Cover Page

Title:
A Phase II Trial of Perioperative Chemotherapy With Leucovorin, Oxaliplatin, Docetaxel and S-1 (LOTS) For Patients With Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

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Abstract

Background

Gastric cancer ranks the third most deadly cancers worldwide. Adjuvant or perioperative chemotherapies improve the surgical outcome and reduce distant failure. Several perioperative chemotherapies are efficacious in patients with locally advanced gastric cancer. S-1 is an orally available fluoropyrimidine that demonstrates a good efficacy and synergistic effect with other chemotherapeutic partners. However, S-1, docetaxel and oxaliplatin triplet has not been investigated as perioperative therapy in locally advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Objectives

The aim of the trial is to investigate the clinical efficacy and toxicity of perioperative leucovorin, oxaliplatin, docetaxel and S-1 (LOTS) in patients with locally advanced gastric or GEJ adenocarcinoma who receive a curative surgery. The primary outcome is pathological response or curative resection rate. The secondary outcome includes recurrence-free survival, overall survival, disease control rate, protocol completion rate and adverse events.

Study design and accrual

The study is an open-label, single-arm and multi-center phase II investigator-initiated trial with Simon two-stage design. Subjects with ≥cT3 or N+ resectable gastric or GEJ adenocarcinoma who are eligible for curative D2 gastrectomy are included. A total of 56 subjects will be enrolled. The minimal sample size is 23 when the treatment response is of the lower threshold. Trial accrual date is 01/Apr/2021.

Treatment protocol

LOTS (14 days as a cycle) 4 cycles every 2 weeks, followed by operation and another 4 cycles every 2 weeks post-operatively. Leucovorin (30 mg) twice daily per oral on day 1 to 7, oxaliplatin (85 mg/m^2) intravenously on day 1, docetaxel (40 mg/m^2) intravenously on day 1 and S-1 (35 mg/m^2) twice daily per oral on day 1 to 7.

Anticipated results

The study will prove the feasibility of perioperative LOTS in gastric or GEJ adenocarcinoma. The, provide an alternative to current regimens and warrant more clinical studies in the future.

SYNOPSIS

Title of the study:	Phase II trial of perioperative leucovorin, oxaliplatin, docetaxel and S-1 (LOTS) for patients with locally advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma
Drug supplier:	S-1 (TS-1®), leucovorin (Folina®) and Oxaliplatin (Oxalip®) are supported by TTY Biopharm Co., Ltd, Taiwan. Docetaxel (Taxotere®) is supported by Sanofi-Aventis, France.
Objectives:	The objective of the study is to evaluate the following outcome parameters with perioperative LOTS and curative surgery in patients with resectable locally advanced (≥cT3, lymph node-positive or both) gastric cancer. Primary outcome: ▪ Pathological response (complete and partial) or curative resection rate (R0 resection). Secondary outcome: ▪ Recurrence-free survival (RFS) ▪ Overall survival (OS) ▪ Disease control rate (objective response plus stable disease ≥ 3 months) ▪ Protocol completion rate ▪ Adverse events related to protocol chemotherapy and/or curative surgery ▪ Predictive biomarkers
Design:	The proposed study is an open-label, single-arm, single-country and multi-center phase II investigator-initiated trial with Simon two-stage design.
Sample size:	We assume the statistical power of 90% (β=0.1) and the probability of type I error by two-tailed α at 0.1, along with an estimated good response rate (P1) of 60% and a poor rate (P0) of 35%. Stage 1: 14 subjects Stage 2: 25 subjects with a total of 39 subjects Minimal sample size: 23 subjects A total of 56 subjects will be enrolled under the assumption of a 30% of drop-out and operation ineligibility rate per protocol.
Criteria for inclusion:	1. Subjects have histologically-confirmed gastric or GEJ (classified as Siewert type III) adenocarcinoma with a clinical stage of T3 or above, lymph node involvement (N+) or both

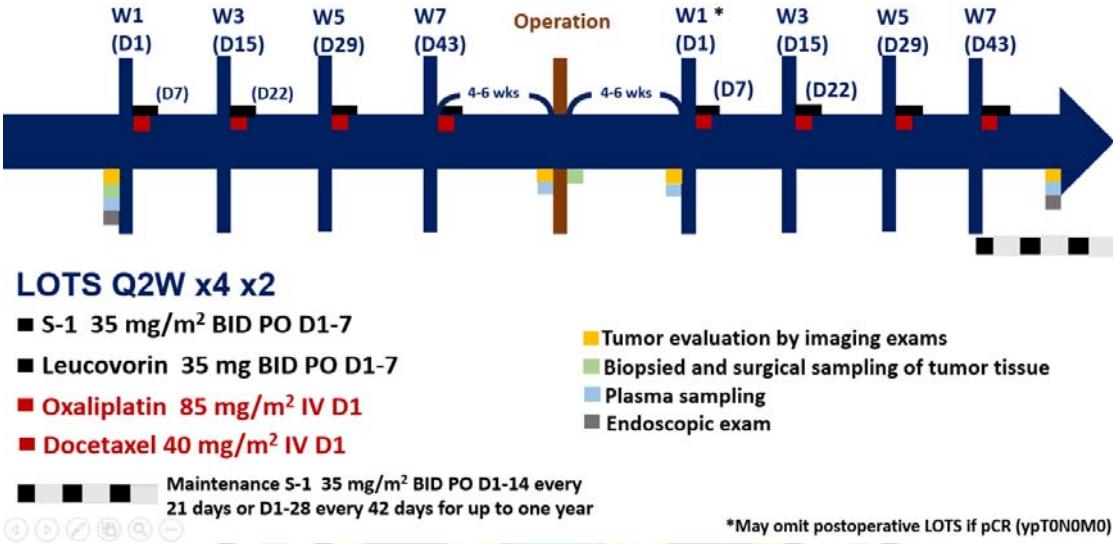
	according to American Joint Cancer Committee staging system, 8th edition (AJCC 8th). 2. Subjects present with at least one measurable lesion which can be accurately assessed by conventional techniques at least 2.0 cm or 1.0 cm by computed tomography (CT) or magnetic resonance imaging (MRI). 3. Subjects have a lymph node-positive disease in which that at least one of the nodes with a diameter greater or equal to 0.8 cm in the long axis. If subjects do not have a node-positive disease, a clinical stage of T3 or above and a measurable tumor is required for inclusion. 4. Subjects are above 20 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, have a life expectancy >3 months, have surgically resectable disease and are physically competent and willing to receive a curative operation. 5. Subjects have adequate organ functions, including bone marrow reserve with a leukocyte count ≥3,000 /μL and platelet count ≥100,000 /μL, hepatic reserve with a serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 times of upper limits and total bilirubin ≤2.0 mg/dL, renal reserve with a creatinine clearance ≥60 mL/min and cardiac reserve with a left ventricular ejection fraction (LVEF) ≥50% by echocardiography at baseline. 6. Subjects have, or agree to establish a vascular access that permits systemic intravenous chemotherapy and are capable of ingesting capsules per oral. 7. Subjects with reproductive potentials are willing to accept contraceptive measures during the trial. 8. Subjects are functionally and cognitively capable to be informed of the trial contents and objectives (including obtaining blood and tumor tissue for the trial investigation), and agree to sign the written consent for enrollment.
Criteria for exclusion:	1. Subjects have metastatic (M1, including washing cytology positive for peritoneal carcinomatosis), recurrent gastric/gastroesophageal junction cancer (defined by an interval time less than five years from the current diagnosis to the prior initial disease), or any other underlying primary malignancies excluding carcinoma in situ or resectable skin cancer.

	2. Subjects have received chemotherapies within 2 years, or a major abdominal surgery or radiotherapy within 4 weeks before the trial enrollment. 3. Subjects are known to be allergic to any of the studied chemotherapeutics. 4. Subjects have underlying chronic illnesses, including cardiopulmonary diseases, ischemic heart disease, inflammatory bowel disease, poorly-controlled diabetes mellitus, liver cirrhosis and/or peripheral neuropathy of any etiologies. 5 Subjects have active bacterial, viral, fungal or mycobacterial infections that require systemic therapy, including active infection with human immunodeficiency virus (HIV), hepatitis B or C virus (HBV or HCV) (For details please refer to 5.2.5). 6. Subjects are planning to conceive or already in pregnancy or breastfeeding. 7. Subjects are currently participating in any other clinical trials or studies.
Protocol treatment:	<u>Perioperative chemotherapy:</u> LOTS (14 days as one cycle) 4 cycles every 2 weeks as preoperative therapy, followed by curative operation and another 4 cycles every 2 weeks as postoperative therapy. Leucovorin 30 mg twice daily per oral on day 1 to 7. Oxaliplatin 85 mg/m^2 on day 1. Docetaxel 40 mg/m^2 on day 1. S-1 35 mg/m^2 twice daily (daily total dose as determined by body surface area (BSA): <1.25 m^2, 80 mg; 1.25-1.50 m^2, 100 mg; ≥1.50 m^2, 120 mg) per oral on day 1 to 7. <u>Operation:</u> Radical total, subtotal or partial gastrectomy (laparotomic, laparoscopic or robotic) plus perigastric and celiac axial lymph node dissection (D2 at least) in a curative intent. <u>Post perioperative treatment</u> Patients who achieve a pathological complete response (ypT0N0M0) after the preoperative chemotherapy plus curative surgery in the absence of any residual tumors might omit the

	postoperative therapy under the investigator's discretion. After the postoperative chemotherapy per protocol (in a total of 8 cycles), patients will be maintained by S-1 monotherapy on D1 to D14 every 21 days or D1 to D28 every 42 days for up to one year with the same dose in perioperative therapy according to the NHI practice and reimbursement guideline. <u>Pre-medications:</u> Intravenous antihistamine and serotonin receptor blocker with/without 10 mg of dexamethasone are administered before the intravenous chemotherapy. Therapeutic granulocyte stimulating factors (GCSF) or granulocyte-macrophage stimulating factors (GM-CSF) are allowed for grade 3 to 4 neutropenia or febrile neutropenia under the investigator's discretion according to the NHI practice and reimbursement guideline. Prophylactic GCSF or GM-CSF is not permitted. Antibiotic and supportive treatments for febrile neutropenia or infections are allowed according to the practice guidance. <u>Pre-treatment preparation:</u> After the enrollment, subjects are required to establish a viable vascular access for systemic chemotherapy, such as port-A or peripherally inserted central venous catheter. Chemotherapy will be initiated right after the access is established.

TRIAL SCHEMA

A Phase II Trial of Perioperative Chemotherapy With Leucovorin, Oxaliplatin, Docetaxel and S-1 (LOTS) For Patients With Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma



Primary endpoint: pathological response (complete and partial) or curative resection rate

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List of abbreviations and definition of terms

AJCC	American Joint Committee on Cancer
ALT/AST	alanine aminotransferase/aspartate aminotransferase
ANC	absolute neutrophil count
CT	computed tomography
CCRT	concurrent chemoradiotherapy
eGFR	estimated glomerular filtration rate
ECOG	Eastern Cooperative Oncology Group
EGDscopy	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GM-CSF	granulocyte-macrophage stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficient virus
LVEF	left ventricular ejection fraction
OS	overall survival
PBMC	peripheral blood mononuclear cell
RFS	recurrence-free survival
SAE	serious adverse event
SJS/TEN	Steven-Johnson syndrome/toxic epidermal necrolysis
SUSAR	suspected unexpected serious adverse reactions
TS	thymidylate synthase
TRG	tumor regression grade
PET	positron emission tomography
PLT	platelet
PSN	peripheral sensory neuropathy

1. OBJECTIVES

1.1 Objective of the study:

To investigate the clinical efficacy and toxicity of perioperative chemotherapy of leucovorin, oxaliplatin, docetaxel and S-1 (LOTS) in patients with resectable and locally advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who receive a curative surgery.

1.2 Primary objective:

Pathological response (complete and partial) of study chemotherapy or curative resection rate.

1.3 Secondary objectives:

Recurrence-free survival (RFS), overall survival (OS), disease control rate (objective response plus stable disease ≥ 3 months), protocol completion rate, adverse events related to study chemotherapy or curative surgery and predictive biomarkers.

2. BACKGROUNDS

Adjuvant or perioperative chemotherapies in gastric cancer

Gastric cancer ranks the third most deadly cancers worldwide.[1] Despite the improvements in the early detection and curative treatment, nearly two thirds of high-risk patients still encounter a recurrence or progression of the disease.[2] Adjuvant or perioperative chemotherapies have introduced substantial attentions for consolidating the surgical outcome and reducing distant failure.[3-6] Indeed, operation alone in high-risk patients, such as those who have an above T2 or nodal positive (N+) disease, is no longer a standard of treatment. Introduction of perioperative therapies, such as chemotherapies or concurrent chemoradiotherapies (CCRT), facilitates the optimal resection of the tumor and prolongs overall survival in the selected population.[7,8] However, given aggressive salvage therapies, patients with recurrent or advanced gastric cancer still have a dismal outcome with survival barely exceeds more than one year.[9]

The UK MAGIC trial investigated perioperative epirubicin, infusional fluorouracil (5-FU) and cisplatin (ECF) in stage II or higher gastric cancer and observed significantly prolonged progression-free and overall survival as compared with operation alone. The probability of curative resection (79.3% vs. 70.3%; p=0.03) and pathological staging of T1-2 tumors (51.7% vs. 36.8%; p=0.002) were more prevalent in patients who received perioperative ECF.[3] Ychou and the French group also reported

a favorable curative resection rate (84% vs. 73%; p=0.04) and survival outcome with perioperative 5-FU and cisplatin (CF), at the cost of more treatment-related neutropenia (20.2%) but not operation-related morbidity.[5] On the success of triplet regimens, the role of anthracycline had been questioned as an ideal partner due to a poor tolerability in perioperative therapies. In the phase II NeoFLOT trial, patients with clinical stage T3 or T4 and lymph node-positive disease received perioperative chemotherapy with a modified combination of 5-FU, leucovorin, oxaliplatin and docetaxel (FLOT). The pathological complete response rate (pCR) plus near complete histological remission (<10% residual tumor) was 40% with a median disease-free survival of 32.9 months.[10] The German group further investigated docetaxel-based triplet in comparison with anthracyclines in the similar group of high-risk patients in phase II/III FLOT4-AIO study. The results confirmed that the perioperative FLOT was superior to ECF in efficacy and comparable in tolerability.[6] On the success of these clinical trials, perioperative chemotherapies have changed the paradigm in patients with resectable gastric cancer harboring high risk of recurrence. Although the ideal partners in the triplet combinations remain undetermined, emerging evidence has supported the anthracycline-free regimens with a favorable efficacy and comparable toxicity.

S-1 in gastric cancer

S-1 is an oral chemotherapeutic composed of tegafur (a prodrug of 5-FU), gimeracil (preventing dihydropyrimidine dehydrogenase-mediated degradation of 5-FU) and oteracil (reducing the toxic effects of 5-FU) with excellent bioavailability and efficacy in various types of cancers.[11,12] S-1 has been shown to improve the outcome in gastric cancer patients who have received optimal gastrectomy with D2 dissection and approved in several Asian countries rather than in the US.[4] Yoshida et al. reported that adjuvant S-1 plus docetaxel prolonged the RFS and OS in stage III gastric cancer with few additional safety concerns.[13] A combination of S-1 with cisplatin or oxaliplatin has also been intensively investigated in resectable gastric cancer as neoadjuvant or adjuvant alternatives to capecitabine/oxaliplatin (XELOX) and other platinum-based doublets.[14-17] In the phase III JCOG0501 trial, patients with linitis plastica or large ulcero-invasive gastric cancer in whom that the prognosis is dismal, received neoadjuvant S-1 plus cisplatin and followed by adjuvant S-1 postoperatively. The results indicated a shorter operation time and a similar morbidity as compared to those not receiving neoadjuvant chemotherapy.[18] In general, S-1-based doublets were well-tolerated without active warning toxicities and yielded some potentials for the development of a three-drug combination.

To date, the optimal S-1-based triplet chemotherapies have not been well-established.

In the phase II KDOG1001 trial, neoadjuvant docetaxel, cisplatin and S-1 (DCS) contributed to a pathological response of 57.5% and a grade 3 histological remission of 8% in patients with high-risk locally advanced gastric cancer.[19] Similar results can also be observed in the phase III PRODIGY trial, in which that neoadjuvant docetaxel, oxaliplatin and S-1 (DOS) followed by adjuvant S-1 correlated with a significantly prolonged PFS as compared with adjuvant S-1 alone.[20] However, the role of S-1 in perioperative therapies are not yet delineated in patients with borderline resectable and advanced gastric cancer who have a greater risk of recurrence, progression or failure on margin-free resection. Ongoing clinical studies are investigating the addition of immune checkpoint inhibitors to standard perioperative chemotherapies.[21-23] However, the predictive biomarkers for efficacy and treatment response are still under investigations. More clinical trials are warranted to demonstrate the role of S-1 as an ideal partner in triplet perioperative chemotherapy.[24]

The proposed trial: perioperative LOTS

S-1 is a feasible companion chemotherapeutic in various cancers. In the preclinical studies, the combination of S-1 and leucovorin enhances the antineoplastic activity as compared with S-1 alone.[25] S-1 plus leucovorin has also been confirmed of the therapeutic efficacy in patients with metastatic colorectal cancer in several phase II trials, as an alternative to intravenous 5-FU.[26-28] Furthermore, The oral formulation of the agents provides significantly favorable clinical convenience and accessibility as compared with prolonged intravenous infusions of high-dose 5-FU. A meta-analysis incorporating Asian patients with advanced gastrointestinal cancers indicated that S-1 was an ideal alternative to intravenous 5-FU due to comparable efficacy and better tolerability.[29]

In addition to gastric cancer, a combination of S-1, leucovorin, oxaliplatin and gemcitabine (SLOG) has been evaluated in advanced pancreatic adenocarcinoma and concluded that the dosage of S-1 at 35 mg/m^2 BID per oral in Asian population was acceptable.[30] The grade 3 to 4 adverse events were less than 5% in the absence of warning toxicities other than anemia, neutropenia, diarrhea and mucositis. In the phase II TCOG T1211 study, SLOG demonstrated good efficacy in chemotherapy-naïve metastatic pancreatic adenocarcinoma.[31] Furthermore, SLOG had been investigated as a frontline therapy in the advanced biliary tract cancer comparing with gemcitabine/cisplatin.[32] Given the success and feasibility of the regimen, LOTS is a promising novel combination in locally advanced gastric cancer.

The proposed trial will investigate the triplet S-1, oxaliplatin, docetaxel and

leucovorin as perioperative chemotherapy for resectable and clinical stage of above T3 and nodal-positive gastric cancer. The study will evaluate the therapeutic efficacy, such as pathological tumor response, curative resection, protocol completion, tolerability and potential adverse reactions. In the published literature, the triplet FLOT was considered an optimal regimen in the dosage of docetaxel no more than 50 mg/m^2 and oxaliplatin at 85 mg/m^2 biweekly, with an acceptable tumor response and toxicity in high-risk resectable gastric cancer.[6] The dosage and treatment schedule will be carefully incorporated in the proposed trial. Together the results will prove the feasibility of S-1-containing triplet perioperative therapies in gastric cancer, provide an alternative to current standard of treatment and warrant more clinical studies in the future.

3. STUDY DRUG INFORMATION

3.1 Leucovorin:

3.1.1 Mechanism of action:

Leucovorin calcium (Folina tab, TTY Biopharm) is utilized to reverse the hematological and metabolic toxicities to normal cells by methotrexate and other antifolate-metabolites. It serves as a reduced folate cofactor in the *de novo* production of thymidylate from dUMP upon intracellular conversion to 5,10-methylenetetrahydrofolate (CH2FH4). Administration of leucovorin enhances the stability of the covalent complex of fluorodeoxyuridine monophosphate (FdUMP) and thymidylate synthase (TS) and thus sensitizes the antineoplastic activity of 5-FU and its derivatives.

3.1.2 Adverse events:

Allergic reactions such as anaphylactoid response or urticaria, have been reported following both oral and parenteral administration of leucovorin with an incidence lower than 1%. The co-administration of leucovorin and 5-FU may augment the toxicity confined to 5-FU.

3.1.3 Clinical formulation:

Leucovorin calcium is commercially available as “Folina® tab” containing 15 mg of calcium folinate per tablet. It is recommended that Folina® is administered orally twice daily for every 6 hours in concordance with the administration of 5-FU and its derivatives. The pregnancy safety category of leucovorin is “C”.

3.2 Oxaliplatin:

3.2.1 Mechanism of action:

Oxaliplatin is a diaminocyclohexane (DACH) carrier ligand-based platinum compound that inhibits DNA synthesis and repair. The major antineoplastic action involves in the formation of intra-strand platinum-DNA adducts by a cross-link between activated platinum species and specific base sequences, such as two adjacent guanine residues or guanine-adenine bases. Oxaliplatin also produces inter-strand cross-links but it accounts for less than 5% in the total platinum-DNA adducts. The features of the adducts resemble that of other platinum chemotherapeutics such as cisplatin and carboplatin but the disruption of DNA synthesis and cytotoxicity are more prevalent with the oxaliplatin-mediated DACH-platinum adducts as compared with other platinums. The bulky DACH carrier ligand of oxaliplatin contributes to the enhanced antineoplastic activity in the absence of cross-resistance with other platinums. Oxaliplatin administration also compromises DNA repair by preventing the assembly of the repair machinery proteins, notably mismatch repair enzyme complex, and thereby sensitizes the DNA breakage and subsequent cell death.

3.2.2 Adverse effects:

3.2.2.1 Neurotoxicity:

The dose and duration-limiting toxicity of oxaliplatin is sensory neuropathy. Oxaliplatin related peripheral sensory neuropathy (PSN) presents with two distinctive forms. The first features by tingling of the face and extremities and may be subsided spontaneously. Cumulative administrations of oxaliplatin correlate with the increase severity and duration of PSN. Severe PSNs, such as laryngopharyngeal spasm/vocal cord palsy, temperature dysesthesia and hyperesthesia are observed in 1 to 2% of patients treated with oxaliplatin. The symptoms may resolve with prolongation or discontinuation of oxaliplatin infusion and the related mortality is extremely rare. The second form involves solely on the extremities and augments with accumulative dosing. Persistent irreversible functional impairment, including disability of fine sensor-motor executive actions or neuropathic pain, requires a dose reduction, delay and event permanent discontinuation of oxaliplatin. The risk of oxaliplatin related PSN at a cumulative dose of 780 mg/m^2 is reported 10% while of 1,170 mg/m^2 is 50%, respectively.

3.2.2.2 Nephrotoxicity:

Oxaliplatin is relatively renal-sparing as compared with other platinums. Drug related renal insufficiency was reported 3% in of all treated populations and grade 3 to 4 events were less than 1%. In addition, pharmacokinetic studies revealed that oxaliplatin does not increase the risk of renal toxicity or impair the metabolite clearance in patients with moderate renal insufficiency (eGFR 30 to 60 ml/min).

3.2.2.3 Hepatic toxicity:
A transient elevation of liver enzymes may occur in patients treated with oxaliplatin. However, clinically relevant hepatotoxicity has not been reported to be a dose-limiting event from oxaliplatin administrations.

3.2.2.4 Gastrointestinal toxicity:
Nausea and vomiting were observed in patients treated with oxaliplatin but could be managed by conventional medications, such as 5-HT3 (serotonin) antagonists. Oxaliplatin is recognized as moderately emetogenic as compared with cisplatin, and does not cause delayed emesis. Diarrhea was reported in 41% of patients but the grade 3 to 4 events were fewer than 5%. Mucositis occurs in only 4% of patients and does not require additional managements.

3.2.2.5 Hematological toxicity:
Myelosuppression is reported less than 5% in oxaliplatin monotherapy. However, the risk of hematological toxicity is increased in combinatorial regimens. The myelosuppressive effects are short in durations, potentially reversible and does not lead to significant complications such as neutropenic sepsis or bleeding.

3.2.2.6 Allergic reactions:
Infrequent allergic reactions have been described. Anaphylactic reactions are reported in 0.5% of patients treated with oxaliplatin but may require permanent discontinuation.

3.2.3 Clinical formulation:
Oxaliplatin (Oxalip®) is produced by TTY Biopharma. It is available in the form of vials of sterile solution. Each vial contains 50/100 mg of oxaliplatin in 10/20 ml solution. The concentration of oxaliplatin in the solution is 5 mg/ml. It is recommended that oxaliplatin should be diluted for infusion in 250 ml to 500 ml of 5% glucose solution. The chemical and physical stability of the reconstituted solution have been demonstrated for 48 hours at 2-8 degree and 30 degree Celsius. Oxaliplatin should not be mixed or administered with saline or other chloride-containing solutions or alkaline media such as basic solutions of 5-FU. The pregnancy safety category of oxaliplatin is “D”.

3.3 Docetaxel:
3.3.1 Mechanism of action:

Docetaxel is an antimitotic chemotherapeutic against various types of cancer. It binds to free tubulin, then promotes the polymerization of tubulin into stable microtubules and inhibits microtubule disassembly, resulting in blockade of cellular mitotic and interphase functions. Consequently, docetaxel promotes tumor cell death by interfering the mitotic division process and demonstrates cell-cycle dependent cytotoxicity. Unlike paclitaxel and other taxanes in clinical application, docetaxel does not alter the number of protofilaments in the bound microtubules and therefore is not cross-resistant with paclitaxel.

3.3.2 Adverse effects:

3.3.2.1 Hematological toxicity:

The drug-limiting toxicity of docetaxel is myelosuppression. The maximal tolerable dose of docetaxel monotherapy is 100 mg/m^2. The incidence of neutropenia is reported 76% in all grades and 52% in grade 3 to 4 events as monotherapy. Severe treatment-related anemia (8.9%) and thrombocytopenia (0.2%) are also noticed in the phase I/II trials. The associated neutropenic sepsis accounts for less than 5% in patients treated with docetaxel but few cases are reported to have clinically relevant thrombocytopenic bleeding. The risk of myelosuppression is increased when docetaxel incorporates other combinatorial chemotherapeutics, such as fluoropyrimidines, anthracyclines and platinums. Prophylactic or therapeutic growth factor treatment is recommended given in high-risk settings. The risk of treatment-related deaths associated with myelosuppression is rare and reported less than 1%.

3.3.2.2 Gastrointestinal toxicity:

Diarrhea, anorexia and mucositis are observed in patients treated with docetaxel but can be safely managed by conventional measures. The incidence of grade 3 to 4 mucositis is 5.3%, diarrhea 4.0%, anorexia 4.0% and vomiting 0.8% at a dose of 100 mg/m^2, respectively. However, the events rarely result in the discontinuation or dose reduction of docetaxel and no toxicity-related deaths are reported.

3.3.2.3 Hepatic toxicity:

Docetaxel is associated with a risk of transient elevations in hepatocellular enzymes and bilirubin. The incidence of grade 3 to 4 hepatotoxicity is 5% in hyperbilirubinemia and less than 3% in transaminitis of in patients treated with docetaxel at a dose of 100 mg/m^2. However, the hepatotoxic reaction is idiosyncratic and does not positively correlate with the dosage.

3.3.2.4 Allergic reactions:

Allergic reactions such as anaphylaxis, bronchospasm, angioedema, hypotension and generalized skin rashes are reported. The risk is exponentially higher in the first infusion of docetaxel. Grade 1 to 2 reactions can be managed by slower infusion rate, corticosteroid and/or antihistamine treatments. Although the risk of grade 3 to 4 reaction is low (less than 1%), medical personnel should prepare emergent management and procedures for life-threatening anaphylaxis prior to the administrations. If the patient encounters an above grade 3 allergic event, discontinuation of docetaxel is required.

3.3.2.5 Neurotoxicity:

Docetaxel is associated with an increased risk of PSN. The incidence of grade 3 to 4 PSN is 3% to 4% in patients treated with docetaxel. Rare cases of ageusia and anosmia are reported but the incidence is lower than 0.1%. Generally, grade 1 to 2 PSN improves spontaneously after the completion of treatment. However, persistent irreversible PSN, including hyperesthesia or neuropathic pain, requires a dose reduction, delay and event permanent discontinuation of docetaxel.

3.3.2.6 Vesicant reactions:

Docetaxel is a moderate vesicant and irritant and should be carefully managed when extravasation occurs. Local ice packing for 15 minutes every hour by 3 to 5 hours and hyaluronidase 150 unit local injections to the affected site are suggested to alleviate the symptoms.

3.2.2.7 Cardiovascular toxicity:

Docetaxel has been reported to be associated with fluid retentions such as pleural, pericardial and peritoneal effusions. However, such reactions are only seen in few scattered reports.

3.3.2.8 Alopecia:

Docetaxel may induce clinically significant alopecia.

3.3.3 Clinical formulation:

Docetaxel (Taxotere®) is produced by Sanofi-Aventis, France. It is available in the form of vials in sterile solution. Each vial contains 20 mg or 80 mg of docetaxel in 1.0 to 4.0 ml anhydrous ethanol since the content is lipophilic. The concentration of docetaxel in the solution is 20 mg/ml. Patients who are allergic to the excipient polysorbate 800 should avoid the infusion of docetaxel. It is recommended that docetaxel not to be infused or diluted with polyene (PVC) bags. The chemical and

physical stability of the reconstituted solution have been demonstrated for 48 hours at 2-8 degree and 30 degree Celsius. The pregnancy safety category of docetaxel is “D”.

3.4 S-1:

3.4.1 Mechanism of action:

S1 is an orally available fluoropyrimidine chemotherapeutic based on a biochemical modulation of 5-FU. S-1 contains tegafur, a prodrug of 5-FU; gimeracil, an inhibitor of dihydropyrimidine dehydrogenase which prevents the rapid degradation of 5-FU; oteracil, which inhibits the phosphorylation of 5-FU and thereby facilitates the clearance of toxic metabolites and reduces the gastrointestinal toxicity, by a molar ratio of 1:0.4:1, respectively.

3.4.2 Adverse events

3.4.2.1 Hematological toxicity:

The maximal tolerable dose of S-1 is 150 mg per day according to the phase I clinical study. However, pharmacogenetic variations are reported in different ethnical backgrounds, as the Caucasian patients require robust dose reductions to 75 mg per day due to the heterogeneous activity of cytochrome 2A6 (CYP2A6) as compared with Asian. The dose limiting toxicity of S-1 is myelosuppression. The incidence of myelosuppression is reported 78% in all grades and 20% in grade 3 to 4 events at a dose of 80 mg/m^2 per day. Among the hematological reactions, neutropenia is the most common event with an incidence of 39%, followed by anemia of 31%, and thrombocytopenia of 11%. The phase III ACTS-GC trial incorporated 529 patients to receive S-1 monotherapy at a dose of 80 mg/m^2 with the maximum of 120 mg daily and concluded that the grade 3 to 4 hematological events were neutropenia (1.2%), anemia (1.2%) and thrombocytopenia (0.2%), in the absence of neutropenic infections or severe bleeding. There were no treatment-related deaths associated with myelosuppression and all the events can be managed safely by conventional measures.

3.4.2.2 Gastrointestinal toxicity:

Diarrhea, anorexia and vomiting are observed in patients treated with S-1 and require no dose delays or reductions. The incidence of gastrointestinal toxicity is reported in the phase I/II studies, in which that mucositis (24%), diarrhea (12%) and anorexia/vomiting (12%) are the most prevalent events. In the ACTS-GC trial, grade 3 to 4 anorexia (6.0%), nausea (3.7%), diarrhea (3.1%) and mucositis (0.2%) are reported and safely managed by conventional measures.

3.4.2.3 Nephrotoxicity:

S-1 has not been reported to be associated with clinically relevant renal toxicity. However, scattered cases of grade 3 to 4 proteinuria are reported but the incidence is lower than 0.5%.

3.4.2.4 Dermatotoxicity:
S-1 has not been reported to be associated with severe dermatotoxicity such as Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). However, 16% of the patients treated with S-1 developed drug-related allergic dermatitis in the phase I/II trials. Grade 3 to 4 allergic dermatitis accounts for only 1%. In addition, skin hyperpigmentation is observed in 22% to 37% in patients receiving S-1 but it does not require medical attentions other than cosmetic issues.

3.4.2.5 Hepatic toxicity:
A transient elevation of liver enzymes may occur in patients treated with S-1. Grade 3 to 4 transaminitis are reported 1.2% to 1.7% in large-scale phase III trials. However, clinically relevant hepatotoxicity has not been reported to be a dose-limiting event in the literature.

3.4.3 Clinical formulation:
S-1 (Taiho Pharmaceutical) is commercially available as a capsule containing 20 mg of tegafur. The tegafur component is utilized as the dose level representative of S-1. It is recommended that S-1 is administered orally once or twice daily after meals. S-1 should be taken orally by swallowing and not be divided, grinded or dissolved in solution for feeding tube administration. The pregnancy safety category of oxaliplatinS-1 is “D”.

4. STAGING CRITERIA AND TOOLS

The TNM staging system, including the clinical, pathological or re-staging definitions which are described in American Joint Committee on Cancer Manual for Staging of Cancer (8th edition), will be used. A supplementary staging system incorporating Japanese Classification of Gastric Cancer, 3rd English edition is also utilized but not mandatory for stratification and analysis.

5. PATIENT SELECTION

5.1 Inclusion criteria

5.1.1. Subjects have histologically-confirmed gastric or gastroesophageal junction (classified as Siewert type III) adenocarcinoma with a clinical stage of T3 or above, lymph node involvement (N+) or both according to American Joint Cancer Committee

staging system, 8th edition (AJCC 8th).

5.1.2. Subjects present with at least one measurable lesion which can be accurately assessed by conventional techniques in one dimension at least 2.0 cm or 1.0 cm by computed tomography or magnetic resonance imaging.

5.1.3. Subjects have a lymph node-positive disease in which that at least one of the nodes with a diameter greater or equal to 0.8 cm in the long axis. If subjects do not have a node-positive disease, a clinical stage of T3 or above and a measurable tumor is required for inclusion (5.1.1 and 5.1.2).

5.1.4. Subjects are above 20 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, have a life expectancy >3 months, have surgically resectable disease and are physically competent and willing to receive a curative operation.

5.1.5. Subjects have adequate organ functions, including bone marrow reserve with a leukocyte count ≥3,000 /μL and platelet count ≥100,000 /μL, hepatic reserve with a serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 times of upper limits and total bilirubin ≤2.0 mg/dL, renal reserve with a creatinine clearance ≥60 mL/min and cardiac reserve with a left ventricular ejection fraction (LVEF) ≥50% by echocardiography at baseline.

5.1.6. Subjects have, or agree to establish a vascular access that permits systemic intravenous chemotherapy and are capable of ingesting capsules per oral.

5.1.7. Subjects with reproductive potentials are willing to accept contraceptive measures during the trial.

5.1.8. Subjects are functionally and cognitively capable to be informed of the trial contents and objectives (including blood and tumor tissue for the trial investigation), and agree to sign the written consent for enrollment.

5.2 Exclusion criteria

5.2.1. Subjects have metastatic (M1, including washing cytology positive for peritoneal carcinomatosis), recurrent gastric/gastroesophageal junction cancer (defined by an interval time less than five years from the current diagnosis to the prior initial disease), or any other underlying primary malignancies excluding carcinoma *in situ* or resectable

skin cancer.

5.2.2. Subjects have received chemotherapies within 2 years, or a major abdominal surgery or radiotherapy within 4 weeks before the trial enrollment.

5.2.3. Subjects are known to be allergic to any of the studied chemotherapeutics.

5.2.4. Subjects have underlying chronic illnesses, including cardiopulmonary diseases, ischemic heart disease, inflammatory bowel disease, poorly-controlled diabetes mellitus, liver cirrhosis and/or peripheral neuropathy of any etiologies.

5.2.5 Subjects have active bacterial, viral, fungal or mycobacterial infections that require systemic therapy, including active infection with human immunodeficiency virus (HIV) (defined as positive immunoblotting confirmatory test for HIV) hepatitis B or C virus (HBV or HCV) (defined as positive HBV surface antigen (HBs Ag) with a viral load ≥500 IU/mL obtained within 28 days prior to the study in the absence of any anti-HBV therapies; positive HCV antibody with a detectable viral load obtained within 28 days prior to the study in the absence of any anti-HCV therapies). However, patients with positive HBs Ag, a viral load <500 IU/mL and are treated with anti-HBV therapies for at least 14 days, positive HCV antibody with an undetectable viral load and positive HIV testing with peripheral blood CD4 T cells ≥350 cells/μL, a viral load <400 IU/mL and are treated with anti-retroviral therapies for at least 28 days do not preclude from the enrollment.

5.2.6. Subjects are planning to conceive or already in pregnancy or breastfeeding.

5.2.7. Subjects are currently participating in any other clinical trials or studies.

6. STUDY DESIGN AND TREATMENT PLANS

The study is an open-label, single-arm, single-country and multi-center phase II investigator-initiated trial with Simon two-stage design. The primary objective is to investigate the therapeutic efficacy of perioperative chemotherapy LOTS in resectable locally advanced gastric cancer. The primary endpoint is the treatment response rate, as in pathological partial or complete response. The secondary objectives are to evaluate the survival outcome, such as RFS, OS, the treatment duration, protocol completion, adverse events and predictive biomarkers for efficacy.

Enrolled subjects will receive the protocol therapies until its completion, disease

progression, death at any causes, intolerable toxicities, subject's refusal, investigator's discretion or the trial termination according to the major study principal investigator.

6.1 Overall protocol

6.1.1 Perioperative LOTS

LOTS (14 days as one cycle) 4 cycles every 2 weeks as preoperative therapy, followed by curative operation and another 4 cycles every 2 weeks as postoperative therapy.

Leucovorin 30 mg twice daily as a fixed dose per oral on day 1 to 7.

Oxaliplatin 85 mg/m^2 in 250 mL of 5% dextrose water, administered as a 3-hour intravenous infusion on day 1.

Docetaxel 40 mg/m^2 in 250 mL of normal saline, administered as a 1.5-hour intravenous infusion on day 1.

S-1 35 mg/m^2 twice daily (daily total dose as determined by body surface area (BSA): <1.25 m^2, 80 mg; 1.25-1.50 m^2, 100 mg; ≥1.50 m^2, 120 mg) per oral on day 1 to 7.

6.1.2 Operation

Radical total, subtotal or partial gastrectomy (laparotomic, laparoscopic or robotic) plus perigastric and celiac axial lymph node dissection (D2 at least) in curative intent.

6.1.3 Post perioperative treatment

Patients who achieve a pathological complete response (ypT0N0M0) after the preoperative chemotherapy plus curative surgery in the absence of any residual tumors might omit the postoperative therapy under the investigator's discretion.

After the postoperative chemotherapy per protocol (in a total of 8 cycles), patients will be maintained by S-1 monotherapy on D1 to D21 every 28 days or D1 to D28 every 42 days for up to one year with the same dose in perioperative therapy according to the NHI practice and reimbursement guideline.

6.2 Pre-medication and preparation

6.2.1 Pre-medications before the chemotherapy

Intravenous antihistamine and serotonin receptor blocker with/without 10 mg of dexamethasone are administered before the intravenous chemotherapy.

Therapeutic granulocyte stimulating factors (GCSF) or granulocyte-macrophage stimulating factors (GM-CSF) are allowed for grade 3 to 4 neutropenia or febrile neutropenia under the discretion of the investigator according to the NHI Taiwan reimbursement criteria and guidance. Prophylactic GCSF or GM-CSF is not permitted. Antibiotic and supportive treatments for febrile neutropenia or infections are allowed according to the practice guidance.

6.2.2 Pre-treatment preparation

After the enrollment, subjects are required to establish a viable vascular access for systemic chemotherapy, such as port-A or peripherally inserted central venous catheter. Chemotherapy will be initiated right after the access is established.

6.3 Dose modification and treatment delay

6.3.1 Treatment requirement:

Subjects will receive perioperative LOTS (leucovorin, oxaliplatin, docetaxel and S-1) chemotherapy every 2 weeks for a total of 8 times (4 preoperative and 4 postoperative administrations). Each cycle of treatment will be administered only when the peripheral hemogram (within 72 hours), and physical conditions meet the following requirements: absolute neutrophil count (ANC) ≥1,500/μL, platelet count ≥100×10^3/μL and all the treatment-related adverse events recover to less than or equal to grade 1.

6.3.2 Treatment delay:

If subjects fail to meet the aforementioned requirements, the scheduled cycle of LOTS can be delayed for one consecutive week. The maximum of treatment delay should not exceed 4 consecutive weeks.

6.3.2 Dose reduction and level:

In addition to dose delays, investigators may adjust the dose level of the next cycle of treatment according to the table below. A maximum of two dose reductions is allowed. If the subject fails to tolerate the least dose level (Level -2), the treatment is discontinued and subject withdrawn from the study. Only dose reductions are allowed but not escalations. A discontinuation of a single chemotherapeutic is permitted outside of the dose level restrictions only when it is recognized as the inciting drug responsible for the specific event as described below but the guidance for dose levels is still maintained per protocol. In that if only single agent is preserved in the regimen excluding leucovorin, the subject is also withdrawn from the study.

Dose levels of LOTS

Dose level	0 (standard)	-1	-2
leucovorin	30 mg BID	30 mg BID	30 mg BID
oxaliplatin	85 mg/m^2	60 mg/m^2	45 mg/m^2
docetaxel	40 mg/m^2	30 mg/m^2	20 mg/m^2
S-1	35 mg/m^2 BID	35 mg/m^2 BID	20 mg/m^2 BID

6.3.3 Specific considerations by adverse events:

6.3.3.1 Neutropenia

In the presence of grade 3 neutropenia (ANC 500-1000/μL) or febrile neutropenia for 5-7 days, reduce the dose to Level -1, followed by Level -2 and then discontinue docetaxel. In the presence of grade 4 neutropenia (ANC <500/μL) or febrile neutropenia for >7 days, reduce the dose to Level -2, and then discontinue docetaxel. If the subject still fails to meet the requirements, the subject is withdrawn from the study.

6.3.3.2 Thrombocytopenia

In the presence of grade 3 to 4 thrombocytopenia (PLT <50/μL), reduce the dose to Level -2 and then followed by discontinuation of oxaliplatin. If the subject still fails to meet the requirements, the subject is withdrawn from the study.

6.3.3.3 Renal impairment

Cockcroft & Gault formula (eGFR (ml/min) = (140-age) x (weight in kg) x (0.85 if female) / (72 x serum Cr in ug/dL) is utilized to calculate creatinine clearance. If eGFR=40 to 60 ml/min, reduce the dose to Level -1. If eGFR<40 ml/min, reduce the dose to Level -2 and then followed by discontinuation of oxaliplatin. If the subject still fails to meet the requirements, the subject is withdrawn from the study.

6.3.3.4 Hepatic impairment

If the serum bilirubin is 2 to 3 times of the upper normal limits, reduce the dose to Level -1. If the serum bilirubin is 3 times more than the upper normal limits, reduce the dose to Level -2. If the serum hepatic aminotransferases are 5 to 20 times of the upper normal limits, reduce the dose to Level -1. If the serum hepatic aminotransferases are more than 20 times of the upper normal limits, reduce the dose to Level -2. If the subject still fails to meet the requirements, the subject is withdrawn from the study. However, adequate management for obstructive cholestasis and evaluation of acute hepatitis are required.

6.3.3.5 Diarrhea

In the presence of grade 3 to 4 diarrhea, S-1 is reduced to Level -2 (20 mg/m^2 BID) but

other chemotherapeutics are rather maintained. A further discontinuation of S-1 is suggested in the absence of recovery. If the subject still fails to meet the requirements, the subject is withdrawn from the study.

6.3.3.6 Neurologic toxicity

In the presence of grade 3 to 4 PSN, a dose reduction to Level -2 is required, and followed by discontinuation of oxaliplatin. If the subject still fails to meet the requirements, the subject is withdrawn from the study.

6.3.3.7 Mucositis

In the presence of grade 2 mucositis, S-1 is reduced to Level -2 (20 mg/m^2 BID) but other chemotherapeutics are rather maintained. A further discontinuation of S-1 is suggested in the absence of recovery. If the subject still fails to meet the requirements, the subject is withdrawn from the study.

6.3.3.8 Dermatitis

In the presence of grade 3 to 4 dermatitis, such as SJS/TEN, the treatment is discontinued regardless of the dose levels and subject withdrawn from the study.

6.3.3.9 Allergic reactions

In the presence of grade 3 to 4 allergic events, such as anaphylaxis, angioedema or bronchospasm, the inciting agent is permanently discontinued regardless of the dose levels. If the research team fails to identify the specific inciting agent, or in combinatorial reactions for the severe allergic events, the subject is withdrawn from the study.

6.4 Off-study criteria

Subjects who meet any one of the following conditions will be withdrawn from the study,

- Imaging or tissue evidence of disease progression or recurrence
- Delayed recovery of treatment-related toxicities, which prohibits the protocol treatment for 28 days since the inciting treatment.
- Unacceptable or unanticipated toxicity
- Subject's death
- Subject's refusal
- Investigator's discretion to stop the protocol treatment
- Available and potentially better alternative treatments at the discretion of the investigator

7. STUDY SCHEDULE

7.1 Pre- and Post-treatment Investigations

The following tests are performed within one week before the initiation of therapy (as the baseline data) and then repeated as scheduled and described below

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7.1.1 The first and screening computed tomographic (CT) or magnetic resonance imaging (MRI) scans must be done within 2 weeks prior to the initiation of therapy and then followed by every 8 weeks (including one exam after pre-operative chemotherapy prior to operation and one exam before post-operative chemotherapy after surgery) for 4 times, and then followed by every 12 weeks for 6 times.

7.1.2 Esophagogastroduodenoscopy (EGDscopy) will be conducted within 2 weeks prior to the initiation and 4 weeks after the completion of the protocol therapies. EGDscopy-directed local therapies for hemostasis, biopsy and removal of other non-tumoral lesions are permitted but not the local antineoplastic therapy for the tumor. However, an interim EGDscopy can be arranged when patients are suspicious of local recurrence or progression.

7.1.3 Physical examinations (including body weight), comprehensive medical history, performance status by Eastern Cooperative Oncology Group (ECOG) and peripheral hemogram will be examined every 2 weeks before each infusion within 72 hrs.

7.1.4 Serum creatinine level will be examined and calculated for eGFR (eGFR (ml/min) = (140-age) x (weight in kg) x (0.85 if female) / (72 x serum Cr in ug/dL)) every 2 weeks before each infusion within 72 hrs.

7.1.5 Liver functional tests (albumin, bilirubin direct/indirect, AST/ALT, and alkaline phosphatase) and routine electrolytes (Na, K and Ca) will be examined every 2 weeks before each infusion within 72 hrs.

7.1.6 CEA and CA19-9 will be evaluated by enzyme-linked immunosorbent assay (ELISA) at baseline and every 8 weeks of the protocol for 4 times (including one exam after pre-operative chemotherapy prior to operation and one exam before post-operative chemotherapy after surgery), and then followed by every 12 weeks for 6 times.

7.1.7 Chest roentgenogram will be examined at baseline and at every 2 weeks of the

protocol. Chest CT will only be done when patients are suspicious of lung metastasis.

7.1.8 Positron emission tomography (PET) and Tc-99m bone scintigraphy will only be arranged when patients are suspicious of distant metastasis.

7.1.9 Serum samples (8 mL) will be collected at study entry and then followed by every 8 weeks (including one exam after pre-operative chemotherapy prior to operation and one exam before post-operative chemotherapy after surgery) for 4 times, and then followed by every 12 weeks for 6 times.

7.1.10 20 paired pre and post-treatment tumoral and peri-tumoral microscopic slides (4-10 μm) are obtained and prepared for immunohistochemical staining, tissue microarray and whole/targeted-exome sequencing following next-generation sequencing procedures and practice guidelines.

7.2 Time table for examinations

	Baseline	Q2W	Q4W	Q8W	Additional
PE (including BW)	X	X			
Performance status, ECOG	X	X			
Hemogram	X	X			
LFT and Lytes	X	X			
Serum creatinine (eGFR)	X	X			
CEA, CA19-9	X			X	X[a, b]
PT/aPTT/INR	X	X			
Chest roentgenogram	X	X			
CT or MRI of abdomen	X			X	X[a, b]
PET or bone scintigraphy					X[c]
Serum samples	X			X	X[a, b]
Tumoral/peritumoral tissue	X				X[d]

a. one exam after pre-operative chemotherapy prior to operation and one exam before post-operative chemotherapy after surgery. If the time interval between the additional exam to the scheduled one is less than 4 weeks, the investigator may omit one of the exams.

b. the scheduled exams for 4 times, and then followed by every 12 weeks for 6 times

c. only when in suspicion of distal metastasis.

d. pre and post-treatment paired samples without a defined time interval.

7.3 Serum and tumor sample collections

7.3.1 Serum samples

In each sampling, 15.0 ml of peripheral blood will be drawn for plasma collection, which is stored in 3 separate vials after centrifugation. Buffy coat-rich plasma will also be collected for the storage of peripheral blood mononuclear cells (PBMCs). All samples will be collected by research nurses of the participating institutes at -20 degree Celsius and sent to NCKUH Biobank, Tainan in dry ice batches for further investigations, such as cell-free tumor DNAs, circulating tumor cells, inflammatory cytokines and other serum biomarkers.

7.3.2 Tumor and peritumor samples

Tumor/peritumor slides will be prepared for Hematoxylin & Eosin and IHC staining. Tumor infiltrating immune cells will be evaluated and quantified via IHC stains. Tumor DNA will be extracted from the formalin-fixed paraffin-embedded tissue (FFPE) samples (archival or fresh) and sent for whole/targeted-exome sequencing with a list of cancer- or immune-related genes. Tumor mutation burdens will be quantified via tumor-specific mutation loads deducted by germline ones as defined by the PBMCs from an identical subject.

8. EVALUATION OF THERAPEUTIC EFFICACY

8.1 Tumor response evaluation

8.1.1 Specification by methods of measurements:

The identical assessment methods should be implemented to each lesion at baseline, during the protocol treatment and in the follow-up periods. Image-based evaluation tools are preferred than clinical ones for the accurate measurement of treatment effect. In addition, pathological response of the complete resected tumor will be evaluated.

8.1.2 Tumor response criteria

Tumor response will be evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines version 1.1.[33] Pathological response will be assessed by Chevallier system with tumor regression grading (TRG) according to the guidance described by Mandard et al..[34,35]

8.1.3 Definition of measurable disease

At baseline, tumor lesions will be categorized as measurable and non-measurable.

Measurable: Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as U ≥20 mm with conventional techniques or as ≥10 mm with

CT, MRI or PET images.

Non-measurable: All other lesions excluding measurable ones (longest diameter <20 mm with conventional techniques or <10 mm with CT, MRI or PET images).

8.1.4 "Target" and "Non-target" lesions.
Target lesions: All measurable lesions up to a maximum of 2 per organ or up to 5 in total that represent all the involved organs at baseline. Target lesions should be based on their sizes (in the longest diameter) and the reproducibility for repeated measurements. A sum of the longest diameter for all target lesions will be calculated as the baseline sum and be utilized as a reference for the calculation of objective response.

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 of these lesions are not mandatory, but the presence or absence of each should be recorded in the follow-up periods alone with their responses.

8.1.5 Image response Criteria
8.1.5.1 Evaluation of target lesions.
Complete response (CR): The disappearance of all target lesions.

Partial response (PR): At least a 30% decrease in the sum of the longest diameter of target lesions.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor increase to qualify for PD.

Progressive disease (PD): At least a 20% increase in the sum of the longest diameter of target lesions plus an increased diameter of any of the target lesions at least 0.5 cm, the development of at least one new measurable lesion, the reappearance of lesions that were previously disappeared, or frank deteriorations of any assessable disease.

8.1.5.2 Evaluation of non-target lesion
Complete response (CR): The resolution of all non-target lesions.
Incomplete response/stable disease (iCR/SD): The persistence of at least one non-target lesion.
Progressive disease (PD): The development of at least one new lesion and progression of pre-existing non-target lesions.

8.1.5.3 Evaluation of best overall response

The assignment of the best overall response is defined by both the measurement and confirmation criteria. An overall response will be recorded when the assessment is performed every 8 weeks for 4 times and consists of all combinations of tumor responses in target and non-target lesions. When a status of PR or CR is assigned, it requires the tumor response to last at least 4 weeks and be confirmed by the subsequent assessment by any time intervals. In cases of SD, the clinical status must fulfill the SD criteria at a minimal interval of 4 weeks.

Overall response criteria

Target lesion	Non-target lesion	New lesion	**Overall response**
CR	CR	No	**CR**
CR	iCR/SD	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**

8.1.6 Pathological response criteria

Pathological complete response (pCR): defined as the complete resolution of all the tumor and negative lymph nodes, as classified by tumor regression grade 1 (TRG 1).

Pathological partial response (pPR): defined as presence of any residual tumor cells with partial tumor regression, as classified by TRG 2 to 4.

Pathological no response (pNR): defined as absence of any regressions or changes of the tumor, as classified by TRG 5.

9. STATISTICAL CONSIDERATION

In the proposed study, a Simon two-stage design is utilized for calculation of the optimal sample size. We assume a statistical power of 90% (β=0.1) and the probability of type I error by two-tailed α at 0.1. According to the published studies, the response rate of preoperative chemotherapies for locally advanced gastric cancer were 30% to 40%. We estimate a good treatment response rate (P1) of 60% and a poor rate (P0) of 35%. In the optimum model, 14 subjects will be enrolled in the stage 1. A maximum of 5 subjects is required to reject the futility of the trial in stage 1. In the stage 2, an additional 25 subjects (39 in total) will be enrolled with a maximum of 18 in total to reject the futility

of the trial. The minimal estimated sample size is 23 if the treatment response is poor (P0). In summary, a total of 56 subjects will be enrolled under the assumption of a 30% of drop-out and operation ineligibility rate per protocol, respectively. The treatment completion rate of the published trials is presented below, along with the estimated subjects in the proposed trial.

Treatment completion in the literature and estimated subjects in the proposed trial

	Enrolled patients, n	Preoperative CT completion, n (%)	Operation completion, n (%)	Postoperative CT completion, n (%)
MAGIC: ECF arm[3]	250	215 (86)	209 (84)	104 (42)
FNCLCC-FFCD: CF arm[5]	113	105 (93)	101 (89)	54 (48)
AIO-FLOT4[6]				
FLOT arm	356	352 (99)	345 (97)	213 (60)
ECX/EFX arm	360	353 (98)	341 (95)	187 (52)
Pooled completion rate	-	(95)	(88)	(50)
Proposed trial: LOTS arm	56	53	49	28

10. REPORTING OF SEVERE ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARD (IRB) OF ETHICS

10.1 Reporting events to IRB

All investigators must receive adequate professional training according to the Good Clinical Practice (GCP) guideline, be approved by the IRB, abide to the related obligations and be accredited for clinical trial investigations. Serious adverse events/Suspected unexpected serious adverse reactions/Unanticipated problems (SAE/SUSAR/UP) must be reported in written form to the PI immediately. The PI will then report to IRB within 72 hours. The events are defined as any of those described in sections 10.1.1 to 10.1.6 below. However, serious events occurring after the subject is withdrawn from the study do to warrant mandatory reporting under the investigator's discretion. Events which are anticipated morbidities associated with malignancy and chemotherapy are waived from the reporting.

10.1.1 Causes death

Study-specific clinical outcomes of death because of disease progression are excluded from the reporting unless the investigator deems the death related to the study treatment.

10.1.2 Are life-threatening.

10.1.3 Causes severe or permanent disability.

10.1.4 Causes prolonged inpatient hospitalization.
Hospitalization for study drug administration or hospitalization due to anticipated morbidity related to chemotherapy and malignancy is waived from the reporting. Therefore, hospitalization due to therapy-related myelosuppression, fever, nausea, vomiting, weight loss, fatigue, electrolyte disturbance, pain management, anxiety, or palliative care is waived from the reporting. However, investigator is authorized to report events in which the severity inconsistent with anticipated risks.

10.1.5 Causes congenital anomaly.

10.1.6 Is significant for any other reasons.

11. OTHERS

11.1 All patients must have a signed Informed Consent form and an on-study (confirmation of eligibility) form filled out and signed by a responsible investigator before entry.

11.2 The responsible study investigators and research nurses must approach each patient prior to study drug administration. All required pre-treatment and interim information should be available and the investigators must decide if a re-evaluation is needed and the grade of treatment-related toxicity if presents.

11.3 Data must be recorded before a course of therapy can be given. A brief explanation for required but missing data should be recorded as a comment.

11.4 Data from patients enrolled at the Cooperative Ward of the Cancer Clinical Research Center (CCRC) of National Health Research Institutes (NHRI) will be entered into the Clinical Data Management System of CCRC.

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