alone [8, 9, 15]. In the BEAT study, Van Cutsem et al. [13] reported the safety and efficacy of bevacizumab with various chemotherapy regimens for metastatic colorectal cancer.

The results of randomized controlled trials (RCTs) in patients with advanced colorectal cancer demonstrated that the median overall survival was 16–23 months in the patients who received bevacizumab with fluoropyrimidine-based chemotherapy, including 5-FU/folinic acid (FA), irinotecan plus 5-FU/leucovorin (IFL), 5-FU/leucovorin plus oxaliplatin (FOLFOX), and capecitabine plus oxaliplatin (XELOX), as 1st line chemotherapy [8, 9, 16]. A Japanese clinical trial of XELOX plus bevacizumab in patients with mCRC reported that the median overall survival was 27.4 months [10]. Although our analysis was based on bevacizumab combined with various regimens, the overall survivals of both the 1st line patients and the patients with further lines of treatment in our study are in no way inferior to those in the previous reports. However, our 1st line patients showed significantly better survival in comparison to the latter patients ($P = 0.005$). It is suggested that the initiation of bevacizumab in the 1st line treatment provided long-term survival.

In the BRiTE study, the authors reported that there was a survival benefit associated with the continuation of bevacizumab beyond PD in patients who received bevacizumab-containing 1st line therapy [17]. There were no significant differences in survival between the groups with and without post-PD treatment with bevacizumab in the present study. However, the group who had post-PD treatment with bevacizumab showed a longer survival time, because many patients in that group had stable disease. The benefit of continuous administration of bevacizumab beyond PD is controversial. Disclosure of the results of two prospective randomized trials (the ML18147 study and the SPIRITT study) could resolve this issue.

The incidences of grade 3 or greater adverse events related to bevacizumab reported in previous studies [8, 9, 13, 15, 17–23] were: hypertension in 3.7–11.0 % of patients, proteinuria in 0.6–0.8 %, hemorrhage in 1.9–3.1 %, wound-healing complications in 0.8–2.0 %, venous thrombosis in 3.4–7.8 %, arterial thrombosis in 1.1–1.7 %, and GI perforation in 0.7–1.7 %. In the present study, there were no differences in the incidence of bevacizumab-related grade 3 or greater adverse events compared with the findings in previous studies, except for the incidence of GI perforation. The incidence of GI perforation in our study was higher than that in the previous studies.

Some risk factors for GI perforation associated with bevacizumab have been reported in CRC patients. A univariate analysis showed that patients with intact primary tumors, a history of sigmoidoscopy or colonoscopy within 1 month of the initiation of bevacizumab therapy, or a history of previous adjuvant radiotherapy might have an increased risk of GI perforation [24]. In addition, patients with ovarian cancer might share similar risk factors, as many have peritoneal carcinomatosis, a history of multiple surgeries, radiation exposure, and invasion of the GI tract by the tumor [25]. Most of the GI perforations in our series occurred during the early period after the initiation of bevacizumab, and these patients also had some risk factors for this complication. It is possible that the perforation events might have been directly related to the bevacizumab treatment. Therefore, identifying patients at high risk of developing a GI perforation will be an important initial step in reducing the risk of such complications. In addition, in patients receiving bevacizumab, physicians should be highly vigilant to detect any sign of perforation as early as possible.

The present study has several potential limitations because it was a retrospective analysis and a multicenter study. These factors made it difficult to obtain some detailed information. Although our survey study likely revealed the current situation in Japan, a prospective multicenter study is needed in this country.

In conclusion, this study revealed that the survival benefit of bevacizumab in Japanese patients with mCRC was similar to that observed in previous clinical trials from other countries. On the other hand, this study showed a higher incidence of GI perforation compared with findings in previous studies. The careful selection of patients with fewer risk factors for a GI perforation will allow for greater patient benefit from bevacizumab.

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Conflict of interest None of the authors has any conflict of interest.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

AQ:A-B

GEST: Gemcitabine and S-1 Trial

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ABSTRACT

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

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

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

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

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INTRODUCTION

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

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

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

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

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

PATIENTS AND METHODS

Study Design

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

Patients

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

Treatment

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

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

Assessments

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

EQ-5D: EuroQol 5 Dimension

Statistical Analysis

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

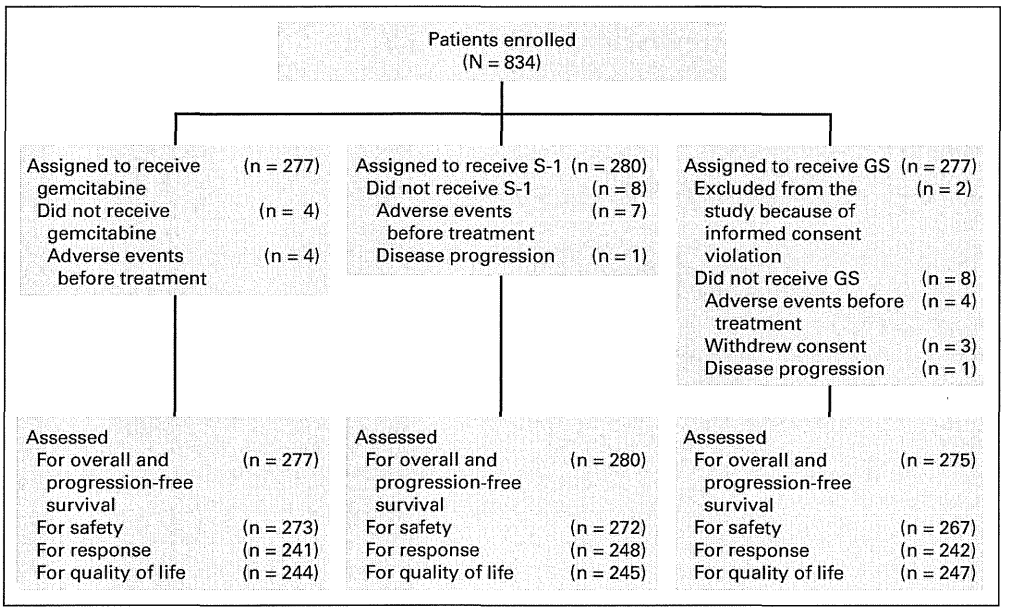

Fig 1. CONSORT diagram. GS, gemcitabine plus S-1.

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

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

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

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

RESULTS

Patients

Between July 2007 and October 2009, a total of 834 patients were enrolled from 75 institutions in Japan and Taiwan (768 in Japan and 66 in Taiwan). Two patients in the GS group were excluded from the study because enrollment was conducted before obtaining written informed consent. The remaining 832 patients were included in the full analysis set and used to calculate OS and PFS (Fig 1). The three treatment groups were well balanced with respect to demographic and baseline characteristics (Table 1). F1, AQ:D T1

Study Treatment

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

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

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

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

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

Survival

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

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

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

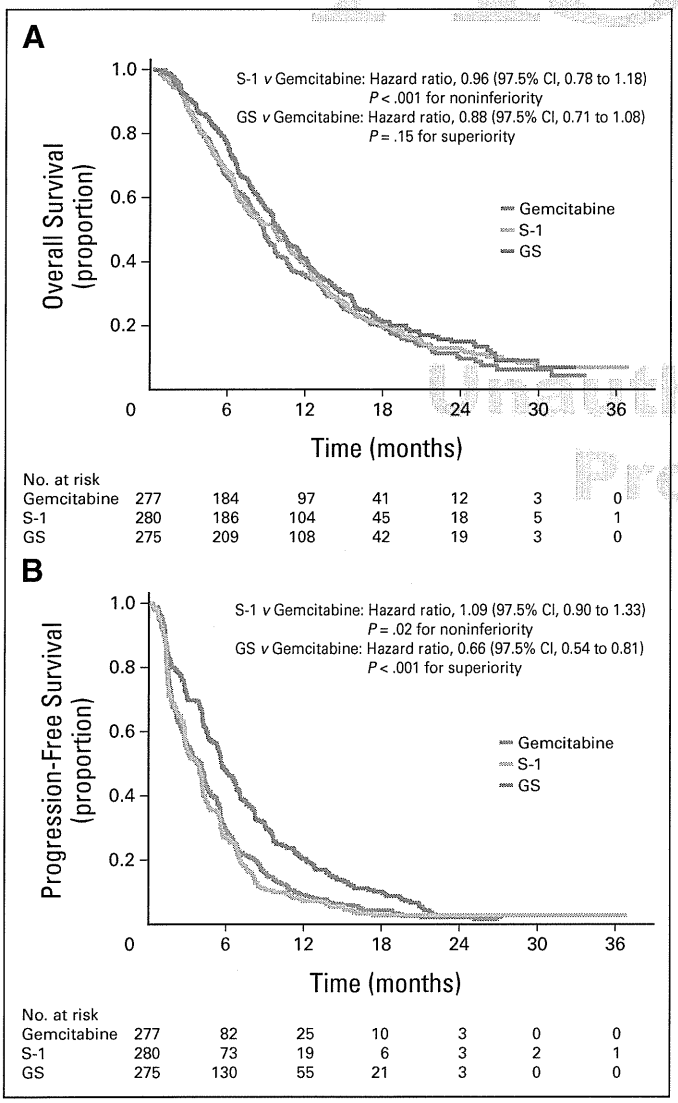

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival according to treatment group. GS, gemcitabine plus S-1.

Response to Therapy

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

Second-Line Chemotherapy

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

Adverse Events and Quality-Adjusted Life Years

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

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

vomiting,

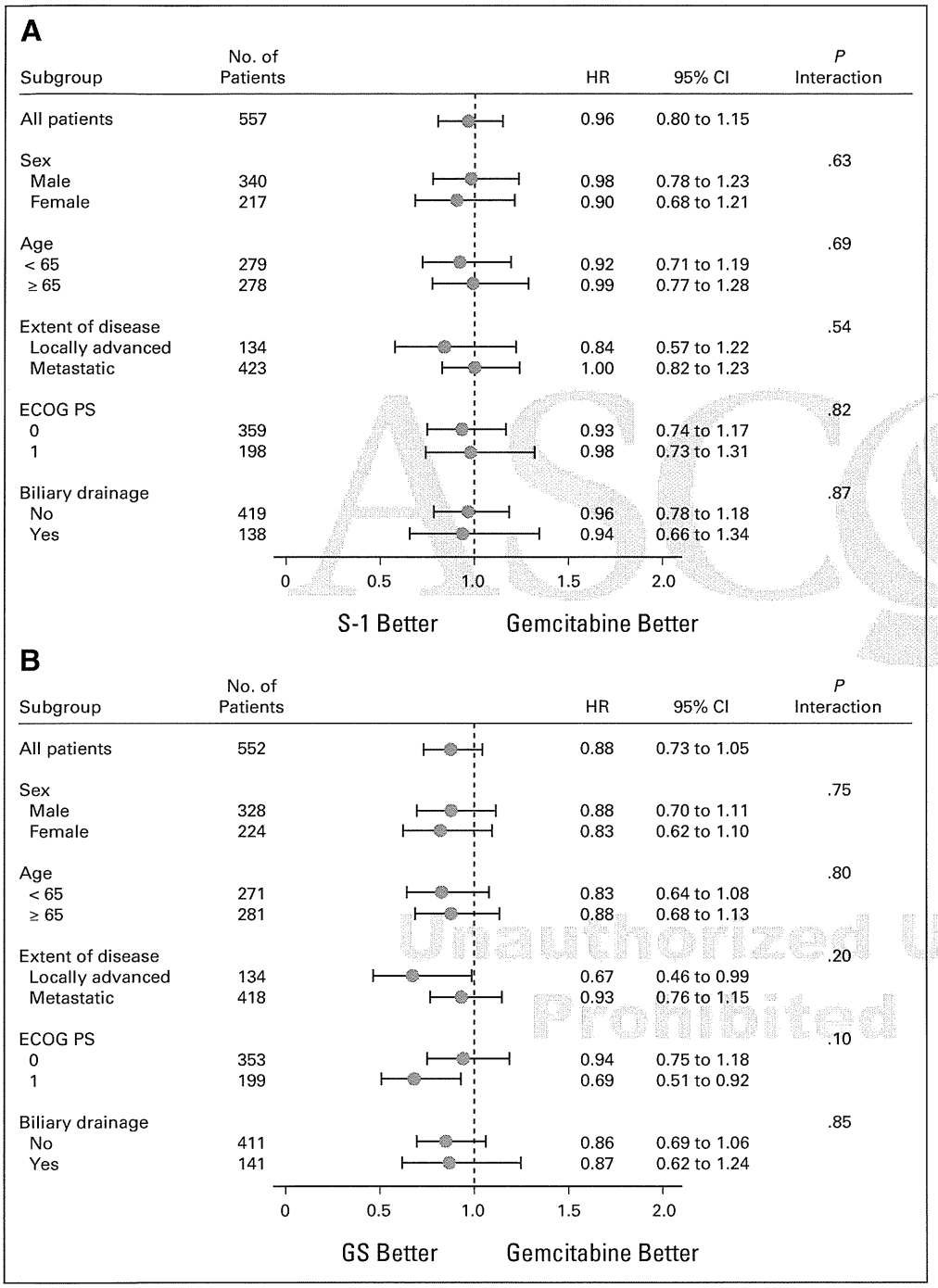

Fig 3. Forest plots of treatment effects on overall survival in subgroup analyses. Forest plots show effects on overall survival of patients in each subgroup. (A) S-1; (B) gemcitabine plus S-1 (GS). Each black circle shows the treatment response. ECOG PS, Eastern Cooperative Oncology Group performance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

blue

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

DISCUSSION

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

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

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

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

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

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

Table 3. Grade 3 or Higher Adverse Events (Safety Population)

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

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

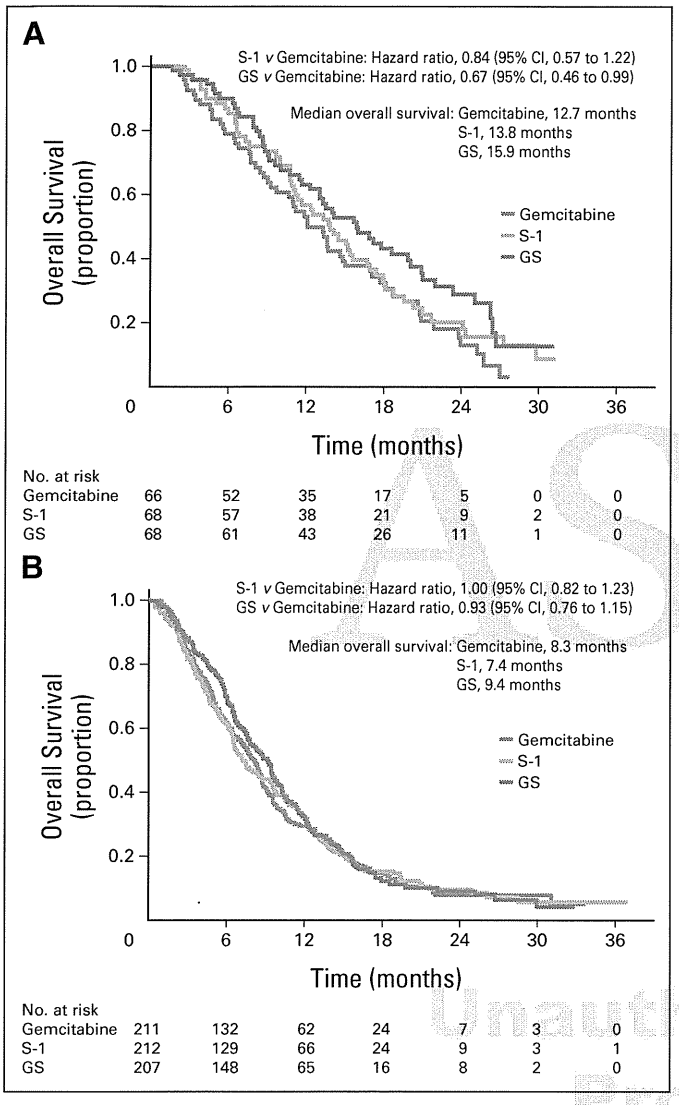

Fig 4. Kaplan-Meier estimates of overall survival in (A) locally advanced disease and (B) metastatic disease. GS, gemcitabine plus S-1.

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

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

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

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

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

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

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

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Details of Adequate Organ Functions in Enrollment Criteria and Main Exclusion Criteria

Adequate organ functions were defined as follows: leukocyte count $\geq$ 3,500/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, hemoglobin level $\geq$ 9.0 g/dL, serum creatinine level $\leq$ 1.2 mg/dL, creatinine clearance $\geq$ 50 mL/min, serum AST and ALT levels $\leq$ 150 U/L, and serum total bilirubin level $\leq$ 2.0 mg/dL or $\leq$ 3.0 mg/dL if biliary drainage was performed.

Main exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; and serious complications such as heart failure, peptic ulcer bleeding, or poorly controlled diabetes. Pancreatic cancers other than adenocarcinoma or adenosquamous carcinoma (eg, anaplastic carcinoma) were excluded from the study.

Dosage Adjustment Guideline for Toxicities

All treatment cycles were repeated until disease progression, unacceptable toxicity, or patient refusal. If patients had a leukocyte count of less than 2,000/μL, a neutrophil count of less than 1,000/μL, a platelet count of less than 70×10^3/μL, or grade 3 or worse rash, the administration of anticancer agents was postponed. S-1 was temporarily halted both in S-1 and in GS groups if patients had a creatinine level of 1.5 mg/dL or higher or grade 2 or worse diarrhea or stomatitis. Treatment was discontinued if these events did not resolve within

4 weeks after treatment suspension. In patients who experienced febrile neutropenia, grade 4 leukopenia, neutropenia, or thrombocytopenia or grade 3 or worse rash, the dose of gemcitabine was reduced by 200 mg/m^2. In patients with febrile neutropenia; grade 4 leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

A—AUTHOR: Please define GEST in title, footnotes, abstract, and text.

B—**AUTHOR: You are responsible for detecting any errors in this proof.** Confirm that all dosing information and treatment regimens are complete and accurate in text, tables, and figures, if applicable to article content.

C—AUTHOR: Please define EQ-5D.

D—**AUTHOR:** Figures in your article have been edited and redrawn to conform to JCO style. **As author, it is your responsibility to review all figure content carefully and completely for accuracy, including dosing information, axis labels, and legends, if applicable.** At this advanced stage of production, changes to figures should only be made to correct data/factual errors or errors that severely compromise clarity or meaning.

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A: GEST: Gemcitabine and S-1 Trial
B: OK
C: EQ-5D: EuroQol 5 Dimension
D: OK
E: OK
F: OK
G: OK
H: OK

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Safety of UFT/LV and S-1 as adjuvant therapy for stage III colon cancer in phase III trial: ACTS-CC trial

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BACKGROUND: The Adjuvant Chemotherapy Trial of TS-1 for Colon Cancer (ACTS-CC) is a phase III trial designed to validate the non-inferiority of S-1 to UFT/leucovorin (LV) as postoperative adjuvant chemotherapy for stage III colon cancer. We report the results of a planned safety analysis.

METHODS: Patients aged 20–80 years with curatively resected stage III colon cancer were randomly assigned to receive UFT/LV (UFT, 300 mg m^{-2} per day as tegafur; LV, 75 mg per day on days 1–28, every 35 days, 5 courses) or S-1 (80, 100, or 120 mg per day on days 1–28, every 42 days, 4 courses). Treatment status and safety were evaluated.

RESULTS: Of 1535 enrolled patients, a total of 1504 (756 allocated to S-1 and 748 to UFT/LV) were analysed. The completion rate of protocol treatment was 77% in the S-1 group and 73% in the UFT/LV group. The overall incidence of adverse events (AEs) were 80% in S-1 and 74% in UFT/LV. Stomatitis, anorexia, hyperpigmentation, and haematological toxicities were common in S-1, whereas increased alanine aminotransferase and aspartate aminotransferase were common in UFT/LV. The incidences of ⩾grade 3 AEs were 16% and 14%, respectively.

CONCLUSION: Although AE profiles differed between the groups, feasibility of the protocol treatment was good. Both S-1 and UFT/LV could be safely used as adjuvant chemotherapy.

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Keywords: colon cancer; adjuvant chemotherapy; phase III; S-1; UFT

Colorectal cancer (CRC) was the second most common cancer in Japan, affecting over 100 000 individuals (Cancer statistics in Japan, 2010). The Japanese Society for Cancer of the Colon and Rectum (JSCCR) reported that recurrence rates were 3.7% for stage I disease, 13.3% for stage II, and 30.8% for stage III (Kobayashi *et al*, 2007). Postoperative adjuvant chemotherapy for patients with stage III CRC is now internationally accepted as a standard care to improve outcomes. In the mid-1990s, 6 months of intravenous (i.v.) therapy with 5-fluorouracil (5-FU)/leucovorin (LV) was established to be standard adjuvant chemotherapy for colon cancer. Subsequently, the benefits of adding oxaliplatin to 5-FU/LV were evaluated. At present, 5-FU/LV combined with oxaliplatin is regarded as the standard adjuvant chemotherapy for stage III colon cancer in western countries (Labianca *et al*, 2010; National comprehensive cancer network (NCCN), 2011).

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The JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer (Japanese Society for Cancer of the Colon and Rectum, 2010) recommend four regimens as adjuvant therapy for stage III CRC: i.v. 5-FU/LV, UFT/LV, capecitabine, and FOLFOX (5-FU/LV plus oxaliplatin). However, large population database demonstrated that outcomes differ among subgroups of patients with stage III disease (Gunderson *et al*, 2010). Consequently, in Japan, considering expected benefits and possible risks of increased toxicity, a consensus has not been reached as to whether adjuvant regimens containing oxaliplatin should be given to all patients with stage III disease. Actually, in Japan, several oral 5-FU derivatives are available, and oral 5-FU agents have been preferred because of their convenience. About 80% of CRC patients received adjuvant chemotherapy using oral 5-FU agents. UFT/LV is one of the most widely used regimens for adjuvant chemotherapy of stage III CRC in Japan.

UFT (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral 5-FU derivative that combines tegafur with uracil in a molar ratio of 1:4. Tegafur is a prodrug of 5-FU, and uracil competitively inhibits the degradation of 5-FU by dihydropyrimidine dehydrogenase (DPD). Concomitant use of the oral folic acid derivative LV with UFT promotes stabilising the ternary complex and augmenting the inhibition of thymidylate synthase (TS) by 5-FU. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-06 trial, which enrolled 1608 patients with stage II or III colon cancer in the United States, demonstrated non-inferiority of UFT/LV to i.v. 5-FU/LV in terms of efficacy and safety (Lembersky *et al*, 2006), and demonstrated better convenience of UFT/LV (Kopec *et al*, 2007).

S-1 (TS-1; Taiho Pharmaceutical Co., Ltd) is another oral 5-FU derivative available for CRC in Japan. It combines tegafur, gimeracil, and oteracil, in a molar ratio of 1:0.4:1 (Shirasaka *et al*, 1996). Gimeracil, a DPD inhibitor, is about 200-fold more potent than uracil. Oteracil inhibits the conversion of 5-FU to active metabolites in the gastrointestinal tract, resulting in reduction of gastrointestinal toxicity of 5-FU. The phase II trial of monotherapy with S-1 for metastatic CRC showed response rates about 35%, which were higher than that of UFT/LV (Ohtsu *et al*, 2000). In a large phase III study in patients with stage II and III gastric cancer (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial), 1 year of postoperative adjuvant chemotherapy with S-1 compared with surgery alone disclosed significantly prolonged relapse-free survival and overall survival (Sakuramoto *et al*, 2007). S-1 is now widely used as the standard adjuvant chemotherapy for GC. However, the efficacy of S-1 as adjuvant chemotherapy on CRC has not been established.

S-1 has several advantages, including slightly higher antitumour activity, low costs, and easy administration, that is, twice daily after meals (UFT/LV is given three times daily, more than 1 h after or before meals). In addition, because of differences in the mechanisms of action, S-1 may be useful in a different subset of patients and have a distinct toxicity profile from that of UFT/LV. S-1 may thus become a new, more convenient option of adjuvant regimen.

We designed a study named ACTS-CC (ACTS for Colon Cancer) to verify the non-inferiority of S-1 to UFT/LV, and thereby confirm the usefulness of adjuvant chemotherapy with S-1 for stage III CRC (ClinicalTrials.gov: no. NCT00660894). The primary endpoint is disease-free survival rate at 3 years after finishing enrolment. Enrolment started in April 2008 and was completed in June 2009. Final conclusions regarding the therapeutic usefulness of these regimens will be open in 2012. But, safety data of UFT/LV and S-1 from large trials with CRC is still unclear, although they are now widely used clinically in Japan. We therefore report the results of a planned interim analysis limited to the safety data in this study, to contribute to the safer use of these regimens in clinical practice.

MATERIALS AND METHODS

Enrolment and assignment

This study was conducted in accordance with the 'Declaration of Helsinki' and the 'Ethical Guidelines for Clinical Research', and was approved by the Institutional Review Boards of each participating institute. Written informed consent was obtained from all patients before enrolment.

Eligible patients were centrally registered by using a Web enrolment system. The main eligible criteria were as follows: aged 20–80 years, histologically confirmed stage III colon adenocarcinoma after curative surgery, starting chemotherapy within 8 weeks after surgery, performance status of 0–1, adequate oral intake, and preserved major organ functions.

Randomisation and masking

After confirming eligibility, enrolled patients were randomly assigned to receive either UFT/LV or S-1 at the central registration centre by a computer programme, by use of a minimisation method with stratification by lymph node metastasis (N1 or N2) and institution. Assignment of patients was concealed from the investigator. Treatment assignment was not masked from the investigators or patients.

Protocol treatment

In the UFT/LV arm, UFT was given at a dose of 300 mg m^{-2} per day as tegafur in three divided doses (every 8 h) more than 1 h after or before meals. A quantity of 75 mg per body per day of LV was given in three divided doses simultaneously with UFT. These drugs were orally administered for 28 consecutive days, followed by a 7-day rest. This 5-week treatment comprised one course. A total of five courses (25 weeks) were delivered.

In the S-1 arm, S-1 was orally given at a dose according to body surface area (BSA; 40 mg with BSA <1.25 m^2; 50 mg with BSA 1.25–1.5 m^2; 60 mg with BSA >1.5 m^2) twice daily after meals for 28 consecutive days, followed by a 14-day rest. This 6-week treatment comprised one course. A total of four courses (24 weeks) were delivered.

Assigned treatment was started within 8 weeks after surgery. During protocol treatment, clinical findings and laboratory values were evaluated every 2 to 3 weeks (evaluations at the time of starting each course were mandatory). Protocol treatment in each course was started and continued when the patients fulfilled the criteria included: leukocytes $\geqslant$3000/mm^3, platelets $\geqslant$100 000/mm^3, haemoglobin $\geqslant$9.0 g dl^{-1}, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant$100 IU l^{-1}, total bilirubin $\leqslant$2.0 mg dl^{-1}, creatinine $<$1.5 mg dl^{-1}, no greater than grade 1 anorexia, nausea, vomiting, and diarrhoea. If the criteria for starting/continuing treatment are not met, treatment was postponed or temporarily suspended until adverse events (AEs) had become to meet the criteria. Depending upon the severity of AEs, the dose of UFT or S-1 was reduced in accordance with the protocol when the treatment was resumed. Once the dose had been reduced, it was not to be increased at a later time. In the UFT/LV group, the dose of LV was not modified.

Protocol treatment was discontinued in the cases included: recurrence or other malignancies developed, treatment failed to be resumed within 14 days after being postponed or temporarily suspended (the pre-defined drug rest for each group is not included), further dose reduction was necessary because of AEs, and so on, even after the specified dose was reduced by two levels or to minimal dose level, the physician judged that the protocol treatment was difficult to continue, the patient requested discontinuation of protocol treatment, and the patients withdrew informed consent.

Data collection

Treatment status Physicians reported the treatment status (i.e., the number of days of administration in each course) by a Web-based case report system.

The drug compliance for each course was defined as the ratio of the actually taken dose to the prescribed dose, and was classified to the following four categories: (1) ⩾90% taken, (2) ⩾75% to <90% taken, (3) ⩾50% to <75% taken, and (4) <50% taken.

Using reported information in the case report form, taken dose per course was calculated for each patient as follows: (prescribed daily dose) × (number of days of administration) × (oral drug compliance for each course). Relative dose intensity for each patient was defined as the ratio of cumulative taken dose during the entire treatment period to scheduled total dose per protocol.

Completion rate of protocol treatment was defined as the ratio of the number of patients who completed four courses of S-1 treatment or five courses of UFT/LV treatment to the number of patients included in the safety analysis set of each group.

Safety profile The types and severities of AEs from the start of protocol treatment to 30 days after the last administration were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (National Cancer Institute, Bethesda, MD, USA). The most severe grade of each AE during each course was reported. The following AEs were required to report as 'priority survey items': leukocytes, haemoglobin, platelets, total bilirubin, AST, ALT, creatinine, stomatitis, anorexia, nausea, vomiting, diarrhoea, rash/desquamation, hyperpigmentation, and fatigue.

Statistical analysis

Data were analysed using SAS (Statistical Analysis System) version 9.1.2 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics such as means, s.d., and medians were calculated. The incidences of categorised discrete values were expressed as percentages for each group.

RESULTS

Patients' characteristics

From April 2008 through June 2009, a total of 1535 patients were enrolled from 358 hospitals in Japan. After excluding 31 patients because of the reasons shown in Figure 1, 1504 were included in the safety analysis (756 in the S-1 group and 748 in the UFT/LV group). The data were cut off on 11 August 2010. The characteristics of the 1504 patients are shown in Table 1.

Table 1 Patients' characteristics

		S-1		UFT/LV	
		n=756	(%)	*n*=748	(%)
Age (years)	Median (range)	66 (23–80)	—	65 (32–80)	—
	⩾70 years	279	(36.9)	252	(33.7)
Gender	Male	411	(54.4)	397	(53.1)
	Female	345	(45.6)	351	(46.9)
PS (ECOG)	0	720	(95.2)	716	(95.7)
	1	36	(4.8)	32	(4.3)
Tumour location	Right colon (C, A, T)	324	(42.9)	262	(35.0)
	Left colon (D, S)	277	(36.6)	309	(41.3)
	Rectosigmoid	155	(20.5)	177	(23.7)
Depth of tumour invasion (TNM 7th)	T1	40	(5.3)	46	(6.1)
	T2	76	(10.1)	77	(10.3)
	T3	428	(56.6)	425	(56.8)
	T4	212	(28.0)	200	(26.8)
Extent of LN dissection[a]	D1	5	(0.7)	5	(0.7)
	D2	142	(18.8)	150	(20.1)
	D3	609	(80.6)	593	(79.3)
No. of LN examined	Median (range)	18 (1–78)		16 (1-78)	
	<12	181	(24.1)	206	(27.5)
	⩾12	575	(75.9)	542	(72.5)
LN metastasis (TNM 7th)	N1a	330	(43.7)	325	(43.4)
	N1b	265	(35.1)	263	(35.2)
	N2a	116	(15.3)	113	(15.1)
	N2b	45	(6.0)	47	(6.3)
Stage (TNM 7th)	IIIA	105	(13.9)	118	(15.8)
	IIIB	550	(72.8)	516	(69.0)
	IIIC	101	(13.4)	114	(15.2)

Abbreviations: ECOG = The Eastern Cooperative Oncology Group; LN = lymph node; LV = leucovorin; PS = performance status. D1: complete dissection of pericolic/perirectal lymph nodes D2: complete dissection of pericolic/perirectal and intermediate lymph nodes D3: complete dissection of all regional lymph nodes. [a]Extent of lymph node dissection according to Japanese Classification of Colorectal Carcinoma.

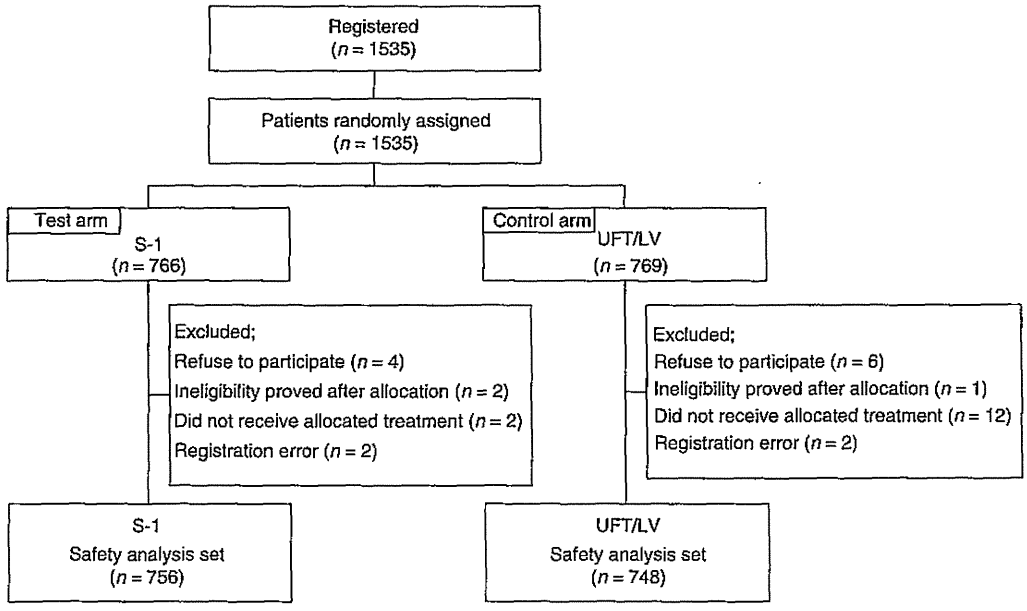

Figure 1 CONSORT diagram.

Treatment status

Completion rate of protocol treatment was 76.5% in the S-1 group and 73.4% in the UFT/LV group (Table 2). Discontinuation of protocol treatment was most common during course 1 and then decreased with courses. Among the 377 patients with discontinuation of the protocol treatments, 138 (77.5% of 178 discontinuation cases) in the S-1 group and 133 (66.8% of 199 discontinuation cases) in the UFT/LV group did within the first two courses (Table 2). Treatment discontinuation because of AEs was observed in 132 patients in the S-1 group and in 134 in the UFT/LV group. Among these patients, treatment was discontinued in 54 patients by the AEs listed in the discontinuation criteria of the protocol, in 34 by physician's decision for other than protocol criteria, and in 44 by patient's refusal related to AEs of the S-1 group, and in 67, 34, 41 of the UFT/LV group, respectively.

As for drug compliance, more than 90% of patients in both groups were reported to take '⩾90%' of prescribed dose for each course (Figure 2). The mean of relative dose intensity, including discontinuation cases, was 76.5% in the S-1 group and 76.0% in the UFT/LV group; the median was 95% in both groups.

Safety profile

A total of 605 patients (80.8%) in the S-1 group and 551 (73.7%) in the UFT/LV group experienced AEs (any grades). In all, 121 patients (16.0%) in the S-1 group and 108 (14.4%) in the UFT/LV group experienced ⩾grade 3 AEs. The incidences of AEs pre-specified as 'priority survey items' are shown in Table 3. The common AEs in any grades were anorexia, diarrhoea, fatigue, anaemia, and hyperbilirubinemia. Stomatitis, anorexia, rash/desquamation, hyperpigmentation, leukopenia, anaemia, and thrombocytopenia were more frequent in the S-1 group. Increased ALT and AST levels were more frequent in the UFT/LV group.

In the UFT/LV group, 5 patients (0.7%) experienced grade 4 increased ALT levels, and 3 (0.4%) had grade 4 increased AST levels (some overlap). One patient in the S-1 group had grade 4 increased AST level. All these events occurred during course 1.

Table 2 Discontinuation and completion of protocol treatment

	S-1		UFT/LV	
	n = 756	(%)	*n* = 748	(%)
No. of patients completed the protocol treatment	578	(76.5)	549	(73.4)
No. of patients with discontinuation	178	(23.5)	199	(26.6)
During course 1	86	(11.4)	78	(10.4)
During course 2	52	(6.9)	55	(7.4)
During course 3	37	(4.9)	34	(4.5)
During course 4	3	(0.4)	27	(3.6)
During course 5	—	—	5	(0.7)

Abbreviation: LV = leucovorin.

Table 3 Incidence of AEs for entire treatment period (worst grade)

	S-1 *n* = 756				UFT/LV *n* = 748			
	Any grades		⩾Grade 3		Any grades		⩾Grade 3	
Events	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Clinical findings								
Stomatitis	146	(19.3)	9	(1.2)	103	(13.8)	3	(0.4)
Anorexia	242	(32.0)	37	(4.9)	187	(25.0)	26	(3.5)
Nausea	166	(22.0)	12	(1.6)	142	(19.0)	9	(1.2)
Vomiting	48	(6.3)	6	(0.8)	58	(7.8)	6	(0.8)
Diarrhoea	177	(23.4)	33	(4.4)	178	(23.8)	41	(5.5)
Rash/Desquamation	114	(15.1)	2	(0.3)	75	(10.0)	4	(0.5)
Hyperpigmentation	201	(26.6)	—	—	95	(12.7)	—	—
Fatigue	208	(27.5)	18	(2.4)	186	(24.9)	11	(1.5)
Laboratory findings								
Leukocytes	136	(18.0)	5	(0.7)	93	(12.4)	3	(0.4)
Haemoglobin	246	(32.5)	7	(0.9)	199	(26.6)	1	(0.1)
Platelets	96	(12.7)	1	(0.1)	55	(7.4)	3	(0.4)
Total bilirubin	195	(25.8)	9	(1.2)	173	(23.1)	11	(1.5)
AST	114	(15.1)	6	(0.8)	152	(20.3)	16	(2.1)
ALT	100	(13.2)	8	(1.1)	160	(21.4)	25	(3.3)
Creatinine	36	(4.8)	0	(0)	34	(4.5)	4	(0.5)

Abbreviations: AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LV = leucovorin.

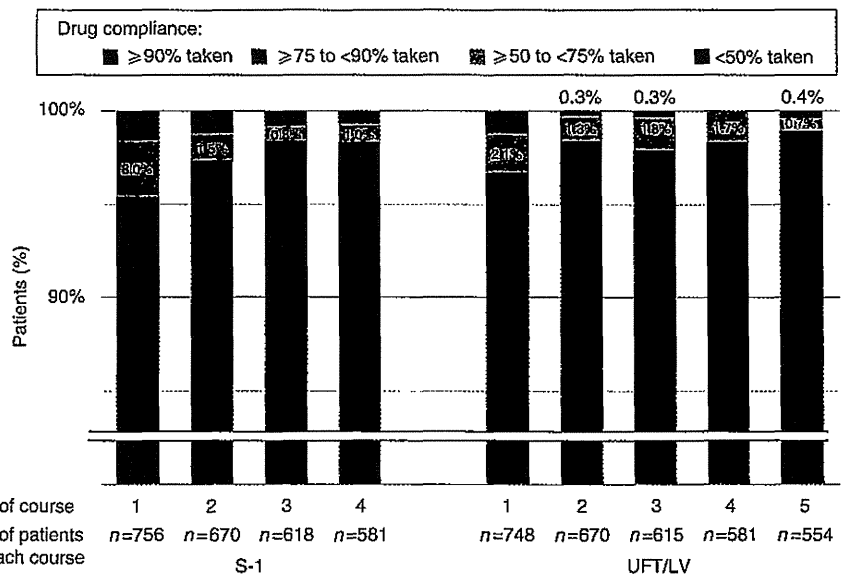

Figure 2 Drug compliance in each course. Each shaded region represents the percentage of patients receiving the indicated proportion of the scheduled dose per protocol in a given course. Abbreviation: LV = leucovorin.

Grade 4 haematological toxicities were as follows: anaemia in one patient, leukocytopenia in two, neutropenia in one in the S-1 group (some overlap), and anaemia in one patient in the UFT/LV group. Grade 3 neutropenia was developed in 10 patients (1.3%) in the S-1 group and 2 (0.3%) in the UFT/LV group.

The other common AEs in any grades were taste alteration (4.0% in the S-1 group and 3.2% in the UFT/LV group) and eye-related symptoms, including tearing, keratitis, and conjunctivitis (3.8% in the S-1 group and 0.4% in the UFT/LV group).

There were two deaths in the UFT/LV group, which was not ruled out to be related to the protocol treatment. One patient had diarrhoea leading to dehydration, metabolic acidosis, and acute respiratory distress syndrome during the first course. In the other patient, aspiration pneumonia associated with postoperative bowel obstruction, which developed during course 5, lead to respiratory failure.

DISCUSSION

This paper reported the results of an interim analysis of safety data obtained from the phase III study of 1504 patients with stage III colon cancer, who received postoperative adjuvant chemotherapy with UFT/LV or S-1.

The overall incidence of AEs (any grades) was 80.0% in the S-1 group and 73.7% in the UFT/LV group, and that of ⩾ grade 3 AEs were 16.0% and 14.4%, respectively. In short, about 80% of AEs were mild or moderate AEs such as grade 1 to 2. The completion rate of protocol treatment was favourable (76.5% in the S-1 group and 73.4% in the UFT/LV group), and treatment was discontinued in some patients during the early courses in both groups. Careful watch in early courses, adequate supportive care, and temporary suspension is important to complete the adjuvant chemotherapy with UFT/LV or S-1.

The present study is the first large trial of adjuvant chemotherapy with S-1 in patients with CRC. As compared, AEs of the S-1 group in this study with those of the ACTS-GC trial in which 1-year S-1 was used for adjuvant chemotherapy in GC (Sakuramoto *et al*, 2007), AE profiles in both trials were similar; the common AEs were anaemia, anorexia, diarrhoea, fatigue, and hyperpigmentation. However, the overall incidence of AEs was higher in the ACTS-GC trial. It may be because of the longer treatment duration of S-1 in the ACTS-GC trial. The proportion of patients who were in treatment at 6 months was similar: 77.9% in the ACTS-GC trial and 76.5% in this study.

On the other hand, potential racial differences of the tolerability for fluoropyrimidines had been reported (Haller *et al*, 2008). When the pharmacokinetics and pharmacodynamics of S-1 were compared between Caucasian and East Asian patients with solid malignancy including CRC, grade 3–4 gastrointestinal toxicities were more common in Caucasians than Asians, although exposure to 5-FU concentration was similar in both groups (Chuah *et al*, 2011).

In the NSABP C-06 trial (Lembersky *et al*, 2006), which was conducted in the United States, AEs in 774 patients who received UFT/LV was observed in 93.5% (⩾ grade 3, in 38.2%). Gastrointestinal toxicity (i.e., diarrhoea, nausea, and vomiting) was considerably less developed in this study, whereas the incidence of haematological toxicity was similar in both studies (Table 4). The difference of AE profiles between Japan and the United States of the bridging study of UFT/LV for unresectable CRC showed similar tendency (Shirao *et al*, 2004).

The UFT/LV treatment sometimes causes liver dysfunction (i.e., increased AST, ALT levels, and hyperbilirubinemia). In this study, five patients (0.7%) in the UFT/LV group had grade 4 liver dysfunction; all cases developed during course 1. The survey performed by the pharmaceutical company reported the similar observations of liver dysfunction caused by UFT, with the highest incidence within 2 months after start of treatment. Therefore, patients treated with UFT/LV are better to be watched carefully about liver dysfunction, and liver function is recommended to be regularly evaluated in early period in treatment.

Because of the different mechanisms of action between S-1 and UFT/LV, AE profiles were expected to differ between two groups. The common AEs were stomatitis, anorexia, rash/desquamation, hyperpigmentation, leukopenia, anaemia, and thrombocytopenia in the S-1 group, and increased ALT and AST levels in the UFT/LV group. Derivatives of 5-FU have been reported to cause keratoconjunctival epithelial disorders due to impaired DNA synthesis, which lead to secondary tear-duct occlusion accompanied by lacrimation (Hassan *et al*, 1998). This study disclosed that the incidence of eye-related symptoms differs between S-1 and UFT/LV. This study is designed to investigate mRNA expression levels and DNA copy numbers of 5-FU-related enzymes, and to clarify relationship between AEs profiles and the results

Table 4 Reported incidence of AEs with other regimens

	Lembersky *et al* (2006)				Twelves *et al* (2005)		André *et al* (2004)	
	UFT/LV ($n=774$)		i.v. 5-FU/LV[a] ($n=759$)		Capecitabine ($n=995$)		FOLFOX4 ($n=1108$)	
Events	Any grades (%)	⩾Grade 3 (%)	Any grades (%)	⩾Grade 3 (%)	Any grades (%)	⩾Grade 3 (%)	Any grades (%)	⩾Grade 3 (%)
Clinical findings								
Stomatitis	26	1.3	24	0.5	22	2	42	3
Nausea	54	7	65	7	36	3	74	5
Vomiting	28	4	31	7			47	6
Diarrhoea	75	29	79	29	46	11	56	11
Skin disorders	22[b]	1.3[b]	20[b]	1.1[b]	—	—	32[b]	2[b]
HFS	—	0.7	—	0.2	60	17	—	—
Paraesthesia	—	—	—	—	—	—	92	12
Laboratory findings								
Leukocytes	17	0	22	0.7	<10	—	—	—
Granulocytes	20	1.3	27	1.3	32	2	79	41
Haemoglobin	—	—	—	—	<10	—	76	0.8
Platelets	—	—	—	—	<10	—	77	1.7
Total bilirubin	7	0.3	4	—	50	20	—	—

Abbreviations: AEs = adverse events; FOLFOX = 5-FU/LV plus oxaliplatin; HFS = hand–foot syndrome; i.v. = intravenous; LV = leucovorin. [a]Treatment schedule reported from the Roswell Park Memorial Institute. [b]Including HFS.

of molecular study. When final results will be open, causes of different profiles of AEs will be disclosed.

The profiles and severity of AEs in this study were not worse than the reported AEs with other regimens of adjuvant chemotherapy (Table 4), and were acceptable. Hand–foot syndrome (HFS) was more common in capecitabine (Twelves *et al*, 2005), whereas ⩾grade 3 HFS in this study was 1.3% in the S-1 group and 0.9% in the UFT/LV group. Haematological toxicities were more common in the regimens containing oxaliplatin (André *et al*, 2004). As mentioned above, gastrointestinal toxicities were fewer in this study, possibly because of racial differences.

In conclusion, the present analysis showed that the AE profiles differed between UFT/LV and S-1, whereas the incidence of ⩾grade 3 AEs was low in both groups. The high completion rate of the protocol treatment with good drug compliance may indicate both regimens are acceptable treatment as adjuvant chemotherapy for CRC.

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Clinical Studies

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