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FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study[†]

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Background: A targeted agent combined with chemotherapy is the standard treatment in patients with metastatic colorectal cancer (mCRC). The present phase III study was conducted to compare two doses of bevacizumab combined with irinotecan, 5-fluorouracil/leucovorin (FOLFIRI) in the second-line setting after first-line therapy with bevacizumab plus oxaliplatin-based therapy.

Patients and methods: Patients were randomly assigned to receive FOLFIRI plus bevacizumab 5 or 10 mg/kg in 2-week cycles until disease progression. The primary end point was progression-free survival (PFS), and secondary end points included overall survival (OS), time to treatment failure (TTF), and safety.

Results: Three hundred and eighty-seven patients were randomized between September 2009 and January 2012 from 100 institutions in Japan. Baseline patient characteristics were well balanced between the two groups. Efficacy was evaluated in 369 patients (5 mg/kg, $n = 181$ and 10 mg/kg, $n = 188$). Safety was evaluated in 365 patients (5 mg/kg, $n = 180$ and 10 mg/kg, $n = 185$). The median PFS was 6.1 versus 6.4 months (hazard ratio, 0.95; 95% confidence interval [CI] 0.75–1.21; $P = 0.676$), and median TTF was 5.2 versus 5.2 months (hazard ratio, 1.01; 95% CI 0.81–1.25; $P = 0.967$), respectively, for the bevacizumab 5 and 10 mg/kg groups. Follow-up of OS is currently ongoing. Adverse events, including hypertension and hemorrhage, occurred at similar rates in both groups.

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Conclusion: Bevacizumab 10 mg/kg plus FOLFIRI as the second-line treatment did not prolong PFS compared with bevacizumab 5 mg/kg plus FOLFIRI in patients with mCRC. If bevacizumab is continued after first-line therapy in mCRC, a dose of 5 mg/kg is appropriate for use as second-line treatment.

Clinical trial identifier: UMIN00002557.

Key words: bevacizumab, chemotherapy, metastatic colorectal cancer, dose, second-line therapy, randomized controlled trial

introduction

In 2012, an estimated 1.3 million people had colorectal cancer, making it the third most common cancer worldwide [1]. In Japan, the incidence and mortality rates of colorectal cancer increased between 1958 and the mid-1990s, and have since stabilized or decreased slightly [2]. Based on data published in 2012, colorectal cancer is the third most common cause of death in women and the fourth most common cause of death in men in Japan [3].

Standard chemotherapy combinations for the treatment of metastatic colorectal cancer (mCRC) are either 5-fluorouracil plus leucovorin combined with oxaliplatin (e.g. FOLFOX) or irinotecan (e.g. FOLFIRI) combined with a targeted agent directed against vascular endothelial growth factor (VEGF), epithelial growth factor receptor (EGFR), or multiple targets. Bevacizumab (Avastin[®]; Genentech), a recombinant, humanized monoclonal antibody directed against VEGF, is well established in the first-line treatment of mCRC [4, 5]. However, four questions regarding its continued use after disease progression remain: (i) Does continuous bevacizumab as second-line treatment offer any benefit? (ii) Is it preferable to treat with an anti-VEGF inhibitor or an anti-EGFR inhibitor? (iii) What is the optimal dose of bevacizumab?, and (iv) Which is the best anti-angiogenic agent?

The first question was answered by the ML18147 study, which showed that median overall survival (OS) was significantly prolonged with continuation of bevacizumab 5 mg/kg after progression compared with chemotherapy alone [6]. The second question was investigated in a randomized phase II study (SPIRITT), which reported similar efficacy with panitumumab plus FOLFIRI and bevacizumab plus FOLFIRI in patients with previously treated wild-type *KRAS* mCRC [7], although further trials are needed. The last two questions remain unanswered.

Regarding the optimal dose of bevacizumab as second-line therapy, the E3200 study showed that bevacizumab 10 mg/kg biweekly plus chemotherapy improved median OS, compared with chemotherapy alone and bevacizumab alone, in bevacizumab-naïve patients [8]; yet, a lower dose of 5 mg/kg biweekly was tested in the registration trials of bevacizumab as first-line therapy [4, 5]. Furthermore, there is some evidence that the effects of bevacizumab may be dose-related [9, 10].

We compared the efficacy and safety of bevacizumab 5 mg/kg plus FOLFIRI with that of bevacizumab 10 mg/kg plus FOLFIRI in the second-line setting in Japanese patients with mCRC following disease progression or toxicity with bevacizumab plus an oxaliplatin-based regimen (EAGLE study).

patients and methods

study design and patient selection

The EAGLE study was a randomized, multicenter, open-label, two-arm phase III study designed to evaluate the superiority of bevacizumab 10 mg/

kg plus FOLFIRI compared with bevacizumab 5 mg/kg plus FOLFIRI as second-line therapy in patients with mCRC previously treated with first-line bevacizumab plus an oxaliplatin-based regimen. Patients were recruited in Japanese institutions. Written informed consent was obtained from all participating patients. The study was conducted in compliance with the 2008 Declaration of Helsinki and approved by institutional review boards. Details of the trial design have been published elsewhere [11]. The trial was registered on the University Hospital Medical Information Network (<http://www.umin.ac.jp/ctr/>; identifier: UMIN00002557).

The enrolled patients were randomized 1:1 at the data center (ECRIN Datacenter, Kyoto, Japan). Dynamic randomization was based on the minimization method with the following stratification factors: Eastern Cooperative Oncology Group (ECOG) performance status (0/1), number of metastatic organs (<2/≥2), reason for starting second-line treatment (disease progression/toxicity), early recurrence within 6 months from adjuvant chemotherapy (yes/no), and institution.

Eligibility criteria included patients with cytologically or histologically confirmed colorectal cancer, with disease progression or toxicity after receiving bevacizumab plus oxaliplatin-based therapy as first-line treatment of more than four cycles, 20 years of age or older, ECOG performance status of 0 or 1, life expectancy of 3 months or longer, and sufficient organ function. Patients who had received prior irinotecan treatment were not eligible.

treatment plan

FOLFIRI plus bevacizumab consisted of bevacizumab 5 or 10 mg/kg as a 30-min infusion and L-leucovorin 200 mg/m² as a 2-h infusion with concurrent irinotecan 150 mg/m² as a 90-min infusion followed by bolus 5-fluorouracil 400 mg/m² within 15 min and then a 46-h infusion of 5-fluorouracil 2400 mg/m². Study treatment was given in 2-week cycles until disease progression, which was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

Dose reductions due to adverse events were allowed for 5-fluorouracil (bolus and infusion doses), irinotecan, and bevacizumab 10 mg/kg. 5-Fluorouracil and irinotecan doses were reduced on the occurrence of grade 4 neutropenia, grade 3 or 4 febrile neutropenia, grade 3 or 4 thrombocytopenia, and all non-hematological adverse events of grade 3 or higher. Bevacizumab 10 mg/kg was reduced in two steps (i.e. 7.5 and 5 mg/kg) on the occurrence of grade 2 hemorrhage, grade 2 or 3 proteinuria, grade 3 hypertension, and grade 3 or 4 hepatic toxicity. Study treatment was discontinued when the following adverse events occurred: grade 3 or 4 venous thrombosis, grade 2 or higher arterial thrombosis, posterior reversible encephalopathy syndrome, gastrointestinal perforation, and grade 3 allergic reactions. Dose reduction of bevacizumab was not allowed in the bevacizumab 5 mg/kg group.

assessments

Disease progression and the occurrence of new disease were monitored using abdominal radiography, abdominal computed tomography (CT) or magnetic resonance imaging, and thoracic CT every 8 weeks (RECIST 1.1), and by measuring levels of tumor markers (i.e. carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) every 4 weeks. Blood tests

and monitoring for adverse events were conducted throughout the treatment period. The follow-up period was 1 year after registration of the last patient.

outcomes

The primary end point was progression-free survival (PFS). The secondary end points included: OS, time from the start of first-line treatment until progression after the protocol treatment (second PFS), tumor response rate, time to treatment failure (TTF), and safety. PFS was defined as the time from the date of randomization to the first date of documented progression or death as a result of any cause. If no PFS event was observed, PFS was censored at the date of the last evaluable tumor assessment. OS was defined as the time from date of randomization to date of death due to any cause. TTF was defined as the time from the date of randomization to the date of each of the following, whichever occurred first: discontinuation of treatment, disease progression, or death from any cause. Response rate was assessed by using RECIST, version 1.1.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. In addition, dose intensity for the treatment period was calculated as the total cumulative dose divided by the duration of dosing (i.e. [start date of last cycle] – [start date of first cycle] + 14). Relative dose intensity was calculated as the dose intensity divided by the planned dose intensity, multiplied by 100. Planned dose intensities per cycle were 5 or 10 mg/kg for bevacizumab and 150 mg/m² for irinotecan. If a patient continued study treatment, relative dose intensity was calculated using the latest treatment cycle as the last cycle.

statistical considerations

The median PFS of the bevacizumab 5 mg/kg group in this trial was assumed to be 5.0 months based on previous studies [8, 12], and prolongation of the median PFS to 7.0 months in the bevacizumab 10 mg/kg group was considered to be a clinically relevant increase (i.e. risk reduction of 30%). The required sample size to detect a 30% risk reduction with 90% power using a log-rank test with a two-sided significance level of 0.05 was 358 patients (330 events), assuming an accrual time of 2 years and a follow-up period of 1 year [13]. Taking some drop-outs into account, the total sample size was set at 370 patients.

Statistical analysis was conducted in the full analysis set (modified intention-to-treat), which was as close as possible to the intention-to-treat principle of including all randomized subjects [14]. The full analysis set excluded patients who failed to satisfy major eligibility criteria based on the pre-randomization variable, patients without any post-randomization data, and those who withdrew consent. The safety evaluation was carried out in patients based on the actual treatment received (safety analysis set).

Time-to-event end points were depicted by the Kaplan–Meier method and compared between groups using a stratified log-rank test (using all stratification factors, except for institute) at a two-sided significance level of 5%. A stratified Cox proportional hazards model was used to assess the hazard ratio with Wald-type 95% confidence intervals (CIs). Comparisons of response rates were conducted using the Fisher's exact test. Response rates were estimated with exact 95% CI. Subgroup analyses were also carried out in which the *P*-value for interaction was calculated with a Cox model including treatment group, baseline characteristics, and their interaction term. All analyses were carried out using SAS version 9.3.

results

patients' characteristics

A total of 387 patients were randomized between September 2009 and January 2012 from 100 institutions. The final follow-up of the study was on 28 September 2013. The median duration

of follow-up was 394 (95% CI 344–432) days. Of the 369 patients included in the full analysis set, 181 patients were assigned to the bevacizumab 5 mg/kg group and 188 patients were assigned to the bevacizumab 10 mg/kg group. The number of patients included in the safety analysis set was 365, which excluded 4 patients who did not receive study treatment (5 mg/kg group, *n* = 1 and 10 mg/kg group, *n* = 3). A CONSORT flow-chart is presented in supplementary Figure S1, available at *Annals of Oncology* online. Patient characteristics at baseline were well balanced between the two groups (Table 1). Time on first-line treatment (supplementary Figure S2, available at *Annals of Oncology* online) and the treatment-free interval between the end of first-line treatment and the start of second-line treatment (supplementary Figure S3, available at *Annals of Oncology* online) were similar in both treatment arms.

dose administration

One patient in each two groups, were treated with different bevacizumab doses to those allocated, i.e. one patient was treated with bevacizumab 10 mg/kg although they were in the 5 mg/kg group, and one patient received 5 mg/kg although they were in the 10 mg/kg group. After excluding these two patients, the median and mean relative dose intensity of bevacizumab was 82% and 80% in the 5 mg/kg group, and 80% and 77% in the 10 mg/kg group, respectively. The median and mean relative dose intensity of irinotecan was 78% and 76% in the 5 mg/kg group, and 73% and 72% in the 10 mg/kg group, respectively (supplementary Table S1, available at *Annals of Oncology* online).

efficacy

The number of PFS events was 174 in the bevacizumab 5 mg/kg group and 176 in the bevacizumab 10 mg/kg group. As shown in Figure 1, the median PFS was 6.1 (95% CI 5.3–7.0) months in the bevacizumab 5 mg/kg group and 6.4 (95% CI 5.6–7.4) months in the bevacizumab 10 mg/kg group (hazard ratio, 0.95; 95% CI 0.75–1.21; log-rank *P* = 0.676). The median second PFS, defined as time from the start of the first-line treatment to progression after receiving the study treatment, was 17.4 (95% CI 16.1–19.4) months in the bevacizumab 5 mg/kg group and 17.6 (95% CI 16.0–18.9) months in the bevacizumab 10 mg/kg group (hazard ratio, 1.00; 95% CI 0.79–1.26; log-rank *P* = 0.976). The number of TTF events was 179 in the bevacizumab 5 mg/kg group and 188 in the bevacizumab 10 mg/kg group. Median TTF was 5.2 (95% CI 4.5–5.8) months in the bevacizumab 5 mg/kg group and 5.2 (95% CI 4.4–5.7) months in the bevacizumab 10 mg/kg group (hazard ratio, 1.01; 95% CI 0.81–1.25; log-rank *P* = 0.967). Response to treatment was similar in the two groups with partial responses reported in 20 patients (11%) in the bevacizumab 5 mg/kg group and 20 patients (11%) in the bevacizumab 10 mg/kg group (supplementary Table S2, available at *Annals of Oncology* online). The number of deaths was 126 and 133 in the bevacizumab 5 and 10 mg/kg groups, respectively. Median OS was 16.3 (95% CI 14.1–21.2) months in the bevacizumab 5 mg/kg group and 17.0 (95% CI 14.6–19.1) months in the bevacizumab 10 mg/kg group (hazard ratio, 1.08; 95% CI 0.75–1.57; log-rank *P* = 0.667), although follow-up of OS is ongoing.

Table 1. Baseline characteristics

	Bevacizumab 5 mg/kg plus FOLFIRI (n = 181)		Bevacizumab 10 mg/kg plus FOLFIRI (n = 188)	
	N	%	N	%
Age, years				
Median	66		65	
Range	36–84		31–88	
Sex				
Male	102	56	107	57
Female	79	44	81	43
ECOG performance status				
0	155	86	163	87
1	26	14	25	13
No. of metastases				
<2	84	46	84	45
≥2	97	54	104	55
Reason for starting second-line treatment				
Progressive disease	154	85	158	84
Toxicity	27	15	30	16
Time to recurrence after adjuvant therapy				
≤6 months	23	13	25	13
>6 months	158	87	163	87
Primary cancer				
Colon	115	64	104	55
Rectum	66	37	84	45
Cancer type				
Adenocarcinoma	168	93	178	95
Other	9	5	7	4
Unknown	4	2	3	2
Site of metastases/recurrence				
Liver	118	65	113	60
Lung	75	41	88	47
Lymph nodes	56	31	61	32
Peritoneum	35	19	36	19
Other ^a	25	14	28	15
First-line chemotherapy regimen				
mFOLFOX6	105	58	110	59
XELOX	27	15	36	19
Other	49	27	42	22
Resection status				
Resected	153	85	149	79
Non-resected	27	15	39	21
Cycles of first-line oxaliplatin, n				
Median	12		12	
Range	4–33		4–30	
Cycles of first-line bevacizumab, n				
Median	15		15	
Range	4–54		4–64	
	n = 176		n = 179	
CEA, ng/ml				
Median	23.2		18.2	
Range	0.40–9279		0.70–2049	
	n = 175		n = 178	
CA19-9, ng/ml				
Median	38.3		36.1	
Range	0.60–48019		0.10–50 000	

Continued

Table 1. Continued

	Bevacizumab 5 mg/kg plus FOLFIRI (n = 181)		Bevacizumab 10 mg/kg plus FOLFIRI (n = 188)	
	N	%	N	%
Sum of target lesions, ^b mm				
Median	50.0		44.4	
Range	4.40–254		10–246	

Percentages may not add up to 100% because of rounding.
CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, 5-fluorouracil/leucovorin plus irinotecan; mFOLFOX6, modified 5-fluorouracil/leucovorin plus oxaliplatin; XELOX, capecitabine plus oxaliplatin.
^aData missing for one patient (bevacizumab 5 mg/kg plus FOLFIRI).
^bTarget lesions defined using RECIST, version 1.1.

safety

A summary of all-grade and grade 3–5 adverse events is given in supplementary Table S3, available at *Annals of Oncology* online. The incidence of all-grade hematological and non-hematological adverse events was similar between the two treatment groups. Bevacizumab-related adverse events of grade 3 or greater, including hemorrhage or bleeding, were also similar between the two treatment groups. The reported incidence rates in the bevacizumab 5 versus 10 mg/kg groups were gastrointestinal hemorrhage 0.6% versus 0.0%, nasal hemorrhage 0.0% versus 0.5%, and hypertension 1.1% versus 1.6%, respectively. Treatment-related deaths occurred in 2 (1.1%) patients in each group (5 mg/kg group: aspiration pneumonia, n = 1; acute myocardial infarction, n = 1; 10 mg/kg group: interstitial lung disease, n = 1; unknown, n = 1).

subgroup analysis

The prespecified subgroup analysis of PFS is shown in supplementary Figure S4, available at *Annals of Oncology* online. Possible differences of treatment effect between the bevacizumab 5 and 10 mg/kg groups were observed for patients when analyzed according to tumor type, CEA level, or tumor size.

discussion

The EAGLE study was designed to evaluate the superiority of bevacizumab 10 mg/kg plus FOLFIRI compared with bevacizumab 5 mg/kg plus FOLFIRI as second-line therapy in patients with mCRC previously treated with a first-line bevacizumab plus an oxaliplatin-based regimen. PFS, the primary study end point, was similar in both treatment groups with a hazard ratio of 0.95 (95% CI 0.75–1.21). Secondary efficacy outcomes, specifically second PFS, TTF, and tumor response rates, were also similar between the two treatment groups and were supportive of the primary result. Follow-up of OS is ongoing. The incidence of adverse events, including bevacizumab-related events, was similar in both groups. These findings suggest that a higher

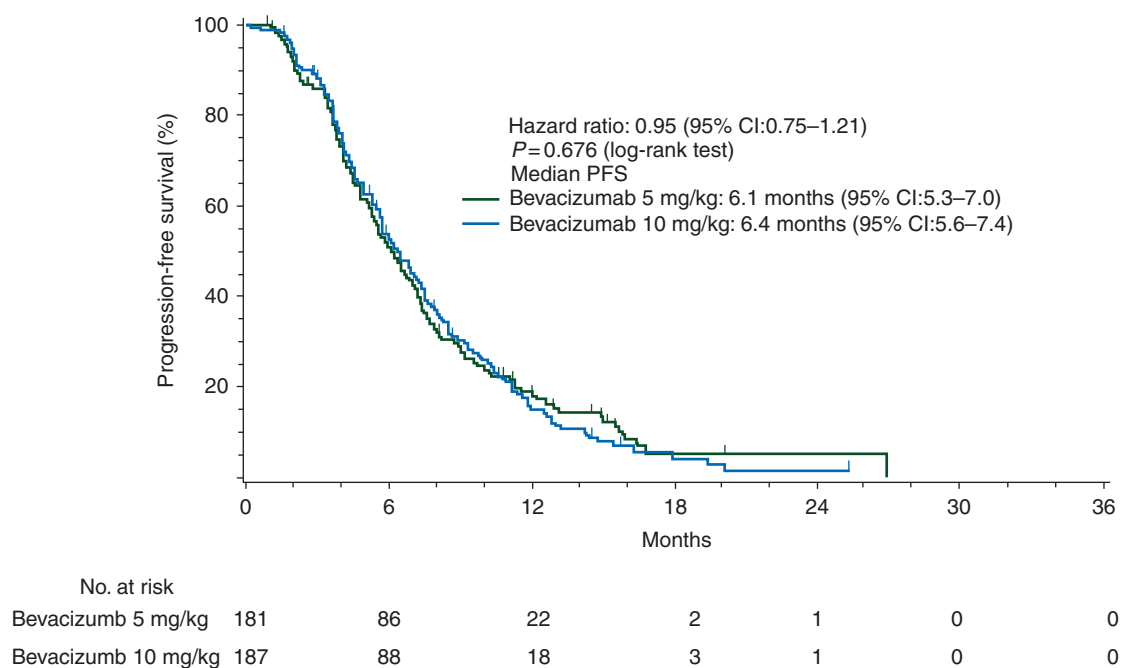


Figure 1. Progression-free survival (PFS).

bevacizumab dose of 10 mg/kg offers no clear clinical benefit compared with a 5 mg/kg dose in this setting.

The reason why the higher bevacizumab dose was not more effective is unclear. Kabbinavar et al. [15] previously showed slightly improved efficacy with bevacizumab 5 mg/kg plus chemotherapy versus bevacizumab 10 mg/kg plus chemotherapy as first-line therapy in mCRC, although the study was small and there were imbalances favoring the low-dose group at randomization. It has, however, been shown that free serum VEGF concentrations drop below detectable limits with bevacizumab doses as low as 0.3 mg/kg [9], suggesting that higher doses may not be necessary for optimal activity in humans.

Our data are consistent with the results from previous studies, which showed a beneficial effect of continued anti-VEGF treatment after first disease progression in patients with mCRC [6, 16]. In our study, the median PFS was 6.1 and 6.4 months in the bevacizumab 5 and 10 mg/kg groups, respectively. In the ML18147 study, patients who had received standard first-line bevacizumab-based therapy were randomly assigned to receive bevacizumab plus standard second-line chemotherapy or standard second-line chemotherapy alone after disease progression. The median PFS in the bevacizumab-treated group was 5.7 months [6]. In the VELOUR study, patients previously treated with an oxaliplatin-based regimen were randomly assigned to receive the anti-angiogenic agent aflibercept plus FOLFIRI or FOLFIRI alone [16]. A subgroup analysis of this study showed that the median PFS of patients who had been previously treated with bevacizumab was 6.7 months [17].

The profile of bevacizumab-related adverse events observed in our study was consistent with previous studies of bevacizumab in combination with FOLFIRI. No unknown toxicities were observed in the bevacizumab 10 mg/kg group of our study. A pooled analysis of 16 published studies which investigated bevacizumab plus FOLFIRI in mCRC reported weighted mean rates of grade 3–4 bevacizumab-related toxicities of 6% for

hypertension, 9% for venous/arterial thromboembolic events, 2% for bleeding events, and 0.7% for proteinuria [18]. In our study, the reporting rates of grade ≥ 3 bevacizumab-related toxicities in the total safety population were 1% for hypertension, 1% for thrombosis venous events, 0.8% for thrombosis artery events, 0.5% for bleeding events, and 0.8% for proteinuria. The adverse events reporting rates in the present study were lower compared with previous studies, even with the higher bevacizumab dose of 10 mg/kg. The incidence of the adverse events in our study was more consistent with results from post-marketing surveillance conducted in Japan [19]. Possible reasons for the differences in the reporting rates between our study and other published studies could be due to differences in patient performance status, ethnicity, and/or standard medical practice/cancer care in Japan.

We conducted a subgroup analysis of PFS (supplementary Figure S4, available at *Annals of Oncology* online) to identify possible patient groups that might respond differently to the two bevacizumab doses. There was one strong interaction (tumor type) and two modest interactions (CEA level or tumor size) between treatment and subgroups. However, it is unclear why the higher dose was more effective in one subgroup, and the lower dose apparently better in the complementary subgroup. It is, therefore, likely that such findings are false-positives. They should be interpreted with caution, and need confirmation in other studies.

The EAGLE study was conducted only in centers in Japan. The generalizability of the study findings to other regions is unknown. The dose of irinotecan used in the FOLFIRI regimen (150 mg/m²) was the approved dose in Japan, but is slightly lower than that used in the USA and Europe (180 mg/m²), although, as discussed above, the median PFS durations in our study were similar to other recent studies in this setting.

In conclusion, bevacizumab 10 mg/kg plus FOLFIRI as second-line treatment did not prolong PFS compared with

bevacizumab 5 mg/kg plus FOLFIRI in patients with mCRC following first-line treatment with a bevacizumab-based regimen. No differences in safety profile were observed between the bevacizumab 5 and 10 mg/kg groups. If bevacizumab is continued after first-line therapy in mCRC, our data suggest that a dose of 5 mg/kg is appropriate to use as second-line treatment.

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appendix

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