Randomized Phase III Trial of Ramucirumab Beyond Progression Plus Irinotecan in Patients With Ramucirumab-Refractory Advanced Gastric Cancer: RINDBeRG Trial

Daisuke Sakai, MD[1,2]; Shigenori Kadowaki, MD, PhD[3]; Ryohei Kawabata, MD, PhD[4]; Hiroki Hara, MD[5]; Hironaga Satake, MD, PhD[6]; Masazumi Takahashi, MD, PhD[7]; Atsushi Takeno, MD, PhD[8]; Hiroo Imai, MD, PhD[9]; Keiko Minashi, MD[10]; Takeshi Kawakami, MD, PhD[11]; Shogen Boku, MD, PhD[12]; Jin Matsuyama, MD, PhD[13]; Yasuhiro Sakamoto, MD, PhD[14]; Kentaro Sawada, MD, PhD[15]; Masato Kataoka, MD, PhD[16]; Hisato Kawakami, MD, PhD[9,17]; Toshio Shimokawa, PhD[18]; Narikazu Boku, MD, PhD[19]; and Taroh Satoh, MD, PhD[2]

DOI https://doi.org/10.1200/JCO.24.01119

ABSTRACT

PURPOSE Continuous use of antiangiogenic agents has demonstrated survival benefits in various cancers. This trial aimed to compare the efficacy and safety of ramucirumab plus irinotecan with irinotecan monotherapy as a third- or later-line treatment for patients with advanced or recurrent gastric or gastroesophageal cancer (AGC) that has progressed on previous ramucirumab-based chemotherapy.

METHODS Patients age 20 years and older with AGC, who had experienced disease progression during ramucirumab-based chemotherapy, were randomly assigned to receive either ramucirumab plus irinotecan or irinotecan monotherapy. The primary end point was overall survival (OS) expecting a hazard ratio (HR) of 0.77 (a power of 80% and a significance level of one-sided 0.05). Secondary end points included progression-free survival (PFS), response rate, disease control rate (DCR), and safety.

RESULTS Between February 2017 and August 2022, 402 patients in Japan were randomly assigned to receive ramucirumab plus irinotecan (n = 202) or irinotecan monotherapy (n = 200). The median OS was 9.4 months in the combination arm and 8.5 months in the monotherapy arm, with an adjusted HR of 0.91 (95% CI, 0.74 to 1.12; $P = .49$). PFS was improved (median, 3.8 *v* 2.8 months; HR, 0.72 [95% CI, 0.59 to 0.89]; $P = .002$), while the DCR was significantly better (64.4% *v* 52.1%; $P = .03$) with the combination therapy. The adverse events of the combination therapy were manageable.

CONCLUSION Adding ramucirumab to irinotecan does not provide a significant advantage in OS over irinotecan alone in patients with AGC who have progressed during ramucirumab-containing chemotherapy.

Accepted February 19, 2025

Published May 23, 2025

J Clin Oncol 00:1-12

INTRODUCTION

Gastric cancer is the fifth most common malignancy worldwide and is the third leading cause of cancer-related mortality.[1] Systemic chemotherapy is the standard of care for patients with advanced unresectable or recurrent gastric cancer (AGC), to improve survival and quality of life. However, the prognosis remains poor, highlighting the urgent need for innovative therapeutic strategies.[2]

In Japan, third- or later-line chemotherapy is recommended for AGC patients with good performance status (PS), for whom irinotecan is an important option. In the WJOG4007 study, which compared paclitaxel and irinotecan in a second-line setting in a Japanese population, 89% and 72% of patients in the paclitaxel and irinotecan groups, respectively, received third-line therapy.[3] Moreover, to improve patient survival after second-line treatment, a powerful treatment strategy is needed.

Ramucirumab is a human monoclonal antibody (IgG1) specifically targeting the vascular endothelial growth factor receptor 2 (VEGFR-2). It inhibits angiogenesis by blocking the binding of VEGFR ligands, such as VEGF-A, VEGF-C, and

CONTEXT

Key Objective

This study aimed to assess the efficacy and safety of adding ramucirumab to irinotecan in patients with advanced gastric cancer who have progressed on previous ramucirumab-based chemotherapies.

Knowledge Generated

To our knowledge, this phase III trial is the first to investigate the efficacy of sustained antiangiogenic therapy in advanced gastric cancer. There was no significant improvement in overall survival with the combination therapy compared with irinotecan monotherapy.

Relevance *(E.M. O'Reilly)*

The authors address a clinically relevant question of whether there is value to continuation of an anti–vascular endothelial growth factor agent (in conjunction with a cytotoxic agent switch) in a third-line setting following disease progression. The results of this phase III trial provide definitive proof that this strategy is ineffective in late-line treatment of gastroesophageal cancers.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD, FASCO.

VEGF-D. Angiogenesis inhibitors not only block tumor angiogenesis and induce tumor regression but also remodel the vasculature,[4,5] promoting anticancer drug delivery at the tumor site.[6,7] Two pivotal international randomized phase III trials have demonstrated the survival benefit conferred by ramucirumab,[8,9] while ramucirumab plus paclitaxel has been recognized as the gold standard second-line chemotherapy for AGC.[2] Preclinical data have suggested that sustained VEGF inhibition can maintain tumor regression in AGC.[10] The continuous use of antiangiogenic agents beyond progression has shown clinical benefits in colorectal, lung, kidney, and breast cancers. For colorectal cancer, in randomized phase III trials (ML18147 and BEBYP studies), continuation of bevacizumab in patients who experienced disease progression in first-line bevacizumab-containing regimens demonstrated a statistically significant survival benefit.[11,12] Moreover, in the RAISE study, fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus ramucirumab demonstrated the superiority over FOLFIRI alone[13] in patients with colorectal cancer who were refractory to bevacizumab-containing first-line chemotherapy. These data suggested the potential benefits of continuing ramucirumab treatment beyond disease progression in patients with AGC.

On the basis of these findings, we hypothesized that continuous use of ramucirumab beyond progression during the previous chemotherapy containing antiangiogenic agents would also have a survival benefit for patients with AGC. This phase III trial (RINDBeRG) investigated the clinical effectiveness of adding ramucirumab to irinotecan as the third- or later-line chemotherapy in patients with AGC who experienced disease progression during previous ramucirumab-containing chemotherapy.

METHODS

Trial Design

This open-label, randomized, phase III trial evaluated the efficacy and safety of adding ramucirumab to irinotecan compared with irinotecan monotherapy in patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer who experienced disease progression during previous ramucirumab-containing chemotherapy. This investigator-initiated intergroup trial was conducted in the Japanese Cancer Trial Network (Appendix Table A1, online only), and the data center was established in the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG). The study protocol was approved by the Protocol Review Committee of the OGSG in July 2016 and by the Institutional Review Committee in the Osaka University Hospital (approved number: 16075-2).

This trial was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000023065) and transferred to the Japan Registry of Clinical Trials (jRCTs051180187) in accordance with the change in the clinical research registry system in Japan.

Patients

Eligible patients were ≥20 years old with histologically confirmed gastric or GEJ adenocarcinoma, regardless of any molecular profile, unresectable or recurrent disease which had progressed during previous ramucirumab-containing chemotherapy. Included patients had failure of chemotherapy with fluoropyrimidines, platinum, and taxane but no previous use of irinotecan. After amendment in February

2022, patients who had early recurrence during or within 180 days after perioperative adjuvant chemotherapy with fluoropyrimidine alone, which was counted as the first-line chemotherapy, and received second-line chemotherapy containing ramucirumab were eligible. They had at least one evaluable lesion on computed tomography (CT) or magnetic resonance images (MRI), according to RECIST version 1.1. They had Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1; sufficient oral intake, not required nutrition support, judged by physician; and adequate organ function including bone marrow, heart, lung, liver, and kidney.

Written informed consent was obtained before any study-specific procedure. Full eligibility criteria are provided in the Protocol (online only).

Randomization

Patients were randomly assigned in a 1:1 ratio to the ramucirumab plus irinotecan arm or the irinotecan monotherapy arm using the stratification factors of (1) PS (0 *v* 1), (2) duration of ramucirumab administration in a previous treatment (<3 months *v* ≥3 months), and (3) the presence or absence of peritoneal metastasis on radiographic imaging (yes *v* no). A randomization sequence using the block randomization method within each stratum was blinded to the investigators. The enrollment by investigators at institutions and randomization was performed in an interactive web response system. The assigned treatment was not masked.

Treatment

In the irinotecan arm, irinotecan was administered at 150 mg/m² intravenously (IV) once every 2 weeks in accordance with the standard dose and schedule in East Asia.[3,14] In the ramucirumab plus irinotecan arm, patients received ramucirumab 8 mg/kg IV and irinotecan 150 mg/m² IV once every 2 weeks on the same day. Although a *UGT1A1* test was not mandatory, patients known to have homozygous or doubly heterozygous *UGT1A1* polymorphisms received a reduced irinotecan dose of 120 mg/m² once every 2 weeks. In the ramucirumab plus irinotecan arm, ramucirumab (8 mg/kg) was administered once every 2 weeks on the same day as irinotecan. Treatment continued until disease progression or unacceptable toxicity was encountered, or upon patient consent withdrawal. Treatment modifications are shown in the Protocol.

Assessments

Tumors were assessed using CT or MRI at baseline and every 8 weeks by the investigator, and evaluated according to the RECIST v1.1. Physical examination, safety, and laboratory tests were checked before administration of the agents. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events v4.00 for up to 30 days after the last dose of the study drug or until the initiation of a new anticancer therapy, whichever came first.

End Points

The primary end point was overall survival (OS), defined as the time from the date of random assignment to the date of death due to any cause. The secondary end points included progression-free survival (PFS), defined as the time from the date of random assignment to the earlier date of the first documentation of objective disease progression or death; overall response rate (ORR), defined as the proportion of participants who showed a best overall response (BOR) of complete response (CR) or partial response (PR); disease control rate (DCR), defined as the proportion of participants who had a BOR of CR, PR, or stable disease; and safety. The list of the study end points is provided in the Protocol.

Statistical Analysis

Primary analyses were performed in the full analysis set (FAS), defined as all enrolled patients excluding those found ineligible by the central eligibility review after random assignment. The intention-to-treat (ITT) population was defined as all enrolled patients regardless of eligibility and protocol adherence, and the per-protocol set (PPS) was defined as all eligible patients, excluding those in whom efficacy was not evaluated because of inadequate observations and those with serious deviations or violations of the study protocol. The safety analysis set was defined as all patients who received at least one dose of the assigned treatment.

The median OS of patients treated with irinotecan monotherapy was assumed to be 5.0 months, on the basis of previous reports. The addition of ramucirumab was expected to prolong median OS to be 6.5 months, corresponding to a hazard ratio (HR) of 0.77. A one-sided significance level of 0.05 and a power of 80% would require 362 events. Planning an enrollment period of 48 months and a follow-up period of 6 months would require 396 patients. The final sample size was set to 400 patients. The primary analysis of OS was performed using a stratified log-rank test with the randomization stratification factors.

An interim efficacy analysis was performed when half (n = 181) of the total expected events (n = 362) were observed. The significance level of the interim and final analyses was adjusted for multiplicity using the Lan and DeMets alpha spending function, and OS was compared using the O'Brien and Fleming alpha spending function. For the interim efficacy analysis, the significance level was set at 0.0057.

RESULTS

Patients

Between February 2017 and August 2022, 402 patients were enrolled and randomly assigned to receive ramucirumab plus irinotecan (n = 202) or irinotecan monotherapy (n = 200) at 89 centers in nine clinical trial groups in Japan (Appendix

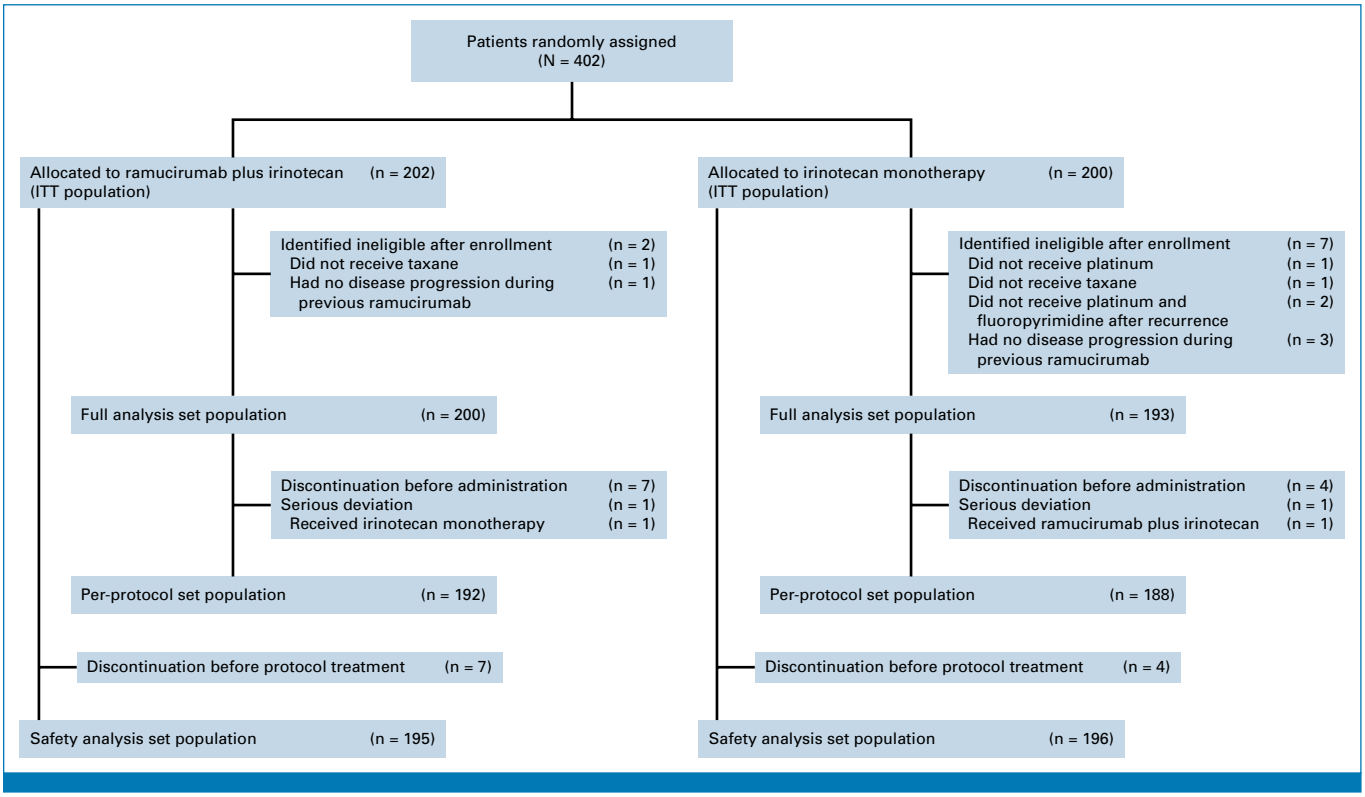

FIG 1. CONSORT diagram of the study. ITT, intention-to-treat.

Table A2). Figure 1 shows the CONSORT diagram of the trial. The FAS included 393 patients: 200 patients in the ramucirumab plus irinotecan arm, and 193 patients in the irinotecan monotherapy arm. Nine patients who were revealed to be ineligible after random assignment by the central review were excluded. The reason for ineligibility were previous treatment history, two patients had not received fluoropyrimidine and platinum after recurrence, two had not received taxane, one had not received platinum, and four had no progression during previous ramucirumab treatment. The baseline characteristics of the patients and their tumors were generally well balanced between the two arms (Table 1). By the data cutoff date (August 11, 2023), with a median follow-up time of 8.9 months, 362 (90.0%) of 402 patients had died. Three (1.0%) patients in the ramucirumab plus irinotecan arm, but none in the irinotecan monotherapy arm, were still on treatment.

Efficacy

In the FAS, among the 200 patients in the ramucirumab plus irinotecan arm, 182 died, while among the 193 patients in the irinotecan monotherapy arm, 173 died. Table 2 summarizes the OS, PFS, and ORR. The median OS was 9.4 months (95% CI, 8.0 to 10.5) in the ramucirumab plus irinotecan arm and 8.5 months (95% CI, 8.0 to 9.3) in the irinotecan monotherapy arm. The HR adjusted for stratification factors was 0.92 (95% CI, 0.74 to 1.13) and the *P* value was .49 (Table 2, Fig 2A). The 6-month OS rate was 71.0% (95% CI, 64.2 to 76.8) in the ramucirumab plus irinotecan arm, and 69.8% (95% CI, 62.8 to 75.8) in the irinotecan monotherapy arm. The 12-month OS rate was 36.5% (95% CI, 29.8 to 43.1) and 32.2% (95% CI, 25.7 to 38.9), respectively. OS did not differ in any of the prespecified subgroups (Fig 3A).

PFS was significantly longer in the ramucirumab plus irinotecan than in the irinotecan monotherapy arm (median, 3.8 months [95% CI, 3.4 to 4.6] *v* 2.8 months [95% CI, 2.2 to 3.5]; HR, 0.73 [95% CI, 0.59 to 0.89]; $P = .002$; Table 2, Fig 2B). The 6-month PFS rate was 31.5% (95% CI, 25.2 to 38.0) in the ramucirumab plus irinotecan arm and 17.6% (95% CI, 12.6 to 23.3) in the irinotecan monotherapy arm. Benefit of ramucirumab for PFS was observed across several prespecified subgroups (Fig 3B), including female sex, GEJ cancer, human epidermal growth factor receptor 2 (HER2) positivity, previous gastrectomy, and previous treatment with immune checkpoint inhibitors (ICIs).

ORR in patients with measurable lesions was not improved significantly by adding ramucirumab (22.1% *v* 15.6%; odds ratio, 1.52; $P = .15$), while the DCR differed significantly (64.4% *v* 52.1%; odds ratio, 1.66; $P = .03$; Table 2, Appendix Fig A1).

An exploratory analysis was also performed on the ITT and PPS populations. In the ITT population, median OS was

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	Ramucirumab Plus Irinotecan (n = 202)	Irinotecan Monotherapy (n = 200)
Age, years, median (range)	68 (40-87)	68 (31-82)
Sex, No. (%)		
Male	156 (77.2)	159 (79.5)
Female	46 (22.8)	41 (20.5)
ECOG PS, No. (%)		
0	102 (50.5)	104 (52.0)
1	100 (49.5)	96 (48.0)
Site of primary tumor, No. (%)		
Gastric	169 (83.7)	170 (85.0)
GEJ	33 (16.3)	30 (15.0)
Pathologic subtype, No. (%)		
Intestinal	102 (50.5)	104 (52.0)
Diffuse	100 (49.5)	96 (48.0)
HER2 status, No. (%)		
Positive	36 (17.8)	43 (21.6)
Negative	166 (82.2)	156 (78.4)
Primary tumor present, No. (%)		
Yes	104 (51.5)	100 (50.0)
No	98 (48.5)	100 (50.0)
Peritoneal metastasis, No. (%)		
Yes	78 (38.6)	74 (37.0)
No	124 (61.4)	126 (63.0)
Measurable lesion, No. (%)		
Yes	151 (74.8)	171 (85.5)
No	51 (25.2)	29 (14.5)
Previous treatment, No. (%)		
Ramucirumab	202 (100.0)	200 (100.0)
Fluoropyrimidine[a]	202 (100.0)	198 (99.0)
Platinum[b]	199 (98.5)	193 (93.5)
Taxane[c]	200 (99.0)	199 (99.5)
ICIs[d]	120 (59.4)	123 (38.5)
Trifluridine/tipiracil	11 (5.4)	10 (5.0)
Trastuzumab	35 (17.4)	38 (19.0)
Number of previous chemotherapy lines, No. (%)		
2	75 (37.1)	80 (40.0)
3	101 (50.0)	79 (39.5)
4	23 (11.4)	34 (17.0)
≥5	3 (1.5)	7 (3.5)
Duration of previous ramucirumab, months, No. (%)		
≥3	147 (72.8)	144 (72.0)
<3	55 (27.2)	56 (28.0)
Treatment pattern of previous ramucirumab, No. (%)		
Continue	91 (45.0)	93 (46.5)
Rechallenge	111 (55.0)	107 (53.5)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICIs, immune checkpoint inhibitors.

[a]Fluoropyrimidine included fluorouracil, capecitabine, and tegafur/gimeracil/oteracil.

[b]Platinum included oxaliplatin and cisplatin.

[c]Taxane included paclitaxel, nab-paclitaxel, and docetaxel.

[d]ICIs included nivolumab and pembrolizumab.

TABLE 2. Summary of Efficacy Outcome

Outcome	Ramucirumab Plus Irinotecan	Irinotecan Monotherapy	HR (95% CI); *P*
OS			
Events, No./population, No. (%)	182/200 (91.0)	173/193 (89.6)	0.92 (0.74 to 1.13); *P* = .49
Median OS, months (95% CI)	9.4 (8.0 to 10.5)	8.5 (8.0 to 9.3)	
PFS			
No. (events)/No. (population) (%)	193/200 (96.5)	191/193 (99.0)	0.73 (0.59 to 0.89); *P* = .002
Median PFS, months (95% CI)	3.8 (3.4 to 4.6)	2.8 (2.2 to 3.5)	
BOR			
CR events, No./population, No. (%)	1/149 (0.7)	0/165 (0.0)	
PR events, No./population, No. (%)	32/149 (21.5)	26/165 (15.8)	
SD events, No./population, No. (%)	63/149 (42.3)	60/165 (36.4)	
PD events, No./population, No. (%)	41/149 (27.5)	69/165 (41.8)	
Nonevaluable events, No./population, No. (%)	12/149 (8.1)	10/165 (6.1)	
Overall response, % (95% CI)	22.1 (15.8 to 29.7)	15.8 (10.6 to 22.2)	*P* = .15
Disease control, % (95% CI)	64.4 (56.2 to 72.1)	52.1 (44.2 to 59.9)	*P* = .030

Abbreviations: BOR, best overall response; CR, complete response; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

9.4 months in the ramucirumab plus irinotecan arm and 8.5 months in the irinotecan monotherapy arm (HR, 0.94 [95% CI, 0.76 to 1.16]), while median PFS was 3.8 versus 3.0 months (HR, 0.72 [95% CI, 0.59 to 0.88]; *P* = .001). In the PPS populations, median OS was 9.5 months in the ramucirumab plus irinotecan arm and 8.5 months in the irinotecan monotherapy arm (HR, 0.89 [95% CI, 0.72 to 1.10]), while median PFS was 3.8 versus 2.9 months (HR, 0.71 [95% CI, 0.58 to 0.87]; *P* = .001; Appendix Table A3, Appendix Figs A2 and A3).

Treatment Exposure

The median number of irinotecan doses was 6 (range, 1-60) in the ramucirumab plus irinotecan arm, and 4 (range, 1-34) in the irinotecan monotherapy arm. The median number of ramucirumab doses was 6 (range, 1-57) in the ramucirumab plus irinotecan arm. The median relative dose intensities (RDIs) of irinotecan were 91.5% in the ramucirumab plus irinotecan arm and 94.3% in the irinotecan monotherapy arm. The median RDI of ramucirumab was 99.1%. Dose reductions and delays of irinotecan were required in 50.0% (98/196) and 65.3% (128/196) of patients in the ramucirumab plus irinotecan arm and 37.9% (74/195) and 59.5% (116/195) in the irinotecan monotherapy arm, respectively.

Disease progression was the most common reason for treatment discontinuation in both arms (158/202 [78.2%] in the ramucirumab plus irinotecan arm *v* 166/200 [83.0%] in the irinotecan monotherapy arm); 30 (14.9%) and 25 (12.5%) patients, respectively, discontinued treatment due to AEs. Moreover, 283 of 402 patients (70.4%) received post-discontinuation treatment (PDT). Specifically, 134 (66.3%) patients in the ramucirumab plus irinotecan arm and 140 (70.0%) patients in the irinotecan monotherapy arm received systemic chemotherapy, including nivolumab (n = 62 *v* 70) and trifluridine/tipiracil (n = 51 *v* 52; Table 3). Median post-treatment survival time was 5.5 months in the ramucirumab plus irinotecan arm and 6.6 months in the irinotecan monotherapy arm. After treatment discontinuation, five patients underwent palliative surgical procedures. These interventions included gastrectomy for bleeding from the primary tumor, enterostomy for GI obstruction, and oophorectomy for ovarian metastases.

Safety

AEs with a higher incidence of any grade in the ramucirumab plus irinotecan arm than in the irinotecan monotherapy arm involved leukopenia (68.2% *v* 48.0%), neutropenia (76.4% *v* 59.7%), thrombocytopenia (32.8% *v* 21.4%), hypoalbuminemia (50.8% *v* 32.1%), oral mucositis (22.1% *v* 8.2%), malaise (67.2% *v* 54.1%), and diarrhea (58.5% *v* 45.9%). Despite increase of bone marrow suppression, febrile neutropenia was not increased in the ramucirumab plus irinotecan arm (4.1%) compared with the irinotecan monotherapy arm (6.1%; Table 4). Hypertension was notably higher in the ramucirumab plus irinotecan arm at 11.8% for any grade. Severe toxicity in relation to ramucirumab was not observed. One treatment-related death (TRD) occurred in the ramucirumab plus irinotecan arm, while two occurred in the irinotecan monotherapy arm. All TRDs were due to pulmonary infection.

DISCUSSION

The RINDBeRG trial was a phase III trial that evaluated the continuous use of an antiangiogenic agent combined with chemotherapy for AGC, which has not been reported to date.

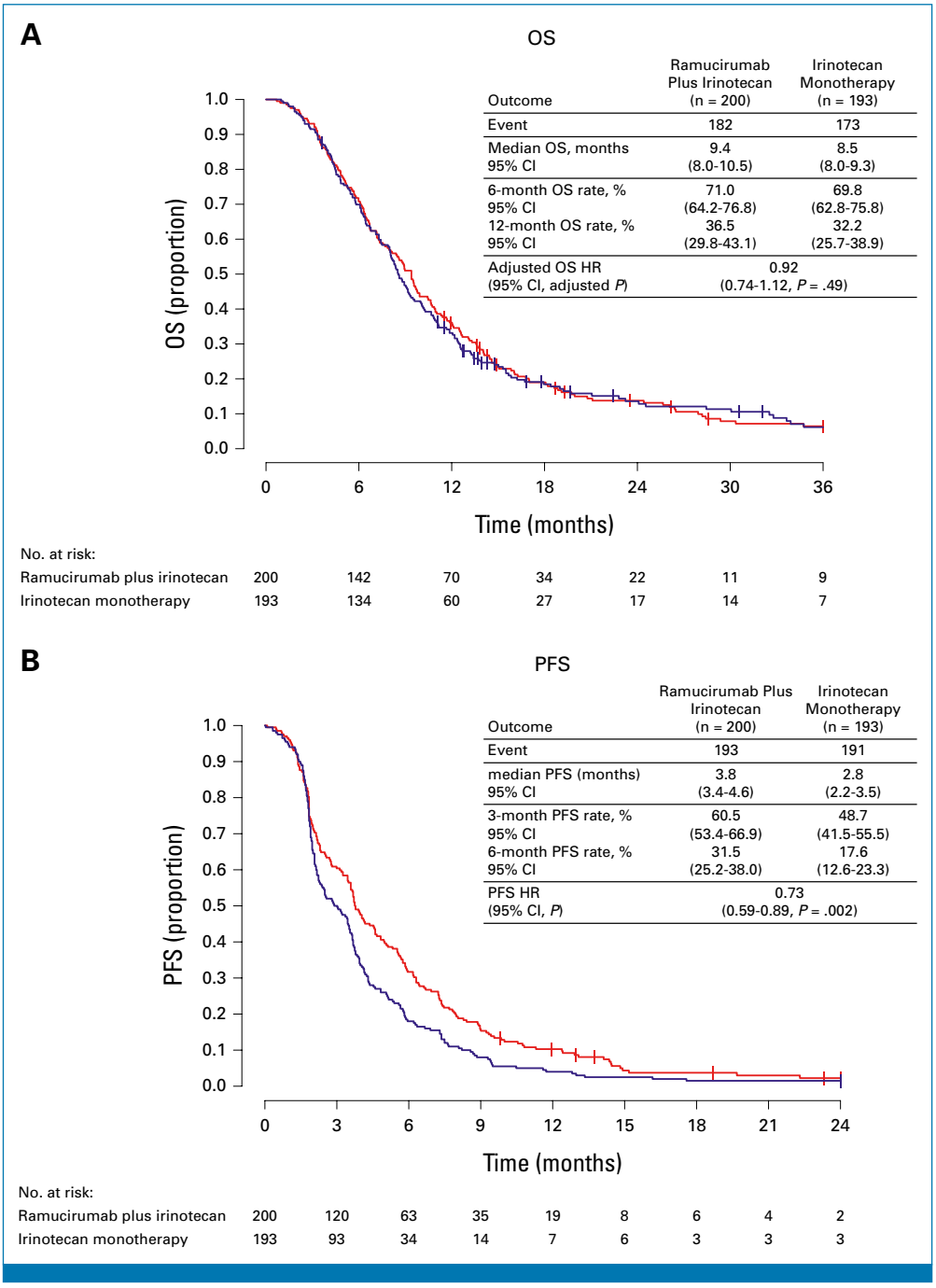

FIG 2. Kaplan-Meier curve of (A) OS and (B) PFS in patients with advanced gastric cancer receiving ramucirumab plus irinotecan or irinotecan monotherapy. OS, overall survival; PFS, progression-free survival.

The primary analysis failed to demonstrate statistical superiority when adding ramucirumab to irinotecan, with a HR of 0.91 (P = .40) and a median OS of 9.4 months for the ramucirumab plus irinotecan arm versus 8.5 months for the irinotecan monotherapy arm. Despite the negative result on the primary end point, improvements were noted in PFS and DCR.

Notably, OS in both arms were more favorable than previously reported for nivolumab or trifluridine/tipiracil as salvage lines for AGC.[15,16] This may have been driven by the high proportion of patients receiving PDT. Several subgroup analyses of phase III trials and meta-analyses of first- or second-line chemotherapy for AGC have demonstrated the contribution of PDT to OS.[17-22] In Japan, where fourth- or further-line chemotherapy is recommended by treatment guidelines if the patient's condition allows,[2] subsequent treatment in any line is administered more frequently than in other countries. For instance, a subgroup analysis in the RAINBOW trial did not demonstrate a clear survival benefit in

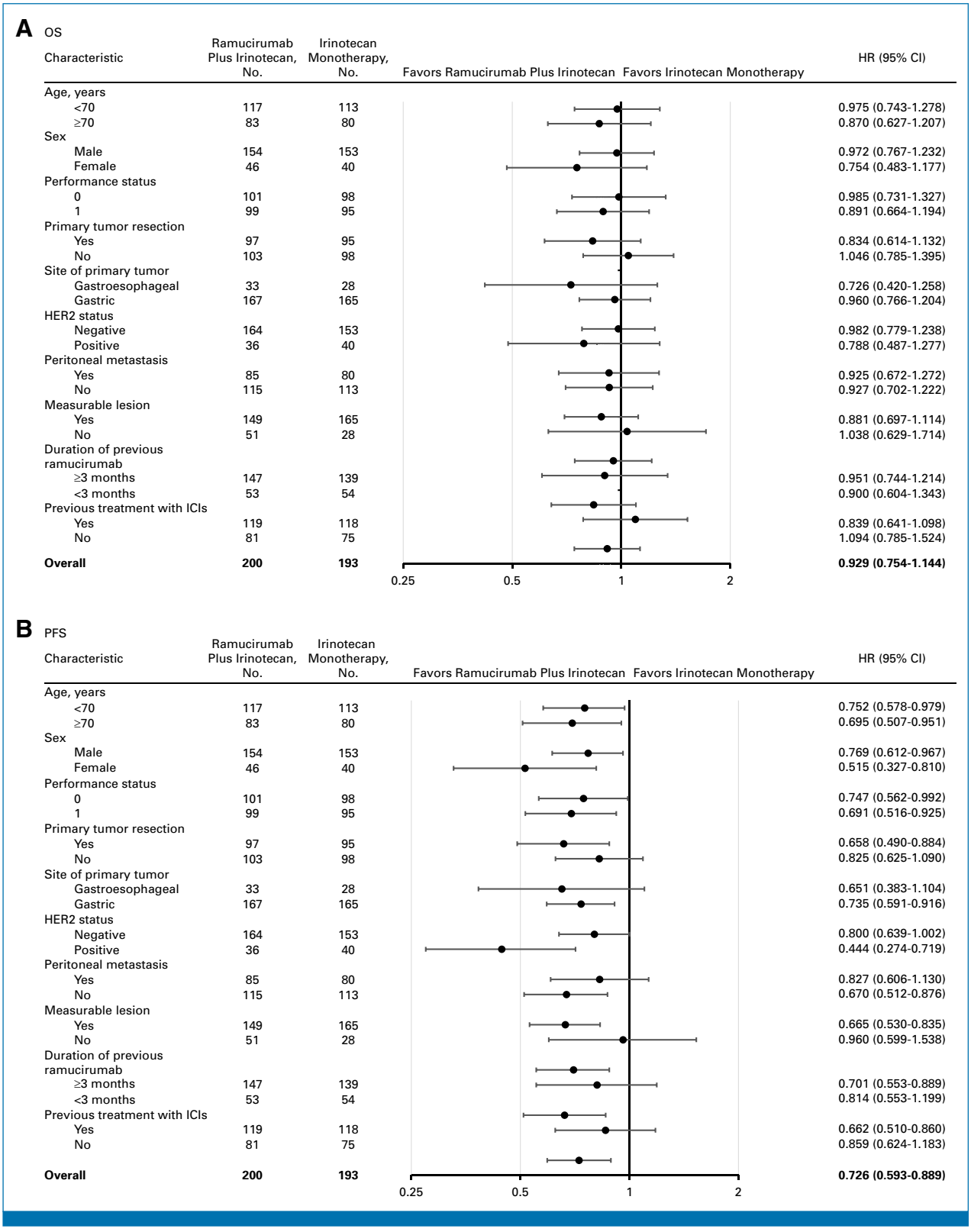

FIG 3. Forest plot of (A) OS and (B) PFS in patients with advanced gastric cancer receiving ramucirumab plus irinotecan or irinotecan monotherapy. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

the Japanese subgroup despite the additional benefit of ramucirumab in terms of PFS and ORR, which may be due to the higher PDT rate (75.0%) in the Japanese population compared with that (37.2%) in the Western population.[9,17] During enrollment period in this study, new active agents such as nivolumab,[15] trifluridine/tipiracil,[16] and trastuzumab

TABLE 3. Post-Discontinuation Treatment on the Intention-to-Treat Population

Treatment	Ramucirumab Plus Irinotecan (n = 202), No. (%)	Irinotecan Monotherapy (n = 200), No. (%)
Post-discontinuation treatment	139 (69.5)	144 (72.0)
Surgery	4 (2.0)	1 (0.5)
Radiotherapy	10 (5.0)	19 (9.4)
Chemotherapy	134 (67.0)	140 (69.3)
Nivolumab	69 (51.5)	62 (44.3)
Trifluridine/tipiracil	52 (38.8)	51 (36.4)
Fluoropyrimidine[a]	21 (15.7)	35 (25.0)
Platinum[b]	17 (12.7)	23 (16.4)
Irinotecan	17 (12.7)	12 (8.6)
Ramucirumab	10 (7.5)	17 (12.1)
Trastuzumab	1 (0.7)	7 (5.0)
Trastuzumab deruxtecan	8 (6.0)	6 (4.3)
Taxane[c]	8 (6.0)	13 (9.3)
Pembrolizumab	2 (1.5)	0 (0.0)
Study drug[d]	12 (9.0)	12 (8.6)

[a]Fluoropyrimidine included fluorouracil, capecitabine, and tegafur/gimeracil/oteracil.
[b]Platinum included oxaliplatin and cisplatin.
[c]Taxane included paclitaxel, nab-paclitaxel, and docetaxel.
[d]Study drug indicated the number of the patients who enrolled in another clinical trial.

deruxtecan[14] were approved as salvage-line chemotherapy for AGC in Japan. The high proportion (approximately 70%) of patients in both arms who received PDT, including these new agents, might have diluted the impact of ramucirumab on OS, despite the significant improvement in PFS.[23,24]

Regional differences in chemotherapy practices for AGC should be taken into consideration. The AVAGAST trial, which evaluated bevacizumab in the first-line treatment of AGC, demonstrated regional differences that OS benefits were observed in Western populations but not in Asian populations.[18] The German pilot phase I/II trial of the combination of trifluridine/tipiracil plus ramucirumab beyond progression demonstrated promising efficacy, compared with historical data of trifluridine/tipiracil monotherapy.[25] Considering these findings, the results of this study may not be applicable to Western populations.

It is concerned that discontinuation of antiangiogenic agents may cause a rapid rebound in tumor growth, through several mechanisms, such as the regression of tumor vasculature normalized by antiangiogenic agent, alterations in the tumor microenvironment that promote angiogenesis, and upregulation of proangiogenic factors.[26] However, post-treatment survival did not differ between the two arms in this study.

Inhibition of angiogenesis remains an attractive therapeutic target in AGC.[27] Multi tyrosine kinase inhibitors (TKIs) with antiangiogenic activity were investigated for AGC. Regorafenib showed a survival benefit as salvage-line treatment of AGC in the randomized phase III trial.[28] Apatinib, another TKI that suppresses VEGFR2, showed efficacy in third- or later-line treatment in Chinese patients with AGC, however failed in the global trial.[29,30] By treating with those or other angiogenesis-inhibiting agents after ramucirumab failure,

TABLE 4. AEs

	Ramucirumab Plus Irinotecan (n = 195), No. (%)		Irinotecan Monotherapy (n = 196), No. (%)	
AE	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Leukopenia	133 (68.2)	49 (25.1)	94 (48)	42 (21.4)
Neutropenia	149 (76.4)	91 (46.7)	117 (59.7)	59 (30.1)
Thrombocytopenia	64 (32.8)	4 (2.1)	42 (21.4)	4 (2)
Hypoalbuminemia	99 (50.8)	11 (5.6)	63 (32.1)	10 (5.1)
Total bilirubin increased	9 (4.6)	1 (0.5)	21 (10.7)	3 (1.5)
AST increased	77 (39.5)	6 (3.1)	58 (29.6)	10 (5.1)
ALT increased	60 (30.8)	3 (1.5)	57 (29.1)	7 (3.6)
Creatinine increased	27 (13.8)	2 (1)	32 (16.3)	3 (1.5)
Diarrhea	114 (58.5)	18 (9.2)	90 (45.9)	11 (5.6)
Oral mucositis	43 (22.1)	2 (1)	16 (8.2)	0 (0)
Nausea	99 (50.8)	6 (3.1)	99 (50.5)	5 (2.6)
Vomiting	49 (25.1)	3 (1.5)	40 (20.4)	4 (2)
Malaise	131 (67.2)	20 (10.3)	106 (54.1)	12 (6.1)
Anorexia	136 (69.7)	26 (13.3)	120 (61.2)	20 (10.2)
Infection	20 (10.3)	12 (6.2)	15 (7.7)	5 (2.6)
Febrile neutropenia	8 (4.1)	8 (4.1)	12 (6.1)	12 (6.1)
Hypertension	23 (11.8)	10 (5.1)	2 (1)	1 (0.5)

Abbreviation: AE, adverse event.

the concept of sustained inhibition of angiogenesis might be a promising strategy. Another randomized trial of trifluridine/tipiracil with or without ramucirumab in patients with AGC who are refractory to ramucirumab is underway in Japan.[31]

Subgroup analysis revealed that the addition of ramucirumab resulted in favorable HRs in specific populations, including females, those with GEJ cancer, HER2 positivity, previous gastrectomy, and previous ICI treatment. In preclinical studies, HER2 signaling pathways upregulate VEGF and VEGF-A expression, which induces transcriptional reprogramming toward angiogenesis.[32,33] In the RAINBOW trial, subgroup analysis of patients who received previous trastuzumab therapy revealed that the second-line ramucirumab and paclitaxel combination had higher efficacies compared with paclitaxel alone.[34] A subgroup analysis of HER2 status from the KCSG-ST19-16 trial, which was a Korean real-world study of second-line ramucirumab plus paclitaxel for AGC, demonstrated that the ORR was higher in HER2-positive than in HER2-negative patients.[35] Furthermore, the results of our subgroup analyses indicated that previous nivolumab treatment enhanced the therapeutic efficacy of ramucirumab. Simultaneous blockade of PD-1 and VEGFR-2 has been reported to enhance T-cell recruitment, activate the local immune status, and induce synergistic antitumor effects.[36,37] A prospective observational study on chemotherapy after nivolumab treatment for AGC showed a positive synergistic antitumor outcome.[38]

The safety profile of ramucirumab plus irinotecan was consistent with that previously reported.[39-42] Patients in the ramucirumab plus irinotecan arm experienced higher frequencies of irinotecan-associated toxicities, such as neutropenia, anorexia, malaise, diarrhea, and nausea, than those in the irinotecan monotherapy arm, similar to the RAINBOW trial in which paclitaxel plus ramucirumab caused more severe hematologic toxicities than paclitaxel alone.[9,17] Certainly the dose of irinotecan was reduced more frequently in the irinotecan plus ramucirumab arm, but discontinuations due to AEs did not differ between the two arms and the median number of irinotecan doses was higher in the irinotecan plus ramucirumab arm. Moreover, the incidence of febrile neutropenia and other severe toxicities did not increase with the irinotecan plus ramucirumab arm. It is considered that optimal dose reduction is required in the later-line chemotherapy to maintain general condition of the patients.

This trial had some limitations. First, a placebo was not used because the trial was an investigator-initiated clinical study conducted within the Japanese insurance system. Second, the absence of biomarker data and quality-of-life assessments hindered comprehensive analyses. Third, all the patients enrolled in this study were Asian. Additionally, the inclusion of patients continuously treated as well as those rechallenged with ramucirumab introduced complexity into the patient population and may have confounded the results.

In conclusion, use of ramucirumab beyond as the later-line treatment for AGC disease progression did not improve OS significantly. Given the negative results of this trial, there is no rationale for the use of ramucirumab after ramucirumab failure.

AFFILIATIONS

[1]Osaka International Cancer Institute, Osaka, Japan
[2]Osaka University Hospital, Suita, Japan
[3]Aichi Cancer Center Hospital, Nagoya, Japan
[4]Osaka Rosai Hospital, Sakai, Japan
[5]Saitama Cancer Center, Ina, Japan
[6]Kobe City Medical Center General Hospital, Kobe, Japan
[7]Yokohama Municipal Citizen's Hospital, Yokohama, Japan
[8]National Hospital Organization Osaka National Hospital, Osaka, Japan
[9]Tohoku University Hospital, Sendai, Japan
[10]Chiba Cancer Center, Chiba, Japan
[11]Shizuoka Cancer Center, Sunto-gun, Japan
[12]Kansai Medical University Hospital, Hirakata, Japan
[13]Higashiosaka City Medical Center, Higashi-Osaka, Japan
[14]Osaki Citizen Hospital, Osaki, Japan
[15]Kushiro Rosai Hospital, Kushiro, Japan
[16]National Hospital Organization Nagoya Medical Center, Nagoya, Japan
[17]Kindai University Faculty of Medicine, Osaka-Sayama, Japan
[18]Wakayama Medical University, Wakayama, Japan
[19]IMSUT Hospital, Institute of Medical Science, University of Tokyo, Tokyo, Japan

CORRESPONDING AUTHOR

Narikazu Boku, MD, PhD; e-mail: nboku@ims.u-tokyo.ac.jp.

DISCLAIMER

The funders were not involved in the data collection, analysis, interpretation, or writing of the manuscript.

PRIOR PRESENTATION

Presented in part at the European Society for Medical Oncology Congress 2023, Madrid, Spain, October 20-24, 2023; the ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, January 18-20, 2024; Japanese Society of Medical Oncology Annual Meeting, Nagoya, Japan, February 22-24, 2024; and the Japanese Gastric Cancer Association Annual Meeting, Kyoto, Japan, February 28-March 1, 2024.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.24.01119.

AUTHOR CONTRIBUTIONS

Conception and design: Daisuke Sakai, Jin Matsuyama, Narikazu Boku, Taroh Satoh
Administrative support: Daisuke Sakai
Provision of study materials or patients: Daisuke Sakai, Ryohei Kawabata, Hironaga Satake, Masazumi Takahashi, Keiko Minashi, Jin Matsuyama, Kentaro Sawada, Hisato Kawakami
Collection and assembly of data: Daisuke Sakai, Shigenori Kadowaki, Ryohei Kawabata, Hiroki Hara, Hironaga Satake, Masazumi Takahashi, Atsushi Takeno, Hiroo Imai, Keiko Minashi, Takeshi Kawakami, Shogen Boku, Jin Matsuyama, Yasuhiro Sakamoto, Kentaro Sawada, Masato Kataoka, Hisato Kawakami, Narikazu Boku, Taroh Satoh
Data analysis and interpretation: Daisuke Sakai, Shigenori Kadowaki, Ryohei Kawabata, Hiroki Hara, Hironaga Satake, Takeshi Kawakami, Jin Matsuyama, Hisato Kawakami, Toshio Shimokawa, Narikazu Boku
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank all the patients and their families who participated in this trial as well as the investigators, the team at the Osaka Gastrointestinal Cancer Chemotherapy Study Group datacenter, Ms K. Ota as the manager of the Electronic Data Capture system, Ms Y. Takeda as the statistical analyst for the interim analysis, and the members of the Independent Data Monitoring Committee, Dr Y. Goto, Dr N. Kiyota, and Dr K. Tamura. The authors also thank the leaders of the nine clinical trial groups (CCOG, HGCSG, JACCRO, JCOG, KSCC, OGSG, T-CORE, TCOG, and WJOG) included in the Japanese Cancer Trial Network Intergroup in Japan.
The study was facilitated by the Research Support Program (National Cancer Center Research and Development Funds: 26-A-22 and 29-A-15). The authors are also grateful to Eli Lilly Japan K.K. for financial support for this study.

REFERENCES

1. Bray F, Laversanne M, Sung H, et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74:229-263, 2024
2. Japanese Gastric Cancer Association: Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer 26:1-25, 2023
3. Hironaka S, Ueda S, Yasui H, et al: Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 31:4438-4444, 2013
4. Willett CG, Boucher Y, di Tomaso E, et al: Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 10:145-147, 2004
5. O'Connor JPB, Carano RAD, Clamp AR, et al: Quantifying antivascular effects of monoclonal antibodies to vascular endothelial growth factor: Insights from imaging. Clin Cancer Res 15:6674-6682, 2009
6. Dickson PV, Hamner JB, Sims TL, et al: Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. Clin Cancer Res 13:3942-3950, 2007
7. Yanagisawa M, Yorozu K, Kurasawa M, et al: Bevacizumab improves the delivery and efficacy of paclitaxel. Anticancer Drugs 21:687-694, 2010
8. Fuchs CS, Tomasek J, Yong CJ, et al: Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383:31-39, 2014
9. Wilke H, Muro K, Van Cutsem E, et al: Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 15:1224-11235, 2014
10. Bagri A, Berry L, Gunter B, et al: Effects of anti-VEGF treatment duration on tumor growth, tumor regrowth, and treatment efficacy. Clin Cancer Res 16:3887-3900, 2010
11. Bennouna J, Sastre J, Arnold D, et al: Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial. Lancet Oncol 14:29-37, 2013
12. Falcone A, Salvatore L, Boni L, et al: Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: Final results of the randomized BEBYP trial. Ann Oncol 26:724-730, 2015
13. Tabernero J, Yoshino T, Cohn AL, et al: Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blin. Lancet Oncol 16:499-508, 2015
14. Shitara K, Bang Y-J, Iwasa S, et al: Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. New Eng J Med 382:2419-2430, 2020
15. Kang YK, Boku N, Satoh T, et al: Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390:2461-2471, 2017
16. Shitara K, Doi T, Dvorkin M, et al: Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 19:1437-1448, 2018
17. Shitara K, Muro K, Shimada Y, et al: Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: A randomized clinical trial in second-line treatment of gastric cancer. Gastric Cancer 19:927-938, 2016
18. Ohtsu A, Shah MA, Van Cutsem E, et al: 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, 2011
19. Takashima A, Iizumi S, Boku N: 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, 2017
20. Iizumi S, Takashima A, Sakamaki K, et al: Survival impact of post-progression chemotherapy in advanced gastric cancer: Systematic review and meta-analysis. Cancer Chemother Pharmacol 81: 981-989, 2018
21. Iwasa S, Kudo T, Takahari D, et al: Practical guidance for the evaluation of disease progression and the decision to change treatment in patients with advanced gastric cancer receiving chemotherapy. Int J Clin Oncol 25:1223-1232, 2020
22. Kato K, Satoh T, Muro K, et al: A subanalysis of Japanese patients in a randomized, double-blind, placebo-controlled, phase 3 trial of nivolumab for patients with advanced gastric or gastro-esophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2). Gastric Cancer 22:344-354, 2019
23. Davidson M, Chau I: Variations in outcome for advanced gastric cancer between Japanese and Western patients: A subgroup analysis of the RAINBOW trial. Transl Gastroenterol Hepatol 1:46, 2016
24. Korn EL, Freidlin B, Abrams JS: Overall survival as the outcome for randomized clinical trials with effective subsequent therapies. J Clin Oncol 29:2439-2442, 2011
25. Goetze TO, Stein A, Lorenzen S, et al: Ramucirumab beyond progression plus TAS-102 in patients with advanced or metastatic esophagogastric adenocarcinoma, after treatment failure on a ramucirumab-based therapy. Int J Cancer 153:1726-1733, 2023
26. Ebos JML, Lee CR, Cruz-Munoz W, et al: Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 15:232-239, 2009
27. Nakayama I, Takahari D: The role of angiogenesis targeted therapies in metastatic advanced gastric cancer: A narrative review. J Clin Med 12:3226, 2023
28. Pavlakis N, Sjoquist KM, Martin AJ, et al: Regorafenib for the treatment of advanced gastric cancer (INTEGRATE): A multinational placebo-controlled phase II trial. J Clin Oncol 34:2728-2735, 2016
29. Li J, Qin S, Xu J, et al: Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 34:1448-1454, 2016
30. Kang YK, Ryu MH, Di Bartolomeo M, et al: Rivoceranib, a VEGFR-2 inhibitor, monotherapy in previously treated patients with advanced or metastatic gastric or gastroesophageal junction cancer (ANGEL study): An international, randomized, placebo-controlled, phase 3 trial. Gastric Cancer 27:375-386, 2024
31. Takahashi N, Hara H, Nagashima K, et al: Randomised phase II trial of trifluridine/tipiracil (FTD/TPI) plus ramucirumab (RAM) versus trifluridine/tipiracil for previously treated patients with advanced gastric or esophagogastric junction adenocarcinoma (RETRIEVE study, WJOG15822G). BMC Cancer 23:1-8, 2023
32. Kim CG, Jung M, Kim HS, et al: Trastuzumab combined with ramucirumab and paclitaxel in patients with previously treated human epidermal growth factor receptor 2-positive advanced gastric or gastroesophageal junction cancer. J Clin Oncol 41:4394-4405, 2023

33. Alameddine RS, Otrock ZK, Awada A, et al: Crosstalk between HER2 signaling and angiogenesis in breast cancer: Molecular basis, clinical applications and challenges. Curr Opin Oncol 25:313-324, 2013
34. De Vita F, Borg C, Farina G, et al: Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: Subgroup analysis from RAINBOW study. Future Oncol 15:2723-2731, 2019
35. Kim BJ, Jee HJ, Rha SY, et al: Ramucirumab plus paclitaxel as a second-line treatment in HER2-positive gastric cancer: Subgroup analysis of a nationwide, real-world study in Korea (KCSG-ST19-16). Gastric Cancer 25:609-618, 2022
36. Lee WS, Yang H, Chon HJ, et al: Combination of anti-angiogenic therapy and immune checkpoint blockade normalizes vascular-immune crosstalk to potentiate cancer immunity. Exp Mol Med 52: 1475-1485, 2020
37. Herbst RS, Arkenau H-T, Santana-Davila R, et al: Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): A multicohort, non-randomised, open-label, phase 1a/b trial. Lancet Oncol 20:1109-1123, 2019
38. Narita Y, Matsushima T, Sakamoto Y, et al: Chemotherapy after nivolumab for advanced gastric cancer (REVIVE): A prospective observational study. ESMO Open 8:102071, 2023
39. Satake H, Sagawa T, Fujikawa K, et al: Phase Ib study of irinotecan and ramucirumab for advanced gastric cancer previously treated with fluoropyrimidine with/without platinum and taxane. Cancer Chemother Pharmacol 82:839-845, 2018
40. Kawamoto Y, Yuki S, Sawada K, et al: Phase II study of ramucirumab plus irinotecan combination therapy as second-line treatment in patients with advanced gastric cancer: HGCSG1603. Oncologist 27:E642-E649, 2022
41. Vogl UM, Vormittag L, Winkler T, et al: Ramucirumab plus paclitaxel or FOLFIRI in platinum-refractory advanced or metastatic gastric or gastroesophageal junction adenocarcinoma—experience at two centres. J Gastrointest Oncol 11:366-375, 2020
42. Lorenzen S, Thuss-Patience P, Pauligk C, et al: FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel—Results from the phase II RAMIRIS Study of the German Gastric Can. Eur J Cancer 165:48-57, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial of Ramucirumab Beyond Progression Plus Irinotecan in Patients With Ramucirumab-Refractory Advanced Gastric Cancer: RINDBeRG Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Daisuke Sakai
Speakers' Bureau: Chugai Pharma, Daiichi Sankyo/UCB Japan
Research Funding: Chugai Pharma (Inst), Yakult Honsha (Inst), Ono Pharmaceutical (Inst), Daiichi Sankyo, Lilly Japan, Astellas Pharma (Inst), Incyte (Inst), Taiho Pharmaceutical (Inst), Eisai (Inst)

Shigenori Kadowaki
Honoraria: Bayer, Bristol Myers Squibb, Chugai Pharma, Ono Pharmaceutical, Merck KGaA, Daiichi Sankyo, Eisai, MSD, Taiho Pharmaceutical, Novartis
Research Funding: Ono Pharmaceutical (Inst), Lilly (Inst), MSD (Inst), Chugai Pharma (Inst), Nobelpharma (Inst), Daiichi Sankyo (Inst), Bayer (Inst), AstraZeneca (Inst)

Hiroki Hara
Honoraria: Chugai Pharma, Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Lilly, Ono Pharmaceutical, Takeda, Bristol Myers Squibb, MSD, Daiichi Sankyo/UCB Japan, Miyarisan pharmaceutical, Nippon Kayaku, Astellas Pharma
Consulting or Advisory Role: Boehringer Ingelheim, Chugai Pharma, Daiichi Sankyo/UCB Japan
Research Funding: AstraZeneca (Inst), Merck Serono (Inst), MSD (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Daiichi Sankyo (Inst), Astellas Pharma (Inst), Bayer (Inst), Amgen (Inst), Chugai Pharma (Inst), Janssen Oncology (Inst), ALX Oncology (Inst), Bristol Myers Squibb Japan (Inst), Jazz Pharmaceuticals (Inst), AbbVie (Inst), Henlius (Inst)

Hironaga Satake
Honoraria: Bayer, Bristol Myers Squibb, Chugai Pharma, Daiichi Sankyo, Lilly Japan, Merck, MSD, Ono Pharmaceutical, Sanofi, Taiho Pharmaceutical, Takeda, Yakult Honsha, Asahi KASEI, AstraZeneca, Astellas Pharma
Research Funding: Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Daiichi Sankyo (Inst), Takeda (Inst), Sanofi (Inst), Asahi Kasei (Inst), MSD (Inst)

Masazumi Takahashi
Honoraria: Bristol Myers Squibb Japan, Taiho Pharmaceutical, Lilly Japan, Ono Pharmaceutical

Keiko Minashi
Research Funding: MSD (Inst), Daiichi Sankyo/UCB Japan (Inst), Taiho Pharmaceutical (Inst), PPD-SNBL (Inst)

Takeshi Kawakami
Honoraria: Taiho Pharmaceutical, Bayer Yakuhin, Takeda, Ono Pharmaceutical, Bristol Myers Squibb Japan, Yakult Honsha, Lilly, Daiichi Sankyo
Consulting or Advisory Role: Daiichi Sankyo

Shogen Boku
Speakers' Bureau: Chugai Pharma, Taiho Pharmaceutical, Bristol Myers Squibb Japan, MSD, Eisai, Ono Pharmaceutical
Research Funding: Daiichi Sankyo Co, Ltd (Inst)

Yasuhiro Sakamoto
Honoraria: Lilly Japan, MSD K.K, Ono Pharmaceutical, Daiichi-Sankyo Co, Ltd, Taiho Pharmaceutical, Chugai Pharma, Takeda, Yakult Honsha, Bristol Myers Squibb Co, Ltd, Nippon Kayaku K.K. Kyowa Kirin K.K

Hisato Kawakami
Honoraria: Chugai/Roche, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb Japan, Yakult Pharmaceutical, Takeda, MSD K.K, Merck Serono, Lilly Japan, Daiichi Sankyo, Astellas Pharma, GlaxoSmithKline, Amgen, Nippon Kayaku
Consulting or Advisory Role: Daiichi Sankyo Co, Ltd, Astellas Pharma, AbbVie
Research Funding: Eisai (Inst), Kobayashi Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Bristol Myers Squibb Foundation (Inst)
Patents, Royalties, Other Intellectual Property: Medical & Biological Laboratories Co, Ltd for Integrin avß6 autoantibody assay kit in the diagnosis of irAE enteritis

Narikazu Boku
Honoraria: Taiho Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb Japan, Daiichi Sankyo, Lilly

Taroh Satoh
Honoraria: Chugai Pharma, Merck Serono, Bristol Myers Squibb, Takeda, Yakult Honsha, Lilly, Bayer Yakuhin, Ono Pharmaceutical, Merck, Astellas Pharma, Taiho Pharmaceutical, Nihonkayaku, Daiichi Sankyo
Consulting or Advisory Role: Bayer Yakuhin, Lilly, Ono Pharmaceutical, Takara Bio, Merck Serono, Nihonkayaku
Research Funding: Yakult Honsha (Inst), Chugai Pharma (Inst), Ono Pharmaceutical (Inst), Sanofi (Inst), Lilly (Inst), Daiichi Sankyo (Inst), Merck (Inst), Merck Serono (Inst), Gilead Sciences (Inst), Dainippon Sumitomo Pharma (Inst), IQVIA (Inst), SHIONOGI (Inst)

No other potential conflicts of interest were reported.

APPENDIX

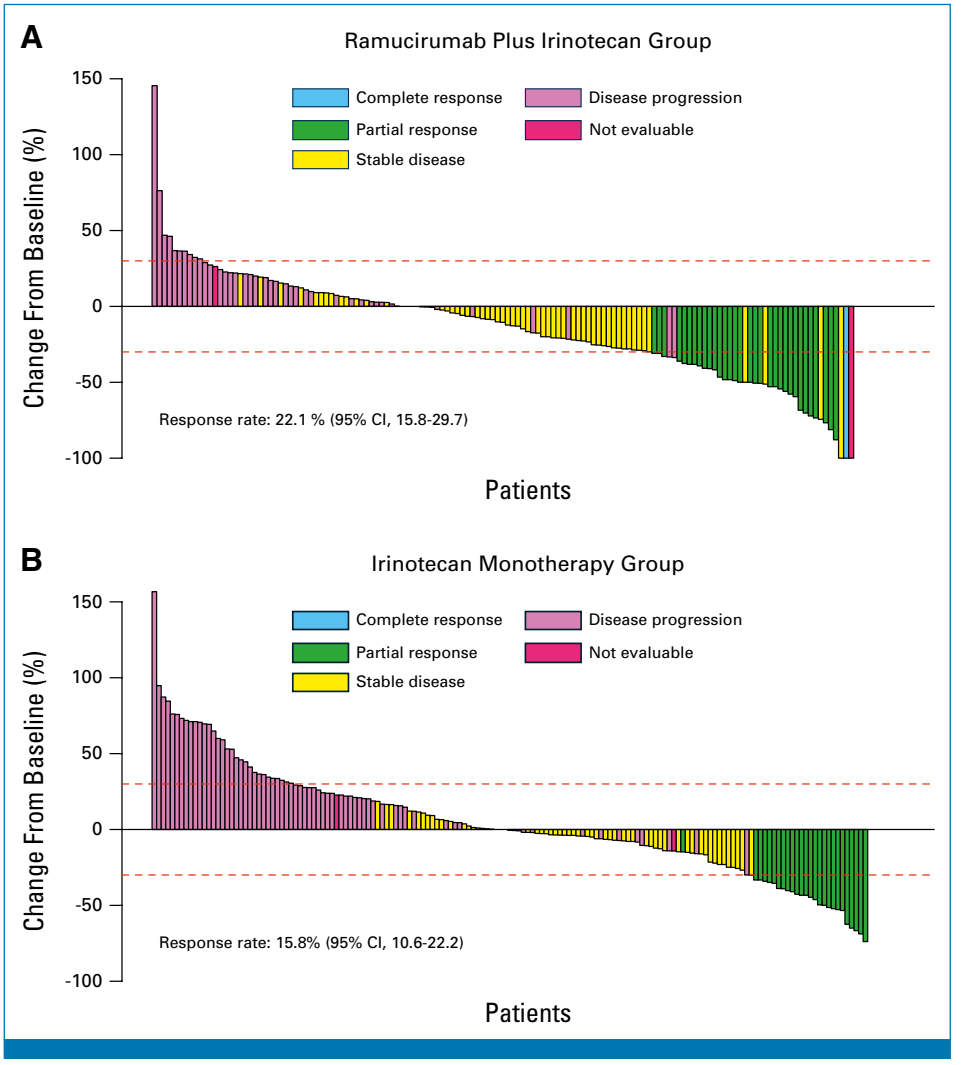

FIG A1. Waterfall plot of (A) the ramucirumab plus irinotecan group and (B) the irinotecan monotherapy group.

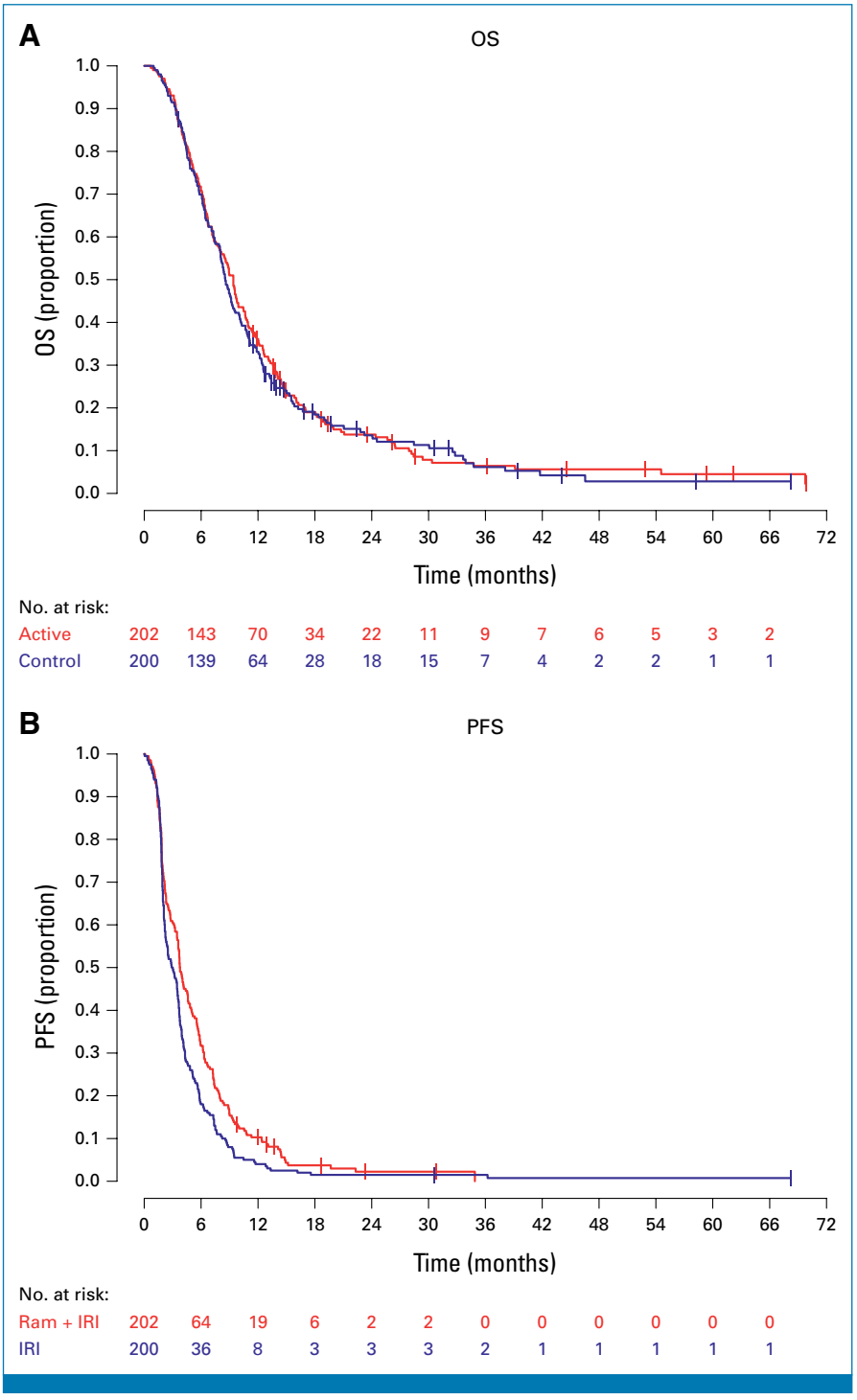

FIG A2. Kaplan-Meier curves for (A) OS and (B) PFS in the intention-to-treat population. OS, overall survival; PFS, progression-free survival.

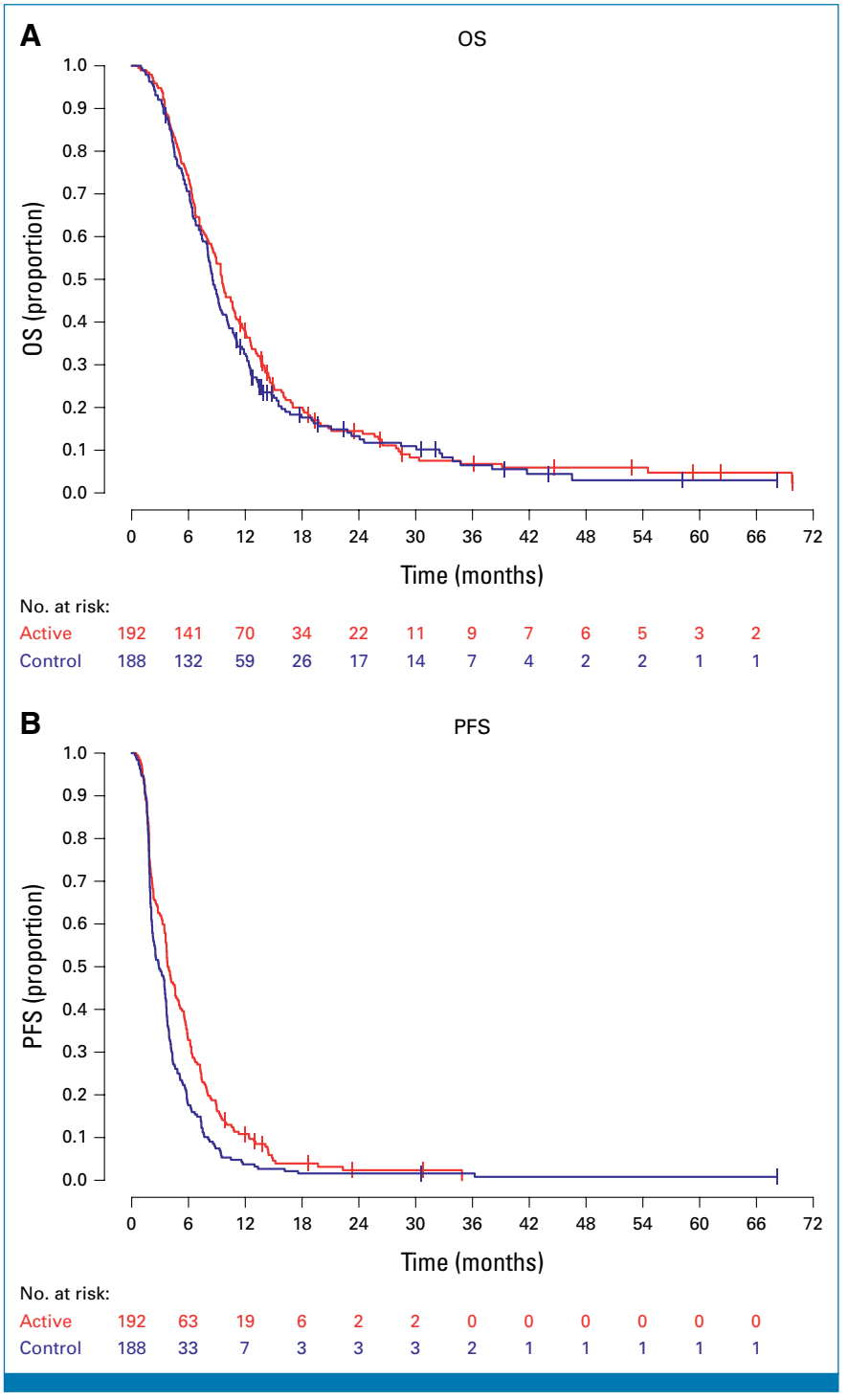

FIG A3. Kaplan-Meier curves for (A) OS and (B) PFS in the per-protocol set population. OS, overall survival; PFS, progression-free survival.

TABLE A1. Participating Clinical Study Groups (listed in alphabetic order)

Clinical Study Group
Chubu Clinical Oncology Group (CCOG)
Hokkaido Gastrointestinal Cancer Study Group (HGCSG)
Japan Clinical Cancer Research Organization (JACCRO)
Japan Clinical Oncology Group (JCOG)
Kyushu Study group of Clinical Cancer (KSCC)
Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG)
Tohoku Clinical Oncology Research and Education Society (T-CORE)
Tokyo Cooperative Oncology Group (TCOG)
West Japan Oncology Group (WJOG)

TABLE A2. Participating Institutions (listed in alphabetic order)

Institution
Aichi Cancer Center Aichi Hospital
Aichi Cancer Center Hospital
Aizawa Hospital
Chiba Cancer Center
Chiba University Hospital
Gifu Municipal Hospital
Hakodate Municipal Hospital
Higashiosaka City Medical Center
Hirosaki University Hospital
Hiroshima City North Medical Center Asa Citizens Hospital
Hokkaido Gastroenterology Hospital
Hokkaido University Hospital
Hyogo Cancer Center
Hyogo Medical University Hospital
Ibaraki Prefectural Central Hospital
Ichinomiya Municipal Hospital
Ikeda City Hospital
Ina Central Hospital
Ishikawa Prefectural Central Hospital
Japanese Red Cross Ishinomaki Hospital
Japanese Red Cross Society Himeji Hospital
Jichi Medical University Hospital
Kagawa University Hospital
Kagoshima University Hospital
Kaizuka City Hospital
Kanagawa Cancer Center
Kansai Electric Power Hospital
Kansai Medical University Hospital
Kansai Rosai Hospital
Keio University Hospital
Keiyukai Sapporo Hospital
Kindai University Hospital
Kindai University Nara Hospital
Kitano Hospital, Tazuke Kofukai Medical Research Institute
Kobe City Medical Center General Hospital
Kobe University Hospital
Komaki City Hospital
Konan Kosei Hospital
Kumamoto University Hospital
Kurume University Hospital
Kushiro Rosai Hospital
Kyoto University Hospital
Kyushu University Hospital
Matsuyama Red Cross Hospital
Mimihara General Hospital
Minoh City Hospital
Nagasaki Harbor Medical Center
Nagoya University Hospital
Nakadori General Hospital

(continued in next column)

TABLE A2. Participating Institutions (listed in alphabetic order) (continued)

Institution
National Cancer Center Hospital
National Hospital Organization Fukuyama Medical Center
National Hospital Organization Kure Medical Center and Chugoku Cancer Center
National Hospital Organization Kyushu Medical Center
National Hospital Organization Nagoya Medical Center
National Hospital Organization Okayama Medical Center
National Hospital Organization Osaka National Hospital
Niigata Cancer Center Hospital
Oita University Hospital
Osaka City General Hospital
Osaka General Medical Center
Osaka International Cancer Institute
Osaka Medical and Pharmaceutical University Hospital
Osaka Metropolitan University Hospital
Osaka Rosai Hospital
Osaka University Hospital
Osaki Citizen Hospital
Rinku General Medical Center
Saga University Hospital
Saitama Cancer Center
Saitama Medical Center
Sakai City Medical Center
Shizuoka Cancer Center
St. Marianna University Hospital
Teine Keijinkai Hospital
The Cancer Institute Hospital Of JFCR
Tohoku University Hospital
Tokai Central Hospital, Public School Mutual Aid Association
Tokyo Metropolitan Toshima Hospital
Tonan Hospital
Toranomon Hospital
Tosei General Hospital
Toyonaka Municipal Hospital
University Hospital Kyoto Prefectural University of Medicine
University of Tsukuba Hospital
Wakayama Rosai Hospital
Yamagata Prefectural Central Hospital
Yamaguchi University Hospital
Yao Municipal Hospital
Yokohama Municipal Citizen's Hospital

TABLE A3. Summary of Efficacy in the Intention-to-Treat Population and the PPS Population

	Intention-to-Treat Population		PPS Population	
Variable	Ramucirumab Plus Irinotecan	Irinotecan Monotherapy	Ramucirumab Plus Irinotecan	Irinotecan Monotherapy
No.	202	200	192	188
OS events, No.	184	178	174	168
Median, months	9.4	8.5	9.5	8.5
HR (95% CI)	0.94 (0.76 to 1.16), $P = .55$		0.89 (0.724 to 1.10), $P = .30$	
PFS events, No.	195	198	185	186
Median, months	3.8	3.0	3.8	2.9
HR (95% CI)	0.72 (0.59 to 0.88), $P = .001$		0.71, (0.58 to 0.87), $P = .001$	

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPS, per protocol set.