Abbreviated Title: HIPEC for Gastric Cancer

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Title: Phase II Trial of Heated Intraperitoneal Chemotherapy and Gastrectomy for Gastric Cancer with Positive Peritoneal Cytology

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
Email: jeremy.davis@nih.gov

Investigational Agents: None

Commercial Agents: Cisplatin, Mitomycin C, Sodium Thiosulfate

PRÉCIS

Background:

- An estimated 24,590 cases of gastric adenocarcinoma are diagnosed annually in the U.S.
- The peritoneal surface is a site of metastasis found often at time of diagnosis and is a common (40%) site of recurrence.
- Laparoscopy with peritoneal lavage and cytopathologic analysis is a staging modality that can identify a subset of patients with microscopic peritoneal metastasis prior to consideration for definitive surgical therapy.
- Intraperitoneal chemotherapy has been employed in advanced gastric cancers and as an adjuvant with an associated improvement in survival in systematic reviews.

Objective:

- Determine the overall survival in patients with cytology-positive gastric cancer treated with HIPEC and gastrectomy.

Eligibility:

- Histologically confirmed adenocarcinoma of the stomach.
- Cytopathologic evidence of peritoneal carcinomatosis.
- Medically fit for systemic chemotherapy, HIPEC and gastrectomy.

Design:

- Single arm, Phase II study of HIPEC and gastrectomy.

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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 overall survival (OS) in patients with cytology-positive gastric cancer treated with HIPEC and gastrectomy.

1.1.2 Secondary Objectives

- Determine intraperitoneal progression free survival (iPFS).
- Determine distant (extra-peritoneal) disease free survival.
- Describe the morbidity of this treatment strategy.

1.2 BACKGROUND AND RATIONALE

Gastric cancer was diagnosed in an estimated 24,590 people in the United States in 2015 and 10,720 were estimated to die of the disease.[1] Worldwide, there are nearly 1 million estimated new cases of gastric cancer per year with over 700,000 estimated deaths, making it the third most common cause of cancer-related death.[2] An estimated 40% of patients will develop some form of peritoneal metastasis during the course of the disease.[3,4] The 5-year overall survival for patients presenting with gastric adenocarcinoma in the U.S. is approximately 25–30%.[5,6] Although the current treatment paradigm of surgical resection and systemic therapy aims to increase recurrence-free and overall survival, peritoneal tumor dissemination remains a source of major morbidity and often a leading contributor to mortality.[3]

The process of peritoneal dissemination begins early, as retrospective studies have shown that positive peritoneal cytology is present in 7% of patients at time of curative surgery, in the absence of macroscopic metastasis.[7] Patients with positive peritoneal cytology (cyto+) experience cancer-specific outcomes similar to those with gross metastatic disease (**Figure 1**).[8-10]

Therefore, in addition to staging laparoscopy, peritoneal lavage with cytopathologic examination is designed to detect this subset of patients with occult metastatic disease and avoid non-curative gastric resection.[7] Laparoscopic staging can prevent non-curative laparotomy in 23–31% of patients harboring metastasis not detected by radiography in patients with resectable gastric cancer.[11,12] This is an important distinction between gastric cancer and other gastrointestinal malignancies because microscopic peritoneal (cyto+ M1) disease is an indication for palliative systemic chemotherapy. The median survival for patients with cyto+ M1 gastric cancer is 12 months.[13] It follows that, outside of a clinical trial, gastrectomy has not been advocated routinely for patients with positive peritoneal cytology, even as the only site of metastatic disease.

The primary risk factor associated with detection of occult peritoneal metastasis is advanced tumor stage. Detection rates rise with increasing pathologic T-stage, such that patients with T0-T2 gastric cancers have a low rate (2%) of positive cytology whereas T3-T4 tumors, or tumors with gross serosal invasion, have a 10-12% rate of positive cytology[7,14]. Increased incidence of positive cytology has been associated also with preoperative TNM stage, such that clinical stage III tumors (AJCC 6th ed.) have an 11% incidence of positive peritoneal cytology[7]. Comparatively, two-thirds of patients with visible carcinomatosis will have positive peritoneal cytology. Most interesting is that metastases may be limited to the peritoneum in up to 73% of patients with peritoneal carcinomatosis.[3,11,12]

The natural history of patients with positive peritoneal cytology was studied by Mezhir and colleagues.[13] The incidence of positive cytology was 23% (291 of 1241) in gastric cancer patients undergoing staging laparoscopy with peritoneal washings. Of those 291 patients, 32% (93 of 291) had positive cytology in the absence of gross metastatic disease. While the median disease-specific survival for the entire cohort was 1 year, a subset of patients who received systemic chemotherapy and then underwent repeat laparoscopy was analyzed. Patients who converted to negative cytology experienced significantly improved survival compared to those with persistently positive peritoneal cytology (2.5 vs 1.4 years, p=0.0003). This finding resembles that of neoadjuvant therapy trials in gastric cancer demonstrating survival is associated with pathologic response to pre-operative therapy[5,15]. In an analysis of patients experiencing a pathologic complete response (pCR) to neoadjuvant therapy, Fields et al. demonstrated recurrence rates at 5 years were significantly lower for patients who achieved a pCR versus a non-pCR (27% vs. 51%)[16]. Taken together, these data suggest that effective systemic and regional therapy combined may improve survival in patients with cytologic M1 disease if a pathologic complete response to therapy can be achieved.

1.2.1 Rationale for Palliative Gastrectomy and Regional Therapy in Gastric Cancer

We hypothesize that gastrectomy to remove the primary tumor combined with multi-modality treatment of microscopic peritoneal metastasis may improve survival in patients with gastric cancer. The clinical indications for palliative gastrectomy include relief of obstruction and refractory bleeding. An oncologic justification for palliative gastrectomy is wanted despite an association with improved survival reported in multiple retrospective studies.[17,18] Hartgrink et al. reported an overall survival advantage associated with gastrectomy in patients with non-curable gastric cancer that was evident only in patients with one site (versus multiple sites) of metastasis, thus implicating differential tumor biology.[17] To date, a single prospective randomized trial has been performed to evaluate the role of palliative gastrectomy (without metastasectomy) prior to systemic therapy for patients with limited (solitary site) gastric cancer metastasis.[19] Although there

was no difference in survival between treatment arms, the study did not allow for metastasectomy in these patients with limited metastatic disease. Resection of the primary tumor in the setting of metastatic disease has been studied prospectively, notably in renal cell carcinoma, and demonstrated improved overall survival for patients undergoing nephrectomy and systemic therapy compared to systemic therapy alone.[20,21] Some explanations of these findings echo the classic 'seed and soil' hypothesis of Paget, the proponents of which contend that therapies should not only address the source of cancer cells (the 'seed'), but also the unique microenvironment of different organs (the 'soil'). In support of completely eliminating the 'seed', detection of circulating tumor cells after curative resection for colorectal cancer has been associated with worse cancer specific outcomes.[22] In a study of metastatic colorectal cancer detection of circulating tumor cells in peripheral blood was associated with progression free survival in patients undergoing cytoreductive surgery and intraperitoneal chemotherapy.[23]

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[24-26]. Subsequent clinical studies have established IP chemotherapy as the optimal treatment for patients with ovarian carcinomatosis, primary peritoneal mesothelioma and appendiceal mucinous neoplasms[27-29]. A prospective study of cytoreductive surgery, gastrectomy and HIPEC with or without systemic chemotherapy in patients with metastatic gastric cancer was performed in the Surgery Branch by Rudloff et al[30]. Although underpowered, the study demonstrated that patients with peritoneal carcinomatosis and limited disease burden could achieve prolonged survival with cytoreduction, including gastrectomy, and IP chemotherapy.

In order to understand the potential role for regional therapy in patients with gastric cancer we performed a systematic review of the literature to identify studies that utilized adjuvant IP chemotherapy in gastric cancer. Our review encompassed 2,042 patients enrolled in phase II randomized controlled trials (RCTs; n=13) or high-quality comparative case control studies (n=4) that examined adjuvant IP chemotherapy for gastric cancer (**Table 1: Systematic Review**). Adjuvant IP chemotherapy was well-tolerated; the most common side effects reported were hematologic and infectious and there were no treatment-related mortalities reported in the IP therapy arms. Despite the heterogeneity of studies with respect to patient accrual, timing of IP drug delivery, and chemotherapy selection, several themes emerged. Primarily, there was an associated improvement in five-year overall survival in studies that administered adjuvant IP chemotherapy in any form. Furthermore, IP treatment appeared most beneficial when it was administered intra-operatively. **Figure 2** depicts the results of a random effects model that includes studies reporting five-year survival data. Although survival rates across studies varied, two systematic reviews have concluded the use of adjuvant IP chemotherapy for resectable gastric cancer is associated with improved survival[39,40,41,42,43].

While these data suggest an incremental benefit of intra-operative IP chemotherapy it is possible that enrichment for patients at highest risk for peritoneal carcinomatosis would show a clearer benefit of this strategy. Importantly, the majority of these randomized prospective studies were performed in Asia. The difference in gastric cancer-specific outcomes between Asian and Western patients is well-documented; therefore, the results of these trials must be viewed with caution[44,45].

1.2.2 **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[46,47]. These studies have revealed novel correlations of molecular subtypes with distinct tumor phenotypes and clinical outcomes[47]. Consequently, these provocative data are expected to aid in identification of novel therapeutic targets and patient-specific therapies. The proposed molecular sub-classifications of gastric cancer have yet to be validated prospectively, however, and are not currently applied to clinical decision making.

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[4]. Somatic gene alterations that impair E-cadherin protein expression are also a recurring feature of sporadic diffuse-type gastric cancers[48]. 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[49]. 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.[50,51] Better understanding of molecular alterations associated with unique patterns of metastasis may uncover key drivers of distinct malignant phenotypes [52].

Currently, two biologic agents are approved for use in advanced gastric cancer: anti-VEGF and anti-HER2 antibodies. While anti-VEGF therapy is not based on known molecular alterations in gastric cancers, the over-expression of HER2 in about 20% of gastric adenocarcinomas forms the basis of its use in HER2+ metastatic disease. Even so, the clinical benefit of anti-HER2 therapy is associated with only a modest improvement in median survival of 2.7 months.[53] Notably, diffuse-type gastric cancers rarely overexpress HER2 compared to intestinal-type tumors (6.1% and 31.8%, respectively) based on data from the ToGA trial[54]. Therefore, clinically meaningful and targeted therapy for diverse subtypes of gastric cancers is needed.

The Cancer Genome Atlas (TCGA) Research Network published a comprehensive analysis of gastric adenocarcinomas resulting in a proposed molecular sub-classification[46]. In their report the genomically stable (GS) subtype of cancers were majority (70%) diffuse-type histology and harbored frequent *CDH1* mutations (37%). *CDH1* germline mutations are linked to hereditary diffuse gastric cancer (HDGC), while sporadic forms of diffuse gastric cancer are marked by E-cadherin loss through somatic mutation of *CDH1* or promoter hypermethylation[55,56]. Recurrent mutations in *RHOA* also have been described in up to 25% of patients with diffuse gastric cancer[51,57]. RhoA, a GTPase encoded by *RHOA,* and a downstream effector, ROCK1 (Rho-associated protein kinase 1), are regulators of cytoskeletal elements and cellular motility. The *RHOA/ROCK1* signaling pathway is important also for epithelial-to-mesenchymal transition and is implicated in gastric cancer metastasis[58-61]. Work by Kakiuchi and colleagues was performed to explore possible driver mutations in diffuse-type gastric cancer (DGC)[51]. Whole-exome sequencing of DGC samples revealed 25.3% (22/87) of tumors with recurrent mutations in *RHOA*, with mutation hotspots affecting the protein at Tyr42, Arg5 and Gly17 residues. A similar *RHOA* mutation profile was reported by Wang and coworkers with a recurring hotspot altering Tyr42 whereas no *RHOA* mutations seen in intestinal-type tumors[57]. The Tyr42 residue of RhoA is

important for interaction with effector molecules such as RhoGEF (Rho GDP/GTP-exchange factor) thus affecting downstream RhoA signaling.

Using a provisional TCGA data set accessed via cBioPortal, 289 samples of gastric adenocarcinoma with available sequencing data were queried for alterations in *CDH1*, *RHOA*, and *ROCK1*[62,63]. Somatic alterations in *CDH1*, *RHOA* and *ROCK1* were found in 25% (71/289) of tumors and there was a trend toward co-occurrence of *CDH1* and *RHOA* mutations (**Figure 3**; these results are in whole based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/.) A similar finding by Kakiuchi et al. reported *CDH1* mutations in 32% (28/87) of diffuse cancers, and, along with the *RHOA* mutants, these alterations appeared almost exclusively in DGC when compared to a set of intestinal-type tumors[51].

The Asian Cancer Research Group (ACRG) selected 300 primary gastric cancer specimens to develop a molecular classification system[47]. Unlike the TCGA data set, these samples were uniformly obtained from patients operated at a single center in Korea. Four distinct subtypes of gastric adenocarcinoma were proposed: microsatellite instability (MSI), microsatellite stable/epithelial-to-mesenchymal transition (MSS/EMT), and MSS/TP53-activity high (MSS/TP53+) and MSS/TP53-activity low (MSS/TP53-). Clinical phenotypes were associated with molecular subtypes such that the MSS/EMT tumors occurred in younger patients and were majority (80%) diffuse-type histology. The MSS/EMT group also had substantially higher rates of peritoneal metastasis and worse overall survival compared to the other subtypes. Interestingly, *CDH1* and *RHOA* mutations were not frequent in the MSS/EMT group, which is contrary to the TCGA findings in the genomically stable (GS) subtype. These differences indicate the MSS/EMT and TCGA GS subtypes are not equivalent and highlight the need for validation of the proposed molecular classifications of gastric cancer.

Translational 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) will be conducted in parallel to strengthen the search for key drivers of peritoneal metastasis. The current Phase 2 trial of heated intraperitoneal chemotherapy delivered to gastric cancer patients with positive peritoneal cytology is designed to determine overall survival in patients treated with this strategy. A concurrent protocol for patients with heritable gastric cancer syndromes is designed to study the natural history of these syndromes, characterize germline mutations, perform cancer risk-reducing surgery, and genotype-phenotype correlation. It is expected that patients who undergo risk-reducing total gastrectomy, in addition to those receiving gastrectomy and HIPEC on the current protocol, will provide a rare opportunity for detailed analysis of molecular changes associated with gastric cancer initiation, invasion and metastasis.

The goal of the current protocol is to address the challenges outlined above; evaluate a strategy for treating gastric cancers with positive peritoneal cytology, validate molecular subtyping of gastric and associated peritoneal metastases, and discover key drivers of peritoneal tumor dissemination.

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 or gastroesophageal junction (Siewert I-III) adenocarcinoma confirmed by the Laboratory of Pathology, NCI.

2.1.1.2 Must have received systemic chemotherapy, minimum 3 months or maximum 6 months, prior to enrollment:

- Systemic therapy should consist of at least fluoropyrimidine-based and/or platinum-based chemotherapy.
- Trastuzumab may be added for HER2-neu over-expressing cancers as clinically indicated.
- Last dose of chemotherapy within 8 weeks of enrollment with recovery to Grade 1 from chemotherapy-related toxicities.
- Documentation of chemotherapy administration must be obtained.

2.1.1.3 Sub radiographic and/or cytopathologic evidence of peritoneal carcinomatosis found at staging laparoscopy (see **Table 2: Cytopathologic Analysis Definitions**):

- Documentation of cytopathologic diagnosis of malignant peritoneal cytology in the absence of disseminated peritoneal disease must be obtained. If cytologic analysis reveals atypical cells of undetermined significance, a repeat lavage with cytopathologic analysis will be performed and must demonstrate evidence of malignancy.
- Limited peritoneal involvement (≤ P1 or PCI ≤ 10)[64] found at staging laparoscopy or on final pathology that is deemed completely resectable is permitted (see **Appendix C**).

2.1.1.4 Age ≥ 18 years.

2.1.1.5 ECOG performance status ≤ 2 (see **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	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional upper limit of normal
– creatinine	< 1.5 mg/dl
	OR
– eGFR (creatinine clearance)	≥ 60 mL/min/1.73 m^2.

2.1.1.7 Physiologically able to undergo HIPEC and gastrectomy.

2.1.1.8 No history of malignancy within 2 years of enrollment except for basal cell carcinoma of the skin, squamous cell skin cancer or carcinoma in situ of the cervix.

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

2.1.1.10 Previous exploratory laparotomy or laparoscopy with tissue biopsy or peritoneal lavage is permitted. (Prior Surgical Score, PSS, of 0 or 1)[65].

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

2.1.1.12 Subjects must agree to co-enrollment on the tissue collection protocol 13C0176, "Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or Surgical Resection of Solid Tumors".

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any investigational agents.

2.1.2.2 Disseminated extra-peritoneal or solid organ metastases:

- Includes carcinomatosis associated with clinically or radiographically evident ascites (greater than 500 cc).
- Excludes greater omentum and ovarian metastases.

2.1.2.3 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.

2.1.2.4 Pregnant women are excluded from this study because HIPEC and gastrectomy have not been studied in pregnant women and has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with HIPEC and gastrectomy, breastfeeding should be discontinued if the mother is treated on this study.

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

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening Activities Performed Prior to Obtaining Informed Consent

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

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.

- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

A waiver of consent for these activities has been requested in Section **10.6.1**.

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

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

2.2.2.1 Within 8 Weeks Prior to Being Registered for Study Treatment (Unless Otherwise Indicated)

- History and Physical Evaluation:
  - Complete medical history and physical examination (including height, weight, vital signs, EKG, and ECOG performance status).
  - Consultation with NIAID physician in HIV positive subjects.
- Laboratory Evaluation:
  - Hematological Profile: CBC with differential and platelet count.
  - Biochemical Profile: Acute, Hepatic, Mineral Panels
  - Serum or urine pregnancy test for female participants of childbearing age and anatomic ability (for eligibility).
  - HIV test, Hepatitis B surface antigen, and Hepatitis C antibody.
- Laparoscopic Staging (if clinically indicated)

  Note: Patients undergoing re-staging laparoscopy at an outside facility must have operative documentation and pathology slides/tissue submitted for review CT-CAP and PET scan of chest, abdomen and pelvis.
- Histologic Confirmation (at any time point prior to initiation of study therapy, if clinically indicated).

  Note: 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.
- CT chest, abdomen, and pelvis (C/A/P) or PET/CT

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 here.

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
A	Cohort A	Patients with gastric adenocarcinoma or gastroesophageal junction (Siewert I-III) adenocarcinoma.

Arms

Number	Name	Description
1	HIPEC with gastrectomy	Patients will undergo HIPEC with gastrectomy.

Arm Assignment

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

2.4 BASELINE EVALUATION

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

2.4.1 Within 8 Weeks Prior to Treatment with HIPEC

- Patients will need documentation of peritoneal re-staging by CT C/A/P or PET/CT, and/or laparoscopy.

2.4.2 Within 4 Weeks Prior to Treatment with HIPEC

- History and Physical Examination (if clinically indicated):
    - Complete medical history and physical examination (including vital signs, height and weight, as well as EKG and ECOG assessment, and review of systemic treatment records).
- Dietary Assessment (if clinically indicated).
- Concurrent Medication (when clinically indicated).
- Laboratory Evaluation (if clinically indicated):
    - General Labs:
        - CBC with platelets

        - Chem-20 equivalent (Sodium (Na), Potassium (K), Chloride (Cl), total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, Total Protein, total CK.
        - PT/PTT & INR.
    - Nutrition Labs:
        - C-reactive protein, Hg A1c, Ferritin, Prealbumin, Thiamine, Iron panel, Vitamin B12, Methlymalonic acid, Zinc, 25-hydroxy Vitamin D
    - Urinalysis
    - CEA, CA 19-9, CA 15-3, CA 125, CA 27-29 tumor markers
- CT C/A/P or PET/CT
- Quality of Life Questionnaire (**3.4.6**).

2.4.3 Pre-Operation Visit (Prior to Treatment with HIPEC)

- Beta HCG for women of child-bearing potential prior to operation only (within 72 hours prior to initiating treatment).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a Phase II trial designed to determine the efficacy of heated intraperitoneal chemotherapy (HIPEC) in patients with gastric cancer and associated positive peritoneal cytology. Patients with a diagnosis of or clinical suspicion of gastric malignancy may undergo screening and initial evaluation on the 'Profiling of Gastric Tumors' protocol (17C0044). All patients will be discussed at a regular multidisciplinary gastrointestinal malignancies conference.

Patients will receive systemic chemotherapy by their treating oncologist for a minimum of 3 cycles. Staging imaging studies and laparoscopy will be performed to rule out progression of disease. After these staging studies, if patients meet eligibility they will be enrolled on the current protocol. Patients will undergo standard pre-operative evaluation and undergo HIPEC with gastrectomy. Patients found to have distant or diffuse peritoneal carcinomatosis ($\geq$ P2 or Peritoneal Cancer Index, PCI, > 10) that cannot be completely resected will undergo biopsy to document disease, and will not receive the assigned treatment. Although it is anticipated to be an uncommon occurrence, patients who experience refractory bleeding or gastric outlet obstruction may be offered palliative surgical intervention even if they are unable to receive HIPEC and resection.

All tumors will be pathologically staged according to American Joint Committee on Cancer 7th edition criteria[66]. Post-operatively, systemic therapy will be administered at the discretion of the treating medical oncologist.

3.2 DRUG ADMINISTRATION

Intraperitoneal chemotherapy will be delivered via a closed perfusion circuit in the Clinical Center operating room under the direction of the Principal Investigator or designated Associate Investigators. Body surface area for each patient will be calculated.

3.2.1 Cisplatin and Mitomycin

Cisplatin (90 mg/m^2) and mitomycin C 10 mg/m^2 will be diluted in 1L of 1.5% dextrose dialysis solution and administered via circuit to the peritoneal cavity.

Note: Cisplatin and mitomycin C may be provided separately and may be provided in a different diluent if 1.5% dextrose dialysis solution is not available. The alternate diluent is described in Sections 12.1 and 12.2.

3.2.2 Sodium Thiosulfate

Sodium thiosulfate will be administered by continuous intravenous infusion starting immediately prior to the perfusion and continuing for a total of 12 hours.

- A loading dose of 7.5 gm/m2 of sodium thiosulfate will be diluted in 150 cc of 0.9% sodium chloride for injection. This loading dose will be infused over 20 minutes beginning with the addition of cisplatin to the peritoneal perfusion circuit.
- Immediately following this bolus dose an additional 25.56 gm/m2 of sodium thiosulfate will be diluted in 1000 cc of 0.9% sodium chloride for injection for a maintenance infusion of 2.13 gm/m2 per hour for 12 hours. The maintenance infusion will be delivered by infusion pump.

3.3 STUDY CALENDAR

	Screening	**Baseline**	**Operation**	**Post-Op Care** (While in ICU)	**Post-Discharge Visits/Follow-Up**[2] (Months)									**Semi-Annual Follow Up** (Semi-Annually for Years 3-5)	**Annual Follow Up** (Annually after Year 5)[4]
					1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		
Confirmation of Pathology	x														
Concurrent Medications[3]		x													
ECOG Performance Status[3]	x	x[1]			x	x	x	x	x	x	x	x	x	x	x
Physical Examination (Including Vital Signs, Weight and Height)	x	x[1]			x	x	x	x	x	x	x	x	x	x	
Dietary Assessment[3]		x		x	x	x	x	x	x	x	x	x	x	x	x
H&P[3]	x	x[1]													
Focused H&P[3]					x	x	x	x	x	x	x	x	x	x	x

	Screening	**Baseline**	**Operation**	**Post-Op Care** (While in ICU)	**Post-Discharge Visits/Follow-Up**[2] (Months)									**Semi-Annual Follow Up** (Semi-Annually for Years 3-5)	**Annual Follow Up** (Annually after Year 5)[4]
					1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		
Tumor Biopsy[3]	x	x[1]	x												
CT C/A/P or PET-CT[2] (MRI if CT imaging contraindicated)	x	x[1]		x		x	x	x	x	x	x	x	x	x	x
General Labs (listed in Sections **2.4.2** and **3.4**)[3]	x	x[1,3]		x	x	x	x	x	x	x	x	x	x	x	x
HIV, HepB, HepC	x														
Nutrition Labs (as listed in Section **2.4.2**)[3]		x		x	x	x	x	x	x	x	x	x	x		
Tumor Markers (Section **2.4.2**)[3]		x		x											
Urinalysis[3]		x													
Pregnancy Test	x	x													

	Screening	**Baseline**	**Operation**	**Post-Op Care** (While in ICU)	**Post-Discharge Visits/Follow-Up**[2] (Months)									**Semi-Annual Follow Up** (Semi-Annually for Years 3-5)	**Annual Follow Up** (Annually after Year 5)[4]
					1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		
EKG	x	x[1]													
QOL Questionnaire[2]		x			x	x	x	x	x	x	x	x	x		
Consultation with NIAID Physician in HIV Positive Subjects	x														
NIH Advanced Directives Form[5]		x													

[1] Does not need to be repeated at Baseline if test was performed on Screening within the defined timeline (see Section **2.4**).

[2] Post-discharge visits/follow-up will include CT C/A/P or PET/CT as indicated in Section **3.4.5**; completion of QOL questionnaires as indicated in Section **3.4.6**; follow-up physical examination and labs as clinically indicated per Section **3.4.5**. **Note:** For patients who have documented disease progression after HIPEC refer to Section **3.4.5**.

[3] If clinically indicated.

[4] If patients are not able to come to NIH after 5 years or have documented disease progression, they will be followed by phone contact or other NIH approved remote platforms (used in compliance with policy, including HRPP Policy 303) annually for survival, performance status, new cancer treatment (refer to Section **3.4.5**).

[5] As indicated in Section **10.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

3.4 SURGICAL GUIDELINES

3.4.1 Preoperative Patient Management

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

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

3.4.2 Patient Management in the Operating Room

3.4.2.1 At Operation (As Clinically Indicated)

- Patients will undergo resection of the primary tumor along with a modified D2 lymphadenectomy will be performed; this implies nodal dissection of stations 1–11 without obligatory splenectomy or distal pancreatectomy.
- Local invasion of adjacent structures is not a contraindication to resection.
- In patients at risk for splenectomy (proximal T3-T4 lesions) immunization against pneumococcus, meningococcus and haemophilus influenzae will be administered pre-operatively or > 1 week after operation for patients in whom splenectomy was necessary at time of operation.
- If limited (< P1, or PCI < 10) peritoneal tumor implants are encountered, a complete resection will be performed.

3.4.2.2 HIPEC

- Peritoneal perfusion may be performed via open or closed technique, which is described hereafter.
- For closed technique, two large bore catheters will be placed into the abdomen, one over the right liver and one in the pelvis and the catheters connected to a perfusion circuit.
- Drug administration (Section **3.2**) will be performed via the perfusion circuit.
- Intravenous thiosulfate will be administered prior to cisplatin administration and followed by continuous infusion as per Section **3.2**.
- The perfusion flow rate will be maintained at least 1 L/min and a perfusate volume will be maintained which moderately distends the abdominal cavity correlating with intra-abdominal pressures of 5–15 mmHg.
- Stable perfusion parameters are obtained and inflow is set to a target of 41 degrees Celsius prior to starting the clock for perfusion time; the perfused temperature will not exceed 42 degrees Celsius.
- Perfusion will be continued for 60 minutes. During the perfusion, constant physical manipulation of the abdomen (shaking) will be maintained to assure even distribution of perfusate.
- Peritoneal temperature will be measured continuously.

- The patient's core temperature will be measured with esophageal temperature probe and maintained at less than 41 degrees Celsius using a cooling blanket and ice packs around the legs and head.
- At the end of perfusion, the circuit will be flushed with saline solution to irrigate the perfusate from the abdominal cavity; the abdominal cavity will be lavaged as needed.

3.4.2.2.1 Type of Primary Tumor Resection (As Clinically Indicated)

- For tumors of the gastric body or antrum, a subtotal gastrectomy will be performed. This will include ligation of the right gastric, right gastroepiploic, and left gastric arteries (for proximal subtotal resection) at their origins with removal of associated lymphoid tissue. The lesser and greater omentum will be removed.
- For proximal gastric tumors a total gastrectomy with 2–4 cm esophageal margin will be performed when possible.
- For GE junction tumors a standard esophagogastrectomy (Ivor Lewis) will be performed.

3.4.2.2.2 Lymph Node Dissection (As Clinically Indicated)

- Perigastric lymph nodes (stations 1, 3 and 5) and greater curve lymph nodes (stations 2, 4 and 6) will be removed as part of a D1 lymphadenectomy; the lymph nodes around the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9) and splenic artery (stations 10 and 11) will be removed as part of a modified D2 lymphadenectomy, without obligatory splenectomy or distal pancreatectomy.
- The extent of the D2 lymphadenectomy will be determined by the operating surgeon depending on tumor characteristics and whether nodal regions can be accessed safely while sparing the spleen and distal pancreas.

3.4.2.2.3 Peritoneal Metastasectomy (As Clinically Indicated)

- For patients with visible peritoneal metastases (small disease burden, ≤ P1 or PCI < 10) without massive ascites, all visible disease will be resected. Partial (limited) peritonectomy will be performed for these patients as indicated by visible disease.
- Any omental implants will be removed as part of the omentectomy as described with the gastrectomy or esophagogastrectomy procedure.

3.4.3 **Postoperative Care**

3.4.3.1 Patient Monitoring

- The patients will be monitored in the Intensive Care Unit for no less than 12 hours after surgical resection. Routine ICU monitoring of vital signs will be performed according to the patient's clinical status. While in the ICU, an attempt to keep urine output greater than 100 cc/hour will be made when physiologically feasible until the sodium thiosulfate is completed.
- Patients will be discharged from the ICU at the discretion of the treating surgeon and in accordance with the institution policies.
- Following discharge from the ICU, vital signs (blood pressure, temperature, pulse, respirations) will be taken per routine (every 2-6 hours and as clinically indicated).

- Patients will receive routine post-operative care; early ambulation will be encouraged.
- Laboratory evaluations (as clinically indicated) will include:
    - CBC, platelets, acute care, mineral and hepatic panel on post-operative days 1 through 3, and then as clinically indicated until discharge.
    - Patients will be transfused as appropriate to maintain a hemoglobin greater than or equal to 8 g/dl.
    - Tumor markers (CEA, CA 19-9, CA 15-3, CA 125, CA 27-29) for new baseline will be obtained within 5 days of discharge.
    - Imaging studies will be obtained as clinically indicated.

3.4.4 Discharge (As Clinically Indicated)

- Total hospitalization may be approximately 7-21 days.
- Patients who are discharged within this time frame should be able to tolerate an oral diet with or without dietary supplements.
- Patients who have a prolonged hospitalization may be discharged with home rehab/physical therapy and/or the addition of enteral nutritional support via a feeding tube.
- Patients may require evaluation by their referring physician following discharge; any clinically indicated laboratory testing obtained locally will be faxed to the Research Nurse.

3.4.5 Post-Discharge/Follow-Up

3.4.5.1 For Patients Who Return to the NIH Clinical Center

- Patients will return to the NIH CC approximately 1, 3, 6, 9, 12, 15, 18, 21 and 24 months from the date of operation, and then every 6 months for years 3-5, and yearly thereafter except where otherwise indicated. Follow up visits may vary +/- 2 weeks for the first 2 years, and +/- 4 weeks thereafter. At these time points patients will undergo:
    - Physical Examination including ECOG as clinically indicated.
    - Dietary Assessment as clinically indicated.
    - CT C/A/P or PET/CT, except at the 1-month follow-up.
    - General Labs as clinically indicated (refer to list in Section **3.4.3.1**).
    - Nutrition Labs as clinically indicated (refer to Section **3.3**).
    - Completion of QOL questionnaires per schedule in Section **3.4.6**.

Note: Patients with documented disease progression after HIPEC will only be followed thereafter by phone, videocall or other NIH approved remote platform (used in compliance with policy, including HRPP Policy 303) annually for survival, performance status, and new cancer treatment.

3.4.5.2 For Patients Who Are Unable or Unwilling to Return to the NIH Clinical Center

- Patients who are unable or unwilling to return to the CC for follow up evaluation will be followed by telephone, videocall or other NIH approved remote platform contact (used in compliance with policy, including HRPP Policy 303).
- The following information may be obtained:
    - Summary of treatment received since the previous contact as clinically indicated.
    - Estimation of ECOG status as clinically indicated.

- Request for imaging studies, physical exam documentation and laboratory reports to be sent to the PI, as clinically indicated.

3.4.6 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 HIPEC (baseline), at 1 month, 3 months and then every 3 months (+/- 2 weeks) for 2 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 (**Appendix B**)[67]. 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. Patients may complete questionnaires electronically or by phone, videocall or other NIH approved remote platforms (used in compliance with policy, including HRPP Policy 303) as applicable

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 **3.4.5**.

In the event a patient is taken off study, patients will be asked to complete one last set of questionnaires (as appropriate to the point of withdrawal) and the data will be included in the analysis. Patients will be phoned prior to the scheduled date of measurement and asked to complete the questionnaire; the FACT-Ga will then be mailed to the patient with a self-addressed return envelope and a cover letter with the script above as directions. If the questionnaires are not returned within 2 weeks, patients will be phoned again.

3.5 COST AND COMPENSATION

3.5.1 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.

3.5.2 Compensation

Participants will not be compensated on this study.

3.5.3 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.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

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

3.6.1 Criteria for Removal from Protocol Therapy

- Completion of protocol therapy
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Investigator discretion
- Positive pregnancy test

3.6.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Investigator discretion
- Screening failure

- Lost to follow-up
- Death
- PI decision to end the study

3.6.3 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 2 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.

Treatment for Helicobacter pylori will be managed according to standard of care when it is first diagnosed, either at time of initial diagnosis of gastric cancer or at time of surgical intervention. After standard of care medical therapy, follow up testing for eradication will be done either through repeat pathologic analysis (i.e., via the surgical specimen) or via stool antigen testing.

5 CORRELATIVE STUDIES

5.1 BIOSPECIMEN COLLECTION AND PROCESSING FOR RESEARCH

Patients will be co-enrolled on protocol 13C0176. All research specimens will be collected, stored, tracked and disposed of as specified in protocol 13C0176.

All correlative/exploratory studies will be done as indicated on protocol 13C0176. No correlative studies will be done on protocol 17C0070.

Note: See **Appendix D** for a general reference of specimens and collection timepoints, noting that this information is ***only to be used as an overview for reference purposes***; all biospecimens will be collected as indicated on 13C0176.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

For the purposes of the research 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 (pre-operation visit) through 30 days after removal from study treatment or until off-study, whichever comes first. Beyond 30 days after the last dose of study therapy, only adverse events which are serious and related to the study intervention need to be recorded.

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 and for the duration of the study, graded adverse events will be described in the source documents, reviewed by the designated research nurse, and captured in C3D unless otherwise indicated below.

Note: No Grade 1 adverse events will be recorded.

6.1.1.1 Concomitant medications:

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

6.1.1.2 Laboratory Events

Laboratory events will be described in the source documents and captured in C3D as follows:

- **During hospitalization for the HIPEC procedure**, only the following labs will be updated into C3D:
  - Admission labs,
  - First morning labs drawn after 4:00 AM, and
  - Labs that support the diagnosis of a reportable event.
- **In the immediate post-operative period**, only the following values will be captured (including laboratory values obtained at sites other than the NIH Clinical Center):

- 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.

6.1.1.3 Exceptions to Adverse Event Recording

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Is associated with clinical signs or symptoms.
- 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.

Non-laboratory, non-concomitant medication events that will be captured only in the source documents:

- **During hospitalization for surgical resection/HIPEC**
  - Grade 2 events except **unexpected** events that are possibly, probably or definitely related to the research.
- **Post-operative recovery phase (following discharge)**
  - 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 recorded.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

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

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

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository; clinicaltrials.gov.
- Another public repository.
- 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

Genomic testing will not be done under this protocol.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for progression of disease at 3, 6, 9, 12, 15, 18, 21, 24 months and semi-annually (every 6 months) during the 3rd, 4th and 5th years, and then every year after that until off-study. Radiographic or clinical evidence of progression of disease will be confirmed, when necessary, by tissue biopsy.

Intraperitoneal progression of disease will be determined by radiographic evidence of new, large volume ascites with or without associated peritoneal nodularity or thickening. This may be confirmed by PET imaging and/or cytopathology or histopathology obtained by percutaneous biopsy.

Extraperitoneal progression of disease will be confirmed based on characteristic radiographic findings (CT, MRI, and/or PET) and confirmed when indicated by percutaneous tissue biopsy.

Local recurrences will be confirmed endoscopically when necessary.

6.3.1 Methods for Evaluation of 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, Laparoscopy: 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 [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. 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 [*JNCI* 92:1534-1535, 2000].

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT,

additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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

6.3.2 Progression-Free Survival

Intraperitoneal PFS is defined as the duration of time from date of operation (HIPEC and gastrectomy) to the date of first observation of progressive disease within the peritoneal cavity (malignant ascites, peritoneal carcinomatosis), or death, whichever comes first. Extraperitoneal DFS i.e., anything other than peritoneal surface disease progression) is defined as the duration of time from date of surgery to the date of first observation of progressive disease at sites other than the peritoneal surface, such as the liver, intra-abdominal lymph nodes, abdominal wall soft tissues, and any other solid organs.

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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

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 here.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

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 should 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 Dr. Dahut 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 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 or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

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

8 STATISTICAL CONSIDERATIONS

The primary objective of the trial is to determine if there is an improvement in overall survival (OS) in patients who have cytology positive (cyto+M1) gastric cancer when treated with systemic chemotherapy, HIPEC and gastrectomy compared to historical controls. Outcomes reported for patients with positive peritoneal cytology suggest that the median OS for patients receiving systemic chemotherapy is approximately 14 months (range 13–15).[10,13] It was also shown by Mezhir et al that patients who converted to negative cytology had an associated improvement in median overall survival of 24 months. Thus, the goal will be to determine if the treatment strategy of systemic chemotherapy, HIPEC and gastrectomy could be associated with a 24-month median OS compared to 14 months median OS compared to these historical controls.

With 37 evaluable patients receiving the proposed therapy with M1 disease, assuming accrual would take place over approximately 4 years, and that there would be at least 2 years of additional potential follow-up after the last patient has begun the HIPEC therapy, there would be 80% power to determine whether there is a difference between a median 14 month OS and an improved 24 month OS after initiation of systemic treatment, with a one sided 0.10 alpha level test, using the method of Brookmeyer and Crowley (Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. *Biometrics,* 38, 29-41, 1982.). In practice, a Kaplan-Meier curve beginning at the initiation of systemic treatment and appropriate confidence intervals at selected time points will be provided to help interpret results relative to the expected results. At the conclusion of the trial, the patients with poorly differentiated tumors may be evaluated separately

from the remaining patients in order to obtain a preliminary estimate of the efficacy in these two subsets of patients. Evidence of benefit identified may be used to guide future studies evaluating this approach.

Intraperitoneal Progression Free Survival (iPFS) improvement is a secondary objective. Because there is inconsistent and sparse information in the literature about the iPFS of similar patients, the 37 patients determined on the basis of estimating OS, will be used to generate an estimate of the iPFS rates at various time points. This information will be used to help guide subsequent study development as well as providing a publishable, reliable measure of this outcome. To the extent possible, the iPFS results may be informally compared to the few available results to describe the procedure's potential benefit. Other secondary endpoints include distant disease free survival and treatment related morbidity. It is anticipated that 37 total patients can be accrued in approximately 4 years. In order to allow for patients who are inevaluable for the determination of either endpoint, the accrual ceiling will be set at 40 patients.

If the trial is opened to multiple institutions to facilitate patient accrual, the biostatistician will be engaged first to discuss statistical implications or trial design.

9 COLLABORATIVE AGREEMENTS

N/A

10 HUMAN SUBJECTS PROTECTIONS

10.1 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. That is to say, 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.

10.2 PARTICIPATION OF CHILDREN

The surgical regimen used in this protocol is a major procedure which entails serious discomforts and hazards for the subject, such that fatal complications are possible. It is therefore only appropriate to carry out this experimental procedure in the context of life threatening gastric cancer. Since the efficacy of this experimental procedure is unknown, it does not seem reasonable to expose children to this risk without further evidence of benefit. Should results of this study indicate efficacy in treating 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.

10.3 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 **10.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see Section **10.6.1** for consent procedure.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefit to patients undergoing this therapy would be palliation in terms of preventing or delaying intra-abdominal tumor progression and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise. In addition, significant tumor response may extend progression free and overall survival. The risks for this protocol include the risks associated with any abdominal surgery. This includes postoperative bleeding, intra-abdominal infection, wound healing complications including fascial dehiscence, enterocutaneous fistulas, anesthetic mishap and perioperative death. 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.

10.4.1 **Risks**

10.4.1.1 HIPEC

The primary risks of intra-operative perfusion of the abdomen with chemotherapy are bleeding, infection, anastomotic leak, and enterocutaneous fistula. In addition, the chemotherapy may cause bone marrow suppression with decreased blood cell counts in the early post-operative phase.

10.4.1.2 Blood Collection

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

10.4.1.3 Urine Collection

There is no physical risk involved with urine collection.

10.4.1.4 Laparoscopy

Risks include bleeding, infection, hernia, injury to organs in the abdomen, abdominal inflammation, blood clots and adverse reactions to anesthesia.

10.4.1.5 Electrocardiogram (EKG)

This test is safe and side effects are unlikely, but it may be uncomfortable when the electrodes are taken off after the test is completed.

10.4.1.6 Questionnaires

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

10.4.1.7 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 (including gadolinium). 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. Gadolinium for research MRI scans will not be given to patients who have impaired kidney function or who received gadolinium within the previous month.

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

10.4.1.8 Risks of Exposure to Ionizing Radiation

This research study involves the potential for up to 6 CT C/A/P or PET/CT scans, as well as a potential CT-guided biopsy for histologic confirmation, over the course of the first year on study. Subjects will be exposed to approximately 8.0 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 26.7 years of background radiation.

10.4.2 **Potential Benefits**

The potential benefit to subjects undergoing this treatment would be cure, or palliation at a minimum, in terms of preventing or delaying intra-abdominal tumor recurrence and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise.

10.5 RISKS/BENEFITS ANALYSIS

Patients with gastric cancer suffer with recurrent bowel obstructions, nausea, vomiting, crampy abdominal pain and incapacitating ascites. This clinical scenario justifies aggressive treatment strategies as a means of palliation and survival benefit. In Phase I and II trials we have seen long-term remissions after HIPEC in patients who were otherwise terminal with no other therapeutic options available.

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.

10.6 CONSENT PROCESS AND DOCUMENTATION

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

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

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

Manual (Non-Electronic) Signature on Electronic Document:

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

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

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

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

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here.

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

For participants addressed in Section **10.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **10.6**.

10.6.2 Request for Waiver of Consent for Screening Activities

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

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities

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

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 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.

11.2 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.

11.3 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.

11.4 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/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by 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(s) 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.

12 PHARMACEUTICAL INFORMATION

Cisplatin, mitomycin C and sodium thiosulfate are being used off label for the investigation. However, the investigation is not intended to support a new indication for use or any other significant changes to labeling or advertising in any of the commercial agents used on the study. The investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug products, therefore an IND will not be submitted.

For this study, all drugs are commercially available, therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the package insert and other resources. Refer to the package inserts for complete information.

12.1 CISPLATIN

12.1.1 Source

Cisplatin is commercially available as a white lyophilized powder in 10cc and 50cc vials with mannitol and sodium chloride (Platinol, Bristol-Myers, Squibb, Princeton, NJ). It will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

12.1.2 Toxicity

Cisplatin produces renal tubular toxicities associated with renal insufficiency and electrolyte, (i.e. magnesium, potassium, calcium, phosphate, bicarbonate) wasting which may result in significant hypomagnesemia and hypokalemia. Neurotoxicity manifests as both sensory and motor peripheral neuropathies. Cisplatin is also toxic to the 8th cranial nerve producing ototoxicity which consists primarily of deficits in high frequency auditory acuity, but may include vestibular abnormalities. Systemic administration of cisplatin at doses similar to those planned in this study are associated with significant nausea and vomiting and bone marrow suppression, particularly leukopenia and thrombocytopenia. Transient moderate elevations of hepatic transaminases, (i.e. AST, ALT) and acute systemic allergic reactions including anaphylaxis may also occur. The prior Phase I study of CHPP with cisplatin has not identified any regional intraperitoneal toxicity from cisplatin. The dose limiting systemic toxicity was renal toxicity at doses of 350 mg/M2. No other systemic toxicities were identified at that dose level.

12.1.3 Formulation and Preparation

Vials containing 10 and 50 mg of cisplatin will be reconstituted with 10 and 50 cc water for injection, USP, respectively to a concentration of 1 mg/mL. The total dose of cisplatin will be injected into a bag of 0.9% sodium chloride for injection, USP, to make 1 liter of final volume (± 10%) prior to administration.

12.1.4 Stability and Storage

After reconstitution with water for injection, USP, to a concentration of 1 mg/mL, cisplatin is stable at controlled room temperature ($24^0C + 2^0C$) at 37^0C, and at 60^0C for at least 14 days. Further dilution at 0.05 or 0.5 mg/mL with 0.9% sodium chloride injection (NS), USP, yields a solution that is stable for at least 24 hrs at room temperature. Intact vials in reconstituted solution should be maintained at room temperature.

12.1.5 Administration Procedures

Cisplatin at a dose of 90 mg/m2 diluted in 1L of 1.5% dextrose dialysis solution will be added to a stable perfusion system at a flow rate of 1 L/min after draining an equivalent volume. If dialysis solution is not available, then 0.9% sodium chloride will be used.

12.1.6 Incompatibilities

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

12.2 MITOMYCIN

12.2.1 Source

Mitomycin C is commercially available as a white lyophilized powder in 5mg, 20mg or 40mg vials with mannitol (Bedford Laboratories, OH). It will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

12.2.2 Toxicity

Mitomycin is known to cause bone marrow suppression, notably thrombocytopenia and leukopenia which may contribute to infections in an already compromised patient. Hemolytic Uremic Syndrome (HUS) a serious complication of chemotherapy has been reported in patients receiving systemic mitomycin. Other adverse reactions include integument and mucous membrane toxicity, renal toxicity and pulmonary toxicity

12.2.3 Formulation and Preparation

Each vial contains either mitomycin 5 mg and mannitol 10 mg, mitomycin 20 mg and mannitol 40 mg, or mitomycin 40 mg and mannitol 80 mg. To administer, add Sterile Water for Injection, 10 mL, 40 mL, or 80 mL respectively. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

12.2.4 Stability and Storage

Unreconstituted mitomycin is stored at room temperature is stable for the lot life indicated on the package. Avoid excessive heat (over 40° C, 104° F). Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg per mL, mitomycin is stable for 14 days refrigerated or 7 days at room temperature.

12.2.5 Administration Procedures

Mitomycin 10 mg/m^2 diluted in sterile water will be added to the perfusion circuit via syringe or infusion bag and administered via circuit to the peritoneal cavity.

12.2.6 Incompatibilities

Refer to the package insert for complete information about this product

12.3 SODIUM THIOSULFATE

12.3.1 Source

The commercially available product will be purchased by the NIH Clinical Center Pharmacy Department.

12.3.2 **Toxicity**

Other than osmotic disturbances, sodium thiosulfate is well tolerated in humans. Large orally administered doses are associated with a cathartic effect. In preclinical studies in dogs continuous i.v. administration of sodium thiosulfate has produced hypovolemia presumably due to an osmotic diuretic effect.

There have been no controlled clinical trials conducted to systematically assess the adverse events profile of sodium thiosulfate. The medical literature has reported the following adverse events in association with sodium thiosulfate administration. These adverse events were not reported in the context of controlled trials or with consistent monitoring and reporting methodologies for adverse events. Therefore, frequency of occurrence of these adverse events cannot be assessed.

- Cardiovascular system: hypotension
- Central nervous system: headache, disorientation
- Gastrointestinal system: nausea, vomiting
- Hematological: prolonged bleeding time
- Body as a whole: salty taste in mouth, warm sensation over body

In humans, rapid administration of concentrated solutions or solutions not freshly prepared, and administration of large doses of sodium thiosulfate have been associated with a higher incidence of nausea and vomiting. However, administration of 0.1 g sodium thiosulfate per pound up to a maximum of 15 g in a 10-15% solution over 10-15 minutes was associated with nausea and vomiting in 7 of 26 patients without concomitant cyanide intoxication.

In a series of 11 human subjects, a single intravenous infusion of 50 mL of 50% sodium thiosulfate was associated with increases in clotting time 1-3 days after administration. However, no significant changes were observed in other hematological parameters.

12.3.3 **Formulation and Preparation**

Sodium thiosulfate injection, USP, is commercially available as a sterile nonpyrogenic solution of sodium thiosulfate dissolved in water for injection, USP, at concentrations of 10% (100 mg/mL) at 25% (250 mg/mL). The commercial formulation may also contain boric acid and sodium hydroxide to adjust the pH to 8.5 - 9.0.

12.3.4 **Stability and Storage**

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

12.3.5 **Administration Procedures**

Sodium thiosulfate will be administered will be administered by continuous intravenous infusion starting immediately prior to the perfusion and continuing for a total of 12 hours.

A loading dose of 7.5 gm/m2 of sodium thiosulfate will be diluted in 150cc of 0.9% sodium chloride for injection. This loading dose will be infused over 20 minutes beginning with the addition of cisplatin to the peritoneal perfusion circuit.

Immediately following this bolus dose an additional 25.56 gm/m2 of sodium thiosulfate will be diluted in 1000cc of 0.9% sodium chloride for injection for a maintenance infusion of 2.13 gm/m2 per hour for 12 hours. The maintenance infusion will be delivered by infusion pump.

12.3.6 **Incompatibilities**

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

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14 APPENDICES

14.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

14.2 APPENDIX B: FACT-GA (VERSION 4)

FACT-Ga (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Ga (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Ga (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

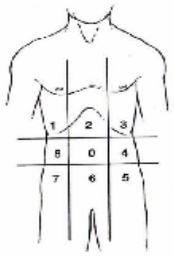
	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
Ga2	I am bothered by reflux or heartburn	0	1	2	3	4
HN1	I am able to eat the foods that I like	0	1	2	3	4
Ga6	I have discomfort or pain when I eat	0	1	2	3	4
Ga5	I have a feeling of fullness or heaviness in my stomach area	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
Ga 12	I have trouble swallowing food	0	1	2	3	4
Ga4	I am bothered by a change in my eating habits	0	1	2	3	4
E6	I am able to enjoy meals with family or friends	0	1	2	3	4
Ga 10	My digestive problems interfere with my usual activities	0	1	2	3	4
Ga9	I avoid going out to eat because of my illness	0	1	2	3	4
Ga7	I have stomach problems that worry me	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4
Ga 14	I am bothered by gas (flatulence)	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
Leu4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

14.3 APPENDIX C: CARCINOMATOSIS EXTENT EVALUATION

Carcinomatosis Extent Evaluation

Patient NIH ID #

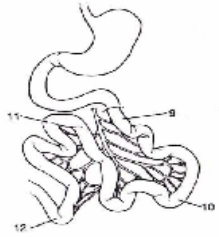
Peritoneal Cancer Index



Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____

PCI ☐

Lesion Size Score
LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



Region	Before Surgery	After Surgery
Region 0		
Region 1		
Region 2		
Region 3		
Region 4		
Region 5		
Region 6		
Region 7		
Region 8		
Region 9		
Region 10		
Region 11		
Region 12		
Total PCI score		

14.4 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 will be as indicated in protocol 13C0176.

Venous research blood and urine samples will be collected at Pre-Op and Post-Op visits, approximately 1, 3, 6, 9, 12, 15, 18, 21 and 24 months from the date of operation, and then every 6 months during Years 3-5, and then yearly thereafter:

- 8 mL blood in an EDTA lavender top tube;
- 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.

Normal and tumor tissue will be collected for research during the clinically indicated surgical operation prior to HIPEC (see Section **3.4.2.1**). These research tissue will be procured according to NIH Clinical Center standard of practice. Peritoneal lavage fluid will be sent for cytopathologic analysis for research purposes.

15 TABLES AND FIGURES

15.1 TABLE 1: SYSTEMATIC REVIEW

Gastric Cancer									
Author, Year (Study Type)	**Total/ (H)IPEC/ Other/ No HIPEC**	**Stage**		**IP Method**	**IP Agent & dose**	**Systemic Tx**	**Median Follow-up**	**Clinical Outcome**	**P-Value**
		I-III	**IV**						
Kang et al., 2013 (RCT)	521 258 263	217 214	46 44	NIPEC Sx & SC	CDDP 100mg in 1L x 2hr	NIPEC: IV MMC, PO DFU, IV CDDP Sx: IV MMC, po DFU, MMC	80.1mo 75.6mo	3yr OS 71% vs 60% 5yr OS: 59% vs 50%	0.006
Miyashiro et al., 2011 (RCT)	268 135 133	135 131	0 2	NIPEC Sx & SC	CDDP 70mg/m2 x2h	IV CDDP 70mg/m2 d14, 5FU 700mg/m2 qd d14-16, po UFT qd 4wk-12mo	6yr	5yr OS 62.0% NIPEC vs 60.9% Sx alone 5yr DFS 57.5% vs 55.6%	0.482
Yonemura et al., 2001 (RCT)	139 48 44 47	35 29 38	13 15 9	HIPEC NIPEC Sx alone	HIPEC: MMC 30mg, CDDP 300mg NIPEC: Same at 37C n/a	ND	5.5yr	5yr OS: 61% HIPEC vs 44% NIPEC or 42% Sx alone	0.021
Fujimoto et al., 1999 (RCT)	141 71 70	58 62	13 8	HIPEC Sx & SC	MMC 10ug/mL in 3-4L	Chemo NOS	ND	2yr OS: 88% HIPEC vs 77% Sx alone 4yr OS: 76% vs 58% 8yr OS: 62% vs 49%	0.0362
Shimoyama et al., 1999 (RCT)	87 30 24 33	30 23 32	1 1 1	NIPEC Portal Sx & SC	NIPEC: MMC 10mg PV: Same	All: IV CDDP & UFT	47mo	1yr OS: 81% (Diffuse type control), vs 94% (Diffuse type NIPEC) 4yr OS: 32%, vs. 73%	 0.049
Rosen et al., 1998 (RCT)	91 46 45	91	0	NIPEC Sx alone	MMC 50mg, CH 375mg x 24hr	ND	597d	Median OS 738.9d NIPEC vs. 515.4d Sx DFS 554.8d vs 380.4d	0.44 0.48
Yu et al., 1998 (RCT)	248 125 123	89 88	36 35	EPIC Sx alone	EPIC: MMC 10mg/m2 POD1, 5FU 700mg/m2 in 1L qd x4 starting POD2	ND	36mo	5yr OS of EPIC 54% vs 38%	0.0278
Ikeguchi et al., 1995 (RCT)	174 78	64	14	HIPEC	MMC 80-100 mg/m2	IV MMC 10mg on d7&14, po UFT 600mg/d d14-6mo	6yr	5yr OS 51% HIPEC vs 46% Sx alone	NS

	96	76	20	Sx & SC		Same MMC on d0,7&14, same UFT			
Takahashi et al., 1995 (RCT)	113 56 57	ND	ND	 NIPEC Sx alone	MMC 50mg in 100mL & CH 375mg x3hr	ND	ND	2yr OS: 66% NIPEC vs 35% control 3yr OS: 66% vs 20%	<0.01
Fujimura et al., 1994 (RCT)	58 22 18 18	 17 13 10	 5 5 8	 HIPEC NIPEC Sx alone	HIPEC: CDDP 300 mg, MMC NIPEC: same at 37-38C	ND	 35mo 37mo 31mo	1yr OS: 95% HIPEC, 81% NIPEC, 43% Sx alone 2yr OS: 89%, 75%, 23% 3yr OS: 68%, 51%, 23%	<0.01
Hamazoe et al., 1994 (RCT)	82 42 40	 38 33	 4 7	 HIPEC Sx alone	MMC 10ug/mL	ND	ND	5yr OS 64.3% HIPEC vs. 52.5% Median OS: 77mo vs 66mos	0.2427
Sautner et al., 1994 (RCT)	67 33 34	 26 27	 7 7	 EPIC Sx alone	POD 10-28: CDDP 90 mg/m2 q1mo	ND	72.5mo	Median OS 17.3 vs. 16.0 mo OS: 1yr - 66.8% vs 57.6%, 3yr - 33.3% vs 30.3%; 5 yr - 21.2% vs 23.6%	0.8 0.6
Kaibara et al., 1989 (RCT)	82 42 40	 42 40	 0 0	 HIPEC Sx alone	MMC 10mg/L	ND	ND	5yr OS 71.5% HIPEC vs 59.7% Sx alone	NS
Koga et al., 1988 (RCT)	60 32 28	 30 24	 2 4	 HIPEC Sx alone	MMC 8-10 mg/L in 2L	ND	ND	30mo OS: 83% HIPEC vs 67.3% Sx alone	NS
Topuz et al., 2002 (PSA)	39	39	0	EPIC	Post-op 3-6wk: CDDP 60 mg/m2, MMC 12 mg/m2, 5FU 600 mg/m2, FA 60 mg/m2 q4wk x 6	ND	23mo	Median DFS 12mo & median OS 19 mo Cumulative 5-yr DFS & OS were 24.7% & 30.7%	n/a
Jones et al., 1994 (PSA)	18	16	2	EPIC	Median 6wk post-op: CDDP 60mg/m2 q21d x4 (x6 if peritoneal washings positive)	ND	ND	Median OS 17 mo	ND
Atiq et al., 1993 (PSA)	35	34	1	EPIC	Post-op14-28d: CDDP 25 mg/m2 & FU 750 mg qd x 4; q28d x 5	FU IV750 mg/m2 x4d	24mo	Median OS 24.9 mo	n/a
Hirose et al., 1999 (PSA/CC)	55 15 40	 12 33	 3 7	 HIPEC Sx & SC	 CDDP 100mg, MMC 20mg, Etoposide 100mg	2-3wk post: IV MMC 6mg/m2, 5FU 375mg/m2 qwk x 3	14.6mo	3yr OS: 48.9% HIPEC vs 28.8% Sx 5yr OS: 39.1% vs 17.3%	0.0142 0.0425

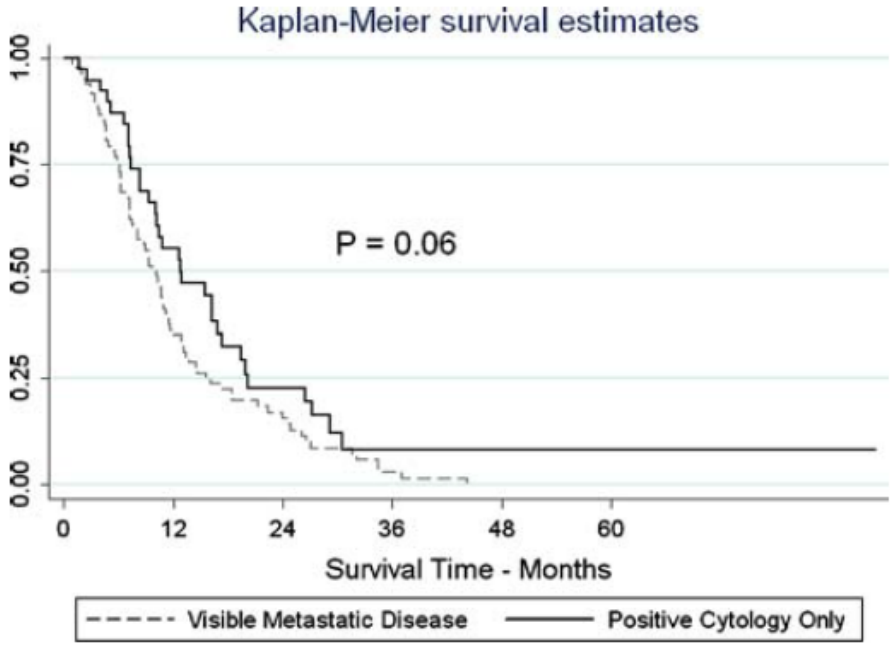
Abbreviations: HIPEC, heated intraperitoneal chemotherapy; Tx, treatment; RCT, randomized control trial; Sx, surgery; MMC, mitomycin-C; CDDP, cisplatin; op, operative; ND, not discussed; OS, overall survival; SC, systemic chemotherapy; IV, intravenous; d, day; UFT, 1-(2-tetrahydrofuryl)-5-fluorouracil/uracil (1:4); NS, non-significant; PSA, prospective single arm; FA, folinic acid; DFS, disease free survival; NOS, not otherwise specified; EPIC, early post-operative intraperitoneal chemotherapy; POD, post-operative day; MMC-CH, mitomycin-C bound to activated carbon particles); DFU, po doxifluridine; CC, case control.

15.2 TABLE 2: CYTOPATHOLOGIC ANALYSIS DEFINITIONS

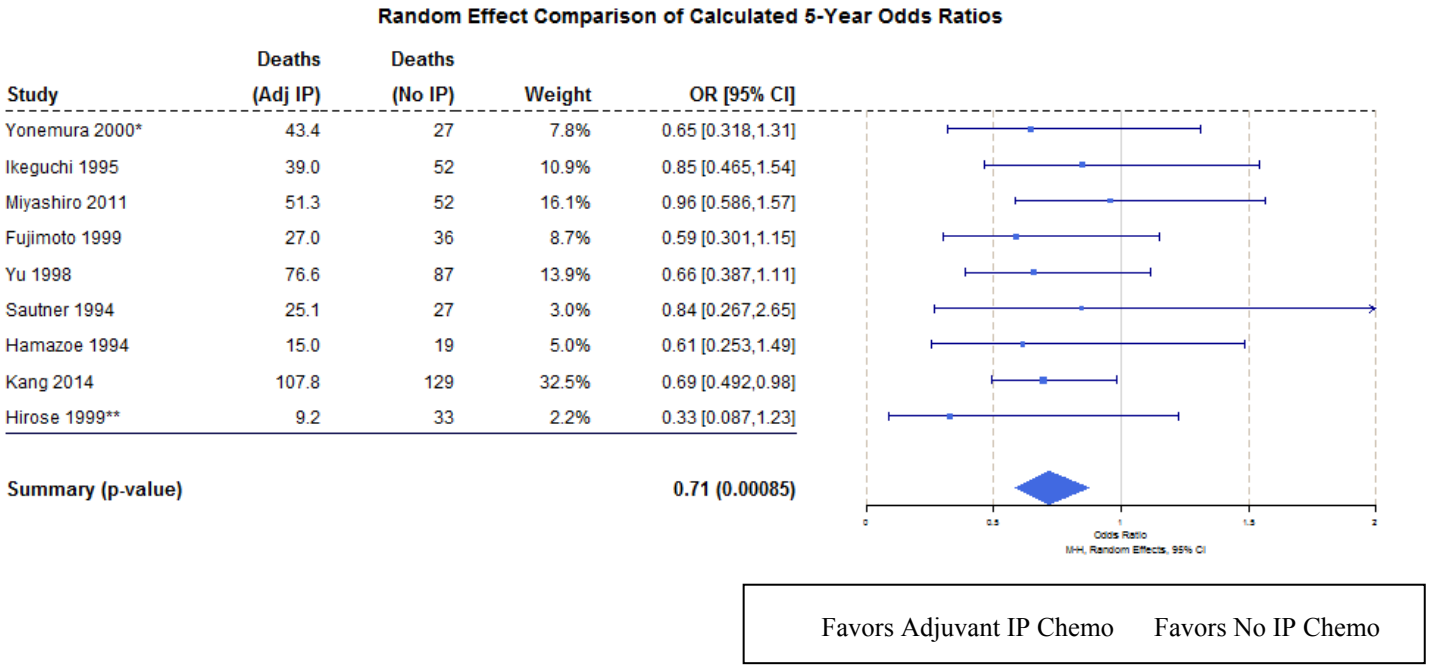
Results	Description
Negative	No evidence of cancerous cells
Malignant (Positive)	Morphologic evidence of cancerous cells
Atypical cells of undetermined significance	Indistinguishable morphologic cellular changes; (Requires repeat cytologic sampling before protocol eligibility can be determined.)
Non-diagnostic	Not enough cellular material or poor cell preservation
Not satisfactory	Not enough cellular material or poor cell preservation

Peritoneal lavage fluid undergoes cytospin and papanicolaou or diff-quik stain for morphologic analysis. Remaining cell block will undergo formalin fixation and paraffin embedding for H&E staining, and immunohistochemistry using an antibody panel of cytokeratin, BerEP4, B72.3 and claudin-4.

15.3 Figure 1: Overall Survival of Patients with Positive Cytology Only Compared to Visible Metastatic Disease at Time of Laparoscopy



15.4 FIGURE 2: RANDOM EFFECT MODEL INDICATING POTENTIAL SURVIVAL ADVANTAGE OF IP CHEMO IN SYSTEMATIC LITERATURE REVIEW



15.5 FIGURE 3: ONCOPRINT INDICATING RECURRING GENOMIC ALTERATIONS IN MULTIPLE GASTRIC ADENOCARCINOMA SUBTYPES