Cancer Chemother Pharmacol (2012) 69:1197–1204
DOI 10.1007/s00280-012-1822-1

ORIGINAL ARTICLE

Randomized phase II study of gemcitabine and S-1 combination versus gemcitabine alone in the treatment of unresectable advanced pancreatic cancer (Japan Clinical Cancer Research Organization PC-01 study)

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Received: 23 November 2011 / Accepted: 31 December 2011 / Published online: 17 January 2012

Abstract
Purpose To evaluate the efficacy and safety of the combination of gemcitabine (GEM) and S-1 (GS) in comparison to GEM alone (G) for unresectable pancreatic cancer.
Methods In this multicenter randomized phase II study, we randomly assigned unresectable pancreatic cancer patients to either the GS group or the G group. The GS group regimen consists of intravenous 1,000 mg/m^2 GEM during 30 min on days 1 and 8, combined with 80 mg/m^2 oral S-1 twice daily on days 1–14, repeated every 3 weeks. On the other hand, the G group regimen consists of intravenous 1,000 mg/m^2 GEM on days 1, 8, and 15, repeated every 4 weeks. The primary endpoint was objective response rate (ORR). Secondary end points included treatment toxicity, clinical response benefit, progression-free survival (PFS), and overall survival.

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Results We registered 117 patients from 16 institutions between June 2007 and August, 2010. The ORR of the GS group was 28.3%, whereas that of the G group was 6.8%. This difference was statistically significant ($P = 0.005$). The disease control rate was 64.2% in the GS group and 44.1% in the G group. Median PFS was 6.15 months in the GS group and 3.78 month in the G group. This was also statistically significant ($P = 0.0007$). Moreover, the median overall survival (OS) of the GS group was significantly longer than that of the G group (13.7 months vs. 8.0 months; $P = 0.035$). The major grade 3–4 adverse events were neutropenia (54.7% in the GS group and 22.0% in the G group), thrombocytopenia (15.1% in the GS group and 5.1% in the G group), and skin rash (9.4% in the GS group). *Conclusions* The GS group showed stronger anticancer activity than the G group, suggesting the need for a large randomized phase III study to confirm GS advantages in a specific subset.

Keywords Unresectable pancreatic cancer · Chemotherapy · Gemcitabine · S-1 · Gemcitabine+S-1

Introduction

Pancreatic cancer (PC) currently is the fifth leading cause of cancer-related mortality in Japan, with an estimated 25,960 deaths attributable to the disease in 2010 [1]. Although surgical complete removal of the tumor is the only chance of cure, almost all PC patients are diagnosed at an advanced unresectable stage, despite recent improvements in diagnostic techniques. Moreover, since PC recurs in about 20% of patients even after surgical resection, development of effective chemotherapy is essential to improve the prognosis of this disease.

Gemcitabine (Gem) is widely used as a standard systemic chemotherapeutic agent for advanced PC [2]. Although some combination therapies including Gem have shown survival benefit, these are not considered as standard regimens [3, 4]. S-1 is a fourth generation oral fluoropyrimidine, which contains tegafur/gimeracil/oteracil potassium at a molar ratio of 1.0:0.4:1.0. The efficacy of S-1 has already been shown in a variety of solid tumors, particularly gastric cancer [5, 6]. A phase II trial of S-1 alone for PC metastatic to other organ has shown a response rate of 37.5% and a median survival of 9.2 months [7, 8]. Moreover, non-randomized phase II trials of a combination of Gem and S-1 (GS) therapy have demonstrated excellent results as to ORR of 44–48% and median survival of 10–12 months [9–13].

The current study (PC-01) was a randomized phase II trial to clarify the effectiveness of GS, prior to an anticipated phase III trial comparing GS with Gem alone, because there are many chemotherapy regimens that did not prove survival benefit despite the fact that one-arm phase II studies showed extremely promising results. Consequently, we, investigators of the Japan Clinical Cancer Research Organization (JACCRO), considered the current study (PC-01) could accurately elucidate the true activity of GS, because selection bias frequently seen in one-arm trials may be minimized by prospective randomization studies.

Patients and methods

Patients

The eligibility criteria for enrollment into this study (March 2007–August 2010) were patients with histologically or cytologically proven pancreatic adenocarcinoma, patients with International Union Against Cancer clinical stage III (locally advanced disease: T4N0-1 and M0) or IV (metastatic disease: T1-4N0-1 and M1), patients with measurable lesions as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines, age $\geq$20 and $\leq$80, no prior anticancer treatment for any malignancies, an Eastern Cooperative Oncology Group performance status (PS) $\leq$2, adequate bone marrow (leukocyte count $\geq$4,000/mm^3, neutrophil $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, and hemoglobin $\geq$8.0 g/dl), adequate renal function (serum creatinine concentration $\leq$1.5 mg/dl and creatinine clearance $\geq$60 ml/min), adequate hepatic function (serum bilirubin level $\leq$2.0 mg/dl, serum alanine and aspartate transaminase levels $\leq$2.5 times the upper limit of the institutional normal; if biliary drainage was performed for jaundice before registration, the former $\leq$5 times the upper limit of the institutional normal and the

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latter ≤2.5 times the upper limit of the institutional normal), oxygen saturation ≥93%, adequate nourishment, no serious complications, life expectancy of at least 8 weeks, and provision of written informed consent from the patient.

Before randomization, a complete history was obtained and physical examination, routine hematology and biochemistry, ECG, chest X-ray, and abdominal computed tomography (CT) scan were performed.

Study design

PC-01 was an open-label, screening design, randomized phase II study. The primary end point was ORR. Secondary end points included treatment toxicity, clinical response benefit, PFS, and OS.

Patients were randomly assigned to the G group or the GS group in a 1:1 ratio. Random assignment was performed centrally by a web-based assistant system (flexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure. Stratification factors were stage (III vs. IV), PS (0 or 1 vs. 2), and pain due to cancer (present vs. absent).

This study protocol was approved by the Protocol Review Committee of the JACCRO and Institutional Review Board of each institution, ClinicalTrials.gov identifier number was NCT00514163.

Protocol treatment

Eligible patients were randomly assigned to either the G group or the GS group. The G group patients received 1,000 mg/m^2 Gem intravenously during 30 min on days 1, 8, and 15, as 1 course repeated every 4 weeks. Patients with grade 4 hematological toxicities or grade 3 non-hematological toxicities underwent dose reduction to 800 mg/m^2 in the next course. The GS group patients received 1,000 mg/m^2 Gem intravenously during 30 min on days 1 and 8, and 40 mg/m^2 S-1 taken orally twice daily on days 1–14, every 3 weeks. When patients developed grade 4 hematological toxicities or grade 3 non-hematological toxicities by day 8, treatment was delayed by 1 week, and the S-1 dose was reduced to 60 mg/m^2 in the next course. In neither arms, prophylactic granulocyte-colony stimulating factor support allowed. Treatment was continued until progression, unacceptable toxicity, or patient refusal to continue the protocol treatment. The discontinuation of the protocol treatment for the reasons mentioned above was defined as protocol cessation.

Response and toxicity assessment

Toxicities were evaluated at each patient visit, according to the Common Terminology Criteria for Adverse Events version 3.0. CT or magnetic resonance imaging scans were performed at the baseline and after every 4 weeks to assess radiological response according to the RECIST version 1.0. Radiological tumor shrinkage of the primary tumor of the pancreas was assessed for all patients in the current study. ORR and DCR were set at the frequency of complete response plus partial response, in addition to stable disease among patients in each arm, respectively.

Clinical response benefit was assessed using daily analgesic consumption (measured in oral morphine-equivalent milligrams). Among patients who required opioid before the protocol treatment, patients whose opioid administration decreased to better than half of the baseline by day 1 of course 3 (8 weeks later in the G group and 6 weeks later in the GS group) were defined to be responders.

Statistical considerations

The primary endpoint was ORR. A sample size of 49 was required for a one-sided alpha value of 0.05 and a beta value of 0.20 with an expected response rate of 30% in the GS group and a threshold response rate of 10% in the G group. The protocol was activated in June 2007, and a total of 110 patients were planned for recruitment accounting for some drop-off

Table 1 Patient characteristics

Characteristics	G group (n = 59)	GS group (n = 53)	P value
	n	*n*	
Gender			
Male	35	32	1.00
Female	24	21	
Age			
<65	31	28	1.00
≥65	28	25	
ECOG PS			
0	45	44	0.66
1 or 2	14	9	
Locally advanced	18	13	0.53
Metastatic	41	40	
Metastatic sites			
Liver	30	28	0.85
Lymph node	10	6	0.43
Peritoneum	7	12	0.14
Lung	3	8	0.11
Ascites and/or pleural effusion			
Present	4	7	0.34
Absent	55	46	
Pain			
Present	20	17	1.00
Absent	39	36	

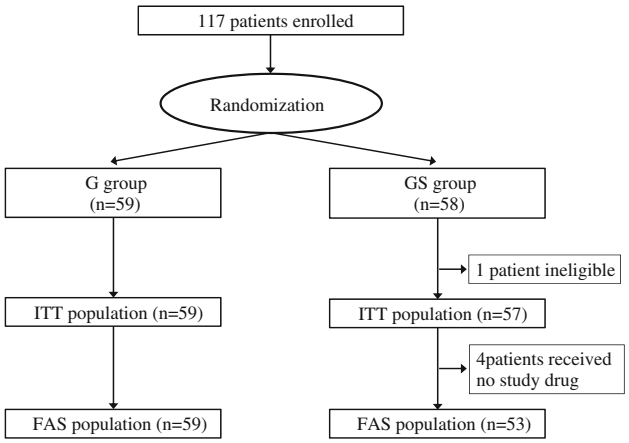

Fig. 1 Trial profile

cases within 1 year. If the null hypothesis (response rate) was not attained, the subsequent phase III trial would be designed to confirm the superiority of GS therapy to Gem alone.

The frequencies of each characteristic in Table 1 and each ORR and DCR in Table 3 were analyzed by the chi-square test.

OS was determined as the time from the date of registration to the date of death due to any cause and was censored at the date of the last follow-up for surviving patients. PFS was measured from the date of registration to the date of the first evidence of radiological or clinical progression, or death due to any cause and was censored at the date of the last follow-up CT for surviving patients with no clinical progression. OS and PFS were estimated by the Kaplan–Meier method, and the confidence interval (CI) was calculated with the Greenwood formula. Comparison of survival probability was conducted by the log-rank test. *P* values of less than 0.05 were considered to indicate statistically significant differences in the current study. The analysis was carried out with the SAS 9.2 statistical software (SAS Institute, Cary, NC, USA).

Results

Because of the poor recruitment rate, the protocol was amended twice, in January 2008 and February 2009, and a total of 117 patients were enrolled by August 2010 from 16 hospitals (see "Appendix"). One patient was judged to be ineligible after registration, because the final pathological diagnosis was not cancer. Accordingly, a total of 116 were allocated into either the G group ($N = 59$) or the GS group ($N = 57$) from among the intent-to-treat (ITT) population. Of the 116 patients, 4 in the GS group received supportive care instead of protocol treatment because of early deterioration or patient refusal. The full analysis set (FAS) consisted of 112, i.e., 59 and 53 patients in the G group and the GS group, respectively (Fig. 1).

Patient data registration was closed in June 2011, 10 months after the last patient registration. At the time of analysis, protocol treatment had been continued in 1 of 53 patients in the GS group. All analyses in comparison between the G group and the GS group were done in the FAS population, except OS.

Patient characteristics

Patient characteristics are shown in Table 1. The median age in the G group was 64 (41–79) years old, and that in the GS group was also 64 (45–77) years old. Although the protocol allowed enrollment of patients with PS 2, almost all patients were in good general condition (PS 0:1:2 was 79%:18%:3%, respectively). Metastatic disease was found in 72% of the patients. Analgesics (including opioids) were used in 33% (19%) of the patients at the baseline.

Toxicity

The major grade 3–4 adverse events are shown in Table 2. Although the frequency of grade 3–4 adverse events in the GS group was higher than that in the G group regarding both hematological and non-hematological toxicities, the toxicities were predictable and manageable. Discontinuation of the protocol treatment due to toxicity was seen in 13 (22%) of 59 protocol-cessation patients in the G group, and 14 (27%) of 52 protocol-cessation patients in the GS group. Treatment-related death was reported in 1 patient in each arm.

Clinical response benefit

At baseline, 12 and 10 patients required opioids in the G group and the GS group, respectively. There were 0 responders to opioids of 12 in the G group, and 2 of 10 in the GS group.

Objective response

Radiological responses are shown in Table 3. There was no complete response. The ORR in the GS group (28.3%) was significantly higher than that in the G group (6.8%), and the null hypothesis was rejected (two-sided $P = 0.005$). Also the DCR in the GS group was significantly higher.

In 31 patients with locally advanced disease, partial response was demonstrated in 1 (5.6%) of 18 patients in the G group, and 3 (23%) of 13 patients in the GS group. In the remaining 81 patients with metastatic disease, partial response was seen in 3 (7.3%) of 41 patients in the G group, and 12 (30%) of 40 patients in the GS group.

Table 2 Summary of maximum toxicity grades

Event	G group ($n = 59$)			GS group ($n = 53$)		
	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)
Hematological						
WBC	5.1	0	5.1	20.8	5.7	26.4
Hemoglobin	5.1	0	5.1	7.5	0	7.5
Neutrophil	20.3	1.7	22.0	41.5	13.2	54.7
Platelet	3.4	1.7	5.1	7.5	7.5	15.1
Non-hematological						
Fatigue	5.1	1.7	6.8	3.8	0	3.8
Anorexia	5.1	0	5.1	3.8	0	3.8
Nausea	1.7	0	1.7	3.8	0	3.8
Diarrhea	0	0	0	3.8	0	3.8
Stomatitis	0	0	0	3.8	0	3.8
Skin rash	0	0	0	7.5	1.9	9.4
AST	3.4	0	3.4	1.9	0	1.9
ALT	6.8	0	6.8	3.8	0	3.8
ALP	6.8	0	6.8	3.8	0	3.8
Bilirubin	6.8	0	6.8	1.9	0	1.9
Albumin	0	0	0	1.9	0	1.9
C-reactive protein	0	0	0	1.9	0	1.9
Treatment-related death	1.7			1.9		

Progression-free survival

PFS curves are shown in Fig. 2. Discontinuation of the protocol treatment due to progression was seen in 34 (58%) of 59 protocol-cessation patients in the G group, and 20 (38%) of 52 protocol-cessation patients in the GS group. The median progression survival time in the GS group (6.15 months) was significantly longer than that in the G group (3.78 months, $P = 0.0007$).

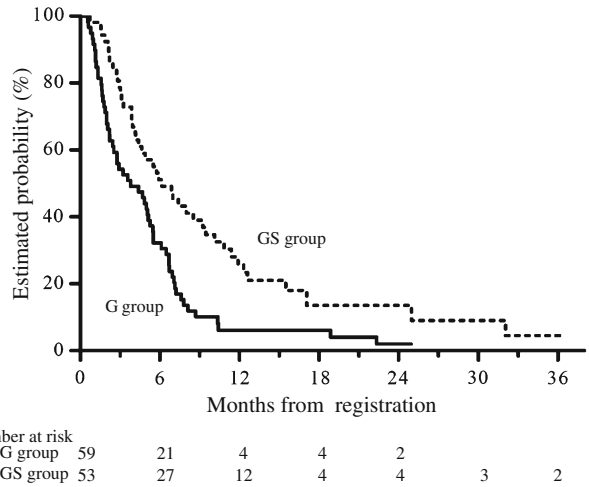

Fig. 2 Kaplan–Meier estimates of progression-free survival ($n = 112$)

Post-study treatment

After discontinuation of the protocol treatment, 37 (67%) of 55 patients in the G group and 23 (44%) of 52 patients in the GS group received various second-line treatments, most of which consisted of Gem or S-1 or both.

Overall survival in the ITT population

OS curves in the G group ($N = 59$) and the GS group ($N = 57$) are shown in Fig. 3. The GS group included 4 patients who deteriorated early or refused before protocol treatment, and subsequently received best supportive care without any anti-cancer treatment. The median survival time and 1-year survival probability in the G group and the GS group were 8.0 months and 29.0%, and 13.7 months and 55.9%, respectively. OS was significantly better in the GS group ($P = 0.035$), and its hazard ratio was 0.63 (95%, 0.41–0.97).

OS curves in the relation to extent of original disease are shown in Figs. 4 and 5. The median survival time in locally advanced and metastatic disease in the G group and the GS group were 8.7 and 7.7 months, and 14.6 and 12.9 months, respectively. OS in metastatic disease was significantly better in the GS group ($P = 0.029$).

Table 3 Objective response

Total (n = 112)	G group (n = 59)	GS group (n = 53)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	4 (6.8)	15 (28.3)	
Stable disease	22 (37.3)	19 (35.9)	
Progressive disease	23 (39.0)	7 (13.2)	
Not evaluable	10 (17.0)	12 (22.6)	
Objective response rate (%)	6.8	28.3	0.005
(95% CI)	(2.7–16.2)	(18.0–41.6)	
Disease control rate (%)	44.1	64.2	0.039
(95% CI)	(32.2–56.7)	(50.7–75.7)	

Locally advanced (n = 31)	G group (n = 18)	GS group (n = 13)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	1 (5.6)	3 (23.1)	
Stable disease	7 (38.9)	5 (38.5)	
Progressive disease	5 (27.8)	0	
Not evaluable	5 (27.8)	5 (38.5)	
Objective response rate (%)	5.6	23.1	0.284
(95% CI)	(1.0–25.8)	(8.2–50.3)	
Disease control rate (%)	44.4	61.5	0.473
(95% CI)	(24.6–66.3)	(35.5–82.3)	

Metastatic (n = 81)	G group (n = 41)	GS group (n = 40)	P value
	n (%)	n (%)	
Complete response	0	0	–
Partial response	3 (7.3)	12 (30.0)	
Stable disease	15 (36.6)	14 (35.0)	
Progressive disease	18 (43.9)	7 (17.5)	
Not evaluable	5 (12.2)	7 (17.5)	
Objective response rate (%)	7.3	30	0.011
(95% CI)	(2.5–19.4)	(18.1–45.4)	
Disease control rate (%)	43.9	65	0.075
(95% CI)	(29.9–59.0)	(49.5–77.9)	

Discussion

We set out to determine whether a combination of S-1 plus GS would obtain better results than GEM alone in a phase II study of unresectable pancreatic cancer.

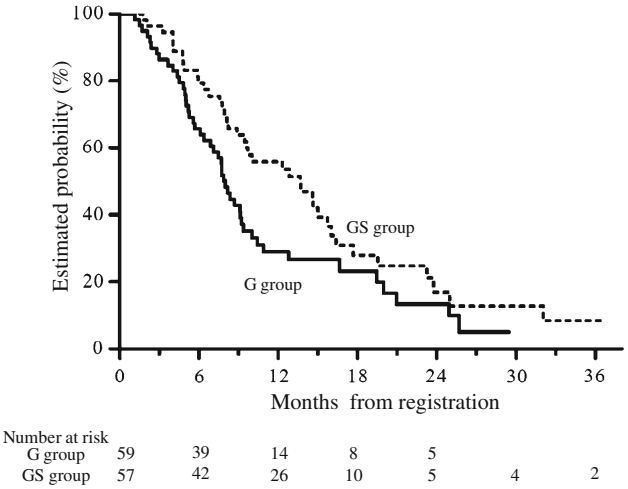

Fig. 3 Kaplan–Meier estimates of overall survival (n = 116)

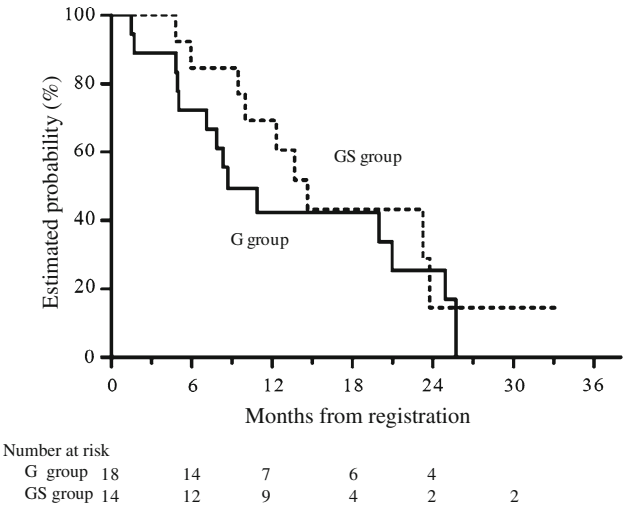

Fig. 4 Kaplan–Meier estimates of overall survival in locally advanced (n = 32)

The current PC-01 study, which was intended to screen GS as a promising investigation for a phase III trial comparing to standard Gem alone, successfully met this primary endpoint. Although the response rate obtained in the current study was lower than that in the previous one-arm phase II trials, the anticancer activity of GS was confirmed to be stronger than Gem alone [9–13]. Favorable results of GS as to PFS and OS data also encouraged us to plan a large phase III study comparing GS to standard Gem alone. However, results of large randomized phase III study of GS and Gem alone, known as the GEST trial, which was started by another Japanese cooperative group after our PC-01, were reported at the latest annual meeting of American Society of Clinical Oncology 2011 [14]. This large-scale (N = 600) GEST did not show OS superiority of GS compared to Gem alone. In terms of the survival benefit, this study seems to contradict the present PC-01 study.

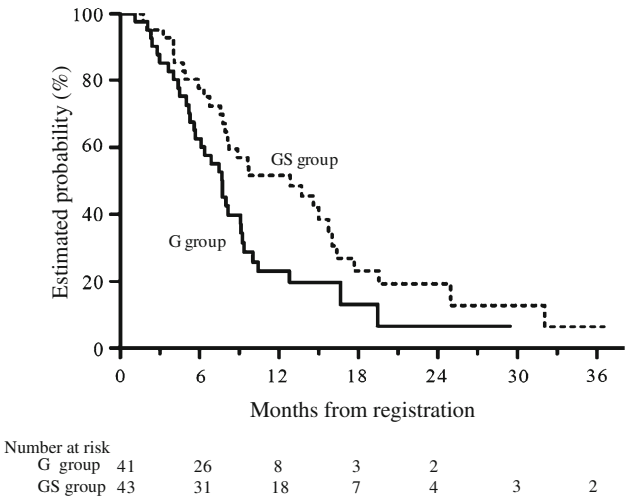

Fig. 5 Kaplan–Meier estimates of overall survival in Metastatic ($n = 84$)

Fluoropyrimidine and its derivatives have been intensively examined in combination with Gem for PC [15, 16]. All of those combinations have failed to show OS superiority compared to Gem alone in phase III settings, whereas relatively favorable results were generally reported in terms of response rate and survival. Accordingly, it may be important to explore a specific population in whom benefit would be maximized by GS therapy, though it may be difficult to develop Gem and fluoropyrimidine combination as a conventional frontline regimen for standard risk cases with advanced PC.

The main limitation of the PC-01 study derived from its inclusion of a relatively large number of patients who were found to be non-evaluable, mainly due to either the deterioration of the disease or patient refusal, which might well have affected the outcome of local response. On the other hand, randomized comparison of GS and Gem alone was one of the strengths of the current study. The ORR of GS in a previous non-randomized phase II study was extremely high, around 40%, perhaps due to selection bias [9–13]. However, in actual practice, since the response rate is usually below 30%, the PC-01 demonstrated a response rate acceptable to medical oncologists. Although PC-01 was not a phase III trial designed to confirm survival benefit, the OS and PFS data in the ITT population were impressive. The GS group showed a significant survival advantage against Gem group, even though the GS group included 3 cases of early deterioration. In the subset analysis, there was some discrepancy for the favorable population for GS between the current PC-01 and the GEST study. For example, GS was favorable in metastatic disease in PC-01; on the other hand, it was favorable in locally advanced disease in the GEST. GEMSAP, another Japanese study group, also carried out a randomized phase II trial of GEM and GS comparison and reported GS superiority to GEM in PFS in ASCO2011 [17].

Further accumulation of GEM and GS data might warrant an integrated meta-analysis to identify the population most likely to benefit from GS. Subsequently, a large randomized phase III trial to confirm GS advantages in a specific patients subset may be justified.

In conclusion, PC-01 demonstrated that GS had strong anticancer activity, and we believe that GS in some situations would be beneficial to give advanced PC patients.

Acknowledgments We are grateful to K. Aiba, Y. Shimada, and R. Kuwatsuru for their kind advice. We also thank T. Sudo and S. Koyama for their data management and Prof M. Takeuchi of Kitasato University for his rigorous statistical analysis. The authors are also indebted to Prof. J. Patrick Barron, Chairman of the Department of International Medical Communications of Tokyo Medical University, who is a remunerated consultant of Taiho Pharmacology for his review of this manuscript. This study was presented in part at the 2011 ASCO Annual Meeting, Chicago, Illinois and the 9th Annual Meeting of the Japanese Society of Medical Oncology, Yokohama, Japan, 2011. This study was supported by JACCRO.

Conflict of interest No authors have any conflict of interest.

Appendix

The following investigators registered patients for this study:

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Yuki Hirose (Japan Red Cross Fukui Hospital, Fukui, Japan); Takaaki Ikari (Tobu Chiiki Hospital Tokyo Metropolitan Health and Medical Treatment Corporation, Tokyo, Japan).

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