIOSPECIMEN COLLECTION TABLE

Test/Assay	**Volume (approx.)**	**Tube Type or Medium***	**Collection Points (+/-48hrs)**	**Location of Specimen Processing/ Storage**	**Location of Specimen Analysis**
Circulating Tumor Cell and Immune Subset Analysis	Blood, 7.5 mL	CellSave Preservation Tubes	Baseline, Weeks 3 and 6, End of Course	Trepel Lab	Trepel Lab
	Peritoneal ascites, ≥ 10 mL **OR** Peritoneal washings, 50 mL (**For Either:** with 50 mL of PBS Buffer)	Specimen Cup with Anti-Coagulant (Heparin)	Baseline, End of Course	Trepel Lab	Trepel Lab
Pharmacokinetic (PK) Studies	Blood, 6 mL	EDTA, Lavender top	Pre-IV/IP infusion, Post-IV/IP infusion at 1, 2, 4, 8,	Blood Processing Core (BPC)	Blood Processing Core (BPC)

			and 24 hours		
	Tumor tissue	Nunc cryovial	Baseline, End of Course	Blood Processing Core (BPC)	Blood Processing Core (BPC)
Pharmacogenetic Studies	Blood, 3 mL	EDTA, Lavender top (K2EDTA BD Biosciences tube preferred)	Baseline	Blood Processing Core (BPC)	Blood Processing Core (BPC)
Proteogenomic Analysis	Tumor tissue with mesothelial metastases	Nunc cryovial	Baseline, End of Course	Blood Processing Core (BPC)	Dr. Hernandez's Lab
* Tubes/media may be adjusted at the time of collection based upon materials available if approved by the PI/laboratory investigator.					

Blood samples for biomarker studies will be processed and stored in the Blood Processing Core (BPC) and sample processing will be per established techniques, unless indicated otherwise.

The amount of blood that may be drawn from adult patients for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

Note: See **Appendix D** for a general reference of specimens and collection timepoints research specimens of IP and IV Paclitaxel patients to be collected, stored, tracked, analyzed for correlative studies and disposed of as specified in protocol 13C0176 specifically for 13C0176 correlative studies, noting that this information is ***only to be used as an overview for reference purposes***; these noted biospecimens will be collected only as indicated on 13C0176, in which the patients will be co-enrolled.

5.2 SAMPLE COLLECTION AND PROCESSING

5.2.1 Circulating Tumor Cell and Immune Subset Analysis

Blood samples and peritoneal ascites or peritoneal washings collected for circulating tumor cell (CTC) and immune subsets analyses will be directly transported to the laboratory of Dr. Jane

Trepel (Neckers), where samples will be freshly analyzed for CTC and barcoded and viably stored for immune subsets analysis. Circulating tumor cell and immune subset samples will be evaluated in order to determine the impact of the study intervention.

5.2.2 Pharmacokinetic (PK) Studies

All collected specimens for pharmacokinetic (PK) analysis will be directly transported to the Blood Processing Core (BPC), where samples will be processed, databased, barcoded, and stored frozen.

Tumor tissue biopsies for will be performed at baseline, and at end of course. Portions of collected tumor tissue will be analyzed for pharmacokinetic (PK) at pre- and post-intervention by measuring the tissue concentrations of paclitaxel using validated assays in the Figg Lab's Clinical Pharmacology Program.

Blood will be collected for PK analysis at pre- and 1, 2, 4, 8, and 24 hours post-IV/IP infusion. Systemic plasma concentrations of paclitaxel in patient blood samples will be analyzed by Dr. Figg's Lab for longitudinal studies.

5.2.3 Pharmacogenetic Studies

All collected specimens for pharmacogenetic analysis will be directly transported to the Blood Processing Core (BPC), where samples will be processed, databased, barcoded, and stored frozen.

One blood sample per patient will be collected in a purple top tube for pharmacogenetic studies to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters (DMET). DNA will be analyzed for 4,627 genetic variations in 1,191 drug disposition genes, including cytochrome P450s (CYPs), Glutathione transferases (GSTs), sulfotransferases (SULTs), as well as genes involved in facilitation of drug transporters, global regulation of drug metabolizing/transporting proteins, drug binding proteins, and drug targets.

5.2.4 Proteogenomic Characterization of Primary and Metastatic Cancers

Peritoneal biopsy tumor tissue with resected mesothelial metastases collected during the study procedure will be sent to Dr. Hernandez's Laboratory for *ex vivo* analysis utilizing the SMART (Sample Microenvironment of Resected Metastatic Tumor) System. *Ex vivo* tumor tissue modeling of peritoneal metastasis will be performed utilizing the SMART Chamber (Section **1.2.4**) and resected mesothelial metastases will undergo *ex vivo* SMART System modeling (as outlined in Section **1.2.5**) in the laboratory to support the identification of underpinnings of interventional chemotherapeutic and immunomodulatory agent effects.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through the 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.

5.3.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.3.1.1 BPC Contact Information

Please e-mail [redacted] at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page [redacted]

For immediate help, call [redacted] (main blood processing core number) or, if no answer, [redacted] (main clinical pharmacology lab number).

For questions regarding sample processing, contact [redacted]

5.3.1.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to subjects without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.3.1.3 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^{0}C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient 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 patient, if so requested). The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

Sample bar-codes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.3.2 Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and

sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not embedded in paraffin is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded.

Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any of these stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. We request that following the completion of LP diagnostic workup, these specimens be allowed use for research purposes on 19C0129 as indicated within Section 5.2 of this protocol.

5.3.3 Dr. Jane Neckers' Trepel Laboratory

Contact the Trepel Lab by email (Dr. Jane Neckers (Trepel): [redacted]; [redacted] and [redacted]) when the patient is scheduled and by phone as soon as the blood is drawn at [redacted].

A lab member will come to pick up the blood. Please keep blood at ambient temperature. Members of the lab will enter the samples into a secure password protected patient's sample tracking database (Translational Pharmacodynamics Research Group Patient Sample Management System) and process the samples.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol. It is critical that the sample remains coded and linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate with these variables.

Blood samples will be stored initially in the Trepel Lab in the Magnuson Clinical Center. If, at any time, a subject 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 patient, if so requested). When a patient withdraws consent the participant's data will be excluded from future distributions, but data that have 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.

5.3.4 Laboratory of Dr. Hernandez

Patient samples, collected for the purpose of research under IRB approved protocols where Dr. Hernandez is Principal Investigator, may be archived in the Laboratory of Dr. Hernandez. All data associated with archived clinical research samples is entered into the NCI Labmatrix database. All staff in Dr. Hernandez's laboratory have received updated NIH/CIT training and maintain standards of computer security.

The data recorded for each sample includes the patient ID, trial name/protocol number, date drawn/collected, treatment cycle/time point, cell source (e.g. peripheral blood, marrow, biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI clinical records. All received samples will receive a unique bar code number, which will be added to the sample NCI Labmatrix

database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the NCI Labmatrix database.

Samples are stored in freezers at -80°C (sera, plasma, tissue samples) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at Dr. Hernandez's laboratory. Access to samples from a protocol for research purposes will be by permission of the Principal Investigator.

5.3.5 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis on this protocol continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

Any specimens that are remaining at the completion of the protocol will be transferred to protocol 13C0176 as all patients will have prospectively consented to this study. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

5.3.6 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. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory.

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

For the purposes of the research sample analyses and correlation with clinical outcomes, demographic information, histology, operative and peri-operative interventions, pathologic findings, laboratory and imaging parameters (performed as part of routine or protocol specified patient care) may be collected on this study. 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 first study intervention, Study Day 1, through 30 days after the subject received the last product administration. After 30 days, 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.

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**.

6.1.1 Routine Data Collection

Following enrollment, graded adverse events will be described in the source documents, reviewed by the designated research nurse, confirmed by the PI and captured in a 21 CFR Part 11-compliant data capture system provided by the NCI CCR. No Grade 1 adverse events will be recorded.

Laboratory events will be captured as follows:

- During hospitalization for the staging laparoscopy and intraperitoneal port placement procedure, only the admission labs, first morning labs drawn after 4 AM, and labs that support the diagnosis of a reportable event will be uploaded into the study database.
- In the post-operative and treatment period, including laboratory values obtained at sites other than the NIH Clinical Center, only the following values will be captured in the study database:
    - Hemoglobin, total white blood cell count, absolute neutrophil count, platelet count.
    - PT, PTT, or INR.
    - Creatinine, ALT, AST, total and direct bilirubin.
    - Any unexpected laboratory abnormality ≥ Grade 2 possibly, probably or definitely related to the surgical intervention.

6.1.1.1 Exclusions to Routine Data Reporting

The following adverse events will be captured only in the source documents and will not be reported in the study database:

For the duration of the study:

- Laboratory values that do not support the diagnosis of a reportable event.

During hospitalization for surgical port placement and staging laparoscopy:

- Grade 2 events except unexpected events that are possibly, probably or definitely related to the research.

During the intraperitoneal and oral chemotherapy phase:

- Grade 2 events except unexpected events that are possibly, probably or definitely related to the research.
- Note: Events that result in hospitalization for convenience will not be reported.

Concomitant medications:

- Only those medications that the patient is taking at baseline on a routine basis, prior to intraperitoneal paclitaxel (as indicated in Section **3.2.1**), or medications that cause an AE will be captured in the study database. (Thus, one-time medications, PRN medications, and medications given to treat adverse events will not be captured in the study database.)

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 an NIH-funded or approved public repository.
- Coded, linked in BTRIS (automatic for activities in the Clinical Center).
- Coded, linked or identified 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

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients will be re-evaluated for response after first course (and after second course if both courses given) of treatment (1 course = 9 weeks) with IP/IV Paclitaxel and PO capecitabine.

Radiographically evident/measurable disease will be evaluated for response and progression in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[43] 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. **The determination of response of subradiographic intraperitoneal disease will be evaluated using the criteria indicated in Section 6.3.1.**

6.3.1 Disease Parameters

Objective response will be declared in patients who meet at least one of the following criteria:

- A reduction in PCI score of greater than or equal to 4 points from baseline PCI.
- Histopathologic evidence of tumor treatment effect in representative peritoneal biopsies obtained at the end of treatment course by re-staging laparoscopy.
- Resolution of small volume ascites for patients in whom ascites was previously documented.

Stable disease will be declared in patients who meet at least one of the following criteria:

- Absence of new intra-peritoneal or extra-peritoneal disease.
- A PCI score within 2 points of baseline PCI (e.g., baseline PCI +/- 2).

Intra-peritoneal (IP) progressive disease will be defined as:

- Increase in PCI of score of greater than 4 points from baseline PCI.
- New ascites requiring repeat (more than 1) therapeutic paracentesis
    - Ascites need not be positive for malignant cytology.
- Malignant bowel obstruction.
- New intraperitoneal nodules or masses concerning for peritoneal metastasis
    - If imaging studies are inconclusive, percutaneous biopsy may be used to confirm.
    - If biopsy is determined not feasible, then repeat interval imaging may be used.
    - In the case of interval imaging, if the previous inconclusive findings are confirmed as disease, then the original date of the inconclusive/suspicious findings will be used for date of progression.
- Decline in performance status not attributed to other medical causes.

Extra-peritoneal (distant) progressive disease will be defined as:

- New extraperitoneal and/or solid organ (i.e., liver) metastasis.

6.3.2 Methods for Evaluation of Measurable Disease

Staging laparoscopy: The PCI scoring system along with tissue biopsy and intra-operative video or image recording will be used to evaluate and document measurable disease.

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: Such techniques may be useful to confirm progression of disease when images are captured and/or biopsies are obtained.

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. 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.

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 FDGPET 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.

Cytology, Histology: These techniques can be used to confirm progression or recurrence of disease. The cytological confirmation of the neoplastic origin of any ascites 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.

6.3.3 Progression-Free Survival

Intraperitoneal PFS is defined as the duration of time from date of placement of intraperitoneal catheter and first dose of IP paclitaxel, to the date of first observation of progressive disease within the peritoneal cavity (increase in PCI from baseline or new ascites requiring repeat drainage; see Section **6.3.1**), or death, whichever comes first. Extraperitoneal DFS (i.e., anything other than peritoneal surface disease progression) is defined as the duration of time from initiation of therapy to the date of first observation of progressive disease at sites other than the peritoneal surface, such as the liver, lymph nodes, and any other solid organs outside the peritoneal cavity.

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).

7 NIH REPORTING REQUIREMENTS/DATA 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 reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

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

To report these deaths, please send an email describing the circumstances of the death to the Clinical Director/designee at 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 regularly on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal 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 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

8.1.1 Primary Endpoint

Separately by cohort based on prior systemic treatment, determine the progression free survival (PFS) in patients with peritoneal metastases from gastric cancer after repeated intraperitoneal chemotherapeutic infusion and systemic paclitaxel administration with concomitant capecitabine therapy.

8.1.2 Secondary Endpoints

- Determine intra-peritoneal PFS (iPFS).
- Determine distant (extra-peritoneal) disease-free survival.
- Determine the frequency of objective histopathologic response to therapy.
- Describe the morbidity of this treatment strategy.
- Determine overall survival.

8.1.3 Exploratory Endpoints

- Evaluate the impact of repeated intraperitoneal chemotherapeutic infusion (IPC) and systemic paclitaxel administration with concomitant capecitabine therapy on circulating tumor cells and immune subsets.
- Determine the pharmacokinetics of repeated intraperitoneal chemotherapeutic infusion (IPC) and systemic paclitaxel administration with concomitant capecitabine therapy in patients with peritoneal metastases from gastric cancer.
- Evaluate the genomic DNA and genotype in patients with peritoneal metastases from gastric cancer in order to determine the most relevant drug metabolizing enzymes and transporters (DMET) through pharmacogenetic analyses.
- Define the risk of developing peritoneal metastasis in gastric cancer, and other associated cancers, through genotype/phenotype correlations.
- Determine the molecular changes and mechanisms of tumor initiation, invasion and metastasis in gastric cancers with peritoneal metastasis.
- Evaluate chemotherapeutic and immunotherapeutic agent effects of systemic paclitaxel administration with concomitant capecitabine therapy in patients with peritoneal metastases from gastric cancer using a novel ex-vivo platform, the SMART System.

8.2 SAMPLE SIZE DETERMINATION

The goal will be to determine if the IV/IP paclitaxel and oral treatment with capecitabine described above could be associated with an 11-month median progression free survival (PFS) compared to a maximum 6 months median PFS based on historical controls.

Patients will enroll in two cohorts: those treated with prior systemic chemo and those who are treatment naïve. In each of these two cohorts, with 32 evaluable patients receiving the proposed therapy,* assuming accrual would take place over approximately 4 years, and that there would be at least 12 months of additional potential follow-up after the last patient has begun the treatment on protocol, there would be 80% power to determine whether there is a difference between a median 5 month PFS beginning at the date IV/IP paclitaxel therapy starts and an improved 9 month PFS, with a one sided 0.10 alpha level test, using the method of Brookmeyer and Crowley.[44] In

practice, a Kaplan-Meier curve beginning at the initiation of treatment, and appropriate confidence intervals at selected time points, will be provided to help interpret results relative to the expected results.

*Note: Per amendment version date 03/09/2021, the dose level of intraperitoneal paclitaxel in this protocol has been increased from 20 mg/m^2 to 60 mg/m^2, and therefore, the primary endpoint evaluation on this study will focus on patients treated at the higher (60 mg/m^2) dose level. Subjects already receiving the study intervention prior to amendment approval will remain at the initial dosage (**1.2.6**); **no** intra-patient dose escalation will occur on this study.

It is expected that 8-10 patients per year may be enrolled to each cohort in this protocol, a total of 16-20 per year; thus, accrual is expected to be completed within approximately 4 years. Following the amendment dated 03/09/2021, in which the dose level of intraperitoneal paclitaxel was increased, the primary endpoint evaluation will focus on patients treated at the higher (60 mg/m^2) dose level. With a requirement for 32+32=64 evaluable patients, to allow for the 4 subjects treated at the lower (20 mg/m^2) dose level of intraperitoneal paclitaxel as well as a small number of inevaluable patients, the accrual ceiling will be set at 74 patients.

8.3 POPULATIONS FOR ANALYSES

Intention to treat: any subjects who enroll onto the trial and provide consent and who receive an intraperitoneal port and receive one cycle of IV/IP chemotherapy will be included in analyses.

8.4 STATISTICAL ANALYSES

8.4.1 General Approach

Determine the progression free survival (PFS) for patients treated on the protocol using a Kaplan-Meier curve.

8.4.2 Analysis of the Primary Endpoints

In each of the cohorts, based on the patients treated at the 60 mg/m^2 dose of intraperitoneal paclitaxel (refer to Section **8.2**), a Kaplan-Meier curve will be constructed for PFS beginning at the date IP chemotherapy begins, and the median PFS in months will be reported along with 80% and 95% two-sided confidence intervals. Progression of disease in any body site will be considered events for this analysis.

8.4.3 Analysis of the Secondary Endpoint

Intra-peritoneal progression free survival (iPFS) will be determined based on the identification of only intraperitoneal sites (e.g., new, malignant ascites, peritoneal nodules, ovarian metastases, etc.) of disease progression using a Kaplan-Meier analysis, using only these progression sites as events. The distant (extra-peritoneal) disease free survival (dDFS) will be determined based on identification of only distant sites of disease progression, such as lungs or intra-parenchymal liver, using a Kaplan-Meier analysis, using only these progression sites as events. A Kaplan-Meier curve will be constructed beginning at the date IP chemotherapy begins and the median iPFS and dDFS in months will be reported along with 80% and 95% two-sided confidence intervals. The frequency of objective histopathologic response to therapy will be based on patients with metastatic tumors that are biopsied at the end of a course of therapy and graded according to standard pathologic techniques.

Overall survival will be estimated by the Kaplan-Meier method, along with the median OS and a 95% confidence interval on the median.

The morbidity of this treatment strategy will be reported using frequencies of complications and adverse events as well as any descriptive material needed for clarification.

8.4.4 Safety Analyses

None, other than description of morbidity of the treatment strategy.

8.4.5 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported.

8.4.6 Planned Interim Analysis

None.

8.4.7 Sub-Group Analysis

None.

8.4.8 Tabulation of Individual Participant Data

None.

8.4.9 Exploratory Analysis

Exploratory analyses on this study will aim to evaluate peritoneal cytology, tumor deposit, and plasma circulating tumor cell response. Peritoneal washings for cytology and peritoneal biopsies taken at baseline and at the end of course will provide information regarding immediate changes due to treatment as well as longitudinal information across treatments. Evaluating the response of circulating tumor cells to intraperitoneal delivery of chemotherapy will provide additional insight into the overall disease response. Tumor cell expression profiles and peritoneal immune cell profiles will be evaluated to identify potential biomarkers that are predictive of response to treatment.

- Evaluation of circulating tumor cell (CTC) and immune subsets will be undertaken in order to determine the impact of the study intervention on the difference in the CTC levels between the time points; the Wilcoxon rank-sum test will be utilized for determination and testing for statistical significance. If multiple statistical tests of these laboratory-based parameters are performed, the results will be reported without any formal correction for multiple comparisons.
- Pharmacokinetic data from pre- and post-intervention analysis of blood and tumor biopsy tissues from study timepoints will be studied using longitudinal and paired analysis methods.
- Analysis of patient blood for pharmacogenetic studies will be done to evaluate the genomic DNA and genotype of targeted drug metabolizing enzymes and transporters (DMET).

Ex vivo analysis of peritoneal biopsy tumor tissue with resected mesothelial metastases by Dr. Hernandez's lab will be performed the SMART System to support the identification of underpinnings of interventional chemotherapeutic and immunomodulatory agent effects.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

Patients with a diagnosis of gastric cancer 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. This is particularly important for this study because of the nature by which the treatment is given. The patients must subject themselves to a major operative procedure with the attendant risks and complications associated with it in order to receive treatment without any assurance of benefit from the treatment.

9.2 PARTICIPATION OF CHILDREN

The chemotherapeutic regimen in this study is not established in children. Both paclitaxel and capecitabine are not medications commonly used in the pediatric population. There is little known regarding the pharmacodynamics or pharmacokinetics in children. Additionally, there has been limited literature in which paclitaxel has been associated with central nervous toxicity and in rare cases death. In addition to the experimental nature of the chemotherapy combination, this protocol calls for repeated surgical intervention resulting in discomfort and hazards for the patients. Should results of this study indicate efficacy in treating gastric 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.

9.3 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 **9.4**), 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 **9.5.1** for consent procedure.

9.4 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, intraabdominal infection, wound healing complications including fascial dehiscence, enterocutaneous fistulas,

anesthetic mishap and perioperative death. 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.

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.

9.4.1 Benefits

The potential benefit is great for these 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.

9.4.2 Risks

Potential complications may arise on this study from both the placement and long-term management of the intraperitoneal infusion system (refer to Sections **3.4** and **11.3.2**) and from risks associated with the use of paclitaxel (**11.1.2**) and capecitabine (**11.2.2**). Protocol risks also include those standardly associated with abdominal laparoscopy, including pain, ileus, ascites, injury to organs in the abdomen (such as the intestines, stomach, bladder and blood vessels) and the possibility of anesthetic mishap. There may be an increased risk of wound healing or infection after surgery due to the use of paclitaxel and capecitabine.

9.4.2.1 Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

9.4.2.2 Electrocardiogram (EKG)

This procedure is associated with minimal discomfort.

9.4.2.3 Questionnaires Risk

Questionnaires may contain questions that are sensitive in nature. The patients are asked to only answer questions they are comfortable with.

9.4.2.4 Tumor Biopsy

Needle biopsy is minimally invasive and is typically a very safe procedure. Depending upon the site being biopsied and the type of biopsy being performed, risks can include infection of the biopsy site, development of a hematoma, and bleeding. Rarely more significant complications can occur when structures near the biopsy target are entered with the needle (e.g., puncture of lung or bowel). Surgical procedures for biopsy specimens will not be conducted for the sole purpose of research specimen collection.

9.4.2.5 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.

9.4.2.6 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.

9.4.2.7 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 catheter 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, or inflammation of the skin and vein with pain and swelling.

9.4.2.8 Risks of Exposure to Ionizing Radiation

This research study involves exposure to radiation from 6 PET/CT scans as well as 3 CT-guided biopsies over the course of the first year. This radiation exposure is not required for medical care and is for research purposes only. Subjects will be exposed to approximately 9.6 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 32.0 years of background radiation.

9.4.2.9 Non-Physical Risks of Genetic Research

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.

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.

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. As previously noted, patients will be notified of any medically significant and actionable incidental findings. Study research results will not be shared with patients.

9.5 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 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 subject 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://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

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

For participants addressed in Section **9.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **9.5**.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 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 study participants, investigator, the sponsor and regulatory authorities. 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, and IRB as applicable.

10.2 QUALITY ASSURANCE AND QUALITY CONTROL

The 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 Conference on Harmonisation 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.

10.3 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 National Cancer Institute 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.

10.4 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.

11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

Paclitaxel for this study will also be used as intraperitoneally. This change in route of administration does not pose any increased risk compared to intravenous administration. There are supporting data that clearly give information that this has been used in many patients without increased risk.[45]

This clinical investigation of two marketed agents is exempt from the IND requirements because all of the criteria for an exemption in 21CFR 312.2(b) are met; including using an alternative route of administration for the paclitaxel in an unapproved indication:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- Additional information on clinical investigations is available on FDA's Web site at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

11.1 PACLITAXEL (TAXOL®)

Refer to the package insert for complete information about this product.

11.1.1 Source

Paclitaxel (Taxol®) is commercially available as a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion in 5, 16.7, and 50 mL vials. (Hospira, Inc) Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Polyoxyl 35 Castor Oil, NF, 49.7% (v/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP. It will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

11.1.2 Toxicity

Paclitaxel has been well studied and toxicities are well defined in the package insert for this FDA approved drug. The most common severe adverse reactions are related to myelosuppression and result in neutropenia, leukopenia and anemia. Additionally, patients with a cardiac history must be monitored during first infusion due to reported conduction abnormalities resulting in AV block and ventricular tachycardia. Patient with known liver disease may experience hepatic enzyme elevation given the high degree of hepatic metabolism. In patients that have received oxaliplatin as previous therapy there is an increased risk of worsening of peripheral neuropathy. In patients who have received radiation therapy there is a risk for radiation recall reactions Less severe reactions such as alopecia, nausea and vomiting have also been noted. When given in an intraperitoneal formulation for gastric cancer the most commonly noted adverse effects were neutropenia and anemia. In limited data no patients experienced abdominal pain due to intraperitoneal formulation. In geriatric patients there is an overall increase in adverse events.

11.1.3 Formulation and Preparation

Please refer to Section **3.2.2** for details.

11.1.4 Stability and Storage

Vials will be stored in original cartons between 20° to 25°C (68° to 77°F) per NIH Clinical Center Pharmacy Department protocol. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25°C) and lighting conditions for up to 27 hours.

11.1.5 Administration Procedures

Please refer to Section **3.2.2** for details.

11.1.6 Incompatibilities

Refer to the package insert for complete information about this product.

11.2 CAPECITABINE (XELODA®)

Refer to the package insert for complete information about this product.

11.2.1 Source

Capecitabine (Xeloda®) is commercially available as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg of capecitabine and each peach-colored tablet contains 500 mg of capecitabine. (Genentech, Inc. San Francisco, CA) It will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

11.2.2 Toxicity

Capecitabine is an FDA approved medication with well-defined adverse events. Nausea, vomiting and dehydration are common events which when severe may lead to dehydration, acute kidney injury and possible renal failure. Additionally, bone marrow suppression has been documented resulting in neutropenia, anemia and thrombocytopenia. Patients with Dihydropyrimidine dehydrogenase deficiency (DPD) are excluded from this study as they may experience serve and life-threatening adverse events due to the inability to metabolize 5-fluorouracil (5-FU). Patients currently on anticoagulation therapy are at an increased risk of bleeding. There are reports of increased PT and INR following initial administration of capecitabine, requiring more frequent PT/INR monitoring as warfarin dose adjustments. Patients with a previous history of coronary artery syndrome are at increased risk of cardiotoxicity including: myocardial infarction, dysrhythmias, electrocardiogram changes, cardiogenic shock and sudden death. Jaundice has been noted in patients with hepatic metastasis on capecitabine, but these patients will be excluded from this protocol. Finally, skin reactions including toxic epidermal necrolysis, Steven Johnson syndrome and palmer-plantar erythrodysesthesia have been reported.

11.2.3 Formulation and Preparation

Capecitabine 150 mg - Color: Light peach; Engraving: XELODA on one side and 150 on the other; 150 mg tablets are packaged in bottles of 60 (NDC 0004-1100-20), individually packaged in a carton.

Capecitabine 500 mg - Color: Peach; Engraving: XELODA on one side and 500 on the other; 500 mg tablets are packaged in bottles of 120 (NDC 0004-1101-50), individually packaged in a carton.

11.2.4 Stability and Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F); storage per NIH Clinical Center Pharmacy Department protocol. Capecitabine is a cytotoxic drug. Follow applicable special handling and disposal procedures. Any unused product should be disposed of in accordance with local requirements, or drug take back programs. If capecitabine tablets must be cut or crushed, this should be done by a professional trained in safe handling of cytotoxic drugs using appropriate equipment and safety procedures.

11.2.5 Administration Procedures

Please refer to Section **3.2.3** for details.

11.2.6 Incompatibilities

Refer to the package insert for complete information about this product.

11.3 SUBCUTANEOUS INTRAPERITONEAL INFUSION PORT

There will be no IDE obtained for the use of the BardPort Titanium Implanted Port with Peritoneal Catheter in this study.

This study meets the criteria for exemption for an IDE as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the BardPort Titanium Implanted Port with Peritoneal Catheter already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve other factors that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of this device.

11.3.1 Source

Subcutaneous intraperitoneal infusion ports are FDA approved and commercially available through Bard Access Systems under the brand name BardPort Titanium Implanted Port with Peritoneal Catheter. The device is made of two components, an injection port with self-sealing silicone septum and a radiopaque silicone rubber catheter.

11.3.2 Possible Complications

There are potential complications with both the placement and long-term management of the intraperitoneal infusion system. These include but are not limited to:

- Bleeding
- Catheter or port erosion
- Catheter or port occlusion
- Catheter or port related sepsis
- Device rotation or extrusion
- Extravasation
- Fibrin sheath formation
- Hematoma
- Intolerance reaction to implanted device
- Inflammation, necrosis, scarring of skin over implanted area
- Laceration of vessels or viscus

- Perforation of vessels or viscus
- Spontaneous catheter tip malposition or retraction

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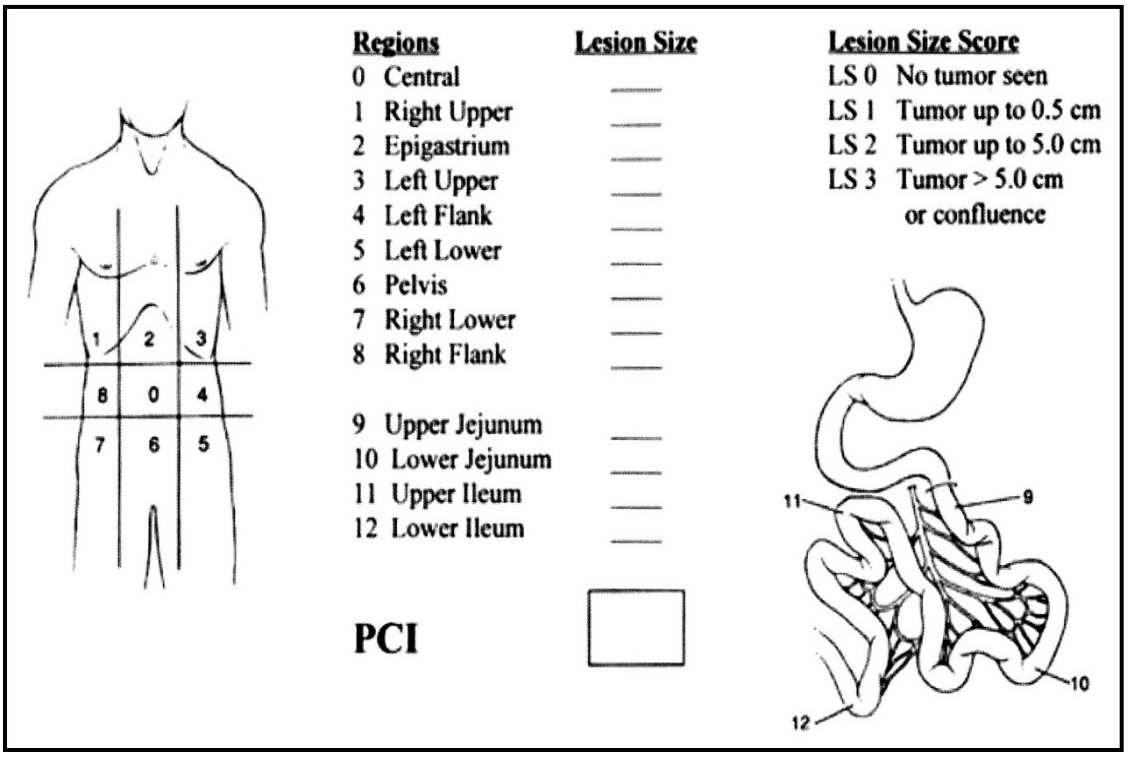
13 APPENDICES

13.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 APPENDIX B: CARCINOMATOSIS EXTENT EVALUATION



13.3 APPENDIX C: ORAL MEDICATION DIARY

Today's Date _____ Cycle #_____

Patient Name_____ (*initials acceptable for patient's name)*

Patient Study ID _____

Please bring your pill bottle and this form to your physician when you go for your next appointment. ***This is required for study compliance.***

INSTRUCTIONS TO THE PATIENT:
1. Complete one form for each cycle (14 days).
2. You will take capecitabine tablets each day twice for 14 days followed by a 7-day rest period during each 3-week cycle. You should be swallowing tablet whole with water within 30 minutes after a meal.
3. Record the date, the number of tablets you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.

Date	**Week/Day**	**# tablets and when taken: Capecitabine**				**Comments**	**Date**	**Week/Day**	**No pills (rest period)**	**Comments**
		#	**AM**	**#**	**PM**					
	W#D1							W#D15		
	W#D2							W#D16		
	W#D3							W#D17		
	W#D4							W#D18		
	W#D5							W#D19		
	W#D6							W#D20		
	W#D7							W#D21		
	W#D8									
	W#D9									
	W#D10									
	W#D11									
	W#D12									
	W#D13									
	W#D14									

Patient's Signature: _____ Date: _____

Study Team will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study _____
3. Patient's planned daily dose_____
4. Total number of pills taken this month _____

Physician/Nurse Practitioner/Nurse's Signature

_____

13.4 APPENDIX D: GENERAL SPECIMEN COLLECTION REFERENCE (REFER TO OFFICIAL TIMEPOINTS IN PROTOCOL 13C0176)

Note: This specimen collection appendix is solely for general reference only. Official specimen collection timepoints for correlative studies on 13C0176 will be as indicated in protocol 13C0176.

The following peripheral blood will be collected for research at Baseline, Weeks 3 and 6, and at End of Course (unless otherwise indicated):

- 8 mL blood in an EDTA Lavender top tube (Baseline only, for genomic DNA);
- 8 mL blood in a CPT Blue/Black top tube;
- 8 mL blood (plasma) in a Sodium Heparin Green top tube;
- 8 mL blood (serum) in SST Gold or Marble top tube;
- 8 mL blood in a Streck Cell Free DNA tube.

Blood and urine samples will be collected at the Pre-Op visit and Follow-Up visits, approximately 1, 3, 6, 9, 12, 15, 18, 21 and 24 months after the last dose of treatment intervention, and then every 6 months during Years 3-5, and then yearly thereafter:

- 8 mL blood in a Streck Cell Free DNA tube;
- 8 mL blood (plasma) in a Sodium Heparin Green top tube;
- 8 mL blood in a CPT Blue/Black top tube;
- 8 mL blood (serum) in SST Gold or Marble top tube;
- 45 mL spot urine sample in a urine clean catch container.

Peritoneal biopsy tumor tissue will be collected as available at Baseline and at End of Course for immunohistochemistry.

Normal and tumor tissue, and tumor tissue with mesothelial metastases for proteogenomic analysis, will be collected for research during the IP port placement (see Section **3.6.2**). Additionally, peritoneal lavage fluid collected during the operation will be sent for cytopathologic analysis for research purposes.