Original Article

A post-marketing safety study of ramucirumab with FOLFIRI in patients with metastatic colorectal cancer

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Background: Ramucirumab [human vascular endothelial growth factor (VEGF) receptor-2 monoclonal antibody] + levofolinate, fluorouracil, and irinotecan (FOLFIRI) was approved for the treatment of metastatic colorectal cancer (CRC) in Japan based on the results from the phase 3 RAISE trial (NCT01183780). However, safety information of ramucirumab + FOLFIRI in the real-world setting is limited. Therefore, the present study was conducted to evaluate the safety of ramucirumab + FOLFIRI under routine clinical practice in patients with metastatic CRC (mCRC) after first-line chemotherapy.

Methods: A single-arm, prospective, multicenter, non-interventional, observational study was conducted between August 2016 and May 2020. Patients with mCRC treated with ramucirumab + FOLFIRI for the first time were included. Patients were observed for 12 months from the start of ramucirumab. Data were recorded using the electronic data capture system.

Results: In total, 362 patients with a mean age of 64.1 years were evaluated for safety, of whom 355 patients were evaluated for effectiveness. A higher proportion of the patients were males (n=200; 55.2%), had metastases and recurrent sites (n=362, 100.0%), and had received prior anti-cancer treatment (n=355; 98.1%). Approximately 83.7% (n=303) and 25.4% (n=92) of patients had medication history of bevacizumab and anti-epidermal growth factor receptor (EGFR) antibodies, respectively. Overall, 84.3% (n=305) of patients experienced any grade adverse events (AEs). Neutrophil count decreased (n=138; 38.1%), hypertension (n=58; 16.0%), and diarrhea (n=57; 15.7%) were observed frequently. The clinically relevant grade ≥3 AEs of special interest (AESIs) with >2% incidence included neutropenia (n=101; 27.9%), hypertension (n=35; 9.7%), proteinuria (n=23; 6.4%), hepatic dysfunction (n=15; 4.1%), febrile neutropenia (n=10; 2.8%), and leukopenia (n=9; 2.5%). The presence of renal disease at baseline increased the risk of proteinuria [risk ratio: 2.1; 95% confidence interval (CI): 1.1–4.2]. Three deaths were reported due to AEs, of which 1 was study treatment related. The 12-month survival rate of the ramucirumab + FOLFIRI regimen was 59%, mortality mainly (90%) occurring due to progressive disease.

Conclusions: Although the current observational study enrolled patients with various medication history, the regimen of ramucirumab + FOLFIRI was manageable under clinical practice. No new safety concerns beyond the findings observed in previous clinical trials were reported.

Keywords: Colorectal cancer (CRC); metastatic; neutropenia; proteinuria; ramucirumab

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Introduction

Colorectal cancer (CRC) is the third most common cancer with an incidence rate of 10% and it is the second most common cause of mortality, accounting for 9.4% of cancer deaths worldwide (1). In Japan, the incidence rate of CRC is 14.4% and the mortality rate is 14.3%, making CRC the most common cancer and second most common cause of cancer-related mortality (2).

About 25% of patients with metastatic CRC (mCRC) are diagnosed initially due to the lack of visible clinical signs and symptoms (3,4). Patients with metastasis have a poor prognosis and a median overall survival (OS) of 30 months (5). The relative 5-year survival rate of stage IV colon cancer is 14% in the United States (6) and 18.8% in Japan (7). Although treatment for patients with mCRC includes surgery, radiotherapy, and chemotherapy, systemic therapy is the standard mode of treatment for unresectable mCRC (8). Systemic therapy comprises chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan, combined with anti-vascular endothelial growth factor (VEGF) inhibitors, and anti-epidermal growth factor receptor (EGFR) antibodies in cases of *RAS* wild-type tumors (5,8).

Ramucirumab is a fully human IgG1 monoclonal antibody that binds to VEGF receptor 2 (VEGFR-2), obstructing VEGF-A, -C, and -D ligand binding, thereby inhibiting tumor angiogenesis (9). Based on the results from the global phase 3 RAISE trial, ramucirumab was approved for second-line mCRC treatment in combination with levofolinate, fluorouracil, and irinotecan (FOLFIRI) in the United States, European Union, and Japan (4,10). The RAISE trial showed a median OS of 13.3 months in patients treated with ramucirumab + FOLFIRI versus 11.7 months in placebo + FOLFIRI [hazard ratio: 0.844; 95% confidence interval (CI): 0.73–0.98; log-rank P=0.02] (10). The safety profile of ramucirumab is similar to other antiangiogenic antibodies (11). The RAISE trial indicated that grade 3 and 4 adverse events (AEs) such as hypertension, neutropenia, and proteinuria were higher in the ramucirumab + FOLFIRI group versus the placebo + FOLFIRI group (10-12). Although the efficacy of ramucirumab in combination with FOLFIRI led to approval of the treatment in patients with mCRC, the safety data of this combination for Japanese patients with mCRC are limited. The objective of this study was to evaluate the safety and confirm the effectiveness of ramucirumab in Japanese patients with mCRC and prior treatment history in the real-world setting. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-863/rc).

Method

Study design

The study was a single-arm, prospective, multicenter, non-interventional, observational study in patients with mCRC who were administered ramucirumab + FOLFIRI under routine clinical practice in Japan. Although the initial dose of irinotecan in FOLFIRI regimen was 180 mg/m^2 in the RAISE trial, 150 mg/m^2 was recommended in Japanese clinical practice. On day 1 of each 2-week cycle, patients received 8 mg/kg ramucirumab as a 60 min intravenous infusion followed by FOLFIRI (150 mg/m^2 intravenous irinotecan given over 90 min concurrent with 200 mg/m^2 intravenous levofolinate given over 120 min, followed by 400 mg/m^2 fluorouracil given as an intravenous bolus injection then 2,400 mg/m^2 given as a continuous infusion over 46 h). However, dosages could be tailored to patient's condition.

Patients were enrolled across 73 medical institutions in Japan. Patients diagnosed with mCRC and treated for the first time with ramucirumab + FOLFIRI were included in the study. The study was conducted between August 2016 and May 2020. Patients were observed for a period of 12 months after ramucirumab initiation. However, if ramucirumab was discontinued, the last day of observation was 30 days after ramucirumab was discontinued or a new treatment was administered, whichever was earlier.

This study was conducted in accordance with the standards of Good Post-marketing Study Practice for drugs (GPSP; Ordinance No. 171, issued 20 December 2004, the Japanese Ministry of Health, Labour and Welfare). The study protocol adhered to applicable local and country-specific laws and regulations pertaining to protection of patient privacy and safety, and was approved by the Pharmaceuticals and Medical Devices Agency (PMDA). In accordance with these laws and regulations, this study did not obtain written informed consent from enrolled patients and ethical approval as these were not required under the GPSP. This study was exempt from World Health Organization registration criteria.

Assessments

The electronic data capture system was used to collect the data points of patients. The investigator entered the

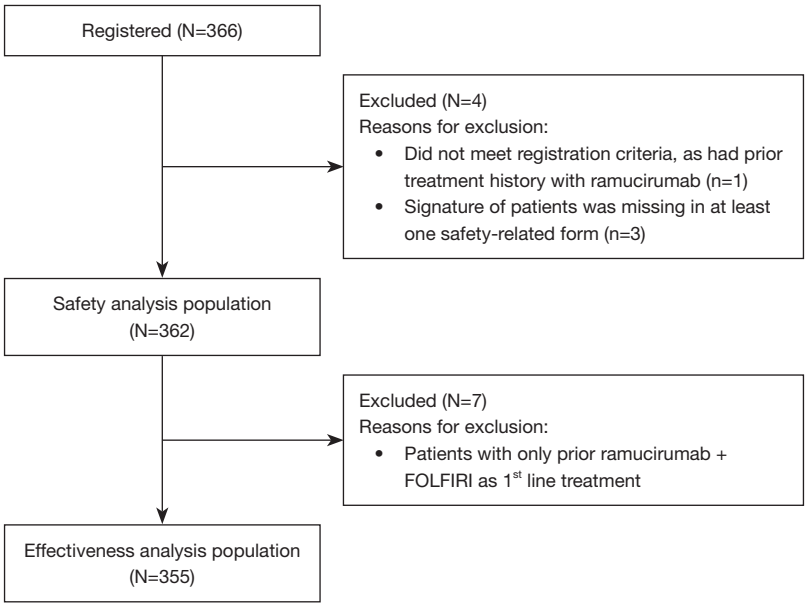


Figure 1 Patient disposition. N, total number of patients; n, number of patients in the category.

parameters including enrollment data, baseline patient characteristics, comorbidity, prior treatment for CRC, concomitant drugs and therapies, performance status, laboratory test values, AEs, laboratory test values related to AEs, survival analysis (investigated 12 months after initiation of ramucirumab), and continuation or discontinuation of ramucirumab, into electronic case report forms. AEs were defined as any unfavorable or unintended disease or sign (including an abnormal laboratory test value) in a patient who was administered ramucirumab + FOLFIRI, with or without a causal relationship to ramucirumab. AEs and laboratory test values related to AEs were graded using Common Terminology Criteria for Adverse Events, version 4.02. Serious AEs (SAEs) were events that resulted in death, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, required inpatient hospitalization or the prolongation of hospitalization, were life-threatening or considered serious for other reasons. AEs of special interest (AESIs) were summarized using consolidated terms comprising one or more Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (Table S1).

Statistical analysis

Statistical analyses for this study were based on estimation as this study was performed under routine clinical practice. Results of statistical analyses were presented using the mean values, incidence proportions, point estimates, and CIs. Continuous variables were summarized using statistics such as mean and standard deviation (SD). Categorical variables, including binary variables, were summarized using statistics such as frequency and incidence proportion. Survival status was estimated using the Kaplan-Meier method, including the 12-month survival rate and associated 95% CI and risk ratio evaluated the impact of patient characteristics on the incidence of proteinuria.

Results

Patient characteristics

A total of 362 patients were included in the safety analysis population and 355 patients in the efficacy analysis population from the 366 patients who registered for the study. Three patients from the safety analysis population were excluded due to absence of signature on at least 1 safety form, and 1 had prior history of ramucirumab treatment; seven patients with only 1st line treatment were excluded from the efficacy analysis population (*Figure 1*).

The mean ± SD age of the population was 64.1±10.9 years and comprised of a higher proportion of males (n=200; 55.2%). The most common primary tumor site was rectum (n=166; 45.9%) and all patients were diagnosed with metastases and recurrent sites (n=362, 100.0%).

Table 1 Baseline and demographic characteristics

Parameter	Analysis population (N=362)
Age, mean ± SD (years)	64.1±10.9
Sex, n (%)	
Male	200 (55.2)
Female	162 (44.8)
BMI, mean ± SD (kg/m^2)	22.4±3.9
Primary tumor site, n (%)*	
Rectal	166 (45.9)
Sigmoid colon	81 (22.4)
Ascending colon	79 (21.8)
Transverse colon	26 (7.2)
Descending colon	20 (5.5)
Metastasis and recurrent sites, n (%)	
Yes	362 (100.0)
No	0 (0.0)
Medication history of anti-cancer drugs, n (%)	
Yes	355 (98.1)
No	7 (1.9)
Medication history of bevacizumab, n (%)	
Yes	303 (83.7)
No	59 (16.3)
Medication history of anti-EGFR antibodies, n (%)	
Yes	92 (25.4)
No	270 (74.6)
ECOG performance status, n (%)	
0	228 (63.0)
1	121 (33.4)
2	13 (3.6)
RAS (*KRAS*/*NRAS*) status, n (%)	
Wild type	151 (41.7)
Mutant	202 (55.8)
Unknown	9 (2.5)
Comorbidity, n (%)	240 (66.3)
Hypertension	156 (43.1)
Diabetes	32 (8.8)
Thromboembolism	25 (6.9)
Renal disease	22 (6.1)
Liver disease	21 (5.8)
Hemorrhagic diathesis and coagulation disorder	4 (1.1)

*, patients could have more than 1 primary tumor site. N, total number of patients; n, number of patients in the category. SD, standard deviation; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; *RAS*, rat sarcoma.

The majority (n=355; 98.1%) of patients had medication history of anti-cancer drugs. Approximately 83.7% (n=303) and 25.4% (n=92) of patients had medication history of bevacizumab and/or anti-EGFR antibodies in combination with chemotherapy, respectively. The frequent regimens were FOLFOX (fluorouracil, levofolinate, oxaliplatin) + bevacizumab (n=153, 42.3%), XELOX (capecitabine, oxaliplatin) + bevacizumab (n=82, 22.7%), FOLFIRI + bevacizumab (n=63, 17.4%), fluorouracil + bevacizumab (n=59, 16.3%), and FOLFOX + anti-EGFR antibodies (n=59, 16.3%). A total of 349 (96.4%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (*Table 1*).

A large proportion (n=240; 66.3%) of the patients suffered from comorbidities, with hypertension (n=156; 43.1%) being the most commonly observed (*Table 1*).

Treatment

Ramucirumab

Overall, 359 patients from the analysis population were treated with ramucirumab for a median of 17 weeks. Three patients were excluded from the analyses due to unavailability of dose information. Each cycle was 14 days, with a median total

Table 2 Use and discontinuation of ramucirumab

Parameter	Value
Use of ramucirumab (N=359), median (min, max)	
Number of cycles (14 days as 1 cycle)	8 (1, 34)
Duration of treatment (week)	17.0 (2.0, 68.0)
Cumulative dose (mg/kg)	39.8 (5.5, 247.2)
Dose intensity (mg/kg/week)	2.9 (0.9, 4.4)
Relative dose intensity (%)	73.2 (21.5, 109.6)
Discontinuation of ramucirumab (N=362)	
Status at 12 months from treatment initiation, n (%)	
Continued	28 (7.7)
Discontinued	331 (91.4)
Reason for discontinuation, n (%)	
Progressive disease	220 (60.8)
AE	58 (16.0)
Physician decision	21 (5.8)
Patient decision	18 (5.0)
Lost to follow-up	7 (1.9)
Death	5 (1.4)
Symptom improvement	2 (0.6)

N, total number of patients; n, number of patients in the category; min, minimum; max, maximum; AE, adverse event.

Table 3 AEs occurring in ≥3% of the population

AEs by MedDRA	Grade ≥3 (N=362), n (%)	Any grade, (N=362), n (%)
Number of patients with any AE	305 (84.3)	
Neutrophil count decrease	90 (24.9)	138 (38.1)
Hypertension	35 (9.7)	58 (16.0)
Proteinuria	18 (5.0)	50 (13.8)
Neutropenia	11 (3.0)	14 (3.9)
Decreased appetite	9 (2.5)	52 (14.4)
Diarrhea	9 (2.5)	57 (15.7)
White blood cell count decrease	8 (2.2)	36 (9.9)
Malaise	4 (1.1)	45 (12.4)
Fatigue	3 (0.8)	23 (6.4)
Platelet count decrease	3 (0.8)	26 (7.2)
Stomatitis	2 (0.6)	36 (9.9)
Epistaxis	1 (0.3)	15 (4.1)
Constipation	1 (0.3)	22 (6.1)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	11 (3.0)
Nausea	0 (0.0)	18 (5.0)
Alopecia	0 (0.0)	14 (3.9)
Pyrexia	0 (0.0)	17 (4.7)

MedDRA, Medical Dictionary for Regulatory Activities (v23.0); N, total number of patients; n, number of patients in the category; AE, adverse event.

number (minimum, maximum) of 8 (1–34) cycles. The median cumulative dose, dose intensity, and relative dose intensity were 39.8 (5.5–247.2) mg/kg, 2.9 (0.9–4.4) mg/kg/week, and 73.2% (21.5–109.6%), respectively (*Table 2*).

FOLFIRI

Dosing and duration of FOLFIRI were performed as per routine standards. The median (minimum, maximum) number of cycles of all 3 drugs was 8 (1–34) cycles. The median duration of treatment was about 16 weeks. The median cumulative doses for levofolinate, fluorouracil (bolus injection + intravenous infusion), and irinotecan were 1,165, 13,500, and 750 mg/m^2, median dose intensity was 80, 977.5, and 54.2 mg/m^2/week, and relative median dose intensity was 80.0%, 69.8%, and 73.2%, respectively (Table S2).

Safety

Overall, at least 1 AE occurred in 305 (84.3%) patients. The most commonly occurring any grade AEs included neutrophil count decreased (n=138; 38.1%), hypertension (n=58, 16.0%), and diarrhea (n=57, 15.7%). Among the grade ≥3 AEs, neutrophil count decreased (n=90; 24.9%), hypertension (n=35; 9.7%), and proteinuria (n=18; 5.0%) were the most frequent (*Table 3*). The most commonly occurring clinically relevant grade ≥3 AESIs included neutropenia (n=101, 27.9%), hypertension (n=35, 9.7%), proteinuria (n=23, 6.4%) (*Table 4*).

SAEs were observed in 19.9% (72/362) of patients. Neutrophil count decreased (n=12, 3.3%), febrile neutropenia (n=7, 1.9%), decreased appetite (n=5, 1.4%), hypertension (n=5, 1.4%), and diarrhea (n=5, 1.4%) were frequently observed.

SAEs led to a total of 3 deaths, of which 1 death was deemed associated with ramucirumab with FOLFIRI treatment. One patient diagnosed with herpes zoster

Table 4 Grade ≥3 AESIs

AESIs	Safety analysis population (N=362)
Neutropenia	101 (27.9%)
Hypertension	35 (9.7%)
Proteinuria	23 (6.4%)
Hepatic dysfunction	15 (4.1%)
Febrile neutropenia	10 (2.8%)
Leukopenia	9 (2.5%)
Hemorrhagic events	3 (0.8%)
Venous thromboembolic events	3 (0.8%)
Gastrointestinal perforation	3 (0.8%)
Interstitial lung disease	2 (0.6%)
Arterial thromboembolic events	1 (0.3%)
Cardiac failure congestive	1 (0.3%)

AESIs were summarized, using consolidated terms comprising one or more MedDRA (Version 23.0) preferred terms (Table S1). N, total number of patients; AESIs, AEs of special interests; AE, adverse event.

meningoencephalitis had prior grade 3 herpes zoster. The herpes zoster meningoencephalitis was deemed associated with ramucirumab + FOLFIRI and varicella zoster virus. The other two patients with ileus and jaundice cholestatic respectively were due to disease progression and not related to ramucirumab + FOLFIRI.

Of the 101 patients with grade ≥3 neutropenia (AESI), 79 patients had only one event. The median time to onset of neutropenia was 21 days. Of 127 grade ≥3 events in 101 patients with neutropenia, granulocyte colony-stimulating factor was concomitantly administered in 46 events (36.2%).

The comorbidity of renal disease based on medical judgment at baseline increased the risk of proteinuria (risk ratio: 2.1; 95% CI: 1.1–4.2). No other parameters including diabetes, hypertension, or ramucirumab cycles increased the risk of proteinuria (*Figure 2*). Furthermore, the effect of urinary protein at baseline was evaluated by urine dipstick levels. Incidence of grade ≥3 proteinuria positively correlated with increased urine protein level at baseline [urine dipstick –/±: 3.6% (8/221); urine dipstick 1+: 14.0% (6/43); urine dipstick ≥2+: 31.6% (6/19)].

Treatment discontinuation

At 12 months (52 weeks) since treatment initiation, 331 (91.4%) patients had discontinued ramucirumab, mainly due to progressive disease (n=220; 60.8%) and AEs (n=58; 16.0%) (*Table 2*). The median time to treatment failure was 17.2 weeks (*Figure 3*). AEs leading to discontinuation included proteinuria (10/58; 17.2%), diarrhea, stomatitis, nephrotic syndrome, and malaise (3/58; 5.2% each).

Effectiveness

Effectiveness was assessed in 355 patients. The 12-month survival rate was 59.0% (95% CI: 53.5–64.4%) (*Figure 4*).

Discussion

The results indicated that the combination of ramucirumab + FOLFIRI had a comparable safety profile and effectiveness to earlier studies (10,13) with no new safety concerns in Japanese patients with mCRC under daily clinical practice.

The most commonly observed AEs in this post-marketing study included neutrophil count decreased, hypertension, and proteinuria. The incidence of grade ≥3 neutropenia (36%) and proteinuria (5%) was similar to a retrospective single-center cohort study in patients with mCRC treated with second-line ramucirumab + FOLFIRI (13). However, the proportion of grade ≥3 neutropenia (56%) was lower than observed in patients treated with ramucirumab + FOLFIRI in a retrospective study (14). Difference in the proportion of patients having no medication history of bevacizumab (49.5%) versus our study (16.3%), could have contributed to the higher proportion of the grade ≥3 neutropenia (14).

The incidence of grade ≥3 AESIs noted in this study were comparable to the RAISE trial (10). Overall, 28% of patients experienced at least 1 grade ≥3 neutropenia; 2 events led to treatment discontinuation. These results were similar to the reports from the RAISE trial (38% in ramucirumab group versus 23% in placebo group) (10). The incidence of grade ≥3 febrile neutropenia in the RAISE trial was 3.4%. Under clinical practice, we confirmed the incidence of febrile neutropenia (2.8%) observed in this study. The majority of patients with neutropenia and febrile neutropenia recovered or were recovering, suggesting that neutropenia and febrile neutropenia associated with ramucirumab + FOLFIRI were well managed under routine clinical practice. Notably, only 0.8% (n=3) of SAEs led to deaths in the study, of which 1 was deemed to be related to ramucirumab treatment. In the RAISE trial, 1.5% (n=8) of

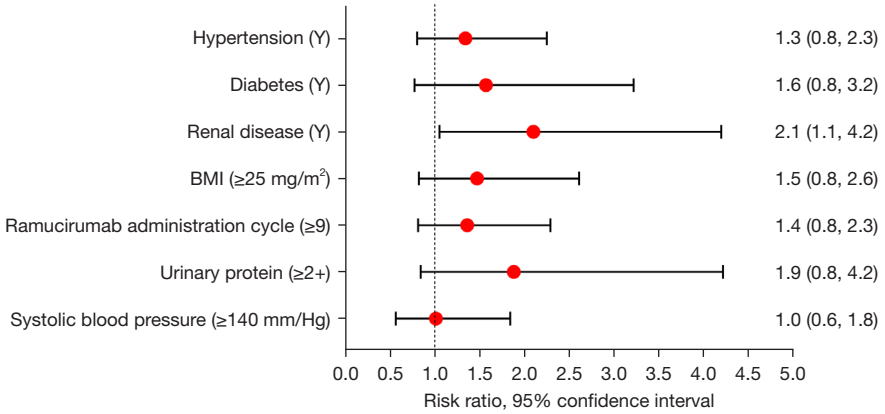
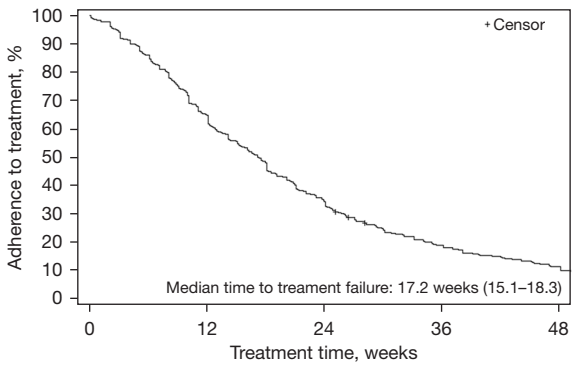
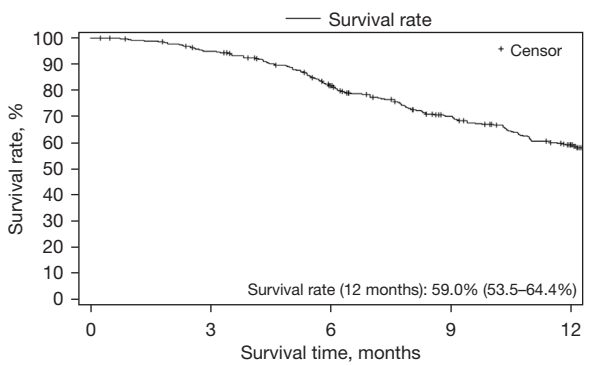


Figure 2 Risk ratio of occurrence of proteinuria. Y, yes; BMI, body mass index.



N	No. of event	No. of censored*	Median TTF	Adherence to treatment			
				12 weeks	24 weeks	36 weeks	48 weeks
362	327 (90.3)	35 (9.7)	17.2 (15.1–18.3)	64.9 (60.0–69.8)	34.8 (29.9–39.7)	18.8 (14.7–22.8)	11.1 (7.8–14.4)

Figure 3 Time to treatment failure. *, censored at 48 weeks, if administration is still on-going at the end on the observational period or at the last administration date and if treatment discontinuation was not confirmed within 48 weeks. TTF, time to treatment failure.



N	No. of death	No. of censored*	Survival rate (%)			
			3 months	6 months	9 months	12 months
355	141 (39.7)	214 (60.3)	94.9 (92.6–97.2)	81.7 (77.6–85.8)	69.9 (64.9–74.9)	59.0 (53.5–64.4)

Figure 4 Survival analysis of patient population. *, censored at the last date when the survival status was confirmed.

deaths occurred in the ramucirumab treatment group and were associated with study treatment (10).

Dysregulation of VEGF-A leads to glomerular disease, characterized by proteinuria and ultimately affecting renal functioning (15). Several studies indicated that proteinuria was a common AE associated with antiangiogenic inhibitors. The development of proteinuria restricted dosing of antiangiogenic inhibitors, thereby reducing efficacy (14,15). Meta-analysis of randomized clinical trials involving bevacizumab administration demonstrated a dose-dependent relationship with proteinuria (16). Pre-existing renal disease, medical history of hypertension and diabetes, and male sex were termed as predisposition factors to proteinuria (16,17). Furthermore, a recent retrospective study indicated that proteinuria occurrence was associated with administration cycles of ≥13, systolic blood pressure, and concomitant use of calcium channel blockers in cancer patients treated with bevacizumab, ramucirumab, or aflibercept (18). Proteinuria is a primary AE leading to discontinuation of ramucirumab combination therapy. In our study, of the 58 patients who discontinued due to AEs, 10 patients discontinued ramucirumab due to proteinuria (17.2%). The presence of renal disease or higher urine protein levels significantly affected the incidence of proteinuria. None of the other baseline parameters including diabetes, hypertension,

or ramucirumab cycles increased the risk of proteinuria. The management of proteinuria caused by ramucirumab combination therapy is key to continue treatment of patients with mCRC. Physicians should pay attention to risk factors including hypertension and monitor proteinuria continuously. Ramucirumab should be temporarily discontinued if proteinuria of ≥2 g/day is reported and resumed with a reduced dose when urine protein levels are <2 g/day. Alternatively, ramucirumab should be permanently discontinued if proteinuria is ≥3 g/day or the onset of nephrotic syndrome appears (12). Antihypertensive drugs and temporary discontinuation of ramucirumab can control hypertension; however, if unmanageable, permanent discontinuation of ramucirumab is vital (12). Additionally, 3 (0.8%) patients suffered from nephrotic syndrome similar to the incidence observed in the RAISE trial (19).

AEs are common concerns in patients treated with chemotherapy; however, the significant and consistent OS benefit in patients with mCRC with prior anti-cancer combination therapy, supports the use of ramucirumab + FOLFIRI in this patient population. In the present study, after 12 months of ramucirumab + FOLFIRI treatment the survival rate was 59.0%, versus 55.9% in the RAISE trial (10), suggesting that benefit of ramucirumab + FOLFIRI is extended to patients with mCRC in the real-world setting.

The study was a prospective and non-interventional design with some limitations such as lack of control group and no specific exclusions criteria in the patient population on treatment history and concomitant medications; therefore, the study data could not be directly compared to the data from prior clinical trials with strict eligibility criteria. Overestimation or underestimation of AEs of ramucirumab + FOLFIRI could have been a possible risk because patients with prior history of various anti-cancer drug treatments were enrolled in this study. Subsequent treatments could increase the incidence of AEs due to worsening of performance status and toxicity from previous treatment or could decrease the incidence of AEs due to relatively shorter treatment period of later lines. Median survival time was not reached as the observational period of the study was 12 months after initiation of ramucirumab + FOLFIRI regimen.

Nevertheless, with these limitations in mind, frequency of AEs and survival rates at 12 months in this study were similar to that in RAISE study, confirming the safety and effectiveness of ramucirumab + FOLFIRI in the real-world setting. Therefore, the results of this observational study encourage health care providers to treat patients with mCRC with this combination.

Conclusions

The current observational study demonstrated that the regimen of ramucirumab + FOLFIRI was manageable for mCRC patients with various medication history including bevacizumab and/or anti-EGFR antibodies in combination with chemotherapy. The most common AE leading to discontinuation of ramucirumab was proteinuria; therefore, it is necessary to appropriately manage proteinuria by periodical proteinuria testing and dose modifications. The results were similar to the RAISE trial and no new safety concerns were noted in the real-world setting.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-863/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-863/dss

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Supplementary

Table S1 Preferred terms included in adverse events of special interest

Adverse event of special interest composite term	MedDRA preferred terms
Neutropenia	Neutropenia, Neutrophil count decreased
Hypertension	Blood pressure increased, Hypertension
Proteinuria	Nephrotic syndrome, Protein urine, Proteinuria, Protein urine present, Urine protein/creatinine ratio abnormal
Hepatic dysfunction	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyl transferase increased, Hepatic function abnormal, Jaundice cholestatic, Liver disorder, Esophageal varices hemorrhage
Leukopenia	Leukopenia, White blood cell count decreased
Febrile neutropenia	Febrile neutropenia
Hemorrhagic events	Conjunctival hemorrhage, Epistaxis, Gingival bleeding, Hematochezia, Hematuria, Esophageal varices hemorrhage, Tumor hemorrhage, Lower gastrointestinal hemorrhage, Post procedural hemorrhage, Hemorrhoidal hemorrhage
Venous thromboembolic events	Pulmonary infarction, Deep vein thrombosis, Embolism, Venous thrombosis limb
Gastrointestinal perforation	Large intestine perforation, Small intestinal perforation
Interstitial lung disease	Interstitial lung disease, Pneumonitis
Arterial thromboembolic events	Cerebral infarction, Pulmonary artery thrombosis
Cardiac failure congestive	Cardiac failure

MedDRA, Medical Dictionary for Regulatory Activities (Version 23.0).

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Table S2 Use of FOLFIRI

Parameter	Median (min, max)
Use of levofolinate	
Number of cycles (14 days as 1 cycle)	8 (1, 34)
Duration of treatment (week)	16.4 (2.0, 68.0)
Cumulative dose (mg/kg)	1,165.0 (0.0, 8,125.0)
Dose intensity (mg/kg/week)	80.0 (0.0, 191.3)
Relative dose intensity (%)	80.0 (0.0, 191.3)
Use of fluorouracil	
Number of cycles (14 days as 1 cycle)	8 (1, 34)
Duration of treatment (week)	16.4 (2.0, 68.0)
Cumulative dose (mg/kg)	13,500 (0.0, 108,000.0)
Dose intensity (mg/kg/week)	977.5 (0.0, 2,837.0)
Relative dose intensity (%)	69.8 (0.0, 202.6)
Use of irinotecan	
Number of cycles (14 days as 1 cycle)	8 (1, 34)
Duration of treatment (week)	16.3 (2.0, 68.0)
Cumulative dose (mg/kg)	750.0 (77.0, 5,760.0)
Dose intensity (mg/kg/week)	54.2 (14.4, 143.6)
Relative dose intensity (%)	73.2 (24.0, 114.7)

min, minimum; max, maximum.

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