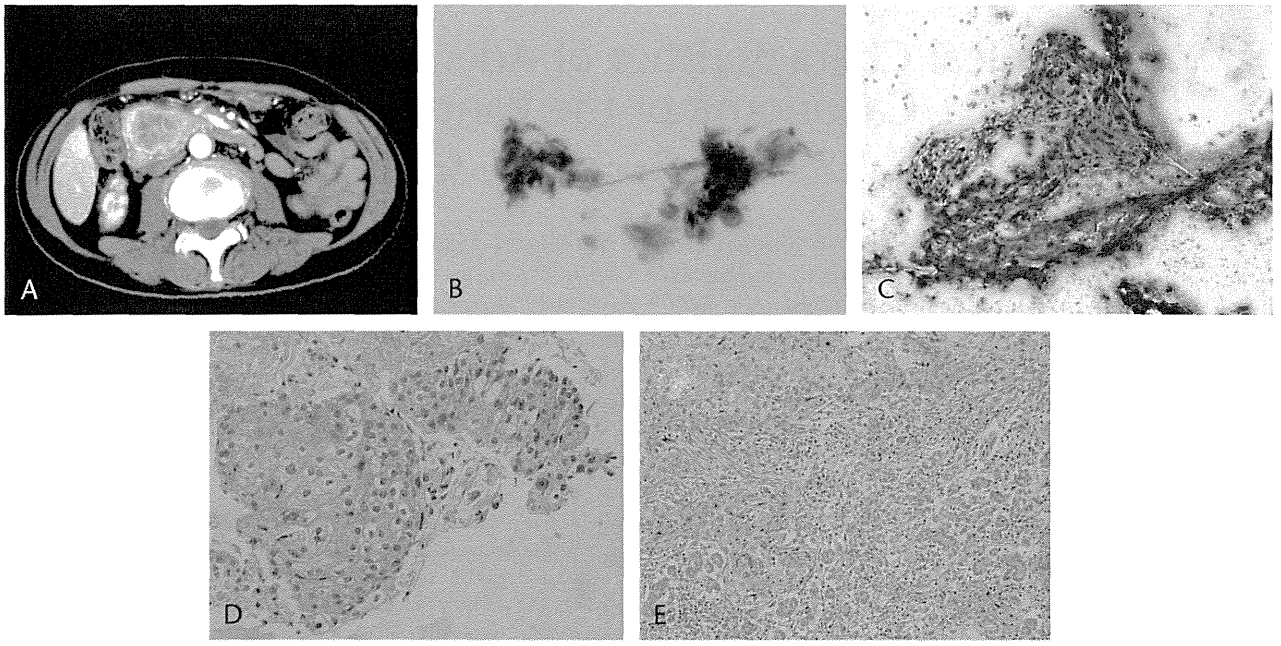

FIGURE 1. Representative images of ASC pathology. A, Computed tomography shows a large heterogeneous mass in the head of the pancreas. In the EUS-FNA specimen, aspirates show atypical keratinized cells with hyperchromatic nucleus and cytoplasmic orangeophilia (Papanicolaou stain, original magnification ×400; B), tissue fragments of neoplastic cells with cytoplasmic opacity and glandular differentiation against a necrotic background (Diff-Quik stain, original magnification ×200; C), and prominent squamous differentiation (hematoxylin and eosin stain, original magnification ×400; D). E, In the surgical specimen, both glandular and squamous differentiation are present (hematoxylin and eosin stain, original magnification ×200).

variables, and using the χ^2 test or the Fisher exact test for categorical variables. Survival was evaluated using the Kaplan-Meier method, and hazard ratios (HRs) were calculated using Cox proportional hazards model. $P < 0.05$ was considered statistically significant, and all P values are 2 sided. Data were analyzed using STATA version 11.1 statistical software (StataCorp, College Station, Tex).

RESULTS

First, we examined clinical characteristics of ASC based on our diagnostic criteria. Of the 914 cases of the pancreatic neoplasms treated between 2001 and 2011, a total of 28 cases (3.0%) of ASC were identified. Patients' characteristics are summarized in Table 1. Median age at diagnosis was 64.0 years (range, 44–79 years). The American Joint Committee on Cancer tumor staging was IIA in 5 patients (17.8%), IIB in 2 patients (7.1%), III in 5 (17.8%), and IV in 16 patients (57.1%). Adenosquamous carcinoma of the pancreas was slightly more common in the body-tail of the pancreas (57.1%). The initial treatment for ASC was curative resection in 6 patients, palliative chemotherapy using gemcitabine (Gem) in 16 cases, Gem plus S-1 in 1 case, 5-fluorouracil-based chemoradiotherapy in 1 case, S-1-based chemoradiotherapy in 1 case, and best supportive care in 3 cases. For the 6 cases of patients (21.4%) who underwent curative resection, pathological tumor staging was IIA in 4 cases and IIB in 2 cases. Three of these cases were located in the pancreatic head, and the others were in the pancreatic body-tail. Five of these cases showed no recurrence, with only 1 case showing recurrence 13.5 months postoperatively (median observation period, 36.6 months [range, 7–90.7 months]).

Next, we clarified the clinical features and prognosis of ASC using a matched case-control study. Characteristics of the control group in the matched case-control study are also shown in Table 1. Demographic and baseline disease characteristics of patients were similar in both ASC and PDAC groups. However, fewer measurable target lymph nodes metastases were seen in the ASC group than in the PDAC group (42.8% vs. 17.8%, $P = 0.014$). In the stage IV patients with ASC, the most common metastatic sites were the liver (81.2%) and lymph nodes (75%). In patients with PDAC, the most common sites were the same, but with different proportions (liver, 59.3%; and lymph nodes, 31.2%). Median duration of follow-up was 14.9 months (95% confidence interval [CI], 11.6–18.1). Median overall survival (OS) was 8.3 months (95% CI, 3.8–16.6 months) in the ASC group, compared to 15.7 months (95% CI, 12.3–32.7 months) in the PDAC group (HR for death, 1.94; 95% CI, 1.07–3.51) (Fig. 2). Overall survival rates at 6, 12, and 24 months were 53.3%, 38.7%, and 12.1%, respectively, in the ASC group compared with 86.9%, 65.3%, and 42.0%, respectively, in the PDAC group.

In unresected patients, the median OS was 4.6 months (95% CI, 3.8–11.8 months) in the ASC group and 12.3 months (95% CI, 8.9–16.0 months) in the PDAC group (HR for death, 2.39; 95% CI, 1.27–4.51) (Fig. 3). Overall survival rates at 6, 12, and 24 months were 43.2%, 24.7%, and 0.0%, respectively, in the ASC group, compared with 83.1%, 55.0%, and 26.9%, respectively, in the PDAC group. Among patients receiving either chemoradiotherapy or chemotherapy, the objective response rate was 10.5% in the ASC group and 13.5% in the PDAC group ($P = 1.000$). On the other hand, among patients receiving palliative chemotherapy using Gem, the objective response rate was 6.25% in the ASC group and 12.5% in the PDAC group ($P = 0.652$). In patients with stage IV disease, the median OS was 3.9 months (95% CI, 3.1–8.3 months) in the ASC group and 9.3 months (95% CI, 6.9–14.8 months) in the PDAC group (HR for death, 2.27; 95% CI, 1.07–4.83). In patients with liver

TABLE 1. Patient Characteristics

	ASC (n = 28)	PDAC (n = 56)	*P*
ECOG performance status score, %			
0–1	27 (96.4)	54 (96.4)	
≥2	1 (3.5)	2 (3.5)	1.000
Initial treatment			
Curative resection	6	12	
Chemoradiation	2	4	
Gem	16	32	
Gem+S-1	1	2	
BSC	3	6	1.000
Tumor stage (AJCC)			
IIA	5	10	
IIB	2	4	
III	5	10	
IV	16	32	1.000
Age, mean ± SD, yr	64.5 ± 9.1	63.8 ± 8.7	0.639
Sex, %			
Male	19 (67.8)	38 (67.8)	
Female	9 (32.1)	18 (32.1)	1.000
Location, %			
Head	12 (42.8)	24 (42.8)	
Body-Tail	16 (57.1)	32 (57.1)	1.000
Measurable metastatic sites, %			
Liver	13 (46.4)	19 (33.9)	0.266
Lymph node	12 (42.8)	10 (17.8)	0.014
Lung	1 (3.5)	6 (10.7)	0.416
Peritoneal	5 (17.8)	12 (21.4)	0.780
Size, mean ± SD, mm	40.6 ± 13.6	35.1 ± 16.3	0.929

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; SD, standard deviation.

metastasis, the median OS was 3.9 months (95% CI, 2.4–8.3 months) in the ASC group and 10.4 months (95% CI, 7.4–14.8 months) in the PDAC group (HR for death, 3.03; 95% CI, 1.26–7.28).

DISCUSSION

Adenosquamous carcinoma of the pancreas is a variant of PDAC that accounts for 3% to 4% of malignant neoplasms of the pancreas.[16–18] Adenosquamous carcinoma of the pancreas has been considered to show poor prognosis owing to its aggressive behavior,[19–21] but the clinical features of ASC have been based primarily on case studies[8] and small surgical series with early-stage cancers.[9] Thus, whether ASC is actually more aggressive than PDAC has remained controversial. Two population-based analyses of ASC have recently been reported.[10,11] Boyd et al[10] described OS after surgical resection of ASC as significantly worse compared to that after resection of PDAC. On the other hand, Katz et al[11] reported that median OS for ASC was 4 months, similar to that for PDAC. They also mentioned that treatment of patients with ASC by surgical resection was associated with a favorable prognosis.[11] These reports about the prognosis of ASC have shown several problems. One is the prejudiced staging of disease. Although ASC has been regarded as a more progressive malignancy, reports have mainly mentioned locoregional disease, not metastatic disease. The other drawback is a

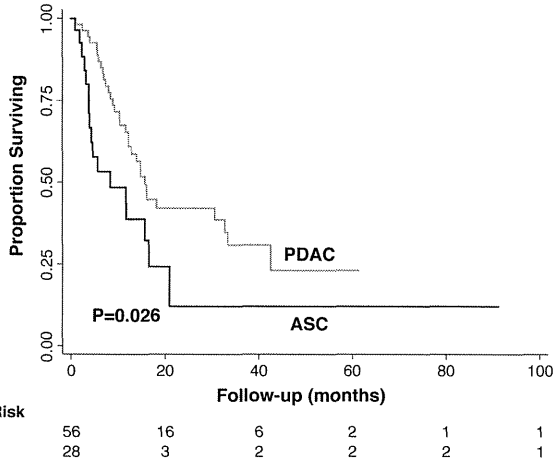

FIGURE 2. Kaplan-Meier curve comparing ASC with PDAC. Kaplan-Meier estimates show overall survival, with median values of 8.3 months in the ASC group and 15.7 months in the PDAC group.

lack of specific information about treatment. Based on registry data, they did not mention detailed palliative treatments in unresectable cases. This information seems essential to clarify the real clinical characteristics and behaviors of ASC. This study therefore examined the clinical characteristics and prognosis of ASC in a matched case-control study.

The present study examined the clinical characteristics and prognosis of ASC. Among all pancreatic neoplasms, 28 cases (3.06%) of ASC were identified. Adenosquamous carcinoma of the pancreas predominantly affected males (67.8%), and the mean age at diagnosis was 64.5 years. These findings resemble the results from other reports for ASC[17,22] and shared clinical characteristics with conventional PDAC. On the other hand, our matched case-control study showed that ASC metastasizes to lymph nodes more frequently than PDAC. Although the difference was not significant, tumors also tended to be larger in ASC than PDAC. Boyd et al[10] reported in a population-based analysis that ASC was more likely to be larger and node

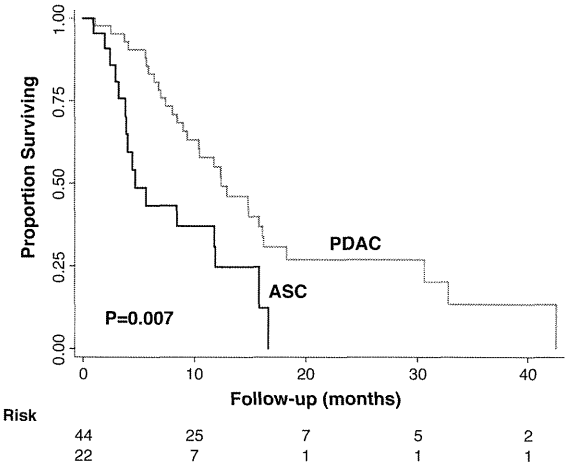

FIGURE 3. Kaplan-Meier curve comparing ASC with PDAC in unresected patients. Kaplan-Meier estimates show overall survival, with median values of 4.6 months in the ASC group and 12.3 months in the PDAC group.

positive compared with PDAC. Results from our matched case-control study support their findings. Because we used cancer stage as a matching valuable, we could not examine the frequency of distant metastases in patients with ASC compared with PDAC. However, ASC being more likely to be larger and node-positive may indicate more aggressive behavior of ASC compared with PDAC.

Our results clearly show that ASC was more progressive than conventional PDAC. The median OS was significantly worse for ASC (8.38 months) than for PDAC (15.75 months). Of the 22 unresected cases, OS was significantly worse for ASC than for PDAC, with an HR of 2.39 (95% CI, 1.27–4.51; $P = 0.007$; median, 4.67 months vs 12.36 months). This seems attributable to the aggressive behavior of ASC. As previously mentioned, ASC tends to metastasize to lymph nodes more frequently than PDAC, even within the same cancer stage. Furthermore, in patients with stage IV disease, simultaneous metastases to the liver and lymph nodes were seen more frequently in the ASC group (43.7%) than in the PDAC group (3.1%, $P = 0.001$). This aggressiveness may contribute to the poor prognosis. We suppose that stronger chemotherapy is one promising option for patients with ASC. In this study, Gem was the most frequently administered agent as palliative chemotherapy. However, Gem shows modest survival benefit in patients with pancreatic cancer. Other newer combination chemotherapeutic regimens, such as GEM+erlotinib[23] and FOLFIRINOX,[24] may thus offer promising therapies for ASC.

In summary, we investigated the clinical characteristics and prognosis of ASC using a matched case-control study. The present results show that ASC was more progressive than conventional PDAC. Conversely, in resectable cases, surgical resection can provide a better prognosis for these patients.

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Invest New Drugs (2013) 31:1265–1274
DOI 10.1007/s10637-012-9910-y

PHASE II STUDIES

Phase II study of sunitinib in Japanese patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumor

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Received: 4 September 2012 / Accepted: 3 December 2012 / Published online: 27 December 2012

Summary *Background.* Pancreatic neuroendocrine tumors (NETs) are rare but are frequently diagnosed at advanced stages and require systemic therapy. *Patients and methods.* This multicenter, open-label, phase II study evaluated sunitinib in Japanese patients with well-differentiated pancreatic NET. Patients received sunitinib 37.5 mg/day on a continuous daily dosing (CDD) schedule. The primary endpoint was clinical benefit rate (CBR; percentage of complete responses [CRs] plus partial responses [PRs] plus stable disease [SD] ≥24 weeks). Secondary endpoints included objective response rate (ORR), tumor shrinkage, progression-free survival (PFS) probability, safety, pharmacokinetics, and biomarkers. *Results.* Twelve patients received treatment. The CBR was 75 % (95 % confidence interval [CI], 43–94) and included 6 patients with a PR and 3 with SD. The ORR was 50 % (95 % CI, 21–79). PFS probability was 91 % (95 % CI, 54–99) at 6 months and 71 % (95 % CI, 34–90) at 12 months. Commonly reported treatment-emergent (all-causality), any-grade adverse events included diarrhea ($n=10$), hand–foot syndrome and hypertension (both $n=8$), fatigue and headache (both $n=7$), and neutropenia ($n=6$). No deaths on study were reported; one death due to disease progression occurred >28 days after end of treatment. Sunitinib on a CDD schedule resulted in sustained drug concentrations without accumulation across cycles. Tumor

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Electronic supplementary material The online version of this article (doi:10.1007/s10637-012-9910-y) contains supplementary material, which is available to authorized users.

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responses in all 12 patients did not appear to correlate with decreases in chromogranin A levels. *Conclusions.* Sunitinib 37.5 mg/day on a CDD schedule demonstrated antitumor activity in Japanese patients with unresectable, well-differentiated pancreatic NET. Commonly reported adverse events were consistent with the known safety profile of sunitinib.

Keywords Efficacy · Japanese · Pancreatic neuroendocrine tumor · Pharmacokinetics · Phase II · Sunitinib

Introduction

Pancreatic neuroendocrine tumors (NETs) are rare malignancies with a prevalence of 2.23 per 100,000 population in Japan [1]. The incidence rate of pancreatic NET per year in Japan (1.01 per 100,000 population) appears higher than in Western countries (0.32/100,000 in the overall US population and 0.25 in Asian Americans [2]). Surgery, if feasible, is the optimal treatment approach [3]. However, the majority of patients present with unresectable disease. When the current study was initiated, treatment options available for symptomatic patients with unresectable disease included somatostatin analogs (e.g. octreotide, alone or in combination with interferon-alpha) and the alkylating agent streptozocin (alone or in combination with doxorubicin), both of which have limited efficacy in patients with advanced disease [4–6]. Subsequently, targeted anticancer agents have been shown to improve progression-free survival (PFS) compared with placebo in phase III studies that included primarily Caucasian patients with advanced pancreatic NET [7–9].

Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are key drivers of angiogenesis in pancreatic NETs [10, 11]. Sunitinib malate (SUTENT®), an oral multitargeted inhibitor of numerous receptor tyrosine kinases including VEGF receptors and PDGF receptors [12–14], has been shown to delay tumor growth in a RIP1-Tag2 transgenic mouse model of pancreatic islet-cell tumors [15, 16]. In a phase II trial, sunitinib demonstrated antitumor activity in patients with pancreatic NET [17], and in a subsequent phase III trial, oral sunitinib 37.5 mg/day on a continuous daily dosing (CDD) schedule prolonged median PFS relative to placebo in Caucasian and Asian patients with locally advanced and/or metastatic, well-differentiated pancreatic NET [7]. Sunitinib was also associated with a greater objective tumor response rate than placebo. In an updated analysis, median overall survival (OS) favored sunitinib (hazard ratio [HR] 0.71, 95 % confidence interval [CI]: 0.47–1.09; P=0.11), despite crossover to sunitinib for most of the patients randomized to placebo, although statistical significance was not reached [18]. On the basis of these findings, sunitinib has been approved multinationally for the treatment of patients with unresectable or metastatic, well-differentiated pancreatic NET with disease progression.

We carried out a phase II, open-label, multicenter trial (NCT01121562) to evaluate the clinical benefit rate (CBR) of sunitinib in Japanese patients with pancreatic NET. The sunitinib dose investigated was 37.5 mg/day on the CDD schedule, which was the same regimen used in a Western phase III study [7]. Secondary objectives were to assess objective response rate (ORR) and PFS, to evaluate safety and tolerability, and to determine the pharmacokinetic (PK) profile of sunitinib in this patient population.

Patients and methods

Study population

Japanese patients ≥20 years old with histologically or cytologically proven, well-differentiated pancreatic NET (according to the World Health Organization 2004 classification [19]) and progressive unresectable advanced or metastatic disease were eligible to participate. Inclusion criteria comprised documented evidence of disease progression within 12 months of study start (by computed tomography [CT] or magnetic resonance imaging [MRI]), and disease not amenable to surgery, radiation, or combined modality therapy with curative intent. At least one measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [20] was required, along with adequate organ function, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and a life expectancy of at least 3 months. Patients were excluded if they had poorly differentiated tumors, prior treatment with any tyrosine kinase or anti-VEGF angiogenic inhibitors, brain metastases, cardiovascular disease ≤12 months prior to study start, uncontrolled hypertension, an uncontrolled thyroid abnormality, ongoing cardiac dysrhythmias with medical intervention or a prolonged QT interval corrected for heart rate (QTc), symptomatic brain metastases, or a left ventricular ejection fraction of ≤50 %.

Study design and treatment

In this multicenter, open-label, phase II study, all patients received oral sunitinib37.5 mg/day on a CDD schedule, and each treatment cycle lasted 28 days. Patients were monitored for toxicity, and dose reductions to 25 mg/day were permitted based on individual tolerability. The sunitinib dose could also be increased to 50 mg/day (if no response was observed in the first 8 weeks and if individual tolerability permitted). The primary endpoint was CBR, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) or stable disease (SD) for ≥24 weeks. CBR was selected as the primary endpoint because maintaining

prolonged SD over about half of a year (24 weeks) was deemed beneficial and clinically meaningful for patients with pancreatic NET, based on the median PFS of 5.5 months reported for placebo treatment in a previous global, pivotal, phase III study [7]. Secondary efficacy endpoints included ORR, defined as the proportion of patients with a confirmed CR or PR; tumor shrinkage, defined as the percentage change from baseline in the sum of the longest diameter of target lesions; PFS; safety; and PK.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws. Approval from the institutional review board or independent ethics committee of each participating center was required, and written informed consent was obtained from all patients before screening.

Study assessments

Investigator-assessed tumor imaging by CT, spiral CT, or MRI was performed at screening and weeks 5 and 9, and then at 8-week intervals during the study. Additional scans were performed when disease progression was suspected or to confirm a CR or PR based on RECIST. Safety was assessed at regular intervals by physical examination and analysis of adverse events (AEs), laboratory abnormalities (hematology and blood chemistry), vital signs, 12-lead electrocardiograms (ECGs), and ECOG PS. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. QTc intervals were determined using 12-lead ECGs in triplicate at baseline, on day 1 of cycles 2 and 3, every 8 weeks thereafter, and as clinically indicated.

Blood samples were collected before dosing on day 15 (±1) of cycle 1 and on day 1 of cycles 2–4 to evaluate trough concentrations (C_{trough}) of sunitinib and its active metabolite SU12662 using a validated high- performance liquid chromatography–tandem mass spectrometry method (Bioanalytical Systems Inc., West Lafayette, Indiana, USA). An exploratory analysis investigated potential differences in steady-state C_{trough} values of sunitinib, SU12662, and total drug (sunitinib plus SU12662) in Japanese versus non-Japanese patient populations and in patients with different tumor types. C_{trough} from this Japanese study, a Western pancreatic NET trial [15], and from studies of Japanese patients with GIST or RCC [21, 22] were dose-corrected to 37.5 mg and compared.

Blood samples were obtained at screening, week 5, and week 9, and then every 8 weeks to assess chromogranin A (CgA) levels (all patients) and hormone levels (patients with functional tumors only). Patients were required to fast for ≥10 h prior to each scheduled visit. In an exploratory analysis of CgA levels, a biochemical response was defined as a ≥50 % decrease in CgA levels among patients with elevated CgA levels at baseline.

Statistical methods

As pancreatic NETs are rare, a target sample size of at least 10 patients was determined based on feasibility of study conduct rather than statistical requirements. All enrolled patients who received at least one dose of study treatment were included in the efficacy and safety analyses.

Descriptive statistics were used to summarize patient characteristics, treatment administration/compliance, safety parameters, and PK variables. For the analysis of the primary endpoint, the CBR and its exact 95 % CI were calculated. For the analysis of the secondary endpoints, the ORR and its exact 95 % CI, and the percentage change from baseline in the sum of the longest diameter of target lesions were calculated. Time-to-event endpoints (PFS and OS) were summarized using Kaplan–Meier methods.

Results

Patients and treatment

Between July and December 2010, 12 patients (8 male, 4 female) were enrolled in the study at four centers in Japan. All patients received treatment and were analyzed for efficacy and safety. At data cut-off (March 2012), treatment was ongoing in 5 patients with a PR (n=4) or SD (n=1), and 7 patients had withdrawn from the trial. Study withdrawals were due to tumor progression or recurrence (n=3), withdrawal of consent (n=1), treatment interruption >4 weeks due to a serious adverse event (SAE; grade 4 enterocolitis; n=1), and SAEs (grade 4 convulsion plus grade 4 loss of consciousness; n=1). Demographic and baseline disease characteristics are presented in Table 1. All of the patients had well-differentiated pancreatic NETs, of which 10 were classified as nonfunctional and 2 as functional (both gastrinomas). Six patients had received prior octreotide treatment and continued octreotide therapy during the study.

The median relative sunitinib dose intensity was 51 % (range, 26–94); the median number of treatment cycles started was 16 (range, 3–21; Table 2). The sunitinib dose was interrupted in 11 patients and reduced in 8 patients. The most frequently reported cause of dosing interruptions or reductions was AEs.

Efficacy

Based on investigator assessments, 6 of the 12 patients experienced a PR, and none had a CR (Fig. 1). SD ≥24 weeks was observed in 3 patients, and the CBR was 75 % (95 % CI, 43–94). In total, 5/6 patients with prior or concurrent octreotide treatment and 4/6 patients who did not receive octreotide met the criteria for experiencing clinical

Table 1 Patient characteristics at baseline

Patient characteristic	Sunitinib (N=12)
Age, years	
Median	54
Range	34–79
Sex, *n* (%)	
Male	8 (67)
Female	4 (33)
ECOG performance status, *n* (%)	
0	11 (92)
1	1 (8)
Time since diagnosis, years	
Median	3
Range	0.2–9.0
Tumor functionality, *n* (%)	
Nonfunctioning	10 (83)
Functioning	2 (17)
Gastrinoma	2 (17)
Number of involved disease sites per patient, *n* (%)	
1 site	4 (33)
2 sites	5 (42)
3 sites	2 (17)
4 sites	1 (8)
Presence of distant metastases, *n* (%)	
Any, including hepatic	12 (100)
Extrahepatic	3 (25)
Involved disease sites, *n* (%)	
Liver	12 (100)
Lymph node	4 (33)
Pancreas	4 (33)
Lung	2 (17)
Bone	1 (8)
Peritoneum	1 (8)
Prior surgery, *n* (%)	
Yes	9 (75)
No	3 (25)
Prior radiation therapy, *n* (%)	
Yes	1 (8)
No	11 (92)
Number of prior systemic chemotherapy regimens, *n* (%)	
0	6 (50)
1	4 (33)
2	0
≥3	2 (17)

ECOG Eastern cooperative oncology group

benefit. The overall ORR was 50 % (95 % CI, 21–79; Fig. 1). One patient showed a 100 % decrease in target lesion size. One PR occurred in a patient with gastrinoma and was accompanied by a 93 % decrease in plasma gastrin levels (Patient D; Data Supplement Table S1; see also below). In 11/12 patients, some degree of tumor shrinkage was observed by the first assessment 1 month after initiation of sunitinib treatment (Fig. 2). At the time of data cut-off, ongoing patients had been observed for at least 16.1 months, and the median duration of treatment with sunitinib was 9.8 months (range, 0.7–18.1). Although 4/12 patients had discontinued treatment with sunitinib due to reasons other than progressive disease (PD), median PFS had not yet been reached. Six-month and 12-month PFS probabilities were 91 % (95 % CI, 54–99) and 71 % (95 % CI, 34–90), respectively. Median OS had not yet been reached. One death occurred (due to progression of primary disease) during survival follow-up, more than 28 days after the end of treatment.

Table 2 Sunitinib treatment

	Sunitinib (N=12)
Treatment cycles started, median (range)	16 (3–21)
Months on treatment, median (range)	10 (0.7–18)
Months on study, median (range)	14 (0.7–19)
No. of patients with ≥1 dosing interruption, *n* (%)	11 (92)
No. of patients with ≥1 dose reduction, *n* (%)	8 (67)
Relative dose intensity, median (range), %	51 (26–94)

Safety

As of March 2012, the most common treatment-emergent (all-causality) AEs of any grade were diarrhea (n=10; 83 %), hand–foot syndrome and hypertension (both n=8; 67 %); fatigue and headache (both n=7; 58 %), and neutropenia (n=6; 50 %; Table 3). Grade 3 AEs reported in at least 2 patients were neutropenia (n=6; 50 %) and leukopenia (n=2; 17 %). Four patients (33 %) experienced grade 4 AEs, all of which were judged to be related to treatment (herpes encephalitis, convulsion, and loss of consciousness [n=1], increased lipase [n=2], and enterocolitis [n=1]). No deaths related to sunitinib treatment were reported on study or within 28 days of the end of treatment. One death due to disease progression occurred >28 days after end of treatment.

Three patients (25 %) experienced SAEs, all of which resolved. In two cases, the SAEs were assessed as treatment-related. One patient (patient H; Fig. 2) had a grade 4 convulsion and grade 4 loss of consciousness that were reported to be likely due to herpes encephalitis. These SAEs resulted in a sunitinib dose interruption exceeding 4 weeks that led to study discontinuation, as specified in the protocol. Another patient (patient K; Fig. 2) experienced an SAE of grade 4 enterocolitis and temporarily discontinued therapy due to this SAE.

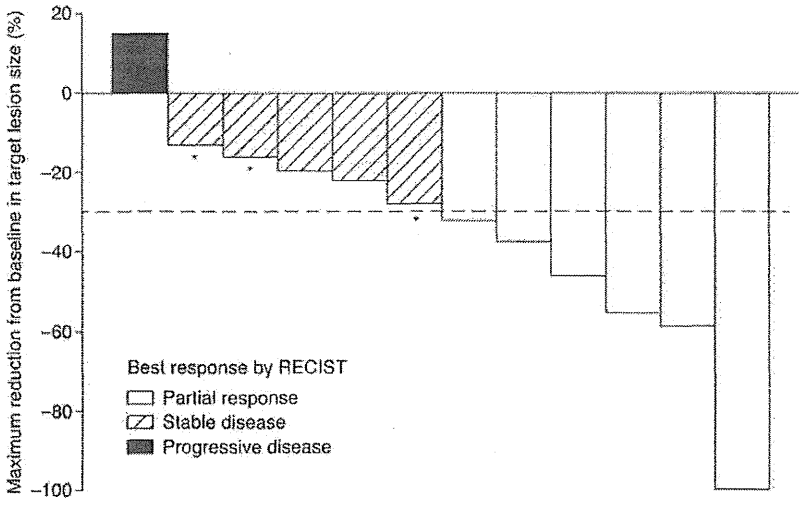


Fig. 1 Maximum percentage reduction from baseline in target lesion size by patient (N= 12). Although one patient had a maximum percentage change in target tumor size from baseline of −100 %, non-target lesions remained and therefore this was not classified as a complete response. *Asterisk* stable disease of ≥24 weeks in duration; *RECIST* Response Evaluation Criteria in Solid Tumors

Pharmacokinetics

Steady-state concentrations of sunitinib, SU12662, and total drug (sunitinib plus SU12662) were reached by day 15 of cycle 1. Subsequent sampling on day 1 of cycles 2–4 showed the concentrations to be sustained following CDD with sunitinib without disproportionate accumulation across cycles (data not shown). Mean dose-corrected (reference dose: 37.5 mg) C_{trough} values were within the ranges of 41.7–53.9 ng/mL for sunitinib, 19.6–25.7 ng/mL for SU12662, and 62.9–77.5 ng/mL for total drug.

We explored potential differences in steady-state C_{trough} values of sunitinib and SU12662 in Japanese versus non-Japanese patient populations and in patients with different tumor types. Dose-corrected steady-state C_{trough} levels from this Japanese study were compared with findings from a Western pancreatic NET population [17], and from studies of Japanese patients with gastrointestinal stromal tumor (GIST) or renal cell carcinoma (RCC) [21, 22]. Steady-state C_{trough} levels of sunitinib, SU12662, or total drug were not significantly different between Japanese and primarily Western patients with pancreatic NET, or between patients with pancreatic NET, GIST, and RCC tumor types (Fig. 3).

Biomarkers

Chromogranin A

Plasma CgA levels were measured in all 12 patients (Fig. 2). At baseline, the median CgA concentration was 9 pmol/mL (range, 3–86 pmol/mL). Six patients had above-median CgA levels at baseline, 3 of whom had a maximum percentage decrease in CgA concentrations of at least −50 %. Among these 3 patients, 2 had a PR and 1 had a best overall response of SD. In the patient with SD, the maximum percentage change in tumor size from baseline was −28 %. Among the 6 patients with below-median CgA levels, 3 experienced a PR and 3 had a best overall response of SD. Tumor responses in all 12 patients did not appear to correlate with the maximum percentage decrease in CgA levels.

Gastrin

Plasma gastrin levels were assessed in the 2 patients with gastrinomas: a 40-year-old female (patient D) and a 34-year-old male (patient L; Data Supplement Table S1). In addition, the relationship between hormonal levels, tumor size, and objective tumor response (based on investigator assessment) was examined in an exploratory analysis. In the male patient, neither gastrin levels nor tumor size decreased after treatment with sunitinib. The best objective response was PD, and the patient discontinued the study at day 79 due to lack of efficacy. In the female patient with gastrinoma, decreases in both gastrin levels (−85 % to −93 %) and tumor size (−31 % to −45 %) were observed during treatment. This patient had a PR on cycle 2 day 1 that was maintained through cycle 7 day 1.

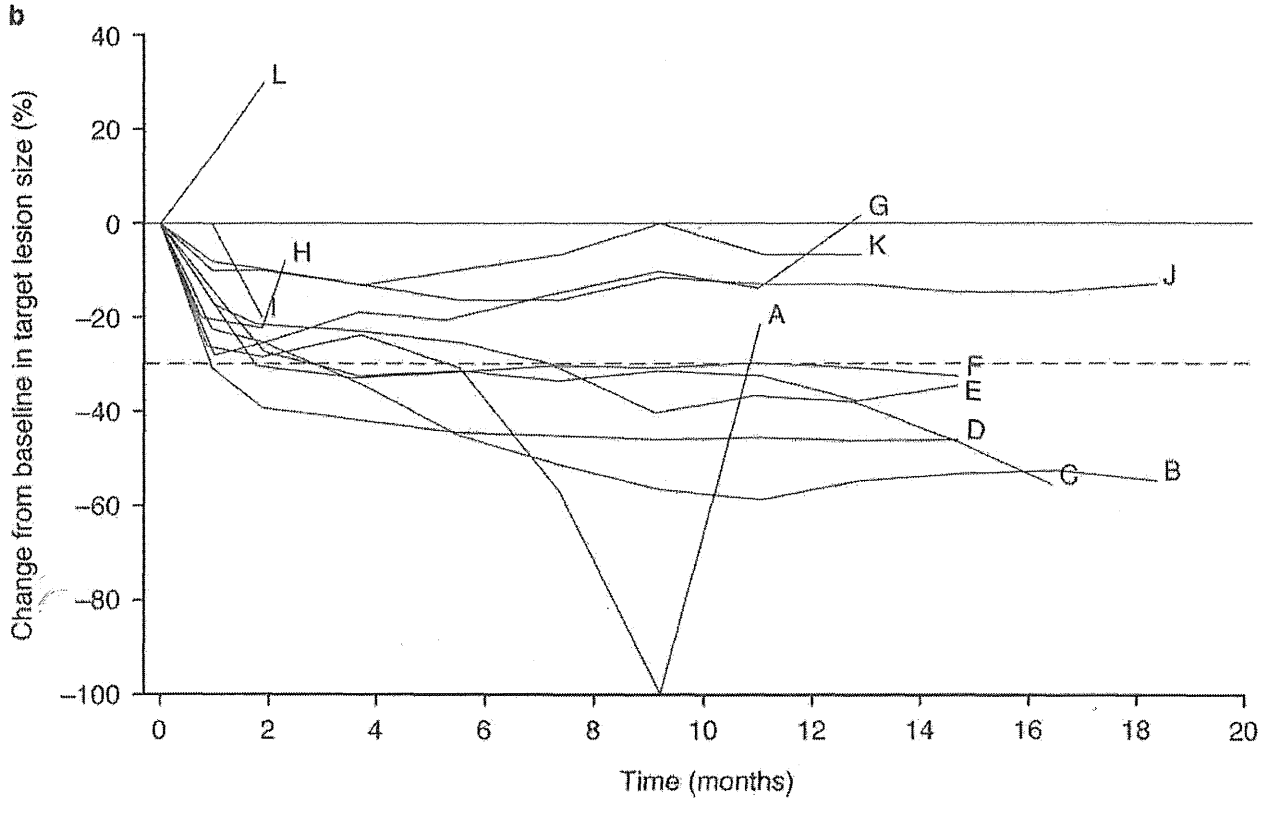
Discussion

This is the first report of sunitinib safety, PK profiles, PFS, and antitumor activity in Japanese patients with unresectable, advanced/metastatic well-differentiated pancreatic NET. While the data are limited by the small sample size, antitumor activity was observed in this population, with a CBR of 75 % and an ORR of 50 %. The ORR was encouraging and higher than the 9 % ORR reported for sunitinib in a randomized, phase III trial in a predominantly non-Asian population [7]. In the present study, 11 patients had

a

Patient	Age, sex	Tumor functionality	Prior treatment	Maximum change in target lesion size (%)[a]	Best overall response	PFS (months)	Reason for discontinuation	Chromogranin A	
								Baseline concentration (pmol/mL)	Maximum change from baseline (%)[a]
A	62, F	Non-functioning	Gemcitabine, somatostatin analogs	−100	PR	11.1	PD	4	5
B	44, M	Non-functioning	Epirubicin, mitomycin-C	−59	PR	18.6[b]	None – ongoing	3	62
C	64, F	Non-functioning	Epirubicin, somatostatin analogs	−56	PR	16.6[b]	None – ongoing	13	−53
D	40, F	Functioning (gastrinoma)	Somatostatin analogs	−46	PR	15.0[b]	None – ongoing	86	−89
E	64, M	Non-functioning	None	−38	PR	14.8	PD	4	47
F	51, M	Non-functioning	Cisplatin, etoposide, somatostatin analogs	−33	PR	14.8[b]	None – ongoing	10	−5
G	46, M	Non-functioning	Fluorouracil, cisplatin, gemcitabine, streptozocin, tegafur-uracil, somatostatin analogs	−28	SD	9.3	PD	18	−73
H	57, M	Non-functioning	Somatostatin analogs	−22	SD	2.4[b]	Treatment interruption >4 consecutive weeks due to lack of tolerance (serious adverse events of convulsion and loss of consciousness)	7	−37
I	64, F	Non-functioning	None	−20	SD	2.1[b]	Withdrawal of informed consent	16	−1
J	44, M	Non-functioning	Epirubicin, cisplatin, cancer vaccinations, cyclophosphamide	−16	SD	18.5[b]	None – ongoing	6	−19
K	79, M	Non-functioning	None	−13	SD	13.0[b]	Serious adverse event (grade 4 enterocolitis)	8	−29
L	34, M	Functioning (gastrinoma)	None	15	PD	2.0	PD	21	300

b



◀ **Fig. 2** Individual patient profiles and response to treatment (N=12). **a** Summary of patient profiles and changes in tumor-size and chromogranin A levels. **b** Percentage change from baseline in target lesion size over time in individual patients. [a] Maximum % change = [(minimum value after dosing – baseline)/baseline] x 100; [b] Based on censored data; *F* female; *M* male; *PD* progressive disease; *PFS* progression-free survival; *PR* partial response; *SD* stable disease

decreases in target lesion measurements and achieved a best response of a PR or SD. Analysis of the percentage change in target lesion size over time showed a trend in tumor shrinkage from the first assessment 1 month after initiation of treatment with sunitinib. As of March 2012, ongoing patients had been observed for at least 16.1 months, and median PFS had not been reached. The probability of being alive and progression-free at 6 months was 91 % (95 % CI, 54–99) and at 12 months was 71 % (95 % CI, 34–90). In the randomized sunitinib phase III trial, median PFS was 11.4 months [7]. These data suggest that PFS in Japanese patients receiving sunitinib in our study may be equivalent to or greater than that observed in the randomized phase III trial.

The potential effect of octreotide therapy was difficult to evaluate in this study due to the small sample size. The CBR was similar among patients with (n=5/6) or without (n=4/6) octreotide treatment. In an exploratory subpopulation analysis reported in the randomized sunitinib phase III study, the efficacy of sunitinib appeared similar in patients who did and did not receive somatostatin analogues (PFS hazard ratios of 0.43 and 0.41, respectively), suggesting that the efficacy of sunitinib was not affected by somatostatin analogue treatment [7].

AEs reported during sunitinib treatment were manageable with palliative care measures, such as dosing interruption. The AEs observed in this study were similar to those reported in a phase III study in primarily Western patients with pancreatic NET [7], and frequently observed AEs were comparable to those reported in patients with GIST or RCC [21, 22].

In the current study, the median number of treatment cycles started was 16. All patients had grade 3/4 AEs and at least one sunitinib dosing interruption. However, the therapeutic effect of sunitinib did not appear to be reduced by temporary dosing interruptions due to AEs. Neutropenia, the most common grade 3/4 AE, was also the most frequently reported grade 3/4 toxicity in the predominantly Western sunitinib phase III pancreatic NET study [7], although the frequency of this event was markedly higher in our study with Japanese patients (42 % vs. 12 %). Increased rates of grade 3/4 neutropenia have also been observed in sunitinib-treated Japanese patients with GIST (37 % vs. 10 %) or RCC (53 % vs. 18 %), compared with predominantly Western populations [21–24]. The frequency of grade 3/4 thrombocytopenia similarly appeared to be higher in sunitinib-treated Japanese vs. Western patients (GIST: 20 % vs. 4 %; RCC: 55 % vs. 9 %; pancreatic NET:

Table 3 Treatment-emergent (all-causality) adverse events (AEs) reported in ≥25 % of patients, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

	Maximum grade (G), *n* (%)			
AE	G1	G2	G3	Total[a]
Any AE[b]	0	0	8	12 (100)
Diarrhea	4 (33)	5 (42)	1 (8)	10 (83)
Hand–foot syndrome	1 (8)	7 (58)	0	8 (67)
Hypertension	1 (8)	7 (58)	0	8 (67)
Fatigue	1 (8)	6 (50)	0	7 (58)
Headache	4 (33)	3 (25)	0	7 (58)
Neutropenia	0	0	6 (50)	6 (50)
Dysgeusia	5 (42)	0	0	5 (42)
Nasopharyngitis	4 (33)	1 (8)	0	5 (42)
Nausea	4 (33)	1 (8)	0	5 (42)
Pyrexia	2 (17)	2 (17)	1 (8)	5 (42)
Vomiting	5 (42)	0	0	5 (42)
Decreased appetite	4 (33)	0	0	4 (33)
Edema	3 (25)	1 (8)	0	4 (33)
Hypothyroidism	0	4 (33)	0	4 (33)
Leukopenia	0	1 (8)	2 (17)	3 (25)
Mucosal inflammation	2 (17)	1 (8)	0	3 (25)
Muscle spasms	3 (25)	0	0	3 (25)
Prolonged electrocardiogram QT	1 (8)	1 (8)	1 (8)	3 (25)
Thrombocytopenia	1 (8)	1 (8)	1 (8)	3 (25)

[a]Grade 4 AEs were observed in 4 patients: convulsion, loss of consciousness, and herpes encephalitis (n=1), increased lipase (n=2), and enterocolitis (n=1); no grade 5 AEs were reported

[b]Patients were counted once, with only the highest grade AE listed

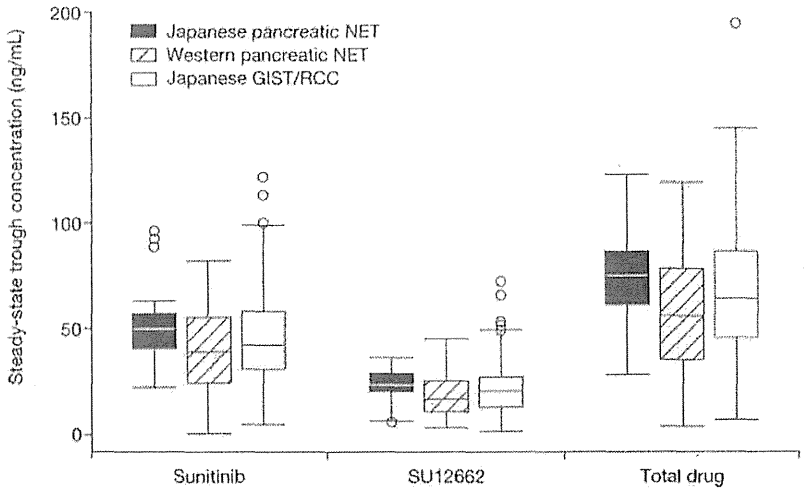


Fig. 3 Trough concentrations of sunitinib, active metabolite SU12662, and total drug (sunitinib plus SU12662) in Japanese patients with pancreatic neuroendocrine tumor (NET; n=11; present study) or gastrointestinal stromal tumor (GIST; n=30) [21] and renal cell carcinoma (RCC; n=38; pooled data) [25], and in predominantly Western patients with pancreatic NET; n=57 [17]. The sunitinib dose in each study was dose-corrected to 37.5 mg. The *upper* and *lower box boundaries* denote the 75th and 25th percentiles, respectively, with the median shown as a line within the box. *Whiskers* indicate minimum and maximum values. Outlying values are denoted as *circles*

17 % vs. 4 %) [21–24]. It should be noted that the sunitinib GIST and RCC trials used a different dosing schedule (sunitinib 50 mg/day, for 4 weeks on therapy, followed by 2 weeks off) than our study and the phase III, pancreatic NET trial.

It is not clear why rates of grade 3/4 hematologic AEs appear to be higher in Japanese versus Western patients who receive sunitinib. Analysis of PK parameters has shown that the area under the concentration–time values of sunitinib and SU12662 are similar in Japanese and Caucasian patients with RCC [22]. In addition, when steady-state C_{trough} values from this Japanese study were compared with those from a Western pancreatic NET population [17] and with C_{trough} values from Japanese patients with GIST or RCC [21, 22], there were no significant differences in the dose-corrected C_{trough} levels of sunitinib, SU12662, or total drug between Japanese and primarily Western patients with pancreatic NET, or among patients with pancreatic NET, GIST, or RCC. In the absence of racial or ethnic differences in the PK of sunitinib, Uemura et al. [25] suggested that the elevated rates of grade 3/4 hematologic AEs in Japanese patients may be due to differences in the expression levels and activity of sunitinib-sensitive kinases involved in the regulation of hematopoiesis.

Everolimus, an inhibitor of the mammalian target of rapamycin, is approved for the treatment of pancreatic NET in Japan, and like sunitinib is commonly associated with skin and gastrointestinal disorders [9]. Additional AEs related to sunitinib treatment include hematotoxicity, cardiovascular disorders and constitutional symptoms [26], while pneumonitis and infections are associated with everolimus therapy [27]. These different safety profiles reflect each compound's distinct mode of action. No racial differences between Japanese and Western patients have been reported for the safety profile of either drug, based on the current study and a subgroup analysis of Japanese patients in the RADIANT-3 everolimus trial [9].

Treatment-emergent changes in CgA levels may provide a means to select patients with pancreatic NET likely to benefit from molecular targeted therapy [28]. However, in this study tumor responses in all 12 patients did not appear to correlate with the maximum percentage decrease in CgA levels, possibly because of small patient numbers with elevated CgA concentrations at baseline. Patient D had the highest baseline CgA levels in the study (86 pmol/mL), and decreased CgA concentrations (−89 %) were subsequently observed in combination with a PR. An increase in CgA levels (300 %) occurred during the study in 1 patient (Patient L) who experienced PD. A potential correlation between changes in CgA levels and clinical benefit was considered in these 2 patients. In patients with elevated baseline CgA concentrations, CgA appeared to be a useful marker in patients with pancreatic NET as reported previously [29].

The use of sunitinib marks a new phase in the development of a more targeted approach to the treatment of advanced-stage pancreatic NET. Results from the current study demonstrate antitumor activity in Japanese patients with unresectable, well-differentiated pancreatic NET and corroborate earlier findings in Western and Asian populations.

Acknowledgments We would like to thank all of the participating patients and their families, as well as the network of investigators, research nurses, study coordinators, and operations staff. We are also grateful to Kyoko Okano and Junichi Tanuma (Pfizer Japan Inc.) for their contributions to study management and to Atsushi Shibata for advice regarding the safety profile of sunitinib. Medical writing support was provided by Molly Heitz at ACUMED® (Tytherington, UK) with funding from Pfizer Inc.

Funding This study was sponsored by Pfizer Inc.

Conflict of interest Richard Chao, Satoshi Hashigaki, Nobuyuki Kimura, and Emiko Ohki are employees of Pfizer, and N. Kimura, E. Ohki, and R. Chao hold Pfizer stock. Mami Murakami was previously employed by Pfizer. Tetsuhide Ito, Takuji Okusaka and Kenji Yamao have received research funding from Pfizer. Toshirou Nishida has received research funding from Pfizer and Novartis Pharmaceuticals. Hisato Igarashi, Nobumasa Mizuno, Kazuo Hara, Chigusa Morizane, Shunsuke Kondo, Akira Sawaki, and Masayuki Imamura have no potential conflicts of interest to disclose.

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VOLUME 31 · NUMBER 13 · MAY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study of Gemcitabine Plus S-1, S-1 Alone, or Gemcitabine Alone in Patients With Locally Advanced and Metastatic Pancreatic Cancer in Japan and Taiwan: GEST Study

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See accompanying editorial on page 1621

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Published online ahead of print at www.jco.org on April 1, 2013.

Written on behalf of the Gemcitabine and S-1 Trial Group.

Supported by Taiho Pharmaceutical and TTY Biopharm.

Presented in part at the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00498225.

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0732-183X/13/3113w-1640w/$20.00

DOI: 10.1200/JCO.2012.43.3680

ABSTRACT

Purpose
The present phase III study was designed to investigate the noninferiority of S-1 alone and superiority of gemcitabine plus S-1 compared with gemcitabine alone with respect to overall survival.

Patients and Methods
The participants were chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive only gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle), only S-1 (80, 100, or 120 mg/d according to body-surface area on days 1 through 28 of a 42-day cycle), or gemcitabine plus S-1 (gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 60, 80, or 100 mg/d according to body-surface area on days 1 through 14 of a 21-day cycle).

Results
In the total of 834 enrolled patients, median overall survival was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The noninferiority of S-1 to gemcitabine was demonstrated (hazard ratio, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority), whereas the superiority of gemcitabine plus S-1 was not (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$). All treatments were generally well tolerated, although hematologic and GI toxicities were more severe in the gemcitabine plus S-1 group than in the gemcitabine group.

Conclusion
Monotherapy with S-1 demonstrated noninferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer.

J Clin Oncol 31:1640-1648. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic cancer (PC) is currently the eighth leading cause of cancer-related mortality worldwide, with an estimated 266,000 deaths in 2008.[1] Gemcitabine became the standard treatment for advanced PC, improving overall survival (OS) compared with fluorouracil.[2] Although various gemcitabine-based combination regimens have been evaluated, only erlotinib added to gemcitabine showed a survival benefit over gemcitabine, and that was marginal.[3]

Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a gemcitabine-free combination regimen, has recently demonstrated a clear survival benefit compared with gemcitabine for patients with metastatic PC who have a performance status of 0 to 1.[4] However, because FOLFIRINOX is associated with significant toxicity, this regimen must be limited to patients with good performance status and requires close monitoring.[5]

In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. S-1

is an oral fluoropyrimidine derivative shown to be effective for gastric and various other types of cancers.[6,7] Phase II studies of S-1 as first-line therapy for metastatic PC resulted in good response rates of 21.1% to 37.5%.[8,9] Consequently, S-1 was approved for the indication of PC in Japan in 2006. Development of gemcitabine plus S-1 (GS) studies have also been initiated, mainly in Japan, and two phase II studies reported high response rates of 44.4% to 48.5% and good median OS of 10.1 to 12.5 months.[10,11]

Because S-1 and GS have shown promising activity in PC, the present randomized phase III study (GEST [Gemcitabine and S-1 Trial] study) was designed to evaluate whether S-1 alone is noninferior to gemcitabine and whether GS is superior to gemcitabine alone for locally advanced and metastatic PC with respect to OS.

PATIENTS AND METHODS

Study Design

This randomized phase III study, sponsored by Taiho Pharmaceutical in Japan and TTY Biopharm in Taiwan, was conducted as a postmarketing study in Japan and as a registration study in Taiwan and was in compliance with the Declaration of Helsinki. Data were collected by a contract research organization contracted by the sponsors and were analyzed by a bio-statistician (Y.O.). An independent data and safety monitoring committee reviewed efficacy and safety data. The study was approved by the ethics committee or institutional review board of each participating center.

Patients

All patients provided written informed consent. Enrollment criteria were locally advanced or metastatic PC, histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events), an Eastern Cooperative Oncology Group performance status score of 0 to 1, and adequate organ functions (see Appendix, online only).

Treatment

Random assignment was performed centrally with stratification by extent of disease (locally advanced disease *v* metastatic disease) and institution using the minimization method. Patients allocated to gemcitabine alone received gemcitabine at a dose of 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Patients allocated to S-1 alone received S-1 orally twice daily at a dose according to the body-surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle. Patients allocated to GS received gemcitabine at a dose of 1,000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose according to the BSA (< 1.25 m^2, 60 mg/d; ≥ 1.25 to < 1.5 m^2, 80 mg/d; ≥ 1.5 m^2, 100 mg/d) on days 1 through 14 of a 21-day cycle. The dose levels of S-1 used in the GS group were based on the results of a previous phase II study of GS, in which 1,000 mg/m^2 of gemcitabine was combined with 120 mg/d, 100 mg/d, and 80 mg/d of S-1. In that study, the rate of treatment withdrawal due to adverse events was 41% (22 of 54 patients), the rate of grade 3 or worse neutropenia was 80%, and the dose was reduced in 56% of the patients (30 of 54 patients).[11] Consequently, 20 mg/d lower doses of S-1 than those used in the S-1 monotherapy group were used in the GS group in the present study.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see Appendix).

Assessments

Physical examinations, CBCs, and biochemistry tests were usually checked at 2-week intervals in the S-1 group and at each time of administration of gemcitabine both in the gemcitabine group and in the GS group. All adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. Computed tomography or magnetic resonance imaging was performed every 6 weeks until disease progression, and response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12] Quality of life was assessed using the EuroQol 5 Dimension questionnaire[13] at baseline and 6, 12, 24, 48, and 72 weeks after the study treatment had begun.

Statistical Analysis

The primary end point was OS, defined as time from date of random assignment to date of death from any cause. Secondary end points were progression-free survival (PFS), objective response rate, safety, and quality of life. PFS was counted from the date of random assignment to the date of death without progression or of progression as confirmed by the investigator's assessment. The median OS was assumed to be 7.5 months in the gemcitabine group, 8.0 months in the S-1 group, and 10.5 months in the GS group. To maintain a one-sided significance level of .025 for the entire study while testing two hypotheses (ie, noninferiority and superiority), the one-sided significance

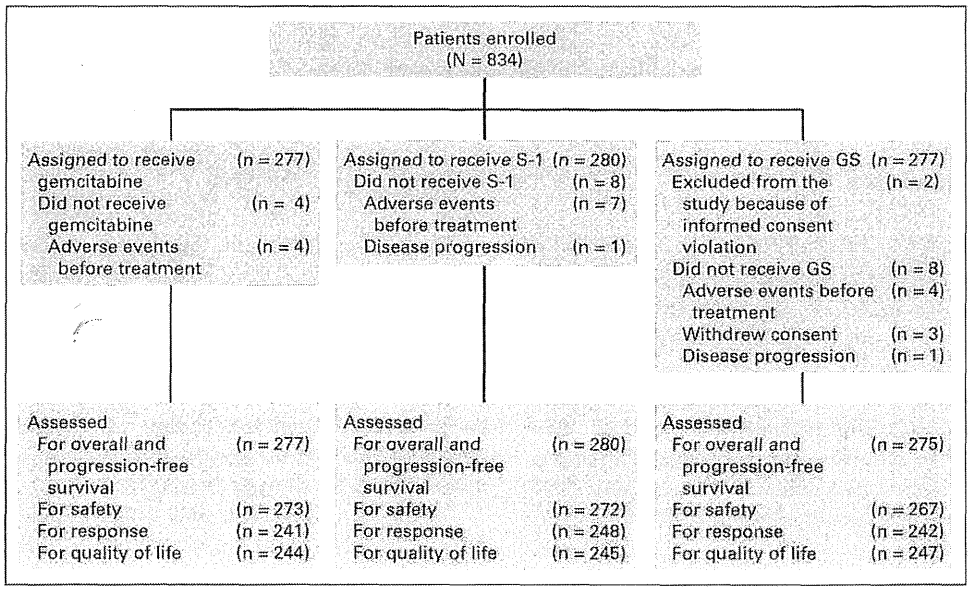

Fig 1. CONSORT diagram. GS, gemcitabine plus S-1.

level for each comparison was set at .0125. The statistical considerations are detailed in the Appendix.

The superiority of GS was evaluated by the stratified log-rank test. To assess the noninferiority of S-1, we used the Cox proportional hazards model to calculate two-sided, 97.5% CIs of the hazard ratio (HR). The noninferiority margin of S-1 was set at 1.33; that is, the null hypothesis was that the median OS with S-1 would be approximately 2 months shorter than with gemcitabine. We decided this setting was justified considering the convenience of S-1 and because there are few effective drugs for the disease. Furthermore, to interpret the obtained data, the Bayesian analysis of the log HR on the basis of the noninformative prior distribution was preplanned. Posterior probability with log HR within a stricter threshold (log 1.15) was also calculated.[14]

In each assigned group, the time-to-event distribution was estimated with the Kaplan-Meier method. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[15] In addition, the Greenwood formula[16] was used to calculate the 95% CI for survival rates. In subgroup analyses, interaction tests were performed to assess the homogeneity of the effect of treatment on OS.

The primary end point was analyzed for the full analysis set. All *P* value evaluations were two-tailed. Data analyses were done with SAS, version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patients

Between July 2007 and October 2009, a total of 834 patients were enrolled from 75 institutions in Japan and Taiwan (768 in Japan and 66 in Taiwan). Two patients in the GS group were excluded from the study because enrollment was conducted before obtaining written informed consent. The remaining 832 patients were included in the full analysis set and used to calculate OS and PFS (Fig 1). The three treatment groups were well balanced with respect to demographic and baseline characteristics (Table 1).

Study Treatment

The median duration of treatment was 2.6 months in the gemcitabine group, 2.6 months in the S-1 group, and 4.3 months in the GS group. The main reasons for treatment discontinuation were either disease progression (202 patients [72.9%] in the gemcitabine group,

Table 1. Demographics and Baseline Characteristics of Patients (full-analysis set population)

Characteristic	Gemcitabine (n = 277)		S-1 (n = 280)		GS (n = 275)		Total (N = 832)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	170	61.4	170	60.7	158	57.5	498	59.9
Female	107	38.6	110	39.3	117	42.5	334	40.1
Age, years								
< 65	134	48.4	145	51.8	137	49.8	416	50.0
≥ 65	143	51.6	135	48.2	138	50.2	416	50.0
ECOG PS								
0	181	65.3	178	63.6	172	62.5	531	63.8
1	96	34.7	102	36.4	103	37.5	301	36.2
Extent of disease								
Locally advanced	66	23.8	68	24.3	68	24.7	202	24.3
Metastatic	211	76.2	212	75.7	207	75.3	630	75.7
Type of tumor								
Adenocarcinoma	272	98.2	276	98.6	272	98.9	820	98.6
Adenosquamous carcinoma	5	1.8	4	1.4	3	1.1	12	1.4
Pancreas excision								
No	254	91.7	264	94.3	248	90.2	766	92.1
Yes	23	8.3	16	5.7	27	9.8	66	7.9
Tumor location*								
Head	122	44.0	110	39.3	116	42.2	348	41.8
Body	88	31.8	124	44.3	102	37.1	314	37.7
Tail	68	24.5	55	19.6	66	24.0	189	22.7
Biliary drainage								
No	202	72.9	217	77.5	209	76.0	628	75.5
Yes	75	27.1	63	22.5	66	24.0	204	24.5
CEA, ng/mL								
Median	5.7		5.6		5.9		5.7	
IQR	3.0-20.1		2.5-18.4		2.5-20.7		2.6-19.5	
CA19-9, U/mL								
Median	1,044		726		441		712	
IQR	52-5,002		64-5,000		45-5,090		55-5,002	
CRP, mg/dL								
Median	0.40		0.50		0.40		0.43	
IQR	0.11-1.38		0.18-1.57		0.15-1.60		0.15-1.57	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; GS, gemcitabine plus S-1; IQR, interquartile range.
*Including patients with tumors involving multiple sites.

215 [76.8%] in the S-1 group, and 162 [58.9%] in the GS group) or adverse events (40 patients [14.4%] in the gemcitabine group, 38 [13.6%] in the S-1 group, and 76 [27.6%] in the GS group). The median relative dose-intensity was 83.0% in the gemcitabine group, 96.1% in the S-1 group, and 83.3% for gemcitabine and 87.4% for S-1 in the GS group.

Survival

The median duration of follow-up for surviving patients was 18.4 months (range, 0.3 to 36.9 months) as of July 31, 2010. The analysis of OS was based on 710 deaths (85.3%) among the 832 patients. The median OS was 8.8 months (95% CI, 8.0 to 9.7) in the gemcitabine group, 9.7 months (95% CI, 7.6 to 10.8) in the S-1 group, and 10.1 months (95% CI, 9.0 to 11.2) in the GS group (Fig 2A). OS rates at 12 and 24 months were respectively 35.4% and 9.2% in the gemcitabine group, 38.7% and 12.7% in the S-1 group, and 40.7% and 14.5% in the GS group. The noninferiority of S-1 to gemcitabine with respect to OS was demonstrated (HR, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority). The Bayesian posterior probability that the HR of S-1 relative to gemcitabine would be less than 1.15 was calculated to be 98% on the basis of the noninformative prior distribution. However, GS failed to improve OS at a statistically significant level as compared with gemcitabine (HR, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$).

The analysis of PFS was based on 793 events (95.3%) among the 832 patients. The median PFS was 4.1 months (95% CI, 3.0 to 4.4) in the gemcitabine group, 3.8 months (95% CI, 2.9 to 4.2) in the S-1 group, and 5.7 months (95% CI, 5.4 to 6.7) in the GS group (Fig 2B). PFS rates at 6 and 12 months were respectively 29.8% and 9.1% in the gemcitabine group, 26.9% and 7.2% in the S-1 group, and 47.9% and 20.3% in the GS group. S-1 was shown to be noninferior to gemcitabine with respect to PFS (HR, 1.09; 97.5% CI, 0.90 to 1.33; $P = .02$ for noninferiority), and GS significantly improved PFS compared with gemcitabine (HR, 0.66; 97.5% CI, 0.54 to 0.81; $P < .001$).

Subgroup analyses of survival according to pretreatment characteristics showed no significant interaction between S-1 and gemcitabine in any subgroup (Fig 3A). However, GS showed a favorable HR compared with gemcitabine in the subsets of patients with locally advanced disease or patients with a performance status of 1 (Fig 3B).

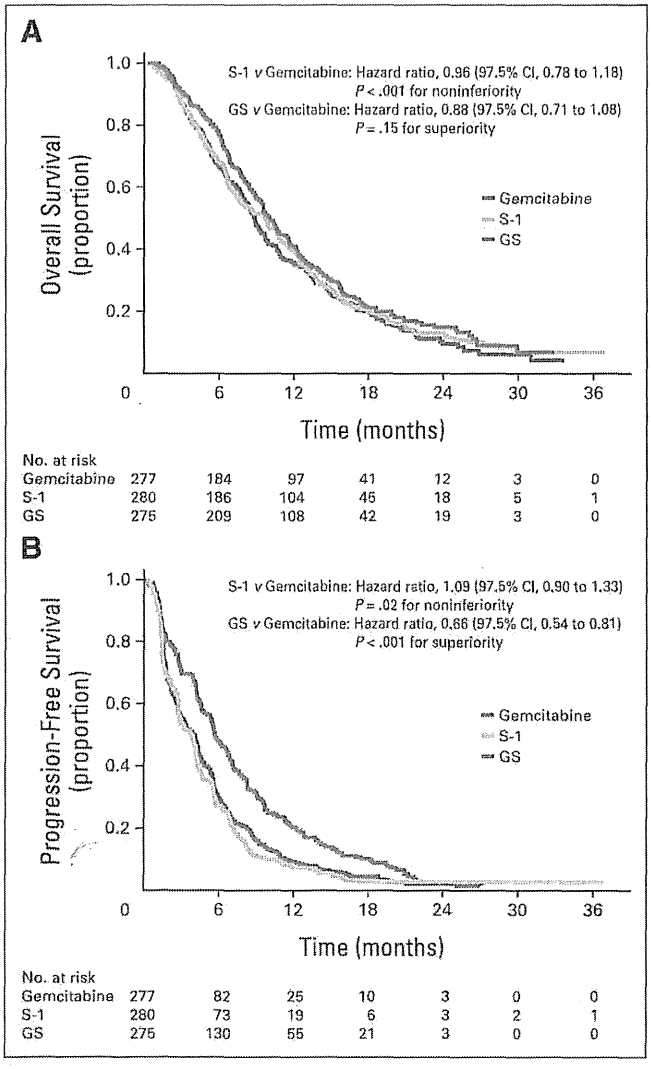

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival according to treatment group. GS, gemcitabine plus S-1.

Response to Therapy

The objective response rate was 13.3% (95% CI, 9.3 to 18.2) in the gemcitabine group, 21.0% (95% CI, 16.1 to 26.6) in the S-1 group, and 29.3% (95% CI, 23.7 to 35.5) in the GS group (Table 2). The objective response rate was significantly higher in the S-1 group ($P = .02$) and in the GS group ($P < .001$) than in the gemcitabine group.

Second-Line Chemotherapy

Second-line chemotherapy was performed in 184 patients (66.4%) in the gemcitabine group, 185 (66.1%) in the S-1 group, and 172 (62.5%) in the GS group. In the gemcitabine group, 140 patients (50.5%) received S-1 alone or S-1–based regimens, and in the S-1 group 162 (57.9%) received gemcitabine alone or gemcitabine-based regimens as second-line chemotherapy. The most common second-line regimens in the GS group were gemcitabine alone (61 patients), GS (53 patients), S-1 alone (24 patients), irinotecan (six patients), and fluorouracil/leucovorin plus oxaliplatin (four patients). In Japan and Taiwan, the use of treatments such as erlotinib, oxaliplatin, and irinotecan for PC was not approved at the time of this study; hence gemcitabine, S-1, or both were used in most patients as second-line chemotherapy.

Adverse Events and Quality-Adjusted Life-Years

The major grade 3 or worse adverse events are listed in Table 3. Patients in the gemcitabine group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, elevated AST levels, and elevated ALT levels as compared with patients in the S-1 group. However, the incidence of grade 3 or worse diarrhea was higher in the S-1 group than in the gemcitabine group. Patients in the GS group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, rash, diarrhea, vomiting, and stomatitis than patients in the gemcitabine group.

There were three deaths considered possibly related to the protocol treatment (interstitial lung disease, sepsis, and acute hepatitis B) in the gemcitabine group, one in the S-1 group (unknown cause), and

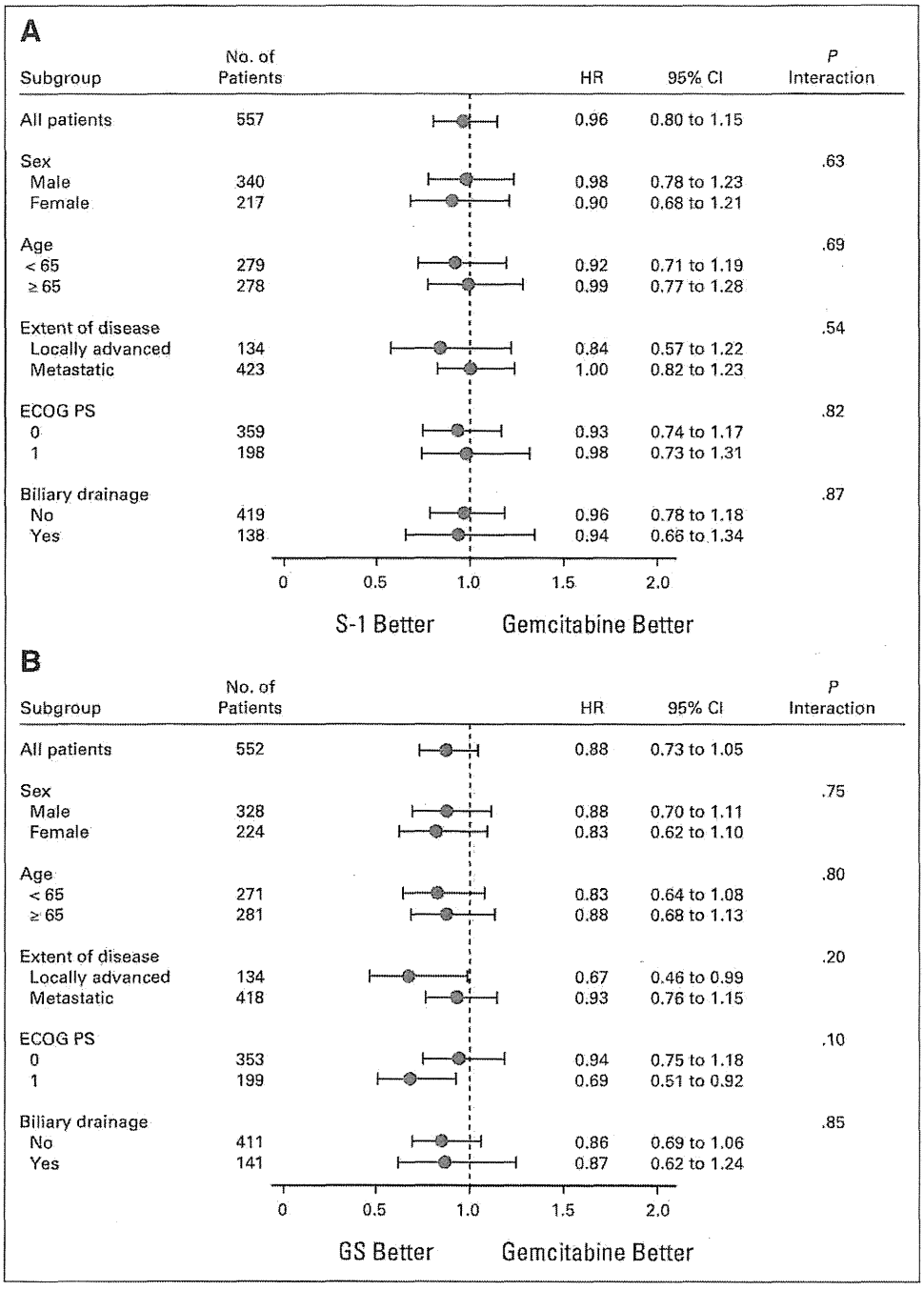

Fig 3. Forest plots of treatment effects on overall survival in subgroup analyses. Forest plots show effects on overall survival of patients in each subgroup. (A) S-1; (B) gemcitabine plus S-1 (GS). Each blue circle shows the treatment response. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

four in the GS group (unknown cause associated with myelosuppression, cerebral infarction, cerebrovascular disorder, and interstitial lung disease). The results of quality-adjusted life-years (QALYs) are in the Appendix and the details of quality-of-life assessments will be reported elsewhere.

DISCUSSION

The overall and PFS curves in the S-1 group were nearly identical to those in the gemcitabine group, confirming the noninferiority of S-1 to gemcitabine in terms of OS and PFS (Fig 2A, 2B). Toxicity profiles of these two drugs differed slightly: gemcitabine tended to show hematologic toxicity, whereas S-1 tended to show GI toxicity. However, both S-1 and gemcitabine were generally well tolerated. Furthermore, the results of QALY evaluation demonstrated that S-1 and gemcitabine were equivalent. Hence our results suggest that S-1 can be used as first-line therapy as a convenient oral alternative for locally advanced and metastatic PC. To the best of our knowledge, this is the first phase III study to demonstrate the noninferiority of a single anticancer agent to gemcitabine alone for locally advanced and metastatic PC.

Table 2. Objective Response Rates (patients with measurable lesions)

Variable	Gemcitabine (n = 241) No.	Gemcitabine (n = 241) %	S-1 (n = 248) No.	S-1 (n = 248) %	GS (n = 242) No.	GS (n = 242) %	*P* (χ^2 test) Gemcitabine *v* S-1	*P* (χ^2 test) Gemcitabine *v* GS
Response								
Complete response	1	0.4	0	0	2	0.8		
Partial response	31	12.9	52	21.0	69	28.5		
Stable disease	119	49.4	105	42.3	102	42.1		
Progressive disease	75	31.1	69	27.8	37	15.3		
Objective response rate*	32	13.3	52	21.0	71	29.3	.02	< .001
95% CI	9.3 to 18.2		16.1 to 26.6		23.7 to 35.5			
Disease control rate†	151	62.7	157	63.3	173	71.5	.88	.04
95% CI	56.2 to 68.8		57.0 to 69.3		65.4 to 77.1			

Abbreviation: GS, gemcitabine plus S-1.
*The objective response rate was defined as the proportion of patients who had a complete response or partial response.
†The disease control rate was defined as the proportion of patients who had a complete response, partial response, or stable disease.

At the time of planning this study, the participants of nearly all phase III trials included both patients with locally advanced as well as those with metastatic PC. However, because locally advanced and metastatic diseases are two clinical entities, it is recently recommended that patients with locally advanced disease should be studied separately from those with metastatic disease.[17] Although this study included locally advanced disease, subgroup analysis of extent of disease showed no significant interaction between S-1 and gemcitabine (Fig 3A). Moreover, the OS curve in the S-1 group was still similar to those in the gemcitabine group in both locally advanced and metastatic disease (Fig 4A, 4B). Regarding pathologic diagnosis, our study included adenosquamous carcinoma, although its percentage was very low (1.4% of whole population). When the data were reanalyzed after excluding patients with adenosquamous carcinoma, the results for OS for gemcitabine versus S-1 was unchanged (HR, 0.96; 95% CI, 0.81 to 1.15). The selection of one treatment over the other will depend primarily on patient preference, clinical factors, or drug costs, as biomarkers indicating effective use of S-1 or gemcitabine do not exist at this time.

Regarding GS, the OS did not differ significantly from gemcitabine, although the PFS was significantly longer in the GS group. Second-line chemotherapy mainly with S-1 in the gemcitabine group may be one reason for this discrepancy. The median OS in the gemcitabine group was 8.8 months, which is longer than those previously reported for gemcitabine in other phase III studies for locally advanced and metastatic PC.[2,3,18-24] Although the efficacy of second-line

Table 3. Grade 3 or Worse Adverse Events (safety population)

Event	Gemcitabine (n = 273) No.	Gemcitabine (n = 273) %	S-1 (n = 272) No.	S-1 (n = 272) %	GS (n = 267) No.	GS (n = 267) %	*P* (Fisher's exact test) Gemcitabine *v* S-1	*P* (Fisher's exact test) Gemcitabine *v* GS
Hematologic								
Leukocytes	51	18.7	10	3.7	101	37.8	< .001	< .001
Neutrophils	112	41.0	24	8.8	166	62.2	< .001	< .001
Platelets	30	11.0	4	1.5	46	17.2	< .001	.05
Hemoglobin	39	14.3	26	9.6	46	17.2	.11	.41
Nonhematologic								
ALT	41	15.0	16	5.9	29	10.9	< .001	.16
AST	41	15.0	21	7.7	32	12.0	.01	.32
Bilirubin	26	9.5	39	14.3	23	8.6	.09	.77
Fatigue	10	3.7	18	6.6	13	4.9	.13	.53
Rash	2	0.7	2	0.7	11	4.1	1.00	.01
Anorexia	20	7.3	31	11.4	25	9.4	.11	.44
Diarrhea	3	1.1	15	5.5	12	4.5	.004	.02
Mucositis/stomatitis	0	0.0	2	0.7	6	2.2	.25	.01
Nausea	5	1.8	5	1.8	12	4.5	1.00	.09
Vomiting	2	0.7	4	1.5	12	4.5	.45	.006
Febrile neutropenia	1	0.4	1	0.4	5	1.9	1.00	.12
Infection with normal ANC	6	2.2	7	2.6	6	2.2	.79	1.00
Pneumonitis	5	1.8	0	0.0	2	0.7	.06	.45

NOTE. Grades of adverse events were defined according to the Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviations: ANC, absolute neutrophil count; GS, gemcitabine plus S-1.

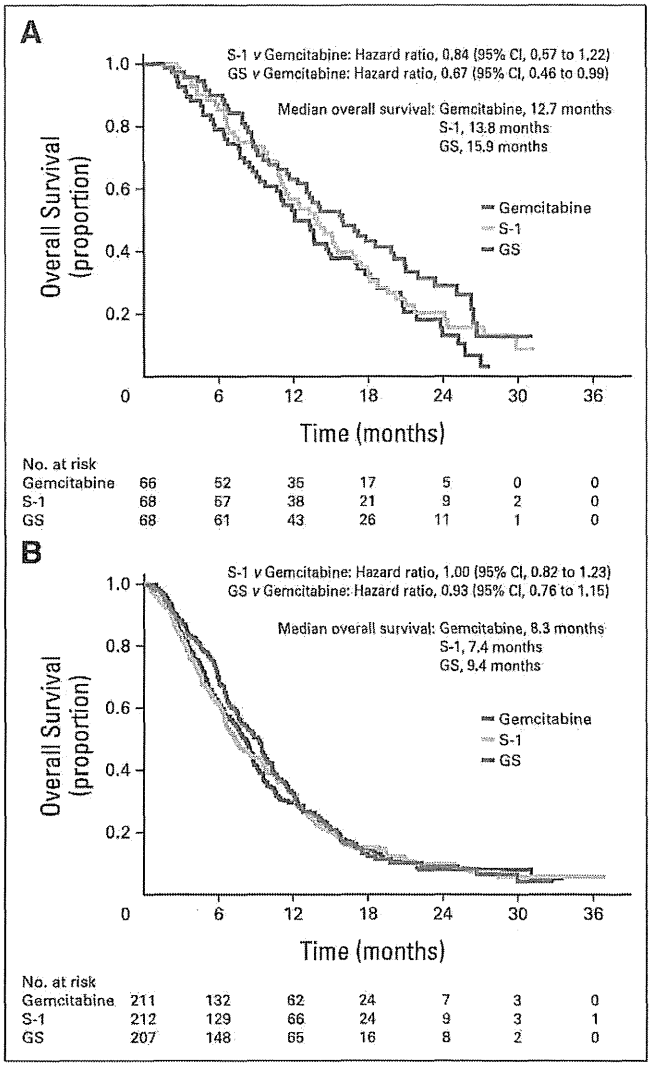

Fig 4. Kaplan-Meier estimates of overall survival in (A) locally advanced disease and (B) metastatic disease. GS, gemcitabine plus S-1.

therapy was not analyzed in this study, a phase II study of second-line S-1 in patients with gemcitabine-refractory PC showed a 15% response rate and 58% disease control rate.[25] Compared with the GS group, which had no promising second-line therapy, the use of S-1 as second-line therapy in the gemcitabine group might have contributed to prolonged survival.

The lack of a significant difference in OS between gemcitabine and GS suggests that gemcitabine and S-1 could be used sequentially rather than concurrently. However, the GS group showed a high response rate and favorable PFS, with a better HR of 0.66 compared with other gemcitabine-based combination regimens in other phase III studies (HR = 0.75 to 1.07).[3,18,20,22,24] Furthermore, the GS group showed a favorable HR for OS in patients with locally advanced disease or patients with a performance status of 1 in the subgroup analyses. Therefore, it is speculated that there may be room to select GS therapy, depending on the profile of the patients and further investigations.

Regarding oral fluoropyrimidines other than S-1, capecitabine has been studied in patients with PC, mainly in the West. In two phase III studies, a combination of gemcitabine plus capecitabine did not significantly prolong survival as compared with gemcitabine alone.[19,20] The results of a meta-analysis of these phase III studies, however, demonstrated that survival was significantly prolonged by combined treatment, with an HR of 0.86,[20] which is similar to the HR for GS in the present study (0.88).

One limitation of our study is that it is uncertain whether our results can be simply extrapolated to Western patients because pharmacokinetics and pharmacodynamics of S-1 between Westerners and East Asians may be different.[26,27] Although S-1 is available for PC only in Japan at the moment, if S-1 is used in Western patients, its effectiveness should be monitored and the dose should be carefully adjusted accordingly. Another potential limitation is that the protocol-specified noninferiority margin of 1.33 may be large. However, the result of point estimate of the HR of S-1 was 0.96 and actual upper limit of the 97.5% CI was 1.18, which was sufficiently lower than the prespecified margin of 1.33. Furthermore, Bayesian posterior probability with log HR within a stricter threshold (log 1.15) was 98%.

Given that most gemcitabine-based combination regimens have not been shown to be significantly superior to gemcitabine alone and that FOLFIRINOX has demonstrated overwhelming superiority to gemcitabine in a phase III study, reporting an HR of 0.57,[4] the development of gemcitabine-free combination regimens for first-line treatment seems to be warranted. However, because FOLFIRINOX requires the placement of a central venous access port for continuous intravenous infusion of fluorouracil, it can be expected that S-1, an oral fluoropyrimidine, will replace the continuous infusion of fluorouracil in the future.

In conclusion, this study has verified the noninferiority of S-1 to gemcitabine, thereby suggesting that S-1 can be used as first-line therapy for locally advanced and metastatic PC. Because S-1 was confirmed to be a key treatment for PC, S-1–based regimens are expected to be developed in the future to improve the management of this formidable disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Hideki Ueno, Taiho Pharmaceutical (C); Tatsuya Ioka, Taiho Pharmaceutical (U); Shinichi Ohkawa, Taiho Pharmaceutical (C); Narikazu Boku, Taiho Pharmaceutical (U); Kenji Yamao, Taiho Pharmaceutical (C); Ann-Lii Cheng, Boehringer Ingelheim (C), sanofi-aventis (C), TTY Biopharm (C); Kazuhiro Mizumoto, Taiho Pharmaceutical (C); Jen-Shi Chen, TTY Biopharm (C); Junji Furuse, Bayer (C), GlaxoSmithKline (C), Kowa (C), Novartis (C), Taiho Pharmaceutical (C); Akihiro Funakoshi, Taiho Pharmaceutical (C); Takashi Hatori, Taiho Pharmaceutical (C); Taketo Yamaguchi, Taiho Pharmaceutical (C); Atsushi Sato, Taiho Pharmaceutical (C); Yasuo Ohashi, Taiho Pharmaceutical (C); Takuji Okusaka, Taiho Pharmaceutical (C); Masao Tanaka, Taiho Pharmaceutical (C) **Stock**