Multicenter Phase II Study of Gemcitabine and S-1 Combination Therapy (GS Therapy) in Patients With Metastatic Pancreatic Cancer†

Hideki Ueno1,* , Takuji Okusaka1, Junji Furuse2,3, Kenji Yamao4, Akihiro Funakoshi5, Narikazu Boku6, Shinichi Ohkawa7, Osamu Yokosuka8, Katsuaki Tanaka9, Fuminori Moriyasu10, Shoji Nakamori11 and Tosiya Sato12

1Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, 2Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital East, Chiba, 3Department of Internal Medicine, Medical Oncology, Kyorin University School of Medicine, Tokyo, 4Department of Gastroenterology, Aichi Cancer Center Hospital, Aichi, 5Department of Gastroenterology, National Kyushu Cancer Center, Fukuoka, 6Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, 7Division of Hepatobiliary and Pancreatic Medical Oncology, Kanagawa Cancer Center Hospital, Kanagawa, 8Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, Chiba, 9Gastroenterological Center, Yokohama City University Medical Center, Kanagawa, 10Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, 11Department of Surgery, National Hospital Organization, Osaka National Hospital, Osaka and 12Department of Biostatistics, Kyoto University School of Public Health, Kyoto, Japan

*For reprints and all correspondence: Hideki Ueno, Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: hiueno@ncc.go.jp

Received May 9, 2011; accepted June 2, 2011

Objective: The aim of this multicenter Phase II study was to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy for metastatic pancreatic cancer.

Methods: Chemotherapy-naïve patients with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. Gemcitabine was administered at a dose of 1000 mg/m² over 30 min on days 1 and 8, and oral S-1 at a dose of 40 mg/m² twice daily from days 1 to 14, repeated every 3 weeks.

Results: A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4% (95% confidence interval: 30.9–58.6%). The median progression-free survival was 5.9 months (95% confidence interval: 4.1–6.9 months) and the median overall survival was 10.1 months (95% confidence interval: 8.5–10.8 months) with a 1-year survival rate of 33.0%. The major Grade 3–4 toxicities were neutropenia (80%), leucopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia.

Conclusions: Gemcitabine and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer. A randomized Phase III study to confirm the efficacy of gemcitabine and S-1 combination therapy is ongoing.

Key words: pancreatic cancer – Phase II – chemotherapy – gemcitabine – S-1

†Part of the content of this report was presented at the ASCO 2007 meeting in the poster presentation (abstract 4550).
INTRODUCTION

Pancreatic cancer is a highly malignant disease and the fifth most common cause of cancer death in Japan. Approximately 80% of patients are ineligible for surgery at diagnosis and more than half of patients have metastatic disease.

Gemcitabine has been the standard chemotherapeutic agent for metastatic pancreatic cancer on the basis of a Phase III study showing clinical and survival benefits over 5-fluorouracil (5-FU) (1). However, the efficacy of gemcitabine monotherapy for advanced pancreatic cancer is limited; most clinical trials have shown response rates of around 10% with a median overall survival of 6–7 months (2–5). Therefore, numerous studies have attempted to increase the efficacy of chemotherapy, but almost all the regimens evaluated in Phase III studies have failed to show survival benefits over gemcitabine. To date, only two randomized trials, gemcitabine plus erlotinib and combination therapy of 5-FU/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) have shown significant prolongation of overall survival (6,7). However, the reported difference in median survival between the gemcitabine plus erlotinib group and the gemcitabine-only group was small (6.24 versus 5.91 months). The results of the FOLFIRINOX trial are more impressive than those of gemcitabine plus erlotinib because FOLFIRINOX led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group. However, the FOLFIRINOX regimen was quite toxic (e.g. 5.4% of patients had Grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger and normal or nearly normal bilirubin levels (8).

S-1, an oral fluoropyrimidine derivative, is now widely used for a variety of malignancies such as gastric cancer (9,10). In Phase II studies of S-1 for metastatic pancreatic cancer, response rates of 21.1–37.5% and median overall survival of 5.6–9.2 months were reported (11,12). Preclinical studies have demonstrated a synergy between gemcitabine and S-1 in tumor cell lines, including pancreatic cancer cells (13). On the basis of these findings, we decided to investigate combination therapy with gemcitabine and S-1 therapy (GS therapy) for pancreatic cancer. We initially conducted a Phase I study of GS therapy in patients with advanced pancreatic cancer (14). In that study, gemcitabine was administered as a 30-min intravenous infusion on days 1 and 8 along with oral S-1 twice daily from day 1 through day 14, concluding that a gemcitabine dose of 1000 mg/m² and an S-1 dose of 40 mg/m² twice daily was recommended in future studies. Since GS therapy showed promising activity, with a 33% response rate and a median survival of 7.6 months, the present multicenter Phase II study was conducted in patients with metastatic pancreatic cancer to evaluate the efficacy and toxicity profile of GS therapy.

PATIENTS AND METHODS

PATIENT SELECTION

Patients were included if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma of the pancreas; at least one measurable metastatic lesion; no history of prior chemotherapy or radiotherapy for pancreatic cancer; age 20–74 years; Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ functions (leucocyte count, 4000–12 000/mm³; neutrophil count, ≥2000/mm³; platelet count, ≥100 000/mm³; hemoglobin level, ≥9.0 g/dl; serum creatinine level, ≤1.5 mg/dl; serum AST and ALT levels, ≤150 U/l and serum total bilirubin level, ≤2.0 mg/dl or ≤3.0 mg/dl if biliary drainage was present).

The exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia; watery diarrhoea; active infection; marked pleural effusion or ascites; central nervous system metastasis; active concomitant malignancy; severe mental disorder; serious complications such as active gastrointestinal ulcer or severe diabetes mellitus and pregnancy or lactation. The study was approved by the institutional review board of each participating center, and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research (the Ministry of Health, Labour and Welfare, Japan). Written informed consent was obtained from all patients. This study is registered in the UMIN Clinical Trials Registry with the identifier C00000173.

TREATMENT

This study was an open-label, multicenter, single-arm Phase II study. The dose schedule of gemcitabine and S-1 was planned based on the results of the previous Phase I study (14): gemcitabine at a dose of 1000 mg/m² was administered as a 30-min intravenous infusion weekly for 2 weeks followed by 1 week of rest. Oral S-1 was administered at a dose of 40 mg/m² twice daily (80 mg/day for body surface area (BSA) <1.25 m², 100 mg/day for 1.25 ≤ BSA <1.50 m² and 120 mg/day for BSA ≥1.50 m²) from days 1 to 14 followed by a 1 week rest period. The treatment was repeated every 3 weeks until disease progression, unacceptable toxicity or patient refusal.

Prophylactic administration of antiemetic agents such as dexamethasone and/or a 5-HT3 receptor antagonist was allowed at the investigator’s discretion. If patients showed a leucocyte count of <2000/mm³ or >12 000/mm³, or a platelet count of <70 000/mm³ during the cycle, administration of both gemcitabine and S-1 was suspended. If patients showed a leucocyte count of <3000/mm³ or >12 000/mm³, platelet count of <100 000/mm³, total bilirubin >3.0 mg/dl, AST and ALT levels >150 U/l, or a creatinine level >1.5 mg/dl, initiation of the next cycle was postponed until recovery. When patients experienced (i) Grade 4 leucopenia or neutropenia, (ii) febrile
neutropenia or infection with Grade 3 leucopenia or neutropenia, (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion or (iv) ≥Grade 3 non-hematological toxicity excluding anorexia, nausea, vomiting, constipation, fatigue and hyperglycemia, the dose of gemcitabine was reduced to 800 mg/m² and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle. The protocol treatment was discontinued if the patients required more than two dose reductions or if the subsequent cycle could not be initiated within 28 days after the final day of the anti-cancer drug administration in the previous cycle.

EVALUATION

All the eligible patients who received at least one dose of GS therapy were included in the response and toxicity evaluations. Physical examination, complete blood cell counts and biochemistry tests were assessed at least on days 1 and 8 in each cycle during chemotherapy. Tumor marker carbohydrate antigen (CA) 19-9 was measured every 4–6 weeks. Objective tumor response was evaluated every 4–6 weeks by computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria In Solid Tumors version 1.0. For the purpose of confirmation of objective response, an interval of at least 4 weeks was required for complete response (CR), partial response (PR) and stable disease (SD) in this study. The response duration was defined as the interval from the first documentation of response (PR or CR) to the first documentation of tumor progression. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Progression-free survival (PFS) was calculated from the date of the initiation of treatment until documented disease progression or death due to any cause (whichever occurred first); overall survival was calculated from the date of treatment initiation to the date of death or censored at the last follow-up. An external review committee confirmed objective responses and adverse events.

STATISTICAL ANALYSIS

The primary endpoint was the response rate (CR and PR) of GS therapy. Forty-nine patients were required based on the assumption of an expected response rate of 25% and the threshold rate of 10%, with α-error of 2.5% (one-sided) and β-error of 20%. In consideration of ineligible patients or those who dropped out, it was planned that 55 patients would be included in this study. We calculated the response rate with 95% confidence interval (CI) in the patients who met eligibility criteria and received at least one GS therapy. The progression-free and overall survival periods were estimated by the Kaplan–Meier method.

RESULTS

PATIENTS

Fifty-five patients were enrolled from 10 institutions between October 2004 and July 2005. Of these 55 patients, one patient was excluded from analysis because he left the study before administration of GS therapy due to an allergic skin reaction caused by insulin. All of the remaining 54 patients received at least one dose of GS therapy and were included in the evaluation of response and toxicity. Patient characteristics of the 54 patients are listed in Table 1. All patients had metastatic disease and no patient received any prior therapies except surgery for pancreatic cancer. Six patients underwent percutaneous transhepatic or endoscopic biliary drainage for obstructive jaundice prior to the study enrollment.

TREATMENTS

The final data were fixed on 31 March 2007. A total of 425 therapy cycles were administered to the 54 patients.

Table 1. Patient characteristics (n = 54)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62 (32–74)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Men</td>
<td>30 (56)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38 (70)</td>
</tr>
<tr>
<td>1</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.59 (1.18–1.83)</td>
</tr>
<tr>
<td>History of surgical resection</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>54 (100)</td>
</tr>
<tr>
<td>Sites of metastasis</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>50 (93)</td>
</tr>
<tr>
<td>Distant lymph nodes</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Lung</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>53 (98)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>28 (52)</td>
</tr>
<tr>
<td>Poor</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (20)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
with a median of 7 cycles each (range, 1–24). GS therapy could generally be administered on an outpatient basis. The gemcitabine on day 8 was administered in 367 (86.4%) of 425 cycles. Dose reduction was required in 30 patients (55.6%), mainly due to leucopenia, neutropenia, rash or gastrointestinal toxicities. At the time of analysis, protocol treatment was discontinued in 52 patients because of disease progression (\(n=30\)) or adverse events (\(n=22\)). The reasons for discontinuation due to adverse events were the second episode of Grade 4 neutropenia after one dose reduction (11), prolonged myelosuppression (3), anorexia or nausea (4), rash (2), cerebral infarction (1) and cholangitis (1). After discontinuation of GS therapy, 30 patients received gemcitabine-based chemotherapy, 6 patients received other anticancer drugs including irinotecan and the remaining 18 patients received only supportive care.

**EFFICACY**

The efficacy results are shown in Table 2. Of the 54 patients, 2 patients could not be assessed for response since they withdrew their consent due to toxicity before the first response evaluation. Although no CR was observed, a PR was achieved in 24 of 54 patients, resulting in an overall response rate of 44.4% (95% CI: 30.9–58.6%). The median response duration was 5.3 months (range, 2.4–15.6 months). SD was noted in 26 patients (48.1%) and progressive disease (PD) in 2 patients (3.7%). The serum CA 19-9 level was reduced to less than half from baseline values in 35 (85.4%) of the 41 patients whose pretreatment levels were >100 U/ml. The median PFS was 5.9 months (95% CI: 4.1–6.9 months) with a median overall survival of 10.1 months (95% CI: 8.5–10.8 months) and a 1-year survival rate of 33.0% (Fig. 1).

**TOXICITY**

The major toxicities observed in the 54 patients are listed in Table 3. The most common toxicity was myelosuppression. Grade 3–4 neutropenia and thrombocytopenia occurred in 80 and 22% of the patients, respectively. The neutrophil and platelet count nadirs typically were observed on day 15. Although most of these hematologic toxicities were transient and recovered without serious events, one patient developed Grade 3 febrile neutropenia. No other unexpected severe toxicities were observed during the study and there were no treatment-related deaths. Although gastrointestinal toxicities and skin rash were frequently observed, most of these were manageable with appropriate medical treatment. There were no cumulative toxicities.

**DISCUSSION**

The major toxicity of GS therapy is myelosuppression, especially neutropenia. Although the incidences of Grade 3–4 neutropenia and thrombocytopenia observed in the current study were high (Table 3), most of these episodes were transient. There was only one episode of neutropenic fever without treatment-related death. Therefore, most patients could be treated on an outpatient basis without receiving granulocyte colony-stimulating factor or a blood transfusion. Although anorexia, nausea, fatigue, rash, pigmentation and aminotransferase elevation were also observed frequently in our study, most of these non-hematological toxicities were manageable with appropriate treatments. Therefore, it is considered that GS therapy in this study is tolerable for patients with metastatic pancreatic cancer.

![Figure 1. Overall survival curve (a) and progression-free survival (b) for 54 patients.](image-url)
To date, several Phase II studies testing the gemcitabine plus S-1 combination as first-line therapy for advanced pancreatic cancer have been published (Table 4) (15–18). One study was conducted in Japan and the remaining studies were in Korea. Although various schedules of gemcitabine and S-1 administration were used, the regimens adopted in all studies including this study were similar: gemcitabine at a dose of 1000–1250 mg administered on days 1 and 8 or 8 and 15 and S-1 at a dose of 60–80 mg/m²/day on days 1–14 of a 21-day cycle. The incidences and severity of toxicities reported in these trials, especially hematological toxicities, have varied widely among the studies. Interestingly, hematological toxicities were more frequently observed in the two Japanese studies, including this study, than the Korean studies. It is well known that the toxicity profile of S-1 differs between Asians and Caucasians (19); Goh and coworkers (20) carried out a study to compare S-1 pharmacokinetics and CYP2A6 activity among Asian and Caucasian patients, and reported that Asian patients had lower 5-FU exposure and lower CYP2A6 activity compared with Caucasian patients. However, the reasons for the discrepancies between the Japanese and Korean studies remain unclear.

In this trial, GS therapy produced a promising efficacy with a response rate of 44.4%. The efficacy of GS therapy reported in the recent studies as well as this study has been consistent (Table 4), with response rates of 27.3–38%, median time to tumor progression of 4.6–5.43 months and median overall survival of 7.89–12.5 months. Recently, the results of a randomized Phase II study comparing GS therapy with gemcitabine alone were reported (21). In that study, 106 patients were randomly assigned at a 1:1 ratio to either the GS group or the gemcitabine-alone group. Patients assigned to GS therapy received gemcitabine at a dose of 1000 mg/m² on days 1 and 15 and S-1 at a dose of 40 mg/m² twice daily on days 1–14, every 4 weeks. The objective response rate was 18.9% in the GS group and 9.4% in the gemcitabine group. Patients in the GS group demonstrated significantly longer PFS than those in the gemcitabine group [median PFS, 5.4 versus 3.6 months; hazard ratio = 0.64 (95% CI: 0.42–0.97); P = 0.036], while overall survival did not differ significantly between the two groups [median

Table 3. Adverse events (n = 54)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Hematological toxicity

- Leucocytes
  - 3
  - 19
  - 31
  - 1
  - 100
  - 59
- Neutrophils
  - 2
  - 9
  - 24
  - 19
  - 100
  - 80
- Hemoglobin
  - 11
  - 29
  - 8
  - 0
  - 89
  - 15
- Platelets
  - 15
  - 23
  - 12
  - 0
  - 83
  - 22

Non-hematological toxicity

- Bilirubin
  - 15
  - 9
  - 3
  - 0
  - 50
  - 6
- AST
  - 23
  - 6
  - 2
  - 0
  - 57
  - 4
- ALT
  - 20
  - 11
  - 4
  - 0
  - 65
  - 7
- Creatinine
  - 7
  - 0
  - 1
  - 0
  - 6
  - 2
- Nausea
  - 19
  - 11
  - 3
  —
  - 61
  - 6
- Vomiting
  - 11
  - 5
  - 1
  - 0
  - 32
  - 2
- Anorexia
  - 18
  - 11
  - 9
  - 0
  - 70
  - 17
- Stomatitis
  - 20
  - 10
  - 1
  - 0
  - 57
  - 2
- Diarrhea
  - 12
  - 5
  - 0
  - 0
  - 32
  - 0
- Constipation
  - 2
  - 0
  - 1
  - 0
  - 6
  - 2
- Ileus
  —
  - 0
  - 1
  - 0
  - 2
  - 2
- Colitis
  —
  - 0
  - 1
  - 0
  - 2
  - 2
- Fatigue
  - 22
  - 14
  - 3
  - 0
  - 72
  - 6
- Fever
  - 15
  - 5
  - 0
  - 0
  - 37
  - 0
- Alopecia
  - 13
  - 2
  —
  —
  - 28
  - 0
- Rash
  - 13
  - 17
  - 4
  - 0
  - 63
  - 7
- Pigmentation changes
  - 27
  - 7
  —
  —
  - 63
  - 0
- Hand-foot skin reaction
  - 3
  - 0
  - 0
  - 0
  - 6
  - 0
- Infection without neutropenia
  - 2
  - 2
  - 2
  - 0
  - 11
  - 4
- Febrile neutropenia
  —
  —
  - 1
  - 0
  - 2
  - 2
- CNS cerebrovascular ischemia
  —
  —
  - 1
  - 1
  - 0
  - 2

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4. Phase II studies of GS therapy for advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Gemcitabine (mg/m²)</th>
<th>S-1 (mg/m²/day)</th>
<th>Cycle (day)</th>
<th>No. of patients</th>
<th>Metastatic disease (%)</th>
<th>RR (%)</th>
<th>Median TTP/PFS (months)</th>
<th>Median OS (months)</th>
<th>Grade 3/4 neutropenia (%)</th>
<th>Grade 3/4 thrombocytopenia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura et al. (15)</td>
<td>1000 (days 8, 15)</td>
<td>60 (days 1–14)</td>
<td>21</td>
<td>33</td>
<td>100</td>
<td>48</td>
<td>5.4</td>
<td>12.5</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>Lee et al. (16)</td>
<td>1250 (days 1, 8)</td>
<td>80 (days 1–14)</td>
<td>21</td>
<td>32</td>
<td>90.6</td>
<td>44</td>
<td>4.92</td>
<td>7.98</td>
<td>28.1</td>
<td>15.6</td>
</tr>
<tr>
<td>Kim et al. (17)</td>
<td>1000 (days 8, 15)</td>
<td>60 (days 1–14)</td>
<td>21</td>
<td>22</td>
<td>86.3</td>
<td>27.3</td>
<td>4.6</td>
<td>8.5</td>
<td>18.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Oh et al. (18)</td>
<td>1000 (days 1, 8)</td>
<td>80 (days 1–14)</td>
<td>21</td>
<td>38</td>
<td>84</td>
<td>29</td>
<td>5.43</td>
<td>8.4</td>
<td>39.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Current study</td>
<td>1000 (days 1, 8)</td>
<td>80 (days 1–14)</td>
<td>21</td>
<td>55</td>
<td>100</td>
<td>44.4</td>
<td>5.9</td>
<td>10.1</td>
<td>80</td>
<td>22</td>
</tr>
</tbody>
</table>

RR, response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival.
overall survival, 14.1 versus 8.7 months; hazard ratio = 0.69 (95% CI: 0.43–1.08); \( P = 0.105 \).

Since it is speculated that combination chemotherapy with S-1 and gemcitabine might be superior to monotherapy with gemcitabine from the results of the recent trials, a Phase III trial was planned to confirm the efficacy of GS therapy (ClinicalTrials.gov, NCT00498225). The Phase III study known as ‘GEST’ is a randomized controlled study involving three arms: gemcitabine monotherapy as a control arm, S-1 monotherapy and GS therapy. The trial was designed to evaluate overall survival as the primary endpoint, non-inferiority of S-1 to gemcitabine and superiority of GS therapy over gemcitabine. The enrollment of 750 patients was planned and has already been completed and the final analysis of the results will be reported in the near future.

In conclusion, the current Phase II study demonstrated encouraging antitumor activity following GS therapy with good overall survival in patients with metastatic pancreatic cancer. The clinical benefits of GS therapy are now investigated in the GEST trial.

Acknowledgements

We are grateful to Drs T. Kosuge, Y. Matsumura and T. Kodama, who served as an Independent Data Monitoring Committee. We thank Drs Y. Ishiguro, N. Moriyama and M. Nagase for their extramural review. We also thank Ms K. Sato who provided advice on ethics, and Ms Y. Yoshimoto, Ms E. Shiokawa, Ms K. Kondo and Ms. R. Mukoyama for their assistance with data management.

Funding

This work was supported by funding from Health and Labor Sciences Research Grant for Clinical Cancer Research, Ministry of Health, Labor and Welfare, Japan.

Conflict of interest statement

None declared.

References


Appendix

In addition to the authors listed in the author field, following are the authors who contributed equally to this study.

Atsushi Makimoto, Division of Pediatrics, National Cancer Center Hospital, Tokyo, Japan.