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ORIGINAL ARTICLE

Safety, pharmacokinetic, and clinical activity profiles of ramucirumab in combination with three platinum/fluoropyrimidine doublets in Japanese patients with chemotherapy-naïve metastatic gastric/gastroesophageal junction cancer

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Abstract

Background We evaluated the safety, tolerability, pharmacokinetics, and tumor response of ramucirumab in combination with one of three platinum/fluoropyrimidine regimens in Japanese patients with chemotherapy-naïve metastatic gastric/gastroesophageal junction cancer.

Methods In this phase 1b study, patients received 8 mg/kg ramucirumab on days 1 and 8 every 3 weeks, following one of three regimens: capecitabine + cisplatin, XP; S-1 + cisplatin, SP; or S-1 + oxaliplatin, SOX. The primary objective was to assess safety and tolerability; the secondary objectives were to evaluate pharmacokinetics and tumor response.

Results Six patients were treated in each cohort. All regimens were generally well tolerated, although 1 patient in SOX was associated with grade 3 enterocolitis, which was considered a dose-limiting toxicity. Common grade 3 or higher adverse events included neutropenia (1 in XP, 3 in SP, and 2 in SOX), decreased appetite (1 in SP), and hypertension (2 in XP). The mean trough ramucirumab concentrations were consistent across all cohorts, and those of most patients exceeded target levels, which were estimated from previous studies of the approved ramucirumab dose (8 mg/kg every 2 weeks). Among the 11 patients with measurable disease, overall response rate and disease control rate were 45.5% and 100.0%, respectively. Median progression-free survival (95% CI) was 7.6 months (6.0 to not estimable).

Conclusion Ramucirumab 8 mg/kg on days 1 and 8 every 3 weeks in combination with XP, SP, or SOX was generally well tolerated and demonstrated preliminary anti-tumor activity in chemotherapy-naïve Japanese metastatic gastric/gastroesophageal junction cancer patients.

Keywords Ramucirumab · IMC-1121B · Anti-VEGF-R2 antibody · Advanced gastric cancer · Japanese

Introduction

Gastric cancer is the fifth most common cancer worldwide and is responsible for 952,000 new diagnoses worldwide and 723,000 deaths annually [1]. In Japan, gastric cancer is the second most frequently diagnosed cancer, with 132,200 reported incidences and 47,900 deaths in 2012 [2], making it the second leading cause of cancer deaths. Although a large proportion of gastric cancer is diagnosed in the early stage as the consequence of screening programs and early access to endoscopy [3], one sixth of patients are still diagnosed at an unresectable stage [4]. For such patients, systemic chemotherapy is the mainstay of treatment [5, 6].

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Combinations with fluoropyrimidines and platinum-based agents such as S-1 plus cisplatin (SP), S-1 plus oxaliplatin (SOX), and capecitabine plus cisplatin (XP) have been used as first-line therapy for metastatic gastric/gastroesophageal junction cancer (mGC), resulting in a median progression-free survival (PFS) of 5–6 months and a median overall survival (OS) of 10–15 months [7–12]. Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), significantly increased the OS of HER2-positive mGC patients, which consist of around 10–20% of all GC patients. However, several subsequent randomized studies failed to show benefits of other molecular targeting agents for mGC in first-line treatment [13–16]; thus, development of more effective combinations is necessary.

Ramucirumab, a fully human IgG1 monoclonal antibody to the extracellular vascular endothelial growth factor (VEGF)-binding domain of VEGFR2, has become one of the standard chemotherapies for mGC on the basis of the findings of two pivotal global phase 3 trials, REGARD and RAINBOW [17, 18]. The REGARD and RAINBOW studies showed prolonged survival benefits for previously treated patients with ramucirumab monotherapy (8 mg/kg biweekly) compared with placebo, and ramucirumab (8 mg/kg biweekly) plus paclitaxel compared with paclitaxel alone, respectively. In the first-line setting, the efficacy of ramucirumab was evaluated in a randomized phase 2 study in patients with advanced gastric or esophageal adenocarcinoma (GEAC) in combination with 5-FU, leucovorin, and oxaliplatin (FOLFOX). However, the addition of ramucirumab to FOLFOX did not improve PFS [19]. A higher rate of discontinuation of study treatment for reasons other than progressive disease in the ramucirumab arm compared with the placebo arm was observed, which led to lower study drug exposure in the experimental arm. Meanwhile, exposure–efficacy response analyses performed on data obtained from REGARD and RAINBOW demonstrated that an increase in exposure is associated with favorable OS and PFS [17]. Further modeling suggested that the target clinically efficacious minimum concentration at steady state is approximately 50 μg/ml; thus, a more intensive dose schedule of ramucirumab (8 mg/kg on days 1 and 8 every 3-week schedule) was planned.

The aim of this phase 1b study in Japanese patients with mGC was to evaluate safety and tolerability as well as the pharmacokinetics (PK) and clinical activity of a new dose schedule of ramucirumab in combination with platinum/fluoropyrimidine chemotherapy as first-line treatment.

Patients and methods

Study design

This was a multi-center, nonrandomized, open-label phase 1b study of ramucirumab (LY3009806; Eli Lilly and Company, Indianapolis, IN, USA) in combination with one of three platinum/fluoropyrimidine doublets including XP, SP, or SOX in chemotherapy-naïve Japanese patients with mGC. The study was conducted at four sites in Japan.

This study was approved by the institutional review boards of each institution and was conducted in accordance with international ethics guidelines, including the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practices Guideline [E6]. This study is registered at ClinicalTrials.gov (NCT02359058).

Patient eligibility

Criteria for patient enrollment in the study included (1) the presence of histologically or cytologically confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma that is metastatic or locally advanced and unresectable; (2) measurable or nonmeasurable, but evaluable, disease was determined using guidelines in the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1); (3) no prior first-line systemic chemotherapy; (4) 20 years of age or older; (5) a life expectancy of 12 weeks or more; (6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1; and (7) adequate hepatic, hematological, and renal functions.

Patients were excluded if they met any of the following exclusion criteria: (1) significant bleeding disorder, vasculitis, or a significant bleeding episode from the gastrointestinal tract within 12 weeks before enrollment; (2) uncontrolled hypertension, despite standard medical management; (3) serious or nonhealing wound or peptic ulcer or bone fracture at enrollment; (3) major surgery within 28 days before enrollment; (4) prior VEGF or VEGF-R targeted therapies; (5) dysphagia for oral medication; and (6) positive HER2 status. Informed consent was obtained from each patient before any protocol procedures or administration of study drug.

Drug administration and dose-limiting toxicity (DLT)

In each cycle, eligible patients received 8 mg/kg ramucirumab on days 1 and 8, every 3 weeks (q3w), in combination with XP q3w: capecitabine (2000 mg/m^2, days

1–14, PO) + cisplatin (80 mg/m^2, day 1, IV); SP every 5 weeks (q5w): S-1 (40 mg/m^2 bid, days 1–21, PO) + cisplatin (60 mg/m^2, day 8, IV); or SOX q3w: S-1 (40 mg/m^2 bid, days 1–14, PO) + oxaliplatin (100 mg/m^2, day 1, IV). Treatment was continued until disease progression, occurrence of unacceptable severe toxicity, or request by subject.

Dose-limiting toxicity (DLT) was defined as an adverse event (AE) during cycle 1 that was possibly related to the treatment, and met any one of the following criteria: Common Terminology Criteria for Adverse Events (CTCAE, version 4.03), ≥grade 3 nonhematological toxicity except for nausea, vomiting, constipation, diarrhea, fatigue, anorexia, hypersensitivity, or electrolyte abnormality that was manageable with appropriate care; grade 3 rash that dissolved within 7 days with appropriate management; grade 3 hypertension, if subsequently controlled, transient (≤7 days); grade 3 liver enzyme elevations, without evidence of other hepatic injury; grade 3 thrombocytopenia associated with significant bleeding that required platelet transfusion, or grade 4 thrombocytopenia; grade 4 neutropenia of >7 days duration; febrile neutropenia; any toxicity that induced a >21-day delay of study treatment.

Relative dose intensity was defined as the ratio of actual dose intensity to the planned dosed intensity. Dose intensity was calculated as the ratio of cumulative dose to the treatment duration per cycle.

Safety assessment

Adverse events were assessed throughout the treatment period up to 30 days after the decision of study treatment discontinuation. Safety assessments were based on medical review of AEs as well as vital sign measurements, physical examination, ECOG performance status, and findings of clinical laboratory test findings.

Pharmacokinetic analysis

Blood samples for determination of serum ramucirumab concentrations were scheduled before infusion (trough or C_{min}) for doses 1–11 and at end of infusion for doses 1, 2, 5, 6, 9, and 10, and at 30-day follow-up. Serum ramucirumab concentrations obtained in each cohort were compared and evaluated whether trough serum ramucirumab concentrations achieved expected target concentration at steady state (∼50 μg/ml).

Tumor response and statistical analysis

Radiologic tumor evaluations were performed by computed tomography at baseline, every 6 weeks after the first dose of study medication, and at the 30-day safety follow-up visit.

Tumor response was evaluated according to RECIST version 1.1. Objective response rate (ORR) was defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR) in patients with measurable disease. Disease control rate (DCR) was defined as the proportion of patients with the best overall response of CR, PR, or stable disease (SD). Progression-free survival (PFS) was assessed for each patient who received at least one dose of ramucirumab, which was defined as the time from the date enrollment until disease progression or death. If a patient had not progressed or discontinued from the study for other reasons, the subject was censored. PFS was estimated together with exact 95% confidence intervals (CIs).

The safety population included all enrolled patients who received any study medication, regardless of their eligibility for the study.

The DLT population included all enrolled patients who completed the first cycle of study medication or discontinued study medication because of a DLT during cycle 1. The DLT population was used for determination of the recommended dose.

Statistical analysis of safety and efficacy was performed with the use of SAS release 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Eighteen patients were enrolled in the study from 18 February 2015 until 4 October 2016 and assigned to one of three treatment cohorts. Median age across all cohorts was 62 years (range, 45–74). Histology was mostly diffuse type. Eleven patients had measurable disease (Table 1).

Tolerability and adverse events

All 18 patients received at least one dose of ramucirumab, which constituted the safety population as well as the DLT population. At the time of data cutoff on 25 January 2017, all patients discontinued study treatment: 12 (66.7%) by progressive disease, 2 (11.1%) by adverse events (AEs), 2 (11.1%) by physician decision, and 2 (11.1%) by patient decision.

Treatment was generally well tolerated, although one patient in SOX had grade 3 enterocolitis, which was considered a DLT. This event was resolved after discontinuation of treatment. Neutropenia was the main cause of dose modification in the SP and SOX cohorts. Dose

Table 1 Patient and tumor characteristics at baseline

Characteristic	XP + RAM ($n = 6$)	SP + RAM ($n = 6$)	SOX + RAM ($n = 6$)	Total ($N = 18$)
Male, *n*	2	0	6	8
Age, median (range), years	57.0 (45–74)	61.0 (48–67)	65.5 (49–68)	62.0 (45–74)
ECOG PS, *n*				
0	6	4	6	16
1	0	2	0	2
Primary site, *n*				
Gastric	5	6	5	16
Gastroesophageal junction	1	0	1	2
Histology, *n*				
Intestinal	1	0	2	3
Diffuse	4	6	3	13
Mixed	1	0	1	2

ECOG PS Eastern Cooperative Oncology Group Performance Status, *RAM* ramucirumab, *SOX* S-1 + oxaliplatin, *SP* S-1 + cisplatin, *TEAE* treatment-emergent adverse event, *XP* capecitabine + cisplatin

Table 2 Treatment-emergent adverse events

AE, *n* (%)	XP + RAM ($n = 6$)		SP + RAM ($n = 6$)		SOX + RAM ($n = 6$)		Total ($N = 18$)	
Grade	Any	3/4	Any	3/4	Any	3/4	Any	3/4
≥1 treatment-related TEAE	6 (100)	2 (33.3)	6 (100)	5 (83.3)	5 (83.3)	4 (66.7)	17 (94.4)	11 (61.1)
Neutropenia	5 (83.3)	1 (16.7)	6 (100)	3 (50.0)	4 (66.7)	2 (33.3)	15 (83.3)	6 (33.3)
Decreased appetite	3 (50.0)	0	6 (100)	1 (16.7)	3 (50.0)	0	12 (66.7)	1 (5.6)
Constipation	5 (83.3)	0	4 (66.7)	0	2 (33.3)	0	11 (61.1)	0
Nausea	3 (50.0)	0	5 (83.3)	0	3 (50.0)	0	11 (61.1)	0
Hypertension	3 (50.0)	2 (33.3)	4 (66.7)	0	2 (33.3)	0	9 (50.0)	2 (11.1)
Palmar-plantar erythrodysesthesia syndrome	3 (50.0)	0	1 (16.7)	0	2 (33.3)	0	6 (33.3)	0
Fatigue	1 (16.7)	0	3 (50.0)	0	0	0	4 (22.2)	0
Thrombocytopenia	0	0	3 (50.0)	2 (33.0)	2 (33.0)	2 (33.0)	5 (27.8)	4 (22.2)
Diarrhea	0	0	2 (33.3)	0	2 (33.0)	0	4 (22.2)	0
Dysgeusia	0	0	4 (66.7)	0	0	0	4 (22.2)	0
Peripheral sensory neuropathy	0	0	1 (16.7)	0	3 (50.0)	0	4 (22.2)	0
≥1 treatment-related AESI	3 (50.0)		6 (100)		3 (50.0)		12 (66.7)	
Hypertension	3 (50.0)		4 (66.7)		2 (33.3)		9 (50.0)	
GGT increased	0		2 (33.3)		0		2 (11.1)	
ALT increased	0		1 (16.7)		0		1 (5.6)	
AST increased	0		1 (16.7)		0		1 (5.6)	
Proteinuria	0		1 (16.7)		1 (16.7)		2 (11.1)	
Epistaxis	0		1 (16.7)		0		1 (5.6)	
Infusion-related reaction	0		1 (16.7)		0		1 (5.6)	
Creatinine renal clearance decreased	0		1 (16.7)		0		1 (5.6)	
Pelvic venous thrombosis	0		1 (16.7)		0		1 (5.6)	

AE adverse event, *AESI* adverse event of special interest, *RAM* ramucirumab, *SOX* S-1 + oxaliplatin, *SP* S-1 + cisplatin, *TEAE* treatment-emergent adverse event, *XP* capecitabine + cisplatin

modifications for reasons of neutropenia were reported for five patients (83.3%), three patients (50.0%), and four patients (66.7%) in the XP + RAM, SP + RAM, and SOX + RAM cohorts, respectively. Common adverse events of grade 3 or higher were observed, including neutropenia: one (16.7%) in XP, three (50.0%) in SP, and two (33.3%) in SOX; decreased appetite: one (16.7%) in SP; and hypertension: two (33.3%) in XP (Table 2).

Treatment-related serious AEs were observed in three patients: two (33.3%) in SP and one (16.7%) in SOX: these included one (16.7%) with decreased appetite, one (16.7%) with pelvic venous thrombosis in SP, and one (16.7%) with enterocolitis in SOX. There were no treatment-related deaths.

Dose intensity and treatment duration are summarized in Table 3. The median relative dose intensity of ramucirumab during the first two cycles was similar among the three cohorts: that of ramucirumab over all cycles was 91.9% in the XP + RAM cohort, 88.8% in the SP + RAM cohort, and 76.2% in the SOX + RAM cohort, respectively. In terms of ramucirumab and fluoropyrimidine, the SP + RAM cohort and SOX + RAM cohort seemed to show a trend of longer duration of treatment than the XP + RAM cohort. Median duration of treatment for cisplatin was 16.6 and 26.1 weeks in the XP + RAM cohort and SP + RAM cohort, respectively, and that for oxaliplatin was 17.5 weeks in the SOX + RAM cohort.

Pharmacokinetics of ramucirumab

A total of 192 samples from 18 patients were within PK sampling windows and were included in the ramucirumab concentration–time summaries. As shown in Fig. 1, the mean trough concentrations of ramucirumab were consistent across all cohorts, and those of most patients exceeded target levels that were estimated from previous studies of the approved ramucirumab dose (8 mg/kg every 2 weeks). As projected, the dosing regimen of RAM used in the present study resulted in a higher trough serum RAM concentration than those of the biweekly dosing regimen, with most patients achieving concentrations above the biologically relevant target level (~50 μg/ml).

Tumor response

Among the 11 patients with measurable lesions, 5 patients (45.5%) had PR and 6 patients (55.5%) achieved SD (Table 4). Most patients with SD also achieved some degree of tumor shrinkage in target regions (Fig. 2). ORR was 45.5% and DCR was 100.0% (Table 4). Median PFS (95% CI) for all cohorts was 7.6 months (6.0–not estimable) (Fig. 3).

Discussion

In this study, we evaluated the safety, tolerability, PK, and tumor response of the new dosing schedule for ramucirumab in combination with first-line regimens as used in the currently ongoing RAINFALL trial [20]. All regimens were generally well tolerated, although one patient in SOX had a DLT (grade 3 enterocolitis). AEs were similar across regimens and comparable with other studies [8–11]. Neutropenia was the main cause of discontinuation, which is

Table 3 Dose intensity

	XP + RAM ($n = 6$)	SP + RAM ($n = 6$)	SOX + RAM ($n = 6$)
RAM			
Relative dose intensity (median: %)			
First two cycles	100.4	96.9	100.6
All cycles	91.9	88.8	76.2
Duration (median: weeks)	16.1	25.9	23.4
FP	Capecitabine	S-1	S-1
Relative dose intensity (median: %)			
First two cycles	98.2	83.9	81.7
All cycles	77.8	75.4	61.7
Duration (median: weeks)	16.2	26.8	23.1
Platinum	Cisplatin	Cisplatin	Oxaliplatin
Relative dose intensity (median: %)			
First two cycles	99.6	98.5	99.9
All cycles	79.6	90.4	82.4
Duration (median: weeks)	16.6	26.1	17.5

RAM ramucirumab, *SOX* S-1 + oxaliplatin, *SP* S-1 + cisplatin, *XP* capecitabine + cisplatin

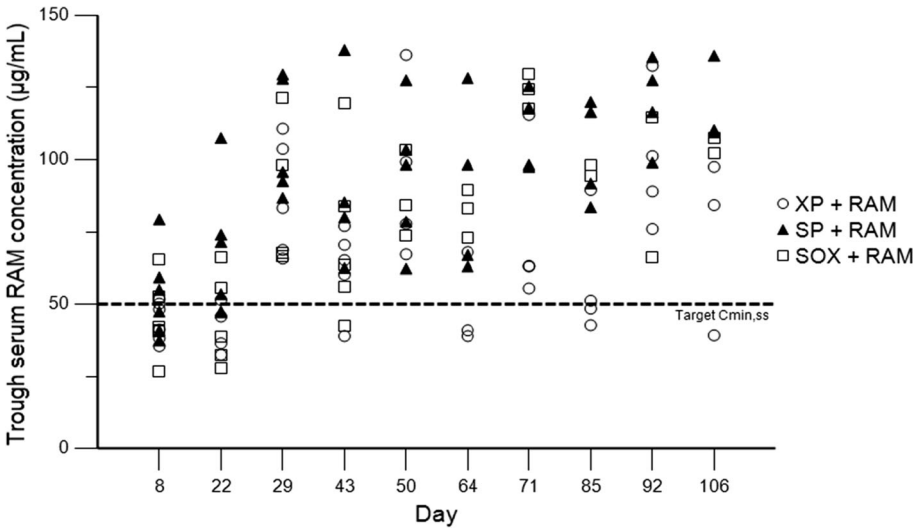

Fig. 1 Individual ramucirumab trough concentrations for Japanese patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following administration of 8 mg/kg ramucirumab on days 1 and 8 every 3 weeks as an intravenous infusion over approximately 1 h in combination with fluoropyrimidines and platinum-based agents. *Cmin,ss* minimum concentration at steady state, *RAM* ramucirumab, *SOX* S-1 + oxaliplatin, *SP* S-1 + cisplatin, *XP* capecitabine + cisplatin. *Dotted line* shows biologically relevant target levels at steady state

Table 4 Tumor response in patients with measurable disease

	XP + RAM ($n = 6$)	SP + RAM ($n = 6$)	SOX + RAM ($n = 6$)	Total ($N = 18$)
Patients with measurable disease, *n*	5	1	5	11
Best overall response				
Complete response, *n*	0	0	0	0
Partial response, *n*	1	1	3	5
Stable disease, *n*	4	0	2	6
Progressive disease, *n*	0	0	0	0
Overall response rate, *n* (%)	1 (20.0)	1 (100)	3 (60.0)	5 (45.5)
Disease control rate, *n* (%)	5 (100)	1 (100)	5 (100)	11 (100)

RAM ramucirumab, *SOX* S-1 + oxaliplatin, *SP* S-1 + cisplatin, *XP* capecitabine + cisplatin

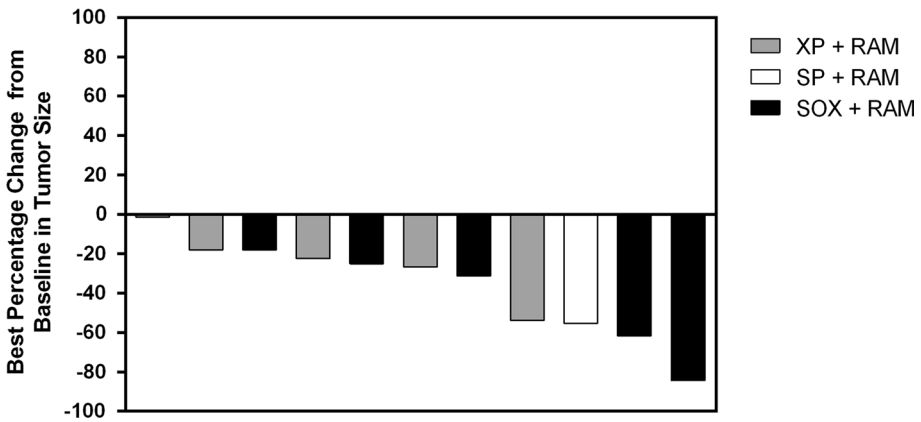

Fig. 2 Waterfall plot of maximal change in tumor size in 11 patients with measurable lesions. *RAM* ramucirumab, *SOX* S-1 + oxaliplatin, *SP* S-1 + cisplatin, *XP* capecitabine + cisplatin

consistent with other studies using fluoropyrimidine-containing regimens [10, 11, 21], as well as ramucirumab in combination with second-line paclitaxel (RAINBOW) [18] and ramucirumab in combination with FOLFOX as front-line therapy [19]. In this study, 33.3% of patients discontinued treatment for reasons other than PD, which is lower

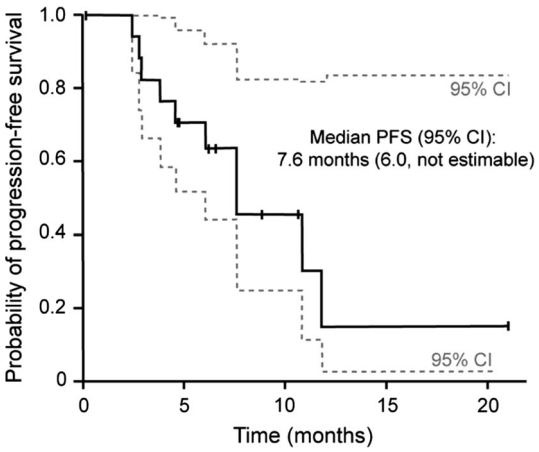

Fig. 3 Probability of progression-free survival (*PFS*) over the treatment period for the safety population ($N = 18$). Median PFS (95% CI) for all cohorts was 7.6 months (6.00–not estimable). *CI* confidence interval, *PFS* progression-free survival, *RECIST* Response Evaluation Criteria in Solid Tumors. "+" indicates a censoring point ("8 patients were censored: 1 patient had no post-baseline measurement and 7 patients were censored at the last measurement during the treatment period"); 1 month = 28 days. PFS is defined as the time from the first dose date until the first date of progressive disease (according to RECIST v.1.1) or death from any cause. Software: R 3.1.0, survfit () function, Kaplan–Meier method

than that in the previous FOLFOX + ramucirumab study (48%) [19]. Hypertension was the most frequently reported AE, which is an on-target and expected side effect of antiangiogenic treatments. Grade 3 hypertension was noted in only a few patients and was manageable with anti-hypertensive agents without discontinuation of ramucirumab. These findings suggest the manageable safety profile of fluoropyrimidine and platinum in combination with ramucirumab.

Despite the small sample size of each cohort and the high standard deviation in the SOX + RAM cohort, the three cohorts appeared to have a similar trend with respect to the dose intensity of ramucirumab.

An exposure–response relationship for ramucirumab was observed in REGARD and RAINBOW studies, in which higher exposures to ramucirumab were associated with improved PFS and OS [22]. Using the new dosing schedule of this study, the mean trough ramucirumab concentrations were consistent across all cohorts and exceeded target levels throughout treatment. Our data suggested that administration of ramucirumab at a dose of 8 mg/kg on days 1 and 8 of a 3qw regimen contributed to a higher trough concentration as compared to the current biweekly administration. However, the hypothesis that patients with higher ramucirumab trough concentrations attained a longer survival benefit than those with lower ones requires further testing by future trials.

The ORR of all cohorts and PFS in this study were comparable with previous studies [7–10]. However, because of the small sample size and lack of a control group as well as the small number of patients with measurable lesions, this study cannot definitively draw conclusions regarding the efficacy of the ramucirumab and XP/SP/SOX combination at the doses used in the study. A randomized, double-blind, placebo-controlled global phase 3 study is currently investigating capecitabine/fluorouracil (5-FU) and cisplatin with or without ramucirumab as first-line therapy for patients with mGC (RAINFALL) [15]. Additionally, a randomized, double-blind, placebo-controlled phase 2 Asian study is currently investigating S-1 and oxaliplatin with or without ramucirumab as first-line therapy in patients with mGC (RAINSTORM) [16].

In conclusion, ramucirumab at a dose of 8 mg/kg on days 1 and 8 of a 3qw regimen in combination with XP, SP, or SOX in the first-line setting was generally well tolerated and demonstrated a preliminary anti-tumor activity in chemotherapy-naïve Japanese patients with mGC. The trough levels of ramucirumab achieved were higher than those with other doses and schedules, without notable increases in toxicity. These results encourage moving forward with the global studies (RAINFALL and RAINSTORM) currently being conducted.

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Author contributions All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. K. Shitara, S. Kadowaki, T. Nishina, D. Sakai, and K. Muro were investigators in the study and were involved in data collection. R. Yoshikawa, Y. Piao, A. Ozeki, K. Inoue, and I. Gritli were involved in the study design and data analyses. A. Ozeki and K. Inoue conducted the statistical and pharmacokinetic analysis, respectively.

Compliance with ethical standards

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Human rights statement All procedures followed were in accordance with the ethical standard of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consents were obtained from all patients for their inclusion in the study.

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