Table 3. Adverse events ($n = 54$)

	Grade				Grades 1–4	Grades 3–4
	1	2	3	4	%	%
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	0	0	13	0
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	4	4

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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/m^2/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/m^2 on days 1 and 15 and S-1 at a dose of 40 mg/m^2 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 4. Phase II studies of GS therapy for advanced pancreatic cancer

Author	Gemcitabine (mg/m^2)	S-1 (mg/m^2/day)	Cycle (day)	No. of patients	Metastatic disease (%)	RR (%)	Median TTP/PFS (months)	Median OS (months)	Grade 3/4 neutropenia (%)	Grade 3/4 thrombocytopenia (%)
Nakamura *et al.* (15)	1000 (days 8, 15)	60 (days 1–14)	21	33	100	48	5.4	12.5	55	15
Lee *et al.* (16)	1250 (days 1, 8)	80 (days 1–14)	21	32	90.6	44	4.92	7.89	28.1	15.6
Kim *et al.* (17)	1000 (days 8, 15)	60 (days 1–14)	21	22	86.3	27.3	4.6	8.5	18.2	4.5
Oh *et al.* (18)	1000 (days 1, 8)	80 (days 1–14)	21	38	84	29	5.43	8.4	39.5	2.6
Current study	1000 (days 1, 8)	80 (days 1–14)	21	55	100	44.4	5.9	10.1	80	22

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.

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Conflict of interest statement

None declared.

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Appendix

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Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study

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Summary

Background Axitinib is a potent, selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. A randomised phase 2 trial of gemcitabine with or without axitinib in advanced pancreatic cancer suggested increased overall survival in axitinib-treated patients. On the basis of these results, we aimed to assess the effect of treatment with gemcitabine plus axitinib on overall survival in a phase 3 trial.

Methods In this double-blind, placebo-controlled, phase 3 study, eligible patients had metastatic or locally advanced pancreatic adenocarcinoma, no uncontrolled hypertension or venous thrombosis, and Eastern Cooperative Oncology Group performance status 0 or 1. Patients, stratified by disease extent (metastatic *vs* locally advanced), were randomly assigned (1:1) to receive gemcitabine 1000 mg/m^2 intravenously on days 1, 8, and 15 every 28 days plus either axitinib or placebo. Axitinib or placebo were administered orally with food at a starting dose of 5 mg twice a day, which could be dose-titrated up to 10 mg twice daily if well tolerated. A centralised randomisation procedure was used to assign patients to each treatment group, with randomised permuted blocks within strata. Patients, investigators, and the trial sponsor were masked to treatment assignments. The primary endpoint was overall survival. All efficacy analyses were done in all patients assigned to treatment groups for whom data were available; safety and treatment administration and compliance assessments were based on treatment received. This study is registered at ClinicalTrials.gov, number NCT00471146.

Findings Between July 27, 2007, and Oct 31, 2008, 632 patients were enrolled and assigned to treatment groups (316 axitinib, 316 placebo). At an interim analysis in January, 2009, the independent data monitoring committee concluded that the futility boundary had been crossed. Median overall survival was 8·5 months (95% CI 6·9–9·5) for gemcitabine plus axitinib (n=314, data missing for two patients) and 8·3 months (6·9–10·3) for gemcitabine plus placebo (n=316; hazard ratio 1·014, 95% CI 0·786–1·309; one-sided p=0·5436). The most common grade 3 or higher adverse events for gemcitabine plus axitinib and gemcitabine plus placebo were hypertension (20 [7%] and 5 [2%] events, respectively), abdominal pain (20 [7%] and 17 [6%]), fatigue (27 [9%] and 21 [7%]), and anorexia (19 [6%] and 11 [4%]).

Interpretation The addition of axitinib to gemcitabine does not improve overall survival in advanced pancreatic cancer. These results add to increasing evidence that targeting of VEGF signalling is an ineffective strategy in this disease.

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Introduction

The prognosis for patients with advanced pancreatic adenocarcinoma is poor, and gemcitabine, the standard of care, offers only slight benefit.[1,2] Despite extensive research, combination regimens with gemcitabine and cytotoxic or molecularly targeted agents have not significantly improved outcomes compared with gemcitabine monotherapy.[3] The addition of erlotinib to gemcitabine resulted in a significant but very small improvement in overall survival.[3,4] There is a pressing need for new treatment options for this disease.

Axitinib is an oral, potent, and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3.[5] A randomised phase 2 study[6] of 103 patients with locally advanced and metastatic pancreatic adenocarcinoma showed an improvement in median overall survival (6·9 *vs* 5·6 months; hazard ratio [HR] 0·71, 95% CI 0·44–1·13) and a greater 1-year survival (37% *vs* 24%) for axitinib plus gemcitabine versus gemcitabine alone. Although not significant, the apparent increase in survival in the combination group provided the rationale for a larger phase 3 study of this regimen. We aimed to assess overall survival in patients with advanced pancreatic cancer treated with gemcitabine plus axitinib versus gemcitabine plus placebo.

Methods

Study design and patients

We undertook a phase 3, randomised, double-blind, global, multicentre, two-group study. Eligible patients were at least 18 years old with histologically or cytologically confirmed metastatic or locally advanced pancreatic adenocarcinoma not amenable to curative resection. Patients were required to have adequate bone marrow, hepatic, and renal function (including urine protein <2 g/24 h); an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and no uncontrolled hypertension (two baseline blood pressure readings ≤140/90 mm Hg). Patients with documented invasion of adjacent hollow organs were excluded. Adjuvant therapy that did not contain gemcitabine was allowed if 4 weeks or longer had passed since the last dose; previous radiation was allowed if there was disease outside the radiation port. Additional exclusion factors included: previous treatment with VEGF or VEGF receptor inhibitors; previous systemic chemotherapy for locally advanced or metastatic disease; use of a thrombolytic agent within 1 month of treatment; central lung lesions involving major blood vessels; recent haemoptysis, myocardial infarction, symptomatic congestive heart failure, cerebrovascular accident, transient ischaemic attack, deep-vein thrombosis, or pulmonary embolism in the past 12 months; peptic ulcer disease needing treatment in the past 6 months; active seizures or gastrointestinal bleeding; malabsorption syndromes; present use of potent cytochrome P450 (CYP) 3A4 inhibitors or CYP3A4 or CYP1A2 inducers; or major surgery within 4 weeks.

The study was undertaken with institutional review board approval and in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, as well as applicable local laws and regulatory requirements. All patients provided written informed consent.

Randomisation and masking

Patients were stratified by disease extent (metastatic *vs* locally advanced) and randomly allocated in a 1:1 ratio to receive gemcitabine plus either axitinib or placebo. A centralised randomisation procedure (interactive voice randomisation system accessible via telephone or internet) was used to assign patients to each treatment group, with randomised permuted blocks within strata. Randomisation was not done by centre, but by stratification category, and use of blocked randomisation made guessing of the next treatment assignment within a block almost impossible. Patients, investigators, and the trial sponsor were masked to treatment assignments.

Procedures

All patients received gemcitabine 1000 mg/m² intravenously during 30 min on days 1, 8, and 15 of each 4-week treatment cycle until disease progression, unacceptable toxic effects, or withdrawal of consent. Dose reductions to 750 mg/m², 550 mg/m², and 425 mg/m² were allowed for management of adverse events. Gemcitabine was discontinued in patients needing a dose interruption longer than 4 weeks or a dose reduction to less than 425 mg/m².

All patients also received either axitinib or placebo, administered orally with food at a starting dose of 5 mg twice a day, which was continued until disease progression, unacceptable toxic effects, or withdrawal of consent. Stepwise dose increases to 7 mg and then 10 mg twice a day were allowed in the absence of axitinib-related or placebo-related grade 3 or higher adverse events for consecutive 2-week periods in patients with blood pressure 150/90 mm Hg or lower who were not receiving antihypertensive drugs. Dose reductions to 3 mg or 2 mg twice daily were allowed for management of adverse events. In patients with systolic blood pressure higher than 150 mm Hg or diastolic blood pressure higher than 100 mm Hg, new or additional antihypertensive treatment was initiated and axitinib or placebo was continued. For patients on maximum antihypertensive treatment, the axitinib or placebo dose was reduced one level. For systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 105 mm Hg, antihypertensive treatment was adjusted, and axitinib or placebo dosing was interrupted and resumed at one lower dose level once blood pressure was lower than 150/100 mm Hg. If proteinuria of 2 g per day or higher occurred, axitinib or placebo dosing was interrupted and resumed at one lower dose level once proteinuria less than 2 g per day was recorded. For all other grade 3 axitinib-related or placebo-related non-haematological adverse events, the axitinib or placebo dose was decreased by one level. For grade 4 axitinib-related or placebo-related non-haematological adverse events or grade 4 haematological adverse events (except lymphopenia), dosing was interrupted and resumed at one lower dose level when the adverse event improved to grade 2 or lower. Treatment was discontinued if a dose interruption for longer than 4 weeks or a dose reduction to less than 2 mg twice a day was needed. If either gemcitabine or axitinib/placebo was interrupted or withdrawn, the remaining therapy was continued.

CT scans were obtained at screening, every 8 weeks during the study, and at follow-up 28 days after the last dose in patients who discontinued without progressive disease. Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST).[7] Safety was monitored by physical examination, urinalysis, haematology, and clinical chemistry tests; assessment of ECOG performance status; and adverse event reporting, based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. An independent data monitoring committee reviewed accumulating unmasked safety and survival data during the study. Blood pressure was monitored in the clinic at baseline, on days 1, 8, and 15 of each 4-week treatment cycle, and at follow-up. Blood pressure was also measured and recorded in diaries by patients before each dose of axitinib or placebo. Thyroid-stimulating hormone (TSH) concentrations were evaluated at baseline, every 2 weeks for the first 6 weeks, and every 8 weeks thereafter.

The primary endpoint was overall survival; secondary endpoints included progression-free survival, objective response rate, duration of response, safety, and health-related quality of life. Health-related quality of life, pancreatic cancer-specific symptoms, pain, and health status were measured with the European Organisation for the Research and Treatment of Cancer quality of life questionnaire–core 30 (QLQ-C30) and pancreatic cancer module (QLQ-PAN26) at baseline, on day 1 of each treatment cycle, and 28 days after the last dose.[8,9]

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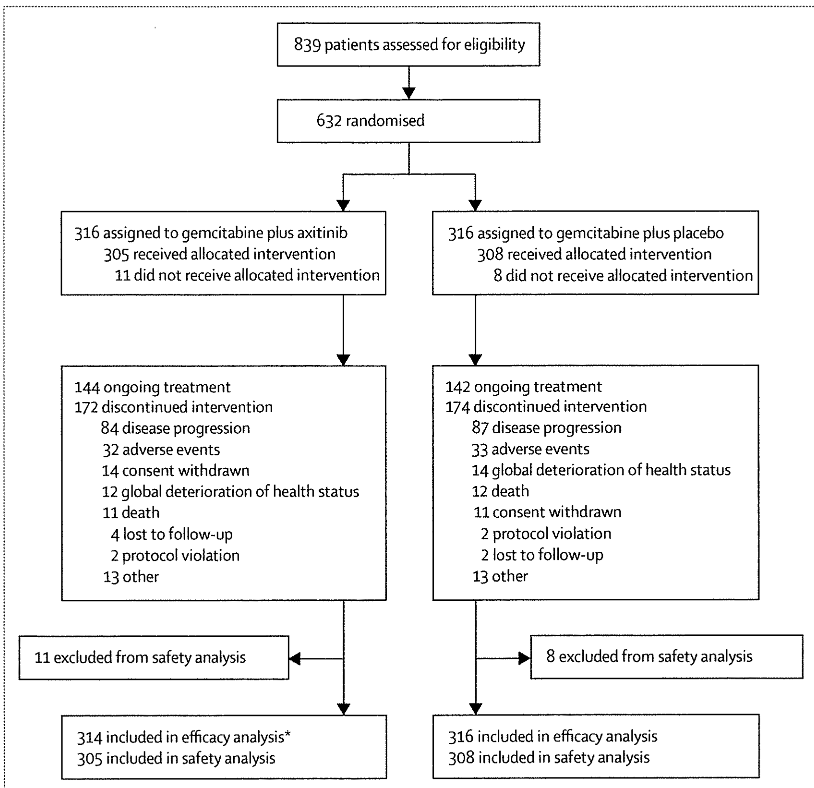

Figure 1: **Trial profile**
*Data missing from database at time of analysis for two patients.

	Axitinib plus gemcitabine (n=314)*	Placebo plus gemcitabine (n=316)
Median age (years)	61 (34–84)	62 (35–89)
Sex		
Male	191 (61%)	188 (59%)
Female	123 (39%)	128 (41%)
ECOG performance status		
0	147 (47%)	158 (50%)
1	162 (52%)	154 (49%)
Missing	5 (2%)	4 (1%)
Disease extent		
Locally advanced	77 (25%)	73 (23%)
Metastatic	226 (72%)	227 (72%)
Missing	11 (4%)	16 (5%)
Metastatic sites		
Liver	146/264 (55%)	135/263 (51%)
Lung	63/264 (24%)	57/263 (22%)
Peritoneum	16/264 (6%)	20/263 (8%)
Previous adjuvant chemotherapy†	12 (4%)	12 (4%)
Mean QLQ-30 global health status/QoL score	54·2 (22·3)‡	57·1 (23·1)§

Data are median (range), n/N (%), or mean (SD). Some data are missing from this table because they were derived from case report forms. ECOG=Eastern Cooperative Oncology Group. QLQ-C30=European Organisation for the Research and Treatment of Cancer quality of life questionnaire, core 30. QoL=quality of life. *Data missing from database at time of analysis for two patients. †Includes neoadjuvant therapy. ‡Data missing from database at time of analysis for 22 patients. §Data missing from database at time of analysis for 28 patients.

Table 1: **Baseline characteristics**

Questionnaires were completed in the clinic before interaction with health-care personnel.

Statistical analysis

On the assumption of a 36·7% improvement in median overall survival from 6 months to 8·2 months in patients allocated axitinib plus gemcitabine and non-uniform accrual (roughly 40% of patients enrolled at 7 months), 460 deaths were needed for a log-rank test with an overall one-sided significance level of 0·025 to have a power of 0·90. The assumed improvement in median overall survival was based on results available from the randomised phase 2 trial[6] at the time that this phase 3 study was designed. Applying a 1:1 randomisation, a planned accrual period of 14 months, and a follow-up of roughly 9 months, we estimated that 596 patients would need to enrol to provide 460 deaths. The nominal significance level for the interim futility and efficacy analysis was established with the Pampallona-Tsiatis power boundary and the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, respectively.[10,11] SAS (version 9.1.3) was used for all analyses.

The primary endpoint of overall survival and other secondary efficacy endpoints were analysed in all patients randomly assigned to treatment groups for whom data were available. Safety and treatment administration and compliance assessments were based on the treatment received. Overall survival was a time-to-event outcome, defined as the time from date of randomisation to date of death from any cause. Objective response rate was defined as the percentage of patients with a confirmed complete or partial response (RECIST). Duration of response was a time-to-event outcome, defined as the time from first documentation of objective tumour response that was subsequently confirmed to first documentation of disease progression or to death from any cause. Time-to-event analyses were done with the Kaplan-Meier method[12] and compared with a one-sided stratified log-rank test at the α=0·025 significance level (the log-rank test was stratified by disease extent [metastatic *vs* locally advanced]); Cox proportional-hazards models were used to explore the effect of baseline characteristics on survival. We compared the proportion of patients with an objective response in each treatment group with a significance level of 0·025 using a one-sided Pearson χ^2 test for unstratified analyses and Cochran-Mantel-Haenszel test for stratified analyses. One-sided significance tests were used because interest centred on whether axitinib plus gemcitabine improved clinical outcomes compared with placebo plus gemcitabine. An interim analysis was planned after roughly half (230) of the deaths had taken place and occurred on Jan 23, 2009.

This study is registered with ClinicalTrials.gov, number NCT00471146.

Role of the funding source

The study was designed by the corresponding author in consultation with the study sponsor. The study sponsor managed all logistical aspects of the study and collected data. Data analysis was done by the sponsor in collaboration with the global team of academic investigators. All authors had full access to the data, and the corresponding author had final responsibility to submit for publication.

Results

Between July 27, 2007, and Oct 31, 2008, 632 patients were randomly assigned to treatment groups (316 to each group). 305 patients in the gemcitabine plus axitinib group and 308 in the gemcitabine plus placebo group received study treatment (figure 1). The baseline characteristics of the treatment groups seemed well balanced (table 1). Most patients (226 [72%] in the gemcitabine plus axitinib and 227 [72%] in the gemcitabine plus placebo group) had metastatic disease and about half had an ECOG performance status of 1.

The median duration of axitinib treatment was 2·8 months (range 0·03–11·0); the median relative dose intensity (actual total dose/intended total dose) was 100%, with the intended total axitinib dose based on 5 mg twice a day. The median duration of gemcitabine exposure was 2·3 months (range 0·03–11·1) with a median relative dose intensity of 77% in combination with axitinib, versus 2·4 months (0·03–11·8) and 79%, respectively, with placebo. The median number of gemcitabine treatment cycles was three in both groups (range 1–13 for gemcitabine plus axitinib, 1–12 for gemcitabine plus placebo). Dose reductions of axitinib or placebo occurred in 74 (25%) of 298 patients in the axitinib group versus 30 (10%) of 301 patients on the placebo group. Axitinib dose titration to more than 5 mg twice daily occurred in 95 (32%) of 298 patients (range 12–20 mg total daily dose), and 36 (12%) of 298 subsequently needed dose reductions. The dose titrations of axitinib to more than 5 mg twice a day led to a median relative dose intensity of 100%, despite dose reductions occurring in 25% of patients.

At a planned interim analysis in January, 2009, the independent data monitoring committee concluded that the futility boundary had been crossed. Patients on treatment were notified, treatment assignments were unmasked, and discontinuation of axitinib was recommended.

Median follow-up for the gemcitabine plus placebo group was 27 weeks (range 0·1–51·7) and for gemcitabine plus axitinib was 27·4 weeks (0·1–55·5). Median overall survival in the efficacy population was similar in both treatment groups: 8·5 months (95% CI 6·9–9·5) for patients allocated axitinib plus gemcitabine and 8·3 months (6·9–10·3) for those allocated placebo plus gemcitabine (HR 1·014, 95% CI 0·786–1·309; Cox model, one-sided p=0·5436, stratified log-rank test; table 2, figure 2). Median progression-free survival, at 4·4 months, was the same for both treatment groups (HR 1·006, 95% CI 0·779–1·298; one-sided p=0·5203; table 2, figure 2).

Disease stage and ECOG performance status, but not treatment, were strong independent predictors of overall survival (Cox proportional-hazards model; table 3). As expected, patients with locally advanced disease lived longer than did those with metastatic disease, and

	Axitinib plus gemcitabine	Placebo plus gemcitabine	Hazard ratio (95% CI)	One-sided p value
Best response*				
Overall objective response rate	12 (5%, 2·5–8·3)	4 (2%, 0·4–4·0)	..	0·0180
Complete response	1 (<1%)	0	..	..
Partial response	11 (4%)	4 (2%)	..	..
Stable disease	74 (30%)	83 (33%)	..	..
Median survival (months)†				
Overall survival	8·5 (6·9–9·5)	8·3 (6·9–10·3)	1·014 (0·786–1·309)	0·5436
Locally advanced	9·5 (7·4–NR)	10·6 (9·9–NR)	..	..
Metastatic	7·0 (5·8–9·3)	6·9 (6·2–8·0)	..	..
Progression-free survival	4·4 (4·0–5·6)	4·4 (3·7–5·2)	1·006 (0·779–1·298)	0·5203
Locally advanced	5·9 (4·2–7·3)	9·1 (5·8–10·6)	..	..
Metastatic	4·2 (3·7–5·4)	3·8 (3·6–4·5)	..	..

Data for best response are n (%, 95% CI); data for survival are median (95% CI). NR=not reached. *Only patients with measurable disease at baseline were included in the analysis; n=247 for axitinib plus gemcitabine, n=255 for placebo plus gemcitabine. †Analysis included all patients randomly assigned to treatment groups; n=314 for axitinib plus gemcitabine (data missing from database at time of analysis for two patients), n=316 for placebo plus gemcitabine.

Table 2: **Efficacy results**

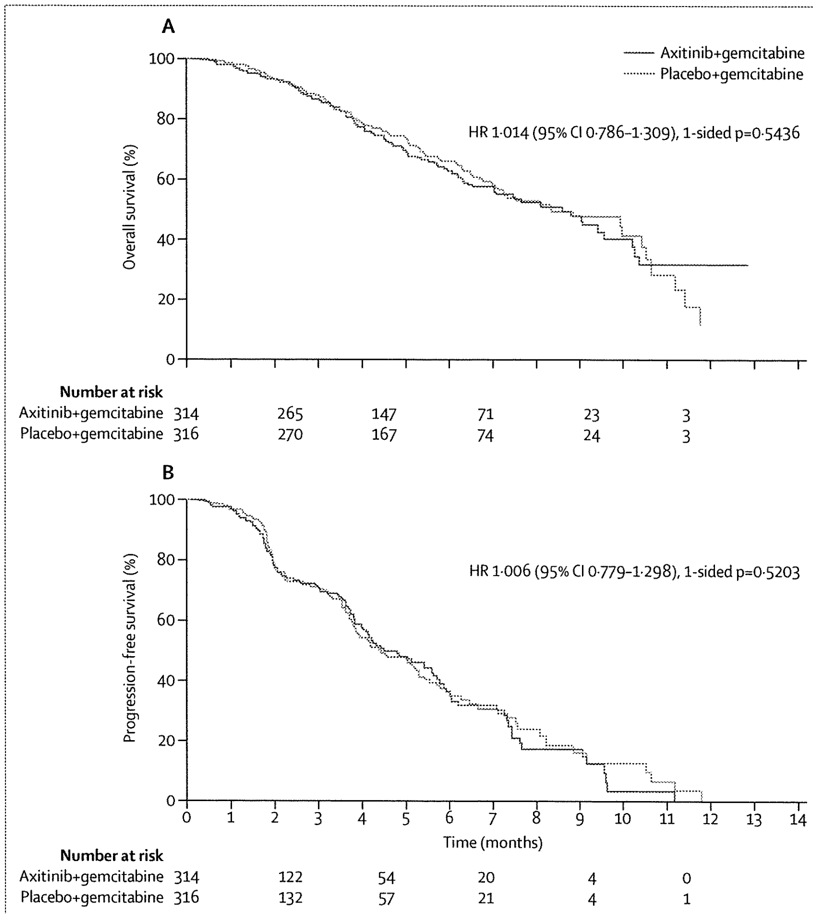

Figure 2: **Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival**

patients with a performance status of 0 lived longer than did those with a status of 1.

502 patients (247 and 255 in the axitinib and placebo groups, respectively) had measurable disease at baseline and could be evaluated for response. The overall objective response rate was 12 (5%) of 247 patients receiving axitinib plus gemcitabine and four (2%) of 255 patients receiving placebo plus gemcitabine (one-sided p=0·0180; table 2). Stable disease was achieved in 74 (30%) of 247 and 83 (33%) of 255 patients in the axitinib and placebo groups, respectively.

	Hazard ratio (95% CI)	p value*
Treatment (axitinib plus gemcitabine vs placebo plus gemcitabine)	0·994 (0·770–1·284)	0·9657
Disease stage (locally advanced vs metastatic)	0·433 (0·301–0·623)	<0·0001
ECOG performance status (0 vs 1)	0·497 (0·380–0·650)	<0·0001

The initial Cox model included baseline factors significant at the 0·10 level in the individual analyses. Backward stepwise selection using an α level of 0·05 was then used to create the final model while forcing treatment to stay in the model/results. ECOG=Eastern Cooperative Oncology Group. *p values are two-sided (Wald χ^2 test).

Table 3: **Multivariate Cox model analysis of overall survival**

	Axitinib plus gemcitabine (n=305)		Placebo plus gemcitabine (n=308)	
	Grade 1 or 2	Grade ≥3	Grade 1 or 2	Grade ≥3
Non-haematological events				
Nausea	129 (42%)*	13 (4%)	106 (34%)	8 (3%)
Fatigue	100 (33%)	27 (9%)	94 (31%)	21 (7%)
Diarrhoea	97 (32%)*	4 (1%)	63 (20%)	5 (2%)
Anorexia	95 (31%)*	19 (6%)	73 (24%)	11 (4%)
Vomiting	86 (28%)	12 (4%)	92 (30%)	10 (3%)
Constipation	85 (28%)	3 (1%)	89 (29%)	7 (2%)
Dysphonia	67 (22%)*	1 (<1%)	13 (4%)	0
Hypertension	65 (21%)*	20 (7%)*	22 (7%)	5 (2%)
Stomatitis	52 (17%)*	0	11 (4%)	1 (<1%)
Pyrexia	47 (15%)	3 (1%)	47 (15%)	1 (<1%)
Abdominal pain	43 (14%)	20 (7%)	41 (13%)	17 (6%)
Peripheral oedema	23 (8%)	0	48 (16%)*	2 (1%)
Haematological abnormalities				
Neutropenia	0	0	3 (1%)	1 (<1%)
Thrombocytopenia	16 (5%)	0	16 (5%)	1 (<1%)
Anaemia	131 (43%)	0	151 (49%)	2 (1%)
Leucopenia	8 (3%)*	0	18 (6%)	0
Lymphopenia	28 (9%)	3 (1%)	42 (14%)	2 (1%)

Data are n (%). *Significant difference in frequency between treatment groups (two-sided 95% CIs exclude 0 for risk differences and 1 for risk ratios).

Table 4: **Adverse events (all causes) reported in 15% or more of patients, and haematological laboratory abnormalities**

	Axitinib plus gemcitabine (n=305)	Placebo plus gemcitabine (n=308)
Asthenia	16 (5%)*†	6 (2%)
Gastrointestinal perforation	4 (1%)	2 (1%)*
Pulmonary embolism	4 (1%)	7 (2%)
Deep-vein thrombosis	4 (1%)	8 (3%)
Gastrointestinal bleeding	2 (1%)	5 (2%)
Cerebrovascular accident	1 (<1%)	1 (<1%)
Proteinuria	1 (<1%)	0

Data are n (%). VEGF=vascular endothelial growth factor. *Includes one grade 5 event. †Significant difference in frequency between treatment groups (two-sided 95% CIs exclude 0 for risk differences and 1 for risk ratios).

Table 5: **Non-haematological grade 3 or 4 adverse events (all causes) attributable to VEGF inhibition or of clinical interest**

Table 4 shows the most common adverse events of any cause, by maximum CTCAE grade. Non-haematological adverse events attributable to VEGF inhibition are presented in table 5. Nausea, diarrhoea, anorexia, dysphonia, hypertension, and stomatitis occurred more frequently in patients receiving axitinib and gemcitabine; peripheral oedema occurred more frequently in patients receiving placebo. Grade 3 or 4 asthenia and hypertension occurred more often in patients on axitinib. Overall, there were two grade 5 events in the placebo group (one cardiac arrest and one cardiac failure) and five in the axitinib group (one each of interstitial lung disease, gastrointestinal haemorrhage, asthenia, acute renal failure, and death).

Grade 3 or 4 deep-vein thrombosis or pulmonary embolism developed in eight (3%) of 305 patients who received axitinib and gemcitabine and 15 (5%) of 308 patients receiving placebo and gemcitabine. Grade 3 or 4 gastrointestinal perforation occurred in four (1%) patients receiving axitinib plus gemcitabine and in two (1%) receiving placebo plus gemcitabine (table 5), mostly associated with tumour involving the bowel wall. Grade 3 or 4 gastrointestinal haemorrhage, probably related to underlying disease, developed in two (1%) patients who received axitinib plus gemcitabine and five (3%) who received placebo plus gemcitabine (table 5).

At study entry, normal concentrations of TSH (<5 μU/mL) were noted in 104 (91%) of 114 patients in the axitinib group and 123 (93%) of 132 patients in the placebo group. Post-treatment increases of TSH (≥5 μU/mL) occurred in 48 (42%) of 114 patients receiving axitinib and gemcitabine and 15 (11%) of 132 patients receiving placebo and gemcitabine, and hypothyroidism as an adverse event was reported in 18 (6%) of 305 patients in the axitinib group and four (1%) of 308 patients taking placebo. 13 of 18 patients who developed hypothyroidism on axitinib plus gemcitabine had asthenia or fatigue, or both, including four grade 3 or 4 cases.

At baseline, the mean scores on the global health status/quality of life scale of the QLQ-C30 did not differ significantly between the two groups (table 1). For patients with a baseline and cycle 4, day 1, value for the global health status scale, after three cycles the mean difference from baseline was 0·1 (n=132) for axitinib plus gemcitabine and 2·8 (n=132) for the placebo group. Patients in the axitinib and gemcitabine group reported a 5-point or more mean change from baseline in pain, constipation, insomnia, and financial difficulties (all improved), and physical functioning, dyspnoea, diarrhoea, and fatigue (all worsened) on the QLQ-C30; on the QLQ-PAN26, patients who received axitinib and gemcitabine reported improvement in pancreatic pain and worsening in body image, changes in bowel habits, treatment-related side-effects, and ability to plan for the future (data not shown). Patients on placebo reported a 5-point or more mean change from baseline in emotional functioning, pain, constipation, insomnia, and loss of appetite (all improved) on the QLQ-C30; similar changes were seen in pancreatic pain, fear of future health, and cachexia (all improved) on the QLQ-PAN26 (data not shown).

Discussion

This randomised phase 3 trial clearly shows that the addition of axitinib to gemcitabine does not improve survival in patients with locally advanced or metastatic pancreatic cancer. These data also confirm the findings obtained in previous phase 3 studies of the VEGF inhibitors bevacizumab and aflibercept that inhibition of this pathway is ineffective in patients with this disease (panel).[13–15]

In view of the long history of promising phase 2 single-group trials that have yielded negative phase 3 results, some investigators have concluded that a randomised phase 2 trial is the optimum method to predict the benefit of a novel agent in the phase 3 setting.[16] The randomised phase 2 trial design reduces the bias of a comparison with historical data, as well as the patient selection bias. As our study shows, the results of hypothesis-generating, exploratory, randomised, phase 2 studies are not always replicated in randomised phase 3 trials. Indeed, the results of this trial underscore the importance of implementation of phase 3 testing only after a robust signal from appropriately designed phase 2 trials.[17]

The decision to evaluate axitinib in a phase 3 study was based on the results of a fairly small (103 patients), exploratory, randomised, phase 2 study in which gemcitabine plus axitinib showed a non-significant improvement in median overall survival compared with gemcitabine (6·9 months, 95% CI 5·3–10·1 *vs* 5·6 months, 3·9–8·8; HR 0·71, 95% CI 0·44–1·13).[6] That phase 2 study was neither intended nor powered to show a significant difference between the two groups, and the confidence intervals for median overall survival overlapped. Additionally, the confidence interval for the HR contained 1·0. When the decision was made to move forward into phase 3, the HR for overall survival in the phase 2 study was 0·74 in favour of the axitinib plus gemcitabine group. Statistical modelling that took this treatment effect into account, as well as its variability, determined that there was a roughly 65% chance that the phase 3 study would have positive results. We regarded this finding as sufficient justification to undertake this phase 3 trial, although we recognised the significant risk in moving forward from a small phase 2 study to a large phase 3 trial.

The treatment effect in the randomised phase 2 trial was greatest in patients with locally advanced disease and in those with ECOG performance statuses of 0 and 1. The inclusion of 25% of patients with locally advanced disease and almost 50% of patients with performance status 0, plus the exclusion of patients with any thrombosis requiring anticoagulation (who tend to have reduced survival rates), clearly account for the longer-than-anticipated median survival of more than 8 months that was recorded in the control group of this trial. A retrospective analysis from a phase 3 study of gemcitabine and erlotinib plus either bevacizumab or placebo suggests that clinical outcomes might correlate with a genetic locus in the tyrosine kinase domain of VEGF receptor 1.[18] Pharmacogenetic analyses are underway for the present study.

The addition of axitinib to gemcitabine resulted in acceptable tolerability, with a similar incidence of grade 3 or higher adverse events in both groups. Only grade 3 or higher asthenia and hypertension occurred more frequently in patients receiving axitinib than in those allocated placebo. Hypertension was manageable with antihypertensive drugs or axitinib dose reductions, or both. Although venous thrombosis, gastrointestinal bleeding, and gastrointestinal perforations have often been reported with VEGF inhibitors, these were not increased in the axitinib group of this trial.

Analysis of health-related quality of life showed improvements in pancreatic cancer symptoms of pain in both treatment groups. In the axitinib plus gemcitabine group, minor worsening was reported in diarrhoea, fatigue, and changes in bowel habits—side-effects that are typically associated with VEGF inhibition.

Despite the 42% incidence of increased TSH concentration (≥5 μU/mL) in the axitinib plus gemcitabine group, only 6% of patients were diagnosed with hypothyroidism and received hormone replacement therapy. Whether any patients with TSH increase had subclinical hypothyroidism,

Panel: Research in context

Systematic review

Although a systematic review was not done as part of the planning for this trial, the existing evidence in this area was identified by literature (Medline) searches. Medline search terms included "pancreatic cancer", "chemotherapy", "gemcitabine"; search limited to English language, 1997–2007. Previous key trials of gemcitabine-based regimens in pancreatic adenocarcinoma have shown poor outcomes and low survival rates. An exploratory randomised phase 2 trial[6] showed that the combination of gemcitabine and axitinib in this setting resulted in a numerical improvement in median overall survival compared with gemcitabine alone. The rationale for the present phase 3 trial of axitinib plus gemcitabine was to further investigate and to confirm findings from the phase 2 study.

Interpretation

Results from this trial show that the addition of axitinib to gemcitabine does not improve survival for patients with advanced pancreatic cancer. The data thus add to increasing evidence that targeting of vascular endothelial growth factor (VEGF) signalling is an ineffective strategy in advanced pancreatic cancer. This conclusion is supported by results of phase 3 trials showing that addition of other VEGF inhibitors such as bevacizumab or aflibercept to gemcitabine did not improve survival compared with gemcitabine plus placebo in patients with advanced pancreatic cancer. On the basis of data from this trial, we recommend that no changes to treatment paradigms for advanced pancreatic cancer are indicated.

or whether hormone replacement therapy would have been beneficial, is uncertain.

In conclusion, the addition of axitinib to gemcitabine does not improve survival for patients with advanced pancreatic cancer. These results add to increasing evidence that targeting of VEGF signalling is an ineffective strategy in this disease.

Contributors

HLK contributed to study design, data collection, analysis, and interpretation, literature search, and writing of the report. TI contributed to data collection and interpretation and review of the report. DJR contributed to patient inclusion, data interpretation, and writing and review of the report. JB contributed to inclusion of patients in the study and writing of the report. RL contributed to recruitment and follow-up of patients and review of the report. TO contributed to recruitment and management of patients, data collection, and review of the report. AF contributed to data collection and interpretation and review of the report. JF contributed to study design, data collection and interpretation, and review of the report. YSP contributed to data collection and interpretation and writing and review of the report. SO contributed to data collection and interpretation and review of the report. GMS contributed to data collection and writing of the report. HSW provided study design advice and contributed to recruitment of study participants, UK ethics submission, and report review and contribution. PCT contributed to study design, data analysis and interpretation, and writing of the report. PB contributed to study design, data collection and analysis, data interpretation, and writing of the report. ADR contributed to study design, data collection, analysis, and interpretation, and writing of the report. SK contributed to design, writing of the protocol, data analysis and interpretation, and editing of the report. EVC contributed to data collection, analysis, and interpretation and writing of the report. All authors provided final approval of the report.

Conflicts of interest

Pfizer provided TI with a flight ticket and accommodation for attending an investigator meeting for the reported study (the meeting was sponsored by Pfizer); Pfizer paid TI's institution the necessary cost to conduct the study. JB has received compensation for board membership from Roche, Bayer, and Boehringer; and payment for lectures, including service on speakers' bureaus from Roche and AstraZeneca. RL's institution received a fee per patient from Pfizer for participation in the study (research nurse work, etc). TO's institution has received research funding from Pfizer in relation to the work under consideration for publication; it has also received research funding unrelated to the submitted work from Eli Lilly, Taiho, Dainippon-Sumitomo, Bayer, Chugai, Otsuka, Novartis, Kowa, Pfizer, Yakult, Eisai, Oncotherapy Science, Bristol-Myers Squibb, Abbott, Takeda Bio, and Nippon Kayaku. TO received travel expenses for the study from Pfizer; he has also received payment for lectures unrelated to the submitted work from Taiho, Eli Lilly, Asuka, Bayer, Chugai, Novartis, Torii, Nippon Kayaku, Pfizer, Janssen, AstraZeneca, Dainippon-Sumitomo, Wyeth, and Ajinomoto. Pfizer provided AF with a flight ticket and accommodation for attending an investigator meeting for the reported study (the meeting was sponsored by Pfizer); Pfizer paid AF's institution the necessary cost to conduct the study. JF has received payment for lectures, including service on speakers' bureaus from Bayer, Taiho, Eli Lilly, and Eisai; Pfizer paid JF's institution the necessary cost to conduct the study. Pfizer paid SO's institution the necessary cost to conduct the study; SO's institution has received research funding from Eli Lilly, Taiho, Chugai, Yakult, Oncotherapy Science, Abbott, and Dainippon-Sumitomo. SO has received payment for lectures from Eli Lilly, Taiho, Kyowa Hakko Kirin, and Hisamitsu. GMS's institution has received a grant from Pfizer in relation to the work under consideration for publication. HSW's institution received money from Pfizer for running the trial and per patient payments to cover trial costs; HSW has received compensation from Pfizer for participation in two advisory boards during the past year (clinical trial and scientific development programmes by Pfizer). EVC's institution received a grant from Pfizer in relation to the work under consideration for publication; and it also has grants or grants pending from Pfizer outside of the submitted work. PCT, PB, ADR, and SK are compensated as employees of Pfizer and own stock or stock options in Pfizer. HLK, DJR, and YSP declare that they have no conflicts of interest.

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Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer

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Erlotinib combined with gemcitabine has not been evaluated in Japanese patients with unresectable pancreatic cancer. This two-step phase II study assessed the safety and pharmacokinetics of erlotinib 100 mg/day (oral) plus gemcitabine 1000 mg/m^2 (i.v. days 1, 8, 15) in a 28-day cycle in the first step, and efficacy and safety in the second step. The primary end-point was safety. One hundred and seven patients were enrolled (first step, *n* = 6; second step, *n* = 101). The most common adverse event was RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) in 93.4% of patients. One treatment-related death occurred. While interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%), all patients recovered or improved. The median overall survival, the 1-year survival rate and median progression-free survival were 9.23 months, 33.0% and 3.48 months, respectively. The overall response and disease control rates were 20.3% and 50.0%, respectively. In Japanese patients with unresectable pancreatic cancer, erlotinib plus gemcitabine had acceptable toxicity and efficacy that was not inferior to that seen in Western patients. (*Cancer Sci* 2011; 102: 425–431)

Approximately 232 000 individuals are diagnosed with pancreatic cancer worldwide each year, with an annual death rate estimated at 227 000.[1] In Japan, approximately 22 000 new cases were reported in 2005.[2] Furthermore, data from 2007 show that around 24 000 individuals in Japan died from pancreatic cancer, making this tumor type the fifth leading cause of cancer-related death.[3] The majority of pancreatic cancer cases are diagnosed at an unresectable stage when prognosis is extremely poor.

Current treatment for advanced pancreatic cancer is based on systemic chemotherapy with gemcitabine. Single-agent gemcitabine has been shown to extend median overall survival (OS) to 5.65 months in chemonaïve patients compared with 4.41 months in patients who received fluorouracil.[4] Addition of other cytotoxic agents to gemcitabine has not demonstrated survival benefits over gemcitabine alone.[5–13] The potential of combining gemcitabine with biological agents in patients with advanced pancreatic cancer has also been evaluated in several phase III studies, but these trials failed to show a survival benefit.[14–19]

Epidermal growth factor receptor (EGFR)-mediated signaling is associated with various cellular processes, and the dysregulation of these processes is common in tumorigenesis.[20,21] Furthermore, EGFR is overexpressed in many tumors and its overexpression is often associated with poor prognosis.[22–26] EGFR tyrosine-kinase inhibitors (TKI, such as erlotinib) are used in the treatment of various types of solid tumors.

Erlotinib has demonstrated antitumor activity in pancreatic cell lines[27] and was subsequently assessed as a potential therapeutic agent in pancreatic cancer. In the PA.3 study (*n* = 569), the risk of death with erlotinib plus gemcitabine was reduced by 18% versus gemcitabine alone (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69–0.99; $P = 0.038$ after adjustment for stratification factors), with a median OS of 6.24 months *vs* 5.91 months, respectively. Erlotinib plus gemcitabine combination therapy provided significant improvements in the 1-year survival rate (23% *vs* 17%; $P = 0.023$) and progression-free survival (PFS; HR 0.77; 95% CI, 0.64–0.92; $P = 0.004$).[28] As a result, this combination was approved for use in pancreatic cancer in many countries.

In Japanese patients with non-small-cell lung cancer (NSCLC), a phase II study has specifically shown that erlotinib monotherapy is well tolerated and has promising antitumor activity.[29] However, there are no data on the use of erlotinib combined with gemcitabine in Japanese patients with pancreatic cancer. This phase II study evaluated the safety and efficacy of erlotinib in combination with gemcitabine in Japanese patients with unresectable locally advanced or metastatic pancreatic cancer.

Methods

Patients. Patients aged 20–80 years with histological/cytological evidence of unresectable locally advanced or metastatic adenocarcinoma/adenosquamous carcinoma of the pancreas were eligible for inclusion in the present study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, adequate hematological, renal and hepatic function and a life expectancy of at least 2 months. No more than one prior regimen for pancreatic cancer was permitted. Patients who had received prior gemcitabine and/or a TKI were excluded from participation, as were those who had previously been exposed to a human epidermal growth factor receptor 2 (HER2) or EGFR inhibitor. Other key

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Clinical trial registry: JAPIC Clinical Trials Information (see links below). http://rctportal.niph.go.jp/examDetail.php?center=3&center_seq=698 http://www.clinicaltrials.jp/user/cteDetail.jsp?clinicalTrialId=839&language=ja. Trial registration number: JapicCTI-060337.

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exclusion criteria were: symptomatic cerebral metastases; a concurrent lung disorder (such as idiopathic pulmonary fibrosis, interstitial lung disease [ILD] or pneumoconiosis); concurrent or previous drug-induced pneumonia; or a history of radiation to the chest.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients, and the protocol was approved by ethics committees at all participating institutions.

Study design and treatment. This was a phase II, multicentre, open-label, two-step study. In the first step, six patients were enrolled into the study and treated with oral erlotinib 100 mg/day on days 3–28, plus i.v. gemcitabine 1000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle. The starting doses of erlotinib and gemcitabine were chosen in reference to the PA.3 study. Dose-limiting toxicities (DLT) were assessed in these study participants using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE, National Cancer Institute, Bethesda, MD, USA). Dose-limiting toxicities were defined in conformity to the P1b study as follows:[30] (i) grade 4 decrease (i.e. to <500/mm^3) in neutrophil count >5 days; (ii) grade ≥3 decrease (i.e. to <1000/mm^3) in neutrophil count with associated fever (≥38.5°C); (iii) grade 4 decrease in platelet count (i.e. to <25 000/mm^3); (iv) any grade ILD; (v) grade 4 elevation of alanine transaminase (ALT)/aspartate transaminase (AST) levels, or grade 3 elevation of ALT/AST levels >7 days; (vi) grade ≥3 non-hematological toxicity (excluding rash, hyperglycemia, γ-GTP and events that were judged to be transient/had no effect on study continuation); and (vii) dose-reduction/interruption required due to persistent adverse events (AE), which meant that the second cycle could not be started.

If treatment-related DLT occurred in no more than two of the six patients, transition to the second step of the study was permissible with approval of the Data Safety and Monitoring Committee (DSMC). If DLT occurred in three or more patients, transition to the second step was limited to those cases that were judged to be safe for this study after the DSMC had evaluated the safety data of the patients with a DLT. In the second step, it was planned that 94 patients would be treated with the same dose as the first step. Treatment was continued until disease progression, death, unacceptable toxicity or patient/investigator request.

The primary end-point of the study was safety, with secondary end-points including OS, 1-year survival rate, PFS, overall response rate (ORR), disease control rate (DCR = complete response [CR] + partial response [PR] + stable disease), pharmacokinetics (PK) and correlation of *EGFR* mutation status with outcomes.

Toxicity evaluation. Adverse events were monitored and graded using NCI-CTCAE v3.0. Clinical and laboratory assessments were conducted throughout the study. Adverse events prespecified in the study to be monitored carefully were rash, diarrhea, vomiting, liver dysfunction and ILD-like events. Chest X-ray examination to assess pulmonary toxicity was conducted weekly until week 4 and every 2 weeks thereafter. In addition, chest computed tomography (CT) scan was performed every 4 weeks. The DSMC reviewed the images and clinical data associated with all potential ILD-like events. All ILD-like events were reported to be serious AE (SAE), regardless of the grade.

Efficacy evaluation. The tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) in patients who had at least one measurable target lesion. Tumors were measured using computed tomography (CT) at baseline and on day 22 of every two cycles thereafter. Median PFS, ORR and DCR were estimated by the extramural review. The relationship between efficacy and the severity of RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) was also examined.

Pharmacokinetic evaluation. Pharmacokinetic evaluation of erlotinib and its O-desmethylated metabolite (OSI-420) was performed in the six patients enrolled in the first step of the study. Venous blood samples were taken prior to erlotinib dosing on day 3 and day 8 of cycle 1 at 0.5, 1, 2, 4, 6, 8 and 24 h after erlotinib administration. Samples were also taken prior to gemcitabine infusion on days 1 and 8 at 0.5, 0.75, 1, 1.5, 2.5 and 4.5 h after dosing.

The plasma concentrations of erlotinib, OSI-420 and gemcitabine were measured by liquid chromatography, tandem mass spectrometry (LC-MS-MS). The LC-MS-MS analytical methods have been described previously.[31,32] Derived PK parameters included the maximum plasma drug concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration-time curve to the last plasma sample (AUC_{last}), terminal half-life ($t_{½}$) and oral clearance (Cl/F).

Biomarker analysis. *EGFR* mutations were assessed in patients with available tumor tissue specimens, which were formalin fixed and paraffin embedded. Samples were analyzed at a central laboratory where DNA was extracted and exons 18–21 sequenced using a nested PCR.

Statistical analysis. Progression-free survival and OS were estimated using the Kaplan–Meier method in all patients who received at least one dose of the study treatment, with 95% CI for the median duration calculated using Greenwood's formula. The Clopper–Pearson method was used to calculate the 95% CI around the ORR, DCR and AE rate. Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model. Baseline characteristics investigated for this analysis included gender, age, lung metastasis, emphysema and various baseline laboratory values. The target enrollment was 100 patients, as this was required to evaluate the safety of erlotinib.

Results

Patient characteristics. Between December 2006 and October 2007, a total of 107 patients were enrolled (first step, n = 6; second step, n = 101) from 12 institutions (Fig. 1). One patient who enrolled into the second step did not receive treatment due to deterioration in PS prior to the start of treatment. A total of 106 patients were evaluable for safety (safety population, full analysis set).

The patient demographics and baseline characteristics are shown in Table 1. The median age was 62 years (range, 36–78) and 52.8% of patients were male. Almost all patients were chemonaïve (95.3%). The majority (75.5%) of patients had an ECOG PS of 0 and most (83.0%) had metastatic disease. Over half (63.2%) of the patients had a history of current or past smoking.

Toxicity and dose modifications. The median duration of erlotinib exposure was 102.5 days and its median dose intensity was 100.0 mg/day, with the majority of patients (78.3%) receiving more than 90% of the relative dose intensity. The median duration of gemcitabine treatment was 4.0 cycles and its median dose intensity was 688.0 mg/m^2 per week, with approximately half of the patients (51.4%) receiving more than 90% of the relative dose intensity.

As only one patient had a DLT (grade 3 diarrhea) in the first step, the second step of the study was initiated. One hundred and six patients received at least one dose of erlotinib; these patients were assessable for toxicity. Treatment-related AE and treatment-related changes in laboratory values are summarized in Table 2; most of these were mild to moderate in severity. The most frequently reported AE was RASH, which occurred in

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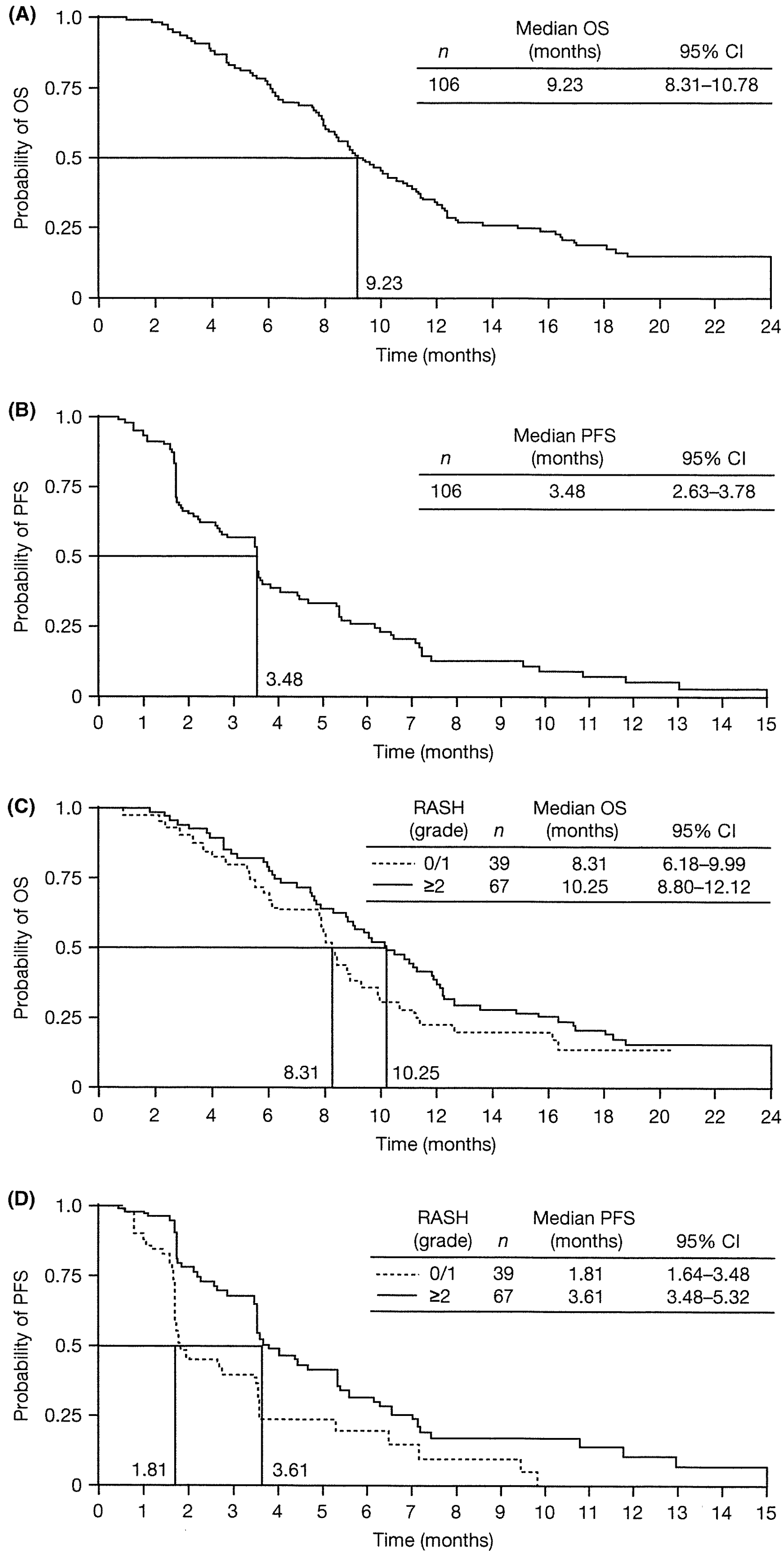

Fig. 1. Kaplan–Meier estimates of (A) overall survival (OS) and (B) progression-free survival (PFS) in the study population (n = 106); (C) OS and (D) PFS according to the severity of RASH (grade ≤1 [n = 39] *vs* grade ≥2 [n = 67]). RASH is a composite of the terms: rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash. CI, confidence interval.

Table 1. Baseline characteristics and demographics (n = 106)

Characteristic	
Median age (range) (years)	62 (36–78)
Gender, n (%)	
Male	56 (52.8)
Female	50 (47.2)
Median bodyweight (range) (kg)	52.3 (33.1–95.0)
Smoking history,† n (%)	
Never smoker	39 (36.8)
Past smoker	37 (34.9)
Current smoker	30 (28.3)
ECOG PS, n (%)	
0	80 (75.5)
1	26 (24.5)
2	0 (0)
Disease status, n (%)	
Metastatic	88 (83.0)
Locally advanced	18 (17.0)
Primary tumor identified, n (%)	92 (86.8)
Primary sites, n (%)	
Head	46 (43.4)
Body and tail	23 (21.7)
Body	22 (20.8)
Tail	10 (9.4)
Other	5 (4.7)‡
Biliary drainage, n (%)	19 (17.9)
Sites of distant metastases, n (%)	
Liver	56 (52.8)
Distant lymph nodes	39 (36.8)
Lung	17 (16.0)
Other	26 (24.5)
Prior lines of therapy, n (%)	
None	101 (95.3)
One regimen	5 (4.7)§
Median CA19–9 (range) (U/mL)	
Median	776 (0–435 000)
Median CEA (range) (ng/mL)	
Median	4.8 (0.6–1100.1)

†Never smoker, never/hardly smoked; past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). ‡Whole of pancreas (n = 1); head and body (n = 3); other (n = 1). §Tegafur, gimeracil, oteracil potassium (S-1) (n = 3); 5-fluorouracil plus leucovorin (n = 2). CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Co-Operative Group.

93.4% of the patients; most cases were mild to moderate in severity (87.7%, grade ≤2; 5.7%, grade ≥3). Other common non-hematological AE included anorexia, pruritus, fatigue, nausea and diarrhea. Most patients experienced some degree of hematological toxicity, with grade 3 or 4 neutropenia (neutrophil decreased), leucopenia (white blood cell count decreased) and anemia (hemoglobin decreased) occurring in 34.9%, 29.2% and 14.2% of patients, respectively. Only one treatment-related death occurred (due to gastrointestinal hemorrhage), which was probably due to arterial bleeding caused by the invasion of the primary tumor into the gastrointestinal tract. Although the likelihood of this event being treatment-related was deemed remote, a causal relationship could not be completely excluded because the event occurred during the study treatment administration period.

Treatment-related SAE were reported in 26 (24.5%) patients. These included nine ILD-like events (8.5%), the majority of which (n = 7) were grade 1–2 in severity. Importantly, all of these nine patients recovered or improved, and four of these patients did so without any treatment for ILD-like events. Other

Table 2. Treatment-related adverse events occurring in >30% of patients treated with erlotinib and gemcitabine (n = 106)

	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Non-hematological			
Rash	78 (73.6)	3 (2.8)	0 (0)
Anorexia	75 (70.8)	15 (14.2)	0 (0)
Pruritus	57 (53.8)	1 (0.9)	0 (0)
Fatigue	56 (52.8)	3 (2.8)	0 (0)
Nausea	56 (52.8)	6 (5.7)	0 (0)
Diarrhea	52 (49.1)	2 (1.9)	0 (0)
Dry skin	49 (46.2)	0 (0)	0 (0)
Stomatitis	38 (35.8)	0 (0)	0 (0)
Pyrexia	32 (30.2)	0 (0)	0 (0)
Hematological			
White blood cell count decreased	85 (80.2)	31 (29.2)	0 (0)
Platelet count decreased	77 (72.6)	9 (8.5)	0 (0)
Hemoglobin decreased	76 (71.7)	13 (12.3)	2 (1.9)
Hematocrit decreased	73 (68.9)	8 (7.5)	0 (0)
Neutrophil decreased	73 (68.9)	32 (30.2)	5 (4.7)
Red blood cell count decreased	72 (67.9)	8 (7.5)	0 (0)
ALT increased	59 (55.7)	10 (9.4)	0 (0)
AST increased	57 (53.8)	4 (3.8)	1 (0.9)
Weight decreased	53 (50.0)	3 (2.8)	0 (0)
Lymphocyte count decreased	46 (43.4)	14 (13.2)	0 (0)
Blood albumin decreased	35 (33.0)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	35 (33.0)	12 (11.3)	1 (0.9)

ALT, alanine amino transferase; AST, aspartate amino transferase.

treatment-related SAE were anorexia (3.8%), vomiting, pyrexia and abnormal hepatic function (1.9% each). The baseline characteristics, treatment and outcomes of patients who developed treatment-related ILD-like events during the study are detailed in Table 3. The onset times of ILD-like events ranged from 7 to 187 days after the start of treatment. In these patients, a relatively long survival was observed (from 119 to 568+ days), and five patients received post-study therapy. All of these nine patients were past or current smokers, and six had emphysema at baseline (not detected prior to treatment, but diagnosed at the extramural review by a radiologist in the DSMC). Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model and emphysema at baseline was indicated as a risk factor for onset of ILD-like events (odds ratio [95% CI], 12.13 [1.01–145.7]; P = 0.0491).

Adverse events led to erlotinib discontinuation in 30 patients (28.3%) and gemcitabine discontinuation in 27 patients (25.5%). The main reasons for treatment discontinuation were ILD (n = 6) and anorexia (n = 3); no patient discontinued treatment due to RASH or diarrhea. Due to the onset of AE, a total of 65 patients (61.3%) required one or more interruptions of erlotinib (36 patients [34.0%] for longer than seven consecutive days and 17 patients [16.0%] for longer than 14 consecutive days) and 56 patients (52.8%) had one or more skip of gemcitabine. Modifications in the erlotinib or gemcitabine dosage were required in 17 (16.0%) and 11 (10.4%) patients, respectively, due to AE.

Efficacy. The median OS was 9.23 months (95% CI, 8.31–10.78; Fig. 1A) and the 1-year survival rate was 33% (95% CI, 24–42). Median PFS was 3.48 months (95% CI, 2.63–3.78; Fig. 1B). Among the patients evaluable for tumor response (n = 64), the ORR was 20.3% (13/64; 95% CI, 11.3–32.2) and the DCR was 50.0% (95% CI, 37.2–62.8; CR, n = 0; PR, n = 13; stable disease, n = 19).

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Table 3. Characteristics, treatment and outcomes of patients with treatment-related ILD-like events (n = 9)

Event	Gender	Age (years)	Smoking status†	Days on treatment	ILD maximum grade	Suspicious findings of ILD	Steroids	Oxygen	ILD outcome	Presence of emphysema (assessed by radiologist)	Survival outcome (days)	Post-therapy (chemotherapy)
Lymphoid ILD	M	62	Past	82	1	Pyrexia	None	No	Improved	Yes	362	Yes
ILD	M	42	Current	50	3	Pyrexia	Pulse	Yes	Recovered	Yes	517	Yes
Organising pneumonia	M	60	Past	183	2	Respiratory symptoms	None	No	Improved	Yes	568+	Yes
ILD	F	62	Past	113	2	Cough	Oral	No	Recovered	Yes	376	No
ILD	F	74	Past	111	3	Cough, dyspnea	Pulse	Yes	Improved	None	183	No
ILD	M	60	Current	25	1	Pyrexia	Pulse	No	Recovered	None	119	Yes
ILD	M	77	Past	7	1	X-ray	None	No	Recovered	Yes	255	No
ILD	M	55	Past	187	1	CT	None	No	Recovered	Yes	415	No
ILD	F	60	Current	76	2	Cough	Oral	No	Recovered	None	346	Yes

†Past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). CT, computed tomography; F, female; ILD, interstitial lung disease; M, male.

The median OS was longer in patients who experienced RASH of grade ≥2 (n = 67) than in those with RASH of grade ≤1 (n = 39) (10.25 months [95% CI, 8.80–12.12] *vs* 8.31 months [95% CI, 6.18–9.99], respectively; Fig. 1C) and the 1-year survival rate was higher (39% [95% CI, 27–50] *vs* 23% [95% CI, 10–36], respectively). Similarly, the median PFS was longer in patients with RASH of grade ≥2 versus those with RASH grade ≤1 (3.61 months [95% CI, 3.48–5.32] *vs* 1.81 months [95% CI, 1.64–3.48]; Fig. 1D). While there was no notable difference in ORR between patients with RASH grade ≥2 and those with grade ≤1 (21.1% [95% CI, 9.6–37.3] *vs* 19.2% [95% CI, 6.6–39.4]), the DCR was higher in those with more severe RASH (60.5% [95% CI, 43.4–76.0] *vs* 34.6% [95% CI, 17.2–55.7]).

Pharmacokinetics. Plasma sampling for PK analyses was performed in all six patients enrolled in the first step. On day 8, the values of C_{max} were 1760 ± 456.9 ng/mL (mean ± SD) for erlotinib, 169.7 ± 64.5 ng/mL for OSI-420 and 22 700 ± 3272.9 ng/mL for gemcitabine. The AUC_{last} was 29 001 ± 6560 h ng/mL, 2748 ± 788 h ng/mL and 10 717 ± 1458 h ng/mL (mean ± SD), respectively. The mean t_{max} was 8.0 h (range, 2.0–23.9 h), 9.0 h (2.0–23.9 h) and 0.51 h (0.45–0.57 h), respectively. Also on day 8, the mean plasma $t_{1/2}$ was 54.92 h (range, 9.25–144.61 h), 32.79 h (10.36–60.46 h), and 0.63 h (0.31–1.14 h), respectively. The Cl/F of erlotinib and gemcitabine showed interindividual variability; the Cl/F on day 8 was 3972.6 ± 772.1 mL/h (mean ± SD; coefficient of variation 19.4%) and 146 580.4 ± 31 101.3 mL/h (21.2%), respectively.

Biomarker analysis. Of the 106 patients enrolled, *EGFR* mutation status was evaluated in 47 patients (44.3%), all of whom had wild-type *EGFR*. The mutation status of the remaining patients was classified as unknown because samples were not available (30.2%), not examined (9.4%) or the results following sequencing were inconclusive (16.0%).

Discussion

This study was designed to initially assess the safety of erlotinib with gemcitabine for Japanese patients with pancreatic cancer, in whom there had been no prior exposure to either drug. As no significant safety concerns were raised in the first step of the study, enrollment of a further 101 patients was performed. Although the incidence of AE in this study was higher than in the PA.3 study, the incidence of grade 3–4 AE was similar.[28] Despite these results, no new AE specific to Japanese patients were observed. As expected, RASH and gastrointestinal events were among the most common AE in this study, and most of these cases were mild to moderate in severity.

Interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%) in the current study, while its incidence was reported to be 2.4% in patients treated in the erlotinib plus gemcitabine arm of the PA.3 study.[28] In addition, in Japanese patients with advanced pancreatic cancer, ILD-like events were reported in two (6.1%) of 33 patients treated with gemcitabine plus S-1, and were reported in three (1.1%) of 264 patients with gemcitabine monotherapy, respectively.[33,34] Likewise, the higher incidence of ILD-like events were documented using S-1 or erlotinib in combination with gemcitabine compared with gemcitabine as monotherapy in patients with pancreatic and biliary tract cancer.[35] On another front, outside of Japan, a high incidence of ILD-like events was reported in gemcitabine and paclitaxel combination therapy in patients with NSCLC.[36] From the above information, considering the higher incidence of ILD when gemcitabine is used in combination, an additive effect from such combinations cannot be ruled out.

In NSCLC, Japanese patients have an increased risk of developing ILD-like events when treated with EGFR TKI.[29,37–39] Fatal cases of ILD-like events have been reported following EGFR TKI administration for the treatment of NSCLC.[37–41] Importantly, however, no patients died due to an ILD-like event in this study. Seven patients experienced ILD-like events of grade 1–2 in severity. This may be due to active management of ILD-like cases during the study period. This management included regular and immediate chest X-rays, in addition to diagnosis with CT scans after any early signs and symptoms were observed (e.g. pyrexia, cough or dyspnea), timely discontinuation of the antitumor drugs (as a precautionary measure in case these drugs were associated with the symptoms) and appropriate treatment for the events (including oral/pulse steroids). By appropriately treating the early symptoms of ILD-like events, patients could restart antitumor therapy (chemotherapy: treatment change). In this study, the onset time for ILD-like events varied markedly between patients (7–187 days). It is therefore necessary to monitor the patients throughout the treatment period.

All of the patients who developed ILD in this study were current or past smokers, and smoking status has been shown to be a risk factor for ILD in the NSCLC population.[38] Results from the multivariate analyses in this study suggest that emphysema is also a risk factor for developing ILD; six of the nine patients with ILD-like events were diagnosed with emphysema at baseline. Although the number of reports of an ILD-like event may have been artificially elevated due to underlying patient baseline characteristics and the active management of ILD-like events, these results demonstrate the need to consider the risk of ILD-like events in Japanese patients treated with TKI. In particular, it is important that chest CT scans are closely checked for the presence of emphysema or comorbid ILD and that pulmonary status is assessed prior to treatment administration.

This study corroborates the results of the combination of gemcitabine and erlotinib shown in the PA.3 study. The median OS in this study of 9.23 months was longer than those reported in trials with gemcitabine alone. In this study, patients who experienced skin toxicity of grade ≥2 had better outcomes than those with less severe toxicity or the overall study population. Retrospective analyses of data from the PA.3 and AViTA studies have found a significant association between the development of skin toxicity and efficacy in patients with pancreatic cancer treated with erlotinib-based therapy, although the precise mechanisms for the association between skin toxicity and effectiveness are unknown.[28,41,42]

Although the presence of mutations in the tyrosine-kinase region of the *EGFR* gene appears to predict a better response to erlotinib in NSCLC,[43,44] this has not yet been evaluated in pancreatic cancer. *EGFR* mutations are very rare in patients with pancreatic cancer;[45–47] indeed in the present study, no *EGFR* mutations were detected. Further work is required to determine whether *EGFR* mutations can be used as predictive markers for improved survival in Japanese patients receiving erlotinib and gemcitabine as treatment for advanced pancreatic cancer.

In conclusion, the present study shows that erlotinib in combination with gemcitabine is generally well tolerated in Japanese patients with advanced pancreatic cancer. This combination is associated with efficacy and survival outcomes, and the results of this study are consistent with the findings of the global PA.3 study.

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ORIGINAL ARTICLE

Phase I/II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients

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Abstract
Purpose There is no standard regimen for gemcitabine (Gem)-refractory pancreatic cancer (PC) patients. In a previous phase II trial, S-1 was found to exhibit marginal efficacy. Gem administration by fixed dose rate infusion of 10 mg/m^2/min (FDR-Gem) should maximize the rate of intracellular accumulation of gemcitabine triphosphate and might improve clinical efficacy. We conducted the phase I/II of FDR-Gem and S-1 (FGS) in patients with Gem-refractory PC.
Methods The patients received FDR-Gem on day 1 and S-1 orally twice daily on days 1–7. Cycles were repeated every 14 days. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels in the phase I: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4). Forty patients were enrolled in the phase II study at recommended dose.
Results The recommended dose was the level 3. In the phase II, a partial response has been confirmed in seven patients (18%). The median overall survival time and median progression-free survival time are 7.0 and 2.8 months, respectively. The common adverse reactions were anorexia, leukocytopenia and neutropenia.
Conclusion This combination regimen of FGS is active and well tolerated in patients with Gem-refractory PC.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Gemcitabine · S-1 · Salvage · Fixed dose rate infusion

The registration number of this clinical trial is UMIN ID, C000000450.

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Introduction

Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. In the recent phase III study, the first-line FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group [4]. 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 [13]. Therefore, this combination therapy was considered to be one of the treatment options for patients in good general condition, and gemcitabine remains the mainstay of care for patients with advanced pancreatic cancer. However, after disease progression during first-line gemcitabine-containing chemotherapy, the options for further anticancer treatment are limited. S-1 is an orally administered anticancer drug that consists of a combination of tegafur, 5-chloro-2,4-dihydroxypyridine and oteracil potassium in a 1 : 0.4 : 1 molar ratio [27]. The antitumor effect of S-1 has already been demonstrated in a variety of solid tumors including pancreatic cancer [7, 11, 12, 14, 20, 21, 25, 26, 32, 33]. In patients with chemo-naïve pancreatic cancer, an overall response rate of 21.1% was achieved, and the median time-to-progression and median overall survival period were 3.7 and 8.3 months, respectively [32]. In gemcitabine-refractory metastatic pancreatic cancer, our recent phase II study of S-1 yielded results that demonstrated marginal activity including a response rate of 15%, a median progression-free survival time of 2.0 months and a median overall survival time of 4.5 months, with a favorable toxicity profile [17]. In addition, other reports also demonstrated marginal antitumor activity [1, 28]. Gemcitabine administration via infusion at a fixed dose rate of 10 mg/m^2/min (FDR-Gem) has been found to increase the intracellular drug concentrations, compared with gemcitabine at a standard dose rate infusion over a period of 30 min. A recent phase II study of combination therapy consisting of FDR-Gem and oxaliplatin (GEMOX) yielded results that demonstrated activity in gemcitabine-refractory advanced pancreatic cancer [5], although oxaliplatin is inactive against pancreatic cancer when used as a single agent [6]. The increased intracellular concentrations of gemcitabine as a result of FDR infusion and/or the synergistic effect of gemcitabine and oxaliplatin may play an important role in the antitumor effect of GEMOX. This finding is of interest when considering the effect of combination therapy consisting of FDR-Gem and some other agent that exhibits a synergistic effect with gemcitabine in patients with metastatic pancreatic cancer who failed standard dose rate gemcitabine.

The inhibition of ribonucleotide reductase by gemcitabine is considered to enhance the effect of the 5-FU metabolite 5-FdUMP by reducing the concentration of its physiological competitor [10]. Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells [3, 23]. S-1 is a fluoropyrimidine, and several phase II studies of S-1 and gemcitabine combination therapy have yielded results that demonstrated a promising activity in chemo-naïve advanced pancreatic cancer patients, including a response rate of 32–48% and a median survival times of 7.89–12.5 months [16, 18, 19, 31].

Therefore, we conducted the present phase I/II study to determine the recommended doses of FDR-Gem and S-1 (FGS) to use for combination therapy and to evaluate the toxicity and efficacy at the recommended doses in patients with gemcitabine-refractory pancreatic cancer.

Materials and methods

Eligibility criteria

The eligibility criteria were histologically proven pancreatic adenocarcinoma with measurable metastatic lesions, disease progression during gemcitabine-based first-line chemotherapy, age 20 years or over, ECOG performance status of 0–2 points, more than 2-week interval between the final dose of the prior chemotherapy regimen and study entry, adequate bone marrow function (leukocyte count $\geq$ 3,500/mm^3, neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin concentration $\geq$ 9.0 g/dL), adequate renal function (serum creatinine level $\leq$ 1.1 mg/dL) and adequate liver function (serum total bilirubin level $\leq$ 2.0 mg/dL, transaminase levels $\leq$ 100 U/L). Patients with obstructive jaundice or liver metastasis were considered eligible if their total bilirubin level $\leq$ 3.0 mg/dL and transaminase levels could be reduced to 150 U/L by biliary drainage. The exclusion criteria were regular use of phenytoin, warfarin or flucytosine, history of fluorinated pyrimidine use, severe mental disorder, active infection, ileus, watery diarrhea, interstitial pneumonitis or pulmonary fibrosis, refractory diabetes mellitus, heart failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, brain metastasis, and active concomitant malignancy. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board of the National Cancer Center of Japan.

Treatment

Considering the patients' quality of life, we adopted biweekly schedule. Gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) was administered by FDR intravenous infusion of 10 mg/m^2/min on day 1. S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally twice daily on day 1 to day 7, followed by a 1-week rest. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred. If blood examination revealed leukocytopenia < 2,000/mm^3, thrombocytopenia < 75,000/mm^3, total bilirubin > 3.0 mg/dL, aspartate aminotransferase or alanine aminotransferase level > 150 U/L, or creatinine > 1.5 mg/dL, both gemcitabine and S-1 were withheld until recovery. If a patient experienced dose-limiting toxicity (DLT), the dose of gemcitabine and S-1 was reduced by one level in the subsequent cycle. If a rest period of more than 15 days was required because of toxicity, the patient was withdrawn from the study. Patients were scheduled to receive gemcitabine and S-1 at four dosage levels (Table 1). Two dosage levels of S-1 were established according to the body

Table 1 Dosage levels of gemcitabine and S-1

Dosage level	Gemcitabine	S-1
Level 0	600 mg/m^2/60 min	Dosage A
Level 1[a]	800 mg/m^2/80 min	Dosage A
Level 2	1,000 mg/m^2/100 min	Dosage A
Level 3	1,200 mg/m^2/120 min	Dosage A
Level 4	1,200 mg/m^2/120 min	Dosage B

[a] Starting dosage

surface area as dosage A, about 80 mg/m^2/day, and dosage B, about 100 mg/m^2/day (Table 2). At the first dose level (level 1), gemcitabine was administered at a dosage of 800 mg/m^2 administered as a 80-min infusion, and S-1 was administered at dosage A. At the next dose level (level 2), the gemcitabine dosage was increased to 1,000 mg/m^2 administered as a 100-min infusion, and S-1 was administered at the same dosage. At the next dose level (level 3), the gemcitabine dosage was increased to 1,200 mg/m^2 administered as a 120-min infusion, and S-1 was administered at the same dosage. At the final dosage level (level 4), gemcitabine administered at the same dosage, and S-1 was administered at dosage B.

Study design

This study was an open-label, four-center, single-arm phase I/II study performed in two steps. The objective of step 1 (phase I) was to evaluate the frequency of DLT during first 2 cycles (4 weeks) and then use the frequency of DLT to determine which of the four dosages tested to recommend (Table 1). At least 3 patients were enrolled at each dosage level. If DLT was observed in the initial three patients, up to three additional patients were entered at the same dosage level. The highest dosage level that did not cause DLT in 3 of the 3 or $\geq$3 of the 6 patients treated at that level during the first two cycles of treatment was considered the maximum-tolerated dosage (MTD). DLT was defined as (1) grade 4 leucopenia or grade 4 neutropenia or febrile neutropenia, (2) grade 4 thrombocytopenia or thrombocytopenia requiring transfusion, (3) grade 3 or 4 non-hematological toxicity excluding hyperglycemia and electrolyte disturbances, (4) serum transaminases levels, γ-glutamyl transpeptidase level and alkaline phosphatase level $\geq$10 times UNL, (5) serum creatinine level $\geq$ 2.0 mg/dL and (6) any toxicity that necessitated a treatment delay of more than 15 days. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In step 2, the recommended dosages (RD) of FGS were then administered, and the effect of this combination therapy on objective tumor response was evaluated in patients who were given the RD (phase II). The number of patients to be enrolled in phase II was determined by using a SWOG's standard design (attained design) [8, 9]. The phase II included the patients who received the RD in the step 1. The null hypothesis was that the overall response rate would be $\leq$5%, and the alternative hypothesis was that the overall response rate would be $\geq$20%. The α error was 5% (one-tailed), and the β error was 10% (one-tailed). The alternative hypothesis was established based on the preferable data in previous reports [5, 15, 24, 30, 34]. Interim analysis was planned when 20 patients were enrolled. If none of the first 20 patients had a partial response or complete response, the study was to be ended. If a response was detected in any of the first 20 patients, an additional 20 patients were to be included in a second stage of accrual to more precisely estimate the actual response rate. If the number of objective responses after completing the trial was 5 or more among the 40 patients, then we would reject the null hypothesis and conclude that FGS was effective, and we would proceed to the next large-scale study. The severity of adverse events and progression-free survival and overall survival were investigated as secondary objectives in phase II.

Table 2 Dosage of S-1 (tegafur equivalent)

Body surface area (m^2)	Dosage A (≒80 mg/m^2/day)	Dosage B (≒100 mg/m^2/day)
<1.25	40 mg × 2/day	50 mg × 2/day
1.25–<1.5	50 mg × 2/day	60 mg × 2/day
$\geq$1.5	60 mg × 2/day	75 mg × 2/day

Results

Patient characteristics

Between June 2006 and March 2009, 49 patients were enrolled in this study. Fifteen patients (level 1: 3 patients, level 2: 3 patients, level 3: 6 patients, level 4: 3 patients) were enrolled into the phase I (STEP 1), and an additional 34 patients were enrolled into the phase II (STEP2) at dose level 3. Table 3 shows the baseline characteristics of the patients in step 1 and step 2. A total of the 40 patients who were given the recommended dose, 6 patients and 34 patients who entered into the study at phase I and phase II, respectively, were evaluated for efficacy and detailed safety profile.

Phase I (STEP 1)

No DLT occurred during the first 2 cycles (4 weeks) at level 1 or level 2. At dose level 3, three patients were

Table 3 Patient characteristics

Characteristic	Step 1				Step 2	Total at the recommended dose (level 3)
	Level 1	Level 2	Level 3	Level 4	Level 3	
No. of patients	3	3	6	3	34	40
Age, years						
Median	66	58	64	62	63.5	64
Range	55–69	51–58	48–71	52–70	40–80	40–80
Sex, *n* (%)						
Male	1 (33)	3 (100)	4 (67)	1 (33)	19 (56)	23 (58)
Female	2 (67)	0	2 (33)	2 (67)	15 (44)	17 (48)
ECOG performance status, *n* (%)						
0	2 (67)	2 (67)	5 (83)	2 (67)	22 (65)	27 (68)
1	1 (33)	1 (33)	1 (17)	1 (33)	12 (35)	13 (33)
Primary tumor, *n* (%)						
Head	1 (33)	2 (67)	2 (33)	2 (67)	17 (50)	19 (48)
Body/tail	2 (67)	1 (33)	4 (67)	1 (33)	17 (50)	21 (53)
Metastatic site, *n* (%)						
Liver	3 (100)	3 (100)	6 (100)	1 (33)	25 (74)	31 (78)
Lung	1 (33)	0	0	2 (67)	7 (21)	7 (18)
Peritoneum	1 (33)	1 (33)	0	1 (33)	11 (32)	11 (28)
Lymph node	0	2 (67)	0	0	11 (32)	11 (28)
Tumor stage at the start of prior treatment, *n* (%)						
Locally advanced	0	0	0	1 (33)	7 (21)	7 (18)
Metastatic	3 (100)	3 (100)	6 (100)	2 (67)	27 (79)	33 (83)
Prior treatment, *n* (%)						
Gemcitabine alone	3 (100)	3 (100)	5 (83)	3 (100)	26 (76)	31 (78)
Gem + Axitinib	0	0	0	0	2 (6)	2 (5)
Gem + Erlotinib	0	0	1 (17)	0	6 (18)	7 (18)

evaluated first, and none developed DLT. Since all 3 patients experienced DLT at dose level 4 (grade 4 neutropenia in two patients, grade 3 stomatitis in one patient), 3 additional patients were evaluated at dose level 3. A DLT (grade 4 neutropenia) was experienced by 2 of the 3 patients in this additional cohort in dose level 3, and dose level 3 was determined to be the MTD. Based on these results, the RD was determined to be level 3.

Phase II (efficacy and safety profile in the 40 patients treated at dose level 3)

In step 2, the RD of FDR-Gem and S-1 was administered to an additional 34 patients, and a total 40 patients were treated at dose level 3 to evaluate the objective tumor response to this combination therapy. As of the date of the analysis, the protocol treatment had been concluded in 39 of the 40 patients, and a total of 286 courses (median: 5 courses; range 1–31 courses) had been administered at level 3. The actual mean weekly dose administered were gemcitabine 545 mg/m^2/week (90.8% of planned dosage) and 90.1% of planned dosage of S-1. Dose reduction was required in 10 patients because of grade 4 neutropenia (five patients), grade 3 fatigue (1 patient), grade 2 fatigue with grade 2 appetite loss (one patient), grade 2 nausea (two patients) and grade 3 rash (1). The reasons for treatment discontinuation in phase II were radiological disease progression (33 patients), clinical disease progression (two patients), recurrent grade 4 neutropenia despite dose reduction due to grade 4 neutropenia (two patients), grade 4 myocardial infarction (one patients) and patient request to return to his distant hometown (one patient). All patients who discontinued treatment because of adverse events recovered from the toxicities after discontinuation. Twelve patients received third-line chemotherapy after discontinuation of FGS: S-1 monotherapy in four patients, gemcitabine + S-1 combination therapy on another treatment schedule in three patients, chemoradiotherapy with S-1 in one patient and new molecularly targeted agents in four patients who participated in a different clinical trial. Twenty-two patients received best supportive care, the other five patients transferred to another hospital, and no