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Impact of Anti-angiogenic Agents on Chemotherapy Efficacy in Patients With Metastatic Colorectal Cancer: Second-line FOLFIRI Plus Bevacizumab or Aflibercept

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Abstract. *Background/Aim: We compared the efficacy and safety of second-line FOLFIRI with bevacizumab (Bmab) or aflibercept (AFL) in patients with unresectable metastatic colorectal cancer (mCRC) to clarify selection criteria for anti-angiogenic agents. Patients and Methods: The subjects were patients with mCRC who received second-line FOLFIRI in combination with Bmab or AFL. The primary endpoint was median overall survival (OS). Secondary endpoints were median time to treatment failure (TTF), overall response rate (ORR) and incidence of adverse events. Results: Data from 26 patients in the Bmab group and 19 in the AFL group were analyzed. Median OS was slightly longer in the AFL group compared to the Bmab group, whereas median TTF was similar. ORR tended to be higher in the AFL group. The incidence of ≥grade 2 diarrhea and proteinuria was significantly higher in the AFL group than the Bmab group. Conclusion: In patients given combination treatment with FOLFIRI for second-line treatment of mCRC, AFL can increase response rates compared to Bmab, which may contribute to longer survival.*

Anti-angiogenic agents such as bevacizumab (Bmab) and aflibercept (AFL) are effective in the treatment of unresectable metastatic colorectal cancer (mCRC), which remains one of the most common causes of cancer-related mortality in the world (1). Bmab binds to and inhibits vascular epithelial growth factor (VEGF)-A, which suppresses the migration and proliferation of vascular endothelial cells (2). In randomized clinical studies, Bmab improved clinical outcomes of patients with mCRC receiving chemotherapies (fluoropyrimidines, irinotecan and oxaliplatin) in both first-line (3-5) and second-line (6-8) settings. Moreover, in the ML18147 study, Bennouna *et al*. reported the efficacy of second-line Bmab in patients with disease progression following first-line Bmab in combination with standard chemotherapy [median overall survival (OS): 11.2 months in Bmab + chemotherapy group *vs*. 9.8 months in chemotherapy group, hazard ratio (HR)=0.81, 95% confidence interval (CI)=0.69-0.94, p=0.0062] (9). Bevacizumab beyond first progression (BBP) is a widely used option for patients with mCRC receiving Bmab plus first-line chemotherapy.

AFL is a soluble decoy receptor which blocks the activity of VEGF-A, VEGF-B and placental growth factor (PIGF) 1 and 2, with higher affinity than endogenous receptors (10). In the VELOUR study, a Phase III randomized trial in patients with mCRC previously treated with an oxaliplatin-based regimen, addition of AFL to FOLFIRI significantly improved median OS and progression-free survival (PFS) in comparison with placebo plus FOLFIRI (median OS: 13.50 *vs*. 12.06 months, HR=0.817, 95%CI=0.713-0.937, p=0.0032, median PFS: 6.90 *vs*. 4.67 months, HR=0.758, 95%CI=0.661-0.869, p<0.0001) (11). Furthermore, prespecified subgroup analyses in this study showed that there was no significant interaction between treatment and stratification by prior exposure to Bmab (12). AFL is expected to be a chemotherapy option for mCRC previously treated with an oxaliplatin-based regimen. In a phase II trial, AFL in combination with FOLFIRI showed a clinical benefit in Japanese patients with mCRC, with tolerable toxicity (13).

Although several clinical reports have compared the efficacy and safety of AFL and Bmab, the findings are inconsistent and a conclusive result has yet to be obtained

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(14-16). Further, these two anti-angiogenic agents have not been compared in randomized clinical studies. As a result, criteria for their selection in second-line treatment for mCRC have not been established.

Here, we conducted a retrospective study to compare the efficacy and safety of second-line FOLFIRI with Bmab or AFL in patients with mCRC who were previously treated with an oxaliplatin-based regimen.

Patients and Methods

Patients. The study subjects were patients with mCRC who had been previously treated with an oxaliplatin-based regimen and received second-line FOLFIRI plus Bmab or AFL in our outpatient chemotherapy clinic between January 2014 and January 2020. Data were obtained from patients' electronic medical records and retrospectively analyzed. Exclusion criteria were two or more prior treatments, no previous treatment with oxaliplatin, and previous treatment with irinotecan.

This study was conducted in accordance with the guidelines for human studies adopted by the ethics committee of Gifu University Graduate School of Medicine and notified by the Japanese government (Institutional review board approval No.2020-109). In view of the retrospective nature of the study, the need for informed consent from the patients was not mandated.

Chemotherapy. Patients were treated with FOLFIRI every 2 weeks, consisting of 1.5 h injection of irinotecan at 150 mg/m^2, 2 h bolus injection of L-leucovorin at 200 mg/m^2, and 10 min bolus injection of 5-FU at 400 mg/m^2, followed by continuous infusion of 5-FU for 46 h at 2400 mg/m^2 with Bmab (5 mg/kg bodyweight, administered by intravenous bolus for 30 min every 2 weeks) or with AFL (4 mg/kg bodyweight, administered by intravenous bolus for 1 h every 2 weeks). Treatment was continued until disease progression or unacceptable adverse events.

Patients who had experienced severe adverse events in previous treatment and those with a poor general condition were administered a reduced initial dose of chemotherapy in the first cycle.

Patients who experienced severe adverse events underwent dose reduction in the subsequent chemotherapy cycle. Briefly, FOLFIRI treatment was delayed and FOLFIRI dose was reduced when one or more of the following adverse events occurred: grade 4 neutropenia or thrombocytopenia; grade ≥3 non-hematotoxicity; or when the treating physician judged that discontinuation was necessary due to adverse events. Bmab was delayed when proteinuria (≥3+) occurred. AFL was postponed when urine protein/creatinine ratio (UPCR) was ≥2.0 or hematuria occurred, and was discontinued when UPCR was >3.0.

Efficacy of chemotherapy. Efficacy indicators were compared between patients who received FOLFIRI plus Bmab (Bmab group) and those who received FOLFIRI plus AFL (AFL group). In addition, efficacy between the groups was also compared in patients with prior Bmab treatment. Primary endpoint for the efficacy of FOLFIRI plus anti-angiogenic agents was OS. Tumor response rate and time to treatment failure (TTF) were used as secondary endpoints. OS was defined as the time from the start of therapy to death, and TTF as the time from the start of therapy to the end of therapy. A censored patient who was still alive at the end of the follow-up period was considered lost to follow-up.

Tumor response was evaluated from computed tomography (CT) scans as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors guideline version 1.1 (17). Overall response rate (ORR) was defined as CR plus PR, and disease control rate (DCR) as CR+PR+SD.

Assessment of adverse events. Adverse events included hematological toxicities such as neutropenia and thrombocytopenia, and non-hematological toxicities, including nausea, vomiting, diarrhea, stomatitis, malaise, proteinuria and hypertension. Symptoms of adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 (18). Incidence rates of adverse events were compared between the Bmab and AFL groups. In addition, safety was compared between the Bmab and AFL groups in those patients with prior Bmab treatment.

Statistical analysis. Data were analyzed using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan) and R software version 3.5.1. p-Values less than 0.05 were considered significant. Patient characteristics are summarized as median with 25th and 75th percentiles for continuous variables and as frequency and percentage for categorical variables. For the primary analysis, OS and TTF between the AFL and Bmab groups were assessed by a Kaplan–Meier estimate and the log-rank test. Categorical variables such as ORR, DCR and the incidence of adverse events between the AFL group and the Bmab were compared using the chi-squared test.

Results

Patients. Fifty-eight patients with mCRC received FOLFIRI plus Bmab or plus AFL during the study period. Among these, 13 patients were excluded because they had two or more prior treatments, (n=6), no previous treatment with oxaliplatin (n=3), or previous treatment with irinotecan (n=4). The remaining 45 patients with mCRC were analyzed (Figure 1), 26 in the Bmab group and 19 in the AFL group (Table I). Of these, 50% (13 patients) in the Bmab group and 73.7% (14 patients) in the AFL group had received Bmab in first-line treatment.

Relative dose intensity (RDI) of anti-angiogenic agents was significantly lower in the AFL group than in the Bmab group [0.85 (0.74-0.97) *vs*. 0.58 (0.43-0.77), p=0.001]. In contrast, RDI did not significantly differ between the groups for other agents such as irinotecan, 5-FU bolus and 5-FU continuous infusion. Post-treatment, consisting of TAS-102, regorafenib, and EGFR antibodies was administered in 50%, 34.6%, 34.6% of patients in the Bmab group and 63.2%, 15.8%, and 26.3% in the AFL group, respectively.

Efficacy of FOLFIRI plus anti-angiogenic agents. Median OS was slightly longer in the AFL group than the Bmab group (14.0 *vs*. 10.5 months, HR=0.89, 95%CI=0.44-1.80, p=0.742, Figure 2A). Median TTF showed no remarkable difference between two groups (3.9 *vs*. 3.8 months, HR=0.94, 95%CI=0.51-1.73, p=0.845, Table II). On the

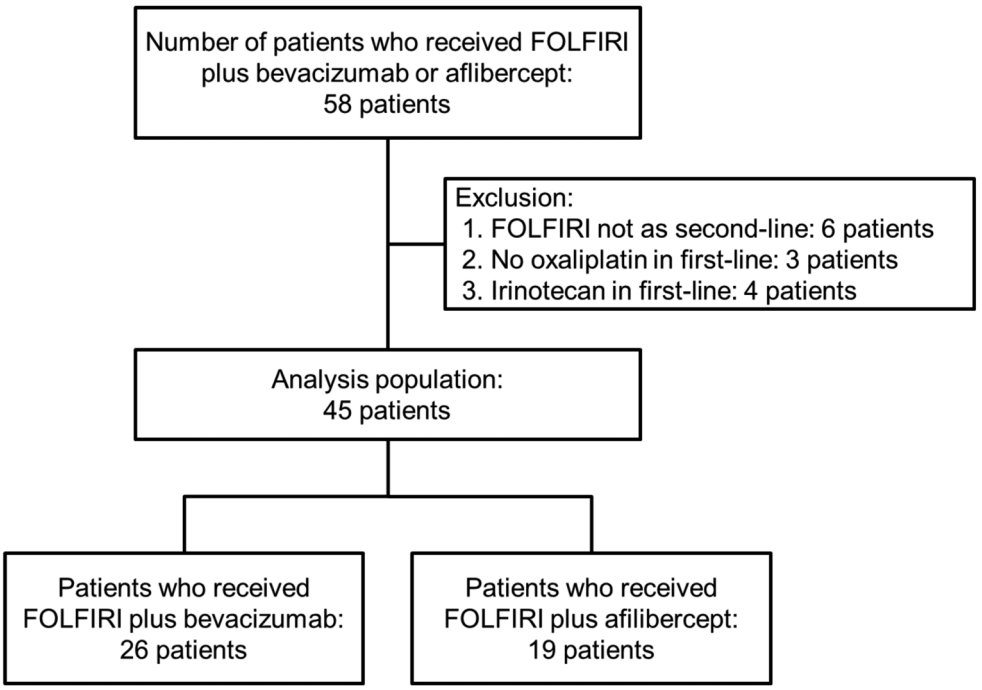

Figure 1. *Consolidated Standards of Reporting Trials (CONSORT) flow diagram.*

other hand, ORR tended to be higher in AFL group than Bmab group (26.5 *vs*. 3.8%, odds ratio: 8.93, 95%CI=0.95-84.3, p=0.069, Table II). Waterfall plot analysis revealed that tumor regression was more frequent in the AFL group than the Bmab group (Figure 3). Among patients with evaluable tumors, rate of PR was 5.2% in Bmab group and 35.7% in the AFL group.

We compared efficacy in the AFL and Bmab groups in patients who had received prior Bmab in first-line chemotherapy. Median OS was slightly longer in the AFL group than in the Bmab group (15.3 *vs*. 10.5 months, HR=0.69, 95%CI=0.30-1.07, p=0.823, Figure 2B). Median TTF was also slightly longer in the AFL group (4.3 *vs*. 2.0 months, HR=0.46, 95%CI=0.002-0.92, p=0.318, Table III). ORR tended to be higher in AFL group than Bmab group (28.6 *vs*. 0.0%, p=0.097, Table III).

Adverse events of FOLFIRI plus anti-angiogenic agents. The incidence rates of diarrhea (Grade ≥2) and proteinuria (Grade ≥2) were significantly higher in the AFL group than the Bmab group (diarrhea: 11.5% *vs*. 42.1%, p=0.033, proteinuria: 11.5% *vs*. 52.6%, p=0.006, Table IV). Similar results were seen in patients who had received Bmab in prior therapy (Table V). There were no significant differences between the two groups in the incidence rates of other adverse events, albeit that patients in the AFL group tended to have a higher frequency of stomatitis and hypertension.

Discussion

In this study, we compared clinical outcomes between FOLFIRI plus Bmab and FOLFIRI plus AFL in patients with mCRC who were previously treated with an oxaliplatin-based regimen. Results showed that median OS was slightly longer in the AFL group, whereas median TTF was similar. Further, ORR tended to be higher in the AFL group. These results suggest that AFL increases response rates compared to Bmab in these patients, and that this may contribute to longer survival.

In detail, median OS was slightly longer in the AFL group than the Bmab group (14.0 months *vs*. 10.5 months, HR=0.89, 95%CI=0.44-1.80, p=0.742), whereas median TTF was similar between the two groups (3.9 months *vs*. 3.8 months, HR=0.94, 95%CI=0.51-1.73, p=0.845). ORR tended to be higher in the AFL group (26.5% *vs*. 3.8%, OR=8.93, 95%CI=0.95-84.3, p=0.069). Furthermore, among patients with tumor-evaluable lesions, patients showing tumor shrinkage (≥1%) were 71.4% in the AFL group compared to 21% in the Bmab group. While there was no significant association between OS and combination of AFL in Cox proportional hazard regression analysis, clinical responses, including OS and ORR, tend to be better in patients receiving AFL than in those receiving Bmab. As TTF did not differ between the two groups, the effect of sustained disease control between the two groups may be comparable;

Table I. *Patient demographics and baseline characteristics in patients who received FOLFIRI plus bevacizumab (Bmab group) and FOLFIRI plus aflibercept (AFL group).*

	All patients		Patients with prior Bmab	
	Bmab group (n=26)	AFL group (n=19)	Bmab group (n=13)	AFL group (n=14)
Gender (male/female)	20/6	15/4	11/2	10/4
Age, median	65.0 42.0-82.0	66.0 45.0-79.0	66.0 48.0-74.0	65.5 49.0-79.0
ECOG-PS				
0	20 (76.9%)	13 (68.4%)	10 (76.9%)	9 (64.3%)
1	6 (23.1%)	6 (31.6%)	3 (23.1%)	5 (35.7%)
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Carcinoembryonic antigen (CEA, U/ml)	40 14-157	37 15-102	83 28-160	38 15-113
Carbohydrate antigen 19-9 (CA19-9, U/ml)	125 12-839	111 35-245	554 31-1637	173 97-311
Time from start of first-line chemotherapy (months)	8.4 7.2-11.9	5.9 4.0-13.0	8.4 7.1-9.6	7.1 3.6-14.5
Primary site (colon/rectal)	14/12	12/7	9/4	7/7
Primary site (right/left)	7/19	5/14	2/11	4/10
Number of metastatic organs/sites (1/≥2)	8/18	9/10	6/7	6/8
Number of metastatic organs/sites				
1	8 (30.8%)	9 (47.4%)	6 (46.2%)	6 (42.9%)
2	14 (53.8%)	7 (36.8%)	6 (46.2%)	5 (35.7%)
3	3 (11.5%)	3 (15.8%)	1 (7.7%)	3 (21.4%)
4	1 (3.8%)	0 (0%)	0 (0%)	0 (0%)
Metastatic organ				
Liver	21 (80.8%)	14 (73.7%)	11 (84.6%)	10 (71.4%)
Lung	14 (53.8%)	5 (26.3%)	6 (46.2%)	4 (28.6%)
Lymph nodes	8 (30.8%)	2 (10.5%)	2 (15.4%)	2 (14.3%)
Peritoneum	3 (11.5%)	6 (31.6%)	1 (7.7%)	4 (28.6%)
UGT1A1 gene (wild or heterozygous/homozygous)	24/2	17/2	11/2	13/1
RAS (wild/mutant/NA)	12/9/5	9/8/2	11/1/1	9/4/1
KRAS (wild/mutant/NA)	12/14/0	8/10/1	11/2/0	8/6/0
Prior bevacizumab (yes/no)	13/13	14/5	13/0	14/0

Data indicate median with 25th and 75th percentiles or number. NA: Not available/not evaluable.

however, transient tumor shrinkage may have had a positive impact on OS for mCRC patients who received second-line chemotherapy. Indeed, several clinical studies in patients with mCRC have reported an association between early tumor shrinkage and survival parameters, and a meta-analysis confirmed that early tumor shrinkage is a good predictor of survival in first-line chemotherapy for mCRC (19). To date, however, few such reports have appeared regarding second-line chemotherapy.

In fact, the ML18147 (9), RAISE (20) and VELOUR trials (12), which added the VEGF/VEGF receptor (VEGFR) inhibitors Bmab (9), ramucirumab (Rmab) (20) and AFL (12) to second-line chemotherapy which included fluoropyrimidines plus oxaliplatin or irinotecan, showed that all of the VEGF/VEGFR inhibitors were superior to chemotherapy alone in terms of OS and PFS. However, AFL was the only VEGF/VEGFR inhibitor in these trials with a higher response rate than chemotherapy alone (ML18147 trial: 5% *vs*. 4%, RAISE trial: 13.4% *vs*. 12.5%, VELOUR trial: 19.8% *vs*. 11.8%). In our study, AFL also tended to provide a higher response rate than Bmab (26.5% *vs*. 3.8%). These results suggest that AFL may be the preferred agent for second-line treatment in situations where conversion or palliation by tumor reduction is expected.

Several possible interpretations may explain the greater efficacy of AFL in tumor shrinkage than Bmab. First, AFL is a recombinant fusion protein consisting of the Fc portion of the human immunoglobulin G1 and extracellular domains of human VEGF receptors 1 and 2, targeting not only VEGF-A but also VEGF-B and PIGF (10). AFL, with a molecular weight of about 115,000 moles, is administered at a dose of 4 mg/kg/2 weeks, whereas Bmab, with a molecular weight of about 149,000 moles, is administered at 5 mg/kg/2 weeks, both in combination with FOLFIRI. AFL is able to trap VEGF-A with markedly higher affinity than Bmab (Kd for Bmab: 58-4456 pM, Kd for AFL: 0.49-9263 pM) and with strikingly stronger potency, which is expressed by the half maximal inhibitory concentration (IC_{50}) (IC_{50} for Bmab: 500-1476 pM, IC_{50} for AFL: 16-90 pM) (21). In their patient-derived xenograft colorectal cancer models, Marielle

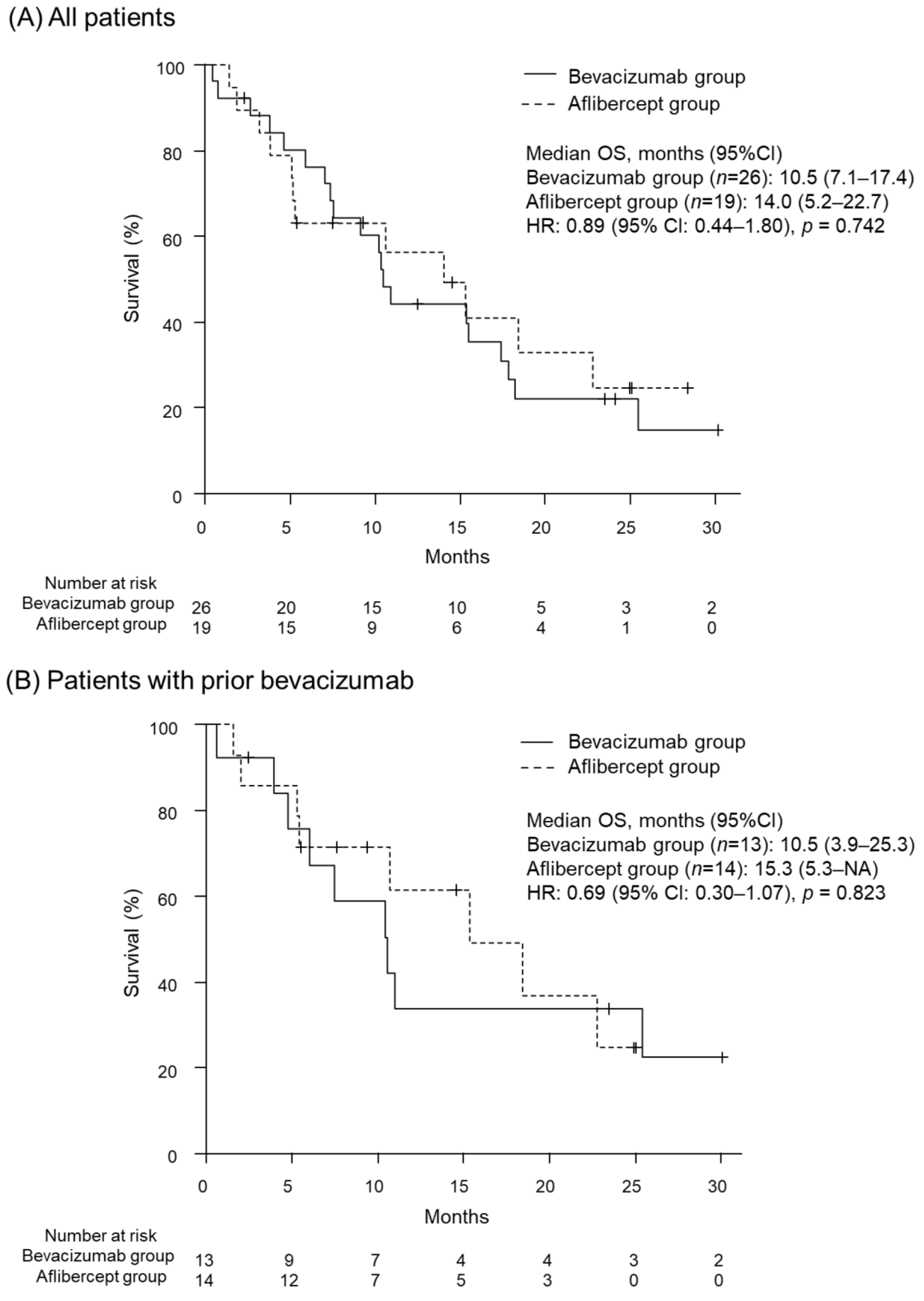

Figure 2. *Kaplan-Meier curves comparing overall survival between patients with metastatic colorectal cancer who received FOLFIRI plus bevacizumab and those who received FOLFIRI plus aflibercept, in all patients (A) and in patients with prior bevacizumab (B).*

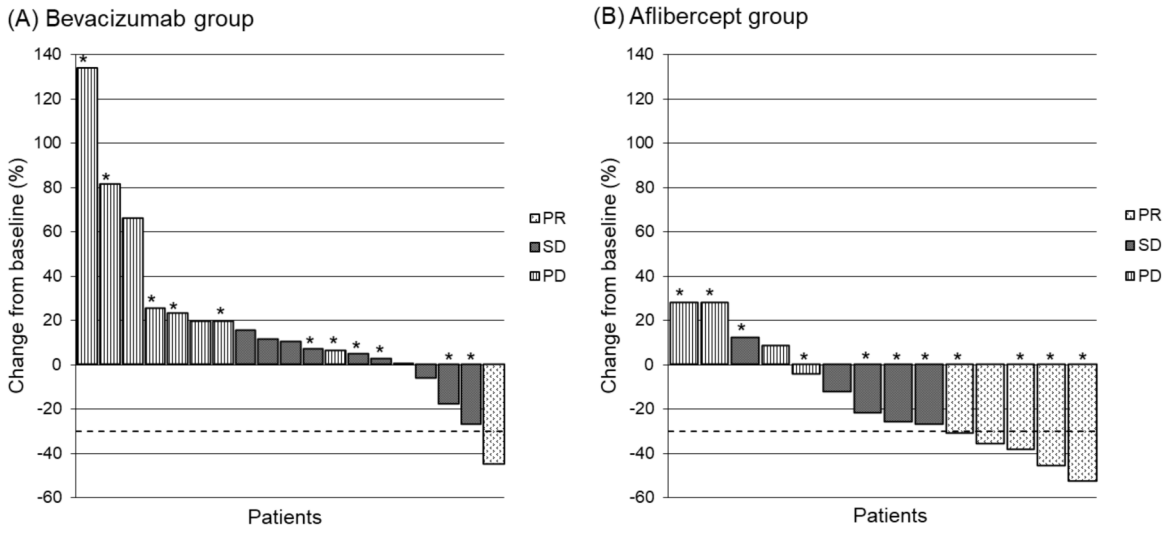

Figure 3. *Waterfall plot of best objective tumor change from baseline in patients with metastatic colorectal cancer who received FOLFIRI plus bevacizumab (A) and those who received FOLFIRI plus aflibercept (B). *Patients with prior bevacizumab.*

Table II. *Comparison of median time to treatment failure and disease control rate in patients with metastatic colorectal cancer between FOLFIRI plus bevacizumab (Bmab group) and FOLFIRI plus aflibercept (AFL group) in all patients.*

Effect	Bmab group (n=26)		AFL group (n=19)		*p*-Value
Median time to treatment failure (months, 95%CI)	3.5	(0.5-6.5)	3.9	(1.9-5.9)	0.974[a]
Tumor response rate (%)					
Response rate (CR+PR)	3.8	(1/26)	26.3	(5/19)	0.069[b]
Disease control rate (CR+PR+SD)	61.5	(16/26)	68.4	(13/19)	0.757[b]
One-year survival (%)	42.3	(11/26)	42.1	(8/19)	1.000[b]

Data were statistically analyzed by [a]log-lank test and [b]Fisher's exact probability test. CI: Confidence interval; CR: complete response; PR: partial response; SD: stable disease.

Table III. *Comparison of median time to treatment failure and disease control rate in patients with metastatic colorectal cancer between FOLFIRI plus bevacizumab (Bmab group) and FOLFIRI plus aflibercept (AFL group) in patients with prior Bmab.*

Effect	Bmab group (n=13)		AFL group (n=14)		*p*-Value
Median time to treatment failure (months, 95%CI)	2.0	(0.5-6.5)	4.3	(2.0-7.4)	0.318[a]
Tumor response rate (%)					
Response rate (CR+PR)	0.0	(0/13)	28.6	(4/14)	0.978[b]
Disease control rate (CR+PR+SD)	46.2	(6/13)	71.4	(10/14)	0.252[b]
One-year survival (%)	30.8	(4/13)	42.9	(6/14)	0.695[b]

Data were statistically analyzed by [a]log-lank test and [b]Fisher's exact probability test. CI: Confidence interval; CR: complete response; PR: partial response; SD: stable disease.

et al. reported that AFL demonstrated greater antitumor activity than Bmab in 39 of 48 models based on statistical analysis (22). In addition, VEGF, VEGFR, and PIGF levels suggested that the antitumor activity may have been due to neutralization of VEGFR-1, which is activated by VEGF derived from tumor cells, and of PIGF, which is primarily produced by tumor stroma. Thus, it is possible that AFL has a superior clinical benefit in patients with mCRC than Bmab.

Table IV. *Comparison of the incidence of adverse events between patients with metastatic colorectal cancer who received FOLFIRI plus bevacizumab (Bmab group) and those who received FOLFIRI plus aflibercept (AFL group) in all patients.*

Adverse event	Bmab group (n=26)		AFL group (n=19)		*p*-Value
	%	(presence/absence)	%	(presence/absence)	
Neutropenia (Grade ≥3)	57.7	(15/11)	68.4	(13/6)	0.673
Thrombocytopenia (Grade ≥2)	15.4	(4/22)	21.1	(4/15)	0.636
Nausea (Grade ≥2)	23.1	(6/20)	36.8	(7/12)	0.501
Vomiting (Grade ≥1)	11.5	(3/23)	15.8	(3/16)	0.686
Diarrhea (Grade ≥2)	11.5	(3/23)	42.1	(8/11)	0.033
Stomatitis (Grade ≥2)	7.7	(2/24)	26.3	(5/14)	0.114
Malaise (Grade ≥2)	34.6	(9/17)	31.6	(6/13)	1.000
Proteinuria (Grade ≥2)	11.5	(3/23)	52.6	(10/9)	0.006
Hypertension (Grade ≥2)	15.4	(4/22)	42.1	(8/11)	0.086

Table V. *Comparison of the incidence of adverse events between patients with metastatic colorectal cancer who received FOLFIRI plus bevacizumab (Bmab group) and those who received FOLFIRI plus aflibercept (AFL group) in patients with prior Bmab.*

Adverse event	Bmab group (n=13)		AFL group (n=14)		p-Value
	%	(presence/absence)	%	(presence/absence)	
Neutropenia (Grade ≥3)	61.5	(8/5)	64.3	(9/5)	1.000
Thrombocytopenia (Grade ≥2)	15,4	(2/11)	14.3	(2/12)	1.000
Nausea (Grade ≥2)	15.4	(2/11)	42.9	(6/8)	0.209
Vomiting (Grade ≥1)	7.7	(1/12)	21.4	(3/11)	0.596
Diarrhea (Grade ≥2)	7.7	(1/12)	42.9	(6/8)	0.077
Stomatitis (Grade ≥2)	15.4	(2/11)	28.6	(4/10)	0.648
Malaise (Grade ≥2)	30.8	(4/9)	21.4	(3/11)	0.678
Proteinuria (Grade ≥2)	15.4	(2/11)	50.0	(7/7)	0.103
Hypertension (Grade ≥2)	7.7	(1/12)	50.0	(7/7)	0.032

Data were statistically analyzed by Fisher's exact probability test.

Among our patients who received prior Bmab in first-line chemotherapy, median OS was longer in the AFL group than in the Bmab group, and tumor shrinkage was greater. In a post hoc study analysis of the VELOUR study, a correlation between prior Bmab therapy and efficacy of AFL was investigated based on biomarker levels for VEGF-A and PIGF, which were suggested to correlate with the acquisition of resistance to Bmab in patients with mCRC (23). Results showed that they were significantly increased in patients who had received prior Bmab compared with those who had not. Moreover, OS and PFS of patients in the AFL plus FOLFIRI group were prolonged compared with placebo, regardless of VEGF-A and PIGF levels at baseline. Thus, AFL may improve the prognosis of patients with resistance to Bmab.

Regarding adverse events, however, the incidence rates of diarrhea and stomatitis were higher in the AFL group than Bmab group. Ghiringhelli *et al*. reported AFL-induced microscopic colitis which was treated with mesalazine and budesonide, and discussed these findings with regard to the mechanism of action of AFL (24). Hindryckx *et al*. showed that a deficit in PIGF by genetic invalidation increased the severity of colitis in a mice model of induced acute colitis (25). Thus, AFL might more strongly exacerbate the gastrointestinal mucosal disorder induced by irinotecan than Bmab, warranting the need for care in treatment with FOLFIRI plus AFL. The frequency of proteinuria and hypertension were also higher in the AFL group than in the Bmab group. Hypertension requires the addition of antihypertensive agents. In addition, proteinuria is an adverse event that often requires the withdrawal of angiogenesis inhibitors, and accordingly the RDI of our AFL group was lower than that of the Bmab group. However, despite the low RDI of AFL, a tumor-shrinkage effect was observed in the AFL group, suggesting that an effect can be obtained even if appropriate AFL withdrawal for proteinuria is performed.

This study should be interpreted in light of several limitations. First, the study was conducted under a

retrospective design at a single center. Second, consideration of confounding factors may have been insufficient, because the sample size was small and the number of factors included in the multivariable analysis was limited to avoid overfitting. Validation of these results in a large-scale prospective study is warranted. In particular, adding bevacizumab to chemotherapy in mCRC may be beneficial only in patients with left-sided primary tumor, whereas patients with right-sided primary tumors may have no additional benefit from the addition of bevacizumab (26), and this point needs to be examined in the future.

In conclusion, AFL showed a higher tumor shrinkage effect than Bmab, suggesting that it may contribute to the extension of survival time in second-line chemotherapy for mCRC patients with FOLFIRI plus anti-angiogenic agents. However, clinicians need to be aware of the possibility of gastrointestinal mucosal disorder and anti-angiogenic agent-induced toxicities, such as proteinuria and hypertension, and consider the withdrawal of AFL in severe cases.

Conflicts of Interest

K. Yoshida has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Yakult Honsha Co., Ltd., Merck Sharp & Dohme Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Johnson & Johnson Co., Ltd., Covidien Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., Asahi Kasei Co., Ltd., Tsumura Co., Ltd., EA Pharma Co., Ltd., Bayer Yakuhin Co., Ltd., Olympus Co., Ltd., Terumo Co., Ltd., Bristol-Myers Squibb Co., Ltd., Denka Co., Ltd., Teijin Co., Ltd., SBI Pharmaceuticals Co., Ltd., Intuitive Surgical Co., Ltd., Novartis Pharma K.K., and Pfizer Inc.; and research funding from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Yakult Honsha Co., Ltd., Merck Sharp & Dohme Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Johnson & Johnson Co., Ltd., Covidien Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., Asahi Kasei Co., Ltd., Tsumura Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma Co., Ltd., Toyama Chemical Co., Ltd., Kinetic Concepts Co., Ltd., Abbott Japan Co., Ltd., and Toray Industries, Co., Ltd. outside the submitted work. A. Makiyama has received honoraria for lectures from Eli Lilly and Company, Taiho Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. The other Authors have no conflicts of interest in relation to this study.

Authors' Contributions

Hironori Fujii and Nobuhisa Matsuhashi conceptualized this study. Yunami Yamada, Nobuhisa Matsuhashi and Hironori Fujii acquired the clinical data. Akitaka Makiyama, Hirotoshi Iihara, Takao Takahashi, Daichi Watanabe, Ryo Kobayashi, Akio Suzuki, Akio Suzuki and Kazuhiro Yoshida were responsible for the data interpretation. Yunami Yamada, Nobuhisa Matsuhashi and Hironori Fujii drafted the manuscript. All Authors have read and approved the current version of the manuscript.

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