

JASPAC 01

Pharma Valley Center Clinical Research Development Project

Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)

Protocol for comparative phase III trial of gemcitabine versus S-1 as adjuvant chemotherapy in patients with resected pancreatic cancer

Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer

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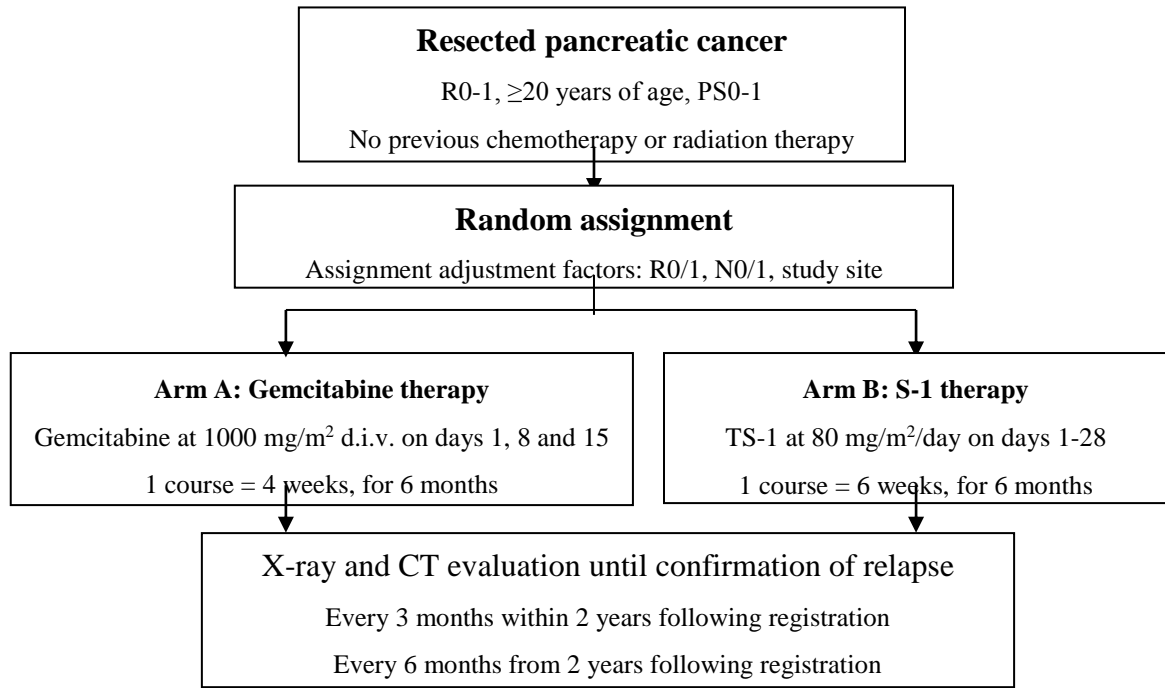
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0. Synopsis

0.1. Outline



0.2. Objectives

To verify in terms of overall survival the non-inferiority of S-1 therapy against gemcitabine therapy as adjuvant chemotherapy after resected pancreatic cancer.

Primary Endpoint: Overall survival

Secondary Endpoints: Incidence of adverse events, relapse-free survival, health-related quality of life (HRQOL)

0.3. Subjects

- 1) Patients with resected pancreatic cancer that was a histologically verified invasive ductal carcinoma of the pancreas (based on Classification of Pancreatic Carcinoma 5th Edition²¹, but excluding cystadenocarcinoma).
- 2) Patients with macroscopic total resection of the primary tumor, and residual primary tumor that satisfies all of the below according to the UICC 6th Edition²² histopathologic staging system.
 - Stage II or lower, or stage III where resection included the celiac artery
 - Local residual tumor classified as R0 or R1
 - Cytologic examination negative upon intraoperative peritoneal lavage
- 3) Absence of distant metastases and malignant ascites
- 4) Adequate oral intake is possible
- 5) Age of 20 years or above
- 6) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1
- 7) Absence of chemotherapy or radiotherapy within past 3 years
- 8) Within 10 weeks following resection of pancreatic cancer
- 9) Major organ functions adequately conserved as shown below (bone marrow, lungs, kidneys)
Satisfies all the criteria below in measurements taken from 7 days prior to registration
 - White blood cell count: $\geq 3,000/\text{mm}^3$, $\leq 12,000/\text{mm}^3$
 - Platelet count: $\geq 100,000/\text{mm}^3$
 - Hemoglobin: ≥ 8.0 g/dL
 - Total bilirubin: ≤ 2.0 mg/dL
 - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT): ≤ 100 IU/L
 - Serum creatinine: ≤ 1.2 mg/dL
- 10) Written informed consent given

0.4. Treatment

Arm A: Gemcitabine therapy

Gemcitabine at 1000 mg/m² d.i.v. Administered on days 1, 8 and 15. One course = 4 weeks.

Treatment for 6 months or until confirmation of recurrence

Arm B: S-1 therapy

TS-1 at 80mg/m²/day. Administered on days 1-28. One course = 6 weeks.

Four courses of treatment or until confirmation of recurrence

0.5. Planned number of registered patients and study period

Planned number of registered patients: 360.

Registration period: 3 years and 3 months. Follow-up period: 5 years after end of registration (by June 30th 2015). Review period after follow-up period: 1 year. Total study period: 9 years 3 months.

0.6. Contact details

Matters that require clinical judgment, such as eligibility criteria and criteria for change of treatment: Study administrators (Cover page, 17.2)

Registration procedure, filling records forms (case report forms), etc.: Study administrators (Cover page, 17.2), CSPOR data center (17.7)

Adverse event reports: Study administrators/study representative, CSPOR data center (17.7)

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1. Objectives

To verify the non-inferiority of S-1 therapy against gemcitabine as adjuvant chemotherapy for resected pancreatic cancer in terms of overall survival.

Primary Endpoint: Overall survival

Secondary Endpoints: Incidence of adverse events, relapse-free survival, health-related quality of life (HRQOL)

2. Background and rationale for the study plan

2.1. Target disease

The number of deaths caused by pancreatic cancer is increasing every year in Japan, with approximately 23,000 deaths caused by pancreatic cancer in 2005. This accounts for 7.0% of deaths caused by cancer in Japan, placing it 5th among causes of cancer death after lung, stomach, colon and liver cancers¹.

Although surgical resection is the only curative treatment option for pancreatic cancer, only approximately 10-20% of cases are resectable²⁻³. Even when resection is performed, there is a reported 95% rate of recurrence within 2 years of surgery⁴, a median overall survival of 11-16.9 months and a 5-year survival rate of just 8-18%⁵⁻⁹. Development of a more effective, multimodal treatment is necessary as resection alone provides limited results in terms of therapeutic outcome.

2.2. Standard treatments for the target disease

Postoperative adjuvant therapies have been developed to improve treatment outcomes for resected pancreatic cancers.

The first prospective study of adjuvant radiochemotherapy for pancreatic cancer (GITSG 9173) reported an improvement in overall survival in a group given combined 5-Fluorouracil (5-FU) and concurrent radiotherapy compared to an observation group (MST: 20 months compared to 11 months, $P = 0.03$)⁵. This study was terminated, however, after less than half of the planned registered subjects was reached after a significant improvement in overall survival was observed at an interim analysis, and due to the time required for patient accrual. Furthermore, because many subjects deviated from the prescribed treatment in the study and 5-FU administration was continued for 2 years after ending radiochemotherapy, there were doubts as to the clinical significance of adjuvant radiochemotherapy shown in this study. Acknowledging the results of this study, a large-scale comparative study (EORTC) that limited the duration 5-FU treatment to the duration of radiotherapy and was a well-managed study of good quality observed no significant difference in overall survival between a combined 5-FU and radiotherapy group and an observation group (MST: 17.1 months and 12.6 months, $P = 0.099$)⁶.

Another study compared an adjuvant chemotherapy of combined 5-FU, doxorubicin and mitomycin C (FAM) with just observation, reporting an improvement in overall survival in the FAM group over the observation group (MST: 23 months and 11 months, $P = 0.02$). However, in this study no difference in the 2-year survival rate was observed (2-year survival rate: 43% and 32%, $P = 0.10$) and severe toxicity was observed in the FAM group⁷.

Another large-scale study (ESPAC-1) investigated both adjuvant chemotherapy and adjuvant radiochemotherapy, dividing subjects into a concomitant 5-FU and radiotherapy group (1), chemotherapy (5-FU and folonic acid) group (2), combined therapy ((2) following (1)) group (3), and observation group (4). Overall survival was improved in patients who received any chemotherapy (groups (2) and (3)) over those who received no chemotherapy (groups (1) and (4)) (MST: 20.1 months and 15.5 months, $P = 0.009$), while overall survival was inferior in patients who received radiochemotherapy (groups (1) and (3)) compared to those who received no radiochemotherapy (groups (2) and (4)) (MST: 15.9 months and 17.9 months, $P = 0.05$)⁸. However, there was probably bias in the results of this study since it employed a complex method of examination, there was no significant difference in overall survival between the individual groups, and it was possible to choose what kind of comparison was examined (radiochemotherapy only and chemotherapy only).

Gemcitabine (GEM) started to be used in studies of postoperative adjuvant therapies in 1997, when it was shown that GEM was significantly more beneficial than 5-FU for the treatment of patients with unresectable advanced pancreatic cancers and distant metastases¹⁰. In the 2006 ASCO Annual Meeting, a study was reported that compared the administration of GEM or 5-FU before

and after concomitant 5-FU and radiotherapy (RTOG-9704), and improved overall survival using GEM treatment over 5-FU treatment was only found in patients with pancreatic head cancer (MST: 20.6 months and 16.9 months, $P = 0.33$)¹¹. A study published in January 2007 that compared adjuvant chemotherapy using GEM and just observation (CONKO-001) reported an improvement in relapse-free survival in the GEM group (DFS: 13.4 months compared with 6.9 months, $P < 0.001$)¹².

Currently ongoing is a study that compares GEM therapy, 5-FU + folinic acid therapy and observation (ESPAC-3) and a study that compares GEM therapy only and combined GEM and radiotherapy (EORTC-40013). The ESPAC-3 study terminated its observation group based on the results of the ESPAC-1 study, so that both the above ESPAC-3 and EORTC-40013 studies have no observation group and are using GEM as the control group.

2.3. Protocol treatments

2.3.1. Drugs

a) Gemcitabine (Generic name: Gemzar®)

Gemcitabine is classified as an antimetabolite anticancer agent. It is metabolized intracellularly to gemcitabine triphosphate and inhibits DNA synthesis. The concentration of gemcitabine triphosphate is maintained intracellularly for a long period and it exhibits a strong cytotoxic action against solid cancer¹³⁻¹⁵. In Japan, its use for non-small cell lung cancer, pancreatic cancer and biliary tract cancer is approved for health insurance coverage.

b) S-1 (Generic name: TS-1®)

S-1 is an oral fluorinated pyrimidine anticancer drug that contains tegafur (FT, a prodrug of 5-FU), gimeracil (CDHP, an inhibitor of the enzyme that degrades 5-FU) and oteracil potassium (Oxo, phosphorylation inhibitor). Including gimeracil and oteracil potassium increases the maximum concentration of 5-FU in the blood, enhancing its antitumor effect and mitigating its gastrointestinal toxicity¹⁶⁻¹⁸. In Japan, its use for gastric cancer, head and neck cancer, colorectal cancer, non-small cell lung cancer, inoperable or recurrent breast cancer and pancreatic cancer is approved for health insurance coverage.

2.3.2. Treatment regimen

a) Gemcitabine therapy

The dosage and administration approved in Japan will be used. That is, “1,000 mg/m² administered by 30-minute intravenous infusion, administered once per week for 3 weeks, followed by a 1-week rest period.”

In a phase I trial conducted in Japan¹⁹, the dosage was fixed at 1,000 mg/m² and escalated via two administration schedules. Dose-limiting toxicity (DLT) was not observed during administration schedule 1 (1,000 mg/m²/30 minutes/once per week for 3 weeks, followed by a 1-week rest period). Out of 6 patients on administration schedule 2 (1,000 mg/m²/30 minutes/once per week for 7 weeks followed by a 1-week rest period, then administration for 3 weeks followed by a 1-week rest period thereafter) one patient experienced grade 4 leukocytopenia and grade 4 neutropenia, and one patient experienced grade 4 neutropenia and grade 3 hepatic dysfunction. Administration schedule 1 was chosen as the standard dosage and administration. Adverse events of grade 3 or higher observed in the trial were leukocytopenia, neutropenia, anorexia, fatigue and nausea/vomiting.

Of 384 patients administered gemcitabine monotherapy in Japanese clinical studies, the main adverse drug reactions observed in a safety population including 369 patients have been leukocytopenia (68.0%), neutropenia (61.8%), erythropenia (58.8%), hemoglobin decreased (66.4%), platelets decreased (32.2%), anorexia (45.5%), nausea/vomiting (40.1%), ALT increased (33.5%), pyrexia (32.2%), fatigue (31.2%) and AST increased (30.1%).

b) S-1 therapy

The dosage and administration approved in Japan will be used. That is, “A standard dosage of 80

mg/m²/day, with a daily dosage of 80 mg/day b.i.d. for a body surface area of <1.25 m², 100 mg/day b.i.d. for ≥1.25 m² and <1.5 m², and 120 mg/day b.i.d. for ≥1.5 m², to be administered orally after breakfast and after evening meal. A single course consists of 28 days of administration, followed by a 14-day rest period. This course is then repeated.”

The antitumor effects obtained in a phase II study conducted in Japan²⁰ were CR in 0 patients, PR in 19, MR in 4, NC in 17, PD in 18 and NE in 1, with a response rate of 32.2% (19/59 patients). Adverse drug reactions considered clinically significant that occurred in the 59 patients for whom adverse drug reactions were evaluable were leukocytopenia (32.2%), neutropenia (27.1%), hemoglobin decreased (50.8%), platelets decreased (33.9%), AT increased (18.6%), ALT increased (16.9%), anorexia (61.0%), nausea (55.9%), vomiting (35.6%), diarrhea (37.3%), general malaise (47.5%), stomatitis (25.4%) pigmentation (39.0%) and rash (22.0%).

2.4. Rationale for the study plan

2.4.1. Rationale for the study design

As stated in section 2.2. “Standard treatments for the target disease”, although there is no standard adjuvant therapy for resected pancreatic cancer, there is a global consensus that such an adjuvant therapy is necessary. In phase III studies, GEM has been shown to be significantly superior to 5-FU for the treatment of advanced pancreatic cancer⁹, with good results as an adjuvant therapy also reported¹¹⁻¹², gradually affirming its role as a standard treatment. As for S-1, the mitigated gastrointestinal toxicity and increased maximum blood concentration of 5-FU provided by S-1 promise an enhanced antitumor effect, and a high response rate of 32.2% has been reported with S-1 in a Japanese phase II study¹⁹. Consequently, S-1 is expected to have an equivalent or better effect compared to GEM as an adjuvant chemotherapy. Oral administration also makes S-1 simpler to implement. This trial positions gemcitabine therapy as a standard adjuvant chemotherapy for resected pancreatic cancer, and seeks to verify the non-inferiority of S-1 therapy against gemcitabine therapy in terms of overall survival.

2.4.2. Rationale for selection of evaluation endpoints

2.4.2.1. Primary endpoint

Overall survival is the fundamental objective of postoperative adjuvant chemotherapy, and was chosen as the primary endpoint of this study.

2.4.2.2. Secondary endpoints

Incidence of adverse events, relapse-free survival and HRQOL are possible criteria for determining whether to select GEM therapy or S-1 therapy in the event of equivalent results in terms of the primary endpoint, and were chosen as the secondary endpoints of this study.

2.4.3. Selection of the target population and rationale for selection of assignment adjustment factors

How target populations and assignment adjustment factors were selected has differed in each past and ongoing phase III study, including those mentioned in section 2.2. “Standard treatments for the target disease”.

- Local residual tumor classification (R): Although opinion is divided on whether R1 patients (residual tumor present upon pathological investigation) are a suitable target for adjuvant chemotherapy, both R0 and R1 patients have been used in many clinical studies outside of Japan, and since this study does not include an untreated arm, R1 patients will be included in this study. There are many reports noting local residual tumor classification as a prognostic factor, and as such it was chosen as an assignment adjustment factor.
- Histology: Although some studies have included papillary carcinoma and histologies of

pancreatic cancer (acinar cell carcinoma, cystadenocarcinoma, etc.) other than pancreatic cancer (adenocarcinoma), as these are regarded as separate diseases with different prognoses, this study will only target invasive ductal carcinoma of the pancreas according to Classification of Pancreatic Carcinoma 5th edition (excluding cystadenocarcinoma). Accordingly, intraductal tumor-derived invasive carcinomas are included, but microinvasive carcinomas are not.

- PS: Although many studies include patients with PS from 0-2, due to the likely obstacle PS2 patients would pose to an investigation of the effects of chemotherapy, PS0 and PS1 patients were chosen as the target of this study.
- Lymph node metastasis (N): This is regarded as a prognostic factor and will be included as an assignment adjustment factor.
- Study sites: This is a multicenter study, and variables such as patient background, medical treatment and the like may differ between study sites. Study site has been added as an assignment adjustment factor.

2.4.4. Clinical hypothesis and rationale for number of registered patients

A hazard ratio threshold of 1.25 will be used to verify the non-inferiority of the S-1 arm against the GEM arm in terms of overall survival. Specifically, applying the proportional hazard model, non-inferiority will be verified if the 95% confidence interval of the S-1 arm to GEM arm death hazard ratio does not exceed 1.25. The quality-adjusted life year (QALY), which takes HRQOL into account, will also be calculated and compared between treatment arms. The clinical hypothesis is that the outcome in the S-1 arm is verifiably non-inferior in terms of overall survival and statistically significantly better in terms of QALY than the GEM arm.

As will be stated in detail in section 13.2 “Scheduled number of registrations and follow-up period”, with a true S-1 arm to GEM arm hazard ratio of 1/1.15 and a statistical power of 80%, a total of 240 events (deaths) are required across the treatment arms to verify non-inferiority. The ongoing progress of a study comparing a GEM arm and observation arm (CONKO-001) reported at the 2006 ASCO Annual Meeting stated a 3-year survival rate of 36% in the GEM arm and 21% in an observation arm. Consequently, 36% will be selected as the 3-year survival rate for the GEM arm (based on the above hypothesis, the anticipated 3-year survival rate in the S-1 arm is 41%). An exponential distribution was assumed for the survival function, and presuming 360 patients are registered evenly across both treatment arms during the 3 years, the expected incidence of events at 1 and 2 years after registration is 191 and 237 events, respectively. From the above, with 360 patient registrations, the interim analysis will be performed at 1 year after the end of registration when there is anticipated to be 180 events, and final analysis will be performed at 2 years after the end of registration. (Upon reporting of the final results of the CONKO-001 study in January 2007 the 3-year survival rate had changed to 34% in the GEM arm and 20.5% in the observation arm. This drives up the expected incidence of events by only 3%, which was not deemed significant enough to cause a change in the current study plan.)

Note that the results of the above calculations are strongly dependent on the value of the base 3-year survival rate (36%) and the exponentiality of the survival distribution. Because of differences in patient selection resulting from the inclusion/exclusion criteria, differences in the patient population itself, and survival benefits that are expected to result from posttreatment with S-1 and gemcitabine, the actual number of events may be expected to be fewer than the number anticipated. Furthermore, it is not definite that registration will proceed as planned. Consequently, incidence of events will be monitored during and after registration and examined again at both interim and final analyses.

2.4.5. Expected patient accrual

A questionnaire survey was sent to each facility planning to participate in the study to discover the expected annual patient accrual of each study site. The result was a possible overall annual registration of at least 150 patients. Because this is the first time these a multicenter clinical study of pancreatic cancer will be conducted in these facilities, the actual number of patients they can register is likely to be significantly lower than expected. Consequently, the expected number of registrations was deemed to be approximately 120 patients/year, or 360 patients registered over 3 years.

2.5. Summary of anticipated benefits and disadvantages of participation in the study

2.5.1. Anticipated benefits

The drugs used in this study (gemcitabine and S-1) are approved for health insurance coverage and the treatment methods employed in this study are performed as normal medical practice covered by health insurance. In addition, because all medical treatment costs, including drug costs, incurred during the study period will either be borne by patients' health insurance or as out-of-pocket payments, participation in this study will provide the participant with no special medical or financial benefit compared to normal medical treatment.

2.5.2. Anticipated risks and disadvantages

The main adverse events participants are likely to experience are those cited in section 2.3.2. of this protocol. Treatment will be provided within the dose ranges printed in the package inserts for gemcitabine and S-1, and appropriate supportive therapy (preventive administration of antiemetics, G-CSF, etc.) provided if adverse events are observed. Upon observation of a serious adverse event, utmost effort will be taken to enact safety measures including prompt examination of the entire treatment arm and informing the Efficacy and Safety Evaluation Committee.

In order to minimize the potential risks and disadvantages of adverse events, matters such as patient selection criteria, criteria for treatment change and concomitant therapy/supportive therapy will be examined carefully within each treatment arm. Costs associated with the treatment of injury to health caused by this clinical study will, as a general rule, be borne by the patient or be subject to health insurance coverage if applicable.

2.6. Significance of this study

With reporting of the final results of CONKO-001 a global consensus was reached on the use of gemcitabine as an adjuvant therapy, while the use of gemcitabine as adjuvant therapy is spreading in general medical practice in Japan. Meanwhile, in a Japanese phase II study a high response rate has been reported for S-1 therapy. S-1 is an oral drug that is easy to administer that has an efficacy anticipated to be equivalent to or better than gemcitabine. S-1 is believed to be clinically significant enough to deserve further elucidation of the results of this phase II study.

2.7. Ancillary research

No ancillary research is planned for the start of this study (April 2007). Any ancillary research undertaken after the start of this study will be conducted according to the provisions below.

- (1) Ancillary research that uses only data obtained in the course of this study in full or in part (a data package where personal information on registered patients is masked) will be conducted after the preparation of a separate study protocol and subsequent approval by the Steering Committee and Efficacy and Safety Evaluation Committee.
- (2) Ancillary research that adds new personal information on registered patients to all or some of the data obtained in the course of this study (genetic analysis, etc.) will be conducted after the preparation of a separate study protocol and subsequent approval by the Ethics Review Board (ERB) of each participating study site.

3. Standards and definitions used in this study

The histology of pancreatic cancers will be classified according to Classification of Pancreatic Carcinoma 5th edition²¹, and histopathological staging and regional lymph node definitions will follow the UICC 6th edition²².

3.1. Histology classification

*: Targets of this study are underlined.

(1) Epithelial tumors

A. Exocrine tumors

1. Serous cystic tumors
 - a) Serous cystadenoma
 - b) Serous cystadenocarcinoma
2. Mucinous cystic tumors
 - a) Mucinous cystadenoma
 - b) Mucinous cystadenocarcinoma
3. Intraductal tumors
 - 1) Intraductal papillary-mucinous tumors
 - a) Intraductal papillary-mucinous adenoma
 - b) Intraductal papillary-mucinous carcinoma
 - 2) Intraductal tubular tumor
 - a) Intraductal tubular adenoma
 - b) Intraductal tubular carcinoma
4. Atypical hyperplasia and carcinoma in situ
5. Invasive ductal carcinoma
 - a) Papillary adenocarcinoma
 - b) Tubular adenocarcinoma
 - c) Adenosquamous carcinoma
 - d) Mucinous carcinoma
 - e) Anaplastic carcinoma
 - f) Invasive mucinous cystadenocarcinoma
 - g) Intraductal tumor-derived invasive carcinoma
6. Acinar cell tumors
 - a) Acinar cell adenoma
 - b) Acinar cell adenocarcinoma

B. Endocrine tumors

C. Combined tumors

D. Epithelial tumors of uncertain differentiation

- a) Solid-pseudopapillary tumor
- b) Pancreatoblastoma
- c) Undifferentiated carcinoma

E. Unclassifiable

F. Others

(2) Nonepithelial tumors

- Hemangioma
- Lymphangioma
- Leiomyosarcoma
- Malignant fibrous histiocyoma
- Malignant lymphoma
- Paraganglioma
- Others

3.2. Cancer staging

The below cancer staging of the UICC 6th edition will be used.

| | | N0 | N1 |
|----|-----|-----|-----|
| M0 | Tis | 0 | |
| | T1 | IA | IIB |
| | T2 | IB | IIB |
| | T3 | IIA | IIB |
| | T4 | III | III |
| M1 | | IV | IV |

1) Local tumor

Tis: Carcinoma in situ

T1: Tumor limited to pancreas, 2 cm or less in greatest dimension

T2: Tumor limited to pancreas, more than 2 cm in greatest dimension

T3: Tumor extends beyond pancreas, but without involvement of celiac axis or superior mesenteric artery

T4: Tumor involves celiac axis or superior mesenteric artery

2) Lymph node metastasis

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

3) Distant metastasis

M0: No distant metastasis

M1: Distant metastasis

3.3. Regional lymph nodes

The definition of regional lymph nodes in the UICC 6th edition²² will be used. These definitions are equivalent to the lymph node numbers of the Classification of Pancreatic Carcinoma 5th edition as shown below.

| | UICC 6th edition | Classification of Pancreatic Carcinoma 5th edition |
|----------------|--|--|
| Superior: | Superior to pancreatic head Superior to pancreatic body | 17a, 13a, 12a, 12b, 12p, 12h, 8a, 8p, 11p |
| Inferior: | Inferior to pancreatic head Inferior to pancreatic body | 17b, 13b 18 |
| Anterior: | Anterior pancreaticoduodenal, pyloris (for tumors of head only), and proximal superior mesenteric artery | 17a, 17b 5, 6 14p, 14d |
| Posterior: | Posterior pancreaticoduodenal, common bile duct, and proximal superior mesenteric artery | 13a, 13b 12b 14p, 14d |
| Splenic: | Hilum of spleen and tail of pancreas (for tumors of body and tail only) | 10, 11d |
| Celiac artery: | (for tumors of head only) | 9*, 7 |

*: Because the target of this study is patients with stage II or lower, or stage III where resection included the celiac artery according to the UICC 6th edition²² staging system, lymph node metastases will include regional lymph nodes. Consequently, the lesions below are judged to be distant metastases and not targets of the study. However, though #9 is a pancreatic body-tail lesion, it was judged appropriate to include it among regional lymph nodes and it shall not be considered a distant metastasis.

Distant metastatic lymph nodes

Pancreatic head lesion : 10, 11d, 15, 16

Pancreatic body-tail lesion : 5, 6, 7, 15, 16

Pancreatic lesion : 15, 16

4. Patient selection criteria

4.1. Eligibility criteria (enrolment criteria)

- 1) Patients with a resected pancreatic cancer that was a histologically verified invasive ductal carcinoma of the pancreas (based on Classification of Pancreatic Carcinoma 5th edition²¹, excluding cystadenocarcinoma)
- 2) Patients with a macroscopic total resection of the primary tumor, and residual primary tumor that satisfies all of the items below according to the UICC 6th edition²² histopathologic staging system
 - Stage II or lower, or stage III where resection included the celiac artery
 - Local residual tumor classified as R0 or R1
 - Cytologic examination negative upon intraoperative peritoneal lavage
- 3) Absence of distant metastases and malignant ascites
- 4) Adequate oral intake is possible
- 5) Age of 20 years or above
- 6) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1
- 7) Absence of chemotherapy or radiotherapy within past 3 years
- 8) Within 10 weeks following resection of pancreatic cancer
- 9) Major organ functions adequately conserved as shown below (bone marrow, lungs, kidneys)
Satisfies all the criteria below in measurements taken from 7 days prior to registration.
 - White blood cell count: $\geq 3,000/\text{mm}^3$, $\leq 12,000/\text{mm}^3$
 - Platelet count: $\geq 100,000/\text{mm}^3$
 - Hemoglobin: ≥ 8.0 g/dL
 - Total bilirubin: ≤ 2.0 mg/dL
 - AST and ALT: ≤ 100 IU/L
 - Serum creatinine: ≤ 1.2 mg/dL
- 10) Written informed consent given

4.2. Exclusion criteria

- 1) Patient has been treated with gemcitabine or S-1
- 2) Recurrence confirmed upon investigations conducted prior to registration
*Cases where the tumor marker has not fully declined or where only mild ascites is observed upon CT are not deemed recurrence.
- 3) Moderate or more severe pleural effusion or ascites upon chest X-ray and abdominal CT
- 4) Pulmonary fibrosis or interstitial pneumonia clearly observed in plain chest X-ray findings
- 5) Inadequately controlled watery diarrhea
*Whether a patient has diarrhea 4 or more times a day while receiving adequate supportive therapy will be used as the indicator to determine whether watery diarrhea is inadequately controlled.
- 6) Heart failure of Class III (Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.) or Class IV (Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.) according to the New York Heart Association functional classification
- 7) Myocardial infarction within 6 months following onset of pancreatic cancer
- 8) An active infectious disease (pyrexia of 38°C or higher, etc.) (excluding viral hepatitis)
- 9) Inadequately controlled diabetes mellitus
*Fasting blood sugar ≥ 200 mg/dl, HbA1c ≥ 10.0 , etc. will be used by investigators as indicators to determine whether diabetes mellitus is inadequately controlled. HbA1c measurements are not required if a judgment can be made using fasting and postprandial blood sugar measurement.
- 10) Blood transfusion required within 2 weeks prior to registration
- 11) Other serious complications (heart failure, kidney failure, liver failure, active peptic ulcer, paresis of intestine, etc.)
- 12) Participation in the study by the patient is judged difficult due to a complicating psychiatric disorder or psychological symptoms
- 13) Serious drug allergy
- 14) Active multiple primary cancers (synchronous multiple primary cancer or within 3 years of a disease-free period following unsynchronous multiple primary cancer)
- 15) Pregnant or breast feeding woman, woman of childbearing potential, or woman who is willing to bear children or desires to bear children
- 16) Man who is willing to conceive a child
- 17) Using flucytosine, phenytoin or warfarin potassium
- 18) An investigator judges participation to be incompatible with the safe conduct of the study

5. Registration and assignment

5.1. Registration procedure

Target patients will be confirmed to satisfy all eligibility criteria and no exclusion criteria, and after completing all required sections of a case report form (CRF), the CRF will be sent by fax to the CSPOR data center.

Contact details and reception times for patient registration

CSPOR data center (within NPO Japan Clinical Research Support Unit)

Tel 03-3254-8029

Fax 03-5298-8536

Weekdays: 10am-5pm

(Not open on national holidays, weekends and from December 29 to January

3)

Contact relating to patient selection criteria

Study administrator Akira Fukutomi

Chief Physician, Department of Gastrointestinal Medicine, Shizuoka Cancer

Center

1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777

Tel 055-989-5222

Fax 055-989-5634

E-mail a.fukutomi@scchr.jp

5.1.1. Notes on registration

- 1) Registration after commencement of protocol treatment is not permitted in any circumstance.
- 2) Registration will not be acknowledged until all details/necessary sections of the CRF have been completed.
- 3) The CSPOR data center will confirm patient eligibility, and after assigning an eligible patient to a treatment arm based on the assignment adjustment factors in section 5.2. of this protocol, will issue a registration number and a Registration Confirmation Form (RCF).
- 4) The CSPOR data center will fax the RCF to the fax number of the investigator noted in the CRF. Patients will be deemed registered by the sending of this RCF. RCFs will be retained by each study site.
- 5) Excluding cases of patient withdrawal of consent that include refusing the use of data for research, once registered, patient registration will not be reversed (deleted from the database). In the event of registration duplication, the antecedent registration information (registration number) will be used.
- 6) Discovery of registrations made in error or duplicate registrations will be promptly reported to the CSPOR data center.
- 7) Study sites will be responsible for calculating body surface area and drug dose. (See protocol section 6.1.2.)

5.2. Random assignment and assignment adjustment factors

Upon registration, patients will be randomly assigned to a treatment arm by the CSPOR data center.

During random assignment, to prevent any major imbalance between treatment arms the minimization method will be employed using (1) R(0 vs.1), (2) N(0 vs. 1) and (3) study site as adjustment factors. Detailed procedures on the random assignment method used will not be disclosed to researchers at participating study sites.

5.3. Reporting of registration confirmation and the pre-treatment report

Investigators will confirm patient registration by receipt of the RCF sent by fax from the CSPOR data center. Data management in this study will be performed using an electronic data capture (EDC) system using the PDF file format (the system will be sent by post to participating study sites on removable USB drives). After confirming patient registration, an investigator or clinical research coordinator (CRC) will simultaneously insert into a PC a USB drive containing the EDC system and a USB drive to be used for backup (both sent by the CSPOR data center), start the EDC system, open the CRF (in PDF file format) from the opened browser, and enter the registration number together with the necessary data into the pre-treatment report for the registered, eligible patient. After that, the investigator or CRC will promptly copy the CRF (the pre-treatment report into which the necessary data has been entered that is in PDF file format) from the backup USB drive to another USB drive that is to be used for data submission, and post the data submission USB drive to the CSPOR data center by a prescribed method.

A patient's pre-treatment report will be posted to the CSPOR data center in the same way even if treatment is not started within 15 days of registration and assignment as prescribed.

6. Treatment plan and treatment change criteria

Treatment and changes to treatment will be implemented as described in this section, unless such implementation threatens the safety of the patient.

In cases where following the protocol is judged medically dangerous, treatment changes will be implemented according to the medical judgment of the investigator. These are protocol deviations, but will be regarded as medically appropriate deviations. (See protocol section 14.1.2 “Protocol deviations and violations”.)

6.1. Protocol treatment

Protocol treatment will be started within 15 days of registration.

If treatment is not started within 15 days of registration for a particular reason, that reason will be entered into a records form (comments section of the progress report). If it has been decided that treatment cannot be started, the details of this decision will be entered into the treatment end report as “Protocol treatment discontinued”.

6.1.1. Drugs used

a) Gemcitabine (Ely Lilly: Gemzar®)

200 mg/Vial, 1 g/Vial 200mg, 1g/Vial

200 mg/Vial and 1 g/Vial preparations will be used after dilution in at least 5 ml and 25 ml of physiological saline, respectively.

b) S-1 (Taiho Pharmaceutical: TS-1®)

20 mg/capsule, 25 mg/capsule

Postprandial oral administration, b.i.d.

6.1.2. Administration method

Study sites will be responsible for calculating body surface area and drug dose. Dose corrections made to address changes in body weight after starting treatment will be left to the judgment of each study site.

a) Gemcitabine therapy

- 1,000 mg/m² administered by 30-minute intravenous infusion. (Dose calculated according to body surface area, rounded off to the nearest 100 mg/body.)
- Administered once weekly for 3 weeks, followed by a 1-week rest period.
- Once course lasts 4 weeks and is repeated.

b) S-1 therapy

- 80 mg/m²/day (see initial doses below) b.i.d., taken after breakfast and evening meal.
- Administered daily for 28 days, followed by a 14-day rest period.
- One course lasts 6 weeks and is repeated.

S-1 initial doses

| Body surface area | S-1 initial dose | Morning/Noon/Evening |
|--|---------------------------|----------------------|
| <1.25m ² | 80 mg (20 mg cap ×4)/day | 2 – 0 - 2 |
| ≥1.25m ² , <1.5m ² | 100 mg (25 mg cap ×4)/day | 2 – 0 - 2 |
| ≥1.5m ² | 120 mg (20 mg cap ×6)/day | 3 – 0 - 3 |

6.2. Criteria for protocol treatment completion and discontinuation

6.2.1. Definition of protocol treatment completion

- a) Gemcitabine (Eli Lilly: Gemzar®)
 - Gemcitabine therapy is completed after 6 months. Specifically, the course ongoing at 6 months after starting gemcitabine therapy will be the final course. (A new course will not be started after 6 months has passed.)
- b) S-1 (Toho Pharmaceutical: TS-1®)
 - S-1 therapy is completed after 4 courses.

6.2.2. Criteria for discontinuation of protocol treatment

Adjuvant chemotherapy will be discontinued if any of the below conditions is met.

- 1) Recurrence is confirmed by diagnostic imaging that includes CT, or recurrence is determined clinically^{Note)}
- 2) For gemcitabine therapy, administration could not be started by 28 days after the final administration date
- 3) For gemcitabine therapy, toxicity that meets criteria for dose reduction occurs after the dose has already been reduced to Level 2 after criteria for dose reduction were met
- 4) For S-1 therapy, administration could not be started by 14 days after the scheduled course start date
- 5) For S-1 therapy, toxicity that meets criteria for dose reduction occurs after the dose has already been reduced to Level 1 after criteria for dose reduction were met
- 6) An adverse event that can cause serious sequela, such as interstitial pneumonia
- 7) Continuation of medical examinations has become problematic due to patient circumstances such as moving house, change of physician, being too busy, etc.
- 8) Patient requests to discontinue protocol treatment
- 9) Other cases an investigator finds discontinuation necessary

Note)

- Recurrence will not be diagnosed based on changed symptoms or an increase in tumor markers only. A diagnosis of recurrence requires imaged findings to support the diagnosis.
- As shown below, recurrence will not be diagnosed if doubts remain regarding the imaged findings. Detailed examination will be conducted by further diagnostic imaging or follow-up observation.

| | |
|--------------------------------------|--|
| Tiny hepatic lesion upon CT, etc. | Difficult to differentiate between metastases to liver and liver abscess |
| Lymph nodes enlarged | Difficult to differentiate between metastases to lymph nodes and inflammatory adenopathy |
| Increase of a local soft-tissue mass | Difficult to differentiate between local recurrence and inflammation-induced scarring |
| Ascites | Difficult to differentiate between peritoneal nodules and carcinomatous peritonitis not accompanied by mesenteric thickening |

- The date of recurrence will be date a definite diagnosis of recurrence was made. The date of recurrence will not be changed retroactively upon reexamination of imaged findings, etc.

6.3. Treatment change criteria

The following terminology will be used with respect to change criteria. (Common to both treatment arms.)

Discontinuation: End of ongoing protocol treatment. No possibility of restarting treatment.

Postponement: Delay of the start of a treatment course or of administration of a study drug past the scheduled date.

Dose interruption: Temporary stoppage of treatment, with the possibility of restarting treatment during an ongoing course.

Dose suspension: Temporary stoppage of treatment, with no possibility of restarting treatment during an ongoing course but a possibility of restarting protocol treatment continuing on from the following course.

Skip: Proceeding to the next administration schedule without giving treatment.

6.3.1. Arm A: Treatment change criteria for gemcitabine therapy

6.3.1.1. Course start criteria

The first dose of each treatment course will be started from the scheduled start date or the day before the scheduled start date, after all of the below-described course start criteria have been satisfied. If any of the course start criteria are not satisfied, course start (the first dose) will be delayed by increments of 1 day to 1 week.

If administration is not started by 28 days after the date of final administration, the protocol treatment will be discontinued.

If the third dose of a course (day 15) is skipped, day 22 (± 2 days) will become the scheduled start date of the next course of treatment (day 1 of the next course).

Course start criteria for gemcitabine therapy

- 1) White blood cell count: $\geq 3,000/\text{mm}^3$
- 2) Platelet count: $\geq 100,000/\text{mm}^3$
- 3) Hemoglobin: $\geq 6.5 \text{ g/dL}$
- 4) Total bilirubin $\leq 3 \text{ mg/dL}$
- 5) AST (GOT): $\leq 150 \text{ IU/L}$
- 6) AST(GPT): $\leq 150 \text{ IU/L}$
- 7) No pyrexia of 38°C or above
- 8) No inadequately controlled diarrhea
- 9) No other non-hematological toxicity of Grade 2 or greater for which an investigator judges administration inappropriate

6.3.1.2. Criteria for skipping second (day 8) or third (day 15)

The second dose (day 8) or third dose (day 15) to be given on the scheduled date of administration or the day before the scheduled date of administration will be skipped if any of the adverse events shown below in “Criteria for skipping second (day 8) or third (day 15) dose” is observed.

Criteria for skipping second (day 8) or third (day 15) dose

- 1) White blood cell count: $< 2,000/\text{mm}^3$
- 2) Platelet count: $< 70,000/\text{mm}^3$
- 3) Total bilirubin: $> 3 \text{ mg/dL}$
- 4) AST(GOT): $> 150 \text{ IU/L}$
- 5) ALT(GPT): $> 150 \text{ IU/L}$
- 6) Pyrexia of 38°C or above
- 7) Development of inadequately controlled diarrhea
- 8) Another non-hematological toxicity of Grade 2 or greater for which an investigator judges administration inappropriate

* The date of the second (day 8) and third (day 15) administrations may be changed by ± 2 days. A minimum of 5 days interval will be provided after the previous administration.

* If a long period of national holiday or the like does not allow administration even when the above-allowed changes to the date of administration are applied, administration will be delayed by a maximum of 7 days. In the event of such a delay, the next administration date will be decided as shown below.

| |
|---|
| Delay of second administration → Third administration performed 7 days after (± 2 days) |
| Delay of third administration → First administration of next course performed 14 days after (± 2 days) |

6.3.1.3. Criteria for dose reduction

If any of the below dose reduction criteria is met, the dose level of the next administration will be reduced by one level. The dose will be reduced by a single level irrespective of whether 2 or more of the below dose reduction criteria is met. The dose will not be increased once the dose has been reduced. If criteria are met for dose reduction after the dose has already been reduced to level -2, protocol treatment will be discontinued.

Dose levels

| Drug | Dose level | Dose | |
|------|--------------------|-----------------------------|---|
| GEM | Level 1 (all) | 1000 mg/m ² /day | First (day 1), second (day 8), third (day 15) |
| | Level -1 (minus 1) | 800 mg/m ² /day | First (day 1), second (day 8), third (day 15) |
| | Level -2 (minus 2) | 600 mg/m ² /day | First (day 1), second (day 8), third (day 15) |

Gemcitabine therapy dose reduction criteria

- 1) White blood cell count <1,000/mm³
- 2) Platelet count <25,000/mm³
- 3) Platelet transfusion required*
- 4) Second (day 8) administration skipped
- 5) Third (day 15) administration skipped, AND unable to start next course on day 22 (±2 days)
- 6) Unable to start administration within 14 days after the date of final administration

*: Satisfaction of this criterion will not be based on whether a platelet transfusion is actually performed, but based on the clinical judgement as to whether a platelet transfusion should be performed.

6.3.1.4. Schedule change

If the normal course of 3-week administration and 1-week rest is changed to a course of 2-week administration and 1-week rest on two consecutive courses due to a skipped dose, later courses may be administered using the 2-week administration and 1-week rest schedule. However, if criteria are then satisfied for dose reduction, in addition to reducing the dose level the treatment course will be returned to 3-week administration and 1-week rest.

6.3.2. Arm B: Treatment change criteria for S-1 therapy

6.3.2.1. Course start criteria

The first dose of each treatment course will be started from the scheduled start date or the day before the scheduled start date, after all of the below-described course start criteria have been satisfied. If any of the course start criteria are not satisfied, course start (the first dose) will be delayed by increments of 1 day to 1 week.

If administration is not started by 14 days after the date of final administration, the protocol treatment will be discontinued.

If the period of administration of the previous course has been delayed due to dose interruption, the next course may be started within 2 weeks of the date of final administration of the previous course, providing all the course start criteria have been satisfied.

After dose suspension in the previous course, the next course may be started within 6 weeks of the previous course providing all the course start criteria have been satisfied.

There will be an interval of at least 1 week between the date of final administration of the previous course and the start of the next course.

Course start criteria for S-1 therapy

- 1) White blood cell count: $\geq 3,000/\text{mm}^3$
- 2) Platelet count: $\geq 100,000/\text{mm}^3$
- 3) Hemoglobin: ≥ 6.5 g/dL
- 4) Total bilirubin: ≤ 3 mg/dL
- 5) AST (GOT): ≤ 150 IU/L
- 6) ALT (GPT): ≤ 150 IU/L
- 7) Serum creatinine: ≤ 1.5 mg/dL
- 8) No pyrexia of 38°C or above
- 9) No inadequately controlled diarrhea
- 10) No other non-hematological toxicity of Grade 2 or greater where an investigator judges administration to be inappropriate

6.3.2.2. Dose interruption criteria

Study drug administration will be interrupted if any of the below adverse events is observed.

S-1 therapy dose interruption criteria

- 1) White blood cell count: $<2,000/\text{mm}^3$
- 2) Platelet count: $<50,000/\text{mm}^3$
- 3) Total bilirubin: $>3 \text{ mg/dL}$
- 4) AST (GOT): $>150 \text{ IU/L}$
- 5) ALT (GPT): $>150 \text{ IU/L}$
- 6) Serum creatinine: $>1.5 \text{ mg/dL}$
- 7) Pyrexia of 38°C or above
- 8) Development of inadequately controlled diarrhea
- 9) Another non-hematological toxicity of Grade 2 or greater an investigator judges requires dose interruption

Note

- Dose interruptions will not be implemented by the judgment of the patient herself/himself. Make sure that patients always contact the investigator or an agent of the investigator for instructions first.
- If a patient does not take the study drug for any reason other than those described above, such as forgetting to take a drug or deciding not to take the drug, this will not be regarded as a dose interruption (to be handled as ongoing continued treatment).
- When a dose interruption enacted by the judgment of the patient herself/himself is identified that satisfies any of the above dose interruption criteria, it will be regarded as a dose interruption.
- Although hospital visits normally occur every 2 weeks, after a dose interruption the onset of adverse events will be checked within 8 days of interrupting the dose, if possible.
- It is desirable to check for adverse events once weekly during the first course of treatment.

6.3.2.3. Criteria for restarting treatment after dose interruption

After a first dose interruption, administration will be promptly restarted if all the criteria below are satisfied.

A second dose interruption will be treated as a dose suspension, upon which administration will not be performed within the same course (see criteria for dose suspension).

Administration will be continued even after a restart of treatment occurring after day 28. The treatment that was to be given within the 28-day course of treatment will be completed.

Criteria for restarting treatment after dose interruption for S-1 therapy

- 1) White blood cell count: $\geq 2,800/\text{mm}^3$
- 2) Platelet count: $\geq 70,000/\text{mm}^3$
- 3) Total bilirubin: $\leq 1.5 \text{ mg/dL}$
- 4) AST (GOT): $\leq 150 \text{ IU/L}$
- 5) ALT (GPT): $\leq 150 \text{ IU/L}$
- 6) Serum creatinine: $\leq 1.5 \text{ mg/dL}$
- 7) No pyrexia of 38°C or above
- 8) No inadequately controlled diarrhea
- 9) All non-hematological toxicities that became the reason for dose interruption improved to Grade 1 or below

6.3.2.4. Dose suspension criteria

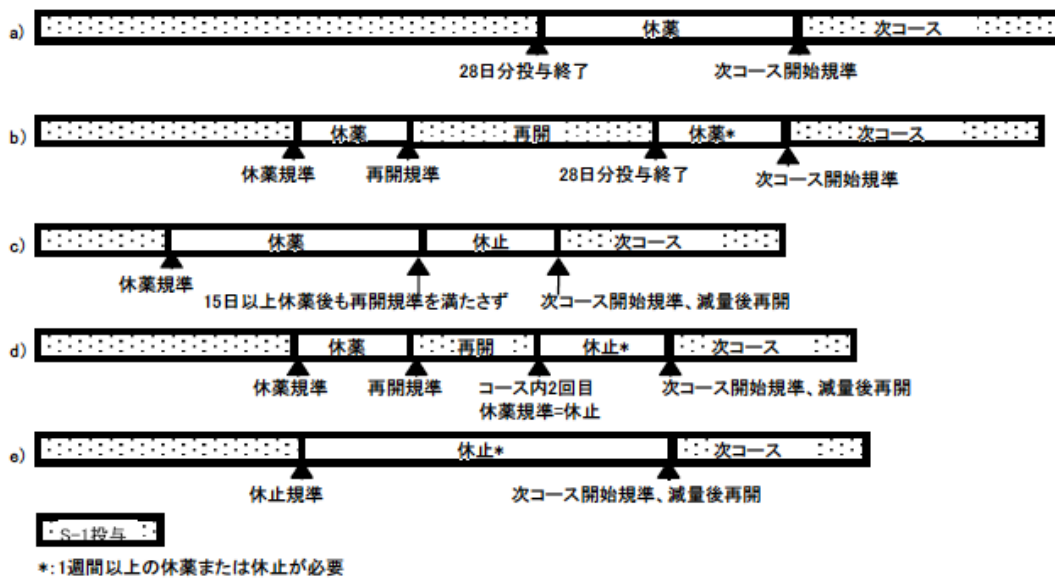
If any of the adverse events below are observed all further administration will be suspended for the ongoing course of treatment.

Dose suspension criteria for S-1 therapy

- 1) White blood cell count: $<1,000/\text{mm}^3$
 - 2) Platelet count: $>25,000/\text{mm}^3$
 - 3) Platelet transfusion required*
 - 4) Hemoglobin: $<6.5 \text{ g/dL}$
 - 5) Non-hematological toxicity of Grade 3 or above
 - 6) Neurological disorder, such as leukoencephalopathy, of Grade 2 or above
 - 7) After dose interruption, no improvement to satisfy criteria for restarting administration within 15 days
 - 8) Dose interruption needed twice within a single course due to adverse events
- *: Satisfaction of this criterion will not be based on whether a platelet transfusion is actually performed, but based on the clinical judgement as to whether a platelet transfusion should be performed.

Note

- If an adverse event does not improve within 8 days of dose suspension, the adverse event will be checked again within 15 days for its improvement, continuation or exacerbation.
- After dose suspension, the next course of treatment will be started with a reduced dose (see section 6.3.2.5.).



| | |
|----------|---------------------------------------|
| 28日分投与終了 | End of 28 days of administration |
| 休薬 | Dose interruption |
| 次コース開始規準 | Criteria for starting next course met |
| 次コース | Next course |
| 休薬規準 | Dose interruption criteria met |

| | |
|--------------------|---|
| 再開規準 | Criteria for restarting treatment met |
| 再開 | Restart |
| 15日以上休薬後も再開規準を満たさず | Criteria for restart not satisfied within 15 days of dose interruption |
| 休止 | Dose suspension |
| 次コース開始規準、減量後再開 | Criteria for starting next course met, restart after dose reduction |
| コース内2回目休薬規準=休止 | Criteria for dose interruption met for second time within single course = dose suspension |
| 休止規準 | Dose suspension criteria met |
| S-1投与 | S-1 administration |
| *:1週間以上の休薬または休止が必要 | *: Dose interruption for 1 week or more, or dose suspension required |

6.3.2.5. Dose reduction criteria

After dose suspension, the next course of treatment will be reduced to dose level -1. There will be no dose increase after a dose reduction. If a criterion for dose suspension is satisfied again after a reduction to level -1, the protocol treatment will be discontinued.

Dose level

| Drug | Dose level | Dose | | |
|------|---------------------|-----------------|-----------------|----------------|
| S-1 | Level 0 (all doses) | 120 mg/body/day | 100 mg/body/day | 80 mg/body/day |
| | Level -1 (minus 1) | 100 mg/body/day | 80 mg/body/day | 50 mg/body/day |

Breakdown of doses after dose reduction

| Body surface area | Dose after S-1 dose reduction | Morning/Noon/Evening |
|--|-------------------------------|----------------------|
| <1.25m ² | 50mg (25 mg cap ×2)/day | 1 – 0 - 1 |
| ≥1.25m ² , <1.5m ² | 80mg (20 mg cap ×4)/day | 2 – 0 - 2 |
| ≥1.5m ² | 100mg (25 mg cap ×4)/day | 2 – 0 - 2 |

6.3.3. Consultations related to treatment changes

Please contact section 16.2. “Study administrators” if there are any questions regarding changes to treatment.

Study administrator contact: Akira Fukutomi

Department of Gastrointestinal Medicine, Shizuoka Cancer Center
 1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777
 Tel 055-989-5222
 Fax 055-989-5634
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6.4. Concomitant therapies/Supportive therapies

6.4.1. Recommended and non-recommended concomitant therapies and supportive therapies

The below are recommended concomitant/supportive therapies. Non-implementation of these therapies will not be regarded as a protocol deviation.

(1) G-CSF

G-CSF will be administered in accordance with its coverage under health insurance as shown in the table below. G-CSF will not be administered preventively.

| | |
|------------------------------|--|
| Timing of start of treatment | <ul style="list-style-type: none"> • When pyrexia (as a general rule, 38°C or higher) is observed with a neutrophil count of <math><1000/\text{mm}^3</math> • When a neutrophil count of 500/mm³ is observed • If, during the previous course, pyrexia (as a general rule, 38°C or higher) and a neutrophil count of <math><1000/\text{mm}^3</math> or if a neutrophil count of 500/mm³ were observed, when a neutrophil count of <math><1000/\text{mm}^3</math> is observed after administering the same chemotherapy |
| Dosage and administration | <ul style="list-style-type: none"> • Filgrastim: Subcutaneous injection of 50 µg/m² q.d. • Nartograstim: Subcutaneous injection of 1 µg/kg q.d. • Lenograstim: Subcutaneous injection of 2 µg/kg q.d. |
| Timing of discontinuation | <ul style="list-style-type: none"> • Administration will be stopped when the neutrophil count reaches 5000/mm³ or greater after reaching its lowest value. • Stopping or reducing the dose will be reviewed if the neutrophil count recovers to 2000/mm³ or greater, there are no symptoms that cause suspicion of an infectious disease, AND it has been judged that the safety of the patient can be assured in terms of her/his reaction to the drug. |

(2) Treatment for pyrexia during a decreased neutrophil count

- 1) If a patient experiences pyrexia of 38°C or higher while having a decreased neutrophil count (neutrophil count $\leq 1,000/\text{mm}^3$) (febrile neutropenia), excluding cases when the pyrexia is judged clinically to be clearly unrelated to an infection, the patient will be regarded as having infection as a complication and antibiotic treatment will promptly be started together with microbiological investigations, such as blood cultures.
- 2) In the event of febrile neutropenia with a relatively severely decreased neutrophil count (neutrophil count $\leq 500/\text{mm}^3$, or neutrophil count $\leq 1,000/\text{mm}^3$ that is expected to further decrease to $\leq 500/\text{mm}^3$), as a general rule, broad-spectrum antibiotics (third- or a higher generation of cepheims, carbapenems, etc.) will be given by intravenous administration.
- 3) Antibiotics will be selected (drug and multi-drug therapy or monotherapy) by a risk judgment based on the neutrophil count (in particular, whether the neutrophil count is $\leq 100/\text{mm}^3$) and monocyte count, period of sustained decreased neutrophil count, whether the neutrophil count is expected to increase, presence of mucous membrane disorders, the situation at the study site with regards to drug-resistant bacteria, previous history of infection and the like. Multi-drug therapies will, as a general rule, consist of concomitant use of a β -lactam antibiotic and an aminoglycoside.
- 4) Whether vancomycin will be used from the start of such treatment will be decided based on the general condition of the patient, the patient's existing normal bacterial flora and the situation in the study site with regards to MRSA.
- 5) The results of blood cultures, etc., the progress of symptoms, the results of investigations to find the infection focus and the like will be reassessed within 3-5 days after starting antibiotics. The arbitrary administration of antibiotics will be avoided, with the antibiotics administered to be changed if pyrexia is not alleviated within 3 days of starting treatment, or if the pathogen is identified.
- 6) Although the use of cytokine preparations such as G-CSF can fall under coverage offered by health insurance, their efficacy in the treatment of infections will not be overestimated. It will

be taken into account that G-CSF is, in particular, slow to have an effect on severe/early onset decreased neutrophil counts.

Note) IDSA guidelines (Clinical Infectious Disease 34: 730-751, 2002), etc. will be referenced with respect to the details of antibiotic selection, methods of risk assessment, duration of antibiotic administration and the like.

6.4.2. Permitted concomitant therapies/supportive therapies

- 1) Selective 5-HT3 receptor antagonists, metoclopramide, steroids, etc. may be used as appropriate to prevent the exacerbation of nausea/vomiting and anorexia, including for preventive use.
- 2) Steroidal drugs may be used as necessary for fatigue, anorexia and emaciation.
- 3) Therapeutic drugs for complications such as hypertension and symptomatic medications such as morphine may be used concomitantly as long as they do not interact with the anticancer drugs being used.

6.4.3. Non-permitted concomitant therapies/supportive therapies

- 1) While protocol treatment is ongoing, anticancer drugs other than those included in the protocol treatment regimen, radiotherapies, hormone therapies other than steroids, and immunotherapies will not be used. (The use of so-called folk remedies and the like will be avoided as possible, though their use according to the wishes of the patient will be left to the judgment of the investigator.)
- 2) G-CSF preparations will not be administered preventively.
- 3) Use of flucytosine, phenytoin and warfarin potassium, which are contraindicated for concomitant use or cautioned against for concomitant use with S-1, will be prohibited during the administration period of this study.

6.5. Posttreatment

No posttreatment will be given after the end of protocol treatment or after discontinuation unless recurrence is observed. Details will not be prescribed in advance with respect to the posttreatment to be given upon confirmation of recurrence. However, because recurrences during protocol treatment or within 6 months of completion of protocol treatment will be identified as cases of unresponsiveness to the protocol treatment, the below crossover treatments will be recommended.

Recurrence during protocol treatment or within 6 months after completion of protocol treatment (recommended)

| Protocol treatment | Treatment after recurrence |
|----------------------------|----------------------------|
| Arm A: Gemcitabine therapy | → S-1 therapy |
| Arm B: S-1 therapy | → Gemcitabine therapy |

7. Drug information and anticipated adverse reactions

7.1. Drug information

This section includes important information on drugs used in this study. Package inserts for the drugs will also be included at the end of the protocol.

7.1.1. Gemcitabine HCl (GEM)

Product name: Gemzar Injection (Eli Lilly Japan K.K.), 200 mg/Vial, 1 g/Vial

Mechanism of action

Gemcitabine (dFdC) is metabolized intracellularly to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. These exhibit cytotoxic action by direct and indirect inhibition of DNA synthesis. dFdCTP inhibits DNA synthesis directly by competing with deoxycytidine triphosphate (dCTP) for incorporation into the DNA chain, after which it induces cell death (apoptosis). dFdCDP inhibits DNA synthesis indirectly by inhibiting ribonucleotide reductase, which reduces the intracellular concentration of dCTP, indirectly enhancing inhibition of DNA synthesis.

Indications

Non-small cell lung cancer, pancreatic cancer, and biliary cancer

Dosage and administration

In adults, normally one dose of 1000 mg/m² is given by 30-minute intravenous infusion. One dose is given once weekly for 3 weeks, followed by a 1-week rest period. One course lasts 4 weeks and is repeated.

Note that the dose will be reduced as appropriate according to age, symptoms or onset of adverse drug reactions.

Main pharmacokinetics

After five patients with advanced cancer were given a 1000 mg/m² intravenous infusion of ¹⁴C-gemcitabine hydrochloride, 92-98% of radioactivity was recovered in patient urine/feces over the following 7 days. Since more than 99% of this radioactivity was recovered in urine, the main excretion pathway for gemcitabine was concluded to be in urine.

Main adverse drug reactions

| | |
|------------------|--|
| Circulatory | 1 to <10%: Tachycardia, blood pressure increased <1%: Blood pressure decreased, anginal pain, palpitations, ventricular extrasystoles, paroxysmal supraventricular tachycardia, abnormal ECG (ST elevation), blood pressure increased |
| Respiratory | ≥10% or incidence unknown: Hypoxemia 1 to <10%: Dyspnea, hypercapnia <1%: PIE (pulmonary infiltration with eosinophilia) syndrome, wheezing, cough, expectoration, shortness of breath |
| Renal | ≥10% or incidence unknown: Total protein decreased, electrolyte abnormality 1 to <10%: Albumin decreased, BUN increased, proteinuria, hematuria, creatinine increased <1%: Oliguria |
| Gastrointestinal | ≥10% or incidence unknown: Anorexia, nausea/vomiting 1 to <10%: Diarrhea, constipation, stomatitis <1%: Stomach discomfort, gingivitis |
| Hepatic | ≥10% or incidence unknown: GGTP increased, AST (GOT) increased, ALT |

| | |
|------------------|--|
| | (GPT) increased, LDH increased, Al-P increased |
| | 1 to <10%: Bilirubin increased, A/G ratio decreased |
| | <1%: Urobilinuria |
| Neuropsychiatric | 1 to <10%: Headache, dizziness |
| | <1%: Paresthesia, sleep loss, lethargy, numbness |
| Dermatologic | ≥10% or incidence unknown: Rash, urticaria |
| | <1%: Alopecia, pruritis |
| Injection site | ≥10% or incidence unknown: Injection site reaction (phlebitis, pain, erythema) |
| Vascular | ≥10% or incidence unknown: Peripheral vasculitis, peripheral gangrene |
| Other | ≥10% or incidence unknown: Fatigue, malaise, asthenia, pyrexia, edema, flu like symptoms (malaise, asthenia, pyrexia, headache, chills, myalgia, sweaty, rhinitis, etc.), CRP increased, radiation recall reaction |
| | 1 to <10%: Platelets increased, weight decreased, urine sugar positive, eosinophilia |
| | <1%: Weight increased, arthralgia, pain, chills, bleeding of ocular fundus, body temperature decreased, hot flush, tinnitus, eye discharge, chest discomfort, dysgeusia, epistaxis |

Severe adverse drug reactions (important adverse drug reactions)

The incidences stated below were observed in domestic (Japanese) clinical studies.

1. Bone marrow depression
Because white blood cells decreased (68.0%, 13.0% decreased to <2000/ μ L), neutrophils decreased (61.8%, 24.5% decreased to <1000/ μ L), platelets decreased (32.2%, 4.6% decreased to <50,000/ μ L), anemia [hemoglobin decreased (66.4%, 15.4% decreased to <8.0 g/dL), red blood cell decrease (58.8%)], etc. have occurred, hematology tests should be conducted frequently, and appropriate action taken such as dose reduction or dose interruption if an abnormal measurement is observed. Note that cases of death caused by sepsis that may be due to severe white blood cells decreased have been reported.
2. Interstitial pneumonia (1.4%)
Because interstitial pneumonia has occurred, patients should be observed carefully including by chest X-ray exams, and if an abnormality is observed administration should be discontinued and appropriate treatment given. Note that cases of death have been reported that may have been caused by interstitial pneumonia.
3. Anaphylactoid symptoms (0.3%)
Because anaphylactoid symptoms including dyspnea have occurred, if any of such symptoms develop administration should be discontinued and appropriate treatment given.
4. Myocardial infarction (0.3%)
Myocardial infarction has been observed in patients with a history of myocardial infarction.
5. Congestive cardiac failure
Congestive cardiac failure has occurred.
6. Pulmonary edema
Pulmonary edema has occurred.
7. Bronchospasm
Bronchospasm has occurred.
8. Adult respiratory distress syndrome (ARDS)
ARDS has occurred.
9. Renal failure
Renal failure has occurred.
10. Hemolytic uremic syndrome (0.3%)
Because hemolytic uremic syndrome has occurred, administration should be discontinued if signs of microangiopathic hemolytic anemia such as a rapid decrease in hemoglobin accompanied by platelets decreased, bilirubin increased, creatinine increased, BUN increased and LDH increased are observed. Renal failure may be reversed by discontinuing

administration, and may require dialytic treatment.

11. Skin disorder (incidence unknown)

Severe skin disorders (erythema, blister, desquamation, etc.) have occurred.

12. Hepatic function disorder, jaundice (incidence unknown)

Severe hepatic function disorders such as AST (GOT), ALT (GPT) and Al-P increased, and jaundice have occurred.

Contraindications

1. Patients with severe bone marrow depression [bone marrow depression may worsen and become fatal.]
2. Patients with interstitial pneumonia or pulmonary fibrosis that is clear on a chest X-ray AND is accompanied by clinical symptoms [symptoms may worsen and become fatal.]
3. Patients undergoing radiotherapy in the chest area [there are reported cases in overseas clinical studies of the concomitant use of gemcitabine and definitive radiotherapy of the chest resulting in serious esophagitis and pneumonitis that have led to death.]
4. Patients with a complicating severe infection [infection may worsen and become fatal.]
5. Patient with a history of a severe hypersensitivity to components of gemcitabine.
6. Pregnant woman or woman of childbearing potential [teratogenic effects and embryofetal lethality are reported in animal studies (mice and rabbit).]

Main interactions

Contraindications for concomitant use

1. Irradiation of the chest

1) Clinical symptoms and interventions

When gemcitabine (1000 mg/m²/day once per week administered prior to irradiation) and definitive radiotherapy of the chest (2 Gy/day 5 times/week) were used concomitantly for 6 weeks in an overseas clinical study, severe esophagitis and pneumonitis were developed that led to death. Since no optimal dose has been established for gemcitabine when used concomitantly with radiation exposure, concomitant use of gemcitabine with radiotherapy of the chest should be avoided as it is expected to have a radiosensitizing effect.

2) Mechanism

In a basic study, the effects of radiation exposure increased dose-dependently with gemcitabine treatment, where the drug was observed to cause increased radiosensitivity.

Precautions for concomitant use

1. Abdominal irradiation

1) Clinical symptoms and interventions

Localized complications that became severe have occurred upon concomitant use of gemcitabine and abdominal radiotherapy (external irradiation). Note that the safety of concomitant gemcitabine use with intraoperative irradiation has not been confirmed.

2) Mechanism

In a basic study, the effects of radiation exposure increased dose-dependently with gemcitabine treatment, where the drug was observed to cause increased radiosensitivity.

2. Other antineoplastic drugs (alkylating agents, antimetabolic agents, antibiotics, alkaloids, etc.)

1) Clinical symptoms and interventions

Bone marrow depression has been exacerbated.

2) Mechanism

Both study drugs cause bone marrow depression.

7.1.2. S-1

Product name: TS-1 capsule (Taiho Pharmaceutical Co., Ltd.), 20 mg/capsule, 25 mg/capsule

Mechanism of action

TS-1 is a preparation composed of tegafur (FT), gimeracil (CDHP) and oteracil potassium (Oxo), and its antitumor effect after oral administration is based on the gradual change of FT to 5-FU within the body.

CDHP selectively and competitively inhibits DPD, which is a catabolic metabolizing enzyme of 5-FU that is mainly distributed in the liver, so increasing the concentration of FT-derived 5-FU. This increase in 5-FU concentration results in sustained high concentrations of 5-fluoronucleotides (phosphorylated metabolites of 5-FU) in the tumor, enhancing their antitumor effect. Furthermore, oral administration of Oxo results in its distribution mainly in digestive tissues where it selectively and competitively inhibits orotate phosphoribosyltransferase, which selectively suppresses the formation of 5-fluoronucleotides from 5-FU. This is believed to mitigate the gastrointestinal toxicity of 5-FU without decreasing the potent antitumor effect of 5-FU.

The main mechanism of action of 5-FU is the binding of its active metabolite FdUMP to dUMP, forming a ternary complex with thymidylate synthase and folate analogs, thereby inhibiting DNA biosynthesis. 5-FU is also said to be changed to FUTP, which impedes RNA function.

Indications

Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, and pancreatic cancer

Dosage and administration

The initial dose (first dose) in adults is normally one of the standard doses below according to the patient's body surface area. It is taken twice daily, once after breakfast and once after evening meal, administered orally for 28 days continuously, followed by a 14-day rest period. This is taken as 1 course of treatment and repeated.

| Body surface area | Initial standard dose (equivalent tegafur dose) |
|---|---|
| >1.25m ² | 40 mg/administration |
| ≥1.25m ² , <1.5 m ² | 50 mg/ administration |
| ≥1.5 m ² | 60 mg/ administration |

Note that the dose will be increased or reduced as appropriate according to the condition of the patient. Dose increases and reductions will take place at steps of 40 mg, 50 mg, 60 mg and 75 mg/administration. The dose will be increased by single steps starting from the initial standard dose if there are no abnormal laboratory measurements (hematology, hepatic and renal function measurements) and no gastrointestinal symptoms that are deemed to be caused by administration of S-1, if there are no problems with safety, and if a dose increase is judged feasible. Dose increases will be limited to a maximum 75 mg/administration. In addition, dose reductions will normally take place by single steps to a minimum dose of 40 mg/administration.

Main pharmacokinetics

In the 72 hours following a single, oral postprandial administration of 32-40 mg/m² of TS-1 in 12 cancer patients, compared to the administered dose, 52.8% of gimeracil (CDHP), 7.8% of tegafur (FT), 2.2% of oteracil potassium (Oxo), 11.4% of the metabolite cyanuric acid (CA) and 7.4% of the metabolite fluorouracil (5-FU) were excreted in patients' urine.

Main adverse drug reactions

| | |
|------------------|--|
| Hematological | <p>≥5%: White blood cells decreased, neutrophils decreased, platelets decreased, red blood cells decreased, hemoglobin decreased, hematocrit decreased</p> <p>0.1 to <5%: Bleeding tendency (subcutaneous bleeding spot, epistaxis, abnormal clotting factor), eosinophilia, white blood cells increased, lymphocytes decreased</p> |
| Hepatic | <p>≥5%: AST (GOT) increased, ALT (GPT) increased, bilirubin increased, Al-P increased</p> <p>0.1 to <5%: Jaundice, urobilinogen urine positive</p> |
| Renal | <p>0.1 to <5%: BUN increased, creatinine increased, proteinuria, hematuria</p> |
| Gastrointestinal | <p>≥5%: Anorexia, nausea/vomiting, diarrhea, stomatitis</p> <p>0.1 to <5%: Abdominal pain, enlarged feeling of abdomen, epigastric pain, gastritis, borborygmus, pale feces, constipation, angular stomatitis, cheilitis, glossitis, thirst, dysgeusia</p> |
| Dermatologic | <p>≥5%: Pigmentation</p> <p>0.1 to <5%: Erythema, desquamation, flushing, blister, hand and foot syndrome, skin ulcer, dermatitis, alopecia, nail abnormality, paronychia, herpes simplex, dry/rough skin</p> <p>Incidence unknown: Photosensitivity, discoid lupus erythematosus-like eruption</p> |
| Hypersensitivity | <p>≥5%: Rash</p> <p>0.1 to <5%: Pruritis</p> |
| Neuropsychiatric | <p>≥5%: General malaise</p> <p>0.1 to <5%: Numbness, headache, headache dull, dizziness</p> <p>Incidence unknown: Light-headedness</p> |
| Circulatory | <p>0.1 to <5%: Blood pressure decreased, blood pressure increased, ECG abnormal, Raynaud symptoms</p> <p>Incidence unknown: Palpitations</p> |
| Ocular | <p>0.1 to <5%: Lacrimation, conjunctivitis, keratitis, eye pain, visual acuity reduced</p> <p>Incidence unknown: Dry eye</p> |
| Other | <p>≥5%: LDH increased, total protein decreased, albumin decreased</p> <p>0.1 to <5%: Pyrexia, generalized hot feeling, whititis, pharyngitis, sputum, glycosuria, sugar blood level increased, edema, myalgia, CK (CPK) increased, arthralgia, electrolyte abnormality (serum sodium increased, serum sodium decreased, serum potassium increased, serum potassium decreased, serum calcium increased, serum calcium decreased, serum chloride increased, serum chloride decreased), weight decreased</p> <p>Incidence unknown: Serum amylase increased</p> |

Serious adverse drug reactions (important adverse drug reactions)

1. Bone marrow depression, hemolytic anemia
Because hemolytic anemia (incidence unknown) and symptoms of severe bone marrow depression such as panhemocytes decreased, agranulocytosis (Symptoms: pyrexia, pharyngeal pain, malaise, etc.), white blood cells decreased, anemia and platelets decreased have occurred, patients should be observed carefully and appropriate action taken such as discontinuation of administration if an abnormality is observed.
2. Disseminated intravascular coagulation (DIC): Because DIC (0.3%) has occurred, patients should be observed carefully and if an abnormal hematology measurement, such as platelet count, serum FDP level or plasma fibrinogen concentration is observed administration should be discontinued and appropriate treatment given.

3. Severe liver disorder, such as fulminant hepatitis (incidence unknown)
4. Dehydration: Because severe diarrhea has occurred and lead to dehydration (incidence unknown), patients should be observed carefully and if such symptoms are observed appropriate action taken such as discontinuation of administration and fluid replacement.
5. Severe enteritis: Because severe enteritis (0.6%) has occurred, patients should be observed carefully and if symptoms such as severe abdominal pain or diarrhea occur administration should be discontinued and appropriate treatment given.
6. Interstitial pneumonia: Because interstitial pneumonia (0.3%) (Initial symptoms: cough, shortness of breath, dyspnea, pyrexia, etc.) has occurred, patients should be observed carefully and if an abnormality is observed appropriate action taken, such as discontinuation of administration, exams such as chest X-rays, and administration of corticosteroids.
7. Severe stomatitis, gastrointestinal ulcers, gastrointestinal hemorrhage and gastrointestinal perforation: Because severe stomatitis (incidence unknown), gastrointestinal ulcers (0.6%), gastrointestinal hemorrhage (incidence unknown) and gastrointestinal perforation (incidence unknown) have occurred, patients should be observed carefully and if an abnormality is observed administration should be discontinued, necessary exams such as abdominal X-rays undertaken and appropriate treatment given.
8. Acute renal failure: Because severe renal disorders (incidence unknown) such as acute renal failure have occurred, patients should be observed carefully and if an abnormality is observed administration should be discontinued and appropriate treatment given.
9. Stevens-Johnson syndrome and Lyell syndrome: Because Stevens-Johnson syndrome and Lyell syndrome (incidence unknown) have occurred, patients should be observed carefully and if an abnormality is observed administration should be discontinued and appropriate treatment given.
10. Neuropsychiatric disorders including leukoencephalopathy, etc.: Because leukoencephalopathy (main symptoms being consciousness disturbed, cerebellar ataxia, dementia-like symptom) and consciousness disturbed, disorientation, somnolence, memory ability decreased, extrapyramidal symptoms, language disorder, quadriplegia, gait disturbance, urinary incontinence, perceptual disturbance (all of which incidence unknown) and the like have occurred, patients should be observed carefully and administration discontinued if any such symptoms are observed.
11. Acute pancreatitis: Because patients acute pancreatitis (incidence unknown) has occurred, patients should be observed carefully and if abdominal pain, serum amylase increased, etc. is observed administration should be discontinued and appropriate treatment given.
12. Rhabdomyolysis: Because rhabdomyolysis (incidence unknown) characterized by myalgia, feelings of weakness, CK (CPK) increased and myoglobin blood/urine increased has occurred, if such symptoms occur administration should be discontinued and appropriate treatment given. In addition, care should be taken to watch for acute renal failure caused by rhabdomyolysis.
13. Anosmia: Because dysosmia has occurred and lead to anosmia (incidence unknown), patients should be observed carefully and appropriate action taken such as discontinuation of administration if an abnormality is observed.

Contraindications

1. Patients with a history of severe hypersensitivity to components of S-1
2. Patients with severe bone marrow depression [bone marrow depression may worsen and become fatal.]
3. Patients with a severe renal disorder [renal excretion of gimeracil, an inhibitor of a catabolic metabolizing enzyme of fluorouracil, may be markedly reduced, increasing the blood concentration of fluorouracil, and causing adverse drug reactions such as bone marrow depression to develop strongly.]
4. Patients with a severe liver disorder [liver disorder may worsen.]
5. Patients currently taking another fluorinated pyrimidine antineoplastic drug (including

concomitant therapy with such drugs)

6. Patients currently taking flucytosine
7. Pregnant women or women of childbearing potential

Main interactions

Contraindications for concomitant use

1. Fluorinated pyrimidine antineoplastic drugs
 - < Fluorouracil (5-FU, etc.), tegafur/uracil combination preparations (UFT, etc.), tegafur (futrafur, etc.), doxifluridine (furtulon), capecitabine (xeloda), carmofur (mifurof) >
 - Folate/tegafur/uracil therapy (Uzel, UFT, etc.)
 - Levofolate/fluorouracil therapy (Isovorin, 5-FU, etc.)
 - Fluorinated pyrimidine antifungal drugs < Flucytosine (Ancotil, Domerajin, Cocol) >
- 1) Clinical symptoms and interventions
 - Concomitant use may quickly cause severe blood disorders and gastrointestinal disorders such as diarrhea and stomatitis. Note that these drugs (therapies) should not be administered within at least 7 days of discontinuing S-1 treatment. Furthermore, when administering S-1 after stopping treatment with of any of these drugs, administration of S-1 should be started after an appropriate period of time considering the effects of these drugs.
- 2) Mechanism
 - Catabolism of administered fluorouracil or fluorouracil derived from administered fluorinated pyrimidine is inhibited by gimeracil, resulting in a marked increase in blood fluorouracil concentration.

Precautions for concomitant use

1. Phenytoin
 - 1) Clinical symptoms and interventions
 - Because phenytoin toxicity (queasy/vomiting, nystagmus, movement disorder, etc.) has occurred, patient condition should be observed carefully. Appropriate action should be taken such as discontinuation of administration if an abnormality is observed.
 - 2) Mechanism
 - Phenytoin metabolism is suppressed by tegafur, resulting in an increase in the blood concentration of phenytoin.
2. Warfarin potassium
 - 1) Clinical symptoms and interventions
 - Because S-1 enhances the action of warfarin potassium, attention should be paid with respect to fluctuations in blood coagulability.
 - 2) Mechanism
 - Mechanism unknown.
3. Other antineoplastics and radiation exposure, etc.
 - 1) Clinical symptoms and interventions
 - Because S-1 exacerbates adverse drug reactions such as blood disorders and gastrointestinal disorders, patient condition should be observed carefully. Appropriate action such as dose reduction or dose interruption should be taken if an abnormality is observed. Because S-1 enhances the action of warfarin potassium, attention should be paid with respect to fluctuations in blood coagulability.
 - 2) Mechanism
 - Adverse drug reactions are exacerbated by drug-drug interactions.

7.2. Anticipated adverse events

Anticipated adverse drug reactions are as shown below.

7.2.1. Anticipated adverse drug reactions caused by chemotherapy

See protocol section 7.1. “Drug information” for information regarding anticipated adverse drug reactions.

7.2.2. Anticipated adverse events caused by recurrence of the primary disease

Anticipated adverse events caused by recurrence of the primary disease will be described using short names from CTCAE ver3.0. These adverse events are only deemed anticipated adverse events after having occurred with the primary disease deemed the potential cause.

General condition: Fatigue, weight loss

Lymphatics: Edema: head and neck, Edema: limb, Edema: trunk/genital, Edema: viscera

Metabolic/laboratory: Hypoalbuminemia, AST, ALT, bilirubin, alkaline phosphatase

Pain: Pain-{site}

7.2.3. Anticipated adverse events caused by concomitant drug use

This section states the main adverse drug reactions for frequently used concomitant drugs. See the package insert of each concomitant drug for more details. These adverse events are only anticipated in the event of concomitant use of the concomitant drugs.

Serotonin (5-HT₃) antagonists

Drugs: Azasetron hydrochloride (Serotone®), gradisetron hydrochloride (Kytril®), tropisetron hydrochloride (Navoban®), ramosetron hydrochloride (Nasea®), ondansetron (Zofran®, Zydys®)

Adverse drug reactions: Headache, feeling of headache, fever, chills, hepatic function abnormal (AST, ALT, LDH, total bilirubin increased), palpitations, rash, diarrhea, constipation

Granulocyte colony-stimulating factor (G-CSF)

Drugs: Nartograstim (Neu-up®), filgrastim (Gran®), lenograstim (Neutrogin®)

Adverse drug reactions: (Severe adverse drug reactions): Interstitial pneumonia, ARDS, splenic rupture

(Other adverse drug reactions): Pyrexia, rash/redness, ALP increased, LDH increased, AST/ALT/bilirubin increased, urate/creatinine increased, CRP increased, bone pain, low back pain, chest pain, arthralgia, nausea/vomiting, headache, malaise, palpitations, skin disorder with neutrophil infiltration/painful erythema/pyrexia

Adrenocortical hormones

Drugs: Dexamethasone (Decadron®), betamethasone (Rinderon®)

Adverse drug reactions: (Severe adverse drug reactions): Inducement/exacerbation of infection, adrenal cortical insufficiency, sugar blood level increased, peptic ulcer, hemorrhage of digestive tract, gastrointestinal perforation, pancreatitis, esophagitis, convulsion, increased intracranial pressure, epidural lipoma, mental aberration, depressive state, osteoporosis, aseptic necrosis (femur, humerus, etc.), myopathy, tendon rupture, glaucoma, ocular hypertension, posterior capsule opacification, thrombosis, cardiac failure congestive, asthma attack exacerbated

(Others): Moon face, buffalo hump, blood pressure increased, Na and water retention (edema), weight increased, hypokalemic alkalosis, Cushing-like symptoms, menstrual disorder, sperm motility/count increased/decreased, acne, hypertrichosis, alopecia, pigmentation, thinning of/fragility of skin, ecchymosis, striae, purpura, facial erythema, panniculitis, hypersensitivity symptom (rash), pruritus, euphoria,

sleep loss, headache, dizziness, paridrosis, polyuria, white blood cells increased, hepatic steatosis, AST/ALT/ALP increased, hyperlipidemia, hypercholesterolemia, steroid nephropathy, nausea/vomiting, gastralgia, heartburn, enlarged feeling of abdomen, thirst, diarrhea, increased appetite, anorexia, retinal disorder caused by central serous chorioretinopathy, proptosis, myalgia, arthralgia, pyrexia, fatigue

Pain relief drugs

Drugs: Morphine (MS Contin®, Kadian®, Anpec®, Prepenon®, Opso®), oxycodone HCl (Oxycontin®)

Adverse drug reactions: Vomiting, constipation, sleepiness, anxiety, depressive state, confusion/hallucination, urination impaired, respiratory depression

Drugs: Fentanyl citrate (Durotep®)

Adverse drug reactions: (Severe adverse drug reactions): Dependency, respiratory depression
(Other adverse drug reactions): Blood pressure increased, tachycardia, bradycardia, blood pressure decreased, sleepiness, unrest, sleep loss, somnolence, amnesia, dizziness, irritability, hallucination, euphoria, headache, confusion, application site pruritus, rash, pruritus, application site erythema, erythema, constipation, queasy, vomiting, diarrhea, thirst, hepatic function abnormal, urinary retention, pyrexia, malaise, sweaty

7.2.4. Anticipated postoperative adverse events and complications

This section describes the anticipated postoperative adverse events and complications. These adverse events are only deemed anticipated adverse events after having occurred with surgery deemed the potential cause.

Gastrointestinal: Gastrointestinal fistula (biliary fistula), gastrointestinal leak (pancreatic fistula), gastrointestinal obstruction (adherent, etc. mechanical ileus), gastrointestinal ileus (paralytic ileus)

Hemorrhage: Gastrointestinal hemorrhage, surgery related hemorrhage (intra-abdominal hemorrhage, wound bleeding, etc.)

Infection: Infection with Grade 0-2 neutrophils decreased (intra-abdominal abscess, cholangitis, peritonitis, wound infection, etc.)

Vascular: Thrombosis (deep vein thrombosis, pulmonary embolus, etc.)

Pain

7.3. Evaluation of adverse events/adverse drug reactions

CTCAE v3.0 Japanese translation JCOG/JSCO will be used to evaluate adverse events/adverse drug reactions.

Adverse events will be graded according to the grade 0-4 definition they most closely resemble. While the original CTCAE regards a treatment-related death as a grade 5 adverse event, in this study, treatment-related deaths will be entered into records forms as a grade 4 adverse event. Observations regarding the causal relationship between an adverse event and death after a treatment-related death will be entered into the “Circumstances at death” field of the clinical trial end report form and follow-up form, and will require expedited reporting. (An investigation conducted later, which will include expedited reporting, will determine whether the adverse event is grade 5.)

The grading of the toxicity-related adverse events noted in protocol section 8.3. “Investigations and assessments during the study period” will be entered into relevant records forms. Other toxicity-related adverse events will be entered by name along with the worst relevant grade into the “Other” field of the progress report, but only for toxicity-related adverse events that are grade 3 or above.

The grade entered into records forms will always also be entered into the medical record.

8. Items for evaluation, laboratory tests and evaluation schedule

*Items for evaluation and laboratory tests will be implemented as described in this section. However, it is recommended that abdominal CT scans be performed from the abdomen to the pelvis, with MRI also available as a substitute to be used in case of a contrast media allergy.

8.1. Items evaluated prior to registration

The below items will be evaluated prior to registration.

8.1.1 Lesion evaluation: Evaluation within 2 weeks prior to registration

- 1) Abdominal CT
- 2) Chest X-ray (2 directions); lung window
- 3) Resting 12-lead ECG

8.1.2 Laboratory tests: Evaluation within 1 week prior to registration

- 4) Hemogram: WBC, RBC, Hb, Ht, Plt, differential white blood count
- 5) Biochemistry: TP, Alb, T-Bil, ALP, AST, ALT, LDH, Na, K, BUN, Cr, Ca, blood sugar
- 6) Blood serum: CRP
- 7) Tumor markers: CEA, CA19-9
- 8) Urinalysis (spot urine): Qualitative urine glucose, qualitative urinary protein

8.1.3 Subjective symptoms: Evaluation on registration day or prior day

- 9) PS (ECOG), body weight, HRQOL

8.2. Categorization of treatment period, observation period and follow-up period

In this study, the protocol treatment period and all periods after protocol treatment has stopped will be divided into the three categories below, with items for evaluation and methods of evaluation prescribed for each period.

Treatment period: From the start of treatment to 30 days after the final day of treatment in order to evaluate adverse events related to protocol treatment. If posttreatment is started before 30 days after the final day of treatment, the treatment period shall be until the day before the start of posttreatment.

Observation period: The period after the completion or discontinuation of protocol treatment during which the patient will be evaluated for recurrence. Consequently, the observation period will be from 31 days after the final day of administration to the day recurrence is confirmed, or the final follow-up observation of this study. There will be no observation period if recurrence is confirmed during the treatment period.

Follow-up period: From the end of the treatment period and observation period until the final follow-up observation of this study or until death.

8.3. Investigations and evaluations during the treatment period

1) Subjective symptoms

The items below will be evaluated at each outpatient visit (at least once fortnightly, or at least once weekly during inpatient care), and the worst measurements/results based on CTCAE v3.0 entered into records forms (case report forms).

| | |
|--------------------------|---|
| Constitutional symptoms: | Fatigue, fever |
| Dermatology/skin | Hyperpigmentation, hand-foot skin reaction |
| Gastrointestinal: | Anorexia, diarrhea, nausea, vomiting, mucositis (functional/symptomatic)-oral cavity |
| Infection: | Infection with Grade 3 or 4 neutrophils (fever of unknown origin) Infection with Grade 3 or 4 neutrophils (documented clinically) -{Catheter-related infection, biliary tree, gallbladder, bronchus, lung (pneumonia), pharynx, upper respiratory NOS, bladder, kidney, urinary tract NOS} Infection with Grade 0 to 2 neutrophils -{Catheter-related infection, biliary tree, gallbladder, bronchus, lung (pneumonia), pharynx, upper respiratory NOS, bladder, kidney, urinary tract NOS} |
| Ocular/visual | Watery eye |

2) Laboratory tests

The items below will be evaluated at each outpatient visit (at least once fortnightly, or at least once weekly during inpatient care), and the worst laboratory measurements entered into records forms (case report forms).

Hemogram: WBC, Hb, Plt, neutrophil count
Biochemistry: Alb, T-Bil, AST, ALT, ALP, Cr, Na, K, Ca

3) Checking for recurrence

Abdominal CT and chest X-ray exams will be conducted at least once every 3 months (3 and 6 months after starting treatment) to check for recurrence.

Tumor markers (CEA, CA19-9) will be examined once monthly.

4) Checking patients' general condition

HRQOL and PS will be checked once every 3 months (3 and 6 months after starting treatment).

8.4. Investigations and evaluations during the observation period

1) Checking for recurrence

Abdominal CT and chest X-ray exams will be conducted at least at the frequencies shown below to check for recurrence.

Within 2 years after registration: Every 3 months

From 2 years after registration: Every 6 months

Tumor markers (CEA, CA19-9) will be examined at least at the frequencies shown below.

Within 2 years after registration: Every 3 months

From 2 years after registration: Every 3 months

2) Checking patients' general condition

HRQOL and PS will be checked once every 6 months.

8.5. Investigations and evaluations during the follow-up period

- Presence of posttreatment
- Site of recurrence
- If posttreatment is being used, the treatment method, start date and general condition at start of posttreatment
- If posttreatment is not being taken, the reasons for its absence
- Date of death, or date of the final confirmation of survival
- In case of death, the cause of death
- HRQOL and PS will be checked once every 6 months. If HRQOL or PS cannot be checked for any reason, the reason will be recorded in the questionnaire form.

Caution

Even when direct patient follow-up is not feasible due to hospital transfer or other reasons, inquiries will be made with the destination of hospital transfer, etc. as possible to confirm whether the patient is alive or dead, and the results of the inquiry will be entered into the medical record.

8.6. Study calendar

| | Before registration | Treatment period* | Observation period Within 2 years after registration | Observation period From 2 years after registration | Follow-up period |
|--|---------------------|------------------------------------|--|--|------------------|
| General condition | | | | | |
| Subjective symptoms | † a) | ‡ | | | |
| Body weight | † a) | § | | | |
| HRQOL, PS | † a) | (3) | (6) | (6) | (6) |
| Laboratory tests | | | | | |
| WBC, RBC, Hb, Ht, Plt, differential white blood count | † b) | | | | |
| WBC, Hb, Plt, neutrophil count | | ‡ | | | |
| TP, Alb, T-Bil, ALP, AST, ALT, LDH, Na, K, BUN, Cr, Ca, blood sugar, CRP | † b) | | | | |
| Alb, T-Bil, AST, ALT, ALP, Cr, Na, K, Ca | | ‡ | | | |
| Urinalysis (qualitative urinary protein/urine glucose) | † b) | | | | |
| 12-lead ECG | † c) | | | | |
| Lesion evaluation | | | | | |
| CEA, CA19-9 | † b) | (1) | (3) | (3) | |
| Chest X-ray (2 directions) | † c) | (3) | (3) | (6) | |
| Abdominal CT (up to pelvis) | † c) | (3) | (3) | (6) | |
| Submission of records forms | | | | | |
| Patient registration card | † | | | | |
| Pre-treatment report | | † | | | |
| Progress report | | † End of each course | | | |
| Treatment end report | | † After end of treatment period | | | |
| Questionnaire about daily living | † a) | (3) | (6) | (6) | (6) |
| Follow-up card | | (6) | (6) | (12) | (12) |

†: Required

‡: Every outpatient visit (at least once fortnightly, or at least once weekly during inpatient care)

§: As necessary

(1): Evaluated every month, (3): Evaluated every 3 months, (6): Evaluated every 6 months, (12): Evaluated every 12 months

a) Evaluation on registration day or day before registration, b) Evaluation within 1 week prior to registration, c) Evaluation within 2 weeks prior to registration

*Note that the treatment period is until 30 days after the final day of administration, or until the day before the start of posttreatment.

9. Data collection

9.1. Records forms (case report forms: CRFs)

9.1.1. Data submission

Excluding the patient registration card, in this study data submission will take place via an EDC system using CRFs in a PDF file format. Investigators or CRCs will submit data via the EDC system to the CSPOR data center during the progress of the study for all registered patients up to completion of the study. If entry or input is performed by a CRC, he/she will obtain confirmation for entry or input from an investigator. Details of the data to be submitted, procedures for submission and the timing of submissions are shown below.

9.1.2. Types of records forms and deadlines for submission

The CRFs to be used in this study and deadlines for submission are shown below.

- | | |
|--|---|
| 1) Case registration card | -Faxed to CSPOR data center |
| 2) Pre-treatment report | -Promptly after the case registration card |
| 3) Progress report | -Promptly at the end of every course |
| 4) Treatment end report | -Promptly after the end of the treatment period |
| 5) Follow-up card | -Every 6 months within 2 years after registration, then every 12 months from 2 years after registration |
| 6) HRQOL survey (questionnaire about daily living) | -By post within 1 month after survey completion |
| 7) Adverse event expedited primary report | -As necessary |
| 8) Adverse event report | -As necessary |

9.1.3. Submission of records forms

- Once the CSPOR data center has been informed of IRB review and approval and conclusion of a clinical trial agreement/contract, three removable USB drives (one USB drive containing the EDC system, one USB drive to be used for backing up, and one USB drive for submission of data) and a study start pack will be sent by post from the CSPOR data center to the principal investigator at the study site.
- Of the CRFs mentioned in protocol section 9.1.2 “Types of records forms and timings for submission”, CRFs 2) to 5) will be included in the EDC system in PDF file format. To submit data to the data center, the USB drive containing the EDC system and the USB drive for backing up will be simultaneously inserted into a PC, the system will be started up, a PDF-format CDF will be navigated to within the opened browser, and the required data entered into the CRF. After entry is complete, data will be copied from the backup USB drive to the USB drive for data submission, and the USB for data submission will be sent by post to the CSPOR data center by a prescribed method (after the data is imported by the data center, the USB for data submission will be returned to the study site by post). After that, if inquiries arise as a result of the centralized monitoring performed at the CSPOR data center, the inquiries will be sent to study sites using print outs of CRFs that contain the submitted data.
- Because patient registration cards and RCFs are needed promptly during registration, they will be sent by fax.
- Regarding follow-up cards, the study site will be contacted every six months within 2 years after registration and every 12 months from 2 years after registration by the CSPOR data center to request the conduct of investigations and to request the submission of data via the EDC system.
- Regarding the HRQOL survey (questionnaire about daily living), the survey form will be collected by a CRC or investigator, whereupon the CRC or investigator will determine the PS and enter it into the survey form. The CRC or investigator will send the survey form to the CSPOR data center by post within 1 month of survey completion.
- In order to avoid the disclosure of personal patient information, patient registration numbers will

be used during communication with the CSPOR data center and study site medical record numbers will not be used.

9.1.4. Correction of records forms

Although the CSPOR data center and study administrators take extreme care during the preparation of records forms, it is possible that missing or inappropriately classified required items and the like are discovered in records forms after commencement of the study. In such cases, records forms will be corrected upon the consent of the head of the data center and a study administrator, provided the change does not mean the scope of the data prescribed for collection in protocol section 8. "Items for evaluation, laboratory tests and evaluation schedule" will be exceeded, and provided the correction is judged not to increase the clinical or financial burden on registered patients. Corrections to records forms that do not require amendment of the protocol itself will not be regarded as protocol amendments. Study site rules will be followed as to whether a records form correction will be reported to the study site IRB.

10. Reporting of adverse events

According to the provisions of this chapter, in the event of a “severe adverse event” or “unanticipated adverse event”, the study site study manager will report the event to the study administrator/study representative.

Note that reports of adverse drug reactions, etc. made to the Minister of Health, Labour and Welfare based on the Pharmaceutical Affairs Act (Contact: Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Fax: 03-3508-4364, <http://www.pharmasys.gr.jp/info/houkoku.html>), reports of severe adverse events, etc. made by each study site to the head of the study site based on ethical guidelines for clinical research (Public Notice of the Ministry of Health, Labour and Welfare, No. 255, <http://www.mhlw.go.jp/topics/2003/07/tp0730-2.html>), and contact made by study sites with corporate enterprises regarding adverse drug reactions should be done appropriately according to the rules of each study site and shall be the responsibility of the study manager of each study site.

10.1. Adverse events of which there is an obligation to report

10.1.1. Adverse events of which there is an obligation for expedited reporting

Adverse events to which any of the below is applicable will be subject to expedited reporting.

(1) All deaths during protocol treatment or within 30 days after the final day of protocol treatment

Expedited reporting irrespective of causal relationship to protocol treatment. Adverse events within 30 days after the final day of protocol treatment will be subject to expedited reporting even if posttreatment has already started after discontinuation of protocol treatment.

(30 days counting day 0 as the final day of protocol treatment)

(2) Unanticipated Grade 4 non-hematological toxicities (adverse events outside the blood/bone marrow category in CTCAE ver3.0)

Grade 4 non-hematological toxicities not included among serious adverse drug reactions in protocol section 7.2 “Anticipated adverse events”. Events that occur during protocol treatment or within 30 days from the final day of protocol treatment will be subject to expedited reporting irrespective of causal relationship, and events that occur from 31 days after the final day of protocol treatment and onwards will be subject to expedited reporting only if a causal relationship to protocol treatment is identified (related or probably related).

10.1.2. Adverse events of which there is an obligation for normal reporting

Adverse events to which any of the below is applicable will be subject to normal reporting.

Of adverse events that fall under (2) and (3) below, events that occur within 30 days from the final day of protocol treatment will be subject to normal reporting irrespective of causal relationship, and events that occur from 31 days after the final day of protocol treatment and onwards will be subject to normal reporting only if a causal relationship to protocol treatment is identified (related or probably related).

(1) Deaths that occur from 31 days after the final day of protocol treatment and onwards for which a causal relationship cannot be ruled out

Applicable to deaths that are suspected to be treatment-related. Not applicable to deaths clearly caused by the primary disease.

(2) Anticipated Grade 4 non-hematological toxicities (adverse events outside the blood/bone marrow category in CTCAE ver3.0)

Grade 4 non-hematological toxicities not included among serious adverse drug reactions in protocol section 7.2 “Anticipated adverse events”. Be aware that severe adverse events will be subject to normal reporting even if they are anticipated.

(3) Unanticipated Grade 2 and 3 adverse events

Grade 2 or 3 adverse events not included in protocol section 7.2. “Anticipated adverse events” or in the drug package insert.

(4) Permanent or significant disability/incapacity

Aplastic anemia, myelodysplastic syndrome, secondary cancer, etc.

(5) Other important medical events

Events that do not fall under (1) or (2) in section 10.1.1., or (1) to (4) in section 10.1.2., but comprise important information that should be shared between participating study sites.

10.2. Reporting obligations of the study site study manager and reporting procedures

10.2.1. Expedited reporting

When an adverse event occurs that is subject to expedited reporting, an investigator will promptly inform the study site study manager. If the study site study manager is not available, a study site coordinator or investigator must take on the responsibilities of the study site study manager.

Primary reporting:

Within 72 hours of learning of an adverse event, the study site study manager will fill in the matters specified in an adverse event expedited primary report, fax it to the study representative and also contact the study representative by phone.

Secondary reporting:

Within 7 days of learning of an adverse event, the study site study manager will fill in the matters specified in an adverse event report, prepare a case report (A4, no restriction on format) that contains more detailed information on the adverse event to accompany the adverse event report, and send both to the study representative by post or by fax. In order to prioritize the prompt communication of information, the report may be sent even if some sections could not be completed.

Tertiary reporting:

Within 15 days of learning of an adverse event, the study site study manager will fill in all sections of an adverse event report that could not previously be completed, and send it to the study representative by post or by fax. In cases of autopsy the postmortem examination will also be appended.

10.2.2. Normal reporting

Within 15 days of learning of an adverse event, the study site study manager will fill in the matters specified in an adverse event report and send it to the study representative by post or by fax.

10.3. Responsibilities of the study representative/study administrators

10.3.1. Determining the need for suspension of registration and urgent notification of study sites

The study representative will determine the degree of urgency, importance and impact of the content of reports received from study site study managers and take measures as necessary such as temporary suspension of registration (by contacting the data center and all participating study sites) and seeking urgent contact with study sites to inform them of matters. Depending on the degree of urgency, the study representative may first contact the data center and study sites by phone then again later in document form within a prompt time frame (by fax, post or email).

10.3.2. Reporting to the Efficacy and Safety Evaluation Committee

If the study representative judges an adverse event learned via either an expedited report or

normal report falls under protocol section 10.1 “Adverse events of which there is an obligation to report”, within 15 days of learning of the adverse event he/she will make a report of same adverse event to the Efficacy and Safety Evaluation Committee in document form and request the Efficacy and Safety Evaluation Committee also reviews the study representative’s own views of the given adverse event and regarding suitable ways of addressing the adverse event.

The study representative should include in the report to the Efficacy and Safety Evaluation Committee the adverse report expedited primary report and adverse event report received from the study site, as well as the conclusions of the study representative’s own examination into how to respond to the adverse event (including a judgment on continuation/discontinuation the study). In addition, for deaths within 30 days as described in section 10.1.1.(1) and deaths from 31 days onwards as described in section 10.1.2.(1) that are judged treatment-related, and for anticipated severe adverse events as described in section 10.2.2.(2), the study representative should also include his/her observations on the progress of individual patients and whether incidence of the given adverse event is within the anticipated range.

10.3.3. Notification of researchers at study sites

If the study representative has made a report to the Efficacy and Safety Evaluation Committee, the study representative will notify the study site study manager of all participating study sites in document form of the review and content of the recommendations of the Efficacy and Safety Evaluation Committee.

If the study representative has not made a report to the Efficacy and Safety Evaluation Committee, he/she will notify the study site study manager of the study site that made the report of the findings of the study representative’s own observations on the matter.

10.3.4. Investigation of adverse events during periodic monitoring

During monitoring, the study representative/study administrators will carefully examine the adverse event reports included within the monitoring reports created by the CSPOR data center in order to verify there are no errors in reports received from study sites. They will also verify that all reported adverse events have been listed in periodic monitoring reports.

10.4. Examination by the Efficacy and Safety Evaluation Committee

The Efficacy and Safety Evaluation Committee will review and examine the content of reports according to procedures for clinical safety data management, and make recommendations to the study representative in document form with respect to how to address matters going forward, including whether to continue registration and whether the protocol needs amendment.

11. Assessment of efficacy and definition of endpoints

11.1. Definition of the analysis population

Periodic monitoring, interim analysis and final analysis will be performed on the analysis populations as defined below.

11.1.1. All registered patients

All patients registered according to protocol section 5.1.1 “Registration procedure”, excluding duplicate registrations and registrations made in error, will be included among All Registered Patients.

11.1.2. All eligible patients

All patients included among All Registered Patients, excluding those identified as ineligible patients upon examination of the treatment arms, will be included among All Eligible Patients. Ineligible patients can only be included among All Eligible Patients by the judgment of an investigator, study site coordinator or the study site study manager. Approval of the study representative is required to identify ineligible patients from treatment arms at final analysis, though at interim analyses and at analyses for academic presentations performed prior to submission of periodic monitoring and the final analysis reports, with the understanding of the study administrator the data center is allowed to exclude patients from among All Eligible Patients when identified as ineligible by a study administrator.

11.1.3. All Treated Patients

All patients among All Registered Patients administered the protocol treatment in whole or in part will be included among All Treated Patients. With the understanding of a study administrator, the data center may identify patients who took none of the protocol treatments as Untreated Patients and decide whether to exclude them from the data aggregation performed for safety.

11.2. Endpoint definitions

11.2.1. Overall survival

The period starting from the registration date until the day of death by any cause.

- The cutoff point for surviving patients will be the date of the final confirmation of survival.
- The cutoff point of patients lost to follow-up will be the date of the final confirmation of survival prior to the patient becoming lost to follow-up.

11.2.2. Relapse-free survival

The period starting from the registration date until the day that recurrence is confirmed.

- The cutoff for relapse-free patients will be the date of the final confirmation of survival.
- If a patient dies for a reason other than the primary disease while relapse-free, it will be deemed an event using the date of death.
- The cutoff for patients lost to follow-up will be the date of the final confirmation of the patient being relapse-free prior to the patient becoming lost to follow-up.

11.2.3. Adverse events**1. Incidence of adverse events**

Taking All Treated Patients as the denominator, the frequency of the worst grade of each of the below adverse events (toxicities) based to the CTCAE ver3.0 Japanese translation JCOG/JSCO edition will be calculated during all courses.

| | |
|-------------------------|---|
| Constitutional symptoms | Fatigue, fever |
| Dermatology/skin: | Hyperpigmentation, hand-foot skin reaction |
| Gastrointestinal: | Anorexia, diarrhea, nausea, vomiting, mucositis (functional/symptomatic)-oral cavity |
| Infection: | Infection with Grade 3 or 4 neutrophils (fever of unknown origin) Infection with Grade 3 or 4 neutrophils (documented clinically) -{Catheter-related infection, biliary tree, gallbladder, bronchus, lung (pneumonia), pharynx, upper respiratory NOS, bladder, kidney, urinary tract NOS} Infection with Grade 0 to 2 neutrophils -{Catheter-related infection, biliary tree, gallbladder, bronchus, lung (pneumonia), pharynx, upper respiratory NOS, bladder, kidney, urinary tract NOS} |
| Ocular/visual: | Watery eye |
| Blood/bone marrow: | Hemoglobin, leukocytes, neutrophils, platelets |
| Metabolic/laboratory: | Hypoalbuminemia, ALT, AST, bilirubin, hypocalcemia, hypercalcemia, creatinine, hyperkalemia, hypokalemia, hyponatremia, hyponatremia |

Other than the above-described adverse events (toxicities), because only adverse events that are non-hematological toxicities (blood/bone marrow category) of Grade 3 or above will be entered in records forms, as a general rule their incidence will not be calculated except for when specific adverse events are observed in high numbers.

2. Incidence of severe adverse events

Taking All Treated Patients as the denominator, the incidence of severe adverse events will be calculated as the proportion of subjects in whom any of the severe adverse events shown below occurs, using the number of patients who experience at least one of these severe adverse events as the numerator.

- 1) All deaths during the protocol treatment period, or within 30 days from the final day of chemotherapy. (Deaths will be counted irrespective of causal relationship to protocol treatment.)
- 2) Deaths from 31 days after the final day of chemotherapy onwards with a causal relationship to protocol treatment that cannot be ruled out.
- 3) Grade 4 non-hematological toxicities (does not include adverse events in the blood/bone marrow category).

11.2.4. Health-related QOL

Details shown in protocol section 12

12. Health-related QOL

12.1. Objectives

Patients' subjective assessment of their HRQOL will be compared as a secondary indicator for evaluation.

- (1) The difference in the impact gemcitabine therapy and S-1 therapy have as adjuvant chemotherapy in patients with resected pancreatic cancer will be compared.
- (2) HRQOL during the entire survival period will be compared between the treatment arms as the QALY.

12.2. HRQOL scale

EQ-5D²³⁻²⁵ will be used as the standardized measure of HRQOL (☞ Appendix). EQ-5D is a simple measure of QOL and will be used to calculate QALY (5 levels of severity).

12.3. HRQOL survey schedule

The first survey will be completed before treatment, then upon entering the third and sixth month of the 6-month protocol treatment period, and every 6 months thereafter.

In this study the administration schedule for the protocol treatment will vary, and some leeway will be allowed with respect to the acceptable time (window) within which surveys are to be completed. While surveys in the protocol treatment period should be completed upon entering the third and sixth months of the protocol treatment period, as a general rule, the surveys may be completed within a window of ± 2 weeks of those times. During the observation period and follow-up period, as a general rule, surveys may be completed within a ± 1 -month window.

12.4. Survey method

As a general rule, surveys will be implemented by a CRC at each survey time point before the start of the next treatment course. Survey forms will be collected by a CRC or investigator. PS will be determined by a CRC or investigator and entered on the survey form. A CRC or investigator will collect survey forms and send them by post to the data center.

Note that in the event a patient is unable to fill in the survey form personally due to worsening of his/her condition, as a general rule the CRC may implement the survey by reading out the survey form to the patient. However, in such cases, this fact will be entered on the survey form.

12.5. Sample size

From experience of conduct of the N-SAS-BC02 trial, the minimum necessary sample size for an HRQOL analysis is deemed to be around 300 patients.

12.6. Method of data analysis

The EQ-5D scores will be aggregated to produce the temporal change in each treatment arm, summarized to produce statistics for smaller numbers as necessary, and compared for an analysis of variance between treatment arms. Propensity scores and weighting, etc. will be used to impute missing data. Details of the analytical plan, including QALY calculation (standard error calculation in particular), will be specified in a separate analytical plan.

13. Statistical considerations

13.1. Main analyses and evaluation criteria

Through applying a proportional hazard model, a hazard ratio threshold of 1.25 will be used to verify the non-inferiority of the S-1 arm against the GEM arm in terms of overall survival. Specifically, applying the proportional hazard model, non-inferiority will be verified if the 95% confidence interval of the S-1 arm to GEM arm death hazard ratio does not exceed 1.25. A standard log-rank test will also be performed between the treatment arms for reference. If non-inferiority is verified, the superiority of the S-1 arm over the GEM arm will also be tested using a log-rank test.

For purposes of interpretation, a normal approximation will be used to calculate the posterior distribution of the log hazard ratio from a noninformative prior distribution, and a posterior probability calculated that includes the log hazard ratio for both inside and outside the above-described threshold ($\pm \log 1.25$) and a stricter threshold of $\pm \log 1.15$. The assumption of this investigation of proportional hazards between the treatment arms will be confirmed using a log-log plot of a Kaplan-Meier curve. If a marked deviation from the proportional hazards assumption is observed, the same investigation as described above will be performed for the 3-year cumulative survival rate.

Note that QALY and Quality Adjusted Disease Free Survival (QADFY), which are measurements of QOL, will be compared between treatment arms in order to provide important judgment criteria on which to base the selection of a primary treatment.

Adverse events and QOL will be examined along with the results of the primary endpoint, and one of the below conclusions will be reached for this study. Moreover, all data relating to endpoints in this study must be presented to, and the final conclusion approved by, the Efficacy and Safety Evaluation Committee.

- 1) If the hazard associated with S-1 therapy is $< 1/1.15$, S-1 therapy will be recommended as adjuvant chemotherapy for resected pancreatic cancer in Japan.
- 2) If the hazard associated with S-1 therapy is < 1 or $\geq 1/1.15$, non-inferiority will almost be verified and S-1 therapy will be deemed a possible option as adjuvant chemotherapy for resected pancreatic cancer in Japan, while citing the probability of inferiority of S-1 therapy compared with GEM therapy.
- 3) If the hazard associated with S-1 therapy is ≥ 1 , the non-inferiority hypothesis will not have been verified. GEM therapy will be the standard treatment as adjuvant chemotherapy for resected pancreatic cancer, and S-1 therapy will not be used as adjuvant chemotherapy for resected pancreatic cancer.

13.2. Planned sample size and follow-up period

With $1/1.15$ chosen as the true hazard ratio between the S-1 arm and GEM arm and with a statistical power of 80%, a total 240 events (deaths) is needed across the treatment arms to verify non-inferiority. The 3-year survival rate of the GEM arm will be set at 36% (and, based on the above assumption, the anticipated 3-year survival rate in the S-1 arm is 41%), and assuming an exponential distribution for the survival function (MST of 27.2 and 28.0 months, respectively) and that 360 patients are registered evenly across both treatment arms during the 3 years, the expected incidence of events at 1, 2 and 3 years after registration is 191, 237 and 270, respectively. From the above, with 360 registered patients, interim analysis will take place at 1 year after the end of registration when there is anticipated to be 180 events, and final analysis will take place at 2 years after the end of registration.

Note that the results of the above calculations are strongly dependent on the value of the base 3-year survival rate (36%) and the exponentiality of the survival distribution. Because of differences in patient selection resulting from the inclusion/exclusion criteria, differences in the patient population itself, and survival benefits that are expected to result from posttreatment with

S-1 and gemcitabine, the actual number of events may be expected to be fewer than the number anticipated. It should be considered that extension of the follow-up period would be highly likely in the case of a GEM arm 3-year survival rate of 40% and a hazard ratio that is lower by about 10%. It is not definite that registration will proceed as planned. Consequently, incidence of events will be monitored during and after registration and examined again at both interim and final analyses.

Although 1.25 is slightly high as a threshold for a non-inferiority study (1.15 to 1.2 is commonly used), when conducted from the perspective of drug approval, a non-inferiority study is essentially a way of obtaining a definite and quick evaluation of a treatment method that is believed to be superior, and is not a methodology used to carry out a relative evaluation to choose between treatments that are considered almost equivalent. Nevertheless, with the amount of information obtained in a non-inferiority study, it is quite possible to carry out a relative comparison between treatment arms using the confidence intervals of the hazard ratio or difference between survival rates. For example, when a Bayesian process is used to calculate the posterior distribution of the log hazard ratio from a noninformative prior distribution, non-inferiority of the S-1 arm against the GEM arm is verified at a hazard ratio of exactly 0.97, where the posterior possibilities for inferiority and non-inferiority of the S-1 arm against the GEM arm are 41% and 59%, respectively. If a stricter threshold of 1.15 and hazard ratio of 1/1.15 (0.87) is used, the posterior probability that the hazard ratio lies outside it is 9.4% for inferiority and 19.7% for non-inferiority, and the posterior probability that the hazard ratio lies inside and can be considered clinically equivalent is 70.9%.

13.3. Patient handling, analysis population and data analysis

Proposals for patient handling, including treatment compliance, will be prepared by the Protocol Drafting Committee prior to the end of registration, and implemented according to criteria determined prior to interim analysis. Patients subject to the main analyses of overall survival and relapse-free survival will be All Eligible Patients in whom study treatment has been started (the so-called full analysis set). Patients subject to analysis of adverse events will be patients in whom study treatment has been started (All Treated Patients). Patients that will be subject to secondary analyses of survival time will be specified in an analytical plan established prior to interim analysis. Analytical methods will also be prescribed in detail in this analytical plan. Separate data handling criteria and a separate analytical plan will be prepared for HRQOL.

13.4. Summarizing patient registration

Patient registration data will be summarized. Discontinuations and dropouts will be summarized based on the handling criteria, and cumulative discontinuations and dropouts will be calculated by the Kaplan-Meier method. To investigate balance between the treatment arms with respect to distribution of the most important background factors, background factors will be summarized with respect to each factor. To measure the degree of balance, tests will be carried out between the treatment arms with respect to each factor as necessary.

13.5. Summarizing and comparing treatment compliance

Treatment compliance will be summarized based on the handling criteria. Reasons for treatment discontinuation will be summarized. The frequency and reasons for changes in treatment other than discontinuation will be summarized.

13.6. Analysis of survival times

The cumulative survival rate will be calculated for each survival time for each treatment arm by

the Kaplan-Meier method. Confidence intervals for the survival rate for each year from the first to the fifth year will be calculated using Greenwood's formula.

13.7. Supplemental analysis of survival times

Subset analyses will be performed for important prognostic factors. The R and N values using during assignment will be included as factors, as may other factors observed to be strongly related to survival time during a blind review. Furthermore, a Cox regression including dummy variables and the factors above will be used to investigate the strength of the effect of prognostic factors on survival time.

13.8. Analysis of the impact of secondary treatments on overall survival

Using an appropriate method of causal inference, there will be an exploratory investigation of the impact of secondary treatments on overall survival after recurrence.

13.9. Analysis of adverse events

Frequencies of adverse events will be summarized for each course of each treatment arm based on grade. Adverse events of high frequency will be investigated for their cumulative status. The worst grade of each adverse event will be calculated for each patient, and the treatment arms compared according to the Mantel test. Only adverse events of Grade 3 or 4 will also be summarized.

13.10. Other analyses

HRQOL will be analyzed according to an analytical plan to be prepared separately, as stated above. Other exploratory analyses, such as a between-study site analysis of survival times, will be performed according to the analytical plan.

13.11. Blinded monitoring

The Steering Committee will monitor registration, treatment compliance, and survival under blinded conditions with the treatment arms masked. The Steering Committee will also investigate the suitability of the rationale used to set the required sample size (number of events) and determine non-inferiority thresholds, the suitability of the interim analyses and final analysis and timing of public release of the same, taking into consideration newly released clinical study results, newly approved anticancer drugs/adjuvant chemotherapies deemed efficacious and the like. When a protocol change is judged necessary, a change to the protocol will be proposed upon discussion with the Protocol Drafting Committee and the change enacted upon deliberation and approval by the Efficacy and Safety Evaluation Committee. The above-described examinations will not be compulsory. The blind review required to determine details of the analytical plan, such as which variables to investigate using the Cox regression model, will be undertaken before the interim analysis.

13.12. Interim analysis

The Efficacy and Safety Evaluation Committee will carry out an interim analysis at 1 year and 2 years after the start of registration to examine treatment compliance and occurrence of adverse events. The Efficacy and Safety Evaluation Committee will offer advice to the Steering Committee on discontinuation of the study and changes to the study plan if such are deemed necessary, taking

into consideration patient registration, newly released clinical study results, newly approved anticancer drugs/adjuvant chemotherapies deemed efficacious and the like.

The Efficacy and Safety Evaluation Committee will carry out an interim analysis of efficacy in terms of overall survival upon observation of 180 events (deaths). The purpose of this interim analysis is to avoid continued administration in a treatment arm in disadvantageous circumstances, when it does not seem possible to verify the non-inferiority of the S-1 arm against the GEM arm or when the S-1 arm is markedly inferior to the GEM arm in terms of safety (futility). Conversely, the purpose of this interim analysis is also to quickly release the results and see the conclusions quickly put into clinical practice when excellent performance is observed in the S-1 arm and non-inferiority is deemed to have already been verified (efficacy). The criterion for determining futility is a Bayesian predictive power of 5% with respect to non-inferiority. This is equivalent to an S-1 arm to GEM arm hazard ratio of 1.13 (log-rank test: one-sided $p = 0.20$). The criterion for determining efficacy is a one-sided p -value of 0.1%. In other words, non-inferiority will be examined using two-sided 98% confidence intervals. If non-inferiority is verified according to this criterion the S-1 arm to GEM arm hazard ratio will be 0.79 (log-rank test: one-sided $p = 0.057$). The Efficacy and Safety Evaluation Committee will, based on the above-described criteria and upon considering information such as adverse events, results of a current analysis of HRQOL, newly released clinical trial results and newly approved anticancer drugs/adjuvant chemotherapies deemed efficacious, offer advice to the Steering Committee to recommend either discontinuation or continuation of the study based on a determination of either futility or efficacy. In the event of a recommendation to discontinue the study based on either futility or efficacy, the Efficacy and Safety Evaluation Committee will recommend publication of the study results at the same time as the final follow-up/final report.

Note that following Korn's proposal²⁶, even if the study is not discontinued at an interim analysis, if the time interval between an interim analysis and final analysis is expected to be at least 1 year the results of the interim analysis may be publicly released once the schedule for the final analysis and report has been stated explicitly.

14. Ethical considerations

14.1. Patient protection

All study collaborators will conduct this study in accordance with the principles of the Declaration of Helsinki (Japan Medical Association: <http://www.med.or.jp/wma/>) and according to Ethical Guidelines for Clinical Studies (MHLW Notice No. 255: <http://www.mhlw.go.jp/topics/2003/07/tp0730-2.html>).

14.2. Informed consent

14.2.1. Explanation to patients

Prior to registration, the investigator will give the patient written information that has been approved by the IRB of the study site (the attached written information or written information modified by the study site), and explain the below-described matters in detail and in person to the patient.

- 1) An explanation of the disease name, disease staging and predicted prognosis
- 2) That this study is a clinical trial
The difference between the terms clinical trial and clinical practice.
- 3) The study design and rationale for the study (rationale with respect to significance, number of registered patients, necessity, objectives, etc.)
- 4) Details of the protocol treatment
Drug names, administration, dose, treatment cycles, duration of the entire protocol treatment, etc.
- 5) Expected effects of the protocol treatment
Survival benefit, tumor regression, relief of symptoms, etc.
- 6) Expected adverse events, complications, sequela and how they will be handled
The severity and frequency of expected adverse events including complications, sequela and treatment-related death, and how they will be handled when they arise.
- 7) Burden of costs and compensation
An explanation that costs associated with treatment will be dealt with under the health insurance system, and that compensation in the event of injury to health will be proportionate with the provision of general treatment, where both costs and compensation will be equivalent with general treatment. Also, an explanation of the burden of costs, etc. in the case of off-label use.
- 8) Alternative treatment
The details, effects, toxicity, etc. of current general treatment (including palliative care) and current standard treatment.
The benefits and disbenefits of choosing an alternative treatment.
- 9) The expected benefits and potential disbenefits to the patient of participation in the study
The benefits it is believed the patient will enjoy and the disbenefits it is believed the patient will suffer upon participating in the study.
- 10) Direct access of medical history
An explanation about accepting audits such as “The direct access of medical histories by the medical staff of other facilities with the permission of the head of the study site for the purposes of quality control”.
- 11) Refusal of consent and withdrawal of consent
That the patient is free to refuse to consent to participate in the study, and that having consented to participate in the study the patient is then free to withdraw to consent to participate in the study, and in either event the patient will experience no unwarranted medical disbenefit.
- 12) Respect for human rights

Maximum efforts will be taken to keep names secret and protect personal information.

13) Secondary use of data

That data may be used for a second time (meta-analysis, etc.), though in a manner that does not connect it to any personally identifying information.

14) Inquiries

In addition to the contact details of investigators, patients will be given the contact details of the study site study manager and study representative (or study administrator) in document form, and informed they are free to ask them questions about the study and the treatment.

14.2.2. Consent

After explaining the study to the patient and confirming that the patient thoroughly understands the content of the study, the patient will be requested to participate in the study. If the patient herself/himself agrees to participate in the study, the investigator who explained the study and the patient who received the explanation and consents to participate in the study will both sign and date the attached informed consent form or an informed consent form that is in a format determined by the study site.

Two copies of the informed consent form will be made, with one copy given to the patient herself/himself and one copy retained by the study site coordinator. The original informed consent form will be retained for the medical record.

14.3. Protection of privacy and patient identification

Participating study sites will not inform the data center of the name, initials, date of birth or medical record number of registered patients.

Registered patients will be identified and cross-referenced using the registration number issued at registration. Consequently, no information that can be used by a third party to directly identify patients will be entered into the database of the CSPOR data center, except via the staff of the study site or via unauthorized access of the database.

14.4. Protocol violations

Study personnel participating in this study will comply with this protocol to the extent it does not interfere with the safety or human rights of the patient.

14.5. Approval of the study site ethical review board (institutional review board)

14.5.1. Approval at the start of study participation

This protocol and the written information for patients must be approved by the ethical review board or IRB of each study site prior to participation in this study.

Once approved by the IRB, the principal investigator or study site coordinator of each study site will fax the statement of IRB approval to a study administrator and the CSPOR data center. The original copy of the statement of IRB approval will be retained by the principal investigator of the study site or the study site coordinator, and the faxed copies of the statement of IRB approval will be retained by the study administrator and CSPOR data center.

Note that the written information for patients may be used after modification by the study site and subsequent approval by the IRB of the same study site, but study sites will not be allowed to change the content of the protocol. The same protocol will be used by all study sites. If it becomes necessary to change the content of the protocol, the protocol used by all study sites will be amended or revised accordingly.

14.5.2. Annual renewal of IRB approval

An annual renewal of the review and approval of this protocol and the written information for

patients by the ethical review board or IRB of each study site may or may not be performed, according to the provisions of each participating study site. Study administrators will not request the submission of written acknowledgment of the annual renewal of IRB approval.

14.6. Changes to the protocol

14.6.1. Types of changes to the protocol

Before making a change (activation), an Application for Protocol Revision must be submitted to and approved by the Efficacy and Safety Evaluation Committee.

Protocol changes made after approval by the Clinical Trial Review Committee will be divided into protocol amendments and protocol revisions. However, because this distinction will be made by the Efficacy and Safety Evaluation Committee, all applications to the committee may be made as an Application for Protocol Revision. Also, the addition of supplementary explanations that do not equal a protocol change will be identified as memoranda. Definitions and handling are shown below.

1) Amendment

A partial change to the protocol that has the potential to increase the risk to patients participating in the study, or is related to the primary endpoint. Requires review and approval by the Efficacy and Safety Evaluation Committee and IRB of each study site. Requires approval by a study administrator and the head of the data center before an application for the change can be made to the Efficacy and Safety Evaluation Committee.

The date of approval by the Efficacy and Safety Evaluation Committee will be shown on the cover page.

2) Revision

A change to the protocol that does not have the potential to increase the risk to patients participating in the study, and is not related to the primary endpoint. Requires review and approval by the Efficacy and Safety Evaluation Committee. Requires approval by a study administrator and the head of the data center before an application for the change can be made to the Efficacy and Safety Evaluation Committee.

Review and approval by study site IRBs will be handled according to the arrangements of individual study sites.

The date of approval by the Efficacy and Safety Evaluation Committee will be shown on the cover page.

3) Memorandum

A supplementary explanation of the protocol to be distributed by the study representative/study administrators to study contributors for the purpose of reducing the variety of possible interpretations of the protocol and in particular to call attention to certain matters; not a protocol change. No prescribed format.

Requires approval by the study representative and head of the data center prior to distribution. Requires a report to be made to the Efficacy and Safety Evaluation Committee either before distribution or promptly after distribution.

Does not need to be shown on the cover page.

14.6.2. Study site IRB approval upon protocol amendment/revision

During the study, when the protocol or written information for patients is amended following approval by the Efficacy and Safety Evaluation Committee, the amended protocol and written information must be approved by the ethical review board (or IRB) at each study site.

When the change is a revision and not an amendment, the decision as to whether its review and approval is required by study site ethical review boards (or IRBs) will be handled according to arrangements at each study site.

When an amendment has been approved by an IRB, the principal investigator or study site coordinator of each study site will fax a copy of the IRB approval statement to a study administrator and the CSPOR data center. The original copy of the IRB approval statement will be retained by the principal investigator or study site coordinator, and copies retained by the study

administrator and CSPOR data center, respectively.

14.6.3. Correction of records forms (reproduction of section 9.1.4.)

Although the CSPOR data center and study administrators take extreme care during the preparation of records forms, it is possible that missing or inappropriately classified required items and the like are discovered in records forms after commencement of the study. In such cases, records forms will be corrected upon the consent of the head of the data center and a study administrator, provided the change does not mean the scope of the data prescribed for collection in protocol section 8. “Items for evaluation, laboratory tests and evaluation schedule” will be exceeded, and provided the correction is judged not to increase the clinical or financial burden on registered patients. Corrections to records forms that do not require amendment of the protocol itself will not be regarded as protocol amendments. Study site rules will be followed as to whether a records form correction will be reported to the study site IRB.

15. Monitoring and audit

15.1. Periodic monitoring

The CSPOR data center will expedite submitted data, review and make inquiries with respect to submitted data, correct data based on the results of such inquiries, and manage its database according to a separately established data management plan (SOPs and manual).

As a general rule, periodic monitoring will be carried out twice annually to check whether the study is being conducted safely and according to the protocol, and whether data is being gathered accurately.

Monitoring will take place by the central monitoring of data entered into records forms (CRFs) collected by the CSPOR data center, and will not take place by visiting study sites to verify submitted data against source documents.

Periodic monitoring reports prepared by the CSPOR data center will be submitted to and examined by the study administrators, study representative and Efficacy and Safety Evaluation Committee.

The CSPOR data center will prepare periodic monitoring reports using entered data, and prepare analytical datasets for statistical analysis.

The objective of periodic monitoring is not to expose problems with the study and at study sites, but to provide feedback on problems in order to improve the scientific and ethical basis of the study. Consequently, the study administrators, study representative and Efficacy and Safety Evaluation Committee will endeavor to resolve problems highlighted in period monitoring reports.

15.1.1. Monitored items

- (1) Status of accrual: Number of registered patients-cumulative/by period, all study sites/by study site
- (2) Eligibility: Ineligible patients/potentially ineligible patients: study site
- (3) By protocol treatment ongoing/treatment ended, reason for discontinuation/ending: study site
- (4) Pretreatment background factors
- (5) Severe adverse events: study site
- (6) Adverse drug reactions/adverse events
- (7) Protocol deviations: study site
- (8) Overall survival: All Registered Patients
- (9) Other problems relating to safety and study progress

15.1.2. Protocol deviations/violations

Protocol deviations will include treatments such as drug administration, radiation exposure and surgical resection, laboratory tests, and toxicity/efficacy evaluations not performed according to the provisions of the protocol.

During monitoring, as a general rule, deviations that exceed specific acceptable ranges decided between the study administrators and study representative will be listed as “Patients with a potential deviation” in the monitoring report, and upon examination by the study administrators and study sites attributed one of the classifications below.

1) Violation

Deviations from the provisions of the protocol will be deemed violations if they are clinically inappropriate, were caused by the investigator/study site, AND fall under any of the following.

- (1) Impact on evaluation of a study endpoint
- (2) Intentional or systemic
- (3) The danger or deviation is of marked severity

Violations will, as a general rule, be described individually upon publication of academic articles.

2) Deviation

Deviations that do not fall under violations in 1), or acceptable deviations in 3).

Particular deviations will be described upon publication of academic articles if they are observed with high frequency.

3) Acceptable range (acceptable deviation)

Deviations from protocol acceptable ranges established before or after commencement of the study by the study group or between the study administrators and study representative.

Deviations within prescribed acceptable ranges will not be written into monitoring reports.

15.2. Study site visit and audit

Visit and audit of study sites will be carried out as necessary.

16. Notice

Central pathological diagnosis and checking for recurrence will not be carried out outside of the study sites.

17. Study organization

Changes to this section do not require review by the Efficacy and Safety Evaluation Committee, but do require approval by the study representative. Changes will be promptly promulgated in document form to all participating study sites and the data center by the study administrators/study representative.

17.1. Study representative

Katsuhiko Uesaka
Department Head, Department of Hepato-Biliary-Pancreatic Surgery, Shizuoka
Cancer Center
1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777
Tel 055-989-5222
Fax 055-989-5634
E-mail k.uesaka@scchr.jp

17.2. Study administrators

Yukiyasu Okamura
Chief Physician, Department of Hepato-Biliary-Pancreatic Surgery, Shizuoka
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1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777
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Akira Fukutomi
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E-mail a.fukutomi@scchr.jp

17.3. Steering Administrator

Clinical Trial Development Department, Public Interest Incorporated Foundation - Shizuoka
Industrial Foundation - Pharma Valley Center
Toshiyuki Soga (Department Director)
1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777
First floor, Research Laboratory, Shizuoka Cancer Center
Tel 055-980-6322
Fax 055-980-6320
E-mail jaspac@fuji-pvc.jp

Public Interest Incorporated Foundation - Shizuoka Industrial Foundation (prior Shizuoka Organization for Creation of Industries) is an incorporated foundation given permit to operate in Shizuoka Prefecture according to Article 34 of the Civil Code in March of 1970 for the purpose of management innovation for SMEs, the promotion of business start ups, the strengthening of management foundations and the advancement of research and development into science and technology.

The Pharma Valley Center promotes world-class research and development in areas spanning

medicine and wellness in order to improve the health of citizens of the prefecture and develop health-related industries, and is an administrative office of the Pharma Valley Project. The clinical trial development department works to promote the development of and promulgation of advanced medical care.

This study will be conducted by the Pharma Valley Center Clinical Research Development Project, which promotes clinical research performed mainly by researchers in Shizuoka prefecture, in order to establish evidence and promote the development of advanced medical care. The Pharma Valley Center Clinical Research Development Project will support activities and expenditures incurred during the conduct of the clinical study with funding obtained from investors sympathetic to the project.

17.4. Participating study sites

This study is a multi-center trial of postoperative adjuvant chemotherapy on a national scale. The organization established for the purpose of this study is named the Japan Adjuvant Study Group of Pancreatic Cancer, which plans to continue its work towards the development of postoperative adjuvant chemotherapies in the field of hepato-biliary-pancreatic medicine building on accumulated knowledge, experience and skills following on from the present study.

| Study site name (medical institution) | Department | Study site study manager | Study site coordinator |
|--|---|--------------------------|------------------------|
| Aichi Cancer Center Hospital | Department of gastrointestinal surgery | Yasuhiro Shimizu | Nobumasa Mizuno |
| Ashikawa Medical University | Department of gastrointestinal surgery | Yohei Kitano | Keisuke Kitano |
| Ogaki Municipal Hospital | Department of surgery | Yuji Kaenoka | Atsuyuki Maeda |
| Kasugai Municipal Hospital | Department of surgery | Ryuzo Yamaguchi | Shinya Watanabe |
| Kanagawa Cancer Center | Department of gastrointestinal surgery, hepato-biliary-pancreatic | Soichiro Morinaga | Shinichi Ohkawa |
| Kyushu Cancer Center | Department of gastrointestinal surgery | Yasuharu Ikeda | Tadashi Kaneshiro |
| Kure Medical Center | Department of surgery | Nobuyoshi Hatanaka | Masahiro Tanemura |
| Gunma Prefectural Cancer Center | Department of gastrointestinal surgery | Hideyuki Nogawa | Yuko Nagashima |
| National Cancer Center Hospital East | Department of epigastric surgery | Masaru Konishi | Masaru Konishi |
| National Hospital Organization Osaka Minami Medical Center | Department of surgery | Shoji Nakamori | Atsushi Miyamoto |
| Saitama Cancer Center | Department of gastrointestinal surgery | Hirohiko Sakamoto | Hirohiko Sakamoto |
| Shizuoka Cancer Center | Department of hepato-biliary-pancreatic surgery | Katsuhiko Uesaka | Yukiyasu Okamura |
| Shizuoka General Hospital | Department of surgery | Yusuke Kyoda | Yusuke Kyoda |
| Jichi Medical University Hospital | Department of gastrointestinal surgery | Naohiro Sata | Yasunari Sakuma |
| Seirei Mikatahara General Hospital | Department of surgery | Kazunori Ogino | Hirofumi Fujita |

| | | | |
|--|---|--------------------|---------------------------------|
| Chiba Cancer Center | Department of gastrointestinal surgery | Hiroshi Yamamoto | Osamu Kainuma |
| University of Tsukuba, Graduate School of Comprehensive Human Sciences | Department of gastrointestinal surgery | Nobuhiro Ohkohchi | Tatsuya Oda Shinji Hashimoto |
| Tochigi Cancer Center | Department of surgery | Shoichi Hishinuma | Moriaki Tomikawa |
| Toyama Prefectural Central Hospital | Department of surgery | Koichi Shimizu | Koichi Shimizu |
| Nagoya University Hospital | Department of gastrointestinal surgery I | Masato Nagino | Yukihiro Yokoyama |
| Fujita Health University | Second department of general surgery (biliary-pancreatic) | Shin Ishihara | Shin Ishihara |
| Hokkaido University Hospital; | Department of oncological surgery | Satoshi Hirano | Satoshi Hirano |
| Yamagata University | Department of gastrointestinal and general surgery | Wataru Kimura | Ichiro Hirai |
| Yokohama City University | Department of gastrointestinal surgery | Endo Itaru | Takao Matsuyama |
| Hyogo Prefectural Nishinomiya Hospital | Department of surgery | Masaki Kashiwazaki | Masaki Kashiwazaki |
| Kobe University Hospital | Department of hepato-biliary-pancreatic surgery | Yonson Ku | Masako Shinzeki |
| Kushiro City General Hospital | Department of surgery | Naoto Hasegawa | |
| Toyohashi Municipal Hospital | Department of general surgery | Takehiko Kato | Takehiko Kato |
| Tokyo Women's Medical University Hospital | Department of gastrointestinal surgery | Masakazu Yamamoto | Takashi Hatori |
| Tokyo Women's Medical University Medical Center East | Department of surgery | Yoshihiko Naritaka | Shunichi Shiozawa |
| Tokyo Womens Medical University Yachiyo Medical Center | Department of hepato-biliary-pancreatic surgery | Tatsuo Araida | Tomoko Murakami |
| Shikoku Cancer Center | Department of gastrointestinal surgery | Minoru Tanada | Akinori Asaki |
| Hirosaki University | Department of gastrointestinal surgery | Kenichi Hakamada | Keinosuke Ishido |

17.5. Steering Committee

| | | |
|-------------|------------------|--------------------------------------|
| Chairperson | Katsuhiko Uesaka | Shizuoka Cancer Center |
| Member | Taira Kinoshita | National Cancer Center Hospital East |
| Member | Masato Nagino | Nagoya University Hospital |
| Member | Narikazu Boku | St. Marianna University |
| Member | Toshiyuki Soga | Pharma Valley Center |

17.6. Efficacy and Safety Evaluation Committee

| | | |
|-------------|-------------------|------------------------------|
| Chairperson | Nobuyuki Yamamoto | Wakayama Medical University |
| Member | Masayuki Shinoda | Aichi Cancer Center Hospital |
| Member | Shuji Saito | Yokohama Medical Center |
| Member | Takeharu Yamanaka | National Cancer Center |

17.7. Study statistician (manager of biostatistical analysis)

Yasuo Ohashi
Professor, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

17.8. Data center

The Public health Research Foundation (CSPOR) will be entrusted with the responsibilities of the data center.

Representative (head of CSPOR data center)
Yasuo Ohashi
Professor, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo/NPO Japan Clinical Research Support Unit Chief Director
1-2-13 Yushima, Bunkyo-ku, Tokyo 113-0034 (within NPO Japan Clinical Research Support Unit)
Tel 03-3254-8029
Fax 03-5298-8536
E-mail jaspac01@crsu.org

17.9. Protocol Drafting Committee

| | | |
|-------------|------------------|--------------------------|
| Chairperson | Katsuhiko Uesaka | Shizuoka Cancer Center |
| Member | Narikazu Boku | St. Marianna University |
| Member | Atsuyuki Maeda | Ogaki Municipal Hospital |
| Member | Akira Fukutomi | Shizuoka Cancer Center |

18. Presentation of study results

Following presentation of the results of this study to the ASCO or similar international academic meetings, they will be submitted for publishing in an English-language journal as a research article. The results of this study will also be presented at academic meetings within Japan as necessary. The Steering Committee will decide who will make presentations and who will author the journal article while taking the number of registered patients into consideration, and definitely include the three study sites with the most registered patients in these decisions. As stated in protocol section 13.12. “Interim analysis”, the results of interim analyses may also be presented if there is expected to be at least a 1-year interval between an interim analysis and the final analysis.

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20. Appendix

- Performance status scale (ECOG)
- Toxicity criteria (CTCAE v3.0 Japanese translation JCOG/JSCO edition)
- Drug package inserts
- Written information/informed consent form
- Complete set of records forms (CRFs)