Phase II Trial of Cytoreduction + Hyperthermic Intraperitoneal Mitomycin-C + Standard Systemic Therapy In Patients With Peritoneal Carcinomatosis for Advanced Non-small Cell Lung Cancer

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1. BACKGROUND:

1.1 Rationale for doing the study

Peritoneal carcinomatosis (PC) refers to extensive dissemination of tumors on the peritoneal surfaces of the abdomen. PC is a common mode of spread of cancers of gastrointestinal origin, gynecologic tumors and occasionally cancers from other sites. PC is a major cause of treatment failure, morbidity and death in cancer patients. It often causes a marked decline in quality of life and presents as pain, ascites, and bowel obstruction. These conditions are caused by progressive involvement of the peritoneal surfaces by tumor seeded within the peritoneal cavity.

PC is a frequent manifestation in the natural history of numerous types of malignancies and has been traditionally regarded as a terminal disease with short median survival [1]. Colorectal cancer presents with metastases to the peritoneum in 10-15% of patients at the time of diagnosis [2]. Cancer recurrence confined to the peritoneum occurs in up to 25% of patients who have been treated curatively [3]. Peritoneal carcinomatosis from gastric cancer can be found in 10% to 20% of patients at the time of initial surgery and in up to 60% of patients who have undergone a curative resection for T3/T4 tumors [4]. The other common primary tumors for nonovarian peritoneal carcinomatosis include peritoneal mesothelioma, pseudomyxoma peritonei, and appendiceal adenocarcinoma[1, 5].

Peritoneal carcinomatosis represents a formidable treatment challenge in oncology. Once considered a variant of systemic spread of disease, peritoneal carcinomatosis of different tumor origins was traditionally treated with palliative systemic chemotherapy alone, with surgery reserved only for palliation of disease- or treatment-related secondary events such as bowel obstruction and ascites. Systemic multi-drug chemotherapy has not altered the natural history of peritoneal carcinomatosis, as patients suffer disease progression and functional deterioration due to visceral obstruction, malignant ascites and cancer cachexia over a limited median survival of 5 to 9 months [6-9].

The biology of peritoneal carcinomatosis is quite different than hematogenous metastasis. Insights into the natural history of peritoneal tumor dissemination have engendered novel multi-modality treatment approaches to address this challenging clinical problem. Tumor dissemination across peritoneal surfaces occurs through established mechanisms of direct tumor extension, transcoelomic tumor cell spread in peritoneal fluid, and malignant peritoneal seeding from surgical manipulation of the tumor, and can occur in the absence of regional or distant nodal or systemic metastases [10-12]. Confinement of disease to the parietal peritoneal surface, in the absence of systemic metastasis, has served as the basis for surgical eradication of disease through aggressive surgical cytoreduction. However, surgery alone may not achieve significant improvement in survival in patients with peritoneal carcinomatosis, as microscopic or grossly apparent disease inevitably remains after even aggressive cytoreduction [13, 14].

The ineffectiveness of systemic chemotherapy for PC can be partially attributed to viable tumor cells that become sequestered in avascular intra-peritoneal adhesions [15]. The presence of an anatomic barrier between the peritoneal cavity and plasma has enabled administration of high

local concentrations of chemotherapy at the peritoneal surface, far in excess of systemically administered agents, when drug delivery is intra-peritoneal [16-19]. High molecular weight agents such as Mitomycin C, and Oxaliplatin (397 Da) have favorable pharmacokinetic profiles (AUC, peritoneal fluid relative to plasma: Mitomycin C, 75:1; Oxaliplatin, 25:1) permitting dose-dense intra-peritoneal therapy over prolonged periods with rapid tissue concentration (in residual tumor deposits and peritoneum), but limited systemic absorption or toxicity[20-23]. This particular therapeutic approach addresses the problem of systemic chemotherapy resistance and with its reduced systemic toxicity provides distinct pharmacological advantage over systemic drug delivery[24, 25].

[6, 31].

Despite the high concentrations of the chemotherapeutic agent at the peritoneal surfaces, a limiting factor is the narrow depth of tissue penetration by the delivered cytostatic agent [32]. Penetration of these commonly used chemotherapeutic agents is limited to ≤ 3 mm from the parietal peritoneal surface [23, 33, 34]. Therefore, the efficacy of hyperthermic intra-peritoneal chemotherapy is inversely proportional to the volume of residual disease. The therapeutic benefit of hyperthermic intra-peritoneal chemotherapy is greatest when all grossly apparent disease is resected (complete cytoreduction), leaving behind only microscopic disease.

This emphasizes the importance of complete cytoreduction which is conducted with the intent to eradicate macroscopic deposits of tumor and optimize the efficacy of hyperthermic chemotherapy in obliterating minimal residual disease. Optimal therapeutic synergy is achieved when intra-peritoneal heated chemotherapy is administered immediately following maximal cytoreduction, thereby minimizing trapping of viable peritoneal tumors cells in fibrin and post-operative adhesions, and maximizing kill of tumor cells shed during resection [35, 36]. Adhesions are lysed during cytoreduction to facilitate uniform distribution of perfusate, maximize direct contact of drug with residual peritoneal tumor cells, and harness the advantage of "thermo-chemotherapeutic" anti-tumor synergism [25, 36-38].

The combination of cytoreductive surgery (CS) and hyperthermic intra-peritoneal chemotherapy can result in longer survival than CS alone in an experimental model with peritoneal carcinomatosis of colorectal origin [36]. This combination has also shown promising oncological outcomes in clinical studies [1, 39, 40].

A multi-center registry study of over 500 patients with peritoneal carcinomatosis of colorectal origin treated with this approach reported median overall survival of 19.2 months, and 3- and 5-year overall survival rates of 39% and 19%, respectively[40]. For patients with no macroscopic residual disease after cytoreduction (CCR0) in that study, 3- and 5-year overall survival was 47% and 31%, with median survival of 32.4 months, similar to outcomes following complete resection of colorectal liver metastases. Treatment with adjuvant systemic chemotherapy after cytoreduction and peri-operative hyperthermic chemotherapy was an independent predictor of improved survival on multivariate analysis. This study, though retrospective in nature, suggested that improved outcomes are indeed possible with a combined modality treatment approach incorporating cytoreductive surgery, regional intra-peritoneal chemotherapy with or without adjuvant systemic therapy in patients that could otherwise expect limited survival ranging from 5-8 months [6, 7, 14]. Overall survival in a large international registry study was consistent with that reported in prior smaller Phase II studies of combined cytoreduction and perioperative hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis of colonic origin and other nonovarian origin [41-49].

A single-institution, randomized controlled (Phase III) trial demonstrated the superiority of this combined modality approach for patients with colorectal peritoneal carcinomatosis over systemic chemotherapy, with or without surgical palliation [50]. One hundred five patients with colorectal peritoneal carcinomatosis were randomly assigned to receive "standard," 5-FU/LV, systemic chemotherapy or hyperthermic intra-peritoneal chemotherapy with Mitomycin C (HIPEC; Mitomycin C, 35 mg/m2 at 41 degrees C for 90 minutes) following aggressive cytoreduction. After a median follow up time of 22 months, median survival was increased significantly in the HIPEC arm of the study: 22.4 vs. 12.9 months; hazard ratio = 0.55: 95% CI, 0.32-0.95. However, the absolute survival benefit of ~10 months in that study was offset by considerable treatment-related morbidity (Grade 4 morbidity = 45%) and mortality (8%) in the study arm. A significant proportion of treatment-associated complications (median operative blood loss 4,000 ml; small bowel fistula, 15%; operative site infection, 6%; renal failure, 6%; pancreatitis, 2%) have been hypothesized to be due to the high dose of intra-peritoneal hyperthermic Mitomycin C, which was administered in the context of the trial. Reductions in intraperitoneal Mitomycin C doses have been recommended on that basis.

Others have demonstrated significantly lesser treatment-related morbidity (23%-35%) and mortality (0-4%) with intra-peritoneal thermo-chemotherapy utilizing reduced Mitomycin C doses [37, 47, 51]. Acceptable therapeutic toxicity has been reported in these studies with relatively lower doses of intra-peritoneal Mitomycin C without apparent compromise in treatment efficacy [37]. The Dutch trial demonstrated benefit of cytoreductive surgery with HIPEC for patients with colorectal carcinomatosis[50]. Patients with peritoneal carcinomatosis with metastatic disease confined to the peritoneal surface treated with complete (CCR0) cytoreduction and HIPEC have demonstrated median survival exceeding 40 months (range 28-60 months) [40-49].

Studies showed that cytoreductive surgery combined with HIPEC is a safe treatment and could improve survival rates of patients with nonovarian peritoneal carcinomatosis [1, 9, 39, 52]. A retrospective, multicenter cohort study included 1290 patients from 25 institutions who underwent 1344 procedures between February 1989 and December 2007. HIPEC was performed in 1154 procedures. The principal origins of PC were colorectal adenocarcinoma (N =523),

pseudomyxoma peritonei (N = 301), gastric adenocarcinoma (N = 159), peritoneal mesothelioma (N = 88), and appendiceal adenocarcinoma (N = 50). The overall morbidity and mortality rates were 33.6% and 4.1%, respectively. In multivariate analysis, patient age, the extent of peritoneal carcinomatosis, and institutional experience had a significant influence on toxicity. The overall median survival was 34 months; and the median survival was 30 months for patients with colorectal origin, not reached for patients with pseudomyxoma peritonei, 9 months for patients with gastric origin, 41 months for patients with peritoneal mesothelioma, and 77 months for patients with peritoneal carcinomatosis from appendiceal adenocarcinoma [1].

In a phase II study, a total of 101 consecutive patients were treated with cytoreductive surgery, HIPEC and early postoperative intraperitoneal chemotherapy [5]. Tumor types included appendiceal (n = 58), colorectal (n = 31), and other (n = 12). Median follow-up was 28 months (range, 0-119 months), with minimum of 24 months among survivors. For appendiceal tumors, median disease-free survival (DFS) was 34 months (range, 0-119 months) and overall survival (OS) has not yet been defined. Three-year and 5-year DFS was 48% and 42%, respectively, and 3-year and 5-year OS was 76% and 62%, respectively. For colorectal carcinomatosis, median DFS and OS was 9 months (range, 0-87 months) and 27 months (range, 0-87 months), respectively. Three-year and 5-year DFS was 34% and 26%, respectively, and 3-year and 5-year OS was 38% and 34%, respectively. The results indicated that long-term survival is achievable for patients with peritoneal carcinomatosis from appendiceal or colorectal primary tumors who received regional treatment with cytoreductive surgery and HIPEC [5].

A single-institution, randomized controlled (Phase III) trial demonstrated the efficacy and safety of a combination of cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) compared to CRS alone for the treatment of peritoneal carcinomatosis from gastric cancer [53]. Sixty-eight gastric peritoneal carcinomatosis patients were randomized into CRS alone (n = 34) or CRS and HIPEC (n = 34) with cisplatin 120 mg and mitomycin C 30 mg each in 6000 ml of normal saline at 43 ± 0.5°C for 60-90 min. At a median follow-up of 32 months (7.5-83.5 months), death occurred in 33 of 34 (97.1%) cases in the CRS group and 29 of 34 (85.3%) cases of the CRS + HIPEC group. The median survival was 6.5 months (95% confidence interval 4.8-8.2 months) in CRS and 11.0 months (95% confidence interval 10.0-11.9 months) in the CRS + HIPEC groups (P = 0.046). Four patients (11.7%) in the CRS group and 5 (14.7%) patients in the CRS + HIPEC group developed serious adverse events (P = 0.839). Multivariate analysis found CRS + HIPEC and no serious adverse events were independent predictors for better survival [53]. Similar results were also observed in another study of 30 patients with peritoneal carcinomatosis of gastric origin [54]. The best indications for this treatment are localized peritoneal carcinomatosis from resectable gastric cancer that can be completely removed during a peritonectomy. Complete cytoreduction and hyperthermic intraperitoneal chemotherapy are essential treatment modalities for improving the survival of patients with peritoneal carcinomatosis from gastric cancer.[54]

A standardized, evidence-based approach is currently lacking for patients with peritoneal surface malignancy from gastrointestinal origin. A clinical trial with surgical quality assurance and modern hyperthermic intraperitoneal chemotherapy incorporating critical assessment of disease burden, determinants of complete cytoreduction, treatment-related toxicity, quality of life and survival is imperative. Theoretically, cytoreductive surgery is performed to treat

macroscopic disease, and hyperthermic intraperitoneal chemotherapy is used to treat microscopic residual disease with the objective of removing disease completely in a single procedure.

This single arm study will be conducted recognizing the importance of surgical standardization and quality control, as well as hyperthermic intraperitoneal mitomycin-C for patients with malignancy of colorectal, appendiceal, pseudomyxoma, peritoneal mesothelioma or gastric origin having resectable dissemination of peritoneal disease, absent apparent hematogenous or distant nodal disease spread, and who are considered suitable candidates for aggressive local-regional therapy with CRS and HIPEC.

1.2 Justification for evaluating Cytoreduction plus Hyperthermic Intraperitoneal Heated Mitomycin C (HIPEC)

Patients with peritoneal surface malignancy from gastrointestinal (GI) cancers almost uniformly succumb to advanced locoregional disease in the form of intractable ascites, malignant visceral obstruction and cancer cachexia. The natural history of pertitoneal carcinomatosis from GI malignancies is inexorably lethal with median overall survival of approximately 5 months [7], as patients with disease confined to the peritoneum remain at increased risk of synchronous occult hematogenous metastases. While systemic therapy improves outcome in patients with hematogenous disease spread, improvements are needed in the control of peritoneal surface malignancy, which is known to be relatively resistant to systemic agents owing principally to the presence of a peritoneal-plasma partition. Moreover, the results of surgical resection alone for peritoneal dissemination of GI cancer have been disappointing given the difficulty in clearing surgically all microscopic disease foci. The infusion of chemotherapy into the peritoneal cavity provides distinct pharmacokinetic advantages. The addition of hyperthermia potentiates the effect of intra-peritoneal chemotherapy through anti-tumor synergism, without systemic drug absorption [35-38].

Mitomycin C is the cytotoxic agent of choice for this purpose, one that has been studied most extensively for hyperthermic intra-peritoneal chemotherapy in patients with peritoneal carcinomatosis of gastrointestinal origin. Mitomycin C has also been shown to demonstrate consistent pharmacokinetics, favorable toxicity profile, and hyperthermia-facilitated tumor cytotoxicity, which is enhanced under conditions of tumor hypoxia; furthermore, Mitomycin C contributes to improved outcomes after optimal cytoreduction [26, 33, 38, 44, 46, 48, 55, 56]. Hence, the delivery of intra-peritoneal heated chemotherapy has the advantage of dose-dense regional delivery of cytotoxic agents with relatively little systemic toxicity. Current clinical experience suggests that adding cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy to modern systemic chemotherapy regimens may significantly improve oncological outcomes.

2. STUDY OBJECTIVES: Review Side Effects and Outcomes

Primary objective:

- This prospective trial will evaluate the technical parameters including completeness of cytoreduction, , morbidity and mortality in patients with peritoneal carcinomatosis of colorectal, gastric, appendiceal, pseudomyxoma peritonei and peritoneal mesothelioma origin undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin C.

Secondary objectives:

- To evaluate time to progression and progression free survival (PFS) for patients with peritoneal carcinomatosis treated with CRS + HIPEC.
- To evaluate overall survival for patients with peritoneal carcinomatosis treated with CRS + HIPEC.

3.0 ENDPOINTS

3.1 Primary endpoint

The primary endpoint for analysis is to evaluate the technical parameters including completeness of cytoreduction, , morbidity and mortality in patients with peritoneal carcinomatosis undergoing CRS and HIPEC with mitomycin C. Patients who have satisfied the inclusion criteria will be taken to the operating room for exploration and cytoreductive surgery. We will record the completeness of cytoreduction (CC 0 – CC 3) as described below. Complete cytoreduction will be defined as a CC 0 or CC1.. Adverse events will be assessed through enrollment following study treatment. The severity of adverse events will be evaluated using NCI-CTCAE version 4. Adverse events which are assessed as possibly, probably, or definitely related to study treatment will be followed until the AE is resolved or the subject is clinically stable. Other safety data including physical examinations, vital signs, hematology, clinical chemistry, and urinalysis will be collected from time of informed consent signed up through subject discontinuation or 12 months after initial study treatment, whichever occurs first.

3.2 Secondary endpoints

3.2.1 Progression-free survival (**PFS**)

PFS is defined as time from operation date to the first documentation of disease progression or death as a result of any cause, whichever comes first. PFS will be censored at the date of last documented progression-free status for patients who are still progression-free, alive or lost to follow-up.

Determination of disease progression will be based on:

- Radiological (CT ± PET), and/or

- Surgical (laparoscopic or open exploration) evidence of recurrent disease. Peritoneal disease progression will be confirmed by cytology or histology revealing cells morphologically consistent with malignant tumor cells

The following events are considered as disease progression/recurrence:

- Symptomatic or new ascites with peritoneal cytology positive for malignancy, 8 or more weeks following operation; and/or,
- Any new peritoneal surface tumors evident after complete cytoreduction by helical computed tomography, and/or biopsy-positive for malignancy; or,
- Fifty percent or greater increase in peritoneal surface tumors evident after incomplete cytoreduction by helical computed tomography (progression of residual disease), 8 or more weeks after operation; or,
- Any post-operative small bowel obstruction requiring re-operation with histologically confirmed malignant obstruction; or
- If other indications progression/recurrence are not present, serum CEA and/or CA19-9 exceeding Upper Limit of Normal (ULN), and increasing ≥50% from last cycle of systemic therapy, verified by two CEA and/or CA19-9 measurements, ≥2 weeks apart, 8 or more weeks after operation.

3.2.2 Overall Survival (**OS**)

OS is defined as the time from operation date to death from any cause. OS will be censored at the date of last follow up visit for patients who are still alive or lost to follow up.

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4.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Patients must satisfy the following conditions to be eligible for study enrollment and participation.

1. Age ≥ 18 years
2. Capable of providing informed consent.
3. The patient who has not previously received hyperthermic intraperitoneal chemotherapy must have histopathologically or cytologically confirmed cancer from peritoneal mesothelioma, pseudomyxoma, or gastrointestinal malignancies (excluding pancreatic and

hepatobiliary) with known synchronous or metachronous disease dissemination limited to the peritoneal surfaces.
4. The patient must have documented disease limited to the peritoneal surface, amenable to complete cytoreduction indicated by:

- Disease confined to the peritoneal surfaces
- No parenchymal liver metastases
- No evidence of clinical, biochemical or radiological biliary obstruction
- Small volume of disease in the gastro-hepatic ligament defined by a < 5cm mass in the epigastric region on cross-sectional imaging
- No clinical or radiological evidence of hematogenous or distant nodal metastasis

5. ECOG performance status of ≤ 1
6. Absolute neutrophil count (ANC) > 1500/mm3, white blood cell count (WBC) > 4000/mm3 and platelet count > 100,000/mm3
7. Adequate hepatic function must be met as evidenced by total serum bilirubin ≤ 1.5 mg/dl (patients with total bilirubin > 1.5 mg/dL eligible only with Gilbert's syndrome);
• alkaline phosphatase < 2.5 times the upper limit of normal; and/or
• AST < 1.5 times upper limit of normal
(alkaline phosphatase and AST cannot both exceed the upper limit of normal)
8. Adequate renal function: Creatinine <1.5x the upper limit of normal (ULN) or calculated creatinine clearance of ≥50ml/min.
9. Satisfactory cardiopulmonary function (no history of severe congestive heart failure or severe pulmonary disease, as indicated by clinically acceptable risks to undergo major abdominal - cytoreductive surgery).

4.1.2 Exclusion criteria:
1. The patients have documented disease beyond the peritoneal surfaces, which prevent achieving complete cytoreduction as indicated by:

- Evidence of distant hematogenous metastatic disease or distant nodal metastases
- Evidence of parenchymal hepatic metastases
- Evidence of clinical, biochemical or radiological biliary obstruction
- Evidence of gross disease of the small bowel mesentery characterized by distortion, thickening or loss of mesenteric vascular clarity which limits ability to obtain complete cytoreduction

2. Significant history of a medical problem or co-morbidity that would preclude the patient from undergoing a major abdominal operation such as a history of severe congestive heart failure or active ischemic heart disease.
3. Active systemic infections, coagulation disorders, or other major medical illnesses precluding major surgery.
4. Childs B or C cirrhosis or with evidence of severe portal hypertension by history, endoscopy or radiologic studies.
5. Significant COPD or other chronic pulmonary restrictive disease with PFTs indicating a FEV1 less than 50% or a DLCO less than 40% predicted for age
6. Psychiatric or addictive disorders or other conditions that would preclude the patient from meeting the study requirements.
7. Patients in pregnant or lactating.
8. Patients with a Body Mass Index (BMI) of 40 or more.

4.2 Screening and follow-up evaluation

All required entry and follow-up studies are listed in the study chart.

Table 1: Required Entry and Follow-up Studies

Required Exams[a]	Screening evaluation (within 6 weeks before registration unless otherwise specified)	After entry, before HIPEC therapy/ operation begins	Follow-up[g]	
			Every 3 months for 1 year	Every 6 months for 4 years thereafter
History, Physical Exam	x		x	x
ECOG Performance	x			
Adverse event assessment			x	x
Laboratory Studies				
Complete Blood Count	x		x	x
CBC Differential	x		x	x
Absolute Neutrophil Count	x		x	x
Pregnancy test (women of reproductive potential)	x			
Chemistries				
Serum Creatinine	x			
Serum BUN	x			
Serum AST	x			
Serum Alkaline Phosphatase	x			
Serum Bilirubin	x			
Tumor Marker				
Serum CEA +/- CA19-9	x		x	x
Scans, Other				
Chest/Abdomen/Pelvis[ef]	x		x	x
Laparoscopy	x[b]			
Cardiac testing	x[c]			
Bone Imaging	x[d]			
Electrocardiogram	x			
Quality of Life Questionnaires[h]	x		x	x

a. History and physical (H&P), hematological studies, chemistries, and appropriate diagnostic testing may be performed at more frequent intervals at the discretion of the principal investigator.

b. Laparoscopy can be used at the discretion of the evaluating surgeon to determine if the patient is a candidate for a complete cytoreductive surgery and HIPEC.

c. Study subjects with intermediate clinical predictors should undergo non-invasive cardiac testing. The need for cardiac testing prior to patient registration will be determined in consultation with internal medicine or cardiology and take into consideration major clinical predictors (unstable coronary syndromes, decompensated CHF, significant arrhythmia, valvular heart disease), functional capacity, and intermediate clinical predictors (mild angina, prior MI, compensated or prior CHF, diabetes).

d. Bone scan is required if alkaline phosphatase is > ULN or if the patient has unexplained bone pain.

e. Spiral CT or MRI is required.

f. Chest/Abdomen/Pelvis imaging should be performed every 3 months for the first 1 year then every 6 months for 4 years. More frequent scanning can be performed at the discretion of the study site principal investigator during the active treatment time period. CT scan should be performed at disease progression or recurrence.

g. Follow up is calculated after surgery and should be every 3 months for 1 year and then every 6 months for 4 years. The window for follow-up procedures is +/- 2 months. As follow-up procedures are standard of care, if subject is seen by other medical providers, we will collect the data from those standard of care visits, including history and physical exams, lab work, and imaging results.

h. Quality of Life questionnaires will be collected at baseline (registration), 6, 12 and 36 months from date of registration.

4.3 Registration Procedures

Authorized staff must register an eligible candidate with the Clinical Trial Office prior to surgery. If necessary, the Clinical Trials Office will then send the registration to the appropriate personnel.

5. STUDY TREATMENT PLAN

5.1 Intra-peritoneal heated chemotherapy

Surgery must start within eight weeks from screening.

5.1.1 Mitomycin C

Mitomycin C must be obtained from commercial sources. Please refer to the current FDA-approved package inserts provided with the medication or the *Physician's Desk Reference* for detailed additional information about possible side effects and instructions for preparation, handling, and storage of the drug. The FDA has not approved Mitomycin C for HIPEC, but numerous Phase II studies have documented a very acceptable morbidity and mortality for the treatment of cytoreductive surgery combined with hyperthermic intra-peritoneal Mitomycin C given at the time of surgery.

Description

Mitomycin C acts as a bi- or tri-functional alkylating agent that inhibits DNA synthesis and cross-links DNA. Its activity is most pronounced during late G1 and early S phases of the cell cycle.

It is soluble in water, saline or dextrose/water. Mitomycin C appears as a bluish-purple crystal. The clinical formulation is supplied in a sterile form in vial. Mitomycin C is available in vials containing 5 mg, 20 mg, and 40 mg.

Mitomycin C is reconstituted with Sterile Water to a concentration of 0.5 mg per mL. Once reconstituted, Mitomycin C is stable for 14 days refrigerated or 7 days at room temperature. The reconstituted solution needs to be protected from light. For the purpose of this study, Mitomycin C 40 mg vial will be mixed with 100 mL of sterile saline for administration in the operating room.

The reconstituted Mitomycin C will be added to normal saline solution as specified below in the *Intra-peritoneal heated perfusion of Mitomycin C protocol* where the first dose of Mitomycin C (30 mg) is administered when intra-peritoneal target temperature of 40.5-42.5°C is reached and the second dose (10 mg) is given 60 minutes later for an additional 30 minutes.

Storage
Mitomycin C must be stored below 25^{o}C and protected from light.

Toxicity [Given the planned doses of Mitomycin C in this study, the likelihood of drug-associated adverse effects listed in the following toxicity profile for Mitomycin C is significantly reduced with intra-peritoneal relative to intravenous administration of the drug.]

Hematologic: Suppression of bone marrow function as manifested by leucopenia, neutropenia, thrombocytopenia and anemia may occur.

Hepatic: Transient elevations of one or both serum transaminases may occur.

Renal: Hypertension, edema, hematuria, proteinuria and rarely hemolytic uremic syndrome (HUS) may occur. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of serum bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Gastrointestinal: Anorexia, nausea, vomiting and stomatitis may occur, most often with intravenous administration of the drug.

Hypersensitivity: Hypersensitivity reactions such as a rash may occur, most often with intravenous administration of the drug. Anaphylactic reactions are rare.

Respiratory: Parenchymal toxicity including interstitial pneumonitis and pulmonary fibrosis has been reported rarely.

Precautions/warnings
Hematological parameters should be monitored closely. Intra-peritoneal drug dose should be reduced by 25% for patients with underlying renal insufficiency (CrCl 10 to 29 mL/minute) Mitomycin should not be given to patients with a serum creatine greater than 1.7 mg/dL.

Avoid intra-thoracic instillation of Mitomycin C. Pregnant women are not eligible for this study.

5.1.2 Pre-perfusion protocol and perfusion circuit set-up and priming
At the conclusion of cytoreductive surgery, hemodynamic stability of the patient will be assured and bleeding points controlled per standard practice.

Systemic body temperature will be monitored. The perfusion system will be assembled per the operator's manual utilizing sterile technique. The perfusion circuit priming will be with a balanced electrolyte solution such as normal saline. In the absence of ascites, approximately 3-4L of perfusate is required for the circuit and priming in an average 70-kg adult. A general guideline is 1.5-2.0 L/m^2 perfusate. The perfusate will be primed, heated to target temperature at the discretion of the operating surgeon and re-circulated.

5.1.3 Placement of inflow and outflow catheters and temperature probes
Peritoneal perfusion catheters and temperature probes will be placed by the operating surgeon in accordance with standards of practice. Inflow catheter positioning in the sub-diaphragmatic region of the peritoneal cavity is preferred. Outflow catheter positioning in the pelvis is preferred. This protocol allows for closed delivery of heated Mitomycin C at surgeon discretion. Timing of intestinal reconstruction and formation of stomas will be at surgeon discretion. Sterile pump lines from the perfusion system will be delivered to the sterile field and the lines will be filled with perfusate to prevent airlocks. The inflow and outflow tubing will be connected and the pre-heated perfusate will be allowed to fill the peritoneal cavity. Usually ~3 liters of solution is required to distend the cavity and achieve desired flow rates.

5.1.4 Intra-peritoneal heated perfusion of Mitomycin C
Once the intra-peritoneal target temperature reaches a consistent inflow temperature of 40.5-42.5°C and outflow temperature of 40.5-42.5°C, the therapeutic interval begins, and Mitomycin C will be added to the perfusate. The Mitomycin C-containing perfusion will be allowed to circulate within the peritoneal cavity for 90 minutes. Mitomycin C, 30 mg, will be administered into the inflow line of the perfusion circuit once target temperature is reached, as directed by the operating surgeon. Perfusate temperatures will be adjusted so as not to exceed target temperature. At the 60 minute time point of the perfusion, Mitomycin C, 10 mg, will be administered into the inflow line of the perfusion circuit. During the entire perfusion, temperature of perfusate, volume of perfusate and flow rate will be recorded at 15 minute intervals. Once the 90-minute perfusion period has elapsed, the perfusate will be drained into the waste reservoir. The peritoneal cavity will be rinsed/washed-out with 10 liters of normal saline. The peritoneal cavity will be re-explored and the remaining fluid drained; the catheters and temperature probes will be removed; the circuit and contents will be discarded in accordance with hospital practices and guidelines for the disposal of chemotherapeutic waste.

5.1.5 Recommended anesthetic management and intra-operative physiological monitoring during HIPEC

An epidural catheter may be placed at the discretion of the operating team (anesthesiologist and surgeon). Broad-spectrum antimicrobial prophylaxis is recommended prior to surgical incision (specific antibiotic at the discretion of the operating surgeon). Radial arterial cannulation may be established for arterial-line blood pressure monitoring. A triple lumen central venous catheter may be placed at the anesthesiologist's discretion. A nasogastric tube is typically placed to decompress the stomach. A transurethral catheter is placed in the bladder. During cytoreductive surgery, careful attention to end tidal carbon dioxide, oxygen saturation and peak airway pressures is made during diaphragmatic stripping assessing for signs of pneumothorax. The patient's core body temperature may be reduced to 35 degrees Celsius (95 degrees Fahrenheit) prior to commencing hyperthermic intraperitoneal chemotherapy. At the start of the hyperthermic chemotherapeutic infusion, the Bair Hugger may be set to blow ambient air flow over the patient. Adequate intravenous fluid hydration with crystalloid and/or colloid prior to initiation of the hyperthermic chemotherapeutic perfusion is important, as systemic vasodilatation occurs during the perfusion. Urinary output during HIPEC should be maintained at 0.5-1.0 ml/kg/hr. Clotting time and INR, serum electrolytes, blood gases, and vital signs are monitored throughout the procedure. Standards of anesthetic practice interventions should occur when clinically appropriate. Fresh frozen plasma and/or Vitamin K are utilized to maintain INR $\leq$ 1.5 as appropriate.

5.2 Cytoreductive surgery

The abdomen is explored through a generous midline incision. If there is a midline wound from a prior operation, it may be resected at the surgeon's discretion. The peritoneal cavity will be explored carefully in order to assess fully the distribution and volume of peritoneal surface disease.

Peritoneal Cancer Index (PCI) will be determined and documented on the basis of tumor size and distribution of the intra-peritoneal nodules for each of the 13 abdomino-pelvic regions. Tumor nodules present at critical anatomical sites (e.g. multiple serosal small bowel implants) will be documented as they portend a poor prognosis irrespective of favorable PCI. The Lesion Size (LS) score will be determined after the lysis of all adhesions and a complete inspection of all parietal and visceral peritoneal surfaces within the abdominopelvic regions. LS-0 indicates no implants seen. LS-1 indicates tumor implants up to 0.5 cm in longest diameter. LS-2 defines implants between 0.5 and 5 cm, and LS-3 implants > 5 cm in longest diameter. A confluence or layering of disease matting abdominal or pelvic structures together will automatically be scored as LS-3 even if it is a thin layer of cancerous implants. The sum of lesion sizes for the abdominopelvic regions will be recorded. The extent of the disease within all regions of the abdomen and pelvis will be indicated by a numerical score from 0 to 39 (PCI).

Any or all of the principal peritonectomy procedures will be undertaken in an effort to achieve as complete a cytoreduction as feasible. Only peritoneal surfaces containing tumor will be stripped surgically. Greater and lesser omentectomy, omental bursectomy, splenectomy, left and right upper quadrant and pelvic peritonectomy, cholecystectomy, total abdominal hysterectomy, low anterior resection and/or gastrectomy will be performed at the surgeon's discretion based on volume and distribution of peritoneal surface malignancy with the aim of achieving complete resection of all grossly apparent disease.

Heated intraoperative intraperitoneal chemotherapy will be delivered as above. At the completion of the perfusion, the abdomen will be re-explored, residual fluid aspirated, bleeding points controlled and reconstructive operation completed if not already done prior to HIPEC (anastomosis with or without diverting stoma).

Completeness of cytoreduction will be estimated and recorded using the CC and RR system shown below. Intra-peritoneal tubes and drains will be placed at the surgeon's discretion and the incision closed in the usual fashion.

CC SCORING	**RR SCORING**
Score Residual Disease	**Score Residual Disease**
CC0 No Disease	**R0** Complete removal of all visible tumor; Negative cytology or microscopic margin
CC1 <= 0.25 cm	**R1** Complete removal of all visible tumor; Positive cytology or microscopic margin
CC2 0.25-2.5 cm	**R2a** Minimal residual tumor, nodule(s) ≤ 0.5 cm
CC3 >=2.5 cm	**R2b** Gross residual tumor, nodule(s), > 0.5, but ≤ 2 cm
	R2c Extensive disease remaining, nodule(s) > 2 cm

5.3 Discontinuation of study treatment

5.3.1 Patient-initiated discontinuation of study

Even after a patient agrees to take part in the study, he or she may stop therapy or withdraw from the study at any time. If the study participant stops treatment but still allows the study physician to submit follow-up information, he/she should continue to be followed clinically according to the study schedule. Alternatively, he/she may choose to have no further interaction regarding the study in which case the investigator must submit the Off Treatment Form indicating patient refusal.

5.3.2 Investigator-initiated discontinuation of study

The investigator may require a study subject to discontinue the study in the event of one of the following:

- the study subject develops a serious side effect that in the opinion of the investigator the patient cannot tolerate HIPEC.
- the study subject, once in surgery, was found to have extensive disease and therefore was not given HIPEC.

5.4 Surgical quality assurance and control (QA/QC)

5.4.1 Surgical QA/QC strategy

For every multi-modality (CRS-HIPEC) case, the following will be required in the context of this clinical trial:

1. Patient eligibility for the trial will be determined and cross-sectional imaging reviewed;
2. Pre-operative PCI score will be determined by CT and/or laparoscopy;
3. Cytoreductive surgery will be undertaken involving any or all of the six principal peritonectomy procedures, based on volume and distribution of peritoneal surface disease, at the surgeon's discretion, in an effort to achieve complete resection of all grossly apparent peritoneal surface disease. Intraoperative PCI will be determined at the beginning of cytoreductive surgery;
4. Heated intra-operative intra-peritoneal chemotherapy will be delivered;
5. At the completion of the perfusion, the abdomen will be re-explored, residual fluid aspirated and reconstruction completed if not already completed prior to HIPEC;
6. Post resection PCI will be determined and completeness of cytoreduction will be estimated and using the CC and RR systems defined above in section 5.2;
7. Intra-peritoneal tubes and drains will be placed and the incision will be left open or closed in the usual fashion at the surgeon's discretion;

5.5 Supportive care

All appropriate supportive care for any side effects or toxicity will be provided by the physicians in the Montefiore-Einstein Center for Cancer Care of MMC. Patients may be admitted as necessary to manage issues related to study treatment procedure.

6. ASSESSMENT OF EFFICACY

6.1 Response criteria in peritoneal surface malignancy:

6.1.1 Clinical (Radiological) Response Evaluation Using RECIST Guideline

Tumor response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [57]. Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

Note: Response/progression evaluation using RECIST Guideline will only be applicable to patients *with measurable disease* at the time of enrollment. Guidance for determination of recurrence/progression listed in **Section 6.2** should be followed for the following situations:

- Disease evaluation for patients with measurable disease at the time of enrollment;
- Disease evaluation after patients receiving cytoreductive surgery;

6.1.1.1 Schedule of Evaluations:

For the purpose of this study, patients should be reevaluated according to **section 4.2**.

6.1.1.2 Definitions of Measurable and Non-Measurable Disease
At time of study enrollment, measurable vs. non-measurable disease status for each patient will be determined according to the following sections.

6.1.1.3 Measurable Peritoneal Surface Disease
Peritoneal surface lesions are considered measurable if at least one lesion whose longest diameter can be accurately measured as > 1.0 cm with spiral CT scan using 5-mm contiguous reconstruction algorithms.

Peritoneal surface lesions in a previously irradiated area are considered nonmeasurable disease.

6.1.1.4 Non-Measurable Peritoneal Surface Disease
All other lesions (or sites of disease), including small lesions (longest diameter < 1 cm) are considered as non-measurable disease. A normal CT scan and biopsy proven malignant peritoneal implants are considered as non-measurable peritoneal surface disease.

6.1.2 Guidelines for Evaluation of Disease

6.1.2.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm, CT imaging must be used for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

6.1.2.2 Acceptable Imaging Modalities for Measurable Disease:
Spiral (helical) chest, abdomen and pelvis CT with 5-mm contiguous reconstruction algorithms will be the primary method of measurement to allow minimum lesion size of 1.0 cm. All images and window settings from each CT will be included for the sake of completeness in the event of central radiology review.

- Adequate volume of oral contrast agent will be utilized to accentuate the bowel against the peritoneal surface and other soft tissue masses. A consistent CT image acquisition method must be used on baseline and subsequent exams.
- Adequate volume of suitable intravenous contrast agents must be used to accentuate liver and other visceral metastases, and distinguish vascular structures from nodal pathology. A consistent method must be used on baseline and subsequent spiral CT examinations.
- Documented lesions (peritoneal surface tumors) must be measured on the same window setting on each spiral CT examination.

6.1.2.3 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 6.1.3.4).
- The cytological confirmation of the malignant neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Fine needle aspiration cytology or core needle biopsy will be utilized in cases where distinguishing residual disease from normal tissue is difficult. When the evaluation of complete response (CR) depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/core needle biopsy) to confirm the CR status.

6.1.3 Measurement of Effect

6.1.3.1 Target Lesions

- All measurable lesions (as defined in Section 6.1.1.3) up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved peritoneal surface, should be identified as target lesions and recorded and measured at baseline. If the protocol specified studies are performed, and there are fewer than 5 lesions identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved peritoneal surface, and should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.
- Baseline Sum of Diameters (BSD): A sum of the diameters [longest for peritoneal surface lesions (see Section 6.1.1.3)] for all target lesions will be calculated and reported as the baseline sum of diameters (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Diameters (PBSD): A sum of the diameters [peritoneal surface lesions (see Section 6.1.1.3)] for all target lesions will be calculated and reported as the post-baseline sum of diameters (PBSD). If the radiologist is able to provide an actual measure for the target lesion, that should be recorded, even if it is below 0.5 cm. If the target lesion is believed to be present and is faintly seen, but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

6.1.3.2 Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed in accordance with table in section 6.1.3.3 below.

6.1.3.3 Response Criteria

All target lesions, as well as non-target lesions followed by spiral CT must be followed and recorded as specified above, on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without re-assessing and measuring all apparent lesions.

- **Evaluation of Target Lesions**

Complete Response (CR)	Complete Disappearance of all peritoneal surface target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameters of the target peritoneal surface lesions taking BSD as the reference (Section 6.1.3.1)
Progression (PD)	At least one of the following must be true: a) at least one new malignant lesion has become apparent; b) at least a 20% increase in the sum of diameters of target peritoneal surface lesions taking MSD as the reference. In addition, the sum must also demonstrate an absolute increase of at least 0.5 cm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking MSD as the reference.

- **Evaluation of Non-Target Lesions**

Complete Response (CR)	All of the following must be true: a) disappearance of all non-target peritoneal surface lesions b) normalization of serum CEA and/or CA19-9
Non-CR/Non-PD	Persistence of one or more non-target peritoneal surface lesions and/or persistence of supra-normal (>ULN) serum CEA and/or CA19-9 levels.
Progression (PD)	At least one of the following must be true: c) at least one new malignant lesion has become apparent; d) unequivocal progression of existing nontarget lesions. (Note: Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.)

6.1.3.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, non-target lesions, and new disease as defined in the following tables:

For Patients with Measurable Peritoneal Surface Disease:

Target Lesions	Non-Target Lesions	New Lesions	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR

PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated	No	SD
SD	CR Non-CR/Non-PD Not All Evaluated	No	SD
Not All Evaluated	CR Non-CR/Non-PD	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated	Yes or No	PD
CR/PR/SD/PD	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD	CR Non-CR/Non-PD Not All Evaluated	Yes	PD

Note: If CEA is above the upper normal limit at time of study entry, it must normalize for a patient to be considered to have had a complete clinical response (CR) when all lesions have been resected or have disappeared radiographically on therapy.

6.1.3.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

6.1.4 Evaluation Based on Peritoneal Cancer Index

In addition to standard **RECIST1.1** criteria to assess response and **PFS** as secondary endpoints in this trial we will include a standard tool for the assessment of peritoneal surface disease burden according to aggregate tumor size and distribution (Peritoneal Cancer Index). The PCI will be used to estimate the volume and extent of carcinomatosis.

6.1.4.1 Schedule of Evaluation:

- Radiologic evaluation: PCI should be evaluated for all patients each time abdominal-pelvic CT examination is obtained. (Schedule see **section 4.2**)
- Surgical evaluation: PCI should be evaluated for patients receiving CRS/HIPEC therapy before, during and after operation.

6.1.4.2 Guidelines for Evaluation of PCI

Measurement Methods:

- The lesion size score (LS) will be used to rate the size of peritoneal surface nodules.
  - o LS-0 indicates no apparent peritoneal surface tumor.
  - o LS-1 denotes tumor implants up to 0.5 cm in longest diameter.
  - o LS-2 defines tumor implants between 0.5 and 5 cm in longest diameter, and
  - o LS-3 indicates tumor implants >5 cm.
  - o If there is a confluence of tumor, the lesion size will be scored as LS-3.

- Distribution of tumor will be assessed in 13 abdominal-pelvic regions.
  - o Regions 0 thru 8 correspond to abdominal regions, and regions 9 thru 12 correspond to small bowel regions that are defined by the intersection of two transverse and two sagittal planes dividing the abdomen into nine abdominopelvic regions (**See figure in Appendix A**).
  - o The small bowel will be assessed separately and designated as abdominopelvic regions 9 through 12 as follows: upper jejunum (region 9), lower jejunum (region 10), upper ileum (region 11) and lower ileum (region 12), respectively.
  - o The summation of the lesion size score in each of the 13-abdominopelvic regions will define the PCI, ranging from a minimum of zero to a maximum score of 39 (3 x 13).
  - o All measurements will be taken and recorded in metric notation (centimeters, cm), using a ruler or calipers.

Accepable imaging modalities for radiologic evaluation:
The same method of measurement and the same technique [at a minimum - spiral (helical) chest, abdomen and pelvis CT with 5-mm contiguous reconstruction algorithms and adequate volume (based on site-specific protocols) of both oral and intravenous contrast agents] will be used to characterize each identified and reported peritoneal surface tumor at baseline and during follow-up.

6.2 Evaluation of Cancer Outcomes

In patients not rendered free of all grossly apparent peritoneal surface malignancy and at time of disease progression, patients will be treated in accordance with standards of practice indefinitely.

6.2.1 Disease progression for patients with measurable tumor at enrollment:

Tumor evaluation should follow the RECIST version 1.1 criteria in section 6.1.1.

6.2.2 Disease progression for patients with non-measurable tumor at enrollment

Serum CEA and/or CA19-9 exceeding Upper Limit of Normal (ULN), and increasing ≥50% from completion of study therapy, verified by two CEA and/or CA19-9 measurements, ≥2 weeks apart, will be considered disease progression. If CEA is above the upper normal limit at time of study entry, it must normalize for a patient to be considered to have had a complete clinical response when all lesions have been resected.

6.2.3 Local-regional recurrence after cytoreductive surgery

- Defined as the development of tumor (one or more lesions) in an area of prior peritoneal surface malignancy that underwent complete response (CR, as defined in Section 6.1.3.3) to treatment or surgical resection, or a new peritoneal surface tumor(s) or mesenteric regional nodal lesions(s)
- Acceptable means of confirmation of local-regional recurrence include cross sectional or functional (e.g. CT-PET) imaging or positive fine needle aspiration cytology or histological biopsy.
- If peritoneal surface or mesenteric nodal lesions show(s) a 20% or greater increase in lesion(s) sum LD on serial imaging, disease recurrence will be confirmed.

6.2.4 Distant recurrence after cytoreductive surgery

- Defined as evidence of tumor in any region of the body, outside the peritoneal surface (e.g. lung, liver, central nervous system, bone marrow, skin, subcutaneous tissue, or distant nodal (retroperitoneal, pelvic, mediastinal, peri-portal or peri-aortic node, etc.) metastases.
- The following methods of diagnosis of extra-peritoneal surface metastases according to site are considered acceptable

Metastatic site	Acceptable Means of Diagnosis
Lung	Needle aspiration cytology, histological biopsy, radiological evidence of multiple pulmonary nodules consistent with lung metastasis
Liver	Cross-sectional, functional imaging or laparoscopy consistent with liver metastasis or liver cytology or tissue biopsy confirming metastasis. Functional imaging is considered evidence of new diseases only if the PET was negative at baseline or corroborated radio graphically.
Central nervous system	Cross-sectional or functional imaging usually in a patient with neurological symptoms consistent with CNS metastases, or cytology or biopsy confirming meningeal metastasis
Bone marrow	Positive cross-sectional or functional imaging, or cytology or biopsy confirming bone marrow metastasis
Skin, soft tissue, distant nodal	Positive cytology, histological biopsy or radiological evidence of metastatic disease in skin, soft tissue, or distant nodes (iliac, para-aortic, vena caval, celiac, portal, mediastinal, hilar, paratracheal, etc.)

6.2.5 Cancer-specific mortality

- Only death confirmed to be related to disease will be considered in disease-related mortality calculations.
- Disease-related, treatment or other cause of death will be captured on the follow up case report form.

7. ADVERSE EVENTS ASSESSMENT AND REPORTING

7.1 Definitions for adverse event reporting

Adverse event (**AE**) assessment, data collection and reporting will be done to ensure the safety of patients enrolled in this study. Adverse events secondary to both cytoreductive surgery and the utilization of intraperitoneal chemotherapy will be monitored closely, recorded appropriately and reported as required. 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).

Timely reporting of serious and unexpected adverse events will be conducted throughout the trial period. Only commercial agents (not provided under IND) will be utilized in this study. The study subject will be informed of the indications, nature, alternatives, expected outcome, risks and benefits of all procedures and therapies provided in the context of this study. Clearly, there are potential, foreseeable risks or discomforts to participants in this study. Detailed information on adverse events or complications, which may be related to HIPEC or operative procedures provided in this trial, will be collected during the course of the study.

The CTEP CTCAE version 4.0 will be used to identify the type, and to grade the severity of adverse events in this trial. An adverse event will be considered a Serious Adverse Event (**SAE**) if that event led to death, resulted in a life-threatening illness or injury, resulted in permanent impairment of a body structure or body function, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function.

An Unanticipated Adverse Event (**UAE**) will be considered any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the commercial agent and/or surgical procedure, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this investigational plan or any other unanticipated serious problem associated with the commercial agent and/or operation that relates to the rights, safety, or welfare of the subjects participating in this study.

7.2 Adverse event assessment

The severity type and grade of the adverse events will be identified using the NCI **CTCAE**. Attribution/treatment relation of adverse events will be defined by the study doctor as Unrelated, Unlikely, Possible, Probable, or Definite.

An adverse event is defined as any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. This includes any occurrence that was new in onset or aggravated in severity or frequency from the baseline condition. Adverse events (AEs) assessments will begin at time of signing of informed consent and will continue until 30 days following study treatment. AEs which are assessed as possibly, probably, or definitely related to study treatment must be followed until the AE is resolved or until the patient

is clinically stable. Other safety assessments, including physical examinations, vital signs, hematology, clinical chemistry, and urinalysis, will be done through subject discontinuation or 12 months after initial study treatment, whichever occurs first.

The condition which is detected by the diagnostic procedure conducted to test the efficacy of the investigational agent is not considered an AE.

Symptoms or clinically significant laboratory or instrumental abnormalities of a pre-existing disease, such as cancer or other disease should not be considered an AE. However, occurrence of new symptoms or laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, is considered AEs.

Abnormal results of diagnostic procedures, including laboratory test abnormalities, are considered adverse events if they result in:

- Discontinuation from the study.
- Treatment or any other therapeutic intervention.
- Further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality).
- Associated clinical signs or symptoms that would have a significant clinical impact, as determined by the Investigator.

Any untoward medical event that occurs from the time of signed informed consent to the time immediately prior to the first study treatment procedure will be reported as a "pre-treatment event" in the Medical History CRF.

All adverse events that occur following study treatment will be documented on the AE CRF with indications of onset, duration, severity (NCI CTCAEs), presumed relationship to study procedure /medication (not related, unlikely, possibly, probably, definitely), remedial actions taken, and outcome.

Surgical complications will be defined as secondary events deviating from the ideal course of convalescence that occurred during or following the operation, resulting in changes in management (diagnostic or therapeutic intervention) and delay in complete recovery and/or adjuvant therapy, or chronic disability.

Surgical complications will be scored according to a five-tier surgical morbidity and mortality scale (according to the intensity of therapy required for the treatment of the defined complication):

Grade Intensity of Treatment

1	oral medications (e.g. oral antibiotics for surgical site infection or bedside care)
2	intravenous medications or nutrition (e.g. antiarrhythmic therapy for supraventricular tachycardia)
3	endoscopy, interventional radiology or reoperation (e.g. operative drainage of an abscess)

4 chronic disability or major organ resection (e.g. reduction in performance status following post respiratory failure)
5 death

7.3 Expedited Reporting of Adverse Events

Expedited adverse event reporting for patients receiving commercial agents is required for:

- All Grade 4 and 5 unexpected adverse events that are possibly, probably or definitely related to therapy.
- All Grade 5 adverse events, regardless of attribution, occurring within 30 days of the end of therapy

Expedited adverse event reporting will NOT be required for the following:

- Adverse events related to surgery
- Adverse events related to radiation
- Adverse events that occur following the first cancer recurrence or second primary cancer development

7.4 Routine Reporting of Adverse Events

All Grade 3-5 **AE**s must be recorded on the appropriate data form. Expedited reporting is in addition to, and does not supplant, the reporting of AEs as part of the data submission requirements for the study.

Adverse events will be categorized by body system (such as cardiovascular-related, renal-related, etc.) and will be reported to the Montefiore institutional review board (IRB) as required by the IRB.

Any serious event, including death from any cause that occurs through 30 days following study treatment, whether or not related to the investigational drug, must be reported to PI immediately (within 24 hours) via telephone, fax, or e-mail. If initially reported via telephone or e-mail, this must be followed-up by a written faxed report to be submitted within 24 hours of the initial report.

Initial Reports

Within 24 hours of the investigator's knowledge of a serious adverse event:

- Complete a Serious Adverse Event Report Form (SAER), sign it, and fax it to the PI.
- Place the initial version of SAER in the subject's file.

Follow-Up Reports

New information received spontaneously or by request of the Medical Monitor or Safety Surveillance. Within 48 hours of the receipt of new information:

- Complete a new SAER with the new information. Sign and fax the form to PI.
- Fax copies of supporting documents (e.g., hospital discharge summaries, lab test results with normal ranges, autopsy or biopsy reports) to PI.
- Place the follow-up version of the SAE and all supporting documentation in the subject's file.

Final Report
Within 48 hours of the receipt of final information:

- Determine that there is no further information available and this update may be considered final.
- Complete a new SAER form with the new and final information. Sign and fax the form to PI. As above, send copies of any additional supporting information.
- Place this version of the final SAER into the subject's file.

It is imperative that IRB be informed within 24 hours of a serious adverse experience so that reporting to the FDA can be met within the required time frame (7 or 15 calendar days).

Because of the need to report to health authorities all serious adverse experiences in a timely manner, it is vitally important that an Investigator report immediately any adverse experiences, which would be considered serious, even if the Investigator does not consider the adverse experience to be clinically significant or drug-related.

Should the Investigator become aware of an SAE (regardless of relationship to study treatment) that occurs while the subject is on the study, the SAE must be reported in accordance with the procedures specified in this protocol.

If the subject is withdrawn less than 30 days after study treatment, any SAEs which occur within 30 days after study treatment must be reported in accordance with the procedures specified in this protocol.

All serious adverse events that are assessed as possibly, probably, or definitely related to study treatment are to be followed until either: the adverse event resolves, the adverse event stabilizes, the adverse event returns to baseline values (if a baseline value is available), or it is shown that the adverse event is not attributable to the study treatment or study conduct.

8.0 ETHICAL CONSIDERATIONS

8.1 IRB review

The study will be conducted in the Montefiore Medical Center, in compliance with Title 21 of the Code of Federal Regulations (CFR), Part 50 (Protection of Human Subjects), and Part 56 (Institutional Review Board) as well as the principles of the Declaration of Helsinki and its amendments. The Montefiore Institutional Review Board (IRB) will review the protocol and informed consent. The study will not be initiated without IRB approval. All subjects will be required to give written informed consent prior to participation in the study. This study will be performed in accordance with Good Clinical Practices (GCP) by qualified Investigators.

The study specifically incorporates the following features:

- Single arm study design
- Prospectively stated objectives and analytical plan
- Accepted, pre-specified outcome measures for safety and efficacy
- Compliance with Good Clinical Practices (GCP), with assessment via regular monitoring.

Quality assurance procedures will be performed to assure that safety and efficacy data were adequate and well documented.

8.2 Informed Consent

Consent will be obtained during patients visiting in physician's office or hospital setting. Investigators or research nurse in the team will provide information to potential subjects and answer questions in the informed consent process. The Investigators will obtain written informed consent from each subject (or their authorized representative) participating in the study. The form must be signed, witnessed and dated.
The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, and the ICH Guideline for Good Clinical Practice, and the terms of the Declaration of Helsinki. Copies of the signed document should be given to the subject and filed in the Investigator's study file, as well as the subject's medical record.

8.3 Subject Protection

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify subjects by initials and assigned subject numbers; subjects should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the personnel of data monitoring committee access to all pertinent medical records in order to verify the data gathered on the case report forms. Regulatory agencies such as the US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the subject as outlined in the subject consent form.

Researchers will ensure the confidentiality of the information gathered in the study by using following methods:

- Paper based records will be kept in a secured location and only accessible to personnel involved in the study.
- All study data will be kept in locked file cabinets and password protected files.
- Computer based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- Prior to accessing any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information.
- Whenever feasible, identifiers will be removed from study-related information.

The selection of subjects for this protocol will not be based on sex, race, or ethnic background.

Because mitomycin C may harm a developing baby, patients in pregnant or lactating will be excluded from this study. Children will not be enrolled in this study.

9. STATISTICAL CONSIDERATION

9.1 Sample size

The target number of patients proposed for this protocol is based on our primary objective, assessing completeness of cytoreduction. The postoperative morbidity and mortality will be important factors at the interim analysis.. The latent goal is to utilize these estimates for generating future research hypotheses and protocol development as well as to benchmark our data against published data.

Sample size calculations are based on our primary objective. Our target sample size is 50 patients unless undue toxicity is encountered or the accrual is terminated at the interim analyses. A sample size of n=50, would produce a two-sided 95% confidence interval with a maximum width of 0.289 for a proportion of 0.5 and 0.267 for a proportion of 0.70. Calculations are based on exact binomial distribution. In a large multi-institutional study, 75% of patients were classified as CCR-0 and 17% CCR-1 [1].

9.2 Statistical Data Analysis

Data will be entered on an excel spreadsheet and analyzed with SAS v9.2. Data analysis will be preceded by quality control of our data which will include checks for accuracy, completeness and internal validity.

Rates of completeness of cytoreduction, and postoperative morbidity and mortality will be computed and reported with their 95% confidence intervals. Descriptive data analysis will be conducted and all adverse events and overall patient characteristics will be described. Bivariate analysis will be conducted to examine factors associated with complete cytoreduction. Categorical variables will be analyzed using the Fisher's exact test. Continuous variables whose distribution meets normality assumptions will be analyzed with the t-test. Variables whose distribution does not approximate normality will be analyzed using the Wilcoxon rank sum test.

For our secondary endpoints to evaluate time to progression, progression-free survival and overall survival we will use Kaplan-Meier methods. Progression-free survival will be calculated from time of surgery to date of recurrence or censored at time patient is last seen. Overall survival will be calculated from time of surgery to time of death or censored at the time patient is last seen. Log-rank test will be used to compare survival of patients who achieved complete cytoreduction with those who did not. We will compute 95% confidence intervals using Greenwood's formula.

QOL data will be collected using the Functional Assessment of Cancer Treatment (FACT-C) instrument. The feasibility of collecting QOL data will be assessed and rates of missing data will be computed. Reasons for missing data will be characterized to the extent possible. In addition to this, QOL data will be described using mean, standard deviation, median, inter-quartiles and range as well as graphically. For exploratory analysis of QOL data over time we will examine the use of hierarchical linear models.

9.2.1 Interim Analysis Decision Rules

Interim analysis will be performed after the first 20 patients are treated, to assess the safety of the proposed treatment. Stopping rules will be based on 30-day postoperative mortality.

The overall mortality rate reported by Glehen et al in the largest retrospective series of patients with Peritoneal Carcinomatosis (PC) treated with Cytoreductive Surgery in combination with HIPEC was 4.1%. Based on Gehen's data, the upper limit of the 95% confidence interval around the 4.1% mortality rate is 5.3%.

While it is anticipated a mortality rate of 5% - comparable to that reported by Glehen - given the variability in origin of PC, given some variability in reports of mortality rates as reported by Koppe et al [58] and given that patients undergoing this approach have very advanced disease and often progress through all other therapies- we will consider a 30-day mortality rate (from the therapy) of greater than 10% to be unacceptable since this rate is higher than one would expect from the largest retrospective series available.

The 30-day mortality will be evaluated after the first 20 patients have been enrolled. If no more than 2 patients (10%) suffer a mortality within 30 days that is attributable to the therapy and not the underlying disease or unrelated to the therapy, we will continue to 50patients. If 3 or more patients suffer a mortality within 30 days of the therapy that is directly attributable to the therapy, we will suspend accrual and will investigate the causes of the higher mortality. After the root cause of the operative mortality has been determined, the study team will confer with the IRB and will make a determination as to whether accrual can be resumed.

9.3 Patient Accrual:

Based on our experience at the Montefiore-Einstein Center for Cancer Care and based on numbers of patients seen during the first half of the year, we expect to screen 30 patients yearly. We estimate 2/3 of these patients will meet inclusion criteria into the study. We expect high rates of participation into this protocol and estimate that it will take us 2-3 years to recruit the proposed sample of 50 patients. We will follow-up these patients until evidence of progression or for a total study time of 5 years.

9.4 Interim Reports

Interim reports will be prepared every 12 months. These will include:

- Monthly patient accrual rate
- Descriptive patient’s demographic characteristics
- Descriptive clinical data
- Frequency and severity of adverse events

10. DATA COLLECTION AND REPORTING

10.1 Data collection

Complete research records or medical records must be maintained on each patient treated on the protocol for both scheduled and unscheduled evaluations. These records should include primary documentation (e.g. laboratory report slips, X-ray reports, scan reports, pathology reports, physician's notes, etc.) which confirm that:

- The patient meet all eligibility criteria
- Signed informed consent will be obtained prior to treatment
- Treatment will be given according to protocol (dated notes about doses given, complications, and clinical outcomes).
- Toxicity will be assessed according to protocol.
- Response will be assessed according to protocol (X-ray, CT-scan, lab reports, date noted on clinical assessment, as appropriate).
- MMC Drug Accountability Records will be kept for each patient.

10.2 Data Safety Monitoring Plan

The PI and the research personnel will meet at least monthly to review all adverse events. Unexpected adverse events and/or serious adverse events will be reported to the MMC IRB. If trends are noted and /or risks warrant it, accrual will be interrupted and /or the protocol and/or consent will be modified accordingly. The MMC IRB will review submitted adverse events monthly to also evaluate trends and will require follow up plans from the principal investigator whenever a trend is identified.

10.3 Data Reporting

All patients must have signed an informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating Investigator before entering on the study.

Patients will be followed at least monthly during therapy for development of toxicity. Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study treatment, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the study treatment and for its seriousness.

10.3.1 Routine Data Reporting:

Data will be captured in the MMC C3D web based reporting system. A minimum of 25% of the data will be source data verified. Grade 1 and 2 lab toxicities and medications used to treat adverse events will be maintained in the source documents but will not be captured in C3D. Only the following outside labs will be captured in C3D:

- Hemoglobin, WBC, ANC, Platelets, ALT/AST, total bilirubin, Creatinine {other labs associated with a serious adverse event may be captured as appropriate}

10.3.2 Expedited Reporting of Deaths on Study and Adverse Events

The protocol PI will report to the MMC-IRB:

- All deaths
- All grade 3 and 4 (CTCAE) events that are **not** listed in the consent form and that are possibly, probably or definitely related to the research
- All serious adverse events (SAEs) that are **not** listed in the consent form, but are possibly, probably or definitely related to the research. An SAE is defined as an untoward medical occurrence that:
    - Resulted in death
    - Was life-threatening
    - Required or prolonged hospitalization
    - Caused persistent or significant disability/incapacity
    - Resulted in congenital anomalies or birth defects
    - Required intervention to prevent permanent impairment or death
    - Is an important medical event
    - Suspected positive Pregnancy

Reports must be received by the MMC IRB within 7 days of notification of the event for Serious Adverse Event Reporting. All reportable serious events and deaths will be reported to the MMC IRB at:

Fax: 718-798-5687
e-mail: koconno@montefiore.org
Phone: 718-798-0406

10.3.3 Adverse Event Reporting in the Continuing Review Report

Data will be submitted for review by the IRB annually. The MMC-IRB requires a summary report of adverse events that have occurred on the protocol since the previous continuing review. The method of presentation should provide the MMC-IRB with the information necessary to clearly identify risks to participants and to make a risk:benefit determination. The summary report is based on the following guidance:

- Any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative.
- Grade 1 events are not required.
- Grade 2 unexpected related to the research events is required.
- Grade 3 and 4 expected and unexpected events related to the research are required.
- All Serious Events regardless of attribution.
- Grade 5 (all) events are included regardless of attribution.

Based on protocol-associated risks to participants, the MMC-IRB retains the authority to establish more frequent Continuing Review periods than the customary annual review period.

10.4 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

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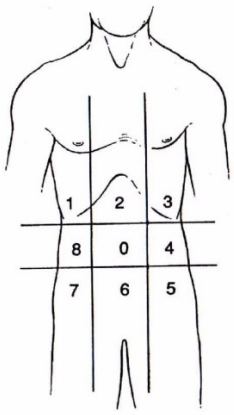
Appendix A: Peritoneal Carcinomatosis Index (PCI) staging system for peritoneal carcinomatosis

Peritoneal Cancer Index

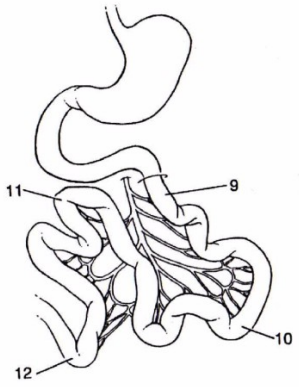


Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____

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



Appendix B: Quality of life questionnaire

Please see attached forms.

1. FACT-C (Version 4)
2. SF-36