PROTOCOL

SHORT TITLE: Laparoscopic HIPEC for metastatic gastric cancer

FULL TITLE: A Phase II study of laparoscopic hyperthermic intraperitoneal chemoperfusion (HIPEC) for gastric carcinomatosis or positive cytology

PROTOCOL TYPE: Standard Clinical

PROTOCOL PHASE: II

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
Cis	Cisplatin
CRF	Case Report Form
CT	Computed Tomography
CXR	Chest X-Ray
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
H & P	History and Physical
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver Function Test
NCI	National Cancer Institute
NYHA	New York Heart Association
OAE	Other Significant Adverse Event
PET	Positron Emission Tomography
RBC	Red Blood Cells
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
STEAE	Serious Treatment Emergent Adverse Event
UA	Urine Analysis
WBC	White Blood Count
WHO	World Health Organization

1.0 OBJECTIVES

Primary: To assess overall survival from the date of diagnosis in subjects with stage IV gastric and gastroesophageal cancer and positive cytology or imaging occult carcinomatosis after laparoscopic hyperthermic intraperitoneal chemotherapy administration.

Secondary:

1) To assess the safety of laparoscopic hyperthermic intraperitoneal chemotherapy administration for subjects with gastric and gastroesophageal cancer and positive cytology or imaging occult carcinomatosis.

2) To assess the gastric resection rate in subjects with stage IV gastric and gastroesophageal cancer representing positive cytology or imaging occult carcinomatosis after laparoscopic hyperthermic intraperitoneal chemotherapy administration.

2.0 BACKGROUND

Peritoneal carcinomatosis and microscopic peritoneal disease represents an aggressive mode of spread for gastric cancer which ultimately results in death. Heated regional peritoneal chemotherapy has been demonstrated to be effective in mesothelioma and appendiceal tumors.[1, 2] In addition, intraperitoneal chemotherapy has been found to improve survival in gastric cancer.[3-5]

From January 1995 to December 2005, 3747 patients presented to M. D. Anderson Cancer Center with gastric or gastroesophageal junction adenocarcinoma. Of those, 381 were without metastatic disease on radiologic imaging and underwent diagnostic laparoscopy for further staging prior to consideration for neoadjuvant treatment. Eighty-three patients had carcinomatosis on laparoscopy while 39 had positive cytology in the absence of carcinomatosis. Carcinomatosis and positive cytology are classified as metastatic or Stage IV disease according to the American Joint Commission on Cancer Staging Manual (7th edition).[6] However, this population of 122 patients had stage IV disease that could be described as a local effect from serosal invasion and peritoneal spread rather than hematologic or lymphatic spread, and therefore are good candidates for local chemotherapy administration. The population of patients with isolated peritoneal disease are also good candidates for a clinical trial as traditional treatment regimens yield dismal survival rates. Median OS (overall survival) for patients with positive peritoneal cytology and no visible metastatic disease at laparoscopy was 12.8 months while median OS was 10.2 months for patients with carcinomatosis at laparoscopy as displayed in Figure 1.[7] For the patients with positive peritoneal cytology and no visible metastatic disease, use of neoadjuvant therapy (most often induction 5-FU and oxaliplatin followed by chemoradiation therapy with 45 Gy) resulted in a 3-year OS rate of 12% versus 0% for patients treated as having incurable stage IV disease. For the patients with carcinomatosis at laparoscopy, outcomes were worse with 0% 3-year OS. For the 122 patients with carcinomatosis at laparoscopy or positive cytology, only 8 (6.7%) underwent resection. The proposed trial will focus on the combined population of patients with radiologically occult carcinomatosis or positive cytology at laparoscopy.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a surgical technique for combining hyperthermia and chemotherapeutic agents to the peritoneal surface via a heated perfusion circuit.[8] Support for the concept of combining heat with chemotherapy is provided through in vivo and in vitro laboratory studies that have established the selective lethal effects of heat on human and murine neoplastic cells.[9] Hyperthermia may work through a direct antitumor effect, augmenting the cytotoxic effects of chemotherapy, or increasing the depth of penetration of chemotherapy into tissues and tumor nodules.

There are many theoretical benefits to a neoadjuvant laparoscopic approach to HIPEC in gastric cancer. Patients would not be subjected to the risks of gastrectomy unless they demonstrated a response to laparoscopic HIPEC. Performing a laparoscopic HIPEC would also allow for clear visualization of the response to treatment as a diagnostic laparoscopy with peritoneal washings should be performed at the intitiation of the procedure. There is also data to suggest that performing laparoscopic HIPEC without cytoreduction and gastrectomy is a low risk procedure. A recent systematic review of laparoscopic hyperthermic intraperitoneal chemotherapy suggests this is a safe procedure with no mortalities and < 10% morbidity in 183 patients. Of note, however, is that only 5 patients in this series underwent this procedure as part of a neoadjuvant approach prior to cancer treatment.[10] Therefore, the purpose of this clinical trial is to determine the efficacy and safety of laparoscopic hyperthermic intraperitoneal chemotherapy with Mitomycin C and Cisplatin in patients with stage IV gastric cancer after treatment with systemic chemotherapy.

3.0 Eligibility: (List All Criteria)

Inclusion:

1) Age 18 years and above. There will be no upper age restriction.

2) ECOG performance status ≤ 2. (See Appendix A –ECOG Performance Status Scale).

3) Cytologic or histologic proof of adenocarcinoma of the stomach or gastroesophageal junction.

4) Adequate renal, and bone marrow function:

   a. Leukocytes >= 3,000/uL

   b. Absolute neutrophil count >= 1,500/uL

   c. Platelets >= 100,000/Ul

   d. Serum creatinine <= 1.5 mg/dL

5) Hepatic function:

   AST (SGOT)/ALT (SGPT) ≤ 5 X institutional ULN.

6) Distant Metastatic Disease limited to peritoneum and radiologically occult (not visualized on preoperative imaging to include CT, U/S, MRI, PET/CT):

a. Positive peritoneal cytology

b. Carcinomatosis on diagnostic laparoscopy or laparotomy.

7) Completion of preoperative systemic chemotherapy.

Exclusion:

1) Distant metastatic disease not limited to peritoneum:

a. Solid organ metastases (liver, central nervous system, lung).

2) Any distant metastatic disease visualized on preoperative imaging:

a. Solid organ metastases

b. Clear radiologic evidence of carcinomatosis.

3) Infections such as pneumonia or wound infections that would preclude protocol therapy.

4) Women with a positive urine or serum pregnancy test are excluded from this study; women of childbearing potential (defined as those who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months) must agree to refrain from breast feeding and practice adequate contraception as specified in the informed consent. Adequate contraception consists of oral contraceptive, implantable contraceptives, injectable contraceptives, a double barrier method, or abstinence.

5) Subjects with unstable angina or New York Heart Association Grade II or greater congestive heart failure.

6) Subjects deemed unable to comply with study and/or follow-up procedures.

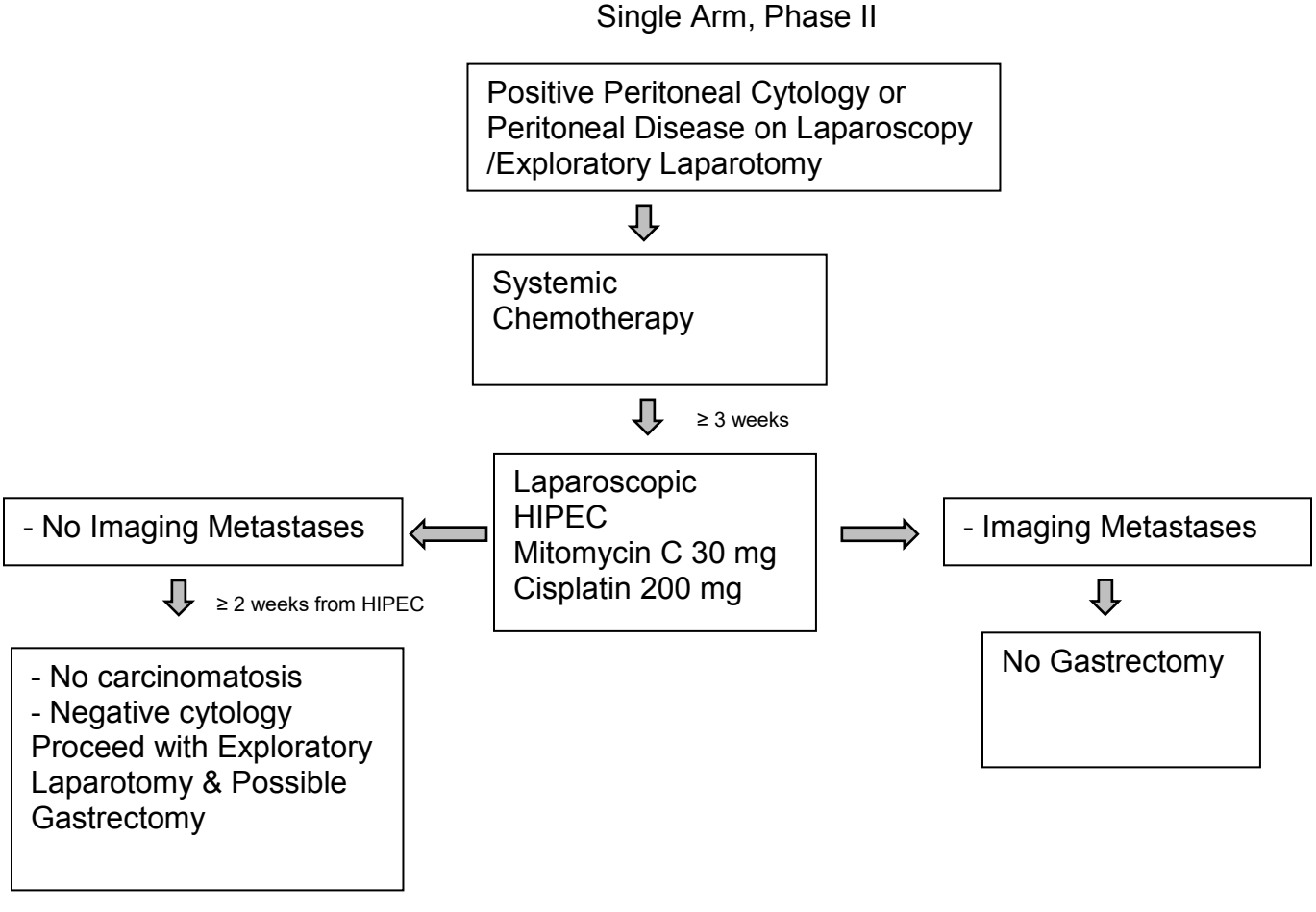
7) Subjects with a known hypersensitivity to protocol systemic chemotherapy that was life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity.

4.0 DESIGN AND METHODS

Subjects with gastric and gastroesophageal adenocarcinoma and positive peritoneal cytology or radiologically-occult carcinomatosis that have completed treatment with systemic chemotherapy will be offered participation in the study. Type and duration of systemic chemotherapy will be left to the discretion of the treating medical oncologist. Subjects may be inpatients or outpatients. Subjects should have a contrast CT scan, MRI, or PET/CT scan within 6 weeks (42 days) of enrollment. Patients will have completed standard systemic therapy prior to enrollment. Lack of imaging evidence of metastatic disease will be defined based on radiologic (CT scan, MRI, or PET/CT)

imaging. Evidence of carcinomatosis or positive cytology will be based on laparoscopic clinical criteria (see eligibility criteria). HIPEC will be administered as defined by the protocol. Patients will undergo laparoscopic HIPEC as displayed in Figure 1. Laparoscopic HIPEC will consist of Mitomycin C 30 mg and Cisplatin 200 mg in 3-7 liters of infusate circulated using an extracorporeal circulation device at a flow rate of 700-1500 mL/minute for 60 minutes, performed no sooner than 3 weeks after completion of systemic chemotherapy. The Laparoscopic HIPEC procedure may be performed up to 5 times, with a minimum of 3 weeks between procedures. At the completion of this treatment, the subjects will undergo restaging CT scan, MRI, or PET/CT scan. Restaging will define two groups of subjects: 1) those whose disease progressed locally or who developed imaging evidence of distant metastatic disease, and 2) those whose disease has responded or remained stable. In addition, diagnostic laparoscopy with peritoneal cytology and biopsy of any suspicious lesions will be performed at the initiation of the laparoscopic HIPEC and will provide clinically significant information regarding the persistence of peritoneal disease. After laparoscopic HIPEC, subjects whose disease did not progress will proceed to surgery with diagnostic laparoscopy and possibly exploratory laparotomy to assess resectability, and if their cancer is resectable will undergo gastrectomy. After completion of study–related treatment, subjects will be followed until recurrence and/or death for up to five years.

Figure 1.



Study Calendar

*See the Study Calendar Footnotes

	STUDY CALENDAR						
	Pre-Treatment Evaluation ≤ 28 days	Treatment Initiation	Post-Treatment (Post-operative) Evaluation	Pre-Gastrectomy Evaluation	Gastrectomy Week ≥ 2 weeks after HIPEC	Post Gastrectomy Evaluation ≤8 weeks after surgery	Survival Follow-up Q 6 months
H&P & Concurrent Meds	X			X		X	X
Consent	X						
Vital Signs[a]	X	X	X	X		X	
ECOG Performance Status	X						
Serum Chemistries[b]	X						
CBC[c]	X						
Pregnancy Test (urine or serum)	X						
Imaging[d]	X			X			X
Adverse Events[e]		X	X	X	X	X	
LS HIPEC[f]		X					
Gastrectomy					X		
Tissue for correlative studies					X		

Study Calendar Footnotes:

a. Vital signs: blood pressure and pulse rate.
b. Serum Chemistries: albumin, alkaline phosphatase, ALT, AST, bilirubin, calcium, chloride, CO2, creatinine, glucose, LDH, magnesium, phosphorus, potassium, sodium,].
c. Complete Blood Count (CBC): Hemoglobin, hematocrit, red blood cells [RBC], white blood cells [WBC], platelets, and differential blood cell counts such as: neutrophils, lymphocytes, monocytes, eosinophils, basophils).
d. Imaging can include CT Chest/Abdomen/Pelvis, Abdominal/Pelvis MRI, or PET/CT scan and may be within 6 weeks of enrollment.
e. All adverse events occurring during any part of the study will be reported appropriately to the IRB.
f. Laparoscopic hyperthermic intraperitoneal chemotherapy administration.

Informed Consent will be obtained.

Type of Study: Prospective phase II, single institution clinical trial.

Procedures and Treatment Plan

1. Laparoscopic HIPEC: Mitomycin C 30 mg and Cisplatin 200 mg in 3-7 liters of infusate will be administered using a rolling pump with hyperthermia for 60 minutes.

Pathology

For those patients that undergo gastrectomy, esophageal, gastric, or duodenal margins will be evaluated on frozen section. Recorded on permanent section will be tumor depth, degree of differentiation, margin status, lymph node status, and degree of treatment effect.

Pretreatment Evaluation

Within 28 days Prior to Study Enrollment the following procedures will be performed:

a) (Complete blood count: hemoglobin, hematocrit, red blood cells [RBC], white blood cells [WBC], platelets, and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils). ;

b) Serum chemistries (albumin, alkaline phosphatase, ALT, AST, bilirubin, calcium, chloride, CO2, creatinine, glucose, LDH, magnesium, phosphorus, potassium, sodium).

c) Pregnancy test) conducted prior to study enrollment to meet eligibility criteria.

d) A history and physical exam.

e) ECOG Performance status.

f) Concurrent medications.

g) Vital signs will also be collected during the pre-treatment evaluation.

h) Within 6 weeks subjects must have undergone staging radiographic studies (CT chest, abdomen and pelvis, Abdominal/Pelvis MRI, or PET/CT scan). These studies are considered standard of care in the evaluation and treatment of patients with gastric cancer.

Post-treatment Evaluation

After laparoscopic HIPEC, patients will be monitored during their inpatient postoperative stay with standard of care postoperative laboratory analysis and daily vital signs.

Expected postoperative hospital length of stay is 3 to 7 days.

Pre-Gastrectomy Evaluation

1. The subjects will be assessed as follows:
    a. Standard of care preoperative laboratory analysis
    b. History and physical and concurrent medications will be collected.
    c. Vital signs (blood pressure and pulse rate) will be collected.
2. After completion of the laparoscopic HIPEC procedures, subjects without peritoneal carcinomatosis or positive cytology will be considered for gastrectomy. Subjects will have a minimum 2 week rest period after the laparoscopic HIPEC to allow for recovery prior to gastrectomy.

Post-resection Evaluation

Within 8 weeks of completion of gastrectomy, the subject will have:

1. History and physical and concurrent medications will be collected.
2. Vital signs (blood pressure and pulse rate) on days of clinic evaluation.
3. Standard of care postoperative laboratory analysis.

Survival

1. The primary endpoint in this study is overall survival, as measured from the time of diagnosis. Patterns of tumor recurrence and survival will be assessed by reviewing routine surveillance imaging.
2. After completion of the treatment (HIPEC or gastrectomy), all subjects will be followed with imaging approximately every 6 months for five years.

Criteria for Removal from Study:

1. Inability of subject to comply with study requirements
2. Determination by the investigator that it is no longer safe for the subject to continue therapy

Correlative Studies: Tissue Banking

All tissue samples will be collected according to MD Anderson Tissue Protocol LAB01-543 SOPs. An IRB approved protocol in standard format is on file with the IRB (PI: Jaffer A. Ajani, M.D.). Patients are consented prior to any endoscopic procedures performed at MD Anderson. Per the protocol and consent, if the patient requires surgery as part of his/her treatment, a portion of the remaining tissue will be stored. No additional surgical maneuvers or procedures are necessary for the collection of study tissues, since all tissue samples will be collected from tissue that has already been removed as part of standard care. When feasible, tissue adequate

for preparation of 50 slides (5 mm thick) will be stored from each collection. In brief, the objectives of this protocol are to:

1. To collect and store, both prospectively and retrospectively, tissue, blood, body fluids and information for the sole purpose of banking pre-malignant and malignant lesions of the gastrointestinal tract. An IRB approved Informed Consent in standard format is on file with the IRB.

2. To collect, store, and analyze, both prospectively and retrospectively, data on disease characterization, treatment and outcomes for patients with suspected premalignant and malignant lesions of the gastrointestinal tract at the University of Texas M. D. Anderson Cancer Center (UTMDACC).

3. To collect, store, and analyze data on patients with gastrointestinal malignancies of the University of Texas M. D. Anderson Cancer Center (UTMDACC) from patients' primary physicians or other treatment centers prior to, during and after the patients' visits at UTMDACC.

4. To collect, store or discard residual tissue, blood and other body fluids obtained during the performance of research activities for which consent and authorization have been obtained from the participant.

5.0 ADVERSE EVENTS REPORTING REQUIREMENTS

Investigators are required to report to the MD Anderson IRB ALL serious treatment emergent adverse event (STEAE) as soon as possible. The methods for collecting safety data are described below.

Adverse Events

1. Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

2. Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), or signs (e.g., tachycardia, enlarged liver). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

3. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

a. Results in death

b. Is immediately life-threatening

c. Requires in-subject hospitalization or prolongation of existing hospitalization

d. Results in persistent or significant disability or incapacity

e. Is a congenital abnormality or birth defect in the offspring of the subject

f. Is an important medical even that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening, or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the drug?”

4. Other Significant Adverse Event (OAE)

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

Recording of Adverse Events:

Any detrimental change in a subject’s condition, subsequent to the subject entering the study should be considered an AE. AE reporting will be performing using CTCAE version 4.0.

Method of detecting AE/SAE:

At each visit the method of detecting AE and SAEs in this study will be by:

1. Information volunteered by the subject, or caregiver

2. Open-ended and non-leading verbal questioning of the subject at every visit such as the following: *How are you feeling? Have you had any (other) medical problems since your last visit*

3. Observation by the investigational team, other care providers or relatives

6.0 STATISTICAL CONSIDERATIONS

For the futility monitoring of overall survival (OS), we have assumed a median OS of 11 months for historical treatment and a median of 15 months (i.e., 4 months improvement) with the experimental therapy based on the preliminary data (Appendix C). For toxicity monitoring, we have assumed that 30% or higher rate of toxicity is intolerable.

This is a single arm phase II study to assess the efficacy and safety of laparoscopic hyperthermic intraperitoneal chemoperfusion for gastric carcinomatosis or positive cytology. The primary objective of this study is to assess the overall survival (OS) in subjects with stage IV gastric cancer representing positive cytology or imaging occult carcinomatosis after laparoscopic hyperthermic intraperitoneal chemotherapy administration.

The study will be continuously monitored for the primary endpoint, OS, using the method of Thall, Wooten, and Tannir.[2] It is assumed that the OS for each patient is exponentially distributed with a median of λ_E among patients who receive the experimental treatment and a median of λ_H for the historical treatment. Further, λ_H was assumed to follow an inverse gamma distribution, i.e., $\lambda_H \sim IG(60, 649)$, which has a mean of 11 months and variance of 2.09. To reflect the little prior knowledge of λ_E we assumed an inverse gamma prior distribution with the same mean of 11 months and a much larger variance of 121, i.e., $\lambda_E \sim IG(3, 22)$. The trial will be stopped early if $Pr(\lambda_E > \lambda_H + \delta \mid data) < pL$, where $\delta = 4$ months and pL=0.03 and this monitoring rule will be first applied when 3 patients have been enrolled. A maximum of 30 patients will be enrolled into this study at an expected accrual rate of 1 to 2 patients per month. The trial will be conducted using the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct/) maintained by the Department of Biostatistics at MDACC.

The operating characteristics of the design, based on an overall assumed accrual rate of 1-2 patients per month with 5000 simulated trials per scenario, are given in the following table:

Scenario	True Median (months)	Pr(Stopped Early)	Mean No. patients	Average Trial Duration (months)
1	7	0.788	19	27.6
2	9	0.475	24	29.9
3	11	0.254	27	31.3
4	13	0.153	28	32.0
5	15	0.075	29	32.4

7.0 Toxicity Monitoring

For the purpose of monitoring, toxicity is defined as > 30% Grade III or Grade IV toxicities occurring during the HIPEC and within 14 days after the HIPEC, as defined by Common Terminology Criteria for Adverse Events v4.0. The toxicity will be monitored using the method of Thall, Simon, and Estey.[11, 12] Following are the rules for the monitoring of toxicities for the experimental treatment: the probability of toxicity is denoted by PE. We assume PE ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement: Pr(PE > 0.30 | data)>0.95. That is, we will stop the study if, at any time during the study, we determine that there is more than 95% chance that the toxicity rate is more than 30%. The stopping boundaries for toxicities, based on these assumptions and monitoring conditions are found in table “Stopping boundaries for toxicities”. We will apply these stopping boundaries starting from the 3rd patient and then in cohorts of 3. For example, accrual will cease if 5 patients experience a toxicity among in the first 6 patients treated. The operating characteristics are summarized in “Operating characteristics for Toxicity Monitoring”. Both the decision rule and operating characteristics were calculated using the stopbound procedure in Stata version 12.1.

Stopping boundaries for toxicities

Stop accrual if the number of toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated.										
The number of patients evaluated for toxicities	3	6	9	12	15	18	21	24	27	30
The number of patients with DLTs	3	5	6	7	8	9	11	12	13	14

Operating characteristics for Toxicity Monitoring

True Toxicity Rate	Early Stopping Probability	Sample Size		
		25th percentile	Median	75th percentile
0.10	0.001	30	30	30
0.20	0.015	30	30	30
0.30	**0.118**	30	30	30
0.40	0.382	15	30	30
0.50	0.750	9	15	27

The joint stopping probabilities for Toxicity and for OS are shown in the table below.

True Toxicity Rate	Pr(Stopping Early)	True Median (months)	Pr(Stopping Early)	Joint Stopping Probability
0.10	0.001	7	0.788	0.788
0.20	0.015	7	0.788	0.791
0.30	0.118	7	0.788	0.813
0.40	0.382	7	0.788	0.869
0.50	0.750	7	0.788	0.947
0.10	0.001	9	0.475	0.476

0.20	0.015	9	0.475	0.483
0.30	0.118	9	0.475	0.567
0.40	0.382	9	0.475	0.676
0.50	0.750	9	0.475	0.869
0.10	0.001	11	0.254	0.255
0.20	0.015	11	0.254	0.265
0.30	**0.118**	**11**	0.254	**0.342**
0.40	0.382	11	0.254	0.539
0.50	0.750	11	0.254	0.814
0.10	0.001	13	0.153	0.154
0.20	0.015	13	0.153	0.166
0.30	0.118	13	0.153	0.253
0.40	0.382	13	0.153	0.477
0.50	0.750	13	0.153	0.788
0.10	0.001	15	0.075	0.076
0.20	0.015	15	0.075	0.089
0.30	0.118	15	0.075	0.184
0.40	0.382	15	0.075	0.428
0.50	0.750	15	0.075	0.769

Statistical Analysis:

All patients who received treatment will be included in the analysis for efficacy and safety. Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. Resection rates will be presented with 95% confidence intervals. The association between resection rates and patient's clinical characteristics will be examined by Wilcoxon's rank sum test or Fisher's exact

test. Overall survival time will be estimated using the Kaplan-Meier method. Patients who drop out of the study will be included in the time to event data as “censored data”. The two-sided log-rank test will be used to assess the differences of time to events between groups.

8.0 AUDITS AND INSPECTIONS

Regulatory authorities or the Institutional Review Board (IRB) may perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

9.0 TRAINING OF STAFF

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). Dr Badgwell will ensure that appropriate training relevant to the study is given to all study staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

A Site Initiation Visit will be conducted at MD Anderson Cancer Center for study staff.

10.0 CHANGES TO THE PROTOCOL

Study procedures will not be changed without approval from the IRB. If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be approved by the MD Anderson IRB, and if applicable, by the local regulatory authority, before implementation. Local and federal (Food and Drug Administration [FDA]) requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB and study sponsor is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to the sub-investigators and staff involved with the study.

11.0 ETHICS

Ethics Review:

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by the MD Anderson IRB. The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually.

Ethical Conduct of the Study:

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Written Informed Consent:

The principal investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Written Informed Consent Form in the subject's medical record as well as his/her study subject file. A copy of the signed Written Informed Consent Form must be given to the subject. The consent process will be documented in the subject's medical records.

Subject Data Protection:

The Written Informed Consent Form will explain that for data verification purposes, a regulatory authority, and the IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

12.0 EMERGENCY PROCEDURES

Procedures in Case of Medical Emergency:

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study.

Procedures in Case of Overdose:

There is currently no known antidote for the systemic chemotherapy in this study. The treatment of AEs associated with overdose should be supportive for the underlying adverse symptoms.

Doses of study treatment in excess of that specified in the clinical study protocol are considered to be an overdose. Overdose, with or without associated symptoms should be handled in the same way as a deviation and sent to IRB. Signs or symptoms of an overdose that meet the criteria of serious should be reported as a SAE in the appropriate timeframes and be documented as clinical sequelae to an overdose.

13.0 DATA SAFETY MONITORING PLAN

The principal investigator and all research staff associated with this trial have received training and certification in human subject protections research and are ultimately responsible for monitoring the safety of this trial.

The PI will continuously monitor this trial and more frequently safety related data. This trial will also be reviewed periodically by physicians and research staff at the Gastric Cancer Multidisciplinary Group meeting.

Monitoring will be provided by the MD Anderson Clinical Research Center for this clinical trial. The monitor will assure that the rights and well – being of human subjects are protected and the data are accurate, complete and verifiable from source documents and the trial is conducted in compliance with currently approved protocol/amendments, with good clinical practice (GCP) and the applicable regulatory requirements.

The monitor will be familiar with the protocol, the informed consent form, any other information provided to the subjects, the standard operating procedures (SOP), GCP and applicable regulatory requirements.

Monitors will have access to subject medical records and other study-related records. The principal investigator agrees to cooperate with the monitor (s) to ensure that any problems detected in the course of these monitoring visits are resolved. Personal contact between the monitor and the investigator will be maintained throughout the clinical trial to assure that the investigator is fulfilling his obligations and the facilities used in the clinical trial remain acceptable.

Investigational Products:

The systemic chemotherapy in this study is the current standard of care for the treatment of gastric cancer.

Monitoring Report:

After each monitoring visit a separate monitoring report will be generated and submitted to the principal investigator and project manager. This report will include significant findings related to deficiencies and deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements and actions taken to prevent recurrence of the detected deviations. The report will make recommendations for actions to be taken to secure compliance.

Continuing Review:

An annual report will be compiled and sent to the IRB to report on number of subjects enrolled in the study and safety events and accrual schedule.

14.0 DATA QUALITY ASSURANCE AND DOCUMENTATION

CRF’s should be filled by qualified personnel, reviewed, dated and signed by the investigator. The forms have to be completed in a neat and legible manner with black or blue ballpoint pen. No entries should be erased or over written or correction fluid or white out be used. Corrections

can only be crossed out with a single line and should have the date and initials of the person making the change.

Source Documents are defined as original documents with original observations and information about the clinical investigation. All electronic source documents should be 21 CFR 11 compliant. Source documents will include progress notes, computer print outs, laboratory data and all recorded data from automated instruments. Monitor will review CRF's against source documentation for accuracy of the information. Subject Confidentiality will be maintained. CRFs will not include any personal identification information such as name etc. Subjects will be identified with Initials and subject study number only.

15.0 RETENTION OF RECORDS

All documentation related to this trial will be retained for 2 years after the investigator is complete.

16.0 REFERENCES

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