Two randomized phase III trials of first-line chemotherapy for AGC [i.e., Japan Clinical Oncology Group (JCOG) 9205 and JCOG9912] conducted by the JCOG involved 5-fluorouracil continuous infusion (5-FUci) as the control arm. In JCOG9205, a combination of 5-FU plus cisplatin did not confer a survival benefit over 5-FUci alone; 5-FUci was regarded as standard chemotherapy in the 1990s [8]. Thereafter, monotherapy with S-1 exhibited non-inferiority to 5-FUci in JCOG9912 in the 2000s [9]. When these two trials are compared directly, the survival of the 5-FUci arm in JCOG9912 is longer than that in JCOG9205 [median survival times: 7.1 months (95 % confidence interval (CI), 5.8–8.2) vs. 10.8 months (95 % CI, 8.9–12.0), respectively].

The periods of patient accrual for JCOG9205 and JCOG9912 were 1992–1997 and 2000–2006, respectively. In Japan, after some new active agents such as S-1, irinotecan, paclitaxel, and docetaxel were approved for AGC in the late 1990s [10–14], they have been used not only in first-line chemotherapy but in second-line chemotherapy as well. The proportions of patients in the 5-FUci arms in JCOG9205 and JCOG9912 who received second-line chemotherapy were 53 and 78 %, respectively. It is speculated that second-line chemotherapy might have contributed to the prolongation of overall survival (OS) in JCOG9912 compared to JCOG9205.

However, survival is possibly affected by other factors including baseline factors. Furthermore, the details of regimens employed as second-line chemotherapy have not been reviewed in either trial. Therefore, it is necessary to adjust the patient backgrounds of JCOG9205 and JCOG9912 to assess the influence of second-line chemotherapy on survival.

This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival even after adjusting the baseline factors of patients who met the common eligibility criteria. If survival prolongation was evident, we aimed to investigate the underlying causes of survival prolongation.

Patients and methods

Patient population

The subjects in this combined analysis were the patients assigned to the 5-FUci arms in JCOG9205 ($N = 105$) and JCOG9912 ($N = 234$). The subjects were selected according to the following eligibility criteria of common to both trials: histologically confirmed unresectable or recurrent gastric adenocarcinoma; adequate self-supported nutrition intake; age 20–75 years; ECOG performance status 0, 1, or 2; no history of chemotherapy or radiotherapy; preserved organ functions; and written informed consent. Patients with intestinal stenosis, who were eligible in JCOG9205 but not JCOG9912, and those with a history of adjuvant chemotherapy, who were eligible in JCOG9912 but not JCOG9205, were excluded from this study.

In both trials, the protocol treatment was continuous infusion of 5-FU (800 mg m^{-2} day^{-1}) from day 1 to 5 repeated every 4 weeks until progressive disease or unacceptable toxicity was observed. The tumor response was evaluated by computed tomography and endoscopy every 4 and 8 weeks in JCOG9205 and JCOG9912, respectively.

The study protocol of this ad hoc combined analysis was approved by the Protocol Review Committee of the JCOG as well as the institutional review boards at the institutions of the study chair and study coordinator in compliance with the Japanese Ethical Guidelines for Clinical Studies.

Statistical analysis

The study endpoints were OS, time to treatment failure (TTF), survival after treatment failure (OS-TTF), the proportions of patients who received second-line chemotherapy, and the type of treatment regimens of second-line chemotherapy.

OS was counted from the date of randomization to the date of death from any cause or was censored at the date of the last follow-up for surviving patients. TTF was defined as the period from the date of randomization to the date of off-treatment from any cause (e.g., death, documentation of disease progression, adverse event, or patient refusal) or was censored at the date of last follow-up for surviving patients on treatment. OS-TTF was calculated by subtracting TTF from OS in each patient or censored in case of survival. OS-TTF was counted as 0 if the protocol treatment (i.e., first-line chemotherapy) was terminated because of death. OS, TTF, and OS-TTF were compared between JCOG9205 and JCOG9912 using the Cox proportional hazard model after adjusting the following baseline factors: age (<65 vs. ≥65 years), sex (male vs. female), performance status (PS, 0–2), macroscopic type (0–5) [15], histological type (intestinal vs. diffuse) [16], prior gastrectomy (+ vs. −), target lesion (+ vs. −), peritoneal metastasis (+ vs. −), and number of metastatic sites (0–2). Prognostic factors for OS-TTF were also analyzed using the Cox proportional hazard model. For Cox regression analysis, all variables were treated as categorical variables.

OS, TTF, and OS-TTF were estimated using the Kaplan–Meier method. All analyses were carried out with SAS release 9.1 (SAS Institute, Cary, NC, USA).

Results

Patients

The study schema is shown in Fig. 1. There were 105 and 234 patients assigned to the 5-FUci arms in JCOG9205 and JCOG9912, respectively. Sixteen and 4 patients in JCOG9205 and JCOG9912 were excluded from this combined analysis because they did not meet the eligibility criteria or had missing data. Finally, 319 patients, 89 from JCOG9205 and 230 from JCOG9912, were included in the combined analysis.

The patients' baseline characteristics are shown in Table 1. JCOG9912 contained more patients ≥65 years old, with better PS, and fewer metastatic sites and fewer patients with peritoneal metastasis compared to JCOG9205. Thus, there appear to be substantial differences in patient background between JCOG9205 and JCOG9912.

Reasons for treatment failure and second-line chemotherapy

The reasons for treatment failure in both trials were similar: disease progression or death in 84 % (disease progression, 68; death, 7/89) and 86 % (disease progression, 197; death, 1/230) in JCOG9205 and JCOG9912, respectively.

Second-line chemotherapy is summarized in Table 2. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 [83 % (190/230) vs. 52 % (46/89), respectively]. The drugs used in second-line chemotherapy largely differed between JCOG9205 and JCOG9912. In JCOG9912, regimens containing new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used as second-line chemotherapy in 178/190 patients (94 %). On the other hand, only 9/46 (20 %) patients received new-generation drugs in JCOG9205.

OS and OS-TTF

TTF adjusted by the Cox model did not differ significantly between trials [adjusted hazard ratio (HR), 0.95; 95 % CI, 0.73–1.26]. However, both OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912 (Fig. 2a–c).

Subgroup analyses by second-line chemotherapy are shown in Fig. 3. Among the patients with second-line chemotherapy, OS-TTF was remarkably longer in JCOG9912 than JCOG9205 (adjusted HR, 0.66; 95 % CI, 0.46–0.95). On the other hand, among the patients who did not receive second-line chemotherapy, OS-TTF was longer in JCOG9205 than JCOG9912 (adjusted HR, 1.37; 95 % CI, 0.74–2.53).

Multivariate analysis was performed to determine the prognostic factors for OS-TTF. PS ($p < 0.001$), gastrectomy ($p = 0.031$), peritoneal metastasis ($p = 0.015$), and number of metastatic sites ($p = 0.011$) were selected as the prognostic factors for OS-TTF (Table 3).

Discussion

Even after selecting patients on the basis of common eligibility criteria and adjusting baseline factors, the OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) of the 5-FUci arm was longer in JCOG9912 than JCOG9205.

We tried to align the two groups as much as possible to maximize comparability. Only the patients from the 5-FUci

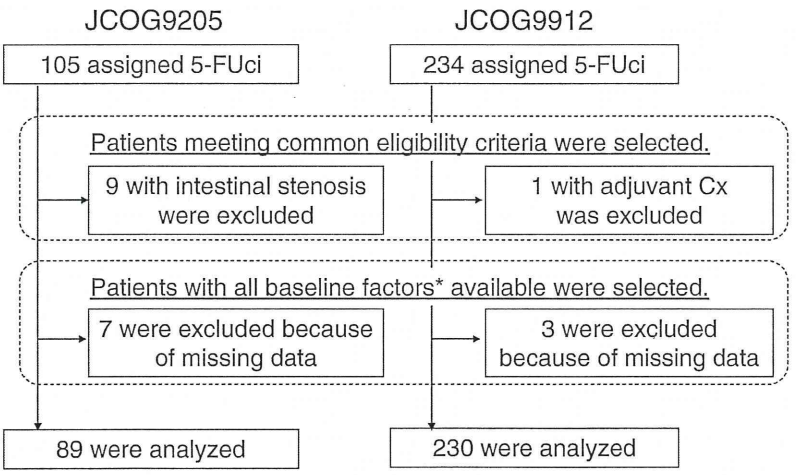

Fig. 1 Study profile. The baseline factors used in this study were age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *Cx* chemotherapy

Table 1 Patient characteristics

	JCOG9205		JCOG9912		*p* value[a]
No. of patients	89	%	230	%	
Age (years)					
Median (range)	63 (27–75)		63 (24–75)		0.4
<65	52	58	119	52	0.06
≥65	37	42	111	48	
Sex					
Male	63	71	172	75	0.48
Female	26	29	58	25	
PS[b]					
0	41	46	149	65	<.0001
1	33	37	78	34	
2	15	17	3	1	
Macroscopic type[c]					
0	0	0	5	2	0.75
1	5	6	8	4	
2	20	22	53	23	
3	45	51	120	52	
4	17	19	40	17	
5	2	2	4	2	
Histological type					
Intestinal	45	51	110	48	0.71
Diffuse	44	49	120	52	
Gastrectomy					
−	69	78	161	70	0.21
+	20	22	69	30	
Target lesions					
−	20	22	59	26	0.66
+	69	78	171	74	
Peritoneal metastasis					
−	76	85	143	62	<.0001
+	13	15	87	38	
Number of metastatic sites					
0	0	0	2	1	0.06
1	51	57	100	43	
≥2	38	43	128	56	

[a] All *p* values are two sided. The Wilcoxon rank-sum test was used to analyze continuous variables, and Fisher's exact test was used to analyze categorical data

[b] PS was evaluated at treatment initiation in JCOG9205 and at registration in JCOG9912

[c] Japanese Classification of Gastric Carcinoma

arms meeting the common eligibility criteria of both trials were analyzed, and baseline characteristics were adjusted in multivariate analysis. In addition, both trials were conducted by the same study group. The results show that TTF (adjusted HR, 0.95; 95 % CI, 0.73–1.26) and the reasons for treatment discontinuation did not differ between trials. This finding indicates that the impact of the first-line chemotherapy with 5-FUci on OS might be comparable between the two trials.

Table 2 Second-line chemotherapy

Second-line chemotherapy	JCOG9205		JCOG9912	
+	46	51.7 %	190	82.6 %
PTX, DTX, irinotecan, or S-1-containing regimen	9	10.1 %	178	77.4 %
PTX/DTX containing	2		60	
Irinotecan containing	6		100	
S-1 containing	1		29	
Other	37	41.6 %	12	5.2 %
5-FU/MTX	25		7	
5-FU/CDDP	6		0	
Other	6		5	
−	39	43.8 %	35	15.2 %
Unknown	4	4.5 %	5	2.2 %

PTX paclitaxel, *DTX* docetaxel, *CDDP* cisplatin, *MTX* methotrexate

To evaluate the effect of second-line chemotherapy, it would be ideal to estimate the time from the start of second-line chemotherapy to death. However, because we did not collect the start date of second-line chemotherapy in the case report form, we adopted OS-TTF as the endpoint. Survival post progression is another endpoint sometimes used to evaluate the effect of second-line chemotherapy. However, protocol treatment is sometimes terminated for reasons other than progression. Moreover, second-line chemotherapy is started before progression. Therefore, we considered OS-TTF to be a more suitable surrogate of the time from the start of second-line chemotherapy than survival post progression.

The present comparison between the two trials performed in different decades is considered to contain some bias. There have been many changes in patient management during this time, leading to better survival in the recent trial. Considering OS was longer in JCOG9912 than JCOG9205, even though TTF did not differ between trials, it can be speculated that patient management after treatment failure might have changed in the era of JCOG9912 compared to that of JCOG9205. One of the major changes that occurred was the availability of antitumor drugs in second-line chemotherapy. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 (83 vs. 52 %, respectively) (Table 2). In particular, new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used more frequently in JCOG9912 than JCOG9205 (77 vs. 10 %, respectively). Moreover, the improvements in OS and OS-TTF from JCOG9205 to JCOG9912 were only observed in the subset of patients who received second-line chemotherapy (HR, 0.66; 95 %

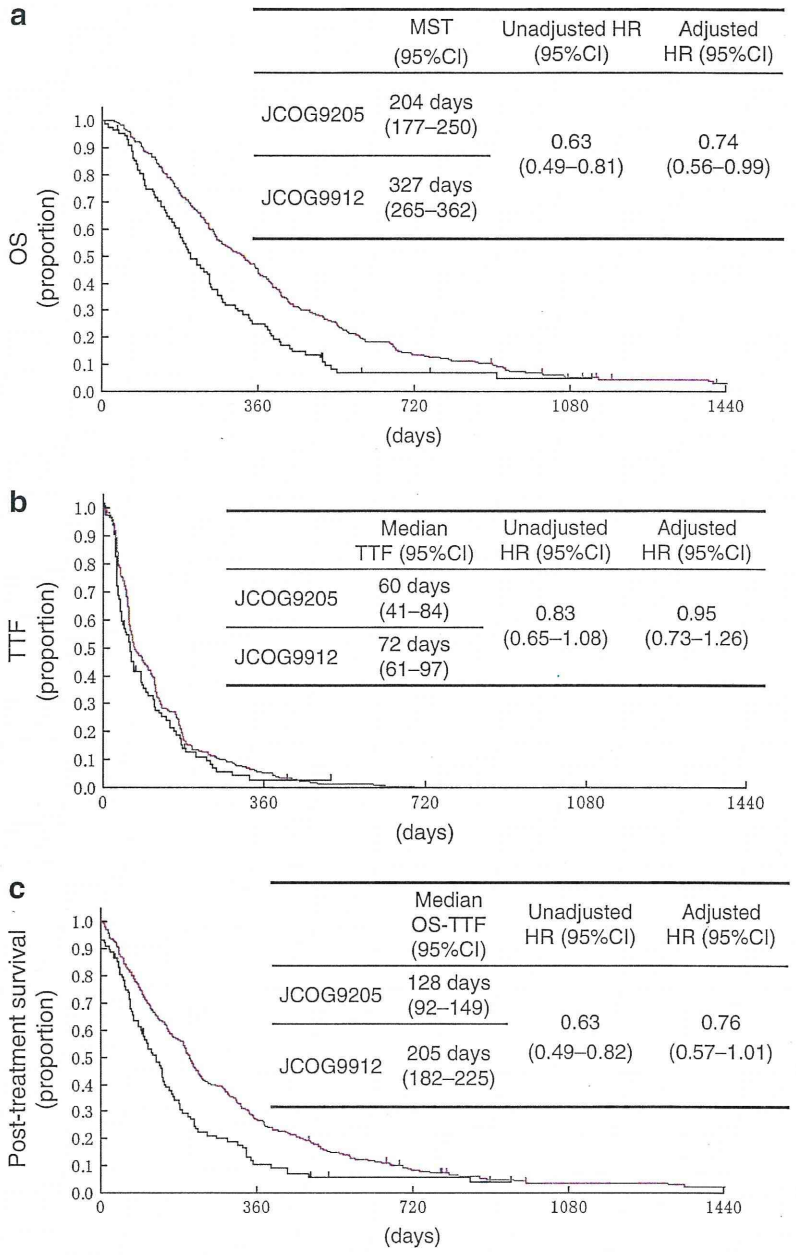

Fig. 2 Overall survival (OS) (**a**), time to treatment failure (TTF) (**b**), and OS-TTF (**c**). Seven patients and one patient in JCOG9205 and JCOG9912, respectively, who died during first-line chemotherapy, were considered to have events on day 0. Adjustment factors included patient age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *MST* median survival time, *OS* overall survival, *TTF* time to treatment failure

CI, 0.46–0.95) (Fig. 3). These results suggest second-line chemotherapy with new-generation drugs might have contributed to survival prolongation. Kawakami et al. [17] reported the post-progression survival (PPS) of AGC is significantly longer in trials published in 2006 or later than in those published before 2005 published trials (5.34 vs. 3.74 months, $p = 0.001$). The present results corroborate these previous results, further indicating the increasing availability of active drugs in subsequent therapies is a potential reason for the observed survival prolongation.

As mentioned in the Introduction, the survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials compared second-line chemotherapy and best supportive care in AGC (6, 7). The first trial compared best supportive care with irinotecan monotherapy [6]. Irinotecan-treated patients had significantly longer survival (median survival time, 4.0 vs. 2.4 months for patients receiving best supportive care alone; HR, 0.48; 95 % CI, 0.25–0.92). These results suggest second-line chemotherapy with irinotecan confers a survival benefit.

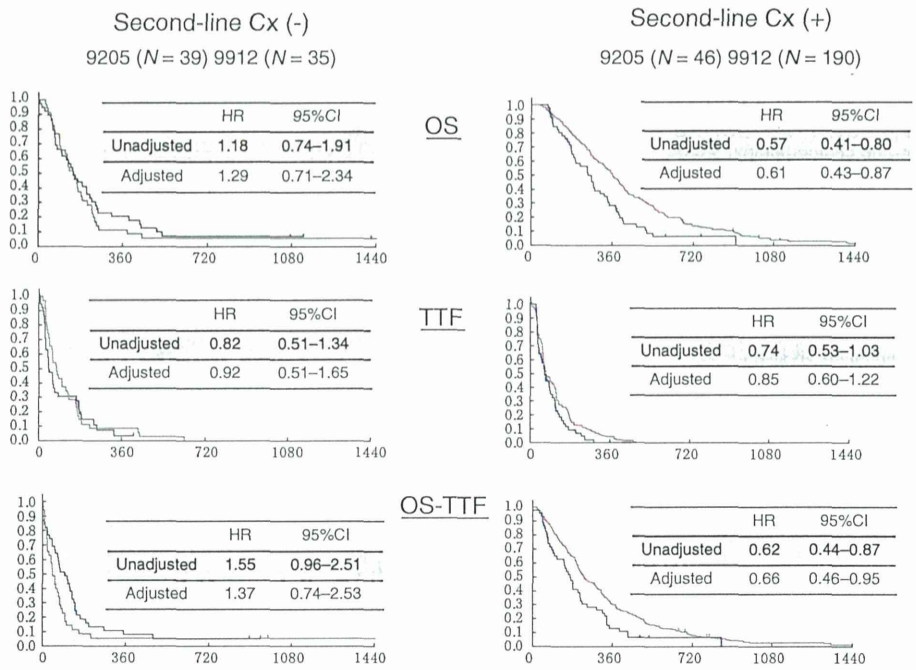

Fig. 3 Subgroup analyses according to the presence of second-line chemotherapy. Adjustment factors included age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and the number of metastatic sites. *Cx* chemotherapy, *MST* median survival time

Table 3 Mutivariate analysis of survival after treatment failure

	HR	95 % CI	*p* value
Trial			
JCOG9912 (vs. JCOG9205)	0.76	0.57–1.01	0.06
Age (years)			
≥65 (vs. ≤64)	1.04	0.82–1.31	0.77
Sex			
Male (vs. female)	0.84	0.63–1.10	0.20
Performance status (PS)			
PS1 (vs. 0)	1.51	1.17–1.95	<0.0001
PS2 (vs. 0)	3.67	2.11–6.37	
Macroscopic type			
1 (vs. 0)	0.61	0.20–1.85	0.63
2 (vs. 0)	0.53	0.21–1.37	
3 (vs. 0)	0.67	0.27–1.69	
4 (vs. 0)	0.61	0.23–1.64	
5 (vs. 0)	0.54	0.15–1.95	
Histological type			
Intestinal (vs. diffuse)	0.97	0.76–1.24	0.78
Gastrectomy			
+ (vs. −)	0.73	0.55–0.97	0.03
Target lesions			
+ (vs. −)	1.08	0.80–1.47	0.61
Peritoneal metastasis			
+ (vs. −)	0.70	0.52–0.93	0.01
Number of metastatic sites			
1 (vs. 0)	2.24	0.30–16.8	0.01
≥2 (vs. 0)	3.26	0.43–24.9	

However, the study was terminated early because of poor accrual. The second study, which compared treatment with irinotecan or docetaxel to best supportive care, also showed a survival benefit of second-line chemotherapy compared to best supportive care (median survival time, 5.3 vs. 3.8 months for patients receiving best supportive care alone; HR, 0.66; 95 % CI, 0.49–0.89) [7]. This result is currently the only evidence from a completed randomized trial justifying the use of second-line chemotherapy for AGC. Besides these two studies, the present results provide additional evidence supporting a survival benefit of second-line chemotherapy in AGC.

The present combined analysis has some limitations. There may be some other reasons for the prolongation of post-treatment failure survival in this analysis, including better general condition at treatment failure in JCOG9912, recent advances in supportive care, lead-time bias of diagnosis of metastasis, and unidentified baseline factors in first-line chemotherapy; however, these factors could not be adjusted in the analysis. In particular, prognostic factors at the failure of first-line chemotherapy that could strongly influence survival after treatment failure, such as PS, were not collected in either trial.

At present, regional differences in clinical outcomes between Asian and Western countries are major obstacles for conducting global trials for AGC [18]. Although better survival in Asian countries is considered to be mainly the result of a higher proportion of patients who receive second-line chemotherapy than in Western countries, the true reason for this difference remains unknown [19]. The

present study suggests "PS," "gastrectomy," "peritoneal metastasis," and "number of metastatic sites" are strongly associated with OS-TTF. These factors are well-known prognostic factors for OS in advanced gastric cancer patients undergoing first-line chemotherapy. Patient condition before both first- and second-line chemotherapy is speculated to substantially impact OS-TTF as well as OS. Therefore, when comparing OS and OS-TF among various regions, the aforementioned patient background characteristics should be considered in addition to second-line chemotherapy. Moreover, collecting the data of prognostic factors at the time of treatment failure is recommended in future trials to clarify the effect of survival after treatment failure.

In conclusion, the longer OS and OS-TTF in JCOG9912 than in JCOG9205, even after adjusting for baseline characteristics, suggest the increasing availability of active drugs (e.g., irinotecan, taxanes, etc.) in subsequent therapies is a potential reason for the observed survival prolongation.

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Conflict of interest The authors have declared no conflicts of interest.

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Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer

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Background: We evaluated the efficacy and safety of S-1 plus oxaliplatin (SOX) as an alternative to cisplatin plus S-1 (CS) in first-line chemotherapy for advanced gastric cancer (AGC).

Patients and methods: In this randomized, open-label, multicenter phase III study, patients were randomly assigned to receive SOX (80–120 mg/day S-1 for 2 weeks with 100 mg/m^2 oxaliplatin on day 1, every 3 weeks) or CS (S-1 for 3 weeks with 60 mg/m^2 cisplatin on day 8, every 5 weeks). The primary end points were noninferiority in progression-free survival (PFS) and relative efficacy in overall survival (OS) for SOX using adjusted hazard ratios (HRs) with stratification factors; performance status and unresectable or recurrent (+adjuvant chemotherapy) disease.

Results: Overall, 685 patients were randomized from January 2010 to October 2011. In per-protocol population, SOX ($n = 318$) was noninferior to CS ($n = 324$) in PFS [median, 5.5 versus 5.4 months; HR 1.004, 95% confidence interval (CI) 0.840–1.199; predefined noninferiority margin 1.30]. The median OS for SOX and CS were 14.1 and 13.1 months, respectively (HR 0.958 with 95% CI 0.803–1.142). In the intention-to-treat population (SOX, $n = 339$; CS, $n = 337$), the HRs in PFS and OS were 0.979 (95% CI 0.821–1.167) and 0.934 (95% CI 0.786–1.108), respectively. The most common ≥grade 3 adverse events (SOX versus CS) were neutropenia (19.5% versus 41.8%), anemia (15.1% versus 32.5%), hyponatremia (4.4% versus 13.4%), febrile neutropenia (0.9% versus 6.9%), and sensory neuropathy (4.7% versus 0%).

Conclusion: SOX is as effective as CS for AGC with favorable safety profile, therefore SOX can replace CS.

Clinical trial number: JapicCTI-101021.

Key words: advanced gastric cancer, oxaliplatin, cisplatin, S-1, phase III study

introduction

Combination therapies using cisplatin and fluoropyrimidines with or without epirubicin or docetaxel have been widely used as first-line treatments for advanced gastric cancer (AGC) [1–4]. The German Arbeitsgemeinschaft Internistische Onkologie (AIO) trial showed that 5-fluorouracil (5-FU)/leucovorin plus oxaliplatin treatment was equivalent to 5-FU/leucovorin plus cisplatin treatment [5]. The randomized two-by-two phase III study (REAL-2) of triplet therapy of epirubicin, 5-FU or capecitabine, and cisplatin or oxaliplatin for advanced esophagogastric cancer showed that oxaliplatin was as effective as cisplatin with respect to overall survival (OS) and progression-free survival (PFS) [6].

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S-1 is an oral anticancer preparation that combines tegafur, a pro-drug of 5-FU, with two modulators, i.e. gimeracil and oteracil [7]. Phase III clinical trials showed that S-1 was noninferior to 5-FU, and that cisplatin plus S-1 (CS) was superior to S-1 (SPIRITS trial) [8, 9]. CS is regarded as a standard first-line treatment of AGC in Japan. A phase III study (FLAGS) suggested that CS could be a substitute for 5-FU plus cisplatin as first-line chemotherapy for AGC [10, 11]. A phase II trial of first-line chemotherapy with S-1 plus oxaliplatin (SOX) yielded promising outcomes, a median PFS and OS of 6.5 and 16.5 months, respectively, with good tolerability [12]. To confirm and extend these results, we carried out a phase III study comparing SOX with CS as first-line chemotherapy for AGC.

methods

patients

The main eligibility criteria included histologically proven, curatively unresectable, advanced or recurrent gastric cancer, age ≥20 years, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, the presence of measurable lesions as confirmed by computed tomography (CT), no previous chemotherapy or radiotherapy, oral intake capability, adequate function of the major organs, and written informed consent of the patient. The main exclusion criteria were active infection, serious concurrent disease, markedly impaired cardiac function, gastrointestinal bleeding, sensory neuropathy, serious diarrhea, ascites beyond the pelvic cavity or pleural effusion, a history of blood transfusion within 3 weeks before enrollment, interstitial pneumonia, or previous treatment with platinum as adjuvant chemotherapy.

This study was carried out according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Each hospital's institutional review board approved this study protocol.

study design

This study was a prospective, multicenter, randomized, open-label, parallel-group phase III clinical trial conducted at 51 centers in Japan. Eligible patients were centrally randomized to CS or SOX in a 1 : 1 ratio, considering the institution, PS, and unresectable or recurrent disease with or without postoperative adjuvant chemotherapy as adjustment factors using the minimization method [13]. The randomization sequence was generated by an independent team from the trial sponsor and investigators. Enrollment was done by a local principal or subinvestigator via a web-based system, which automatically assigned either treatment to a patient. The allocated study treatments were not masked from the patients and investigators.

treatment

In CS, S-1 was given orally twice daily for the first 3 weeks of a 5-week cycle. The dose was 80 mg/day for body surface area (BSA) <1.25 m^2, 100 mg/day for BSA ≥1.25 to <1.5 m^2, and 120 mg/day for BSA ≥1.5 m^2. Cisplatin was administered at 60 mg/m^2 as an i.v. infusion with adequate hydration on day 8 of each cycle [9]. In SOX, S-1 was given as the same way for the first 2 weeks of a 3-week cycle. Oxaliplatin at 100 mg/m^2 was infused for 2 h i.v. on day 1 of each cycle [12]. The treatments were continued until one of the criteria for withdrawal of the study treatment was encountered.

In both treatment groups, the dose of each drug was reduced to ~80%, if the neutrophil count was <500/mm^3, the platelet count was <25 000/mm^3 or ≥grade 3 febrile neutropenia, diarrhea, stomatitis, or hand-foot syndrome developed. In CS, the dose of cisplatin was reduced in the event of grade 3 anorexia suspected to be caused by cisplatin. In SOX, the dose of oxaliplatin was reduced if the platelet count was <75 000/mm^3 on day 29 when the treatment was delayed for a week, or grade 2 sensory neuropathy developed on the first day of a cycle (supplementary Tables S1–S3, available at *Annals of Oncology* online).

assessments

PFS was defined as the time from the randomization to documented progressive disease (PD) or death without prior PD, whichever came first. Patients who were alive and free of progression (i.e. second-line treatment was started due to any cause) were regarded as censored cases at the date of the last assessment. Lesions were evaluated by CT at the baseline and every 6 weeks from the randomization to the initiation of second-line treatment. The assessments were done under the same imaging way as the baseline in all patients. All images for PFS and tumor responses were reviewed by an independent review committee, according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 [14]. OS was defined as the interval from the date of randomization to the date of death from any cause or the last follow-up date. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE version 3.0).

statistical considerations

We aimed to assess two primary end points. One primary end point was to demonstrate noninferiority in PFS for SOX compared with CS which was used for sample size determination. The other primary end point was to evaluate the relative efficacy in OS between SOX and CS. The noninferiority analysis was carried out in the per-protocol population. The noninferiority margin in PFS was defined at 1.30 in reference to the results of SPIRITS trial and phase II study of SOX (supplementary Appendix A1, available at *Annals of Oncology* online). Since the required number of events was estimated as 456 with a one-sided α value of 0.025 and a power of 80%, we estimated that 600 patients would be needed to achieve the required number of events within the patient accrual (1.5 years) and follow-up periods (1 year after the last patient randomization). In February 2011, it appeared to be difficult to achieve the required number of events within the preplanned timetable, and the target number of patients was revised to 680 according to the predefined procedure in the protocol. For OS, the noninferiority margin was defined to be 1.15 as a guide of evaluation. The number of events required for OS analysis was set as 508 with a one-sided α value of 0.025 and a power of 80% when median OS for SOX and CS were expected as 14.5 and 13.0 months, respectively.

Time-to-events were analyzed using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the stratified Cox proportional hazards model. The stratification factors were unresectable or recurrent disease, with or without postoperative adjuvant chemotherapy, and PS of 0, 1, or 2, excluding institution from adjustment factors in randomization. We also did the analyses in the intention-to-treat (ITT) population: all randomized patients excluding patients who took no trial medication. In exploratory analyses, subgroup efficacy and multivariate analyses were carried out on stratification factors and demographic factors in the Cox proportional hazards model. Statistical analyses were carried out using SAS v9.1.3.

results

patients disposition and characteristics

From 14 January 2010 through 17 October 2011, 685 patients were enrolled; 343 and 342 patients were randomly assigned to SOX or CS (Figure 1). The demographic characteristics in the per-protocol population were well balanced between SOX and CS (Table 1).

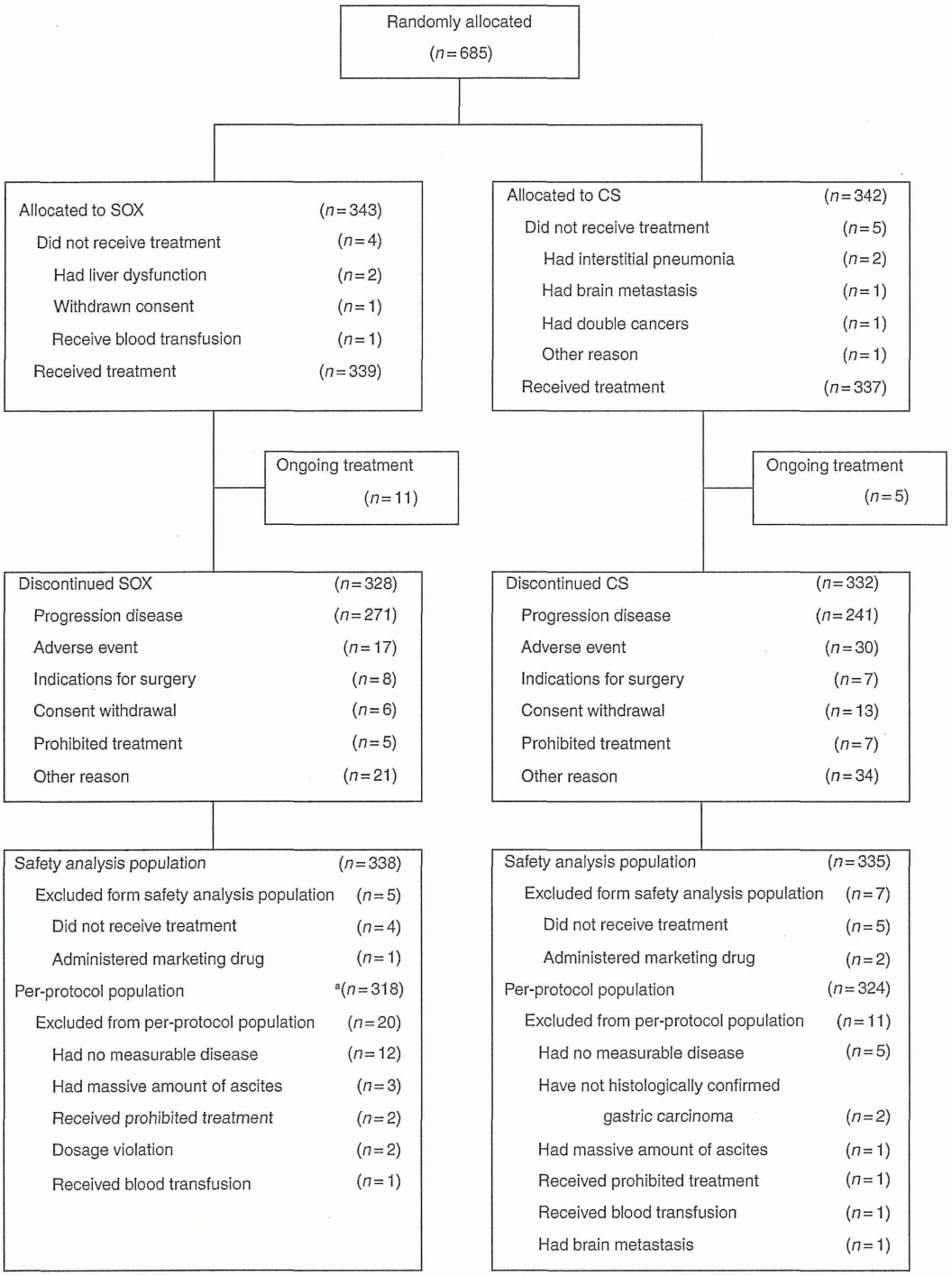

Figure 1. CONSORT diagram. [a]After PFS analysis was fixed, it was verified that one patient did not have gastric carcinoma. This patient was excluded from OS analysis but included in safety analyses because some cycles of assigned treatment were given. SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1.

treatment delivery

The median treatment cycles in SOX and CS were 7.0 (range 1–43) and 5.0 (range 1–19), respectively. The relative dose intensity was 79.0% [interquartile range (IQR), 62.3–95.1] for oxaliplatin and 78.9% (IQR 65.9–91.3) for S-1 in SOX; it was 80.7% (IRQ 64.2–94.6) for cisplatin and 79.8% (IQR 68.1–90.9) for S-1 in CS.

In SOX, 261 of 308 (84.7%) patients who discontinued treatment received second-line chemotherapies: taxanes-containing regimens in 131 of 261 (50.2%) patients, irinotecan-containing

Table 1. Baseline characteristics

	Treatment		
	SOX ($N = 318$)	CS ($N = 324$)	P^a
Gender			
Male	240 (75.5)	237 (73.1)	0.50
Female	78 (24.5)	87 (26.9)	
Age (years)	65 (21–83)	65 (29–85)	–
ECOG performance status			
0	224 (70.4)	228 (70.4)	0.94
1	91 (28.6)	92 (28.4)	
2	3 (0.9)	4 (1.2)	
Unresectable	261 (82.1)	272 (84.0)	0.78
Recurrent	57 (17.9)	52 (16.0)	
Adjuvant chemotherapy (+)	29 (9.1)	25 (7.7)	
Adjuvant chemotherapy (−)	28 (8.8)	27 (8.3)	
Tumor histology			
Intestinal	144 (45.3)	145 (44.8)	0.89
Diffuse	174 (54.7)	179 (55.2)	
Primary tumor			
−	74 (23.3)	72 (22.2)	0.75
+	244 (76.7)	252 (77.8)	
No. of metastatic sites			
1	102 (32.1)	101 (31.2)	0.97
2	136 (42.8)	141 (43.5)	
≥3	80 (25.2)	82 (25.3)	
Metastatic site[b]			
Liver	124 (39.0)	129 (39.8)	
Lung	36 (11.3)	35 (10.8)	
Lymph node	290 (91.2)	287 (88.6)	
Peritoneal	61 (19.2)	64 (19.8)	

Data are presented as *n* (%) or median (range).
[a]χ^2 test; comparing proportion of each characteristic.
[b]Patients can be included in more than one category.
SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ECOG, Eastern Cooperative Oncology Group.

regimens in 87 of 261 (33.3%) patients, and S-1-containing regimens in 20 of 261 (7.7%) patients. In CS, 269 of 319 (84.3%) patients who discontinued treatment received second-line chemotherapies: taxanes-containing regimens in 102 of 269 (37.9%) patients, irinotecan-containing regimens in 84 of 269 (31.2%) patients, and S-1-containing regimens in 46 of 269 (17.1%) patients. Other details are shown in supplementary Appendix A2, available at *Annals of Oncology* online.

efficacy

The median follow-up for PFS was 6.9 months (IQR 2.9–9.6). The median PFS in SOX and CS were 5.5 months (95% CI 4.4–5.7, 260 events) and 5.4 months (95% CI 4.2–5.7, 249 events), respectively (Figure 2A). The HR was 1.004 (95% CI 0.840–1.199, $P_{\text{noninferiority}} = 0.0044$), and the upper limit of 95% CI was less than the noninferiority margin of 1.30.

The median follow-up for OS was 25.9 months (IQR 21.0–29.2). The median OS in SOX and CS were 14.1 months (95% CI 13.0–15.8, 249 events) and 13.1 months (95% CI 12.1–15.1, 259 events), respectively (Figure 2B). The HR was 0.969 (95% CI 0.812–1.157). However, one eligible patient was not included in the stratified analysis. The analysis including all eligible patients resulted in giving that the HR was 0.958 (95% CI 0.803–1.142) (supplementary Appendix A3, available at *Annals of Oncology* online). In the ITT population (SOX, $n = 339$; CS, $n = 337$), the HRs in PFS and OS evaluated by stratified Cox regression with combining stratum were 0.979 (95% CI 0.821–1.167) and 0.934 (95% CI 0.786–1.108), respectively.

The response rate and disease control rate were 55.7% and 85.2% (2 complete response, 175 partial response, and 94 stable disease) in SOX, and 52.2% and 81.8% (4 complete response, 165 partial response, and 96 stable disease) in CS, respectively. The median time from the randomization to the first date that documented to reach 30% tumor reduction were 1.5 months (95% CI 1.4–2.5) in SOX and 1.5 months (95% CI 1.4–1.6) in CS.

Figure 3 summarizes the subgroup analysis of OS. SOX showed significantly longer OS in patients with peritoneal metastasis. Multivariate analyses showed that ECOG PS (1, 2), unresectable disease, diffuse-type, and sum of tumor diameter (≥median) correlated with poor prognosis in OS. The adjusted HR in treatment efficacy for OS was 0.955 (95% CI 0. 802–1.138) (Table 2).

safety

Table 3 summarizes the main adverse events in the safety analysis population. Grade 3 or worse leukopenia, neutropenia, anemia, febrile neutropenia, and hyponatremia were more frequently seen in CS than in SOX. Grade 3 or worse sensory neuropathy was more frequently observed in SOX than in CS. There were no remarkable differences in the incidence of thrombocytopenia between the treatment groups. Grade 3 or worse febrile neutropenia in CS was seen in 12/111 (10.8%) of patients with a creatinine clearance (Ccr) <70 ml/min and 11/224 (4.9%) of patients with Ccr ≥70 ml/min; and in SOX, in 3/113 (2.7%) of patients with Ccr <70 ml/min and 0/225 (0%) of patients with Ccr ≥70 ml/min. Further, grade 3 or worse febrile neutropenia in CS was seen in 12/234 (5.1%) of patients aged <70 years and 11/101 (10.9%) of patients aged ≥70 years; and in SOX, in 1/224 (0.4%) of patients aged <70 years and 2/114 (1.8%) of patients aged ≥70 years. Serious adverse events were more frequently observed in CS than in SOX [127 (37.9%) versus 99 (29.3%), $P = 0.017$]. There were 12 treatment-related deaths (8 in CS and 4 in SOX).

discussion

This randomized phase III study for AGC showed that SOX was noninferior to CS in terms of PFS and OS. As far as we know, this is the first large comparative study of the oxaliplatin plus S-1 doublet with CS. The results of CS in the present study are similar to those observed in the SPIRITS trial that demonstrated the superiority of CS (median PFS 6.0 months and median OS 13.0 months) to S-1, and this suggests the robustness of our results for noninferiority [9].

The adverse events observed for CS and SOX were consistent with previously reported results. Notably, in the present study,