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ORIGINAL ARTICLE

Comparison of S-1–cisplatin every 5 weeks with capecitabine-cisplatin every 3 weeks for HER2-negative gastric cancer (recurrent after S-1 adjuvant therapy or chemotherapy-naïve advanced): pooled analysis of HERBIS-2 (OGSG 1103) and HERBIS-4A (OGSG 1105) trials

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Abstract

Background We previously reported the HERBIS-4A phase II trial comparing S-1 plus cisplatin (SP) with capecitabine plus cisplatin (XP) in chemotherapy-naïve patients with HER2-negative advanced gastric cancer (GC). We performed a pooled analysis of HERBIS-4A and HERBIS-2, the phase II trial comparing SP with XP in HER2-negative recurrent GC patients with a recurrence-free interval after S-1 adjuvant therapy of ≥ 6 months.

Patients and methods Patients were randomly assigned to receive either SP [S-1 (40–60 mg twice daily for 21 days) plus cisplatin (60 mg/m^2 on day 8), every 5 weeks] or XP [capecitabine (1000 mg/m^2 twice daily for 14 days) plus cisplatin (80 mg/m^2 on day 1), every 3 weeks].

Results In the pooled analysis, SP (n = 44–50) showed a longer progression-free survival [6.4 versus 5.1 months; hazard ratio (HR), 0.666; P = 0.062], overall survival (14.8 versus 10.6 months; HR, 0.695; P = 0.099), and time to treatment failure (4.6 versus 3.6 months; HR, 0.668; P = 0.045) as well as a higher disease control rate (86.4% versus 68.1%, P = 0.149) compared with XP (n = 47–51). A significant survival advantage for SP over XP was apparent in patients with a performance status of 0, a differentiated-type tumor histology, or a primary tumor localization to the upper portion of the stomach.

Conclusion Our pooled analysis supports the use of SP in the first-line setting for patients with HER2-negative advanced or recurrent GC with a recurrence-free interval of ≥ 6 months.

Clinical trial registration The HERBIS-2 trial was registered with UMIN-CTR as UMIN000006105.

Keywords Advanced gastric cancer · Recurrent gastric cancer · S-1 · Capecitabine · Cisplatin

Introduction

Gastric cancer (GC) is the second leading cause of cancer death worldwide and the fifth most common malignant disease [1]. Newly diagnosed GC patients often present with unresectable or metastatic disease, for which systemic chemotherapy is the standard of care. For human epidermal growth factor receptor 2 (HER2)–negative disease, which accounts for most cases of advanced GC, such treatment usually consists of doublet chemotherapy with a fluoropyrimidine such as S-1 or capecitabine combined with a platinum agent such as cisplatin or oxaliplatin, whereas trastuzumab in combination with such doublet chemotherapy is the standard treatment for HER2-positive GC [2].

On the basis of the results of the phase III trials JCOG9912 [3] and SPIRITS [4], S-1 plus cisplatin (SP) has become accepted as a standard first-line therapy for HER2-negative advanced GC in Japan. On the other hand, capecitabine plus cisplatin (XP), another standard chemotherapy

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in this setting [5], has been adopted as a standard backbone chemotherapy regimen for combination in several global phase III trials for advanced GC [2, 6, 7]. Against this background, we previously conducted a phase II study, HERBIS-4A, to directly compare SP and XP in chemotherapy-naïve Japanese patients with HER2-negative advanced GC and measurable lesions [8]. XP did not show superior efficacy relative to SP in this trial, providing further support for SP as the preferred first-line chemotherapy for HER2-negative advanced GC in Japan.

On the basis of the results of the ACTS-GC trial [9], S-1 monotherapy for 12 months is the standard treatment for stage II or III GC after curative resection in Japan. The optimal treatment strategy for such patients with recurrent disease after S-1 adjuvant therapy has been unclear, however. A retrospective analysis of patients with recurrent GC after S-1 adjuvant therapy found that those treated with SP achieved a median progression-free survival (PFS) and overall survival (OS) of 4.8 and 12.2 months, respectively. The survival benefit of SP was greater in patients with a recurrence-free interval (RFI) of ≥ 6 months than in those with an RFI of < 6 months, with a median PFS of 6.2 versus 2.3 months and a median OS of 16.6 versus 7.3 months, respectively [10]. On the basis of these findings, SP is administered preferentially in recurrent GC patients with an RFI of ≥ 6 months in Japan. On the other hand, XP showed reasonable efficacy in recurrent GC patients with an RFI of < 6 months after S-1 adjuvant therapy in a phase II trial (XParTS-1) [11], yielding a median PFS and OS of 4.4 and 13.7 months, respectively. However, the efficacy of XP—in particular, in relation to that of SP—in recurrent GC patients with an RFI of ≥ 6 months after S-1 treatment is unclear.

To answer this clinical question, we conducted the HERBIS-2 trial, in which SP and XP were compared in recurrent GC patients with an RFI of ≥ 6 months after S-1 adjuvant therapy. Furthermore, we performed a pooled analysis of the HERBIS-2 and HERBIS-4A trials to better understand the differences between SP and XP for patients with chemotherapy-naïve advanced GC or recurrent GC patients with an RFI of ≥ 6 months after S-1 adjuvant therapy.

Patients and methods

Study design and treatment

The Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 1103 (HERBIS-2) study was designed as an open-label, multicenter, randomized phase II trial to compare the efficacy and safety of XP and SP in HER2-negative recurrent GC patients with an RFI of ≥ 6 months after completion of S-1 adjuvant therapy. The study protocol was approved by the OGSG and the institutional review board of each participating institution. Written informed consent was provided by all participants before inclusion in the trial. This study was registered with UMIN-CTR as UMIN000006105. The study design for HERBIS-4A was described previously [8].

For both HERBIS-2 and HERBIS-4A studies, randomization was stratified by institution and by Eastern Cooperative Oncology Group (ECOG) performance status (PS, 0 versus 1 or 2). Patients received either SP (S-1 at 40–60 mg twice daily for 21 days plus cisplatin at 60 mg/m^2 on day 8, every 5 weeks) or XP (capecitabine at 1000 mg/m^2 twice daily for 14 days plus cisplatin at 80 mg/m^2 on day 1, every 3 weeks) until progression or the development of intolerable toxicity.

Patients

For HERBIS-2, eligible patients were aged 20 years or older and had HER2-negative recurrent GC after treatment with adjuvant chemotherapy including S-1 for > 12 weeks, with relapse occurring ≥ 6 months after completion of such therapy. HER2 positivity was defined as 3 + staining by immunohistochemistry or as *HER2* gene amplification (*HER2:CEP17* signal ratio of ≥ 2.0) as detected by hybridization. Eligible patients were also required to have an ECOG PS of 0–2 as well as adequate bone marrow, cardiac, hepatic, and renal function. Detailed information for the HERBIS-4A trial was provided previously [8].

End points and assessments

The primary end point of HERBIS-2 was OS, with secondary end points including response rate (RR), PFS, time to treatment failure (TTF), and safety. Tumor response and progression were assessed according to RECIST (version 1.1) at baseline and every 8 weeks from randomization until disease progression. RR was defined as the proportion of patients who achieved a confirmed complete or partial response. Tumor histology was determined on the basis of the Japanese classification of GC [12], with differentiated-type tumors being defined as papillary or tubular adenocarcinoma and undifferentiated-type tumors as poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Detailed information for the HERBIS-4A trial was provided previously [8].

Statistical analysis

The planned sample size for HERBIS-2 was initially 80 randomized patients on the basis of an expected 1-year OS rate for SP and XP of 54–70%, respectively, and with a one-sided

significance level (α) of 0.10 and power of 0.80. However, as a result of slow accrual, enrollment was terminated after the inclusion of 20 patients in April 2016.

Survival curves were estimated by the Kaplan–Meier method. The stratified log-rank test with strata of allocation factors other than institution and with or without measurable lesions was applied for comparison of survival curves between arms. Hazard ratios (HRs) and their confidence intervals (CIs) were calculated with a Cox proportional hazards model. The RR was compared between arms with Fisher's exact test. Efficacy outcomes were assessed in the full analysis set (FAS), which consists of all randomized patients with the exception of those who were found to be ineligible after enrollment but before treatment. Toxicity was evaluated in the per protocol set (PPS), which was defined as all patients in the FAS who received treatment at least once and had no major protocol violations. All statistical analysis was performed with the use of R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC). A P value of <0.05 was considered statistically significant.

Results

Pooled analysis for HERBIS-2 and HERBIS-4A

The detailed results of HERBIS-2 are shown in Supplementary material. For pooled analysis, patients who were found to be ineligible after enrollment but before treatment were excluded. A total of 101 patients was therefore included in the FAS, with the SP and XP arms including 50 and 51 patients, respectively (Table 1). For the PPS, two patients were excluded from the SP arm of HERBIS-4A for not receiving any treatment as a result of withdrawal from the study. For RR analysis, four patients in each of the SP and XP arms of HERBIS-2 were excluded for not having measurable lesions (Fig. 1).

The RR was 54.5% (95% CI, 38.8–69.6%) versus 51.1% (95 % CI, 36.1–65.9%) in the SP and XP arms, respectively ($P=1.000$). The disease control rate was higher in the SP arm [86.4% (95% CI, 72.6–94.8%)] than in the XP arm [68.1% (95 % CI, 52.9–80.9%)], although the difference was not statistically significant ($P=0.149$) (Table 2). Waterfall plot analysis for the 84 evaluated patients ($n=42$ in each arm) also revealed a trend toward better disease control in the SP arm (Fig. 2).

The median PFS in the FAS was 6.4 months (95 % CI 4.6–9.3 months) and 5.1 months (95% CI, 3.9–7.7 months) for the SP and XP arms, respectively [HR of 0.666 (95 % CI, 0.435–1.020), $P=0.062$] (Fig. 3a). The difference in median PFS between the SP arm [6.8 months (95 % CI 4.6–9.3 months)] and the XP arm [5.1 months (95 % CI 3.9–7.7 months)] was statistically significant among the PPS [HR of 0.632 (95 % CI 0.410–0.973), $P=0.0037$] (Fig. 3b). For the FAS, median OS in the SP arm [14.8 months (95 % CI 11.5–23.0 months)] tended to be longer than that in the XP arm [10.6 months (95 % CI 7.6– 15.6 months); HR

Table 1 Baseline characteristics of patients in the SP and XP arms for the FAS of the combined analysis of HERBIS-2 and HERBIS-4A

Characteristic	SP ($n=50$)	XP ($n=51$)
Age (years)		
Median	68	65
Range	37–78	34–79
Sex		
Male/female	39/11	42/9
ECOG PS		
0/1	28/22	31/20
Primary tumor site		
Upper	10	17
Middle	26	14
Lower	14	20
Tumor histological type		
Papillary	0	0
Tubular	25	24
Poorly differentiated	20	24
Signet ring cell	3	1
Mucinous	1	2
Undetermined	1	0
T factor at diagnosis		
TX	1	1
T1 (SM)	0	1
T2 (MP)	6	1
T3 (SS)	12	11
T4a (SE)	25	27
T4n (SI)	6	10
N factor at diagnosis		
NX	0	1
N0	4	7
N1 (1–2)	5	10
N2 (3–6)	13	17
N3a (7–15)	20	10
N3b (≥16)	8	5
Missing	0	1
M factor at diagnosis		
MX	2	1
M0	15	12
M1	33	38
Prior gastrectomy		
Yes/no	15/35	10/41
Number of metastases		
1	30	24
≥2	20	27

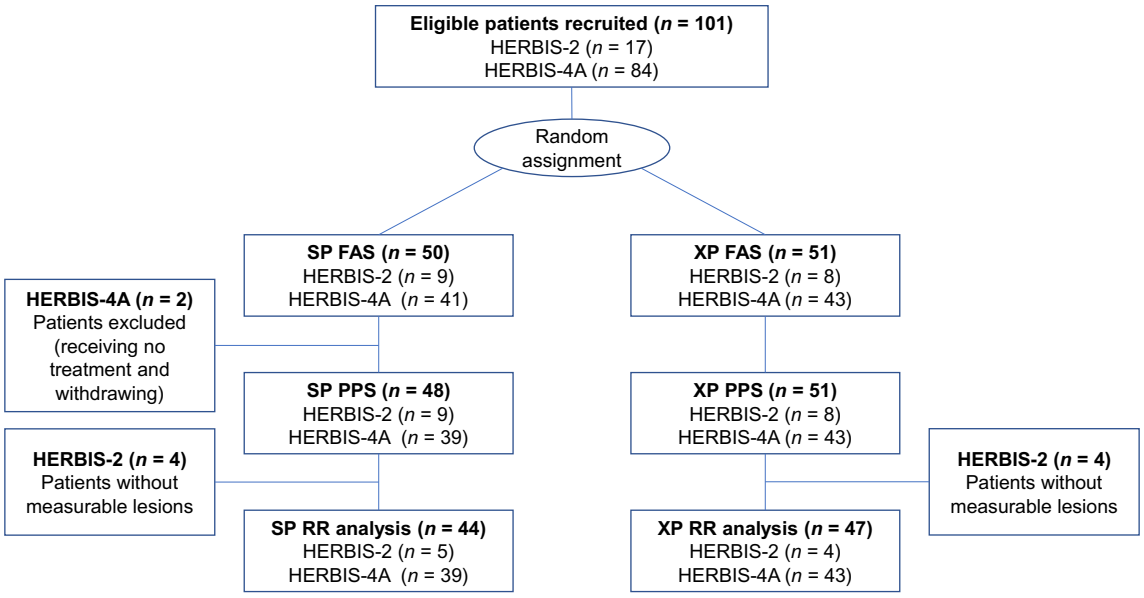

Fig. 1 Patient flow for the combined analysis of the SP and XP arms in HERBIS-2 and HERBIS-4A

Table 2 RR in the pooled analysis of HERBIS-2A and HERBIS-4A

Arm	*n*	CR	PR	SD	PD	NE	RR (95 % CI)	DCR (95 % CI)
SP	44	0	24	14	4	2	54.5% (38.8–69.6%)	86.4% (72.6–94.8%)
XP	47	0	24	8	10	5	51.1% (36.1–65.9%)	68.1% (52.9–80.9%)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *DCR* disease control rate

of 0.695 (95 % CI 0.451–1.071); $P=0.099$] (Fig. 3c). This difference in median OS was more pronounced in the PPS, with values of 14.9 months (95 % CI 12.0–23.8 months) and 10.6 months (95 % CI 7.6–15.6 months) for the SP and XP arms, respectively [HR of 0.656 (95 % CI 0.423–1.018), $P=0.060$] (Fig. 3d). The median TTF in the FAS was significantly longer for the SP arm [4.6 months (95 % CI 3.7–6.4 months)] than for the XP arm [3.6 months (95 % CI 2.7 to 4.1 months); HR of 0.668 (95 % CI 0.450–0.992); $P=0.045$] (Fig. 3e), and this difference was again more evident in the PPS 4.6 months (95 % CI 4.0–6.4 months) in the SP arm versus 3.6 months [95% CI, 2.7–4.1 months] in the XP arm; HR of 0.635 (95 % CI 0.426–0.947); $P=0.026$] (Fig. 3f).

Subgroup analysis for OS according to baseline clinical characteristics showed similar results across all subgroups, although the OS benefit in the SP arm was significantly greater than that in the XP arm for patients with a PS of 0 [HR of 0.544 (95 % CI 0.309–0.959), interaction $P=0.035$], for those with a primary tumor located in the upper region of the stomach [HR of 0.226 (95 % CI 0.070–0.731), interaction $P=0.013$], or for those with differentiated-type cancer [HR of 0.433 (95 % CI 0.228–0.822), interaction $P=0.011$] among the FAS (Fig. 4), and these differences were similar or more pronounced among the PPS [PS of 0, HR = 0.514 (95 % CI 0.289–0.914) and interaction $P=0.023$; tumor arising in upper region of stomach, HR = 0.157 (95 % CI 0.042–0.585) and interaction $P=0.006$; differentiated-type cancer, HR = 0.433 (95 % CI 0.228–0.822) and interaction $P=0.011$].

The median relative dose intensities per patient in the SP arm were 95.2% for S-1 and 88.5% for cisplatin, whereas those in the XP arm were 90.2% for capecitabine and 85.4% for cisplatin.

Discussion

We here first report the results of a phase II study, HERBIS-2, that examined the efficacy and safety of SP versus XP in recurrent GC patients with an RFI of ≥ 6 months after S-1–containing adjuvant therapy. This study was closed

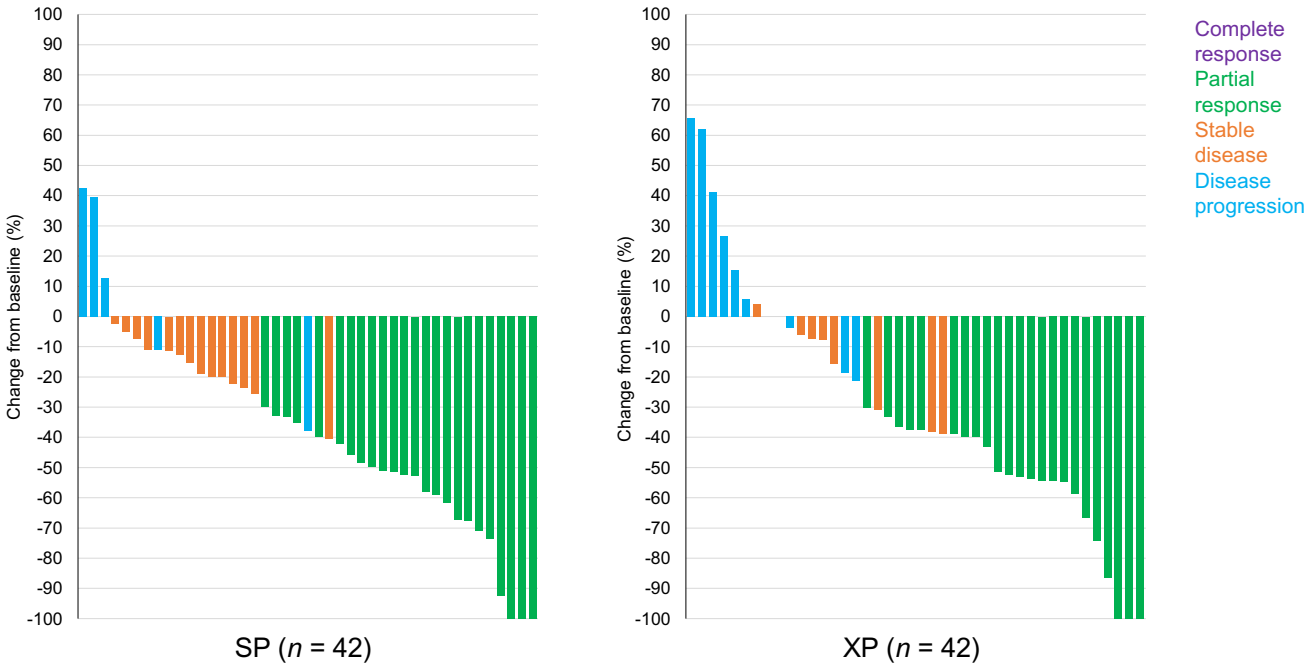

Fig. 2 Waterfall plot of the best confirmed response in combined analysis of the SP and XP arms in HERBIS-2 and HERBIS-4A

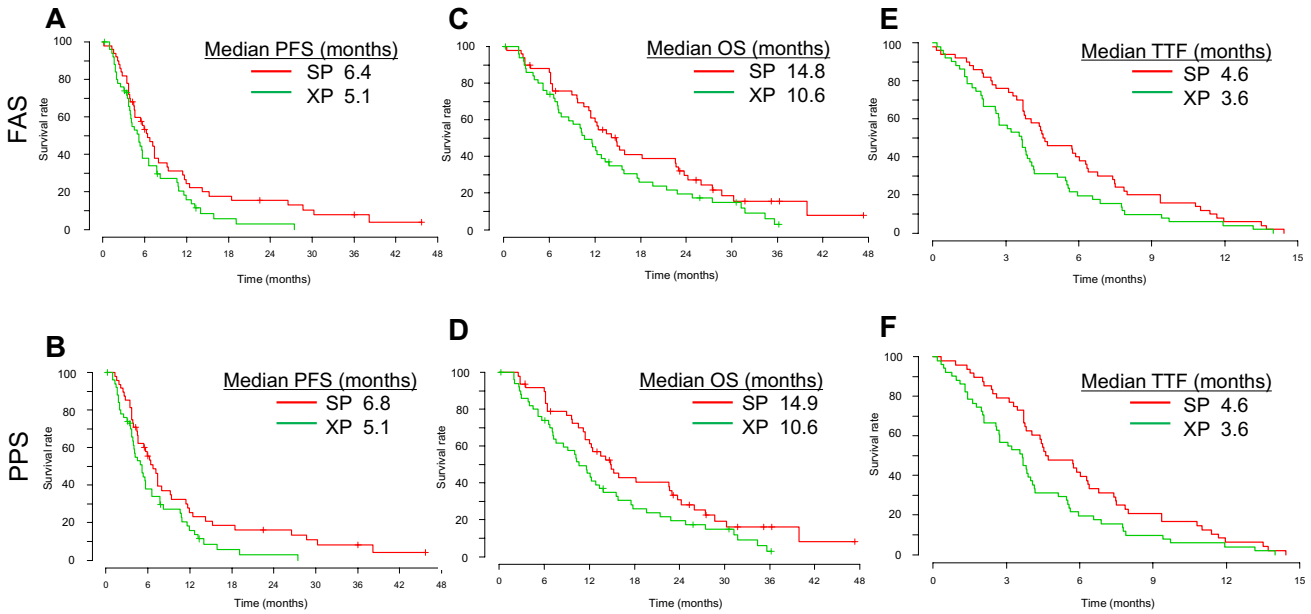

Fig. 3 Kaplan–Meier analysis of PFS (**a**, **b**), OS (**c**, **d**), and TTF (**e**, **f**) in the SP and XP arms for the FAS (**a, c, e**) and PPS (**b, d, f**) in the combined analysis of HERBIS-2 and HERBIS-4A

prematurely because of slow accrual due to the limited size of the target population. However, the data obtained from this trial suggested that the efficacy of SP might be greater than that of XP in this setting. Although the difference was not statistically significant, median OS, the primary end point of this study, was longer in the SP arm than in the XP arm (18.7 versus 13.4 months). Furthermore, median PFS was significantly longer in the SP arm than in the XP arm (9.1 versus 5.7 months), despite the small number of patients enrolled. The median PFS and OS for XP in HERBIS-2 are similar to those for recurrent GC patients who relapsed within 6 months after completion of S-1 adjuvant

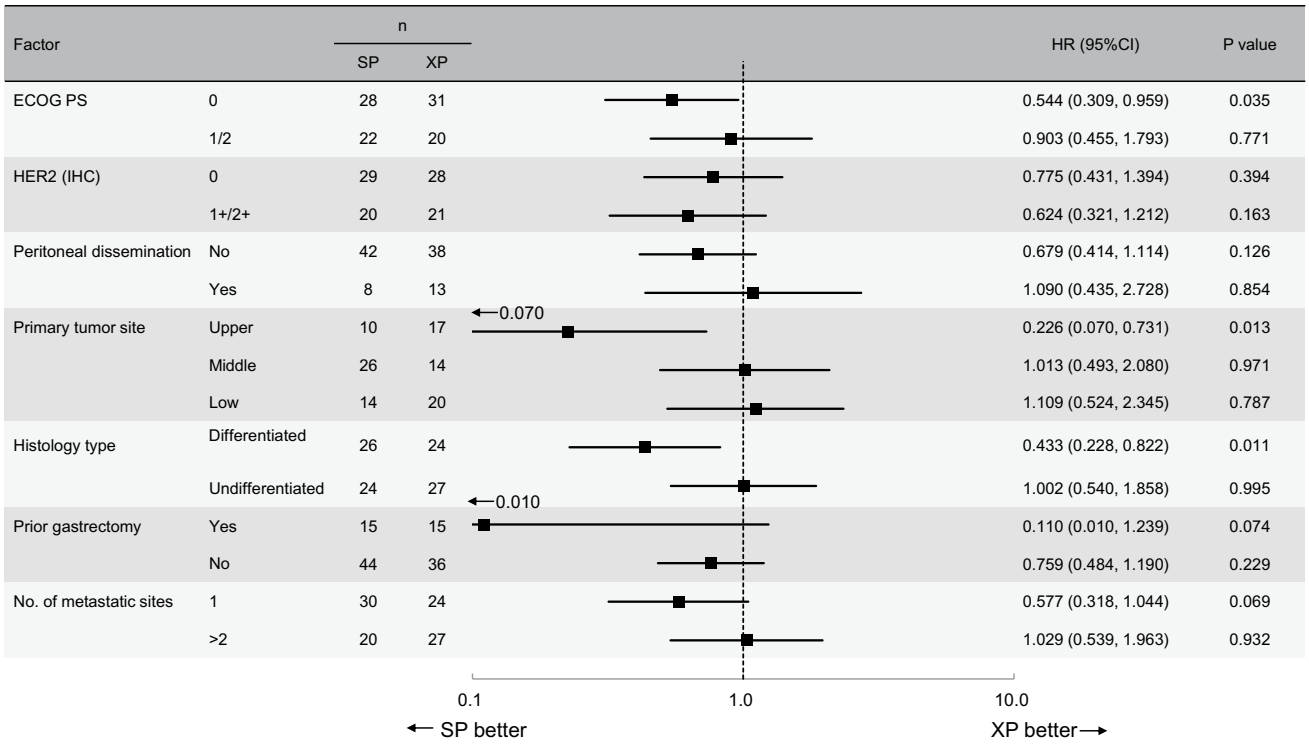

Fig. 4 Hazard ratio (HR) and 95 % CI for OS in patient subgroups of the FAS ($n = 101$) in the combined analysis of HERBIS-2 and HERBIS-4A. Abbreviations not defined in text: IHC, immunohistochemistry

chemotherapy in the XParTS-1 study (4.4 and 13.7 months for PFS and OS, respectively) [11]. These data suggest that the efficacy of XP might be independent of the interval between completions of S-1 therapy and relapse.

We concluded that a combined analysis of data from the HERBIS-2 and HERBIS-4A trials was feasible and valid because the two trials had similar designs even if their primary objectives were different. With the exception of the history of S-1 adjuvant therapy, the inclusion and exclusion criteria were identical in both trials, as were the chemotherapy regimens studied. The objective of pooling the data from the two trials was to improve the statistical power of the survival analysis and therefore to provide a better estimate of the potential benefit of either SP or XP for patients with HER2-negative advanced or recurrent GC. In the HERBIS-4A trial, although the differences were not statistically significant, SP was associated with a better median PFS [5.9 versus 4.1 months; HR of 0.763 (95 % CI 0.462–1.259); $P = 0.284$], OS [13.5 versus 10.0 months; HR of 0.776 (95 % CI 0.485–1.244); $P = 0.290$], and TTF [4.5 versus 3.1 months; HR of 0.651 (95 % CI 0.421–1.006); $P = 0.052$] [8]. This trend toward a better survival for SP revealed by HERBIS-4A was confirmed by the current pooled analysis. We thus detected a better survival outcome for SP relative to XP, with TTF and PFS (in the PPS) being significantly longer and OS tending to be longer for SP. The median relative dose intensities of S-1 and cisplatin were trending higher than capecitabine and cisplatin, which may partially explain the significantly better TTP and PFS in the SP versus XP arm. These results thus suggest that SP may be the preferred option for first-line chemotherapy of HER2-negative advanced GC or of HER2-negative recurrent GC with an RFI of ≥ 6 months after S-1 adjuvant therapy.

Subgroup analysis of the combined HERBIS-2 and HERBIS-4A data revealed that the survival advantage of SP was significant for patients whose tumors were located in the upper part of the stomach. This result should be interpreted with caution, however, given the small sample size for each subgroup. Gastric cancer arising from the upper portion of the stomach, including the gastroesophageal junction and cardia, has been found to be associated with chromosomal instability [13], suggesting that precise biomarker analysis might facilitate the selection of patients most likely to benefit from SP. Our subgroup analysis also showed that patients with differentiated-type cancer benefited significantly from SP compared with XP. Tumor histology has been used as an important classifier in GC, with two major classification systems—the Lauren classification [14] and Japanese classification [15]—having been adopted, and with intestinal type versus diffuse type of the former classification largely corresponding to differentiated type versus undifferentiated type of the latter, respectively. To date, no data are available

regarding the relation between the efficacy of chemotherapy regimens and tumor histological type in GC. It was thought that SP might be effective for diffuse-type GC, given that S-1 contains gimeracil, an inhibitor of dihydropyrimidine dehydrogenase, and that diffuse-type GC expresses this enzyme at a high level [16]. A retrospective analysis of the FLAGS study [17] revealed a better survival for patients with diffuse-type GC treated with an SP regimen (S-1 at 25 mg/m^2 orally twice daily on days 1 through 21 followed by a 7-day rest period; cisplatin at 75 mg/m^2 on day 1 of each 28-day cycle) than for those treated with the combination of 5-fluoruracil and cisplatin [18]. However, the subsequent DIGEST study failed to demonstrate a significant difference in OS between these two regimens for advanced GC patients with diffuse-type tumors [19]. A phase III study of patients with diffuse- or mixed-type GC in China recently showed that oxaliplatin plus S-1 tended to confer a better OS compared with SP in the first-line setting [20]. Further studies are thus warranted to shed light on the relation between tumor histology and the response to chemotherapy regimens.

Limitations of our pooled analysis include the relatively small number of patients. Direct comparison of SP and XP as first-line treatment for HER2-negative GC was also performed in another randomized phase II study (XParTS-II) [21] with metastatic GC patients or recurrent GC patients with an RFI of ≥ 6 months after S-1 adjuvant therapy. No difference in efficacy was apparent between the two regimens, with a median PFS of 5.6 versus 5.1 months [HR of 1.126 (95 % CI 0.753–1.685), $P = 0.5626$] and median OS of 13.5 versus 12.6 months [HR of 0.942 (95 % CI 0.624–1.423), $P = 0.7769$] for SP versus XP, respectively. Furthermore, subgroup analysis according to tumor histology (intestinal versus diffuse type) revealed no significant difference between the two treatments. The reason for the apparent discordance between these findings and our present results is unclear. We therefore plan the integration analysis with the use of individual data from these trials to better understand the characteristic of SP and XP.

In conclusion, despite its small size, the HERBIS-2 study suggests that the efficacy of SP might be better than that of XP in recurrent GC patients with an RFI of ≥ 6 months after S-1 adjuvant therapy. Pooled analysis of HERBIS-2 and HERBIS-4A further revealed a consistent survival advantage of SP over XP in HER2-negative advanced GC or recurrent GC with an RFI of ≥ 6 months after S-1 adjuvant therapy. This advantage will be evaluated further by combined analysis of our trials and the XParTS-II study.

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Compliance with ethical standards

Conflict of interest H.K. has received consulting fees from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Daiichi-Sankyo Co. Ltd., and Taiho Pharmaceutical Co. Ltd; honoraria from Bristol-Myers Squibb Co. Ltd., AstraZeneca K.K., Bayer yakuhin Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd.; lecture fees from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co., Ltd.; and research funding from Chugai Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd, and Eisai Co. Ltd. T. Tamura has received honoraria from Merck Serono Co. Ltd., speaker's bureau fees from Daiichi Sankyo Co. Ltd., and research funding from Takeda Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd. Y. Kurokawa has received lecture fees from Taiho Pharmaceutical Co. Ltd., Yakult Honsha, Ono Pharmaceutical Co. Ltd., MSD K.K., Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Kaken Pharmaceutical, as well as research grants from Taiho Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., and MSD K.K. T. Satoh received research grants from Giliad; consulting fees from Daiichi Sankyo and and Takeda Pharmaceutical, Co. Ltd.; consulting fees, honoraria and research grants from Merck BioPharm, Bristol-Myers K.K., Taiho pharmaceutical, Elli lilly, MSD,, Sanofi, Bristol Myers-Squib; and departmental research grants, research grants, honoraria and consulting fees from Chugai Pharmaceutical Co. Ltd., Ono Pharmaceutical. Co. Ltd. and Yakult Honsha Co. Ltd. All remaining authors declare no conflicts of interest.

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