Protocol

A Phase II Study of S-1, Irinotecan, and Oxaliplatin in Locally-Advanced Pancreatic Cancer (SIROX Study)

- followed by curative surgery and adjuvant chemotherapy

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Protocol summary

Study title: A Phase II Study of S-1, Irinotecan, and Oxaliplatin in Locally-Advanced Pancreatic Cancer (SIROX Study) - followed by curative surgery and adjuvant chemotherapy

Study phase: II

Study objectives:

1. To explore the efficacy and safety of a neoadjuvant chemotherapy regimen with potential feasibility and low toxicity in locally-advanced pancreatic cancer
2. To explore the chemotherapy-associated immune response for further development of immunotherapy in pancreatic cancer

Study endpoints:

Primary endpoint

- resection rate (RsR): (patients with R0 or R1 resection of the primary tumor after study chemotherapy)/patients receiving at least one dose of study chemotherapy

Secondary endpoint

- the efficacy of this therapy in terms of PFS, RR, DCR
- the improvement in CBR (clinical benefit response)
- the OS
- the responses in immune-related biomarkers, including T cell, MDSC, B cell and macrophage and related cytokines (blood and tumor tissue)
- the rates of surgery-related complications

Study population: newly diagnosed, unresectable, locally-advanced, pancreatic adenocarcinoma

Number of patients: 35

Overview of study design: Based on the Simon's two-stage optimum design, the first stage will need at least 2 out of 18 patients to proceed to the second stage. The maximal number of this study after enrollment of both stages will be 35 patients. Total study duration is planned to be 48 months.

We assume α=0.05, β=0.1, P0=0.1, P1=0.3 with a Simon's two-stage design.

Design	Optimum
First stage sample size (n1)	18
Upper Limit For 1st Stage Rejection of Drug (r1)	2
Maximum Sample Size (n)	35
Upper Limit for 2nd Stage Rejection of Drug (r2)	6
Expected Sample Size If Response Probability = P0 (EN0)	22.53
Probability of Early Termination at P0	0.73

n is the total number of subjects

n_1 is the number of subjects accrued during stage 1

r_1, if r_1 or fewer responses are observed during stage 1, the trial is stopped early for futility

r_2, if r_2 or fewer responses are observed by the end of stage two, then no further investigation of the drug is warranted

EN_0 is the expected sample size for the trial when response rate is p_0

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1. Background

1.1 Current chemotherapy in pancreatic cancer

For advanced/recurrent pancreatic cancer, single-agent gemcitabine is the current standard since 1997. The MPACT Study, comparing gemcitabine/nab-paclitaxel to gemcitabine alone, demonstrated significant benefits in median OS (8.5 versus 6.7 months) and RR (23% versus 7%) [1].

As for triplet combination, the randomized phase III ACCORD 11 trial, enrolling patients with advanced pancreatic cancer and comparing FOLFIRINOX (oxaliplatin, irinotecan and 5-FU) to gemcitabine alone for first line therapy was demonstrated to have a high RR of 31.6% and median OS of 11.1 months [2]. To replace 5-FU with S-1 in the GOFL regimen [3], the SLOG regimen in the phase I study was demonstrated RR of 37.5% with median PFS of 4.6 months and MTD of S-1 was determined as 35 mg/m^2 [4]. In general, the RR can be improved from 20% for doublet regimens to ≥ 30% for triplet regimens. However, the toxicities increase significantly without significant improvement in OS. Moreover, these studies only recruited patients with metastatic diseases, and may not reflect the efficacy and outcome in locally-advanced patients [1, 2, 4]. Recently, a meta-analysis focusing on the locally-advanced patients treated with first-line FOLFIRINOX regimen reported promising outcomes. The median OS was 24.2 months and the pooled resection rate was 28%. However, 73% of patients received G-CSF for primary prophylaxis or rescue of neutropenia [5]. By contrast, a meta-analysis demonstrated that the resection rate was 33% in borderline resectable or unresectable patients after combination chemotherapy [6]. Therefore, FOLFIRINOX is a promising regimen in locally-advanced pancreatic cancer with significant hematological toxicities.

Currently, the standard therapy for locally-advanced pancreatic cancer is still chemotherapy. The role of radiotherapy adding to chemotherapy is still controversial [7-9].

Therefore, to develop a regimen with high disease control rate (DCR) and low toxicities is required. However, it is difficult to balance responses and toxicities with chemotherapeutic agents because of overlapping toxicities. Therefore, modification of the FOLFIRINOX regimen with prolongation of drugging intervals of each chemotherapy agent may be a reasonable strategy.

1.2 S-1 + Irinotecan trials

Irinotecan and S-1 are widely used in the treatment for pancreatic cancer, colorectal cancer, and gastric cancer. In pancreatic cancer, a phase I/II study had been performed with irinotecan on D1 and D15 and S-1 on D1-14. Six of the 16 patients had been exposed to gemcitabine. The RR was 43.7% with TTP of 4.9 months and median OS of 11.3 months. Grade 3-4 neutropenia developed in 5 of 16 patients and grade 3 diarrhea in 1 patient [10]. In a phase II/III trial in second-line therapy for metastatic colorectal cancer, irinotecan was given as 125 mg/m^2 on D1 and D15 and S-1 40-60 mg twice daily on D1-14. The most common ≥ grade 3 toxicities were neutropenia (36.2%), leucopenia (18.1%) and diarrhea (20.5%) [11]. In the phase I/II trial using 3 weeks as the

cycle length, S-1 was used with fixed dose of 80 mg/m^2/day on D1-D14 and irinotecan used at 80-120 mg/m^2 on D1 and D8. The phase II recommended dose of irinotecan was 80 mg/m^2. Grade 3 or more neutropenia, leucopenia, and diarrhea occurred in 30%, 10%, and 2.5% of patients, respectively [12].

1.3 S-1 + Oxaliplatin trials

In gemcitabine-refractory pancreatic cancer, the regimen of S-1 (80-120 mg/day, D1-14) plus oxaliplatin (100 mg/m^2, q3w) demonstrated a RR of 20.9% and a median OS of 7.4 months with moderate hematological toxicities [13]. In chemotherapy-naive gastric cancer, the combination of oxaliplatin and S-1 in a 3-week cycle demonstrated comparable toxicity profiles [14]. In metastatic colorectal cancer, the combination of oxaliplatin (130 mg/m^2, D1) and S-1 (40 mg/m^2, bid, D1-14) in a 3-week cycle also demonstrated comparable toxicities [15].

1.4 S-1 + Irinotecan + Oxaliplatin trials

S-1 is an oral prodrug of 5-FU with reliable PK profiles. Therefore, to replace 5-FU of the FOLFIRINOX regimen with S-1 is reasonable. Similarly, the triplet combination had been tested in gastric, colorectal, and pancreatic cancers. In the phase I trial in pancreatic cancer, the DLTs were fatigue and neutropenia. The recommended phase II dose was S-1 (80 mg/m^2, qod), oxaliplatin (85 mg/m^2), and irinotecan 150 mg/m^2) in a 14-days cycle. The RR was 47% and median OS was 13.4 months. However, grade 3/4 leucopenia, neutropenia, fatigue, and anorexia were noted in at least 20% of patients [16]. The recommended dose (RD) in phase II trials was S-1 (80 mg/m^2, per day), oxaliplatin (85 mg/m^2), and irinotecan 150 mg/m^2) in a 14-days cycle in the other three studies [17-19]. The most common grade 3-4 toxicity was neutropenia and occurred in about half of patients [17-19].

1.5 Exploration of immune reaction after chemotherapy

1.5.1 Myeloid-derived suppressor cells (MDSC)

MDSCs are a heterogeneous group of immature myeloid cells and tend to be immunosuppressive. Two distinct subsets of MDSC are identified in mouse models. One is granulocytic MDSC (Gr-MDSC), and the other is monocytic MDSC (Mo-MDSC). In pancreatic cancer, the KRAS-mediated signaling can induce the recruitment of MDSC to the tumor tissues and suppress CD8+ T cell immunity [20, 21]. However, previous data reported that Gr-MDSC but not Mo-MDSC is reduced after gemcitabine [22]. Furthermore, gemcitabine was shown to induce granulocyte macrophage colony-stimulating factor (GM-CSF) – the main cytokine for MDSC recruitment, production from cancer cells and recruitment of Mo-MDSC [23]. However, the effects of 5-FU, oxaliplatin, and irinotecan on MDSC in pancreatic cancer are not reported.

1.5.2 T helper 17 (Th17) cells and associated cytokines

The percentage of Th17 cells detected by flow cytometry analysis and IHC was significantly higher in 46 pancreatic tumor tissues compared with corresponding adjacent normal tissues. The serum levels of Th17 cell-associated cytokines, IL-17 and IL-23, in 20 pancreatic patients detected by ELISA were significantly higher than 15 healthy volunteers [24]. IL-21 is produced by a variety of activated CD4+ T cells including Th17 cells. IL-21 exerts potent antitumor effects due to its ability to induce and expand cytotoxic CD8+ T cells, NK cells and NKT cells, as well as to its capacity to suppress FOXP3 expression and the expansion of regulatory T cells. IL-17, the prototypical cytokine of Th17 cells, was demonstrated to promote pancreas inflammation, formation of pancreatic intraepithelial neoplasm (PanIN) and pancreatic cancer through REG3β–JAK2–STAT3 pathway [25]. IL-21 and IL-23 are associated with Th17 differentiation and maintenance. AsPC-1 pancreatic cancer cells trans-duced with IL-21 and IL-23 were shown to have slower growth in (T-cell defective) SCID mice comparing to wild type cells, and the effects were partially through NK cells [26].

According to our previous unpublished data, IL-17 and IL-21 were elevated in chemotherapy responders. Therefore, the activation of Th17 cells and Th17-related cytokines may be important in the eradication of pancreatic cancer cells.

1.5.3 B cell and B cell-activating factor (BAFF)

The role of tumor-associated B cells is not clear in pancreatic cancer at present. In a retrospective study, CD20+ tertiary lymphoid tissues were associated with better prognosis, while CD20+ tumor-infiltrating B cells were associated with worse prognosis [27]. In mouse pancreatic cancer models, cancer growth was retarded in B cell-deficient mice. Inhibition of Bruton tyrosine kinase (BTK), a key B-cell receptor kinase, with ibrutinib could block macrophage Th2 skewing induced by tumor-associated B cells [28]. BAFF, a proinflammatory cytokine of TNF superfamily, is associated with B cell survival and maturation. Bing of BAFF to its receptors can induce NF-kB pathway. Serum BAFF was significantly higher in pancreatic cancer patients and was associated with tumor size and distant metastasis [29]. In addition, BAFF+ and BAFF-receptor+ B cells infiltrated in pancreatic cancer tumor beds [29]. Pancreatic cancer cell lines also expressed BAFF receptor, and BAFF could induce epithelial-mesenchymal transition in pancreatic cancer cells [29]. The chemotherapy effects on BAFF and B cells remain to be elucidated.

1.5.4 Toll-like receptor (TLR) and immunogenic cell death (ICD)

TLRs are enzymatically-inactive single membrane-spanning proteins, best known for their ability to detect so-called“microbe-associated molecular patterns” (MAMPs). Several TLRs have recently been shown to sense not only exogenous MAMPs but also endogenous “damage-associated molecular patterns” (DAMPs), i.e., molecules released or exposed by stressed, dying or dead cells to convey a danger signal. Oxaliplatin was shown to induce ICD through TLR in various cell lines through the production of HMGB1 by dying cells [30]. The roles of irinotecan and 5-FU in TLR-mediated ICD are not reported.

1.5.5 Immune checkpoints

Currently, cancer therapy with immune checkpoint inhibitors is under active development and becomes standard therapy in a certain cancer types. Programmed death 1/programmed death ligand-1 (PD1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)/CD80/CD86 pathways were upregulated in pancreatic cancer [31]. These pathways are implicated in tumor-associated with immune tolerance, and may be associated with poor survival [31]. Therapeutic targeting to these pathways could improve the survival of chemotherapy alone in mouse models [32]. However, the efficacy of these agent alone or with gemcitabine is limited. The poor clinical activity may be attributed to the strong immunosuppression in the tumor microenvironment associated with MDSC, regulatory T cells, B cells, or the low mutation loads and neoantigen formation of pancreatic cancer [33, 34]. To create more tumor heterogeneity, neoantigen formation, and induce strong anti-tumor immunity, neoadjuvant chemotherapy with multiple agents and even with RT is a reasonable method.

1.5.6 Th1/Th17 and regulatory T cell (Treg)

Recently, accumulating data revealed that intestinal commensal bacteria affect the chemotherapy response. After antibiotic treatment and induced dysbiosis, the response to chemotherapy was reduced. The phenomenon was associated with reduced induction of IFN-γ-producing Th1/Th17 cells, so called pathogenic Th17 cells [35].

However, the phenotype of Th17 cells is dynamic. The origin of Th17 cells can derive from FoxP3+Treg cells. Under the stimulation of IL-1, IL-2, IL-21, and IL-23, Treg cells can differentiate into Th17 cells [36]. Importantly, the transdifferentiation may be through epigenetic regulation [37, 38].

According to our previous unpublished data, IL-17, IL-21, and IFN-γ were elevated in chemotherapy responders. Therefore, the activation of Th1/Th17 cells and Th17-related cytokines may be important in the eradication of pancreatic cancer cells. In addition, the intestinal bacterial species of the patients may be implicated in the response of chemotherapy. The intrinsic nature of immune regulation in the transdifferentiation of Th1/Th17 and Treg cells may be associated with epigenetics of individual patients.

2. Rationale of this study

In terms of clinical activity, the triplet regimen of S-1, irinotecan, and oxaliplatin is a highly active regimen and a reasonable alternative of FOLFIRINOX in advanced pancreatic cancer. However, significant toxicities were still observed and comparable to the FOLFIRINOX regimen. In locally-advanced pancreatic cancer, to increase resectability as much as possible with a triplet regimen is the only chance to prolong survival. However, to reduce toxicity, we will propose this study design.

3.Study objectives

1. To explore the efficacy and safety of a neoadjuvant chemotherapy regimen with potential feasibility and low toxicity in locally-advanced pancreatic cancer
2. To explore the chemotherapy-associated immune response for further development of immunotherapy in pancreatic cancer

4.Study design

4.1 Endpoints:

Primary endpoint:

- resection rate (RsR): (patients with R0 or R1 resection of the primary tumor after study chemotherapy/patients receiving at least one dose of study chemotherapy

Secondary endpoint:

- the efficacy of this therapy in terms of PFS, RR, DCR
- the improvement in CBR (clinical benefit response)
- the OS
- the responses in immune-related biomarkers, including T cell, MDSC, B cell and macrophage and related cytokines (blood and tumor tissue)
- the rates of surgery-related complications

4.2 Design:

Drug	Schedule (3 wk/cycle)
Oxaliplatin (provided by TTY Biopharm)	85 mg/m^2, D1
Irinotecan (provided by TTY Biopharm)	150 mg/m^2, D8
S-1 (covered by National Health Insurance)	40 mg (20 mg/cap) bid, D1-14

Dose reduction schedule (for toxicity)

Oxaliplatin	85 mg/m^2
Level -1	75 mg/m^2
Level -2	65 mg/m^2
Irinotecan	150 mg/m^2
Level -1	135 mg/m^2
Level -2	115 mg/m^2
S-1	80 mg per day (2#/2#)
Level -1	60 mg per day (2#/1#)
Level -2	40 mg per day (1#/1#)

We assume α=0.05, β=0.1, P0=0.1, P1=0.3 with a Simon's two-stage design.

Design	Optimum

First stage sample size (n1)	18
Upper Limit For 1st Stage Rejection of Drug (r1)	2
Maximum Sample Size (n)	35
Upper Limit for 2nd Stage Rejection of Drug (r2)	6
Expected Sample Size If Response Probability = P0 (EN0)	22.53
Probability of Early Termination at P0	0.73

n is the total number of subjects

n_1 is the number of subjects accrued during stage 1

r_1, if r_1 or fewer responses are observed during stage 1, the trial is stopped early for futility

r_2, if r_2 or fewer responses are observed by the end of stage two, then no further investigation of the drug is warranted

EN_0 is the expected sample size for the trial when response rate is p_0

4.3 Inclusion criteria

a. histologically or cytologically proven pancreatic adenocarcinoma

b. newly diagnosed, unresectable, locally-advanced pancreatic cancer; the definition of unresectability will follow the criteria of NCCN guidelines (version 2.2016, PANC-B).

c. no potential of R0 resection at diagnosis

d. presence of measurable pancreatic lesion, which must meet the criteria of being ≥ 10 mm in at least one dimension by conventional CT/MRI

e. age between 20 and 79 years at registration

f. ECOG performance status (PS) of 0 or 1

g. adequate major organ functions, as defined below:

i. WBC ≥ 3,500/mm^3

ii. ANC ≥ 2,000/mm^3

iii. hemoglobin ≥ 9.0 g/dL

iv. platelet ≥ 100,000/mm^3

v. serum total bilirubin ≤ 2.0 mg/dL.

vi. ALT and AST ≤ 2.5 times the ULN

vii. albumin ≥ 3.0 g/dL

viii. serum creatinine ≤ 1.2 mg/dL, and creatinine clearance ≥ 50 ml/min (based upon 24 hours urine collection or calculated by Cockroft-Gault formula)

h. ability to take the oral study medication (S-1)

i. no clinically significant abnormal ECG findings within 28 days (4 weeks) prior to registration

j. voluntarily signed the written informed consent form

4.4 Exclusion criteria

a. pulmonary fibrosis or interstitial pneumonitis diagnosed within 28 days prior to registration

b. presence of diarrhea ≥ CTCAE v.4.03 grade 2

c. concomitant active infection

d. significant co-morbid medical conditions, including, but not limited to , heart failure, renal

failure, hepatic failure, hemorrhagic peptic ulcer, mechanical or paralytic ileus, or poorly controlled diabetes

e. moderate or severe ascites or pleural effusion that requires drainage

f. prior or concurrent malignancies within the last 3 years, with the exception of carcinoma in situ of the cervix, or basal type skin cancer

g. concomitant treatment with flucytosine, phenytoin or warfarin

h. peripheral neuropathy grade of 2 or higher

i. known Gilbert syndrome or homozygosity for UGT1A1 promoter TA repeats prone to high risk of drug toxicity (screening of UGT1A1 genotype will NOT performed routinely before study)

j. pregnant women or nursing mothers, or positive pregnancy test for women of childbearing potential. Patients of childbearing age should have effective contraception for both the patient and his or her partners during the study period

k. severe mental disorder

l. judged ineligible by physician for participation in the study due to safety concern

4.5 Statistical analysis

a. Sample size consideration:

Based on the Simon's two-stage optimum design, the first stage will need at least 2 out of 18 patients to proceed to the second stage. The maximal number of this study after enrolling both stages will be 35 patients.

b. Endpoint:

- RsR (%): (patients with R0 or R1 resection of the primary tumor after study chemotherapy)/patients receiving at least one dose of study chemotherapy
- Safety variables include toxicity grading, AEs and laboratory values: It is characterized by CTCAR v4.03 scale and SAEs. Incidence of adverse drug reactions/adverse events and their 95% confidence intervals (two-sided) will be calculated. Laboratory results will be summarized by descriptive statistics.
- PFS: The Kaplan-Meier method will be used to estimate cumulative PFS rate, median PFS, and annual PFS rate. The 95% confidence interval (two sided) for median PFS and cumulative PFS rate will be calculated.
- OS: The cumulative survival rate, median survival time, and annual survival rate will be presented by Kaplan-Meyer analysis. The 95% confidence interval (two-sided) for median PFS and cumulative PFS rate will be calculated.
- RR/DCR: The RR/DCR and their 95% confidence intervals (two-sided) will be estimated.

4.6 Adjuvant chemotherapy (according to the pancreatic cancer guidelines of NTUH, Appendix)

- Adjuvant chemotherapy with standard S-1 or gemcitabine alone for 24 weeks will be given if the post-operation condition is feasible for further chemotherapy. (estimated: 10 patients) [39]
- Adjuvant CCRT will be optional for patients with R1 resection. The timing of adjuvant CCRT

will be determined by investigators.

4.7 Surgery [40]

- Base on the pancreatic cancer guidelines of NTUH, the definition of "resectable" is:

Superior mesentery artery (SMA)	No extension, normal fat plane, between the tumor and the artery
Celiac axis/hepatic artery	No extension
Superior mesentery vein (SMV)/portal vein (PV)	Patent

- The evaluation of "resectability" after neoadjuvant SIROX will be performed and determined by the PI and CO-PI (radiologist).
- If the subject is resectable after neoadjuvant SIROX, standard pancreatoduodenectomy, distal pancreatectomy or total pancreatectomy will be performed according to the tumor location.
- If the subject does not meet the criteria of "resectable", extended pancreatoduodenectomy, distal pancreatectomy or total pancreatectomy will be performed according to the tumor location if the tumor does not progress.
- Based on the consensus of International Study Group for Pancreatic Surgery (ISGPS), the following surgical procedures will be performed after neoadjuvant SIROX.
  - Standard pancreatoduodenectomy:
    - head of the pancreas and uncinate process;
    - duodenum and first segment of jejunum;
    - common bile duct and gallbladder;
    - lymphadenectomy;
    - sometimes pylorus and/or antrum of stomach; and
    - sometimes elements of the transverse mesocolon exclusive of relevant vasculature (eg, limited soft tissue contiguous to the tumor but not including the colon itself).
  - Standard distal pancreatectomy:
    - body and/or tail of the pancreas;
    - spleen, including splenic vessels;
    - lymphadenectomy;
    - sometimes fascia of Gerota; and
    - sometimes elements of the transverse mesocolon exclusive of relevant vasculature (eg, limited soft tissue contiguous to the tumor, but not including the colon itself).
  - Standard total pancreatectomy:
    - head, neck, body, and tail of the pancreas;
    - duodenum and first segment of jejunum;
    - common bile duct and gallbladder;
    - spleen including splenic vessels;
    - lymphadenectomy;
    - sometimes pylorus and/or antrum of stomach;

- sometimes fascia of Gerota; and
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (eg, limited soft tissue contiguous to the tumor but not including the colon itself).

- Extended pancreatoduodenectomy: Standard pancreatoduodenectomy as defined previously plus any of the following organs involved in continuity:
  - more than the antrum or distal half of the stomach;
  - colon and/or mesocolon with relevant vascular structures of the transverse mesocolon (ileocolic, right, or middle colic vessels);
  - small bowel beyond the first segment of jejunum;
  - portal, superior mesenteric, and/or inferior mesenteric vein;
  - hepatic artery, celiac trunk, and/or superior mesenteric artery;
  - inferior vena cava;
  - right adrenal gland;
  - right kidney and/or its vasculature;
  - liver; and
  - diaphragmatic crura
- Extended distal pancreatectomy: Standard distal pancreatectomy as defined previously plus any of the following organs involved in continuity:
  - any type of gastric resection;
  - colon and/or relevant vascular structures of the transverse mesocolon (middle or left colic vessels);
  - small bowel;
  - portal, superior mesenteric, and/or inferior mesenteric vein;
  - hepatic artery, celiac axis, and/or superior mesenteric artery;
  - inferior vena cava;
  - left adrenal gland;
  - left kidney and/or its vasculature;
  - diaphragmatic crura and/or diaphragm; and
  - liver
- Extended total pancreatectomy: Standard total pancreatectomy as defined previously plus any of the following organs involved in continuity:
  - more than the antrum or distal half of the stomach;
  - colon and/or relevant vascular structures of the transverse mesocolon (ileocolic, right, middle, or left colic vessels);
  - small bowel beyond the first segment of jejunum;
  - portal, superior mesenteric, and/or inferior mesenteric vein;
  - hepatic artery, celiac trunk and/or superior mesenteric artery;
  - inferior vena cava;
  - right and/or left adrenal gland;

- kidney and/or its vasculature;
- diaphragmatic crura and/or diaphragm; and
- liver.

4.8 Salvage therapy (according to the pancreatic cancer guidelines of NTUH, Appendix)

If PD or any distant metastasis is documented by imaging studies, the patient will be withdrawn from this study. Further survival follow-up will be performed until the patient' death or loss of follow-up.

4.9 Adjuvant CCRT

The administration of adjuvant CCRT in subjects with R1 resection will depend on Investigator's discretion. Subjects with R0 resection will not be given RT. The administration of CCRT will start after completion of all adjuvant chemotherapy with prerequisite documentation of no recurrence.

S-1 schedule: D1-16 (dose reduction schedule)

S-1	80 mg per day (2#/2#)
-1	60 mg per day (2#/1#)
-2	40 mg per day (1#/1#)

S-1 will be covered by National Health Insurance.

RT: 36 Gy/12 fractions (Monday to Friday, 12 fractions); The administration of S-1 and RT is concomitant. The dose adjustment will be based on toxicity grading.

4.9.1 Technical Factors

Equipment: > 6 MV photons will be used.

4.9.2 Localization, Simulation, and Immobilization

Simulation will be done with the patient in the supine "arms up" position using a CT-simulator.

4.9.3 Treatment Planning/Target Volumes

Intensity Modulated Radiotherapy (IMRT) treatment planning is required.

4.9.3.1 RT planning

a. The gross tumor volume (GTV) was defined as the primary tumor and any involved nodes by CT or MRI imagines.

b. Standard-risk clinical target volume CTV included the gross tumor volume plus the regional lymph nodes (i.e., peripancreatic, celiac, superior mesenteric, porta hepatic, retroperitoneal).

c. The CTV was expanded to an internal target volume using 4D-CT to account for respiratory motion

d. The planning target volume (PTV) expansion was 3~5 mm of the internal target volume for patients who underwent 4D-CT. For those without 4D-CT, the inferior and superior margins of the CTV were increased to 8 to 10mm in defining the PTV.

4.9.3.2 The normal tissue constraints (Critical Structures)

a. The normal tissue constraints for treatment planning varied during the study period; however, the current constraint guidelines were as follows:
b. Liver: mean liver dose <20 Gy, liver volume receiving30 Gy (V30) <30%
c. Kidney: , volume receiving 20 Gy (V20) for each kidney <30%
d. Stomach: stomach V20 <50%
e. Spinal cord: maximal spinal cord dose 45 Gy.
f. The small bowel contour was confined to the small bowel loops within 3 cm of the PTV and was limited to V40 <33%, V45 <10 cm3, and maximal dose <50Gy.

4.10 Schema

4.11 Pre-study screening

Before entering the study, subjects will be assessed to ensure that the eligibility criteria are met (please refer to Sections 4.3 and 4.4). Every subject must provide written informed consent to the investigators or co-investigators prior to any study-specific procedures.

The following criteria for establishing eligibility of each subject must be evaluated before registration and treatment allocation:
a. medical history review and physical examination
b. tumor pathological/cytological results
c. ECOG PS assessment
d. Laboratory studies
e. Radiological studies

Detailed investigations and observations are as follows:

All the laboratory examinations/procedures will be performed in the National Taiwan University Hospital according to the general practice of cancer care.

Within 14 days prior to registration, the subjects should undergo screening evaluations for eligibility, which include:

a. hematology: CBC/DC, PT, aPTT
b. blood biochemistry: BUN, creatinine, total bilirubin, direct bilirubin, AST, ALT, albumin, ALP, gamma-GT, CRP, Na, K, Cl, Ca, P, Mg, Glucose (AC), HbA1c, TG, total cholesterol, HDL, LDL
c. tumor marker: CEA (RIA), CA 19-9 (RIA)
d. HBsAg, anti-HBc, anti-HCV (not restricted to 14 days). In HBsAg+ patients, HBV DNA, HBeAg, and anti-HBe should be evaluated before chemotherapy (not restricted to 14 days), and HBV carriers will be referred to GI specialists for anti-HBV prophylaxis.
e. creatinine clearance (based on 24-hour urine collection or calculated by Cockroft-gault formula)
f. urine pregnancy test for female patients

g. height, body weight, ECOG PS, vital signs

h. other laboratory tests/observation will be conducted if necessary (depending on symptoms)

i. Baseline tumor assessment by image study (chest, abdominal, and pelvic CT or MRI) should be performed within 28 days prior to registration.
j. Baseline ECG and chest X-ray should be performed within 28 days prior to registration.

4.12 Investigations during investigation
4.12.1 Investigations during and after study period

The following examinations will be performed during the treatment period:

a. hematology: CBC/DC (①) (Table 1, 2)
b. blood biochemistry (BCS): (Table 1, 2)
- (②): BUN, creatinine, total bilirubin, direct bilirubin, AST, ALT, albumin, ALP, gamma-GT, CRP, Na, K, Cl, Ca, P, Mg, Glucose (AC), HbA1c, TG, total cholesterol, HDL, LDL
- (③): creatinine, total bilirubin, ALT, ALP
c. tumor marker: CEA (RIA), CA 19-9 (RIA) (④)(Table 1, 2)
d. body weight, ECOG PS, vital signs (⑤) (Table 1, 2)
e. ECG (when abnormality of cardiac function is suspected)
f. chest X-ray (examination of interstitial pneumonitis) (⑥)(Table 1)
g. presence/absence and content of the AEs other than abnormal test results, eg. diarrhea, rash, nausea, vomiting, fatigue, anorexia etc.
h. tumor assessment by image study including chest, abdominal, and pelvic CT or MRI (⑦); CT or MRI will be evaluated after 4 cycles of SIROX (between D15 and D35 of cycle 4 of SIROX), before adjuvant/during adjuvant/after adjuvant chemotherapy (every 12 weeks) (Table 1, 2)
i. other laboratory tests/observation will be conducted if necessary (depending on symptoms)
j. Endoscopic ultrasound (EUS)-guided pancreatic tumor core biopsy: (Table 1)
- (⑧): within 28 days before SIROX chemotherapy
- (⑨): (window ± 3 days)
  - for patients proceeding to surgery, biopsy will not be done
  - for patients proceeding to salvage therapy, biopsy will be performed before salvage therapy.

k. biomarkers:
- Blood (■): flow cytometry for lymphocytes, MDSC, monocytes; BAFF, IL-17, IL-21, glycosylation enzymes, ICOS, ICD markers
- Biopsy tissue:
  - genetic (PCR, DNA sequencing): KRAS, P53, P16, SMAD4, DNA repair pathways
  - Immune (IHC): CD4+ T cell, CD8+ T cell, B cell, MDSC, glycosylation enzymes, PD-1. PD-L1, IL-17/IL-17R, IL-21/IL-21R, ICOS/ICOS-R, ICD markers, BAFF/NF-kB
- Surgical tissue:
  - genetic(PCR, DNA sequencing): KRAS, P53, P16, SMAD4, DNA repair pathways

- Immune (including tumor part, regional lymph nodes, peripancreatic tissues, spleen): (IHC) CD4+ T cell, CD8+ T cell, B cell, MDSC, glycosylation enzymes, PD-1. PD-L1, IL-17/IL-17R, IL-21/IL-21R, ICOS/ICOS-R, ICD markers, BAFF/NF-kB

Table 1 Flow chart during SIROX chemotherapy (window ± 2 days)

Timing	Before C1D1	D0 (each cycle)	D7 (each cycle)
Hematology		①	①
BCS		②	③
Tumor marker		④	
BW, PS, vital		⑤	⑤
CXR		⑥	
CT/MRI		⑦	
EUS biopsy	⑧	⑨ (refer to 4.12.1; j)	
Biomarker		■	■

Table 2 Flow chart during adjuvant gemcitabine or S-1 chemotherapy

Gemcitabine (D1, 8, 15 of 4wk/cycle schedule)			
Timing	D0	D7	D14
Hematology	①	①	①
BCS	②	③	③
Tumor marker	④		
BW, PS, vital	⑤	⑤	⑤
CXR	⑥		
CT/MRI	⑦		
Biomarker	■		
S-1 (D1-14 of 3 wk/cycle schedule)			
Timing	D0	D7	D14
Hematology	①	①	
BCS	②	③	
Tumor marker	④		
BW, PS, vital	⑤	⑤	
CXR	⑥		
CT/MRI	⑦		
Biomarker	■		

To ensure comparability, the baseline imaging studies and subsequent imaging tests to assess clinical response should be performed using identical techniques. And every effort will be made to follow each confirmed lesion with the same type of radiological examination between baseline and follow-up. AE/toxicity assessment is based on CTCAE v 4.03, and will be evaluated at each treatment visit.

4.12.2 Investigations at termination/end of study treatment

The following examinations will be performed at termination of the study treatment:

a. hematology: CBC/DC

b. blood biochemistry: BUN, creatinine, total bilirubin, direct bilirubin, AST, ALT, albumin, ALP, gamma-GT, CRP, Na, K, Cl, Ca, P, Mg
c. tumor marker: CEA (RIA), CA 19-9 (RIA)
d. body weight, ECOG PS, vital signs

For safety follow-up, each subject will be followed for occurrence of new AE until 30 days after the last dose of study medication, or additional antitumor therapy has been introduced, whichever comes first. Existing AE will be followed until resolution/stabilization, unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying diseases.

Tumor assessment by image study should be continued according to institutional guidelines (pancreatic cancer guidelines of NTUH) until disease progression. Image study should be evaluated before the next evaluation time point (per 12 weeks) if disease progression is suspected according to any symptom or laboratory data.

4.13 Description of study drugs, dosing criteria, and dose reduction rules

4.13.1 Description of Oxaliplatin (Oxalip®)

Abbreviation	Ox
Chemical structure	(R,R)-1,2-diaminocyclohexane(ethanedioate-O,O)platinum
Formulation	50 mg/10 mL/vial (TTY Biopharm Company Limited)
Contents	Each ml contains oxaliplatin 5mg excipient: polyethylene glycol 400 Water for injection
Administration	administered as a 2 hours intravenous infusion in 250 ml of 5% glucose solution

4.13.2 Description of Irinotecan (Irino®)

Abbreviation	Ir
Chemical structure	(S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate
Formulation	Irino 40 mg/2ml brown glass vial Irino 100 mg/5ml brown glass vial (TTY Biopharm Company Limited)
Contents	Each ml contains irinotecan hydrochloride, trihydrate 20.0 mg Excipient: Sorbitol, lactic acid and water for injection

Administration	administered as a 90 minutes intravenous infusion in 250 ml of 0.9% sodium chloride solution

4.13.3 Description of S-1 (TS-1®)

Abbreviation	S
Chemical structure	Tegafur Gimeracil Oteracil potassium
Formulation	20 mg/cap (Taiho Pharmaceutical Co.; TTY Biopharm Company Limited)
Contents	Tegafur 20 mg, Gimeracil 5.8 mg, Oteracil potassium 19.6 mg
Administration	administered twice daily, after breakfast and after the evening meal

4.13.4 Description of gemcitabine (GEMZAR®)

Abbreviation	G
Chemical structure	$C_9H_{11}F_2N_3O_4 \cdot HCl$
Formulation	200 mg/vial (ELI LILLY AND COMPANY, United States)
Contents	Vials of Gemzar® contain either 200 mg of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg) and sodium acetate (12.5 mg) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.
Administration	administered as a 30 minutes intravenous infusion in 250 ml of 0.9% sodium chloride solution

4.13.5 Supply and control of study medication

Gemcitabine (GEMZAR®) and (S-1)TS-1® will be provided by the National Taiwan University Hospital as this two drugs are approved for advanced pancreatic cancer and paid by the National Health Insurance. Oxaliplatin (Oxalip®) and irinotecan (Irino®) are products of the Taiho Pharmaceutical Co., Ltd and will be provided/supported by TTY Biopharm Co., Ltd.

4.13.6 Dose reduction during neoadjuvant SIROX chemotherapy

4.13.6.1 Dose reduction schedule (for toxicity evaluated with Common Terminology Criteria for Adverse Events, CTCAE version 4.03)

Oxaliplatin	85 mg/m^2
Level -1	75 mg/m^2
Level -2	65 mg/m^2

Irinotecan	150 mg/m^2
Level -1	135 mg/m^2
Level -2	115 mg/m^2
S-1	80 mg per day (2#/2#)
Level -1	60 mg per day (2#/1#)
Level -2	40 mg per day (1#/1#)

4.13.6.2 Criteria for dose reduction of oxaliplatin in SIROX

- Simultaneous dose reduction will be done for general toxicities of oxaliplatin, irinotecan, S-1, and gemcitabine. Dose reduction of only specific drugs will depend on drug-specific toxicities.
- For patients who develop acute laryngopharyngeal dysaesthesia, during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours. No dose reduction will be required if the symptoms are not longer than 7 days. If symptoms last longer than 7 days (≦21 days) and are troublesome, the subsequent oxaliplatin dose should be reduced for one dose level. If paraesthesia with functional impairment persists longer than 21 days, oxaliplatin should be discontinued (irinotecan and S-1 should be continued) until the discomforts reduced to a non-significant magnitude. If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered. However, the next oxaliplatin infusion should be administered over 6 hours.
- The dose of adjustment of oxaliplatin for day 1 of subsequent new cycles will be made based on the worst toxicity grade of the AEs experienced during the preceding treatment cycle.
- Hematology
  - If grade 3 toxicities of WBC (< $2.0x10^9$/L – $1.0x10^9$/L), neutrophils (< $1.0x10^9$/L– $0.5x10^9$/L), platelets (< $50x10^9$/L– $25x10^9$/L), or Hb (<8.0 g/dL) occurs, administration of the next course of therapy should be postponed until hematological values return to grade 1. If the postponed duration is ≦21 days, no dose reduction will be done. If the hematological values return to grade 1 between 22 and 35 days, reduction of one dose level will be done. If the hematological values do not return to grade 1 within 35 days, the patient should be withdrawn from this study treatment.
  - If grade 4 toxicities of WBC (< $1.0x10^9$/L), neutrophils ($0.5x10^9$/L), platelets (< $25x10^9$/L), or Hb (life-threatening) occurs, administration of the next course of therapy should be postponed until hematological values return to grade 1. If the postponed duration is ≦21 days, reduction of one dose level will be done.
    - If the hematological values return to grade 2 (but not grade 1) between 22 and 35 days, reduction of two dose levels will be done. However, administration of the next course of therapy should be postponed until hematological values return to grade 1.
    - If the hematological values do not return to grade 1 within 35 days, the patient should be withdrawn from this study treatment.
  - Transfusion will follow the routine practice at our hospital. The administration of G-CSF(covered by National Health Insurance) will follow the guidelines of the National Health

Insurance. Prophylatic transfusion or administration within one day before chemotherapy will not be allowed.

- Gastrointestinal
  - Prophylaxis and/or treatment with potent antiemetic agents is indicated.
  - If grade 3 mucositis/diarrhea/nausea/anorexia/vomiting occur, the next treatment should be delayed until recovery from mucositis/diarrhea to grade 1. If the postponed duration is ≦21 days, no dose reduction will be done. If the toxicities return to grade 1 between 22 and 35 days, reduction of one dose level will be done. If the toxicities do not return to grade 1 within 35 days, the patient should be withdrawn from this study treatment.
  - If grade 4 mucositis/diarrhea/anorexia/vomiting occur, administration of the next course of therapy should be postponed until the toxicities return to grade 1. If the postponed duration is ≦ 21 days, reduction of one dose level will be done.
    - If the toxicities return to grade 2 (but not grade 1) between 22 and 35 days, reduction of two dose levels will be done. However, administration of the next course of therapy should be postponed until the toxicities return to grade 1.
    - If the toxicities do not return to grade 1 within 35 days, the patient should be withdrawn from this study treatment.
- Infection
  - If any grade 3 infection (ie. use of antibiotic) occurs, the next treatment should be delayed until recovery from the infection. If the postponed duration is ≦21 days, no dose reduction will be done. If the infection recovers between 22 and 35 days, reduction of one dose level will be done. If the infection does not recover within 35 days, the patient should be withdrawn from this study treatment.
  - If any grade 4 infection occurs, administration of the next course of therapy should be postponed until recovery from the infection. If the postponed duration is ≦21 days, reduction of one dose level will be done. If the infection recovers between 22 and 35 days, reduction of two dose levels will be done. If the infection does not recover within 35 days, the patient should be withdrawn from this study treatment.
- In the case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease. The continuation of oxaliplatin will be determined by investigators case by case.
- General rules of other toxicities:
  - If any grade 3 toxicity occurs, the next treatment should be delayed until recovery from the toxicity. If the postponed duration is ≦21 days, no dose reduction will be done. If the toxicity recovers between 22 and 35 days, reduction of one dose level will be done. If the toxicity does not recover within 35 days, the patient should be withdrawn from this study treatment.
  - If any grade 4 toxicity occurs, administration of the next course of therapy should be postponed until recovery from the toxicity. If the postponed duration is ≦21 days, reduction of one dose

level will be done. If the infection recovers between 22 and 35 days, reduction of two dose levels will be done. If the toxicity does not recover within 35 days, the patient should be withdrawn from this study treatment.

4.13.6.3 Criteria for dose reduction of irinotecan in SIROX

- The dose reduction criteria of hematology, gastrointestinal, infection, and other toxicities will follow the same rules of oxaliplatin.
- The dose of adjustment of irinotecan for day 1 of subsequent new cycles will be made based on the worst toxicity grade of the AEs experienced during the preceding treatment cycle.
- Atropine (0.25 mg subcutaneously) should be administered before irinotecan unless clinically contraindicated for prophylaxis of acute cholinergic syndrome.
- Delayed diarrhea (occurring more than 24 hours after administration)
  - The currently recommended antidiarrheal treatment consists of high doses of loperamide (4mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours. In addition to the antidiarrheal treatment, a prophylactic broad-spectrum antibiotic should be given, when diarrhea is associated with grade 4 neutropenia.

4.13.6.4 Criteria for dose reduction of S-1 in SIROX

- The starting dose of each cycle of S-1 will follow the dose reduction criteria of oxaliplatin for hematology, gastrointestinal, infection, and other toxicities.
- The dose of adjustment of S-1 for day 1 of subsequent new cycles will be made based on the worst toxicity grade of the AEs experienced during the preceding treatment cycle.
- Dose reduction of S-1 within the same cycle will not be allowed.
- If any grade 3 or 4 toxicities occur within any cycle, S-1 should be hold in the same cycle and restarted with the same dose as soon as the toxicities recover to grade 1 or less. Dose reduction will not be required in the next cycle if the duration without S-1 is <14 days.
  - If the duration without S-1 is ≧ 14 days in any cycle, S-1 will not be restarted in the same cycle. Dose reduction of one level will be done in the next cycle.
- Avoid concomitant use with S-1: fluoropyrimidines, such as fluorouracil(5-FU), tegafur/uracil(UFT), tegafur(futraful), doxifluridine(furtulon), capecitabine(Xeloda), carmofur(mifurol), folic acid+tegafur-uracil (UZEL/UFT), Levofolinate+fluorouracil (Isovorin/5-FU), fluoropyrimidine antifungal, Flucytosine(ancotil)

4.13.7 Dose reduction during adjuvant gemcitabine

- Hematology
  - If grade 3 toxicities of WBC (< $2.0x10^9$/L – $1.0x10^9$/L), neutrophils (< $1.0x10^9$/L– $0.5x10^9$/L), platelets (< $50x10^9$/L– $25x10^9$/L), or Hb (<8.0 g/dL) occurs, administration of the next dose (D8

or D15) should be postponed until hematological values return to grade 1. If the postponed duration is ≦14 days, no dose reduction will be done in the next dosing. If the hematological values return to grade 1 between 15 and 28 days, reduction of one dose level in the next dosing will be done. If the hematological values do not return to grade 1 within 28 days, the patient should be withdrawn from this study treatment.

- If grade 4 toxicities of WBC (< $1.0x10^9$/L), neutrophils ($0.5x10^9$/L), platelets (< $25x10^9$/L), or Hb (life-threatening) occurs, administration of the next dose should be postponed until hematological values return to grade 1. If the postponed duration is ≦14 days, reduction of one dose level will be done.
  - If the hematological values return to grade 2 (but not grade 1) between 15 and 28 days, reduction of two dose levels will be done. However, administration of the next dose should be postponed until hematological values return to grade 1.
  - If the hematological values do not return to grade 1 within 28 days, the patient should be withdrawn from this study treatment.
- Transfusion will follow the routine practice at our hospital. The administration of G-CSF(covered by National Health Insurance) will follow the guidelines of the National Health Insurance. Prophylatic transfusion or administration within one day before chemotherapy will not be allowed.

- Gastrointestinal
  - Prophylaxis and/or treatment with potent antiemetic agents is indicated.
  - If grade 3 mucositis/diarrhea/nausea/anorexia/vomiting occur, the next dose should be delayed until recovery from mucositis/diarrhea to grade 1. If the postponed duration is ≦14 days, no dose reduction will be done. If the toxicities return to grade 1 between 15 and 28 days, reduction of one dose level will be done. If the toxicities do not return to grade 1 within 28 days, the patient should be withdrawn from this study treatment.
  - If grade 4 mucositis/diarrhea/anorexia/vomiting occur, administration of the next dose should be postponed until the toxicities return to grade 1. If the postponed duration is ≦14 days, reduction of one dose level will be done.
    - If the toxicities return to grade 2 (but not grade 1) between 15 and 28 days, reduction of two dose levels will be done. However, administration of the next dose should be postponed until the toxicities return to grade 1.
    - If the toxicities do not return to grade 1 within 28 days, the patient should be withdrawn from this study treatment.
- Infection
  - If any grade 3 infection (ie. use of antibiotic) occurs, the dose should be delayed until recovery from the infection. If the postponed duration is ≦14 days, no dose reduction will be done. If the infection recovers between 15 and 28 days, reduction of one dose level will be done. If the infection does not recover within 28 days, the patient should be withdrawn from this study treatment.

- If any grade 4 infection occurs, administration of the next dose should be postponed until recovery from the infection. If the postponed duration is ≦14 days, reduction of one dose level will be done. If the infection recovers between 15 and 28 days, reduction of two dose levels will be done. If the infection does not recover within 28 days, the patient should be withdrawn from this study treatment.

- General rules of other toxicities:
  - If any grade 3 toxicity occurs, the next dose should be delayed until recovery from the toxicity. If the postponed duration is ≦14 days, no dose reduction will be done. If the toxicity recovers between 15 and 28 days, reduction of one dose level will be done. If the toxicity does not recover within 28 days, the patient should be withdrawn from this study treatment.
  - If any grade 4 toxicity occurs, administration of the next dose should be postponed until recovery from the toxicity. If the postponed duration is ≦14 days, reduction of one dose level will be done. If the infection recovers between 15 and 28 days, reduction of two dose levels will be done. If the toxicity does not recover within 28 days, the patient should be withdrawn from this study treatment.
- The dose adjustment of gemcitabine for day 1 of subsequent new cycles will be made based on the worst toxicity grade of the AEs experienced during the preceding treatment cycle.
- Adjuvant gemcitabine will be given for 6 cycles.
- Dose reduction schedule

Initial dose	Dose reduction level	
1,000 mg/m^2	-1	-2
D1, 8, 15; 28 Days/cycle	800 mg/m^2	600 mg/m^2

4.13.8 Dose reduction during adjuvant S-1

- Adjuvant S-1 will be given for 8 cycles [39]. S-1 will be dosing according to body-surface area (BSA), orally administered twice a day for 14 days followed by a 7-day rest.

-Dosing and dose reduction schedule

BSA	Initial dose	Dose reduction level	
		-1	-2
< 1.25 m^2	80 mg per day	60 mg/day	40 mg/day
1.25 to < 1.5 m^2	100 mg per day	80 mg/day	60 mg/day
≥ 1.5 m^2	120 mg per day	100 mg/day	80 mg/day

- The dose of adjustment of S-1 for day 1 of subsequent new cycles will be made based on the worst toxicity grade of the AEs experienced during the preceding treatment cycle.
- When the subject has experienced any one of the AEs described below, the dose of S-1 should be reduced by one dose level at a time in the subsequent cycles:

- WBC < 1,000/mm^3
- ANC < 500/mm^3
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection accompanied by ANC < 1,000/mm^3, fever ≥ 38.5°C)

- Infection (documented clinically or microbiologically) with ANC < 1,000/mm^3
- Platelet < 25,000/mm^3 or 50,000/mm^3 requiring platelet transfusion
- Creatinine ≥ 1.5 mg/dL
- Diarrhea, stomatitis, or skin rash ≥ grade 3

- S-1 should be hold if grade 3 or 4 toxicities occur and restarted as soon as the toxicities recover to grade 1 or less.
- Subjects who require more than two dose-reduction steps of S-1 must be discontinued from the study treatment.
- Once the dose of S-1 has been reduced for a subject, no further dose re-escalation is allowed even if the condition of the subject returns to normal.

4.13.9 Dosing criteria

- Any administration of oxaliplatin, irinotecan, S-1, and gemcitabine should be performed within a window of plus or minus 1 day of the scheduled visit date.
- Day 1 of cycle 1-4 of SIROX; D1, 8, 15 of cycle 1-6 of adjuvant gemcitabine, D1, 8 of cycle 1-8 of adjuvant S-1
  - The study treatment should be started within 28 days after the registration, and all the criteria below should be met (clinical and laboratory exams should be done within two days of start of study treatment):

- WBC ≥ 3,000/mm^3
- ANC ≥ 1,500/mm^3
- Platelet ≥ 75,000/mm^3
- AST ≤ 3 x ULN
- ALT ≤ 3 x ULN
- Total bilirubin ≤ 1.5 x ULN. For subjects who are treated by biliary drainage due to obstructive jaundice, bilirubin ≤ 3 x ULN will be acceptable.
- Creatinine ≤ 1.5 x ULN
- Diarrhea, stomatitis ≤ grade 1
- Skin rash ≤ grade 1

4.13.10 Intervals between treatment phases

SIROX	D21 of cycle 4 of SIROX	21-42 days	Surgery	28-56 days	D1 of cycle 1 of adjuvant chemotherapy

- If treatment is not initiated within the specified periods, the patient will be withdrawn from this study.

4.13.11 Discontinuation of the study treatment

Subjects must be discontinued from the study treatment for the following reasons:

a. unable to start the first dose of study treatment within 28 days after registration

b. being ineligible after registration
c. objective disease progression after 4 cycles of SIROX
d. recurrence before or during adjuvant therapy
e. requirement for further dose reduction beyond the lowest dose limitation
f. lost to follow-up or unable to adhere to the visit schedule
g. protocol non-compliance: any significant non-medical deviation from the protocol without prior agreement of principal investigator
h. informed consent withdrawn
i. death
j. investigators discretion: experiencing the occurrence of an AE for which the investigator considers discontinuation from the protocol treatment to be in the subject's best interest

4.14 Measurability of tumor lesions

Tumor response will be evaluated basically according to the proposal of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

4.14.1 Definitions:

a. At baseline, tumor lesions will be categorized as measurable and non-measurable.
   1. Measurable: Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
   ■10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
   ■10mm caliper measurement by clinical exam (when superficial)
   ■20mm by chest X-ray (if clearly defined and surrounded by aerated lung)
   2. Non-measurable: Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
b. All measurements should be recorded in metric notation by use of a ruler or calipers.

4.14.2 Specification by methods of measurements:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluate by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

a. Clinical examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography-including a ruler to estimate the size of the lesion-is recommended.

b. Chest-X-ray: Lesions on chest X-ray are acceptable as measurable when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.
c. CT and MRI: CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm. This specification applies to the tumors of the chest, abdomen, and pelvis.

4.14.3 Tumor clinical response evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by histology.

4.14.3.1 Target lesions:

a. All lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions.
b. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
c. A summation of the longest diameter for all target lesions will be calculated and reported as the baseline longest diameter summation. The baseline longest diameter summation will be used as reference for further characterization of the objective tumor response.

4.14.3.2 Non-target lesions:

a. It is required to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up and reported in CRF with their responses.

4.14.3.3 Best overall response:

a. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient’s best response assignment will depend on the achievement of measurement criteria.
b. When an examination cannot be conducted for AE or discontinuation due to the subject’s rejection, the subject will be regarded as NE in best overall response.
c. Summary of target and non-target lesions:

CR	■Target Lesions: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes) ■Non-target Lesions: disappearance of all non - target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis) ●Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
PR	■Target Lesions: At least 30% decrease in the sum of the longest diameter taking as reference the baseline SLD
PD	■Target Lesions: > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir or appearance of one or more new lesions ■Non-target Lesions: Appearance of one or more new lesions; unequivocal progression of existing non-target lesions; tumor marker levels irrelevant.
SD	■Target Lesions: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest SLD since the treatment started. ■Non-target Lesions: Non-CR/Non-PD
NE	An examination cannot be conducted for some reason or the state of the lesion does not fall into categories CR, PR, SD (non-CR/non-PD), PD

d. Summary of overall response:

Target	Non-target	New	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

5 Adverse events (AE) (grading with CTCAE v4.03)

5.1 Definition of AE: an Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

5.2 Serious adverse event (SAE):

Any untoward medical occurrence that falls in the following categories:

a. results in death

b. is life threatening

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

c. requires inpatient hospitalization or prolongation of existing hospitalization

d. results in persistent or significant disability/incapacity

e. is a congenital anomaly/birth defect

f. 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. Examples of such events are intensive treatment in an emergency room or home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.3 Unexpected adverse event:

An AE, the nature or severity of which is not consistent with that described in the Investigator’s Brochure or summary of product characteristics is considered as an unexpected AE.

5.4 Reporting

5.4.1 AE reporting

- All AEs reported spontaneously by the subject or observations by the investigator must be recorded in the CRF.
- Their severity and relationship to the study medication should be evaluated and recorded in the CRF.
- Categories of severity:
  - Mild CTCAE v4.03 grade 1: The AE does not limit usual activity. The subject may experience slight discomfort.
  - Moderate CTCAE v4.03 grade 2: The AE results in some limitation of usual activities. The subjects may experience significant discomfort.
  - Severe CTCAE v4.03 grade 3: The AE results in an inability to carry out usual activities. The subject may experience intolerable discomfort.
  - Life threatening: Disabling, CTCAE v4.03 grade 4; The AE results in a disabling situation. The AE results in a life-threatening situation. The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe
  - DeathCTCAE v4.03 grade 5
- Causality to study treatment: Causal relationship with the study drug/radiotherapy will be judged in consideration of a subject’s systemic conditions, complications, concomitant medications/combination therapies and temporal relationship. Reasonable possibility of a

relationship between an AE and the study drug/radiotherapy is to be categorized as “yes” (presence of reasonable causal relationship) or “no” (absence of reasonable causal relationship) two categories. Definition of causality will be referred to Council for International Organizations of Medical Sciences (CIOMS) VI. In case of “yes” (presence of reasonable causal relationship) will be judged as Adverse Drug reaction (ADR).

5.4.2 SAE reporting:
Any SAE must be reported to the investigator as soon as possible (within 24 hours) following the discovery of the event. The investigator should also report any SAE to the Ethics Committee/Institutional Review Board and Ministry of Health and Welfare, Executive Yuan, R.O. C. (Taiwan) (MOHW) within 15 calendar days.

5.4.3 AE follow up
- For safety follow-up, each subject will be followed for occurrence of new AE until 30 days after the last dose of study medication, or additional antitumor therapy has been introduced, whichever comes first.
- Existing AE will be followed until resolution/stabilization of, unless, in the investigator’s opinion, the condition is unlikely to resolve due to subject’s underlying disease.

6. Analysis

6.1 Interim analysis and premature discontinuation
a. If additional information suggests safety problems with continuation of the study or unpromising efficacy of the study treatment, premature discontinuation will be considered.
b. Interim analysis will not be conducted.

6.2 Final analysis
Final analysis for all endpoints will be conducted after the all endpoints are collected completely or the study period (4 years) is reached.

6.3 Trial monitoring
No trial monitoring will be conducted.

7. Ethical consideration

7.1 Good clinical practice (GCP)
The trial will be carried out in accordance with the World Medical Association’s Declaration of Helsinki as amended in 1996 and in accordance with the GCP principles as defined in the International Conference on Harmonization (ICH) of Technical Requirements for Registration of

Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for good clinical practice.

7.2 Responsibilities of the Investigator

The Investigator is responsible for the conduct of this trial at his/her site. Throughout this clinical trial protocol, Investigartor refers to both the PI and any CO-PI. He/she will ensure that the trial is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, regulations of the responsible authorities, and the GCP principles. The Investigators must ensure that only subjects who have given their informed consent are included in the trial.

7.3 Institutional review board (IRB) approval

The Investigator must submit a copy of the protocol to the local IRB for consideration. The study will not start until IRB has given written approval of the protocol. Investigators are obligated to disclose any conflict of interest which they, their spouses or their dependent children may have in this study. The information is required during the trial.

7.4 Regulatory requirements

The Investigator is responsible for ensuring that the protocol and any supporting documentation are submitted to the relevant regulatory authorities and the necessary approval obtained, prior to the start of the trial (where applicable) according to local regulations.

7.5 Information for participants

The investigator must explain to each participant before handing the objectives and requirements imposed by the study, as well as the nature of the test treatment and potential adverse effects. A patient information sheet drafted in simple language should be given to each participant.

7.6 Informed consent

The investigator is responsible for providing written (patient information sheets) and verbal information to the patient and obtaining written informed consent prior to participation in the trial. A copy of the completed consent form will be given to the patient. The Investigator will confirm in writing that informed consent has been obtained. Before consent may be obtained, the Investigator should provide the prospective subject with ample time and opportunity to inquire about details of the clinical trial and to decide whether or not to participate in this trial. In such cases, the Investigator or the trial coordinator giving supplementary explanation should answer all questions about the trial to the satisfaction of the prospective subject. Depending on national regulations, a person other than the Investigator may inform the subject about the trial and sign the informed consent, as above. After the information is provided by the Investigator, the informed consent must be signed and personally dated by the subject and the Investigator. The signed and dated declaration of the informed consent will remain at the Investigator’s site and must be safely archived by the

Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. Whenever important new information becomes available that may be relevant to the subject's consent, the Investigator will revise the informed consent form provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised informed consent form, the Investigator will explain the changes to the previous version to each trial subject and obtain his/her written consent for continued participation in this trial.

7.7 Subject identification and privacy

A unique subject number will be assigned to each subject at inclusion. Subject number will be assigned immediately after informed consent has been obtained. This number will serve as the subject's identifier in this trial as well as in the clinical trial database. The subjects data collected in this trial will be stored under this number. Only the Investigator and study coordinator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that that are reviewed at the site during source data verification by the monitor, audit, and inspection inspections will be kept strictly confidential. Blood and tumor tissue samples for biomarkers will be stored for up to 10 years after trial completion. After 10 years, the samples will be destroyed or fully anonymized or a new IRB approval and informed consent will be requested to keep the samples for an additional period.

7.8 Emergency medical support

Subjects enrolled in this clinical trial will be provided with the 24-hr contact information of all of PI, CO-PIs, and study coordinators. If the Investigator is available when an event occurs, he/she will answer any questions and provide any adequate further medical support.

7.9 Clinical trial insurance and compensation

None

8. Premature termination of trial

The Investigator has the right to terminate the trial at any time for reasonable medical and/or administrative reasons. Reasons for termination must be documented appropriately.

9. Publication/Presentation

After completion of this clinical study, Investigators will be entitled to publish the study results at the earliest opportunity in international academic papers or present the results at academic meetings.

10. Intellectual property rights

Intellectual property rights arising from the study will belong to the property of the Investigators.

11. Reference

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12. Appendix