ANTICANCER RESEARCH *41*: 3091-3097 (2021)
doi:10.21873/anticanres.15093

Risk–benefit Analysis of FOLFIRI Plus Ramucirumab/Aflibercept as a Third-line Treatment in Metastatic Colorectal Cancer

MICHIO KIMURA[1], EISEKI USAMI[1], HITOMI TERAMACHI[2] and TOMOAKI YOSHIMURA[1]

[1]*Department of Pharmacy, Ogaki Municipal Hospital, Gifu, Japan;*
[2]*Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, Gifu, Japan*

Abstract. *Background/Aim: The efficacy of folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus ramucirumab (F-RAM) or aflibercept (F-AFL) as a second-line treatment in metastatic colorectal cancer (mCRC) is established. In this study, the risks and benefits of F-RAM/AFL as a third-line treatment after first- and second-line bevacizumab for mCRC were evaluated. Patients and Methods: Overall survival (OS) and adverse events (AEs) were compared between groups treated with F-RAM/AFL (n=17) and trifluridine/tipiracil combination tablet (TAS-102) (n=26). Results: Median OS was longer in the third-line F-RAM/AFL group (379 days; 95%CI=157-458 days) than in the TAS-102 group (183 days; 95%CI=80-204 days) (log-rank test, p=0.015). Discontinuation due to AEs was only observed in the F-RAM/AFL group (3 cases). Conclusion: As a third-line treatment for mCRC, F-RAM/AFL should be prioritized over TAS-102 in terms of efficacy; however, the risk of AEs should be considered.*

Angiogenesis is an important therapeutic target in colorectal cancer (CRC) (1). Currently, three products are approved in Japan as angiogenesis inhibitors (VEGF inhibitors), bevacizumab (BV), ramucirumab (RAM), and aflibercept (AFL). In CRC, a larger number of phase III clinical trials have proven the effectiveness of BV compared to RAM and AFL (2-9). These trials support the use of BV in combination with any treatment line or concomitant drug. Phase III clinical trials have only demonstrated the effectiveness of RAM and AFL as a second-line treatment, and the concomitant drug is FOLFIRI therapy (F-RAM/AFL) (10, 11).

For the first-line treatment of metastatic colorectal cancer (mCRC), the combination of fluorouracil/leucovorin and oxaliplatin (FOLFOX) or fluorouracil/leucovorin and irinotecan (FOLFIRI) with BV, cetuximab, or panitumumab molecularly targeted therapeutic agents is recommended (3, 12-16). For cases with *Ras* mutations, the combination of FOLFIRI and BV/RAM/AFL is recommended as the second-line treatment after using FOLFOX plus BV as the first-line treatment (10, 11, 17, 18). BV is often used as a second-line treatment in clinical practice. As third-line treatment in cases that are refractory or intolerant to fluoropyrimidine, oxaliplatin, or irinotecan, the American Society of Clinical Oncology and the National Comprehensive Cancer Center Network recommends the regorafenib or trifluridine/tipiracil combination tablet (TAS-102) as the third-line and later-line treatment for mCRC (19, 20).

In short, there is evidence for the efficacy of F-RAM/AFL as a second-line treatment and for regorafenib and TAS-102 as third-line and later-line treatments. In clinical practice, F-RAM/AFL is often used as a third-line treatment after the use of BV as a second-line treatment; however, the efficacy and safety of F-RAM/AFL in the third-line setting is not clearly established. Therefore, clarifying the risk–benefit of F-RAM/AFL for third-line treatment of mCRC as well as its efficacy and safety will improve treatment selection. In this study, F-RAM/AFL (human IgG-1 monoclonal antibodies targeting the extracellular domain of VEGF receptor 2) and TAS-102 (containing trifluridine, which inhibits thymidylate synthase and tumour growth) have been compared for third-line treatment of mCRC, as there is no difference between F-AFL and F-RAM for second-line treatment (10, 11, 18). The aim of this study was to clarify the risk benefits of F-RAM/AFL with respect to overall survival (OS) and adverse events (AEs) in comparison with those of TAS-102 as a third-line treatment after using BV as first-line and second-line treatment for mCRC.

Correspondence to: Michio Kimura, Department of Pharmacy, Ogaki Municipal Hospital, 4-86 Minaminokawa-cho, Ogaki-shi, Gifu 503-8502, Japan. Tel: +81 584813341, Fax: +81 584770854, e-mail: kimkim0305nao@yahoo.co.jp

Key Words: Ramucirumab, aflibercept, bevacizumab, third-line treatment, overall survival, adverse event, metastatic colorectal cancer.

Table I. *Patient characteristics*.

Characteristic	F-RAM/AFL	TAS-102	*p*-Value
Patients, n	17	26	
Age, years			
Median (range)	67 (36-79)	68 (42-78)	0.775[a]
Gender, n			
Male/female	8/9	16/10	0.349[b]
Height, cm			
Median (range)	156 (145-181)	160 (141-184)	0.882[a]
Weight, kg			
Median (range)	55 (39-89)	57 (38-95)	0.766[a]
BSA			
Median (range)	1.53 (1.28-2.07)	1.59 (1.22-2.04)	0.775[a]
CrCl			
Median (range)	66.3 (28.4-105.5)	78.9 (39.7-122.1)	0.358[a]
Disease status			
Recurrent/advanced, n	6/11	9/17	0.964[b]
Treatment regimen after third line			
TAS-102	7	0	0.017[b,*]
FOLFIRI plus RAM/AFL	2	0	0.289[b]
SOX plus BV	2	0	0.289[b]
Regorafenib	1	6	<0.001[b,*]
Metastatic site, n			
Lymph node	4	7	0.898[b]
Liver	6	16	0.386[b]
Peritoneal	5	10	0.903[b]
Bone	0	1	0.463[b]
Lung	8	15	0.989[b]
Others	3	0	0.015[b,*]

[a]Mann-Whitney *U*-test. [b]Chi-square test of independence. *$p<0.05$. RAM: Ramucirumab; AFL: aflibercept; BSA: body mass index; CrCl: creatinine clearance; FOLFIRI: combination of fluorouracil/leucovorin and irinotecan; F-RAM/AFL: combination of fluorouracil/leucovorin and irinotecan (FOLFIRI) with ramucirumab or aflibercept; TAS-102: trifluridine/tipiracil combination tablet; SOX: tegafur/gimeracil/oteracil potassium plus oxaliplatin.

Patients and Methods

Patients and evaluations. In total, 44 patients treated with F-RAM/AFL or TAS-102 as a third-line treatment after using BV as the first-line and second-line treatment for mCRC at Ogaki Municipal Hospital (Ogaki, Japan) between October 2016 and December 2020 were retrospectively evaluated. However, we excluded one patient who had been transferred to another hospital. Thus, 43 patients were considered eligible for this study. Patient characteristics, OS, AEs, treatment period, and reasons for treatment discontinuation were analyzed using data collected from electronic charts and pharmacy service records. OS was defined as the interval between the initiation of F-RAM/AFL or TAS-102 administration and the date of death from any cause. AEs were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (21), and the most severe grades during chemotherapy were reported. Personal information was protected in aggregated data. This study was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; approval number 20210325-2). The need for informed consent was waived owing to the retrospective nature of the study.

Treatment protocol. In the F-RAM/AFL group, patients received 8 mg/kg RAM/4 mg/kg AFL as a 60-min intravenous infusion, followed by FOLFIRI (150 mg/m^2 irinotecan and 200 mg/m^2 l-leucovorin were concurrently infused intravenously over 120 min, followed by 400 mg/m^2 fluorouracil administered as an intravenous bolus over 2-4 min, and then 2,400 mg/m^2 of fluorouracil as a continuous infusion over 48 h on day 1 every 2 weeks). Oral TAS-102 (35 mg/m^2 per dose) was administered twice daily (after morning and evening meals) for 5 consecutive days, followed by 2 days of rest, for 2 weeks, followed by a 14-day rest period; this constituted one treatment cycle.

Statistical analysis. Between-group comparisons were performed using the F-test. Mann–Whitney *U*-tests or chi-squared tests of independence (Fisher's exact probability tests) were used for comparisons of patient characteristics, AEs, and reasons for discontinuation. The Kaplan–Meier log-rank test was used to compare OS. Significance was defined as $p<0.05$, and all statistical analyses were performed using EZR (v1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (22).

Results

Patient characteristics. The F-RAM/AFL and TAS-102 groups included 17 (F-RAM: 12, F-AFL: 5) and 26 patients, respectively. The characteristics of patients are summarized in Table I. After the third line, TAS-102 (7 cases) was often used in the F-RAM/AFL group (p=0.017). In the TAS-102 group, regorafenib (6 cases) was frequently used (p<0.001).

Hazard ratio for overall survival after third-line treatment. Univariate and multivariate analyses of the prognostic value of baseline and clinical characteristics are presented in Tables II and III. In the univariate analysis, body surface area (>1.50), use of F-RAM/AFL as a third-line treatment (yes), and subsequent treatment (after third-line treatment) (yes) were significantly associated with survival. In the multivariate analysis, the use of F-RAM/AFL in third-line treatment (yes) was independently and significantly associated with survival. Patients who received the F-RAM/AFL regimen on third-line treatment had a death hazard ratio of 0.379 (95%CI=0.164-0.876; p=0.023), which was lower than that of patients who received the TAS-102 regimen as a third-line treatment.

Effect of the third-line treatment on overall survival. Kaplan–Meier survival curves according to third-line treatment for all patients are shown in Figure 1. The median OS of patients who received F-RAM/AFL on third-line treatment (n=17) and those who received TAS-102 (n=26) were 379 days (95%CI=157-458 days) and 183 days (95%CI=80-204 days), respectively (log-rank test, p=0.015) (Figure 1).

Reasons for discontinuation. The discontinuation of treatment due to AEs was more common in F-RAM/AFL (20 cases) than in TAS-102 (26 cases) (p=0.026). Reasons for the discontinuation of F-RAM/AFL or TAS-102 are summarized in Table IV. Treatment was discontinued due to progressive disease, AEs, deterioration of condition, and deterioration in performance status in 6, 3, 2, and 2 patients in the F-RAM/AFL group and in 10, 0, 4, and 10 patients in the TAS-102 group, respectively. The AEs in the F-RAM/AFL group included proteinuria, fatigue, and anorexia.

Analysis of adverse events. The AEs for the F-RAM/AFL group included diarrhoea (n=9, 34.6%), anorexia (n=9, 34.6%), peripheral sensory neuropathy (n=9, 34.6%), and nausea (n=8, 30.8%). The AEs for the TAS-102 group included neutropenia (n=14, 82.4%), anaemia (n=12, 70.6%), and fatigue (n=11, 64.7%). The AEs for the F-RAM/AFL and TAS-102 groups are summarized in Table V. Grade 3 or higher AEs in the F-RAM/AFL group included leucopenia (n=1), neutropenia (n=2), diarrhoea (n=1), fatigue (n=1), proteinuria (n=1), and anorexia (n=1), while those in the TAS-102 group included leucopenia (n=2), neutropenia (n=7), decreased platelet count (n=1), and anaemia (n=2).

Table II. *Univariate analysis of prognostic factors associated with OS in patients with advanced and recurrent colorectal receiving chemotherapy.*

Factor	Hazard ratio	95%CI	p-Value
Age, years			
<71	0.997	0.966-1.028	0.839
Gender			
Male	0.921	0.448-1.893	0.822
BSA, cm			
>1.50	0.442	0.210-0.929	0.031*
CrCl, kg			
<90.4	1.099	0.469-2.570	0.828
Duration of third-line treatment, day			
>64.0	0.585	0.271-1.263	0.172
Use of F-RAM/AFL in third-line			
Yes	0.401	0.186-0.863	0.019*
Treatment after third-line			
Yes	0.392	0.168-0.919	0.031*
Disease status			
Advanced/recurrent	0.917	0.429-1.961	0.822
Number of metastases			
>1	1.333	0.839-2.116	0.226

BSA: Body surface area; CrCl: creatinine clearance; F-RAM/AFL: combination of fluorouracil/leucovorin and irinotecan (FOLFIRI) with ramucirumab or aflibercept; OS: overall survival; CI: confidence interval. *p<0.05.

Table III. *Multivariate analysis of prognostic factors associated with OS in patients with advanced and recurrent colorectal receiving chemotherapy.*

Factor	Hazard ratio	95%CI	p-Value
Age, years			
<71	0.963	0.922-1.005	0.086
Gender			
Male	1.18	0.496-2.805	0.707
BSA, cm			
>1.50	0.533	0.219-1.295	0.165
Use of F-RAM/AFL in third-line			
Yes	0.379	0.164-0.876	0.023*
Treatment after third-line			
Yes	0.409	0.147-1.146	0.089

BSA: Body mass index; F-RAM/AFL: combination of fluorouracil/leucovorin and irinotecan (FOLFIRI) with ramucirumab or aflibercept; OS: overall survival; CI: confidence interval. *p<0.05.

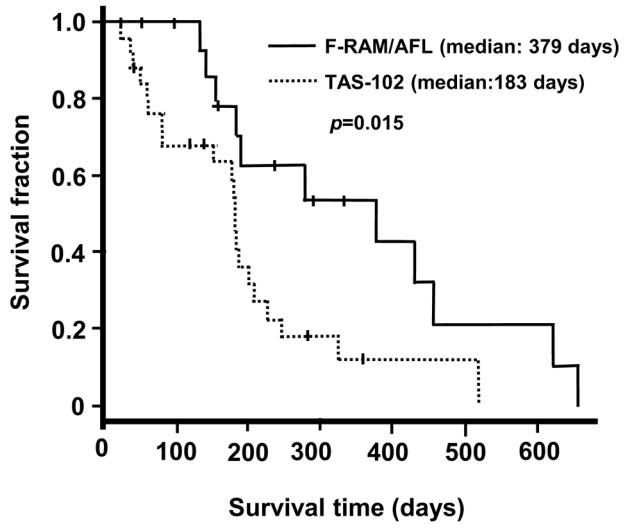

Figure 1. *Kaplan–Meier survival curves of overall survival following third-line therapy with FOLFIRI plus ramucirumab/aflibercept and trifluridine/tipiracil combination tablet. No significant difference in survival was observed between the two groups. The FOLFIRI plus ramucirumab/aflibercept group had a longer survival compared with the rifluridine/tipiracil combination tablet group.*

Table IV. *Reasons for third-line treatment discontinuation.*

	F-RAM/AFL n=17	TAS-102 n=26	*p*-Value
Adverse events	3	0	0.026[a,*]
Progressive disease	6	10	0.834[a]
Deterioration in performance status	2	10	0.056[a]
Deterioration of condition	2	4	0.738[a]
Other	1	1	0.757[a]
On-going	3	1	–

[a]Chi-square test of independence. *$p<0.05$. F-RAM/AFL: Combination of fluorouracil/leucovorin and irinotecan (FOLFIRI) with ramucirumab or aflibercept; TAS-102: trifluridine/tipiracil combination tablet.

Discussion

In this study, we clarified the risks and benefits of F-RAM/AFL as a third-line treatment after the use of BV as the first-line and second-line treatment for mCRC in comparison with those of TAS-102. We observed a longer OS in F-RAM/AFL than in TAS-102. However, F-RAM/AFL yielded more frequent AEs, such as stomatitis and proteinuria, and was discontinued due to AEs, unlike TAS-102.

For the third-line and later treatment of mCRC, Yoshihiro *et al*. reported that F-RAM results in a median OS of 13.0 months (23). F-AFL has not been investigated after the third-line treatment in mCRC. However, in a local phase II trial of TAS-102, the OS was only 9.0 months (19). OS for patients treated with regorafenib is 6.4 months (24). These reports are broadly focused on third-line and later treatment and are not limited to third-line treatment. In our study, the OS estimates for F-RAM/AFL and TAS-102 were 379 days (12.6 months) and 183 days (6.1 months), respectively. Furthermore, the use of F-RAM/AFL as a third-line treatment was identified as a prognostic factor. Accordingly, it is possible that a similar OS can be obtained using F-RAM/AFL or TAS-102 as third-line treatment or third-line and later treatment. In fact, Kimura *et al*. reported that F-RAM and TAS-102 have the same effect on OS. However, comparisons between studies are limited by the previous focus on both third-line and later treatment as well as differences in drugs used as first- and second-line treatments, demographic factors, and the number of cases. In summary, these findings demonstrate the beneficial effect of F-RAM/AFL on prognosis after the use of BV for first- and second-line treatments.

Treatment discontinuation due to urinary protein, malaise, and loss of appetite was observed with F-RAM/AFL, whereas TAS-102 could be continued without discontinuation due to AEs in all cases. AEs in F-RAM included myelosuppression, gastrointestinal toxicity (*e.g.*, nausea and diarrhoea), mouth ulcers, and proteinuria. AE management is important because diarrhoea and mouth ulcers reduce quality of life (24). Grade 3 or higher neutropenia and anaemia were observed in TAS-102; however, treatment was continued by temporarily stopping the drug. In addition, although the frequencies of nausea and malaise were high, these symptoms were mild and did not affect the continuation of treatment. Taken together, F-RAM/AFL frequently produces severe AEs and therefore patient quality of life may be lower for F-RAM/AFL than for TAS-102.

Our findings provide new insights into the potential of F-RAM/AFL and TAS-102 as third-line treatments after using BV as first- and second-line treatments in patients with mCRC. These results can guide the selection of an appropriate third-line therapeutic agent. However, the number of cases was limited, and patient backgrounds differed between groups. Thus, further well-designed studies are needed to resolve these issues and validate our results. The high cost of cancer treatment is a highly debated issue (26). Given the high cost, availability of alternative options, and minimal improvement in survival, the usefulness of RAM in clinical practice has been questioned (27). The estimated annual cost of F-RAM is significantly higher than the estimated cost of TAS-102 (24, 28). The cost-effectiveness ratios for AFL and RAM are JPY 19,836,504 (US $ 179,678) and JPY 41,947,989 (US $ 379,964) per QALY, respectively. AFL is more cost-effective than RAM. However, the addition of AFL or RAM to FOLFIRI as a second-line treatment for

Table V. *Treatment-related adverse events reported in 10% or more of treated patients in either group.*

VEGF (n=26)									TAS-102 (n=17)					
	F-RAM (n=21)				F-AFL (n=5)									
	Grade, n				Grade, n					Grade, n				
Events	1	2	3	4	1	2	3	4	All grades (%)	Events	1	2	3	4	All grades (%)
Leucopenia	4	0	1	0	1	0	0	0	6 (23.1)	Leucopenia	2	2	2	0	6 (35.3)
Neutropenia	3	0	1	1	1	0	0	0	6 (23.1)	Neutropenia	1	6	5	2	14 (82.4)
Platelet count decreased	2	0	0	0	0	1	0	0	3 (11.5)	Platelet count decreased	4	0	1	0	5 (29.4)
Anaemia	2	3	0	0	0	0	0	0	5 (19.2)	Anaemia	3	7	2	0	12 (70.6)
Diarrhoea	3	2	1	0	3	0	0	0	9 (34.6)	AST/ALT increase	4	0	0	0	4 (23.5)
Constipation	1	1	0	0	1	0	0	0	3 (11.5)	T-Bil increase	3	0	0	0	3 (17.6)
Stomatitis	5	1	0	0	1	0	0	0	7 (26.9)	Diarrhoea	3	0	0	0	3 (17.6)
Nausea	3	3	0	0	2	0	0	0	8 (30.8)	Nausea	9	0	0	0	9 (52.9)
Vomiting	3	0	0	0	0	0	0	0	3 (11.5)	Fatigue	11	0	0	-	11 (64.7)
Sensory neuropathy	6	1	0	0	0	2	0	0	9 (34.6)	Anorexia	5	2	0	0	7 (41.2)
Fatigue	4	0	1	-	1	0	0	-	6 (23.1)	Dysgeusia	2	0	0	-	2 (11.8)
Proteinuria	3	1	0	-	0	2	1	-	7 (26.9)						
Anorexia	5	2	0	0	1	0	1	0	9 (34.6)						
Dysgeusia	2	1	0	-	2	0	0	-	5 (19.2)						
Edema limbs	1	0	0	0	2	0	0	0	3 (11.5)						

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; T-Bil: total bilirubin; VEGF: vascular endothelial growth factor; F-RAM: combination of fluorouracil/leucovorin and irinotecan (FOLFIRI) with ramucirumab; F-AFL: combination of fluorouracil/leucovorin and irinotecan (FOLFIRI) with aflibercept.

mCRC is not cost-effective in the Japanese healthcare system (29). In the future, it will be necessary to calculate the cost-effectiveness of RAM and AFL, including TAS-102. The results of this study suggest that F-RAM/AFL is superior to TAS-102 in terms of efficacy in the third-line setting. Furthermore, biomarkers may be used to predict the effect. Various potential prognostic biomarkers after F-AFL have been associated with efficacy endpoints (30).

In conclusion, as a third-line treatment after using BV as a first-line and second-line treatment for mCRC, F-RAM/AFL should be prioritized over TAS-102 in terms of efficacy; however, it is necessary to pay attention to the occurrence of AEs, such as stomatitis and proteinuria.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

MK contributed to the case report design, collected and provided data, was the principal author of the article, and is the guarantor of the article and all data. EU, HT, and TY contributed to the clinical study design, reviewed the article, and supervised the report and publication process. All the Authors approved the final version of the manuscript.

References

1 Battaglin F, Puccini A, Intini R, Schirripa M, Ferro A, Bergamo F, Lonardi S, Zagonel V, Lenz HJ and Loupakis F: The role of tumor angiogenesis as a therapeutic target in colorectal cancer. Expert Rev Anticancer Ther *18(3)*: 251-266, 2018. PMID: 29338550. DOI: 10.1080/14737140.2018.1428092

2 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350(23)*: 2335-2342, 2004. PMID: 15175435. DOI: 10.1056/NEJMoa032691

3 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Cassidy J: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol *26(12)*: 2013-2019, 2008. PMID: 18421054. DOI: 10.1200/JCO.2007.14.9930

4 Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, Schulz J, Richards D, Soufi-Mahjoubi R, Wang B and Barrueco J: Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol *25(30)*: 4779-4786, 2007. PMID: 17947725. DOI: 10.1200/JCO.2007.11.3357

5 Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E, Hambleton J, Novotny WF and Kabbinavar F: Bevacizumab in combination with fluorouracil and leucovorin:

an active regimen for first-line metastatic colorectal cancer. J Clin Oncol *23(15)*: 3502-3508, 2005. PMID: 15908660. DOI: 10.1200/JCO.2005.10.017

6 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB 3rd and Eastern Cooperative Oncology Group Study E3200: 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 *25(12)*: 1539-1544, 2007. PMID: 17442997. DOI: 10.1200/JCO.2006.09.6305

7 Grothey A, Sargent D, Goldberg RM and Schmoll HJ: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol *22(7)*: 1209-1214, 2004. PMID: 15051767. DOI: 10.1200/JCO.2004.11.037

8 Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Saltz L: Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol *26(12)*: 2006-2012, 2008. PMID: 18421053. DOI: 10.1200/JCO.2007.14.9898

9 Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E and Kozloff M: Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol *26(33)*: 5326-5334, 2008. PMID: 18854571. DOI: 10.1200/JCO.2008.16.3212

10 Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, Portnoy DC, Van Cutsem E, Grothey A, Prausová J, Garcia-Alfonso P, Yamazaki K, Clingan PR, Lonardi S, Kim TW, Simms L, Chang SC, Nasroulah F and RAISE Study Investigators: 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 *16(5)*: 499-508, 2015. PMID: 25877855. DOI: 10.1016/S1470-2045(15)70127-0

11 Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R and Allegra C: 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 *30(28)*: 3499-3506, 2012. PMID: 22949147. DOI: 10.1200/JCO.2012.42.8201

12 Kocakova I, Melichar B, Kocak I, Bortlicek Z, Büchler T, Dusek L, Petruzelka L, Kohoutek M, Prausová J, Finek J, Mohelnikova-Duchonova B and Vyzula R: Bevacizumab with FOLFIRI or XELIRI in the first-line therapy of metastatic colorectal carcinoma: results from Czech observational registry. Anticancer Res *35(6)*: 3455-3461, 2015. PMID: 26026110.

13 Van Cutsem E, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P and Ciardiello F: Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol *29(15)*: 2011-2019, 2011. PMID: 21502544. DOI: 10.1200/JCO.2010.33.5091

14 Bokemeyer C, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, Celik I, Schlichting M and Koralewski P: Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol *22(7)*: 1535-1546, 2011. PMID: 21228335. DOI: 10.1093/annonc/mdq632

15 Sasaki Y, Hamaguchi T, Arai T, Goto A, Ura T, Muro K, Yamada Y, Shirao K and Shimada Y: Phase I study of combination therapy with irinotecan, leucovorin, and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for advanced colorectal cancer in Japanese patients. Anticancer Res *34(4)*: 2029-2034, 2014. PMID: 24692743.

16 Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu RH, Kim TW, Ismail F, Tan IB, Yeh KH, Grothey A, Zhang S, Ahn JB, Mastura MY, Chong D, Chen LT, Kopetz S, Eguchi-Nakajima T, Ebi H, Ohtsu A, Cervantes A, Muro K, Tabernero J, Minami H, Ciardiello F and Douillard JY: 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 *29(1)*: 44-70, 2018. PMID: 29155929. DOI: 10.1093/annonc/mdx738

17 Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S and ML18147 Study Investigators: Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol *14(1)*: 29-37, 2013. PMID: 23168366. DOI: 10.1016/S1470-2045(12)70477-1

18 Yoshino T, Yamazaki K, Gotoh M, Nasroulah F, Gao L, Yoshizuka N and Ohtsu A: Safety and pharmacokinetics of second-line ramucirumab plus FOLFIRI in Japanese patients with metastatic colorectal carcinoma. Anticancer Res *35(7)*: 4003-4007, 2015. PMID: 26124348.

19 Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A and RECOURSE Study Group: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med *372(20)*: 1909-1919, 2015. PMID: 25970050. DOI: 10.1056/NEJMoa1414325

20 Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D and CORRECT Study Group: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet *381(9863)*: 303-312, 2013. PMID: 23177514. DOI: 10.1016/S0140-6736(12)61900-X

21 US Department of Health and Human Services: Common terminology criteria for adverse events (CTCAE) version 4.0. United States, National Cancer Institute, 2009. Available at: http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5X7.pdf [Last accessed on February 4, 2021]

22 Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant *48(3)*: 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244

23 Yoshihiro T, Kusaba H, Makiyama A, Kobayashi K, Uenomachi M, Ito M, Doi Y, Mitsugi K, Aikawa T, Takayoshi K, Esaki T, Shimokawa H, Tsuchihashi K, Ariyama H, Akashi K and Baba E: Efficacy and safety of ramucirumab plus modified FOLFIRI for metastatic colorectal cancer. Int J Clin Oncol *24(5)*: 508-515, 2019. PMID: 30604155. DOI: 10.1007/s10147-018-01391-w

24 Kimura M, Usami E, Teramachi H and Yoshimura T: Risk benefit of FOLFIRI plus ramucirumab as third-line and later-line treatment of metastatic colorectal cancer. Anticancer Res *40(3)*: 1605-1611, 2020. PMID: 32132063. DOI: 10.21873/anticanres.14108

25 Al-Batran SE, Hozaeel W, Tauchert FK, Hofheinz RD, Hinke A, Windemuth-Kieselbach C, Hübner A, Burmester M, Koenigsmann M, Wiegand J, Zur Hausen G, Linsse B, Kuhl R and Pauligk C: The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax). Ann Oncol *26(6)*: 1244-1248, 2015. PMID: 25755108. DOI: 10.1093/annonc/mdv129

26 Meropol NJ, Schrag D, Smith TJ, Mulvey TM, Langdon RM Jr, Blum D, Ubel PA, Schnipper LE and American Society of Clinical Oncology: American Society of Clinical Oncology guidance statement: the cost of cancer care. J Clin Oncol *27(23)*: 3868-3874, 2009. PMID: 19581533. DOI: 10.1200/JCO.2009.23.1183

27 Zeichner SB, Kohn CG and Goldstein DA: Economics of ramucirumab for metastatic colorectal cancer. Expert Rev Pharmacoecon Outcomes Res *16(6)*: 733-745, 2016. PMID: 27828732. DOI: 10.1080/14737167.2016.1259070

28 Goldstein DA and El-Rayes BF: Considering efficacy and cost, where does ramucirumab fit in the management of metastatic colorectal cancer? Oncologist *20(9)*: 981-982, 2015. PMID: 26265225. DOI: 10.1634/theoncologist.2015-0028

29 Kashiwa M and Matsushita R: Comparative cost-effectiveness of aflibercept and ramucirumab in combination with irinotecan and fluorouracil-based therapy for the second-line treatment of metastatic colorectal cancer in Japan. Clin Ther *42(7)*: 1361-1375, 2020. PMID: 32616433. DOI: 10.1016/j.clinthera.2020.05.013

30 Hamaguchi T, Denda T, Kudo T, Sugimoto N, Ura T, Yamazaki K, Fujii H, Kajiwara T, Nakajima TE, Takahashi S, Otsu S, Komatsu Y, Nagashima F, Moriwaki T, Esaki T, Sato T, Itabashi M, Oki E, Sasaki T, Chiron M and Yoshino T: Exploration of potential prognostic biomarkers in aflibercept plus FOLFIRI in Japanese patients with metastatic colorectal cancer. Cancer Sci *110(11)*: 3565-3572, 2019. PMID: 31520559. DOI: 10.1111/cas.14198

Received April 8, 2021
Revised April 19, 2021
Accepted April 20, 2021