International Journal of Clinical Oncology (2023) 28:1501–1510
https://doi.org/10.1007/s10147-023-02402-1

ORIGINAL ARTICLE

Meta-analysis of three randomized trials of capecitabine plus cisplatin (XP) versus S-1 plus cisplatin (SP) as first-line treatment for advanced gastric cancer

Kazuhiro Nishikawa[1] · Hisato Kawakami[2] · Toshio Shimokawa[3] · Kazumasa Fujitani[4] · Shigeyuki Tamura[5] · Shunji Endo[6] · Michiya Kobayashi[7] · Junji Kawada[4] · Yukinori Kurokawa[8] · Akira Tsuburaya[9] · Takaki Yoshikawa[10] · Junichi Sakamoto[11] · Taroh Satoh[12] · for HERBIS-2, HERBIS-4A, XParTS I. I. study investigators

Received: 26 June 2023 / Accepted: 7 August 2023 / Published online: 27 August 2023

Abstract

Background S-1 plus cisplatin (SP) and capecitabine plus cisplatin (XP) are standard first-line regimens for advanced gastric cancer (AGC) worldwide. We conducted a meta-analysis using individual participant data (IPD) to investigate which is more suitable.

Methods IPD from three randomized trials were collected. In these trials, patients with AGC were randomly allocated to SP (S-1 80–120 mg for 21 days plus cisplatin 60 mg/m^2 (q5w)) or XP (capecitabine 2000 mg/m^2 for 14 days plus cisplatin 80 mg/m^2 (q3w)).

Results In 211 eligible patients, median overall survival (OS) for SP versus XP was 13.5 and 11.7 months (hazard ratio [HR], 0.787; $p=0.114$), progression-free survival (PFS) was 6.2 and 5.1 months (HR, 0.767; $P=0.076$), and TTF was 5.1 and 4.0 months (HR, 0.611; $P=0.001$). The most common grade ≥ 3 adverse events with SP or XP were neutropenia (18% *vs.* 29%) and anorexia (16% *vs.*18%). Subgroup analysis demonstrated significant interaction between treatment effect and performance status > 1 (HR, 0.685; $P=0.036$), measurable lesion (HR, 0.709; $P=0.049$), primary upper third tumor (HR, 0.539; $P=0.040$), and differentiated type (HR, 0.549; interaction, 0.236; $P=0.019$). For the differentiated type, OS was significantly longer in the SP group (13.2 months) than in the XP group (11.1 months) (HR, 0.549; $P=0.019$). For the undifferentiated type, OS was similar in the SP group (14.2 months) and in the XP group (12.4 months) (HR, 0.868; $P=0.476$).

Conclusions SP and XP were both effective and well tolerated. SP might be suitable for the pathological differentiated subtype of AGC.

Clinical Trial Registration: The HERBIS-2, HERBIS-4A, and XParTS II trials were registered with UMIN-CTR as UMIN000006105, UMIN000006755, and UMIN000006045, respectively.

Keywords Advanced gastric cancer · First-line chemotherapy · S-1 plus cisplatin (SP) · Capecitabine plus cisplatin (XP) · Histological subtypes · Meta-analysis

Introduction

Gastric cancer remains one of the leading causes of cancer-related deaths worldwide [1]. Combination chemotherapy regimens provide better response rates (RRs) and modest survival benefits compared with single-agent therapies [2]. A combination of fluoropyrimidine and platinum is the most commonly used [3, 4]. S-1 or capecitabine can be used as an alternative to infusional 5-fluorouracil (5-FU) in doublet regimens for advanced gastric cancer (AGC).

Based on results from the SPIRITS trials, S-1 combined with cisplatin (SP) has become the accepted standard treatment regimen for AGC in Japan [5]. Conversely, capecitabine plus cisplatin (XP) was reported to have significantly non-inferior median progression-free survival (PFS) compared with 5-FU plus cisplatin (5.6 months vs. 5.0 months; hazard ratio [HR] = 0.81) [6]. More recently, XP therapy was the active comparator in three multinational phase III studies designed to evaluate the potential of molecular targeted

Kazuhiro Nishikawa and Hisato Kawakami have contributed equally to this study.

Extended author information available on the last page of the article

therapeutics for AGC [7–9]. Thus, both SP and XP are listed as first-line treatment in the Japanese guidelines [10].

Three randomized trials compared SP and XP therapy for AGC: the XParTS II [11] trial by the Epidemiological and Clinical Research Information Network (ECRIN) and the HERBIS-2 [12] and HERBIS-4A [13] trials by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG). The XParTS II study found SP and XP lead to comparable PFS (5.6 *vs.* 5.1 months; HR, 1.126; $P=0.5626$) and overall survival (OS) (13.5 *vs.* 12.6 months; HR, 0.942; $P=0.7769$) [11]. On the other hand, in the pooled analysis of HERBIS-2 and HERBIS-4A, SP was associated with longer OS (14.8 *vs.* 10.6 months; HR, 0.695; $P=0.099$) and PFS (6.4 *vs.* 5.1 months; HR, 0.666; $P=0.062$) than XP [12]. One reason for the lack of significant differences in each trial was the limited sample sizes.

Regarding S-1 versus capecitabine not in combination with cisplatin, two randomized trials in elderly patients with AGC have been reported. One involved S-1 or capecitabine monotherapy and the other involved S-1 plus oxaliplatin (SOX) and capecitabine plus oxaliplatin (CAPOX) [14–16]. In addition, several meta-analyses reported in abstracts have compared S-1–based and capecitabine-based chemotherapy [17–19]. All these studies showed that S-1 and capecitabine are almost equally effective. However, there is scant evidence to suggest whether S-1 or capecitabine would be preferable for precision medicine.

Thus, it remains unclear whether SP or XP is more suitable as first-line treatment for AGC. It is also unclear whether clinical and molecular characteristics of patients could assist in deciding whether to use SP or XP. Therefore, we conducted a meta-analysis with individual participant data (IPD).

Patients and methods

Study design

This meta-analysis was planned in 2020 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-IPD [20]. We included all completed and published peer-reviewed randomized clinical trials that investigated the effect of XP or SP as first-line chemotherapy for gastric or gastroesophageal junction adenocarcinoma. We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials up to 30 September 2020. The search terms were "gastric cancer OR gastric carcinoma OR gastroesophageal junction adenocarcinoma" AND "capecitabine" AND "S-1" AND "CDDP OR cisplatin" AND "metastatic OR recurrent OR first-line." The inclusion criteria were as follows: (1) prospective randomized controlled clinical trial; (2) pathological diagnosis of AGC or gastroesophageal junction adenocarcinoma; (3) XP or SP as first-line treatment regimen. Based on PRISMA-IPD, three randomized trials, the ECRIN XParTS II trial, OGSG HEBIS-2 trial, and OGSG HERBIS-4A trial, were included (Fig. 1). All three trials compared SP and XP at the same dose and the treatment methods were identical, and 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). In terms of patient enrollment, inclusion and exclusion criteria were reported previously [11–13].

We first verified the integrity of the IPD from the three trials. All clinical data were extracted and held centrally at the OGSG data center. This study was conducted in compliance with the ethical principles of the Declaration of

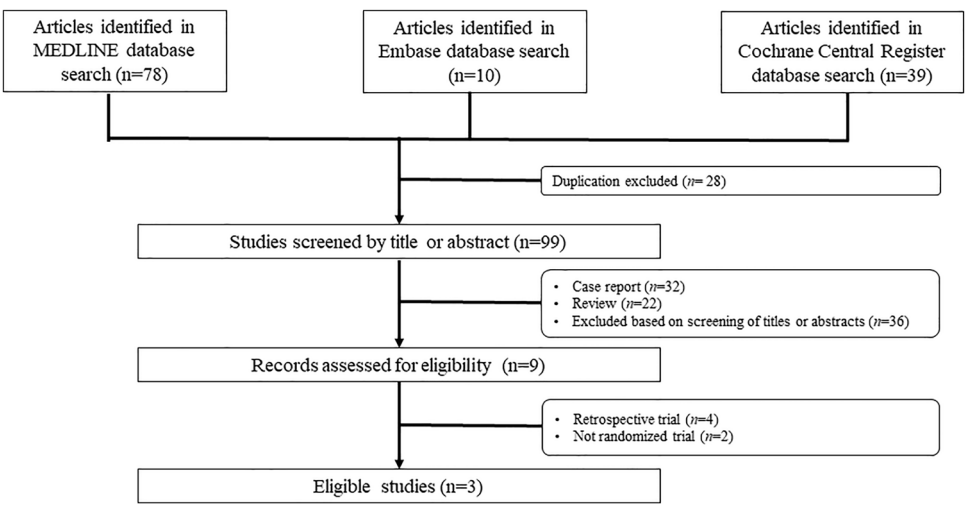

Fig. 1 PRISMA flow diagram of the literature search

Helsinki and the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labour and Welfare.

Patients

Briefly, patients with histologically confirmed HER2-negative AGC were eligible for all three trials. For XParTS II, no previous chemotherapy or radiotherapy was allowed, but prior adjuvant chemotherapy was allowed if more than 6 months have passed since the end of such treatment [11]. For HERBIS-4A, patients were required to be naïve to systemic chemotherapy [13]. Patients who had recurrence within 6 months after the completion of S-1 adjuvant therapy were eligible for HERBIS-2 [12]. Other eligibility criteria were as follows: age ≥ 20 years; written informed consent; Eastern Cooperative Oncology Group performance status (PS) of ≤ 2; adequate organ function (white blood cell count ≥ 3000/mm^3 for HERBIS-2 and HERBIS-4A, neutrophil count ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin level ≥ 8.0 g/dL, aspartate aminotransferase and alanine aminotransferase levels ≤ 100 IU/L for HERBIS-2 and HERBIS-4A or ≤ 2.5 × upper limit of normal (ULN) at each institution (≤ 5 × ULN if there were metastases) for XParTS II, total bilirubin level ≤ 1.50 mg/dL for HERBIS-2 and HERBIS-4A or ≤ 1.5 × ULN at each institution for XParTS II, serum creatinine ≤ 1.20 mg/dL for HERBIS-2 and HERBIS-4A, creatinine clearance ≥ 60 mL/min estimated with Cockcroft-Gault equation. Exclusion criteria consisted of additional malignancies or significant comorbidities.

Assessment

The primary objective of this study was to evaluate prospectively collected IPD from the XParTS II, HERBIS-2, and HERBIS-4A trials to compare SP with XP and to determine the optimal first-line chemotherapy for patients with HER2-negative unresectable advanced or recurrent gastric cancer. The primary endpoint of this study was OS. The secondary endpoints were PFS, time to treatment failure (TTF), post-protocol survival (PPS), overall response rate (ORR), disease control rate (DCR), and adverse events (AEs).

OS was defined as time from randomization to death. PFS was defined as time from randomization to radiographic progression or death. TTF was defined as time from treatment to resistance or progression of disease, transformation to another malignancy, or death from any cause. PPS was defined as time from the end of therapy as per protocol to death. Tumor responses were assessed using Response Evaluation Criteria In Solid Tumors version 1.1 and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on central review. ORR was defined as the proportion of patients with CR or PR. DCR was defined as the proportion of patients with CR, PR, or SD. The DCR of patients without measurable lesions was defined as the proportion of patients with CR or non-CR and non-PD. PFS and RR were monitored with abdominal Computed Tomography or Magnetic Resonance Imaging every 6 weeks and measuring levels of the tumor markers carcinoembryonic antigen and cancer antigen 19–9. AEs were evaluated using the Common Terminology Criteria for Adverse Events version 4.0.

Tumor histology was based on the Japanese classification of gastric carcinoma [10]. Differentiated-type (DIFF) tumor was defined as papillary or tubular adenocarcinoma. Undifferentiated-type (UNDI) tumor was defined as poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma. Other histology types were designated as other.

Statistical analysis

Survival curves were estimated using the Kaplan–Meier method. The log-rank test with stratification of allocation factors was used to compare survival curves between arms. HRs and their 95% confidence intervals (CIs) were calculated with Cox proportional hazards models; 95% CIs were used for median OS, PFS, and TTF. ORR was compared between arms with Fisher's exact test. All statistical analysis was performed with R version 3.3.1 (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

Selected trials

Based on PRISMA-IPD, three randomized phase III trials, the ECRIN XParTS II trial, OGSG HEBIS-2 trial, and OGSG HERBIS-4A trial, were included (Fig. 1).

Patient characteristics

We extracted data from 211 patients eligible for the HERBIS-2 (N = 17), HERBIS-4A trial (N = 84), and XParTS II (N = 110) trials. There were 105 patients (50%) allocated to the SP group and 106 (50%) allocated to the XP group. Both arms were well balanced in terms of baseline clinical characteristics (Table 1).

Adverse events

Toxicity profiles are summarized in Table 2. The incidence of grade ≥ 3 AEs was low in both groups. There were

Table 1 Patient characteristics

Eligible patients, $n=211$	SP	XP
No. of patients	105	106
Age		
Median (range)	66 (37–78)	65 (31–79)
Gender		
Male	69 (65.7%)	87 (82.1%)
Female	36 (34.3%)	19 (17.9%)
ECOG PS		
0	75 (71.4%)	76 (71.7%)
1	29 (27.6%)	28 (26.4%)
2	1 (1.0%)	2 (1.9%)
Body mass index		
Median (range)	20.3 (14.4–29.1)	20.5 (14.4–29.1)
Disease status		
Metastatic	79 (75.2%)	83 (78.3%)
Recurrent	26 (24.8%)	23 (21.7%)
Adjuvant chemotherapy		
Yes	17	15
No	9	8
Primary tumor		
Yes	73 (69.5%)	78 (73.6%)
No	32 (30.5%)	28 (26.4%)
Site of metastasis[a]		
Lymph-node	65 (61.9%)	80 (75.5%)
Peritoneum	32 (30.5%)	39 (36.8%)
Liver	29 (27.6%)	25 (23.6%)
Lung	5 (4.8%)	6 (5.7%)
Bone	7 (6.7%)	5 (4.7%)
Measurable disease		
Yes	79 (76.2%)	83 (78.3%)
No	26 (23.8%)	23 (21.7%)
Histopathological classification[b]		
Differentiated (DIFF)	45 (42.9%)	36 (34.0%)
Undifferentiated (UNDI)	60 (57.1%)	70 (66.0%)

ECOG Eastern cooperative oncology group, *PS* performance status, *HER2* human epidermal growth factor receptor 2, *SP S-1* plus cisplatin, *XP* capecitabine plus cisplatin

[a]Patients can be included in more than one category

[b]Differentiated-type: pap, tub1, tub2; Undifferentiated-type: por, sig, muc

no significant differences in the incidence of grade ≥ 3 AEs between treatment arms, except for diarrhea, which occurred more frequently in the SP group (7% *vs.* 0%; $P=0.006$). There were no deaths resulting from AEs in either arm. The incidence of all-grade neutropenia (52% *vs.* 67%), hyponatremia (22% *vs.* 40%) and peripheral sensory neuropathy (4% *vs.* 18%) was higher in the XP group. The incidence of all-grade abdominal pain (21% *vs.* 8%) was higher in the SP group.

Efficacy

OS was 13.5 months (95% CI 12.1–16.2) in the SP group and 11.7 months (95% CI 10.2–15.0) in the XP group (HR: 0.787; 95% CI 0.584–1.060; $P=0.114$) (Fig. 2a). PFS was 6.2 months (95% CI 4.6–7.4) in the SP group and 5.1 months (95% CI 4.2–5.8) in the XP group (HR: 0.767; 95% CI 0.572–1.029; $P=0.076$) (Fig. 2b). However, TTF was significantly longer in the SP group (5.1 months

Table 2 Adverse events

Neutropenia	SP (N = 103[*1])				XP (N = 106)				p-value (any)	p-value (G3)
	Any Grade (%)		≧G3(%)		Any Grade (%)		≧G3(%)			
Neutropenia	54	(52.4%)	19	(18.4%)	70	(66.7)	30	(28.6%)	0.049	0.104
Febrile neutropenia			5	(4.9)			3	(2.9)		0.494
Anemia	38	(36.9)	13	(12.6)	38	(36.2)	14	(13.3)	0.886	1.000
Thrombocytopenia	49	(47.6)	7	(6.8)	54	(51.4)	6	(5.7)	0.678	0.781
Hypoalbuminemia	63	(61.2)	2	(1.9)	71	(67.6)	3	(2.9)	0.391	1.000
Total bilirubin increased	58	(56.3)	9	(8.7)	57	(54.3)	11	(10.5)	0.781	0.815
AST increased	30	(29.1)	1	(1.0)	24	(22.9)	1	(1.0)	0.343	0.999
ALT increased	17	(16.5)	1	(1.0)	17	(16.2)	0	(0.0)	1.000	0.492
LDH increased	22	(21.4)	0	(0.0)	17	(16.2)	0	(0.0)	0.376	1.000
BUN increased	14	(13.6)	0	(0.0)	18	(17.1)	1	(1.0)	0.566	1.000
Serum creatinine value increased	31	(30.1)	1	(1.0)	33	(31.4)	2	(1.9)	0.881	1.000
Hyponatremia	23	(22.3)	3	(2.9)	42	(40.0)	8	(7.6)	0.007	0.214
Hypokalemia	33	(32.0)	3	(2.9)	35	(33.3)	5	(4.8)	0.883	0.721
Hyperkalemia	35	(34.0)	2	(1.9)	31	(29.5)	1	(1.0)	0.551	0.617
Hypercalcemia	26	(25.2)	5	(4.9)	26	(24.8)	7	(6.7)	1.000	0.767
CRP increased	24	(23.3)	1	(1.0)	27	(25.7)	3	(2.9)	0.749	0.621
Oral mucositis	21	(20.4)	2	(1.9)	21	(20.4)	2	(1.9)	0.999	1.000
Nausea	41	(39.8)	4	(3.9)	57	(55.3)	10	(9.7)	0.052	0.165
Vomiting	15	(14.6)	2	(1.9)	21	(20.4)	2	(1.9)	0.362	1.000
Diarrhea	31	(30.1)	7	(6.8)	20	(19.4)	0	(0.0)	0.076	0.006
Abdominal pain	22	(21.4)	1	(1.0)	8	(7.8)	1	(1.0)	0.005	0.999
Anorexia	70	(68.0)	16	(15.5)	76	(73.8)	18	(17.5)	0.651	0.852
Fatigue	38	(36.9)	3	(2.9)	45	(43.7)	9	(8.7)	0.479	0.134
Malaise	58	(56.3)	0	(0.0)	59	(57.3)	0	(0.0)	1.000	1.000
Fever	17	(16.5)	1	(1.0)	9	(8.7)	1	(1.0)	0.094	0.999
Allergic reaction	2	(1.9)	0	(0.0)	1	(1.0)	0	(0.0)	0.617	1.000
Peripheral sensory neuropathy	4	(3.9)	0	(0.0)	19	(18.4)	2	(1.9)	0.001	0.497
Palmar-plantar erythrodysesthesia syndrome	7	(6.8)	0	(0.0)	32	(31.1)	2	(1.9)	< 0.001	0.497
Weight loss	14	(13.6)	1	(1.0)	15	(14.6)	1	(1.0)	1.000	0.999
Edema	5	(4.9)	0	(0.0)	3	(2.9)	0	(0.0)	0.494	1.000

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *BUN* blood urea nitrogen, *CRP* c-reactive protein, *LDH* lactate dehydrogenase, *SP*, S-1 plus cisplatin, *XP* capecitabine plus cisplatin

[*] Excluding two patients discontinued before treatment

[95% CI 4.4–6.3]) than in the XP group (4.0 months [95% CI 3.5–5.1]) (HR: 0.611; 95% CI 0.461–0.811, $P = 0.001$) (Table 3). PPS was 6.9 months (95% CI 5.9–11.2) in the SP group and 6.5 months (95% CI 5.5–9.7) in the XP group (HR: 0.927; 95% CI 0.688–1.248: $P = 0.614$) (Table 3).

As shown previously, of the 79 patients in the SP group with measurable disease, 2 achieved CR, 36 achieved PR, and 28 achieved SD. Of the 83 patients in the XP group who had measurable disease, 1 achieved CR, 41 achieved PR, and 18 achieved SD. ORR was 47.5% (95% CI 36.2–59.0%) in the SP group and 50.6% (95% CI 39.4–61.8%) in the XP group ($P = 0.755$) [21]. Among patients with measurable disease, DCR was comparable between the SP and XP arms (83.5% [95% CI 73.5–90.9%] *vs.* 72.3% [95% CI 61.4–81.2%]; $P = 0.137$). Of the 25 patients in the SP group who did not have measurable disease, 25 achieved non-CR and non-PD, but none achieved CR; DCR was 88.0% (95% CI 68.9–97.5%). Of the 23 patients in the XP group who did not have measurable disease, 1 achieved CR and 15 achieved non-CR/non-PD; DCR was 69.6% (95% CI 47.1–86.8%) (Table S1). Overall DCR for those with and without measurable lesions combined was significantly higher in the SP group (84.6% [95% CI 77.7–91.5%]) than in the XP group (71.7% [95% CI 63.1–80.3%]) ($P = 0.024$) (Table S2).

Subgroup analysis of OS by age, gender, PS, measurable lesion, peritoneal metastasis, primary lesion, histological

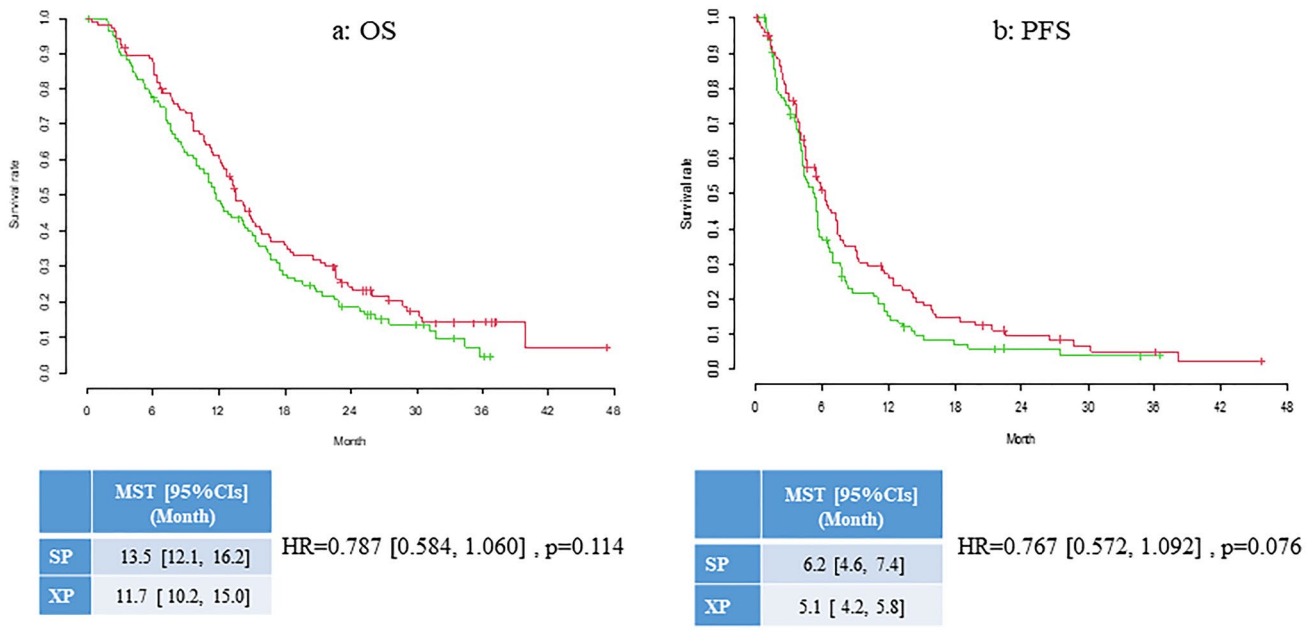

Fig. 2 Kaplan–Meier curves for OS **a** and PFS **b** by treatment group. *OS* overall survival, *PFS* progression-free survival

Table 3 TTF and PPS by treatment group

	SP	XP	HR [95%CI]	P-value
Median TTF (months)	5.1 [4.4–6.3]	4.0 [3.5–5.1]	0.611 [0.461–0.811]	0.001
Median PPS (months)	6.9 [5.9–11.2]	6.5 [5.5–9.7]	0.927 [0.688–1.248]	0.614

TTF time to treatment failure, *PPS* post-protocol survival, *HR* hazard ratio, *95% CI* 95% confident interval

type, prior adjuvant chemotherapy, and prior primary tumor resection demonstrated significant interaction between treatment effect and PS > 1 (HR: 0.685; interaction: 0.165; $P = 0.036$), measurable lesion (HR: 0.709; interaction: 0.248; $P = 0.049$), primary upper third (U) lesion (HR: 0.539; interaction: 0.361; $P = 0.040$), and histological DIFF tumor (HR: 0.549; interaction: 0.236; $P = 0.019$) (Fig. 3).

Histological differences

We focused on the histological types that are likely to be encountered in actual clinical practice. Among patients with pathological DIFF tumors, OS was significantly longer in the SP group (13.2 months [95% CI 11.2–18.2]) than in the XP group (11.1 months [95% CI 8.5–15.6]) (HR: 0.549; 95% CI 0.332–0.907: $P = 0.019$) (Fig. 4a). Among patients with UNDI tumors, OS was similar in the SP group (14.2 months [95% CI 12.1–18.7]) and the XP group (12.4 months [95% CI 9.8–16.7]) (HR: 0.868; 95% CI 0.587–1.282; $P = 0.476$) (Fig. 4b). PFS was 5.9 months (95% CI 4.4–7.6) in the SP group and 5.6 months (95% CI 3.9–8.3) in the XP group (HR: 0.881; 95% CI 0.546–1.421; $P = 0.604$) for DIFF tumors (Fig. S1a). PFS was 7.1 months (95% CI 4.6–9.3) in the SP group and 4.7 months (95% CI 4.2–6.0) in the XP group (HR 0.692; 95% CI 0.468–1.023, $P = 0.065$) for UNDI tumors (Fig. S1b). TTF was 4.4 months (95% CI 3.7–6.4) in the SP group and 3.9 months (95% CI 2.7–5.6) in the XP group (HR: 0.789; 95% CI 0.503–1.238; $P = 0.302$) for DIFF tumors. In contrast, for UNDI tumors, TTF was significantly longer in the SP group (5.9 months [95% CI 5.0–7.5]) than in the XP group (4.0 months [95% CI 3.5–5.1]) (HR: 0.480; 95% CI 0.327–0.706, $P < 0.001$).

DIFF accounted for 69.5% (114/164) of measurable lesions. UNDI was significantly more common (64%; 32/50) among lesions that were not measurable (Table S3).

Discussion

This meta-analysis with IPD is the first report to compare SP and XP regimens in a large sample. With PRISMA-IPD methods, we were able to evaluate efficacy in detail, especially with subgroup analyses. We showed that SP is associated with superior TTF compared to XP as well as non-significantly better OS and PFS. SP and XP achieved

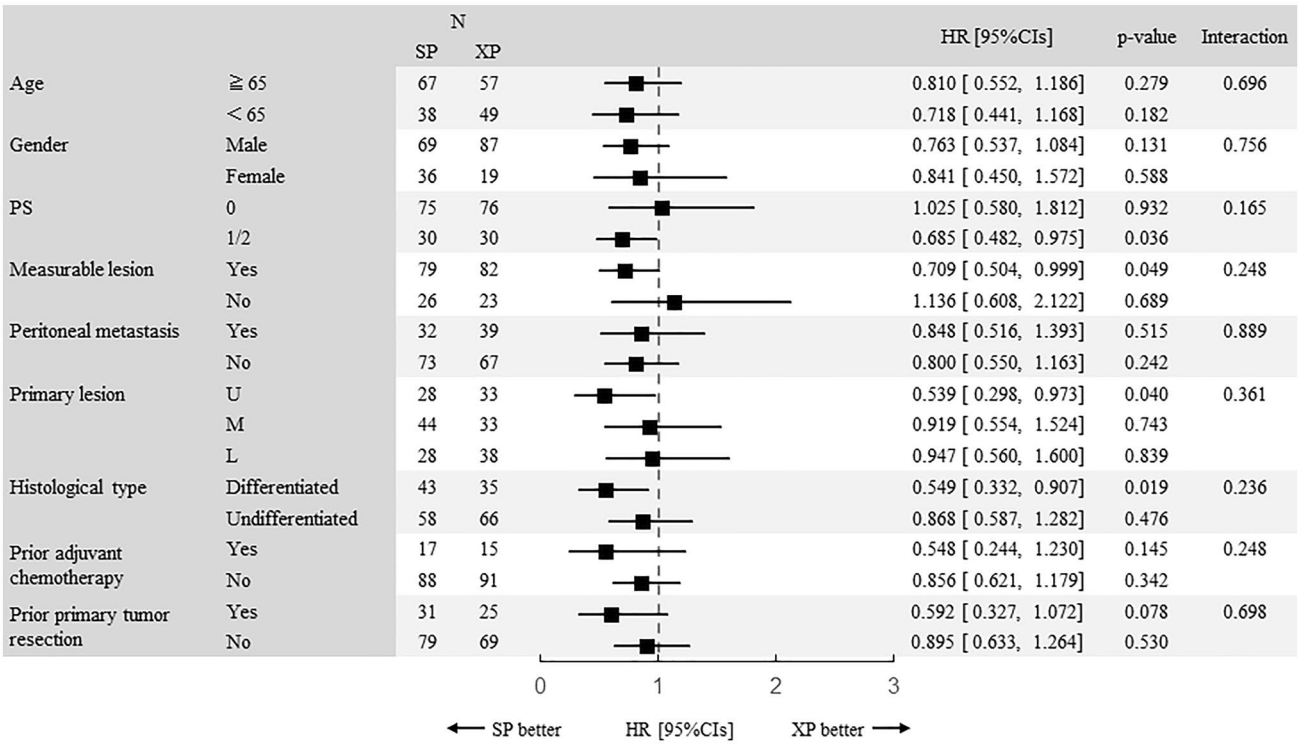

Fig. 3 Subgroup analysis for OS. PS, performance status

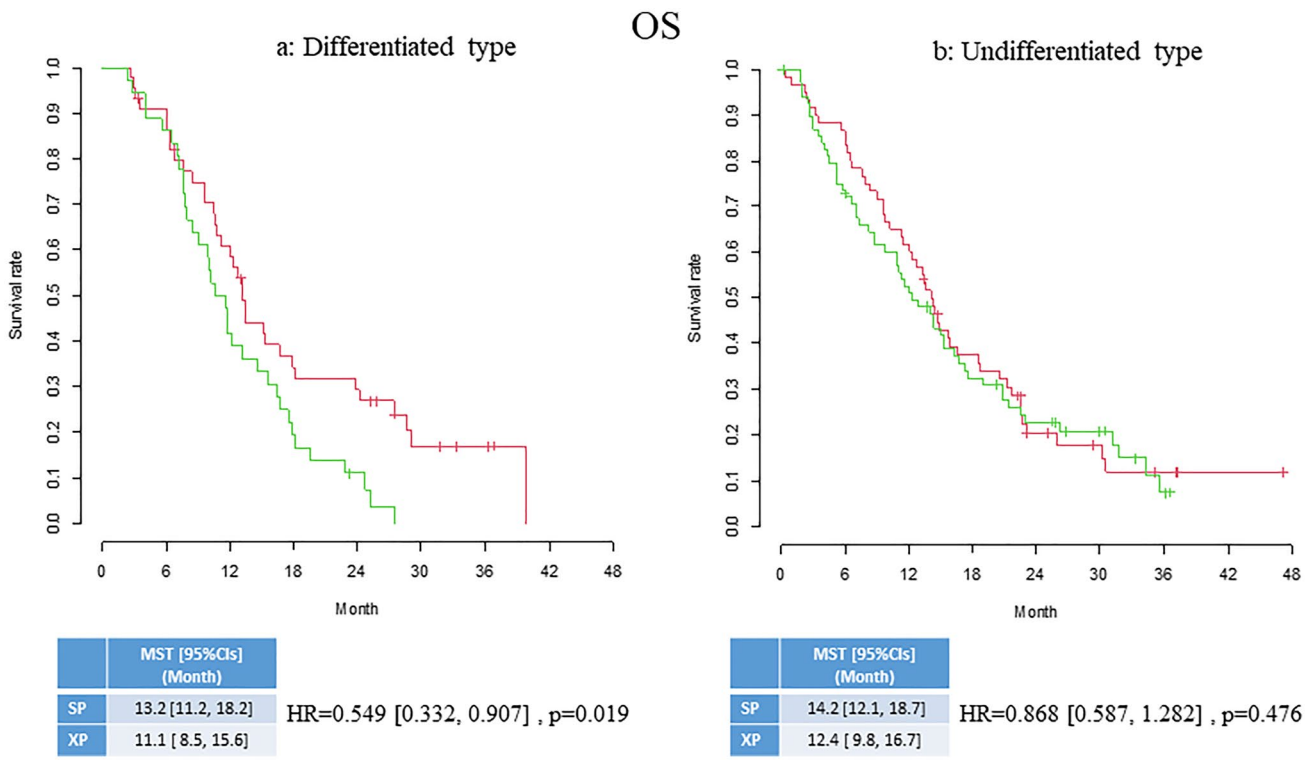

Fig. 4 Kaplan–Meier curves for OS in differentiated type **a** and in undifferentiated type **b** by treatment arm. *OS* overall survival, *SP S-1* plus cisplatin, *XP* capecitabine plus cisplatin.

comparable ORR with acceptable toxicity levels. The overall DCR for SP was significantly higher than for XP.

Various factors could account for the discrepancy between OS and TTF results. In Japan, more than 70% of patients with AGC receive second-line chemotherapy. Demonstrating the superiority of a first-line regimen in terms of OS is difficult because OS is strongly affected by subsequent treatment. Takashima et al. reported strong correlations between the proportion of patients receiving with second-line chemotherapy and post-progression survival and OS, respectively [23]. Although the SP group was able to undergo primary treatment longer due to maintenance treatment with S-1 as a single agent after SP therapy, the XP group might have had more effective treatment after the shift to second-line treatment. Our subgroup analysis of OS revealed a significant interaction between treatment effect and PS > 1 ($P = 0.036$), primary U lesion ($P = 0.040$), measurable lesion ($P = 0.049$), and DIFF type ($P = 0.019$) (Fig. 3).

It is unknown why SP resulted in superior OS in patients with poor performance status. The major difference between SP and XP regimens other than S-1 and capecitabine is the initial dose and cisplatin schedule (SP, 60 mg/m^2, every 5 weeks [12 mg/m^2/week] *vs.* XP, 80 mg/m^2, every 3 weeks [26.7 mg/m^2/week]). In the SOS study, cisplatin 60 mg/m^2 every 3 weeks in combination with S-1 (SP3) was compared to standard every 5 weeks S-1 plus cisplatin (60 mg/m^2) [22]. In this trial, SP3 was slightly superior to standard SP in terms of PFS, but not in OS. However, there were significantly more ≥ grade 3 AEs in the SP3 arm than in the standard SP arm (73% *vs.* 51%). In our study, although AEs with SP and XP were comparable, better tolerability of cisplatin 60 mg/m^2 every 5 weeks might have led to more treatment cycles and longer TTF than cisplatin 60 mg/m^2 every 3 weeks. In addition, SP is more convenient because it can be administered less frequently in hospitals and partially on an outpatient basis given the lower dose of cisplatin. Thus, one possible reason for the favorable prognosis of patients with SP was the better tolerability against cisplatin.

Regarding primary U tumors, gastric cancer arising from the upper portion of the stomach, including the gastroesophageal junction and cardia, is associated with chromosomal instability [24], suggesting that precise biomarker analysis might facilitate the selection of patients most likely to benefit from SP. Further study of the clinical and molecular characteristics of AGC is needed to guide decisions on using SP or XP therapy.

We also showed that OS was significantly better with SP than with XP in patients with pathological DIFF tumors. There are few reports suggesting the use of S-1 or capecitabine based on histological type. Initially, in the subset analysis of the FLAGS trial, S-1 appeared to be superior to 5-FU in the diffuse gastric cancer subgroup [25], but the DIGEST trial following the FLAGS trial failed to demonstrate that S-1 was superior to 5-FU for diffuse-type gastric cancer [26]. A previous study showed that compared to diffuse-type tumors, intestinal-type tumors tend to have lower expression levels of excision repair cross-complementation group 1 (*ERCC1*), a nucleotide excision repair pathway gene that provides protection against platinum-based chemotherapy-induced DNA damage [27]. The better OS of SP compared with XP for differentiated-type tumors might be due to the fact that relatively low doses of platinum (SP: 12 mg/m^2/week *vs.* XP: 26.7 mg/m^2/week) are enough for tumors with low *ERCC1* expression and SP is better tolerated than XP. Further molecular biology studies are needed to determine whether tumor differentiation can be used to select S-1 or capecitabine for AGC. SP yielded superior OS than XP in patients with measurable lesions. We have worked on elucidating as a separate study, and found that in DIFF tumors, the depth of tumor shrinkage in SP is deeper than that in XP, which is why there is no difference in PFS or TTF, but a large difference opens up in OS [21]. On the other hand, in the UNDI tumors, we found differences in PFS and TTF.

This study has several limitations. This study only included Japanese patients and ethnic differences between Asian and Western patients could have affected the overall results; the results should be interpreted with caution. Second, the planned doses of concomitant cisplatin were different, so it is not possible to determine whether S-1 or capecitabine should be used. Lastly, as the platinum agent used in this study was cisplatin, it is unclear what the results would be with other platinum products. Recently, SOX or CAPOX has become more commonly used than SP or XP [28, 29]. Furthermore, the standard of care for HER2-negative AGC is an anti–programmed death receptor-1 antibody with oxaliplatin and fluoropyrimidine [29–31]. Whether SOX or CAPOX should be used as the base combination chemotherapy is debated.

In conclusion, the efficacies of XP were similar to those of SP. SP might be suitable in the differentiated subtype of AGC, although histological subtyping is not adequately sensitive for selecting S-1 or capecitabine. Further research that classifies AGC based on other biomarkers is necessary to enable individualized treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-023-02402-1.

Acknowledgements We deeply appreciate all patients and investigators involved in the XParTS II trial and the OGSG HEBIS-2, -4A trials. We also thank the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) and the Epidemiological & Clinical Research Information Network (ECRIN) for their support.

Funding This study was funded by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG). [No grant numbers apply].

Declarations

Conflict of interests Kazuhiro Nishikawa has received honoraria for lectures from Bristol-Myers Squibb Co. Ltd., Daiichi-Sankyo Co. Ltd., EA Pharma Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd. Hisato Kawakami has received consulting fees from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., and Daiichi-Sankyo Co. Ltd.; honoraria from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., and Daiichi Sankyo Co. Ltd. Yukinori Kurokawa has received honoraria and research funding from Taiho Pharmaceutical. Taroh Satoh has received departmental research grants from Chugai Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., Daiichi-Sankyo Co. Ltd., Hutchmed, Parexell, and BeiGene, and honoraria from Eli Lilly Japan K.K., Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., and Daiichi-Sankyo Co. Ltd. All remaining authors declare no conflicts of interest.

Ethical approval This trial was conducted in compliance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labour and Welfare. This trial was approved by the institutional review boards or ethics committees at all participating centers.

References

1. Sung H, Ferlay J, Siegel RL et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209–249
2. Wagner AD, Grothe W, Haerting J et al (2006) Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 24:2903–2909
3. Van Cutsem E, Moiseyenko VM, Tjulandin S et al (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. J Clin Oncol 24:4991–4997
4. Cunnigham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
5. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
6. Kang YK, Kang WK, Shin DB et al (2009) Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 20:666–673
7. Bang YJ, Van Cutsem E, Feyereislova A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376:687–697
8. Ohtsu A, Shah MA, Van Cutsem E et al (2011) Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 29:3968–3976
9. Lordick F, Kang YK, Chung HC et al (2013) Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 14:490–499
10. Japanese gastric cancer treatment guidelines (2018) 5th edition. Gastric Cancer 2021(24):1–21
11. Nishikawa K, Tsuburaya A, Yoshikawa T et al (2018) A randomised phase II trial of capecitabine plus cisplatin versus S-1 plus cisplatin as a first-line treatment for advanced gastric cancer: Capecitabine plus cisplatin ascertainment versus S-1 plus cisplatin randomised PII trial (XParTS II). Eur J Cancer 101:220–228
12. Kawakami H, Fujitani K, Matsuyama J et al (2020) 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-naive advanced): pooled analysis of HERBIS-2 (OGSG 1103) and HERBIS-4A (OGSG 1105) trials. Int J Clin Oncol 25:1635–1643
13. Kawakami H, Takeno A, Endo S et al (2018) Randomized, open-label phase ii study comparing capecitabine-cisplatin every 3 weeks with S-1-cisplatin every 5 weeks in chemotherapy-naive patients with HER2-negative advanced gastric cancer: OGSG1105, HERBIS-4A trial. Oncologist 23:1411-e147
14. Lee JL, Kang YK, Kang HJ et al (2008) A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 99:584–90
15. Kim MJ, Kong SY, Nam BH et al (2018) A randomized phase II study of S-1 versus capecitabine as first-line chemotherapy in elderly metastatic gastric cancer patients with or without poor performance status: clinical and pharmacogenetic results. Pharmacogenet Genom 28:23–30
16. Kim GM, Jeung HC, Rha SY et al (2012) A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer 48:518–526
17. He MM, Wu WJ, Wang F et al (2013) S-1-based chemotherapy versus capecitabine-based chemotherapy as first-line treatment for advanced gastric carcinoma: a meta-analysis. PLoS ONE 8:e82798
18. Ter Veer E, Mohammad NH, Lodder P et al (2016) The efficacy and safety of S-1-based regimens in the first-line treatment of advanced gastric cancer: a systematic review and meta-analysis. Gastric Cancer 19:696–712
19. Feng Z, Yan P, Hou X et al (2020) The efficacy and safety of capecitabine-based versus S-1-based chemotherapy for metastatic or recurrent gastric cancer: a systematic review and meta-analysis of clinical randomized trials. Ann Palliat Med 9:883–894
20. Stewart LA, Clarke M, Rovers M et al (2015) Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA 313:1657–65
21. Kawakami H, Nishikawa K, Shimokawa T et al (2022) Histology classification highlights differences in efficacy of S-1 versus capecitabine, in combination with cisplatin, for her2-negative unresectable advanced or recurrent gastric cancer with measurable disease. Cancers 14:5673
22. Ryu MH, Baba E, Lee KH et al (2015) Comparison of two different S-1 plus cisplatin dosing schedules as first-line chemotherapy for metastatic and/or recurrent gastric cancer: a multicenter, randomized phase III trial (SOS). Ann Oncol 26:2097–2101
23. Takashima A, Iizumi S, Boku N (2017) Survival after failure of first-line chemotherapy in advanced gastric cancer patients: differences between Japan and the rest of the world. Jpn J Clin Oncol 47:583–589
24. Cancer Genome Atlas Research N (2014) Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513(7517):202–209
25. Ajani JA, Rodriguez W, Bodoky G et al (2010) Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 28:1547–1553

26. Ajani JA, Abramov M, Bondarenko I et al (2017) A phase III trial comparing oral S-1/cisplatin and intravenous 5-fluorouracil/cisplatin in patients with untreated diffuse gastric cancer. Ann Oncol 28:2142–2148
27. Shirasaka T, Shimamato Y, Ohshimo H et al (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–57
28. Yamada Y, Higuchi K, Nishikawa K et al (2015) Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. Ann Oncol 26:141–148
29. Janjigian YY, Shitara K, Moehler M et al (2021) First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. The Lancet 398:27–40
30. Kang YK, Chen LT, Ryu MH et al (2022) Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 23:234–247
31. Boku N, Ryu MH, Kato K et al (2019) Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). Ann Oncol 30:250–58

Authors and Affiliations

Kazuhiro Nishikawa[1] · Hisato Kawakami[2] · Toshio Shimokawa[3] · Kazumasa Fujitani[4] · Shigeyuki Tamura[5] · Shunji Endo[6] · Michiya Kobayashi[7] · Junji Kawada[4] · Yukinori Kurokawa[8] · Akira Tsuburaya[9] · Takaki Yoshikawa[10] · Junichi Sakamoto[11] · Taroh Satoh[12] · for HERBIS-2, HERBIS-4A, XParTS I. I. study investigators

✉ Kazuhiro Nishikawa
kazuno13@hotmail.co.jp

[1] Cancer Treatment Center, Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka 543-0035, Japan

[2] Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

[3] Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan

[4] Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan

[5] Department of Surgery, Yao Municipal Hospital, Yao, Japan

[6] Department of Digestive Surgery, Kawasaki Medical School Hospital, Kurashiki, Japan

[7] Cancer Treatment Center, Kochi Medical School Hospital, Nankoku, Japan

[8] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Japan

[9] Department of Surgery, AOI Nanasawa Rehabilitation Hospital, Atsugi, Japan

[10] Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan

[11] Tokai Central Hospital, Kakamigahara, Japan

[12] Palliative Care Center, Osaka University Hospital, Suita, Japan