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Original Research

A phase II multicenter trial assessing the efficacy and safety of first-line S-1 + ramucirumab in elderly patients with advanced/recurrent gastric cancer: KSCC1701☆

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KEYWORDS
Elderly patient;
gastric cancer;
S-1;
Ramucirumab

Abstract ***Background:*** The mainstream first-line chemotherapy for advanced/recurrent gastric cancer (ARGC) is combination therapy including platinum-based agents. With the progressive aging of the society, the incidence of gastric cancer in elderly patients is increasing. However, elderly patients cannot tolerate these agents because of renal dysfunction or low quality of life. The KSCC1701 study explored the efficacy and safety of S-1 + ramucirumab in elderly patients with ARGC.

Patients and methods: Chemotherapy-naive patients aged ≥70 years with ARGC were eligible. Patients received S-1 (40–60 mg twice daily for 4 weeks in 6-week cycles) and ramucirumab (8 mg/kg every 2 weeks) until disease progression. The primary end-point was the 1-year overall survival (OS) rate. The anticipated lower threshold of 1-year survival was set at 40% in light of previous S-1–based regimens. The secondary end-points included progression-free survival (PFS), OS, the overall response rate (ORR) and safety.

Results: Between September 2017 and November 2019, 48 patients (34 men and 14 women) were enrolled in this study. The median patient age was 77.5 years, and all patients had a performance status of 0 (n = 20) or 1 (n = 28). The 1-year OS rate was 65.2%, which met the primary end-point. The median survival time and median PFS were 16.4 and 5.8 months, respectively. The ORR was 41.9%. The most frequent grade 3/4 (≥15%) adverse events were neutropenia, anorexia and anaemia.

Conclusion: Considering these findings, S-1 + ramucirumab appears to be an excellent treatment option for elderly patients with ARGC. (250 words).

This trial has been registered with the Japan Registry of Clinical Trials Registry under the number jRCTs071180066.

1. Introduction

Gastric cancer remains an important cancer globally, ranking fifth in incidence and fourth in mortality [1]. With the progressive aging of the society, the incidence of gastric cancer in elderly patients is increasing [2]. This trend has been observed in many countries such as China, Korea and Taiwan. The development of new therapies for elderly people is a common challenge in these countries.

The mainstream first-line chemotherapy for advanced/recurrent gastric cancer (ARGC) consists of combination regimens. For example, triplet chemotherapy regimens such as ECF (epirubicin + cisplatin + 5-fluorouracil), EOX (epirubicin + oxaliplatin + capecitabine) and DCF (docetaxel + cisplatin + 5-fluorouracil) are widely used in Western countries [3–5], whereas doublet regimens such as SP (tegafur/gimeracil/oteracil (S-1) + cisplatin) and SOX (S-1 + oxaliplatin) are common in Japan [6].

Many elderly patients are frail, making it difficult for them to receive intensive and toxic regimens such as DCF and SP [7]. S-1 alone is conditionally permitted and often used for elderly patients in Japan [8]. However, S-1 alone is not necessary for the optimal standard therapy in terms of efficacy for elderly patients with ARGC. Thus, new regimens for elderly patients with ARGC with adequate antitumor efficacy and low toxicity are needed in an accelerated aging society.

Incidentally, Yoon et al. reported that FOLFOX + ramucirumab provides significantly longer progression-free survival (PFS) than FOLFOX + placebo in chemotherapy-naive patients with gastric or gastro-esophageal junctional cancer [9], illustrating that ramucirumab combined with existing agents might represent a promising frontline regimen. Moreover, the subset analysis revealed that PFS was also favourable in patients aged ≥65 years who received ramucirumab in the REGARD and RAINBOW trials [10,11]. In addition, in the REGARD trial, performance status (PS) was maintained for significantly longer in the ramucirumab group than in the placebo group [9], which might be favourable for elderly patients. Accordingly, ramucirumab is promising for use in combination with 5-FU in elderly patients.

Therefore, we conducted the KSCC1701 single-arm phase II study to explore the efficacy and safety of S-1 + ramucirumab in elderly patients with ARGC.

2. Patients and Methods

2.1. Study design

This multicenter, open-label, single-arm phase II trial was conducted at 42 institutions in Japan. The primary end-point was the 1-year survival rate, and the secondary end-points included overall survival (OS), PFS, the overall response rate (ORR) and safety. The 1-year OS rate was calculated as the percentage of patients who survived for 1 year from the date of enrolment. PFS was defined as the time from enrolment to the first documentation of disease progression or death from

any cause. OS was defined as the time from enrolment to death from any cause. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria version 4.0. ORR, and the percentage of patients with a complete response (CR) or partial response (PR) was assessed by the investigator of each institution.

The study was conducted in accordance with Good Clinical Practice guidelines and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, and the protocol was approved by the institutional review board or ethics committee at each institution. All patients provided written informed consent.

2.2. Patients

Patients at least 70 years old with histologically confirmed ARGC (HER2-negative or undeterminable) who had measurable disease or assessable disease were eligible for the study. Patients who received previous chemotherapy (including adjuvant therapy within 24 weeks before recurrence) or radiotherapy (excluding palliative purposes, such as bone metastasis) for metastatic disease were excluded. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, adequate organ function, sufficient oral intake and a life expectancy of at least 90 days. All patients provided written informed consent before enrolment. Patients were excluded if they had symptomatic brain metastasis, pre-existing uncontrolled hypertension, ascites or pleural effusion requiring treatment, major surgery or open biopsy within 4 weeks before enrolment, urinary protein ≥2+, daily treatment with high-dose aspirin (≥325 mg/day) or non-steroidal anti-inflammatory medications, concomitant non-malignant disease such as cardiac, pulmonary, renal or hepatic disease or uncontrolled infection.

2.3. Treatment

Ramucirumab (8 mg/kg) was administered every 2 weeks, and S-1 was administered orally twice daily for 14 consecutive days at a dose 40 mg/m^2 based on the patient's body surface area adjusted for creatinine clearance, as calculated by the Cockcroft–Gault formula (Fig. 1). Before our study, this regimen was applied in the TCOG phase II trial (first-line S-1 in patients older than 75 years with ARGC) [12] and the WJOG8315G study (first-line S-1 or SOX in patients ≥70 years old with ARGC). We have applied this regimen to reduce the adverse effects of S-1.

2.4. Statistical hypothesis

The principal hypothesis for this study was that 'subjects receiving the protocol treatment (S-1 + ramucirumab) will have better 1-year survival than historical controls (subjects receiving S-1 alone)'. If this hypothesis is validated, then S-1 + ramucirumab is a promising treatment.

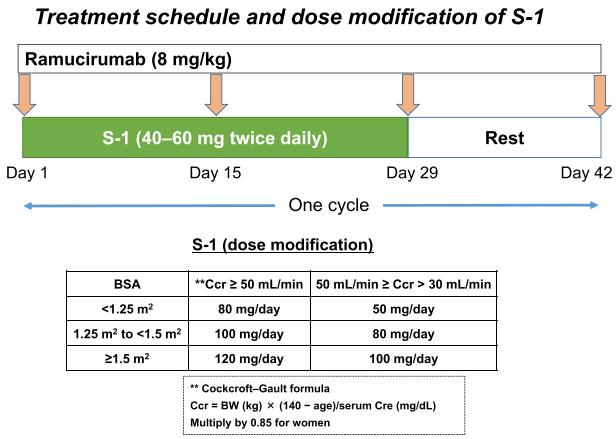

Fig. 1. Method of S-1 + ramucirumab administration. BSA, bovine serum albumin; Ccr, creatinine clearance; BW, body weight; Cre, creatinine.

Previous phase III studies (JCOG9912 and SPIRITS studies) in Japan indicated that the 1-year survival rates for subjects receiving S-1 alone were 47.863% (95% confidence interval [CI] = 41.335%–54.089%) [13] and 46.7% (95% CI = 38.7%–54.7%) [14], respectively. The efficacy of a platinum agent and ramucirumab cannot be compared directly, and the current study was a small phase II study of elderly patients. Given these facts, a 1-year OS rate of approximately 60% would suggest that adding ramucirumab to S-1 has the same benefit as adding a platinum agent. However, if the 1-year survival rate was lower than 40%, which was the lower bound of the 95% CI in the two aforementioned studies, then added ramucirumab presumably offers no benefit. Thus, the threshold for the 1-year survival rate was 40%, and the expected value was 60%. The one-tailed level of significance was 5%, and the power was 80%. Using an exact method based on a binomial distribution, the sample size required to achieve the aforementioned power was 44 patients. Assuming that some patients would become ineligible after enrolment, the target sample size was 48 patients.

2.5. Statistical analysis

The median survival time (MST) and median PFS were calculated using the Kaplan–Meier method. $P < 0.05$ indicated statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Response Evaluation Criteria for Solid Tumors version 1.1 was used to evaluate antitumor effects. The Charlson comorbidity index was recorded at the time of enrolment to examine concomitant diseases, and the G8 screening tool was employed

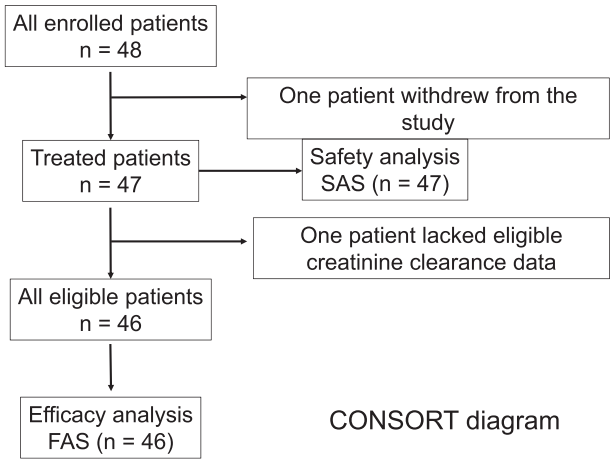

Fig. 2. CONSORT diagram of S-1 + ramucirumab. SAS, safety analysis set; FAS, full analysis set.

before treatment to assess patients' suitability for treatment [7] (see supplementary materials).

3. Results

3.1. Patients' characteristics

Between September 2017 and November 2019, 48 patients were enrolled in this study. The study cohort included 34 men and 14 women with a median age of 77.5 years (range, 71–87), and ECOG PS was 0 in 20 patients and 1 in 28 patients. As shown in Fig. 2, the outcomes of 47 patients in the safety analysis set and 46 patients in the full analysis set were reviewed. The characteristics of the patients are presented in Table 1 [15] (for the full version, see Table S1).

Table 1
Patient characteristics.

Variables		All enrolled patients
		N = 48
Age	Median	77.5 (71–87)
Sex	Male	34 (70.8%)
	Female	14 (29.2%)
Performance status	0	20 (41.7%)
	1	28 (58.3%)
Primary tumour site	EGJ	3 (6.3%)
	Upper	11 (22.9%)
	Middle	15 (31.3%)
	Lower	19 (39.6%)
Liver metastasis	Yes	10 (20.8%)
	No	38 (79.2%)
Pathology	Papillary	2 (4.2%)
	Tubular	18 (37.5%)
	Poorly	20 (41.7%)
	Signet ring	3 (6.3%)
	Mucinous	3 (6.3%)
	Not investigated	2 (4.2%)
Measurable lesions	No	17 (35.4%)
	Yes	31 (64.6%)

EGJ, esophagogastric junction, IHC, immunohistochemistry; FISH, fluorescence in situ hybridization.

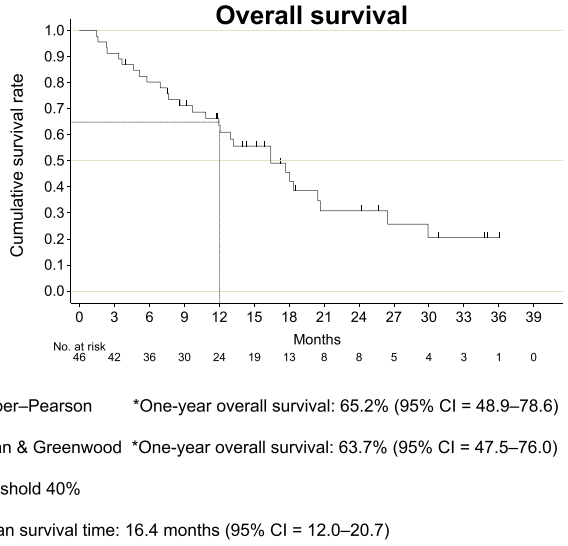

Fig. 3. Kaplan–Meier curve of overall survival for S-1 + ramucirumab, CI, confidence interval.

3.2. Time-to-event measurement

The data cut-off date was December 28, 2020. The median follow-up period was 12.5 months (range, 11.7–36). As shown in Fig. 3, the 1-year OS rate was 63.7% (95% CI = 47.5–76.0) as calculated through Kaplan–Greenwood analysis. This rate exceeded 40%, meaning that this trial met the primary end-point. MST reached 16.4 months (95% CI = 12.0–20.7).

As shown in Fig. 4, median PFS was 5.8 months (95% CI = 4.0–7.2). In the subset analysis, age (<79 versus ≥80), PS (0 versus 1), the presence of measurable lesions

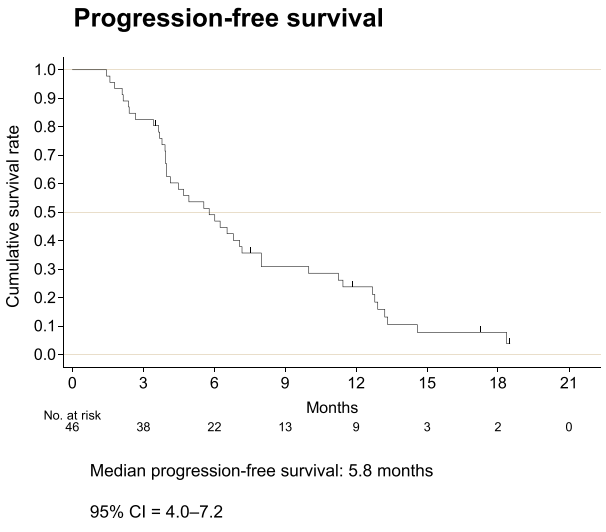

Fig. 4. Kaplan–Meier curve of progression-free survival for S-1 + ramucirumab, CI, confidence interval.

Table 2
Subset analysis of OS and PFS.

Variables	OS, HR (95% CI)	PFS, HR (95% CI)
Age (<79 versus ≥80)	0.708 (0.324–1.548), P = 0.3840	0.603 (0.310–1.173), P = 0.1311
PS (0 versus 1)	0.637 (0.292–1.389), P = 0.2526	0.770 (0.410–1.445), P = 0.4127
Measurable lesions (yes/no)	0.819 (0.370–1.814), P = 0.6221	0.874 (0.453–1.686), P = 0.6856
Gastrectomy (yes/no)	1.018 (0.445–2.328), P = 0.9664	0.725 (0.371–1.416), P = 0.3424

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

(yes/no), and gastrectomy (yes/no) did not influence OS or PFS, as presented in Table 2 (Kaplan–Meier curves are presented in supplementary figures).

Progressive disease (60.4%) and adverse events (20.8%) were the most common reasons for treatment discontinuation. The rate of transition to second-line therapy was 55.3%.

3.3. Antitumor effect and number of treatment courses

As presented in Table 3, the ORR was 41.9% (n = 13). The CR, PR, stable disease and progressive disease rates were 3.2% (n = 1), 38.7% (n = 12), 38.7% (n = 12) and 16.1% (n = 5), respectively, whereas the response was unknown in one patient (3.2%). The median number of treatment courses was four (range, 1–10).

3.4. Adverse events

The most frequent grade 3/4 adverse events were neutropenia (27.7%), anorexia (23.4%), anaemia (19.1%), hypertension (14.9%), leucopaenia (12.8%) and hypoalbuminemia (12.8%, Table 4). No treatment-related deaths were observed (for full data, see Table S2).

3.5. Relationships of G8 scores with overall survival, progression-free survival, overall response rate and adverse events

We examined the associations of G8 scores with various factors. The G8 score ranges from 0 to 17, and a higher score indicates a better health status. The time-dependent receiver operating characteristic curve for 1-year survival revealed that the cut-off for the G8 score was 11 (area under the curve = 0.7844). It was necessary to set an original cut-off for Japanese patients because many elderly Japanese patients have a slender figure. For this reason, the cut-off of the G8 score was lower than that used in Western populations (G8 score = 14).

As shown in Fig. 5, the high G8 score group (≥11) had significant longer OS (P < 0.0001) and PFS (P = 0.0038) than the low G8 score group (<11). Furthermore, the high G8 score group tended to have better ORR and lower adverse event rates than the low G8 score group (Tables 5 and 6). Of the 46 patients, 31 (67.4%) received second-line chemotherapy, including 74.2% (23/31) of patients in the high G8 score group and 53.3% (8/15) of patients in the low G8 score group.

Table 3
Best overall response.

	n = 31
CR	1 (3.2%)
PR	12 (38.7%)
SD	12 (38.7%)
PD	5 (16.1%)
Not evaluable	1 (3.2%)
ORR	41.9% (95% CI = 24.5–60.9)

*Non-target: 15 patients.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CI, confidence interval.

4. Discussion

It is often difficult for elderly patients with ARGC to receive platinum agents in light of their deficient renal function or inadequate quality of life. Therefore, we developed a first-line combination chemotherapy regimen with an anti-VEGF agent without platinum agents. In this study, S-1 + ramucirumab provided longer OS and PFS

Table 4
Adverse events.

Haematological events	N = 47 (%)		
	All-grade	Grade 3	Grade 4
Anaemia	46 (97.9%)	6 (12.8%)	3 (6.4%)
Thrombocytopenia	37 (78.7%)	2 (4.3%)	0 (0.0%)
Neutropenia	36 (76.6%)	12 (25.5%)	1 (2.1%)
Leucopoenia	24 (51.1%)	5 (10.6%)	1 (2.1%)
Non-haematological events	**N = 47**		
	All-grade	Grade 3	Grade 4
Hypoalbuminemia	43 (91.5%)	6 (12.8%)	0 (0.0%)
Anorexia	42 (89.4%)	11 (23.4%)	0 (0.0%)
Hypertension	39 (83.0%)	7 (14.9%)	0 (0.0%)
Hypocalcaemia	34 (72.3%)	1 (2.1%)	1 (2.1%)
Fatigue	31 (66.0%)	1 (2.1%)	0 (0.0%)
Hyponatremia	27 (57.4%)	3 (6.4%)	0 (0.0%)
AST elevation	27 (57.4%)	2 (4.3%)	0 (0.0%)
Nausea	25 (53.2%)	3 (6.4%)	0 (0.0%)
Limb oedema	21 (44.7%)	1 (2.1%)	0 (0.0%)
Diarrhoea	20 (42.6%)	1 (2.1%)	0 (0.0%)
Hyperkalaemia	18 (38.3%)	2 (4.3%)	1 (2.1%)
Hypokalaemia	18 (38.3%)	2 (4.3%)	0 (0.0%)
Oral mucositis	15 (31.9%)	3 (6.4%)	0 (0.0%)
Respiratory disorders	5 (10.6%)	4 (8.5%)	1 (2.1%)
Dehydration	2 (4.3%)	2 (4.3%)	0 (0.0%)
Hypoxia	2 (4.3%)	1 (2.1%)	1 (2.1%)

AST, aspartate aminotransferase.

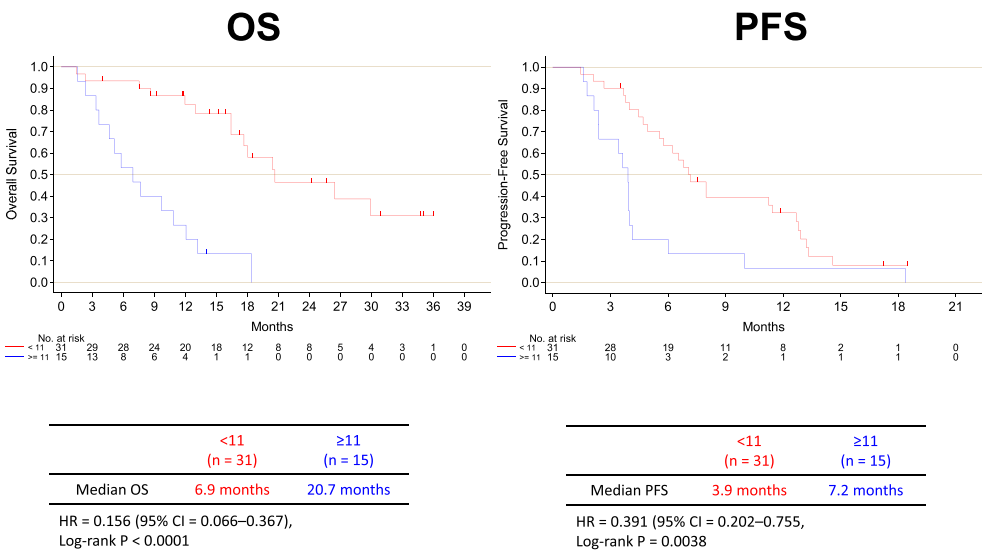

Fig. 5. Kaplan–Meier curves of OS and PFS for S-1 + ramucirumab by the G8 score, Red line, G8 score <11; blue line, G8 score ≥11, OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Table 5
Best response stratified by the G8 score.

	<11 (N = 13)	≥11 (N = 18)
CR	0 (0.0%)	1 (5.6%)
PR	3 (23.1%)	9 (50.0%)
SD	7 (53.8%)	5 (27.8%)
PD	3 (23.1%)	2 (11.1%)
Not evaluable	0 (0.0%)	1 (5.6%)
ORR	23.1% (95% CI: 5.0–53.8)	55.6% (95% CI: 30.8–78.5) P = 0.1392

*Non-target: 15 patients.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CI, confidence interval

Table 6
Adverse event rates stratified by the G8 score.

	<11 (n = 16)	≥11 (n = 31)
<Grade 3	3 (18.8%)	7 (22.6%)
≥Grade 3	13 (23.1%)	9 (77.4%) N.S.

and a better ORR than recorded for S-1 monotherapy in the JCOG9912 and SPIRITS trials [13,14].

Capecitabine + bevacizumab [16] has been recommended and widely used in patients with metastatic colorectal cancer who are elderly or who do not wish to receive a toxic regimen. However, among patients with gastroesophageal cancer, the AVAGAST trial illustrated that the addition of bevacizumab to CDDP + capecitabine/5-FU did not improve survival versus placebo + chemotherapy [17]. Therefore, we did not use an anti-VEGF combination as the frontline therapy for ARGC. Incidentally, the rate of VEGF-C protein expression in patients with gastric cancer was reported to range 26%–51% [18]. Lymphangiosis was also reported to arise in patients with gastric cancer through the Akt/MMR/VEGF-C/VEGF-D signalling pathway [19]. In addition, the combined overexpression of VEGF-A and VEGF-C is significantly correlated with poor survival in patients with gastric cancer [20]. Ramucirumab, which can inhibit VEGF-C and VEGF-D in addition to VEGF-A [21], might be a more appropriate treatment for gastric cancer than bevacizumab, which only inhibits VEGF-A.

Several trials of first-line combination regimens including ramucirumab have been reported [22,23]. In the RAINFALL trial, PFS was prolonged by the addition of ramucirumab to CDDP + 5-FU/capecitabine, but OS was not extended. Meanwhile, neither PFS nor OS was prolonged by the addition of ramucirumab to SOX in the RAINSTORM trial. Given the lack of effects on OS in the RAINFALL and RAINSTORM trials, some detrimental effects may have been induced by the addition of ramucirumab to the regimens. As a frontline treatment, ramucirumab in combination with a 5-FU derivative without platinum agents may be promising.

Elderly patients in fairly good general condition can be administered the combination of platinum and fluoropyrimidine, which is the international standard-of-care first-line chemotherapy for ARGC. The advantages of this combination therapy in elderly patients include higher response rates and longer survival. Its disadvantages include greater rates of toxicity, such as renal failure or peripheral neuropathy, especially in elderly patients. In addition, elderly patients generally tend to experience renal or hepatic dysfunction after chemotherapy.

We have reviewed the difference in outcomes between S-1 + ramucirumab and S-1, SP, and SOX. Data for S-1 and SP were obtained from the SPIRITS trial [14], and those for SOX were taken from the G-SOX study [6]. The rates of all-grade haematological adverse events, anorexia, fatigue, creatinine elevation, and hyponatremia

were higher in the S-1 + ramucirumab group. The incidence of adverse events was generally higher for S-1 + ramucirumab than for S-1 monotherapy but lower than that of SOX or SP (Table S3). Considering that only patients at least 70 years old were included in this study, the safely of S-1 + ramucirumab was acceptable. Because S-1 + ramucirumab was provided to elderly patients, who usually have some complications and lack normal functioning, caution is needed to prevent haematological adverse events (≥50%, all-grade), anorexia, and hypertension. However, unmanageable adverse events and treatment-related deaths were not observed, indicating that S-1 + ramucirumab might represent a safe regimen for elderly patients.

Our results demonstrated that patients with G8 scores of ≥11 had significantly longer OS. Although the cut-off of 11 was determined by the OS analysis, patients with G8 scores of ≥11 also had significantly longer PFS than those with lower scores. Moreover, patients with high G8 scores tended to have better ORR and adverse event rates. These results highlighted the utility of the G8 score for identifying elderly patients with ARGC who are suitable for S-1 + ramucirumab to some extent, although some patients with lower G8 scores may have also been suitable for this regimen.

In patients with HER2-positive tumours, trastuzumab-containing regimens such as 5-FU + CDDP + trastuzumab could have worrisome side-effects. When patients cannot tolerate CDDP because of older age, 5-FU + trastuzumab could be considered.

Recently, immune checkpoint inhibitors (ICIs) have been approved and introduced for the first-line treatment of ARGC. ICIs can be administered to elderly patients, but they require platinum-based regimens. In addition, ICIs carry the possibility of immune-related adverse events. It would be better to use ICIs alone as salvage therapies for elderly patients to reduce adverse events. S-1 + ramucirumab can be a well-balanced regimen for elderly patients even in the era of ICI-containing regimens for ARGC.

One limitation of this phase II study was the small number of cases. Therefore, survival and response might have been overestimated. A larger phase II or phase III study should be conducted to confirm the efficacy of S-1 + ramucirumab.

5. Conclusion

Considering the good antitumor efficacy and acceptable toxicity, the combination of S-1 and ramucirumab appears effective and safe for elderly patients with ARGC.

Authors' contributions

Masaki Mori and Hideo Baba had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of data analysis. Concept and design: Koichi Suyama, Hiroshi Saeki and Akitaka Makiyama. Acquisition, analysis or interpretation of data: All authors. Quality control of data: Eiji Oki, Koichi Suyama, Hiroshi Saeki and Akitaka Makiyama. Drafting of the manuscript: Kazuma Kobayshi, Koichi Suyama and Eiji Oki. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Mototsugu Shimokawa. Administrative, technical or material support: Eiji Oki, Hiroshi Saeki and Akitaka Makiyama. Supervision: Eiji Oki.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.02.028.

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