Phase II Study of Neoadjuvant Chemotherapy with Gemcitabine and S1 for Resectable Pancreatic Carcinoma (PREP-01)

Study Protocol

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0. SYNOPSIS

0.1. Title
Phase II study of Neoadjuvant chemotherapy with Gemcitabine and S1 for resectable pancreatic carcinoma (Prep-01)

0.2. Objectives
Primary endpoint: 2-year survival rate defined by the % of people who are alive for 2 years after enrollment
Secondary endpoint: Adverse event, resection rate, residual tumor (R), nodal involvement (N), pathological effect, recurrence free survival, tumor marker, dose intensity

0.3. Subjects
Subjects in this study are those who meet all the eligibility criteria and none of the exclusion criteria.
1) Pancreatic ductal adenocarcinoma (invasive pancreatic ductal carcinoma) diagnosed on imaging and histological/pathological findings
2) No distant metastases
3) Resectable with no macroscopic residual tumor (R0, 1)
4) Tolerable for curative-intent surgery
5) Treatment naïve
6) ECOG performance status of 0 or 1
7) Adequate functions of major organs (e.g., bone marrow, liver, kidneys, and lungs)
   (i) White blood cell count: ≥3,500/mm³ and <12,000/mm³
   (ii) Neutrophil count: ≥2,000/mm³
   (iii) Hemoglobin content: ≥9.0 g/dL
   (iv) Platelet count: ≥100,000/mm³
   (v) Total bilirubin: ≤2.0 mg/dL*
   (vi) AST: ≤150 U/L
   (vii) ALT: ≤150 U/L
   (viii) Creatinine: ≤1.2 mg/dL
   (ix) Creatinine clearance (Ccr): ≥50 mL/min
8) Able to take medication orally
9) Written informed consent from the patient
10) Age ≥20 years and competency to give consent for this study at the time of enrollment
0.4. Design
Open-label, multicenter, single-arm, prospective phase-II study

- R0/1 resectable PDAC, 20 years and older, PS:0-1, No prior therapy
  - Enrollment after written IC
  - Neoadjuvant chemotherapy (Intervention)
    - Two cycles of GS regimen within 8 weeks
  - Surgery
- Inclusion criteria for on-protocol
  1. R0/1 resection
  2. Postoperative CA19-9 < 2.5 times the upper normal limit of normal
  3. M0
  4. Sufficient recovery for chemotherapy within 10 weeks after surgery
- Exclusion criteria for on-protocol (as off-protocol)
  1. R2 resection or no resection
  2. Postoperative CA19-9 > 2.5 times the upper normal limit of normal
  3. M1
  4. Insufficient recovery for chemotherapy within 10 weeks after surgery

- Standard adjuvant chemotherapy
  - 6 cycles of gemcitabine monotherapy within 24 weeks
- Adequate treatment in each institution

Follow-up
0.5. Treatment

Neoadjuvant chemotherapy

The intervention consists of administering GEM for 2 weeks followed by a 1-week rest, and S-1 for 1 week, starting from the day of each GEM administration, by the oral route twice daily. The goal is to administer a total of 4 doses of GEM and 4 weeks of oral S-1 within 8 weeks. The protocol therapy, however, should not be discontinued for patients who failed to achieve the target number of doses within 8 weeks; they should still undergo surgery. S-1 is to be administered starting from after dinner on the day of GEM administration until after breakfast on Day 8 of each GEM administration.

Adjuvant chemotherapy

For on-protocol patients, standard GEM adjuvant (1g/m²/week, 3 weeks administration followed by 1 week rest, 6 courses) is administered as a practice.

0.6. Sample Size and Study Period

Target sample size: 80 subjects

Study period: 4 years (October 2010 to September 2014)

Enrollment: 2 years (October 2010 to September 2012)

Follow-up: 2 years after final enrollment
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1. STUDY OBJECTIVES

Primary endpoint:
2-year survival rate defined by the % of people who are alive for 2 years after enrollment

Secondary endpoint:
Adverse event, resection rate, residual tumor (R), nodal involvement (N), pathological effect, recurrence free survival, tumor marker, dose intensity

2. BACKGROUND AND RATIONALE

2.1. Background of the Disease

Pancreatic cancer is an un-curable cancer, with a 5-year survival rate of approximately 5%. The number of deaths attributed to pancreatic cancer in 2004 was approximately 22,000, making it the fifth-ranked leading cause of death in Japan.

Histologically, pancreatic tumors are divided into two groups: exocrine and endocrine. Exocrine neoplasms are further classified into cystic neoplasms, intraductal neoplasms, atypical hyperplasia and carcinoma in situ, invasive ductal carcinomas, and acinar cell neoplasms. Approximately 90% of histologically classified pancreatic cancers are invasive ductal carcinoma, among which the most common tissue type is tubular adenocarcinoma.

Pancreatic cancer patients experience symptoms such as jaundice, abdominal/back pain, loss of appetite, gastrointestinal hemorrhage, and weight loss, none of which are symptoms specific to pancreatic cancer. Thus, even with the advances made in imaging diagnoses, early diagnoses are still difficult. The poor survival rate for pancreatic cancer patients is attributable to the facts that most patients are diagnosed with unresectable advanced cancer by the time they are diagnosed because of abdominal pain, jaundice, or diabetic exacerbation, among other symptoms, and that patients who undergo curative resection often develop postoperative early recurrence. Therefore, to extend the survival time of pancreatic cancer patients, it is necessary to develop radiotherapy, chemotherapy, and other nonsurgical treatment. At present, however, no therapies have yet to demonstrate a satisfactory therapeutic effect.
2.2. **Standard Therapy for the Target Disease**

The treatment of pancreatic cancer that offers a chance for long-term survival is surgical resection. Most of the tumors treated, however, are progressing advanced cancer and frequently relapse after resection, making long-term survival difficult. Several European randomized comparative studies of postoperative adjuvant therapy (ESPAC-1, ESPAC-3, CONKO-001) have reported that postoperative adjuvant chemotherapy contributes to the extension of survival. Given such results, the Japanese Guidelines for the Management of Pancreatic Cancer also recommends gemcitabine as postoperative adjuvant chemotherapy. In Japan, a randomized comparative study of gemcitabine as postoperative adjuvant chemotherapy (Ministry of Health, Labour and Welfare, the Kosuga team) also produced results similar to those from CONKO-001. Given the above results, a consensus has emerged that the standard treatment for resectable pancreatic cancer is “resection and postoperative adjuvant chemotherapy with gemcitabine.”

2.3. **Gemcitabine (GEM)**

Gemcitabine [trade name, Gmezar® (Eli Lilly Japan K.K.)]

GEM is an anti-cancer agent classified as antimetabolite. It is intracellularly metabolized into gemcitabine triphosphate, which inhibits DNA synthesis. Furthermore, the intracellular concentration of gemcitabine triphosphate is maintained over a long period of time, which provides a potent cytocidal activity against solid tumors. Presently, GEM is widely used worldwide as first-line therapy for advanced pancreatic cancer. In Japan, as well, it was approved in April 2001 for the additional indication of pancreatic cancer after a phase I study was conducted [response rate 18.2% (2/11)]. GEM has been approved for insurance coverage to treat pancreatic cancer as well as non-small cell lung cancer, bile duct carcinoma, urinary tract carcinoma in situ, inoperable or recurrent breast cancer, and ovarian cancer that worsened after cancer chemotherapy.

2.4. **S-1**

S-1 [trade name, TS-1® (Taiho Pharmaceutical Co., Ltd.)]

S-1 is an oral anti-cancer agent comprising tegafur (a prodrug of 5-FU) combined with two modulators: gimeracil and oteracil potassium. It was developed to enhance the antitumor effect by increasing the blood concentration of 5-FU and to reduce the associated gastrointestinal toxicity.

Clinical studies of S-1 in Japan began in 1993 and have reported response rates of 46.5% for gastric cancer; 32.6%, colorectal cancer; 34.1%, head and neck carcinoma; 18.2%, non-small cell lung cancer (treatment-naïve); and 21.8%, inoperable or recurrent breast cancer. S-1 has received approval for each of
these indications and has been used in general treatment either as a monotherapy or combination therapy.

An early phase II study of advanced pancreatic cancer with distant metastasis reported a response rate of 21.1% (4/19), a time to progression (TTP) of 77 days, and a median survival time (MST) of 169 days; the late phase II study reported a response rate of 37.5% (15/40), a TTP of 113 days, and an MST of 281 days [phase-II overall response rate: 32.2% (19/59)]. It received approval for the additional indication in August 2006. In addition, it was approved for the treatment of bile duct carcinoma in August 2007.

2.5. Gemcitabine and S-1 Combination Therapy (GS therapy)

Preclinical studies have shown that 5-FU (the S-1 metabolite) and GEM inhibit DNA synthesis through different pathways and show synergistic effects. Many phase II studies of the combination therapy with 5-FU and GEM for the treatment of pancreatic cancer have reported the feasibility as well as relatively good response rates (10% to 20%) and survival times (median, 7 to 10 months). There are also two reports available on phase II studies of the combination therapy with GEM and UFT, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine (DIF), which has the same mechanism of action as that of S-1. Those studies reported response rates of 33% and 22.7%, and MST of 11 months and 5.8 months, respectively.

Meanwhile, a phase II study of GEM and S-1 combination therapy (GS therapy) was initiated in October 2004 at the National Cancer Center Hospital, among other study sites. The phase II study enrolled 55 subjects, who repeated 21-day courses of treatment with GEM at 1,000 mg/m² administered on Days 1 and 8, and S-1 at 80 mg/m² administered on consecutive days from Days 1 through 14. Among the 54 subjects who were evaluated (1 subject who discontinued prior to treatment was excluded), the response rate was 44% (24/54); median progression-free survival (PFS), 5.9 months; median survival time (MST), 10.1 months; and the 1-year survival rate, 33.0%. These data suggest that GS therapy is potentially the most effective neoadjuvant chemotherapy.

2.6. Neoadjuvant Chemotherapy

With pancreatic cancer resections giving poor results, some have advocated the administration of neoadjuvant chemoradiotherapy or chemotherapy before surgical resection. If neoadjuvant therapy successfully leads to the down-staging of cancer progression, it can increase the resection rate and reduce the chance for cancer cells to remain and spread during the surgery. In addition, if a distant metastasis is diagnosed during neoadjuvant therapy or if the patient is completely unresponsive to the neoadjuvant therapy, laparotomy can be avoided (Guidelines for the Management of Pancreatic Cancer, 2009 Edition).

Neoadjuvant therapy is becoming an established treatment strategy for other carcinomas. For breast
cancer, neoadjuvant chemotherapy provides the advantages of improving the breast preservation rate and facilitating the prediction of prognosis based upon demonstrated sensitivity to chemotherapy. In cases where postoperative chemotherapy is applicable, neoadjuvant chemotherapy should be considered as it can improve survival just as postoperative chemotherapy (Clinical Practice Guideline of Breast Cancer). For esophageal carcinoma, a randomized comparative study of a combination of neoadjuvant chemotherapy and resection and a combination of resection and postoperative adjuvant chemotherapy (JCOG9907) showed that neoadjuvant chemotherapy (5-FU and CDDP) significantly extended survival.

For pancreatic cancer, Palmer et al. conducted a randomized, phase II comparative study in patients diagnosed with resectable pancreatic cancer, who were divided into two arms that received neoadjuvant chemotherapy with either gemcitabine or a combination of gemcitabine and cisplatin. They reported that the latter was superior in terms of both resection rate and survival. In addition, Sahora et al. administered neoadjuvant chemotherapy with a combination of gemcitabine and oxaliplatin (GemOX regime) to patients with localized advanced pancreatic cancer (borderline resectable or unresectable) and reported satisfactory results similar to those in resectable cases. Prospective studies that took place mainly in Europe have reported promising potential, but the findings on neoadjuvant chemotherapy that have been reported remain scarce. A phase III study of the GemOX regimen in patients with unresectable pancreatic cancer reported a response rate of 26.8%, which is equivalent to that of 29.0% in the phase III study of the abovementioned GS therapy. This suggests that the GS therapy is also a worthy neoadjuvant therapy that should be assessed in a confirmatory comparative study.

3. PATIENT SELECTION CRITERIA

Subjects entered into the study are patients who meet all of the eligibility criteria and none of the exclusion criteria. Laboratory data must have been collected no more than 14 days prior to enrollment and imaging results no older than 28 days prior to enrollment.

3.1. Eligibility Criteria

1) Diagnosis of pancreatic cancer (invasive ductal carcinoma)*

*1 Eligible patients are those with pancreatic cancer diagnosed as “invasive ductal adenocarcinoma” at the time of enrollment. The pre-enrollment diagnosis must include cytological (e.g., pancreatic juice and ductal brushing) or histological diagnosis (e.g., EUS-FNA).

Invasive ductal carcinoma of the pancreas is as defined in the General Rules for the Study of Pancreatic Cancer (The 6th Edition) and includes papillary adenocarcinoma, tubular adenocarcinoma, poorly differentiated
adenocarcinoma, adenosquamous carcinoma, mucinous carcinoma, and anaplastic carcinoma. For cytology, Class V is preferable; however, if the imaging diagnosis is consistent with that of conventional pancreatic cancer, Class IV is also acceptable.

2) No distant metastases*²
*² To be determined based on imaging studies

3) Resectable with no macroscopic residual cancer (R0, 1) on imaging studies*³
*³ The term “resectable pancreatic cancer” refers to T1-3, stage IA to IIB based on the UICC TNM classification [see Criteria and Definitions Used in This Study (vi)].

4) Tolerable for curative surgery (pancreatoduodenectomy, distal or total pancreatectomy)

5) Treatment-naïve

6) ECOG performance status of 0 or 1

7) Adequate function of major organs (e.g., bone marrow, liver, kidneys, and lungs)
   (Meeting the following criteria based on the laboratory data within 14 days before enrollment)
   (i) White blood cell count: \( \geq 3,500/mm^3 \) and \( < 12,000/mm^3 \)
   (ii) Neutrophil count: \( \geq 2,000/mm^3 \)
   (iii) Hemoglobin: \( \geq 9.0 \text{ g/dL} \)
   (iv) Platelet count: \( \geq 100,000/mm^3 \)
   (v) Total bilirubin: \( \leq 2.0 \text{ mg/dL} \)
   \( \leq 3.0 \text{ mg/dL} \) for patients undergoing biliary drainage for obstructive jaundice
   (vi) AST: \( \leq 150 \text{ U/L} \)
   (vii) ALT: \( \leq 150 \text{ U/L} \)
   (viii) Creatinine: \( \leq 1.2 \text{ mg/dL} \)
   (ix) Creatinine clearance: \( \geq 50 \text{ mL/min} \)
   (This criterion should be evaluated based on the actual measurement, if available, or the Cockcroft-Gault*⁴ estimate.)
   *⁴: \( \text{Male Ccr} = \text{body weight} \times (140 - \text{age})/(72 \times \text{creatinine}), \)
   \( \text{Female Ccr} = \text{body weight} \times (140 - \text{age})/(72 \times \text{creatinine}) \times 0.85 \)

8) Able to take medication orally

9) Written informed consent from the patient personally

10) Age \( \geq 20 \text{ years} \) and competency to give consent for this study at the time of enrollment

3.2. Exclusion Criteria

1) Patients with pulmonary fibrosis or interstitial lung disease
2) Patients with poorly controlled watery diarrhea

3) Patients with active double cancers*

*Synchronous double cancers or metachronous double cancers with a disease-free interval of ≤3 years, including sarcoma, lymphoma, and other malignant non-epithelial neoplasms. However, if a radical treatment has been performed on a carcinoma in situ or intramucosal carcinoma, the disease-free interval does not matter.

4) Patients with any active infection (fever of ≥38.0°C; viral hepatitis is excluded)

5) Patients who are HBs-antigen positive

6) Patients who use flucytosine, phenytoin, or warfarin

7) Patients who are pregnant or may be pregnant

8) Any other patients deemed by the attending physician to be unsuitable to allow the feasible for this study

4. ETHICS

4.1. Patient Protection

All investigators involved in this study shall comply with the most up-to-date ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies (Ministry of Health, Labour and Welfare, complete revision, July 31, 2008). Patients’ human rights, welfare, and safety shall be ensured to the maximum extent, and considerations of patients’ well-being shall be given priority over the interests of science and society.

4.2. Consent Acquisition

Prior to enrolling a patient, the attending physician is to provide extensive information on items (1) through (11) below using written information and written consent for the patient that have been approved by the study site’s institutional review board (IRB) or ethics review board (ERB). Patients should be given chances to ask questions and sufficient time to determine whether to participate in the study (where appropriate, obtain consent a day after the explanations are given). After confirming that the patient has an adequate understanding of the study, obtain voluntary written consent to participate in the study from the patient personally. The attending physician is to promptly provide the subject a copy of the written consent that has been signed and sealed or signed, and properly retain the original of the written consent in the specified archive at each study site.
4.3. **Information to be Given**

(1) Name of Disease, medical condition, disease stage, and prognosis

(2) The fact that this study is a clinical study

(3) This study’s design and rationale (e.g., significance, necessity, objectives, and duration)

(4) Study methodology and treatment description
Drug name, method of administration, dose, treatment cycle, and the overall conduct of the study, etc.

(5) Expected effects and adverse drug reactions

(6) Cost burdens and compensations
Explanations that as with the general medical practice, the cost of therapy will be covered by the insurance plan, and compensation in case of health damage will be handled in accordance with the general medical practice

(7) Any alternative therapies and their descriptions

(8) Information concerning direct access to medical history and secondary use of data

(9) Consent refusal and consent withdrawal
The fact that patients are free to refuse consent to participate in the study and free to withdraw consent without suffering any inappropriate disadvantage in medical care

(10) Human rights protection
That the utmost effort will be made to protect the confidentiality of names and other personal information

(11) Free to ask questions
Explanations that the contact information for the attending physician, the study site principal investigator, and the chief investigator (or the secretariat) will be provided in writing and subjects are free to ask questions about the study and treatment

4.4. **Privacy Protection and Patient Identification**

Participating study sites do not provide subjects’ names to the data center. Patients are enrolled into the study using the minimum amount of information, such as gender and patient ID number. The enrollment process uses no medical chart ID numbers or initials of subjects, which can be used to identify individuals. The identification or matching of enrolled subjects is based on the registration number. No subjects’ names or information that allows a third party to identify individuals is included in the database.

As a general rule, with the exception of subject enrollment, the data center and study sites are to exchange subject data by postal mail or direct hand delivery regardless of whether the data are recorded
on paper or electronic medium.

4.5. Protocol Compliance

Investigators who participate in this study shall comply with this study protocol as long as the safety and human rights of subjects are not compromised.

4.6. Approval by Institutional Review Board or Ethics Review Board

Before participating in this study, each institution must submit this study protocol and the written information for the subject to the study site’s IRB or ERB for approval. Upon approval by the IRB or ERB, the principal investigator at each study site sends copies of the written approvals to the data center. The study site retains the originals of the written approvals, and the data center retains the copies.

4.7. Protocol Changes

(1) Classification of protocol changes

Before implementing any protocol change, a “Protocol Revision Application” must be submitted to the efficacy and safety evaluation committee for approval.

For handling purposes, protocol changes are classified into two types: amendment and revision. The head of the efficacy and safety evaluation committee determines the classification of a change. Supplemental information that does not change the protocol is handled as a memorandum.

(i) Amendment

A partial protocol change that may increase the risk to subjects participating in the study or is related to the study’s primary endpoint in useful clinical study results, among other data, obtained during the study period

(ii) Revision

A protocol change that does not increase the risk to subjects participating in the study and is unrelated to the study’s primary endpoint

(iii) Memorandum

Supplemental information to the protocol, distributed by the chief investigator or the study secretariat to relevant parties associated with the study that does not change the protocol but is intended to standardize the interpretation of a certain term or to call for cautions

(2) Approval of a protocol amendment/revision by an IRB or ERB

If an amendment is made during the study to this protocol or the written information for the patient
under the approval of the efficacy and safety evaluation committee, the amendment must be submitted to each study site’s IRB or ERB for approval. When an amendment is approved by the IRB or ERB, the principal investigator at each study site sends a copy of the written approval to the data center. The study site retains the original of the written approval, and the data center retains the copy.

In the event a revision is made, each study site has the discretion to determine whether an approval review by the IRB or ERB is needed.

5. **ENROLLMENT**

5.1 **Study site enrollment**

1) The principal investigator/attending physician at each institution, after obtaining the approval of the study site’s IRB or ERB and before enrolling the first subject at the site, transmits by FAX or e-mail to the data center, a copy of the approval notification form along with a “Site Enrollment Request Form” and a “List of Laboratory Test Reference Values” that have been completed with the required information.

2) The data center registers the institution and the laboratory test reference values and transmits by FAX to the principal investigator/attending physician a “Site Registration Completion Notification” and a “Laboratory Test Reference Values Registration Completion Notification.”

5.2 **Subject enrollment and allocation**

1) The attending physician confirms that the subject selection criteria are met, fills in the required information on the enrollment form, and transmits by FAX to the data center.

2) The data center confirms eligibility based on the enrollment form received.

3) The data center transmits an “Enrollment Result Notification” to the attending physician and the FAX number provided on the enrollment form.

- When the enrollment form for a subject contains information that is incomplete or questionable, the subject will not be enrolled.
- If the enrollment information does not meet the eligibility criteria, the subject will be deemed ineligible, and no registration number will be issued.
- The “enrollment allocation date” provided on the “Enrollment Result Notification” is the day on which the series of enrollment procedures are completed. Transmitting an enrollment form by FAX for a subject to the data center does not complete the enrollment for the subject.
- Promptly contact the data center when there are any questions during enrollment or when it becomes
apparent that a subject is enrolled multiple times or erroneously.

- The attending physician, after confirming the completion of enrollment (that a registration number has been issued), initiates the allocated therapy.

Data Center: Study Secretariat of PREP
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6. TREATMENT PLAN AND MODIFICATION

6.1. Drug Information

For the specifics and handling of study drugs, see their respective package inserts. The study drugs used in this study are as follows. The use of generics is also allowed.

### 6.1.1 Gemcitabine (GEM)

<table>
<thead>
<tr>
<th>Nonproprietary name</th>
<th>Gemcitabine Hydrochloride</th>
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<tr>
<td>Abbreviation</td>
<td>GEM</td>
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<tr>
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<td>![Structural formula image]</td>
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<tr>
<td>Trade name</td>
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<td>Dosage form</td>
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<td>Content</td>
<td>Content of gemcitabine hydrochloride per vial</td>
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<td></td>
<td>228mg</td>
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<td>Storage condition</td>
<td>Store at room temperature</td>
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6.1.2 Tegafur-Gimeracil-Oteracil Potassium Combination Capsules/Granules (S-1)

<table>
<thead>
<tr>
<th>Nonproprietary name</th>
<th>Tegafur-Gimeracil-Oteracil Potassium Combination Capsules/Granules</th>
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</thead>
<tbody>
<tr>
<td>Abbreviation</td>
<td>S-1</td>
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<tr>
<td>Structural formula</td>
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</tr>
<tr>
<td>Trade name</td>
<td>TS1 combination capsules T20, TS1 combination granules T20, TS1 combination capsules T25, TS1 combination granules T25 (Taiho Pharmaceutical Co., Ltd.)</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Hard capsules/granule</td>
</tr>
<tr>
<td>Content</td>
<td>Tegafur, gimeracil, and oteracil potassium contents per capsule/granule 20 mg/5.8 mg/19.6 mg</td>
</tr>
<tr>
<td>Storage condition</td>
<td>Store at room temperature</td>
</tr>
</tbody>
</table>

6.2. Protocol Treatment

After enrollment and allocation, initiate neoadjuvant chemotherapy (GS therapy) within 2 weeks.

Perform surgery (surgical resection). R0/1 resection with M0 (including negative CY) and 2.5 UL<TM is defined as on protocol cohort. Standard adjuvant with GEM (for 6 months) is recommended to administer for on-protocol cohort. Off-protocol cohort is given adequate treatment in each institution.

6.3. Neoadjuvant Chemotherapy: GS Therapy

6.3.1 Schedule of administration

Administer GEM on Days 1 and 8 but not on Day 15 and S-1 by the oral route for 1 week starting from the day of each GEM administration. Such a 3-week course is the standard regimen. The aim is to achieve a total of 4 doses of GEM and 4 weeks of oral administration with S-1 within 8 weeks of initiating the GS therapy. Nonetheless, the protocol therapy should not be discontinued for subjects who failed to achieve the target number of doses within 8
weeks; they are still to undergo surgery. Each dose of GEM (1,000 mg/m$^2$ dissolved in 100 mL of physiological saline) is administered by intravenous drip over 30 minutes. The initial dose of GEM shall be within the range of ±100 mg of the dose calculated from the body surface area. Any correction to the actual dose for body weight changes is up to the discretion of the attending physician. If the administration of GEM cannot take place on the scheduled date due to an issue with the subject’s availability or due to a holiday, it may be administered 1 day before or after the scheduled date. In such cases, do not change or postpone the schedule for the next dose. Refer to Table to determine the initial dose of S-1 based on the body surface area. Divide the daily dose of S-1 into two portions and administer each orally starting from after dinner on the day of GEM administration until after breakfast on Day 8 of GEM administration. During GS therapy, if a subject missed a scheduled dose of S-1 (e.g., forgetting to take a dose), he/she should not subsequently take or attempt to “make up” the missed dose.

**Standard dosing schedule for GS therapy**

<table>
<thead>
<tr>
<th>Body Surface Area</th>
<th>Standard Initial Dose (dose level 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.25 m$^2$</td>
<td>60 mg/day</td>
</tr>
<tr>
<td>≥1.25 m$^2$ to &lt;1.5 m$^2$</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>≥1.5 m$^2$</td>
<td>100 mg/day</td>
</tr>
</tbody>
</table>

**6.3.2 Criteria for initiating GS therapy**

On the day before or the day of the first GEM dose, confirm that the criteria for initiating GS therapy provided in Table are met. When a subject is deemed eligible to begin the therapy, administer the therapeutic drugs. In cases where even one of the criteria is unmet, wait for the laboratory data to recover or symptoms to resolve, then confirm that the criteria are met before initiating therapy.

In cases where the subject is unable to begin therapy despite a postponement of 3 weeks after the date of enrollment/allocation, discontinue the protocol therapy.
### Table Criteria for initiating GS therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>≥3,500/mm$^3$</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>≥2,000/mm$^3$*</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥100,000/mm$^3$</td>
</tr>
<tr>
<td>AST</td>
<td>≤150 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>≤150 U/L</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>≤2.0 mg/dL**</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>≤1.2 mg/dL</td>
</tr>
<tr>
<td>Diarrhea, oral mucositis</td>
<td>≤Grade 1</td>
</tr>
<tr>
<td>Rash</td>
<td>≤Grade 1</td>
</tr>
</tbody>
</table>

* Despite a neutrophil count of <2,000/mm$^3$ (as a general rule, ≥1,500/mm$^3$), a subject may begin therapy at the discretion of the attending physician provided that the white blood cell count is ≥3,500/mm$^3$.

** This criterion is ≤3.0 mg/dL for subjects undergoing biliary drainage for obstructive jaundice. The attending physician also has the discretion to postpone the therapy based on any adverse event other than those described above.

### 6.3.3 Criteria for continuation of dosing

On the day before or the day of the second or a subsequent GEM dose, confirm that all of the criteria for continuation of dosing provided in Table are met. If the criteria are not met, postpone the dose, and cease the administration of both GEM and S-1. If the dose is postponed, reexamine and retest the subject 1 week later. Confirm that the criteria for continuation of dosing are met before resuming the administration of GEM.

In cases where the subject fails to meet the criteria for continuation of dosing for 3 weeks consecutively (failure to meet the criteria for continuation on Day 21 after the day of the last GEM dose), terminate GS therapy and perform surgery within 6 weeks after the day of the last dose of anti-cancer agent. Such cases are not considered a protocol therapy discontinuation. The GS therapy period shall not exceed 8 weeks.
Table Criteria for continuation of dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>≥2,000/mm³ (≤Grade 2)*</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>≥1,000/mm³ (≤Grade 2)**</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥70,000/mm³</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&lt;1.5 mg/dL</td>
</tr>
<tr>
<td>Non-hematotoxicity*</td>
<td>≤Grade 2</td>
</tr>
</tbody>
</table>

*Even if the white blood cell count is slightly below 2,000/mm³, dosing may continue at the discretion of the attending physician if the neutrophil count is ≥1,000/mm³.

**Even if the neutrophil count is slightly below 1,000/mm³, dosing may continue at the discretion of the attending physician if the white blood cell count is ≥2,000/mm³.

**Dosing schedule for GS therapy**

Example 1) The second GEM dose scheduled on Day 8 could not be administered due to Grade 3 AE, but recovery was confirmed a week later. Subsequent progress was without problems and the subject received 4 GEM doses and 4 weeks of S-1 administration.

Example 2) A GEM dose always led to a Grade 3 AE a week later, resulting in doses administered every other week. The dosing was completed in 7 weeks.

Example 3) The GEM dose led to long-term sustained AE even at 3 weeks after 1 dose of GEM and
1-week administration of S-1. GS therapy, thus, was terminated for the subject, who went on to receive surgery. Even if the hematotoxicity improves by Day 57, no GEM dosing should be resumed.

8 weeks

<table>
<thead>
<tr>
<th>GEM</th>
<th>×</th>
<th>×</th>
<th>×</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

Within 6 weeks after the day of the last S-1 oral dose (on Day 8 in this case)

### 6.3.4 Criteria for dose reduction

For subjects who developed any adverse event (Grade 4 hematotoxicity, ≥Grade 3 non-hematotoxicity) corresponding to any of the criteria for dose reduction provided in Table 7-4, the subsequent GEM dose is to be reduced to 800 mg/m². For subjects who developed ≥Grade 3 rash, oral mucositis, loss of appetite, or diarrhea (non-hematotoxicity that are likely attributable to S-1 as well), the subsequent dose of both GEM and S-1 is to be reduced. Reduce the dose of GEM and S-1 to level −1 (by 1 level only); do not increase the dose. For subjects who meet the dose reduction criteria while receiving doses at dose level −1, terminate the GS therapy, and perform surgery within 1 to 6 weeks after the day of the last dose of anti-cancer agent. Such cases are not considered a protocol therapy discontinuation.

| Table Criteria for dose reduction and actions to be taken in case of adverse events |
|----------------------------------|------------------|
| **Hematotoxicity other than platelet count decrease** * |
| Grade | Action to be Taken |
| 1, 2 | Continue dosing |
| 3 | Postpone dosing until recovery to ≤Grade 2 |
| 4 | Postpone dosing until recovery to ≤Grade 2 |
| | Reduce the subsequent GEM doses |
| *Adverse events of “anemia,” “hypocellular marrow,” “lymphocyte count decrease,” “neutrophil count decrease,” “white blood cell count decrease,” “platelet count decrease,” and “CD4 lymphopenia” according to CTCAE v4.0. |

<table>
<thead>
<tr>
<th><strong>Platelet count decrease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion</strong></td>
</tr>
<tr>
<td>≥70,000/mm³</td>
</tr>
<tr>
<td>≥50,000/mm³</td>
</tr>
</tbody>
</table>
**Non-hematotoxicity**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action to be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2</td>
<td>Perform appropriate supportive therapies and continue dosing</td>
</tr>
</tbody>
</table>
| 3     | Perform appropriate supportive therapies and postpone dosing until recovery to ≤ Grade 2  
|       | Reduce subsequent doses |
| 4     | Discontinue the protocol therapy and perform appropriate supportive therapies |

**Adverse events other than “anemia,” “hypocellular marrow,” “lymphocyte count decrease,” “neutrophil count decrease,” “white blood cell count decrease,” “platelet count decrease,” and “CD4 lymphopenia” according to CTCAE v4.0.**

**GEM dose reduction**

<table>
<thead>
<tr>
<th>Level 0 (initial dose)</th>
<th>Level −1 (dose reduction by 1 level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 mg/m²</td>
<td>800 mg/m²</td>
</tr>
</tbody>
</table>

Example 4) The blood sampled on Day 8 showed Grade 3 hematotoxicity, resulting in a postponement. The subject meets the criteria for continuation on Day 15, and GEM and S-1 are administered. The subject developed Grade 4 hematotoxicity on Day 22, resulting in a postponement. On Day 29 the subject meets the criteria for continuation and GEM is administered at a reduced dose of 800 mg/m² (from 1000 mg/m²). The subject developed no subsequent adverse events and moved on to undergo surgery.

6.4. **Pancreatectomy**

Subjects after completion of the neoadjuvant chemotherapy with the GS therapy are evaluated to confirm that all eligibility criteria to receive surgery are met before undergoing the pancreatectomy.
When it is determined that a subject does not meet even one of the criteria before surgery, discontinue the protocol therapy. Although no treatment is specified for subjects for whom the protocol therapy has been discontinued, report the therapies provided on the specified case report form.

6.4.1 Eligibility criteria for pancreatectomy

1) No findings of distant metastasis in an imaging study at the end of GS therapy
2) Macroscopic curable (R0/1-resectable) in an imaging study at the end of GS therapy
3) Tolerable for curative surgery with adequate cardiac, hepatic, renal, and other organ functions
4) No findings of distant metastasis (hepatic metastasis, peritoneal metastasis) during laparotomy or exploratory laparoscopy

6.4.2 Timing of surgery

Perform a radical surgery within 1 to 6 weeks after the day of the last dose of S-1 (preference is for the surgery to be performed between 2 and 4 weeks after the day of the last dose of S-1). If surgery cannot be performed within 6 weeks, discontinue the protocol therapy.

6.4.3 Procedure of Pancreatectomy

Perform an adequate surgery for curative intent that aims to avoid macroscopic residual cancer (R2) and to leave no histologic residual cancer (R0 resection). If curable surgery is performed even with a reduced field of dissection and the reduction is judged to facilitate higher feasibility of the surgery, the field of dissection may be reduced at the discretion of the attending physician.

6.5 Postoperative Adjuvant Chemotherapy: Gemcitabine Monotherapy (On-protocol)

Perform pancreatectomy and confirm that the criteria for curative surgery are met. Administration of standard GEM monotherapy as a postoperative chemotherapy within 10 weeks after surgery is recommended.

6.5.1 Eligibility criteria for postoperative adjuvant chemotherapy

1) R0 or R1 resection achieved
2) Post-surgical tumor marker (CEA, CA19-9) within 2.5 x Upper Normal Limit (within 8 weeks after surgery).
3) Invasive pancreatic ductal adenocarcinoma proven by histopathological exploration of the resected specimens
4) Confirmation of a negative result on cancer cells by a peritoneal lavage cytodiagnosis or an ascites cytodiagnosis
5) Absence of metastases to distant lymph nodes (for example, para-aortic nodes metastases)

### 6.5.2 Method and schedule of administration

![Cycle Schedule Diagram]

Gemcitabine (GEM) at a dose of 1,000mg/m²/week, 3 weeks followed by 1 week rest, is administered for 6 cycles as a standard postoperative adjuvant.

### 6.6. Actions to Take at Discontinuation

Upon discontinuing the protocol therapy, the attending physician records the date of discontinuation, the reason for discontinuation, and other required information on the medical record and the protocol therapy completion report, and forwards the information to the data center. Provide the best intervention if the therapy is discontinued due to an adverse event or if a new adverse event occurs after the completion of therapy.

### 6.7. Prohibited Concomitant Drugs and Therapies

1) Anti-malignant tumor therapy
   During the protocol therapy, except for GEM and S-1, no other chemotherapy, hormone therapy, immunotherapy, antibody therapy, radiation therapy, thermotherapy, or operative treatment that may affect the evaluation in this study is allowed.

2) Investigational/experimental drugs with potential anti-malignant tumor effect

3) Flucytosine

4) Prophylactic administration of G-CSF

### 6.8 Authorized Concomitant Drugs

The concomitant use of drugs other those prohibited for concomitant use and interventions for complications and adverse events are allowed.
(1) Follow the criteria below when administering a G-CSF drug. The preceding shall not apply if the purpose is to ensure subject safety.

(i) Begin administration when a subject with a neutrophil count of <1,000/mm$^3$ develops a fever (temperature $\geq 38.0^\circ$C, as a general rule).

(ii) Begin the administration when the neutrophil count drops to <500/mm$^3$.

(iii) For subjects who have previously received treatment with a G-CSF drug based on one of the above criteria, begin administration the next time neutrophil count drops to <1,000/mm$^3$.

When the neutrophil count recovers to 5,000/mm$^3$ after reaching the lowest level, stop the G-CSF dosing.

(iv) Administer the study drug after an interval of 24 hours or longer following the administration of a G-CSF drug.

(2) Prophylactic treatments with a 5-HT3 receptor antagonist, steroid (e.g., dexamethasone 4–8 mg), or NK-1 receptor antagonist to alleviate nausea or vomiting are permitted.

(3) Drugs may be administered as appropriate to treat complications and adverse events.

(4) The use of opioids such as morphine and fentanyl patch is allowed.

(5) When the use of phenytoin or warfarin potassium is needed after enrollment, administer with care as S-1 may enhance the effect of such drugs.

6.9 Follow-up Treatment

After completion of the protocol treatment, take a wait-and-see approach without further treatment as long as no recurrence or other neoplastic lesions (synchronous or metachronous double cancers) are observed. Although no treatment is specified after the discontinuation of protocol therapy or recurrence, report the administered therapies on the specified case report form.

7. Adverse Events

The following are the major adverse reactions reported in patients with pancreatic cancer in the phase II study of the GEM and S-1 combination therapy (GS therapy) (GEM dose, 1,000 mg/m$^2$; S-1 dose, 80 mg/m$^2$) conducted by the National Cancer Center, and the international multicenter GEST study of the S-1 monotherapy (S-1 dose, 80 mg/m$^2$). The subject (unresectable cancer) of the reference data is more advanced than the subject (resectable cancer) in this study. The incidence and severity of adverse events in this study, therefore, are expected to be less than those in the data shown in the attached table.
Adverse events in phase II study of GS therapy by the National Cancer Center (NCI-CTCv2)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade1-4</th>
<th>Grade3</th>
<th>Grade4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytopenia</td>
<td>54(100%)</td>
<td>31(57%)</td>
<td>1(2%)</td>
</tr>
<tr>
<td>Neutrocytopenia</td>
<td>54(100%)</td>
<td>24(44%)</td>
<td>19(35%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>48(89%)</td>
<td>8(15%)</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>50(93%)</td>
<td>12(22%)</td>
<td>0</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>38(70%)</td>
<td>9(17%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>34(63%)</td>
<td>4(7%)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>35(65%)</td>
<td>4(7%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>33(61%)</td>
<td>3(6%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39(72%)</td>
<td>3(6%)</td>
<td>0</td>
</tr>
<tr>
<td>Infection unaccompanied by neutrophil count decrease</td>
<td>4(7%)</td>
<td>2(4%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17(31%)</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>31(57%)</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>Ileus</td>
<td>1(2%)</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>1(2%)</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>Infection accompanied by Grade 3–4 neutrophil count decrease</td>
<td>1(2%)</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>CNS cerebrovascular ischemia</td>
<td>2(4%)</td>
<td>1(2%)</td>
<td>1(2%)</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>34(63%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20(37%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17(31%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15(28%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>7(13%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>3(6%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

8. OBSERVATIONS, TESTS, SURVEYS, AND THEIR SCHEDULES

8.1. Patient Characteristics (pre-enrollment survey)

Sex, age, height, histological diagnosis or cytology, HBs antigen test, complications, medical history, any biliary drainage

8.2. Pre-enrollment tests and observations

(1) Test within 14 days before enrollment

- Hematological tests: white blood cell count, neutrophil count, hemoglobin level, platelet count
- Biochemical tests: albumin, total bilirubin, AST, ALT, ALP, creatinine, creatinine clearance, Na, K, CRP
- Subjective and objective symptoms and signs: pyrexia, oral mucositis, diarrhea, nausea, vomiting, loss of appetite, rash (maculopapular), fatigue

27
· Body weight, PS
· Tumor markers: CEA, CA19-9, other tumor markers, as needed, such as DUPAN-2*

*If the CA19-9 value is at or below the measurement sensitivity, the subject is likely to be Lewis antigen negative. In such a case, the DUPAN-2 assay is particularly recommended as the CA19-9 value would not reflect the state of disease. Even if all tumor markers are at the normal level before enrollment, scheduled tumor marker tests should still be carried out thereafter.

(2) Test within 28 days before enrollment
· Plain chest radiography or chest CT scan
· Abdominal contrast-enhanced CT scan (MRI also acceptable)** (site occupied by the primary lesion, lesion site, size)

**Perform an abdominal contrast-enhanced CT with a slice width of ≤5 mm. For subjects who have an allergy to iodinated contrast agents, an MRI scan is acceptable. The abdominal CT scan may be started from the chest to include the lung field. The same should apply after enrollment.

**The pre-enrollment pancreatic CT scan preferably should be performed under the recommended conditions with Memorandum 3 as a reference.
· FDG-PET scan (if possible)

8.3. Tests and Observations during Neoadjuvant Chemotherapy (GS therapy)

(1) Tests and observations on the day before or the day of GEM dosing

These observations and tests should also be performed on subjects who discontinued the protocol therapy, within 28 days after the discontinuation (at least once).
· Hematological tests: white blood cell count, neutrophil count, hemoglobin level, platelet count
· Biochemical tests: albumin, total bilirubin, AST, ALT, ALP, creatinine, Na, K
· Subjective and objective symptoms and signs: pyrexia, oral mucositis, diarrhea, nausea, vomiting, loss of appetite, rash (maculopapular), fatigue, febrile neutropenia
· Body weight, PS

(2) Information to be verified during therapy
· Specifics of therapy (day of dosing, dose, any dose delay or reduction)
· Concomitant drug information (any concomitant use, drug names, descriptions of interventions)

8.4. Perioperative Observations

Preoperative observations
For subjects in the control arm, tests performed at the time of enrollment are acceptable. Subjects in the study arm should be evaluated after the neoadjuvant chemotherapy by no later than the day before surgery. Imaging studies used for preoperative evaluation should preferably be performed within 28 days before the day of surgery.

- Hematological tests: white blood cell count, neutrophil count, hemoglobin level, platelet count
- Biochemical tests: albumin, total bilirubin, AST, ALT, ALP, creatinine, Na, K
- Tumor markers: CEA, CA19-9, other tumor markers, as needed, such as DUPAN-2
- Routine chest radiography or chest CT scan
- Abdominal contrast-enhanced CT scan (MRI also acceptable)

**Perioperative observations**
- Surgical procedure
- Duration of procedure
- Volume of operative blood loss
- Peritoneal lavage cytodiagnosis or ascites cytodiagnosis
- Operative and pathological findings

**Postoperative observations**
Follow-up with subjects who underwent surgery regarding the following information:
- Death during postoperative hospital stay or within 60 days postoperative
- Any repeat surgery and a description of the repeat surgery, if any
- Postoperative complications [pancreatic fistula, delayed gastric emptying, hemorrhagic complication, intra-abdominal abscess (including drain infection), wound infection, biliary fistula, gastrointestinal suture insufficiency/stenosis, pneumonia, deep vein thrombosis, cardiovascular disorder, cerebrovascular disorder, or other complications]
- Severity of complication
- Number of days of postoperative hospital stay

**8.5. Tests and Observation during Postoperative Adjuvant Chemotherapy**
(1) Tests and observations to be performed at each outpatient visit (at least once every 2 weeks)
These include the tests and observations to be performed at least once within 28 days after the
protocol therapy completion.

- Hematological tests: white blood cell count, neutrophil count, hemoglobin level, platelet count
- Biochemical tests: albumin, total bilirubin, AST, ALT, ALP, creatinine, Na, K
- Subjective and objective symptoms and signs: pyrexia, oral mucositis, diarrhea, nausea, vomiting, loss of appetite, rash (maculopapular), fatigue
- Body weight, PS

(2) Information to be verified during therapy

- Specifics of therapy (day of dosing, dose, any dose delay or reduction)
- Concomitant drugs information (any concomitant use, drug names, description of interventions)

(3) Perform at least once every 3 months

- Plain chest radiography or chest CT scan
- Abdominal contrast-enhanced CT scan (MRI also acceptable)
- Tumor markers: CEA, CA19-9, other tumor markers, if necessary, such as DUPAN-2

8.6. Evaluation for Recurrence

In the 1 year after surgery, perform imaging diagnoses such as CT and tumor marker test at least once every 3 months until recurrence is confirmed, to investigate whether any recurrent lesions are present. If recurrence is suspected but not confirmed, perform additional imaging diagnosis (e.g., diffusion-weighted MRI or FDG-PET) at the discretion of the attending physician. This study does not specify the interval of tests after recurrence; it is left to the discretion of the attending physician.

- Plain chest radiography or chest CT scan
- Abdominal contrast-enhanced CT scan (MRI also acceptable)
- Tumor markers: CEA, CA19-9, other tumor markers, if necessary, such as DUPAN-2
- Any follow-up treatment and a description of the follow-up treatment, if any

9. ADVERSE EVENTS REPORTING AND ACTIONS TO TAKE

9.1. Actions to Take in Response to Adverse Events

The principal investigator or the attending physician at each study site, upon confirmation of an adverse event, administers appropriate interventions to the subject and reports the event on the case report form. As a general rule, the attending physician follows-up with the subject to the extent possible, irrespective of study drug causality, until the adverse event resolves or the pre-dosing condition is restored. The preceding shall not apply, however, if the follow-up is made difficult because the symptoms
become chronic due to worsening primary disease or complications, or because the subject has transferred to another hospital or begun follow-up treatments.

9.2. **Actions to Take in Response to Serious Adverse Event**

Upon the occurrence of a “serious adverse event” or “unexpected adverse event,” the study site’s principal investigator or attending physician reports the event to the chief investigator and/or the study secretariat.

The principal investigator at each study site bears the responsibility, as mandated by the medical institution, of filing a report to the study site’s head of medical institution, a voluntary report by a medical institution to the Pharmaceutical and Food Affairs Bureau, Ministry of Health, Labour and Welfare according to the MHLW “Pharmaceutical Safety Information Reporting System,” or a voluntary report by a medical institution to a pharmaceutical company through the “Safety Reporting System by Pharmaceutical Companies” based on the Pharmaceutical Affairs Act.

9.3. **Adverse events subject to immediate reporting requirement**

Adverse events that correspond to any of the following categories are subject to the immediate reporting requirement.

1) Any death during the protocol therapy or within 30 days after the last day of the protocol therapy

   Report any such deaths irrespective of whether it is causally related to the protocol therapy. Even for subjects who had discontinued the protocol therapy and begun follow-up treatment, any death within 30 days after the last day of the protocol therapy is subject to the immediate reporting requirement (the term “30 days” refers to 30 days counting from the day after the last day of the protocol therapy, which is Day 0).

2) Any unexpected Grade 4 non-hematotoxicity (adverse event other than those classified under blood/bone marrow in CTCAE v4.0-JCOG)

3) Any unexpected ≥Grade 4 (requiring ICU care) perioperative complication (except events specifically described under Section 8.4 Perioperative Observations) according to Clavien’s classification

9.4. **Adverse events subject to the normal reporting requirement**

Adverse events that correspond to any of the following categories are subject to the normal reporting requirement.

1) Any death more than 30 days after the last day of the protocol therapy for which a causal relationship cannot be ruled out
A suspected treatment-related death is an example that corresponds to this category. Any apparent death from the primary disease does not correspond to this category.

2) Any expected Grade 4 non-hematotoxicity (adverse event other than those classified under blood/bone marrow in CTCAE v4.0-JCOG)

3) Any unexpected Grade 2 or 3 adverse event

4) Any other medically important event
   Adverse event during chemotherapy that requires inpatient hospital care
   Permanent or marked impairment (e.g., aplastic anemia, myelodysplastic syndrome, secondary cancer)
   Any other event considered important information that should be shared with the chief investigator and research groups at all study sites

9.5. Reporting duty of principal investigator at study site and reporting procedure

A study site’s principal investigator or attending physician enters the required information on an “Adverse Event Report Form” and transmits it by FAX to the chief investigator and/or the study secretariat within 72 hours of learning of an adverse event subject to the immediate reporting requirement, or within 15 days after an adverse event subject to the normal reporting requirement.

9.6. Responsibilities of principal investigator/study secretariat

1) Determine whether cessation of enrollment and emergency notification to study sites are needed.

   After receiving a report from a study site’s principal investigator or attending physician, the chief investigator or his representative determines the urgency, importance, and extent of impact of the reported information and takes measures, as appropriate, such as temporary cessation of enrollment (notifying the data center and all participating study sites) or sends an urgent notification of the information to participating study sites. The data center and study sites may be contacted by phone depending on the degree of urgency; in such cases, a written notification (FAX, postal mail, E-mail) should be sent afterward as soon as possible.

2) Report to the efficacy and safety evaluation committee

   If the adverse event reported by a study site in an immediate report or normal report is deemed an “adverse event subject to reporting requirement,” the chief investigator and/or the study secretariat reports the event in writing (FAX, postal mail, E-mail) to the efficacy and safety evaluation committee within 15 days of learning about the occurrence of the adverse event and at the same time requests a review on the
chief investigator’s opinion regarding the event and the justification of actions taken in response to the event. The efficacy and safety evaluation committee notifies the chief investigator of its opinions in writing.

10. OUTCOME MEASUREMENT

(1) Adverse event:

Compile the worst grade by adverse event during therapy for each subject.

(2) Overall survival (OS):

OS is the time from the date of enrollment/allocation to death by any cause. For surviving subjects, OS ends on the last day on which survival was confirmed. For subjects lost to follow-up, OS ends on the last day on which survival was confirmed before lost to follow-up.

(3) Recurrence-free survival (RFS):

RFS is the time from the date of enrollment/allocation to recurrence. For subjects who died (regardless of the cause of death) before the confirmation of recurrence, RFS ends on the day of death. However, all-cause deaths may be included as events and analyzed separately.

Recurrence includes both those determined based on imaging diagnosis and those determined based on worsening condition without imaging diagnosis (clinical recurrence). The date of recurrence is the date on which the imaging study was performed if the recurrence is based on imaging diagnosis, or the date on which the clinical decision was made if the recurrence is a clinical recurrence. An elevated tumor marker level does not indicate recurrence. The date of recurrence is the date of the imaging diagnosis that confirms recurrence or the date on which clinical recurrence is determined based on worsening condition. Do not diagnose recurrence by reexamining past imaging studies or other findings.

If the diagnosis of recurrence is confirmed by a pathological examination of biopsied specimens, the day of recurrence is the day of clinical diagnosis if the clinical recurrence is diagnosable prior to the biopsy, or the day of the biopsy if the recurrence is not diagnosable clinically and is diagnosed based on a pathological examination of biopsied specimens.

(4) Resection rate:
Resection rate = total number of resected subjects/total number of treated subjects

(5) Residual tumor classification (R):
Calculate the percentage of residual tumor classification (R) by study allocation arm.
The attending physician at each study site determines whether a resection is R0, R1, or R2 based on
the perioperative macroscopic findings and the postoperative histopathological exploration of the
resected specimens. When resecting the retroperitoneum or nerve plexus during surgery, it is
necessary to submit the stump for a perioperative pathological test, or observe the resected specimen
and mark the incision surface with a dye to conduct a more accurate pathological examination
concerning residual cancer classification.
Even with a positive peritoneal lavage cytodiagnosis or periaortic lymph node metastasis, local
resection may still be possible provided that there are no other non-resectable factors. R0/R1
determination should be based on a histopathological exploration as described above.

(6) Lymph node metastasis rate:
Based on operative findings, determine the percentage of subjects with positive lymph node
metastasis.

(7) Histological response (pathological response):
Perform post-resection histopathological explorations using the Oboshi-Shimosato classification or
the Evans classification. The histopathology review committee performs a central review of the
pathological preparations from the submitted resected specimens to confirm the extent of response
(extent of tumor destruction or necrosis).

(8) Tumor markers:
Calculate the tumor marker response rate and the tumor marker normalization rate after resection
from the CA19-9 (or DUPAN-2) values.

Rate of response to neoadjuvant chemotherapy (study arm only) =
(Pre-enrollment value – post-neoadjuvant therapy value)/pre-enrollment value

Normalization rate after resection (both arms) =
(Number of normalized subjects 3 to 8 weeks post-resection)/(total number of resected subjects)
*If the CA19-9 value is at or below the measurement sensitivity, the subject is likely to be Lewis antigen negative. In such a case, use the DUPAN-2 assay for evaluation.

Even if all tumor marker levels are within the range of reference values at the study site, as a general rule, the assay should continue to be performed, and the tumor marker response rate and the tumor marker normalization rate after resection should be calculated. However, if all are within the range of the reference value but there is an increased level of another tumor marker (e.g., Span-1) that increases with pancreatic cancer, it is acceptable to perform assays at each of the above mentioned time points and include the calculation of the tumor marker response rate and the tumor marker normalization rate after resection based on the normal upper limit.

(9) Treatment dose intensity (dose intensity):
The dose intensity of preoperative GS therapy is determined for GEM and S-1 individually based on 100% of the planned dose calculated from the body surface area. The dose intensity of the preoperative GS therapy is the mean of the dose intensities calculated for each drug.

A) The planned GEM dose (100% dose intensity) = 4,000 mg/m²

B) The planned S-1 dose (100% dose intensity)

<table>
<thead>
<tr>
<th>Body Surface Area</th>
<th>Standard Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.25 m²</td>
<td>1680 mg = 60 mg × 28 days</td>
</tr>
<tr>
<td>≥1.25 m² to &lt;1.5 m²</td>
<td>2240 mg = 80 mg × 28 days</td>
</tr>
<tr>
<td>≥1.5 m²</td>
<td>2800 mg = 100 mg × 28 days</td>
</tr>
</tbody>
</table>

Calculate the dose intensity of postoperative adjuvant chemotherapy (monotherapy) according to the first dose, with 11,200 mg/body (= 100 mg/body/day × 28 × 4), 8,960 mg/body (= 80 mg/body/day × 28 × 4), or 6,720 mg/body (= 60 mg/body/day × 28 × 4) as 100%, from the actual postoperative dose.

(10) Recurrence pattern (patterns of recurrence):
Compile the percentage of each recurrence pattern (local recurrence, distant metastatic recurrence).

(11) Radiological response rate (Tumor shrinkage rate):
Calculate the tumor shrinkage rate attributable to the neoadjuvant chemotherapy. The imaging review committee performs central reviews to determine tumor sizes.

Tumor shrinkage rate = (Tumor size at enrollment – post-neoadjuvant chemotherapy tumor size)/tumor
11. STATISTICS

Analysis populations are defined as follows.

1) Full analysis set (FAS): This population includes all enrolled subjects excluding those who are ineligible. The final decision on ineligibility requires a consensus within a study group.

2) Per protocol set (PPS): This population includes all enrolled subjects who received a partial or complete protocol therapy.

3) On-protocol cohort: This population includes subjects for R0/1-resected with M0 and sufficient recovery after surgery. Post-surgical TM must be within <2.5 times the upper normal limit.

4) Off-protocol cohort: This population is defined as PPS excluding on-protocol subjects.

All eligible patients were included in the intention-to-treat (ITT) population for efficacy analyses. The primary endpoint was the 2-year OS of the ITT population and on-protocol patients. The historical 2-year survival of up-front surgery followed by standard adjuvant gemcitabine was 47.5% (CONKO-01 study).

The sample size calculation was based on the assumption that the 2-year OS of on-protocol patients (R0/1 resection with M0, postoperative CA19-9 ≤2.5 times ULN, and sufficient recovery within 10 weeks after surgery) would be 45% (null survival probability) to 65% (alternative survival probability). A sample size of 41 on-protocol patients was required to detect an improvement in 2-year OS, with a bilateral 5% type I error and a power of 90%. A total sample size of 90 patients was required, assuming: 1) 30% unresectability including M1; 2) 10% sustained elevation of CA19-9 at >2.5 times the ULN; and 3) 15% insufficient recovery after surgery. OS was defined as the duration from provision of written consent to the protocol to death, and was estimated using the Kaplan-Meier method, with Greenwood's formula used to calculate the standard error of the Kaplan-Meier estimate and the 95% confidence interval. For patients who underwent resection, recurrence-free survival was defined as the time from surgery to first recurrence (local, distant or both) or death, whichever occurred first. Variables were compared using Student’s t-test by JMP version 10.0 software (SAS Inc. Cary, NC, USA).
12. STUDY DISCONTINUATION/INTERUPTION AND COMPLETION

12.1. Discontinuation or Interruption of the Study All or in Part

The Data and Safety Monitoring Committee appropriately assesses the justification for continuing the study. If any situation arises that requires the discontinuation or interruption of the study in part or in whole, the committee issues a recommendation to this study organization on whether to discontinue or interrupt the study. Once a decision is made to discontinue or interrupt the study in compliance with the recommendation, the principal investigator promptly notifies the principal investigator at every institution involved. If a modification of the written information for the patient is deemed necessary, the principal investigator at each study site promptly amends or revises the written information based on the information and submits it to the head of the institution performing the study to obtain the approval of the study site’s review committee members.

12.2. Completion of the Overall Study

After the completion of the study, the Principal investigator notifies the principal investigator at each institution of the completion of the study.

13. MONITORING AND AUDITS

13.1. Periodic Monitoring

As a general rule, conduct periodic monitoring twice annually to verify whether the study is being conducted safely and in accordance with the protocol as well as whether data are being collected correctly. Conduct central monitoring based on data entered into the CRFs that have been collected by the data center; no study-site monitoring, including collation with the raw data by study site visits, will be conducted. The data center prepares and submits periodic monitoring reports to the study secretariat, the principal investigator, and the Data and Safety Monitoring Committee for review.

13.2. Items to Monitoring

(1) Status of achieving the target sample size
(2) Eligibility: ineligible subjects/potential ineligibility
(3) Serious adverse events
(4) Protocol deviations
(5) Any other issues concerning study progress and safety
13.3. **Protocol Deviations and Violations**

Any therapies such as drug administration or surgical resection, laboratory tests, or safety or efficacy evaluations performed without complying with the protocol are considered deviations.

(1) Violation

Unless otherwise specified, protocol deviations corresponding to any of the following items are considered violations.

- Having an impact on end-point evaluations in the study
- Attributable to the attending physician or the study site
- Intentional or systematic
- Dangerous or marked deviation
- Clinically inappropriate

(2) Deviation

Any deviation that corresponds to neither a violation under (1) nor the acceptable deviation under (3)

(3) Acceptable deviation

Each study group sets its own acceptable deviations either ahead of time or afterward.

Do not record deviations that have been established as acceptable in monitoring reports.

14. **STUDY ORGANIZATION**

This study is a multicenter study organized by the Study Group of Preoperative Therapy for Pancreatic Cancer (PREP).

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5. Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University
6. Department of Surgery, Kindai University Faculty of Medicine
7. Department of Surgery, Nara Medical University
8. Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University

14.4. **Data and Safety Monitoring Committee:**
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Ko Miura MD, Miyagi Cancer Center

14.5. **Data Center:** Division of Surgery and Oncology, Tohoku University
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APPENDIX

Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

A. Introduction

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for physicians and other participants in medical research involving human subjects, including research on identifiable human material and data. It is the duty of the physician to promote and safeguard the health of patients. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”

Medical progress is based on research that ultimately must include studies involving human subjects.

In medical research involving human subjects, the well-being of the individual research subject must take precedence over the interests of science and society. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic, and therapeutic interventions. Even the preventive, diagnostic, and therapeutic interventions that have been proven the best must be evaluated continually through research for their efficacy, effectiveness, efficiency, and quality. In current medical practice and in medical research, most preventive, diagnostic and therapeutic interventions involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. Special needs must be recognized for those who are economically and medically disadvantaged. These include those who cannot give or refuse consent for themselves, those who may be vulnerable to coercion or undue influence, those who do not benefit personally from the research, and those whose care is tied to the research.

Physicians should consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable
international norms and standards. No national ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. Basic Principles for All Medical Research

It is the duty of physicians who participate in medical research to protect the life, health, privacy, and dignity of research subjects. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. Appropriate caution must be exercised in the conduct of medical research that may harm the environment, and the welfare of animals used for research must be respected.

The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol must be submitted to a specifically named ethics review committee for discussion, comment, guidance, and, as appropriate, approval. This committee must be independent from the investigator, sponsor, and any other people who may have an undue influence. The independent committee must comply with the laws and regulations of the country or countries in which the research is to be performed. The committee has the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. The researcher must report to the committee for review information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, and incentives for subjects. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed.

Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications and requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the research subjects or third parties.
This does not exclude the participation of healthy volunteers in medical research. All research protocol must be made accessible to the general public.

Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects. This is particularly important in studies where the subjects are healthy volunteers. Medical research is considered justified only if the study population stands a reasonable chance to benefit from the results of the research.

Participation by competent individuals as subjects in medical research must be voluntary and informed. The right to protect a research subject’s integrity must be respected at all times. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental, and social integrity.

In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the potential subject has understood the information, the physician must then seek the potential subject’s freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

When seeking informed consent on a research project, the physician must pay particular attention to whether the research subject is dependent on the physician or whether there is a potential of coerced consent. If there is a risk of such a relationship or coerced consent, the informed consent must be obtained by a physician who is independent from such a relationship, well-informed of the research, and who has no involvement in the research.
For research involving subjects who are legally, physically, or mentally incapable of giving consent, or minors who are legally incapable of giving consent, the researcher must seek informed consent from the legally authorized representative under applicable laws. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject and the research cannot instead be performed with competent persons. When a potential research subject such as a minor who is deemed incompetent is able to give assent to decisions about participation in research, the researcher must seek that assent in addition to the consent of the legally authorized representative.

Research involving individual subjects who are incapable of giving consent, including the unavailability of consent by the legally authorized representative or a prior consent, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by the review committee. The protocol must state that consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

Authors and publishers have ethical obligations with regard to the publication of the results of research. Authors are accountable for the accuracy of their reports when publishing results of research. Negative as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations, and all potential conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic, or therapeutic value. In such cases, further standards to protect the subject as a patient apply.

The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best current proven preventive, diagnostic, and therapeutic
interventions. The use of placebo, or no treatment, however, is acceptable in studies where no current proven preventive, diagnostic, and therapeutic interventions exist.

At the conclusion of the study, all subjects entered into the study are entitled to access to the preventive, diagnostic, and therapeutic interventions proven the best in the study. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven preventive, diagnostic, and therapeutic interventions do not exist or have been ineffective, the physician, with informed consent from the patient, may use an unproven or new preventive, diagnostic, or therapeutic intervention if in the physician’s judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available. Other relevant guidelines must also be complied with in this section.