ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Ramucirumab plus FOLFIRI as second-line treatment for patients with *RAS* wild-type metastatic colorectal cancer previously treated with anti-EGFR antibody: JACCRO CC-16

H. Yasui[1†], Y. Okita[2†], M. Nakamura[3], T. Sagawa[4], T. Watanabe[5], K. Kataoka[6], D. Manaka[7], K. Shiraishi[8], N. Akazawa[9], T. Okuno[10], T. Shimura[11], M. Shiozawa[12], Y. Sunakawa[13], H. Ota[14], M. Kotaka[15], H. Okuyama[2], M. Takeuchi[16], W. Ichikawa[17], M. Fujii[18] & A. Tsuji[2*]

[1]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe; [2]Department of Clinical Oncology, Faculty of Medicine, Kagawa University, Kita-gun; [3]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto; [4]Department of Gastroenterology, National Hospital Organization Hokkaido Cancer Center, Sapporo; [5]Department of Surgery, Japanese Red Cross Society Himeji Hospital, Himeji; [6]Division of Lower GI, Department of Gastroenterological Surgery, Hyogo Medical University, Nishinomiya; [7]Department of Surgery, Gastro-Intestinal Center, Kyoto Katsura Hospital, Kyoto; [8]Department of Medical Oncology, National Hospital Organization Nagoya Medical Center, Nagoya; [9]Department of Gastroenterological Surgery, Sendai City Medical Center Sendai Open Hospital, Sendai; [10]Department of Medical Oncology, Osaka Rosai Hospital, Sakai; [11]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya; [12]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama; [13]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki; [14]Department of Gastroenterological Surgery, Ikeda City Hospital, Ikeda; [15]Gastrointestinal Cancer Center, Sano Hospital, Kobe; [16]Graduate School of Mathematical Sciences, The University of Tokyo, Meguro-ku; [17]Division of Medical Oncology, Showa University Fujigaoka Hospital, Yokohama; [18]Department of Digestive Surgery, Nihon University School of Medicine, Itabashi-ku, Japan

Available online 12 September 2023

Background: Chemotherapy in combination with anti-epidermal growth factor receptor (EGFR) antibody is considered a first-line treatment regimen for *RAS* wild-type and left-sided metastatic colorectal cancer (mCRC), whereas second-line treatment regimens have not yet been established. Few studies have prospectively evaluated second-line treatment with anti-vascular endothelial growth factor antibody after first-line anti-EGFR antibody therapy for *RAS* wild-type mCRC.

Patients and methods: This non-randomized phase II trial investigated the clinical outcomes of second-line ramucirumab (RAM) plus fluorouracil, levofolinate, and irinotecan (FOLFIRI) after first-line anti-EGFR antibody in combination with doublet or triplet regimen in patients with *RAS* wild-type mCRC. The primary endpoint was the 6-month progression-free survival (PFS) rate. The secondary endpoints were PFS, overall survival (OS), objective response rate (ORR), rate of early tumor shrinkage (ETS), and safety. We hypothesized a threshold 6-month PFS rate of 30% and an expected 6-month PFS rate of 45%. Treatment was considered effective if the lower limit of the 90% confidence interval (CI) of the 6-month PFS rate was >0.30.

Results: Ninety-two patients were enrolled in the study. The primary tumor was located on the left side in 86 (95.6%) patients. Twenty (22.0%) patients had received triplet plus cetuximab as previous therapy. Six-month PFS rate was 58.2% (90% CI 49.3% to 66.2%) with a median PFS of 7.0 months (95% CI 5.7-7.6 months). Median OS was 23.6 months (95% CI 16.5-26.3 months). The ORR and ETS rate were 10.7% and 16.9%, respectively, in 83 patients with measurable lesions. The 6-month PFS rate was comparable between patients previously treated with doublet and triplet regimens; however, median PFS was longer for the doublet regimen (7.4 versus 6.4 months, $P = 0.036$).

Conclusions: Our study demonstrated prospectively that RAM plus FOLFIRI is an effective second-line treatment after anti-EGFR antibody-containing first-line therapy in *RAS* wild-type and left-sided mCRC. Furthermore, the results were similar for patients who were previously treated with triplet regimen.

Key words: ramucirumab, colorectal cancer, *RAS* wild-type, chemotherapy

INTRODUCTION

Colorectal cancer is the third most common carcinoma in the world in terms of the number of cases, and is the second leading cause of cancer-related death in Japan.[1,2] Regardless of *RAS* gene mutation, the use of anti-vascular endothelial growth factor (VEGF) antibody drugs as

*Correspondence to: Dr Akihito Tsuji, Department of Clinical Oncology, Faculty of Medicine, Kagawa University, 1750-1, Miki-Cho, Kita-gun, Kagawa 761-0793, Japan. Tel: +81-898-5111

E-mail: tsuji.akihito@kagawa-u.ac.jp (A. Tsuji).

†These authors contributed equally to this work.

2059-7029/© 2023 The Author(s). Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

second-line chemotherapy for patients who failed or were intolerant to first-line chemotherapy with anti-VEGF antibody drugs is the standard of care in metastatic colorectal cancer (mCRC).[2-7] Ramucirumab (RAM) is a fully human immunoglobulin G1 monoclonal antibody VEGF receptor-2 antagonist that prevents ligand binding and receptor-mediated pathway activation in endothelial cells.[8] Based on the results of the RAISE trial, RAM plus fluorouracil, levofolinate, and irinotecan (FOLFIRI) is considered one of the standard treatments for second-line chemotherapy.[2] Based on the results of several clinical trials, combination chemotherapy with anti-EGFR antibody has been positioned as the standard of care for first-line treatment in patients with *RAS* wild-type mCRC.[9-12] In particular, doublet plus anti-EGFR antibody regimen has been considered a first-line treatment regimen for *RAS* wild-type and left-sided mCRC;[12] however, second-line treatment regimens for *RAS* wild-type and left-sided mCRC have not yet been established. Few studies have prospectively evaluated second-line treatment in combination with anti-VEGF antibody after first-line anti-EGFR antibody-containing therapy for *RAS* wild-type mCRC.

We therefore conducted a prospective trial to investigate the efficacy and safety of RAM plus FOLFIRI as second-line treatment in patients with *RAS* wild-type mCRC who were refractory or intolerant to oxaliplatin and fluorouracil (doublet) or oxaliplatin, irinotecan and fluorouracil (triplet) plus anti-EGFR antibody chemotherapy.

PATIENTS AND METHODS

Patients

An investigator-initiated, single-arm, non-randomized, multicenter, phase II trial of RAM plus FOLFIRI as second-line therapy was carried out at 45 institutions in Japan. The eligibility criteria were as follows: age $\geq$20 years, histologically confirmed adenocarcinoma of colon or rectum with wild-type *RAS*, Eastern Cooperative Oncology Group performance status score of 0 or 1 and normal organ function, neutrophil cell count $\geq 1.5 \times 10^3$ cells per mm^3, hemoglobin count $\geq$9.0 g/dl, platelet count $\geq 10.0 \times 10^4$ per mm^3, urine protein test $<$1+, prothrombin time-international normalized ratio $<$1.5, and activated partial thromboplastin time no higher than the upper limit of normal plus 5 s. Eligible patients were refractory or intolerant to first-line doublet or triplet chemotherapy in combination with anti-EGFR antibody. In addition, patients who did not obtain early tumor shrinkage (ETS) in first-line treatment could participate in this study even if there was no disease progression. The exclusion criteria were evidence of symptomatic central nervous system metastasis or any other condition or therapy that in the investigators' opinion might pose a risk to the patient or interfere with the study objectives.

All patients provided written informed consent before enrollment. The protocol was approved by central and local ethics review boards and the study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. This trial is registered in jRCT (jRCTs061180002).

Protocol treatment

On day 1 of each 2-week cycle, patients received RAM 8 mg/kg as a 60-min intravenous infusion, followed by the FOLFIRI regimen (intravenous irinotecan 150 mg/m^2 given over 90 min followed by or concurrent with intravenous levofolinate 200 mg/m^2 given over 120 min, followed by fluorouracil 400 mg/m^2 given as an intravenous bolus infusion, and then 2400 mg/m^2 given as a continuous infusion over 48 h). Irinotecan dose reduction (125 mg/m^2 or 100 mg/m^2) was acceptable at the discretion of the attending physician for patients with uridine diphosphate glucuronosyltransferase family 1 member A1 (*UGT1A1*) gene polymorphisms of a homozygous *28 or *6, and compound heterozygous *28 and *6. Treatment was continued until radiographic confirmation of disease progression.

Study endpoints

The primary endpoint was 6-month progression-free survival (PFS) rate, which was defined as the rate of patients who did not experience disease progression or death from any cause during the period from randomization to 6 months. Secondary endpoints included PFS, overall survival (OS), objective response rate (ORR), rate of ETS (defined as a $>$20% reduction of the sum of the longest diameters of the target lesion at 8 weeks after treatment), and safety. The investigators assessed tumor response at baseline and every 8 weeks based on RECIST version 1.1. The response was confirmed in additional imaging carried out 4 weeks later. Safety was assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.

Statistical considerations

The median PFS of doublet plus molecular targeted therapy in second-line treatment has been reported as ~6 months in mCRC.[2-4,13,14] In the ML18147, RAISE, and VELOUR trials, which evaluated the efficacy of doublet plus anti-VEGF inhibitor after bevacizumab-containing doublet chemotherapy, the 6-month PFS rate was 40%-46%.[2-4] The 6-month PFS rate was ~30% for patients who received doublet chemotherapy without a molecular targeted drug as second-line therapy.[2-4,13,14] We hypothesized a threshold 6-month PFS rate of 30% and an expected 6-month PFS rate of 45% for the protocol treatment. A sample size of 74 patients was required (one-sided $\alpha = 0.05$; $\beta = 0.2$). Considering that some patients would be excluded from the analysis due to ineligibility after enrollment and the decrease in power due to the existence of censoring, 90 cases would be required to maintain a power $>$80%.

Survival analysis for PFS was carried out using the Kaplan–Meier method, and the Greenwood formula was

Table 1. Patient characteristics

Characteristics	Items	$n = 91$
Age, years	Median (range)	66.0 (29-84)
Sex, *n* (%)	Male/female	49 (53.8)/42 (46.2)
PS, *n* (%)	0/1	74 (81.3)/17 (18.7)
Previous therapy, *n* (%)	Doublet + anti-EGFR	68 (74.7)
	Doublet + anti-EGFR (ETS not achieved)	3 (3.3)
	Triplet + anti-EGFR	20 (22.0)
Primary tumor, *n* (%)	Present	36 (39.6)
	Resected	55 (60.4)
Primary tumor location, *n* (%)	Left	86 (95.6)
	Right	4 (4.4)
Metastatic site, *n* (%)	Liver	64 (70.3)
	Lung	38 (41.8)
	Para-aortic lymph nodes	21 (23.1)
	Regional lymph nodes[a]	18 (19.8)
	Peritoneum	18 (19.8)
	Pleural effusion	1 (1.1)
	Bone	3 (3.3)
UGT1A1 polymorphism, *n* (%)	−/−	40 (40.4)
	−/*28 or −/*6	30 (33.0)
	*28/*28, *6/*6, or *28/*6	6 (6.6)
Prior baseline chemotherapy, *n* (%)	FOLFOXIRI	19 (20.9)
	FOLFOX	70 (76.9)
	CAPOX	2 (2.2)
Prior anti-EGFR antibody, *n* (%)	Cetuximab	48 (52.7)
	Panitumumab	43 (47.3)

CAPOX, capecitabine and oxaliplatin; EGFR, epidermal growth factor receptor; ETS, early tumor shrinkage; FOLFOX, fluorouracil, levofolinate, and oxaliplatin; FOLFOXIRI, fluorouracil, levofolinate, oxaliplatin, and irinotecan; PS, performance status.
[a]All patients with regional lymph nodes also had distant organ metastases.

used to obtain a 90% confidence interval (CI) when estimating the probability of PFS at 6 months. The lower limit of the 90% CI was set as the threshold PFS probability at 6 months. If the lower limit of the 90% CI was >0.30, which was set as the threshold PFS probability at 6 months, the treatment was considered to be effective.

RESULTS

Ninety-two patients were enrolled in the study between October 2018 and December 2020. A safety analysis was carried out on all patients before initiation of treatment. One patient did not receive anti-EGFR antibody as first-line therapy and was excluded from the efficacy evaluation. The primary tumor was located in the left-sided colon or rectum in 86 (95.6%) patients. Twenty (22.0%) patients had received triplet plus cetuximab as previous therapy (Table 1). All patients with regional lymph nodes also had distant organ metastases.

At the data cut-off of 31 August 2022, the median number of treatment cycles was 11 (range 1-53 cycles) and one (1.1%) patient still received the protocol treatment at the end of the follow-up period. The dose intensity (actual/planned) values for the agents were as follows: RAM, 73.5%; irinotecan, 60.6%; levofolinate, 71.3%; bolus fluorouracil, 47.5%; and continuous fluorouracil, 69.6%. The

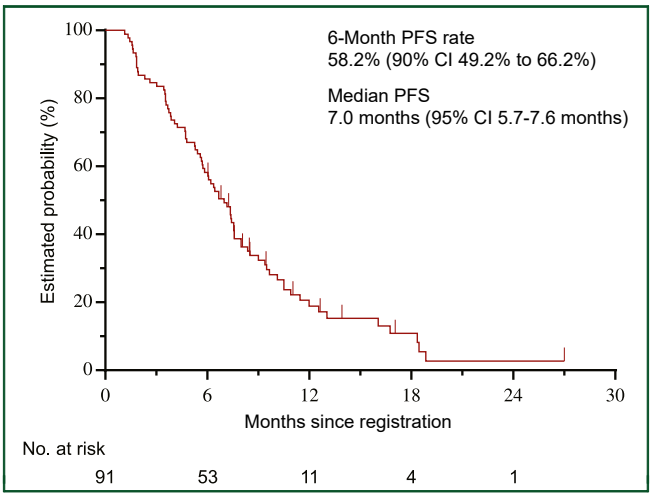


Figure 1. Progression-free survival (PFS).
CI, confidence interval.

reason for discontinuation of treatment was disease progression in 63 (70.0%) patients, delayed administration of >28 days due to adverse events in 13 (14.4%), adverse events in 6 (6.7%), withdrawal of patient consent in 4 (4.4%), and other in 4 (4.4%).

Efficacy

The primary endpoint of 6-month PFS rate was 58.2% (90% CI 49.3% to 66.2%), which met the expected 6-month PFS rate of 45%. Median PFS was 7.0 months (95% CI 5.7-7.6 months) (Figure 1). Median OS was 23.6 months (95% CI 16.5-26.3 months) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101636).

One (1.2%) patient achieved complete response and 8 (9.5%) achieved partial response. The confirmed ORR was 10.7% (95% CI 4.1% to 17.3%). The remaining 64 (76.2%) patients had stable disease, thus achieving a disease control rate (DCR) of 86.9% (95% CI 79.7% to 94.1%). Fourteen (16.9%) of 84 measurable patients achieved ETS at the first assessment of tumor shrinkage (Figure 2). As an exploratory analysis, the treatment effect was analyzed separately for patients with and without ETS. Median PFS was 5.9 months (95% CI 4.1-7.4 months) in patients with ETS and 10.1 months (95% CI 3.7-13.0 months) in those without ETS ($P = 0.027$) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101636).

The 6-month PFS rate was 58.3% (95% CI 46.1% to 68.7%) and 57.9% (95% CI 33.2% to 76.3%) in patients who had received doublet and triplet regimens, respectively, in first-line treatment. Median PFS was significantly longer in the doublet regimen group compared to the triplet regimen group: 7.4 months (95% CI 5.7-9.0 months) versus 6.4 months (95% CI 3.8-7.4 months), $P = 0.036$ (Figure 3). The ORR was 12.1% (95% CI 4.2% to 20.0%) in the doublet regimen group and 5.6% (95% CI 0.0% to 16.1%) in the triplet regimen group; however, DCR was 84.8% (95% CI 76.2% to 93.5%) in the doublet regimen group and 94.4% (95% CI 83.9% to 100%) in the triplet regimen group.

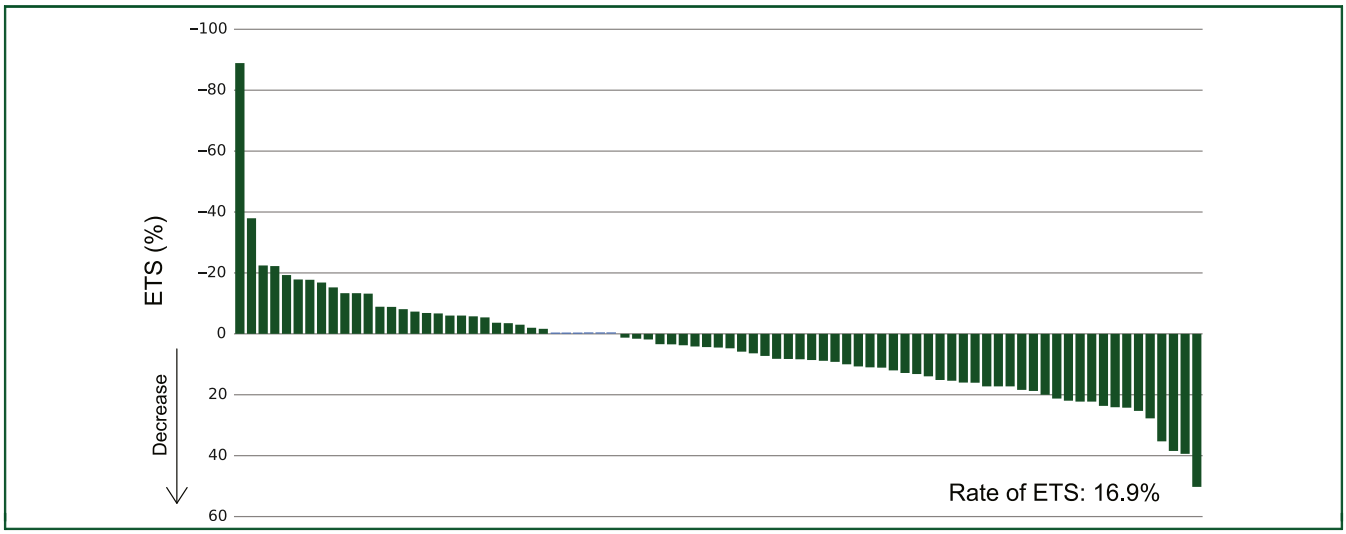


Figure 2. Percentage change from baseline in the sum of diameters of measurable tumors at the first.
ETS, early tumor shrinkage.

Safety and adverse events

Safety analysis was carried out on all 92 patients. The overall incidences of hematological and non-hematological toxicities are shown in Table 2. There were no treatment-related deaths. Grade 3 or 4 neutropenia was the most common adverse event, which occurred in 69 (47.8%) patients. In addition, three (3.3%) patients had grade 3 febrile neutropenia. The common grade 3 or 4 non-hematological toxicities were hypertension (27.2%), hypoalbuminemia (13.1%), anorexia (2.2%), and pneumonitis (2.2%). All-grade proteinuria and thromboembolism, which were considered adverse events related to RAM, occurred in 33.7% and 1.1% of patients, respectively. There were no grade 3 or 4 cases of proteinuria or thromboembolism.

DISCUSSION

Our study prospectively showed the efficacy and safety of RAM plus FOLFIRI in *RAS* wild-type mCRC patients who were refractory or intolerant to anti-EGFR antibody-containing first-line chemotherapy; in particular, 95% of the patients in this study were left-sided primary cases. To the best of our knowledge, this is the first clinical and prospective trial to demonstrate the efficacy of second-line chemotherapy in combination with anti-VEGF drug after anti-EGFR antibody-containing therapy in mCRC with *RAS* wild-type and left-sided primary tumors.

The present results demonstrated a 6-month PFS rate of 58.2%, a median PFS of 7.0 months, and a median OS of 23.6 months for second-line RAM plus FOLFIRI. The 6-month PFS rate, median PFS, and median OS were 43.7%, 5.7 months, and 13.3 months, respectively, in the RAISE trial, whereas subgroup analysis in the ML18147 trial found a median PFS of 6.4 months and a median OS of 15.4 months in *KRAS* wild-type patients.[2,15] In a subgroup analysis of the FIRE-3 trial for *RAS* wild-type mCRC, median PFS and median OS were 7.3 and 16.3 months, respectively, for FOLFOX plus bevacizumab in second-line treatment after FOLFIRI plus cetuximab, which possibly indicates a better therapeutic effect of anti-VEGF antibody in patients with *RAS* wild-type mCRC.[14] As most of the patients in the present study were *RAS* wild-type, it is difficult to directly compare present results with those of the RAISE trial, which included *RAS* mutations.[2] However, a subgroup analysis of the RAISE trial showed a median PFS of 5.7 months for *RAS* wild-type patients in the RAM plus FOLFIRI group.[16] Based on these historical data, anti-VEGF antibody may be more effective in RAS wild-type mCRC when administered after anti-EGFR antibody compared with continued administration of anti-VEGF antibody after tumor progression. The results of this study are comparable with those of other studies, despite expecting the results to be worse because 20% of the enrolled patients received triplet regimen in first-line treatment. OS data were prolonged compared to previous reports. We believe this was because drugs such as trifluridine—tipiracil and regorafenib were likely not administered in previous studies and are likely to have been given post-treatment in many patients in this study. Our findings support the favorable clinical outcomes of second-line treatment with anti-VEGF antibody-containing regimen in patients with *RAS* wild-type mCRC after first-line treatment with anti-EGFR antibody plus doublet or triplet regimen. From a preclinical perspective, the present results are supported by an animal model in which resistance to anti-EGFR antibody was accompanied by increased expression of VEGF and corresponding sensitivity to anti-VEGF agents.[17,18] In the GI-SCREEN Ukit study, VEGF-D levels in blood increased after use of anti-EGFR antibody drugs.[19] In the RAISE study, patients with higher VEGF-D levels in blood before RAM plus FOLFIRI therapy showed better treatment response.[20] These results confirm that anti-EGFR antibody-containing treatment in first-line therapy followed by anti-VEGF antibody-containing treatment is a reasonable strategy in patients with *RAS* wild-type mCRC.

Two randomized phase II trials (PRODIGE-18 and SPIRITT) have shown that combining anti-VEGF antibodies in first-line

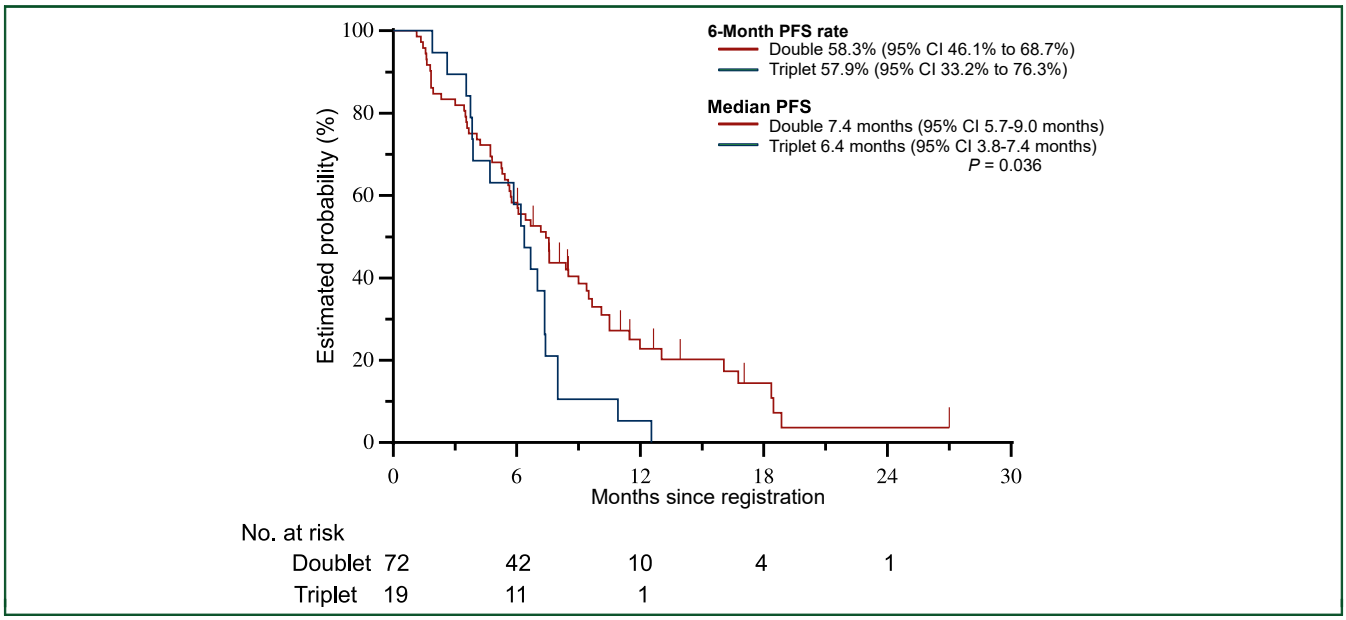


Figure 3. Progression-free survival (PFS) by previous treatment (doublet or triplet).
CI, confidence interval.

therapy with anti-EGFR antibodies in second-line therapy for patients with *RAS* wild-type mCRC does not prolong survival, although the ORR was higher than continuing to use anti-VEGF antibodies beyond progressive disease.[21,22] However, in the STRATEGIC-1 trial, designed to compare treatment strategies for patients with *RAS*/*BRAF* wild-type mCRC, comparison between FOLFIRI plus cetuximab followed by FOLFOX plus bevacizumab and OPTIMOX plus bevacizumab followed by FOLFOX plus bevacizumab followed by anti-EGFR antibody found a tendency for longer median OS in the former group (34.4 versus 37.8 months), although the difference was not statistically significant.[23] The PARADIGM trial recently showed that the standard of care for first-line treatment of *RAS* wild-type, left-sided mCRC is FOLFOX plus anti-EGFR antibody.[12] These results suggest that a standard regimen is an irinotecan-based chemotherapy with anti-VEGF antibody in second-line treatment for mCRC with *RAS* wild-type and left-sided primary tumors. The present data suggest that RAM plus FOLFIRI will be a clinically applicable regimen in clinical practice.

Table 2. Adverse events in the safety population (n = 92)

	All grades *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Hematological			
Leucopenia	61 (66.3)	18 (19.6)	0
Neutropenia	69 (75.0)	31 (33.7)	13 (14.1)
Anemia	44 (47.8)	5 (5.4)	0
Thrombocytopenia	42 (45.7)	7 (7.6)	2 (2.2)
Febrile neutropenia	3 (3.3)	3 (3.3)	0
Non-hematological			
Hypertension	54 (58.7)	25 (27.2)	0
Malaise	43 (46.7)	0	0
Hypoalbuminemia	40 (43.5)	9 (9.8)	3 (3.3)
Anorexia	39 (42.4)	2 (2.2)	0
Diarrhea	30 (32.6)	0	0
Oral mucositis	33 (35.9)	1 (1.1)	0
Proteinuria	31 (33.7)	4 (4.3)	0
Fatigue	30 (32.6)	1 (1.1)	0
Increased AST	29 (31.5)	3 (3.3)	0
Nausea	28 (30.4)	0	0
Increased ALT	27 (29.3)	2 (2.2)	0
Increased alkaline phosphatase	22 (23.9)	1 (1.1)	0
Alopecia	21 (22.8)	0	0
Fever	14 (15.2)	0	0
Hypokalemia	12 (13.0)	2 (2.2)	0
Hyponatremia	10 (10.9)	0	0
Gastrointestinal bleeding	4 (4.3)	0	0
Pneumonitis	2 (2.2)	2 (2.2)	0
Thromboembolism	1 (1.1)	1 (1.1)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The frequency of hypertension in patients who received RAM plus FOLFIRI in the RAISE trial was 53% in all grades, but was higher in the present study. The reason for this difference may be that in the RAISE study, patients had been previously treated with bevacizumab, and management for adverse events of hypertension had already begun, whereas in our study, patients had not been previously treated with anti-VEGF antibody drugs, and hypertension appeared after initiation of treatment.[2] In addition, the dose intensity was ∼10% lower in the present study than in the RAISE study, in which the mean dose intensity of each agent was 86.0% for RAM, 75.5% for irinotecan, 80.8% for levofolinate, and 69.8% for fluorouracil.[2] There was no significant difference in the dose reduction criteria between the two trials. As more severe toxicities such as myelosuppression were observed in our study, the intensity of treatment may have been slightly lower in the present Japanese patients than in the patient population in the RAISE trial.

The present study has several limitations. This study is a single-arm non-randomized trial. At this time, there are no comparative studies of anti-VEGF antibody drugs such as bevacizumab, aflibercept, and RAM in second-line

https://doi.org/10.1016/j.esmoop.2023.101636

treatment after first-line treatment with bevacizumab. Therefore, it is unclear which of the three drugs should be applied in second-line therapy after anti-EGFR antibody drugs. However, our promising results indicate clearly that RAM in second-line treatment after first-line treatment with bevacizumab should be the treatment of choice. Participants in this study included a variety of cases with differences in prior treatment, and those who were refractory to irinotecan and who did not experience ETS and disease progression in the previous treatment were eligible for enrollment. There have been no prospective trials of subsequent treatment of patients who received triplet or doublet regimen in combination with anti-EGFR antibody; therefore, we designed this trial with atypical eligibility criteria to enable the collection of novel evidence regarding second-line treatment for mCRC. Another limitation of this paper is the inclusion of a heterogeneous treatment population, which included not only patients who received doublet as primary treatment but also those who received triplet as primary treatment. The results of the TRIPLETE trial, a phase III trial, which compared triplet plus panitumumab and doublet plus panitumumab in the first-line treatment of *RAS* wild-type mCRC with the primary endpoint of ORR, did not demonstrate superiority of the triplet plus panitumumab group.[24] However, the DEEPER trial, a phase II trial that compared triplet plus cetuximab and triplet plus bevacizumab in the first-line treatment of *RAS* wild-type mCRC with the primary endpoint of deepness of response, met its primary endpoint.[25] Although the present exploratory results should be interpreted with caution, we consider that they suggest the clinical utility of RAM plus FOLFIRI after triplet treatment.

In conclusion, this study is the first prospective trial to demonstrate the efficacy of anti-VEGF antibody combination chemotherapy as second-line therapy after first-line combination chemotherapy with anti-EGFR antibody in patients with *RAS* wild-type mCRC. Our results indicate that anti-VEGF antibody including RAM plus FOLFIRI is a clinically useful second-line treatment for patients with *RAS* wild-type, left-sided primary mCRC, and is the first treatment regimen to demonstrate efficacy and safety, specifically after first-line anti-EGFR antibody combination therapy. Because efficacy was not impaired by the triplet regimen in first-line treatment, RAM plus FOLFIRI could be used as a treatment option after first-line triplet plus anti-EGFR antibody.

ACKNOWLEDGEMENTS

We thank the patients, their families, investigators, institutions involved in this study, and the members of the JACCRO Data Center and Support Office. We also thank Kenji Omura, Michio Itabashi, and Kohei Akazawa for the independent data and safety monitoring committee.

FUNDING

This work was supported by Eli Lilly Japan K.K. (no grant number) and the Japan Clinical Cancer Research Organization (JACCRO, 061180002). The funders did not have any involvement in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article or the decision to submit the article for publication.

DISCLOSURE

MN declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Eli Lilly Japan, Bristol-Myers Squibb, Daiichi Sankyo, Ono Pharmaceutical, Taiho Pharmaceutical, Yakult Honsha, Bayer Yakuhin, Chugai Pharmaceutical, Merck BioPharma, Otsuka Pharmaceutical, and Takeda; KK declares grants or contracts from the Japanese Society of Clinical Oncology and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Eli Lilly Japan and Merck BioPharma; MS declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Eli Lilly Japan; YS declares grants from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda, Sanofi, Ohtsuka Pharmaceutical, and Eli Lilly Japan, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Eli Lilly Japan, Bristol-Myers Squibb, Chugai Pharmaceutical, Takeda, Ono Pharmaceutical, Merck BioPharma, Taiho Pharmaceutical, Bayer, Daiichi-Sankyo, MSD, Sysmex, and Guardant Health, and participation in a data safety monitoring board or advisory board from Merck BioPharma, Ono Pharmaceutical, and Guardant Health; WI declares grants from Taiho Pharmaceutical, Chugai Pharmaceutical, Shionogi, and Daiichi-Sankyo, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Chugai Pharmaceutical, Yakult Honsha, AstraZeneca, Taiho Pharmaceutical, Nihonkayaku, Bayer, Merck BioPharma, Kyowa Kirin, and Bristol-Myers Squibb; AT declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Merck BioPharma, Bayer, Ono Pharmaceutical, and Daiichi-Sankyo. All other authors have declared no conflicts of interest.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. 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-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16(5):499-508.
3. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30(28):3499-3506.
4. 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*. 2013;14(1):29-37.

5. Chiorean EG, Nandakumar G, Fadelu T, et al. Treatment of patients with late-stage colorectal cancer: ASCO resource-stratified guideline. *JCO Glob Oncol*. 2020;6:414-438.
6. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. *Ann Oncol*. 2018;29(1):44-70.
7. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2020;25(1):1-42.
8. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol*. 2010;28(5):780-787.
9. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1065-1075.
10. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705.
11. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2017;317(23):2392-2401.
12. Watanabe J, Muro K, Shitara K, et al. Panitumumab vs bevacizumab added to standard first-line chemotherapy and overall survival among patients with RAS wild-type, left-sided metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2023;329(15):1271-1282.
13. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;25(12):1539-1544.
14. Modest DP, Stintzing S, von Weikersthal LF, et al. Impact of subsequent therapies on outcome of the FIRE-3/AIO KRK0306 trial: first-line therapy with FOLFIRI plus cetuximab or bevacizumab in patients with KRAS wild-type tumors in metastatic colorectal cancer. *J Clin Oncol*. 2015;33(32):3718-3726.
15. Kubicka S, Greil R, Andre T, et al. Bevacizumab plus chemotherapy continued beyond first progression in patients with metastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings. *Ann Oncol*. 2013;24(9):2342-2349.
16. Obermannova R, Van Cutsem E, Yoshino T, et al. Subgroup analysis in RAISE: a randomized, double-blind phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab or placebo in patients with metastatic colorectal carcinoma progression. *Ann Oncol*. 2016;27(11):2082-2090.
17. Viloria-Petit A, Crombet T, Jothy S, et al. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. *Cancer Res*. 2001;61(13):5090-5101.
18. Ciardiello F, Bianco R, Caputo R, et al. Antitumor activity of ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to antiepidermal growth factor receptor therapy. *Clin Cancer Res*. 2004;10(2):784-793.
19. Taniguchi H, Yuki S, Shiozawa M, et al. Plasma VEGF-D and PlGF levels according to prior use of biologics among metastatic colorectal cancer: preliminary results from GI-SCREEN CRC-Ukit study. *J Clin Oncol*. 2020;38(suppl 4):178.
20. Taniguchi H, Yoshino T, Yamaguchi K, et al. Clinical development and evaluation of a VEGF-D assay in plasma from patients with metastatic colorectal cancer in the RAISE study. *Curr Med Res Opin*. 2021;37(10):1769-1778.
21. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT: a randomized, multicenter, phase II study of panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment in patients with unresectable wild type KRAS metastatic colorectal cancer. *Clin Colorectal Cancer*. 2015;14(2):72-80.
22. Bennouna J, Hiret S, Bertaut A, et al. Continuation of bevacizumab vs cetuximab plus chemotherapy after first progression in KRAS wild-type metastatic colorectal cancer. *JAMA Oncol*. 2019;5(1):83-90.
23. Chibaudel B, Dourthe L, Andre T, et al. STRATEGIC-1: multi-line therapy trial in unresectable wild-type KRAS/NRAS/BRAF metastatic colorectal cancer—a GERCOR-PRODIGE randomized open-label phase III study. *J Clin Oncol*. 2022;40(suppl 16):3504.
24. Rossini D, Antoniotti C, Lonardi S, et al. Upfront modified fluorouracil, leucovorin, oxaliplatin, and irinotecan plus panitumumab versus fluorouracil, leucovorin, and oxaliplatin plus panitumumab for patients with RAS/BRAF wild-type metastatic colorectal cancer: the phase III TRIPLETE study by GONO. *J Clin Oncol*. 2022;40(25):2878-2888.
25. Tsuji A, Ohori H, Yamaguchi T, et al. The randomized phase II study of FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab as the first-line treatment in metastatic colorectal cancer with RAS wild-type tumors: the DEEPER trial (JACCRO CC-13). *J Clin Oncol*. 2021;39(suppl 15):3501.