An observational study of vascular endothelial growth factor inhibitors as second-line treatment for metastatic colorectal cancer treated with bevacizumab plus FOLFIRI beyond progression: the association with RAS mutation and tumor sidedness

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Background: The BRiTE and ARIES studies suggested that the continued use of bevacizumab beyond progression (BBP) was beneficial. This study investigated the efficacy and safety of the vascular endothelial growth factor inhibitors (VEGFis) bevacizumab and aflibercept as second-line treatments for patients with metastatic colorectal cancer (mCRC) that progressed following the application of bevacizumab-containing chemotherapy as a first-line treatment.

Methods: This observational cohort study (OCS) analyzed the medical records of 73 patients with mCRC divided into a no-VEGFi group (n=48) and a VEGFi group (n=25). Progression-free survival (PFS) was the primary endpoint, and the overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety were secondary endpoints.

Results: The results revealed that the PFS, ORR, and DCR of the VEGFi group were significantly superior to those of the no-VEGFi group, even in those with wild-type and mutant-type RAS or left-sided mCRC (all P<0.05); however, OS did not differ significantly between the two groups (all P>0.05). Patients with primary left-sided lesions and continued use of VEGFi exhibited the most marked effect on PFS (P=0.001). No significant differences were observed in the incidence of grade 3 or 4 adverse events (AEs) between the two groups (P=0.133).

Conclusions: These results support the use of VEGFi as a second-line treatment after bevacizumab beyond the initial progression in this OCS. Bevacizumab or aflibercept combined with second-line chemotherapy in mCRC has an acceptable safety profile and is relatively active. Regardless of the RAS gene type, VEGFi plus FOLOFX6 exhibited superior PFS to that of FLFOX6 as a second-line treatment, and a greater improvement in PFS was obtained for the left-sided lesions than for the right-sided lesions.

Keywords: Vascular endothelial growth factor inhibitor (VEGFis); bevacizumab beyond progression (BBP); second-line treatment; RAS mutation; tumor sidedness
Introduction

Curative surgical resection is a treatment for initial colorectal cancer (CRC) (1). If resection is unfeasible, then chemotherapy or target therapy is used to prolong life expectancy.

Several second-line treatment options are now available for patients for whom initial therapy had failed. The common treatment options for patients who tolerate intensive therapy include the triple drug regimen or biologic agents in combination with a chemotherapy regimen in the initial metastatic CRC (mCRC) diagnosis (2). In some phase II and III studies, bevacizumab was added to the standard 5-fluorouracil (5-FU)-based chemotherapy regimen because it improves the survival rate compared with chemotherapy alone, as demonstrated in patients with mCRC (3-5). The bevacizumab plus FOLFOX4 regimen resulted in improved median overall survival (OS) (12.9 vs. 10.8 months) and median progression-free survival (PFS) (7.3 vs. 4.7 months) compared with the FOLFOX4 regimen (6). The ML18147 study revealed that maintenance of the vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) with standard second-line chemotherapy beyond disease progression has clinical benefits for patients with mCRC (7). The RAISE study reported that adopting ramucirumab plus FOLFIRI as a second-line treatment significantly improved OS in patients with mCRC (8). In addition, the VELOUR study revealed that the addition of aflibercept to second-line FOLFIRI had benefits in patients with mCRC regardless of the timing for the first-line disease progression; no unexpected safety concerns were noted (9). However, few clinical studies have evaluated the efficacy and safety of VEGFi combined with standard chemotherapy regimens in patients with mCRC who exhibited disease progression after receiving bevacizumab plus FOLFIRI as a first-line therapy.

Methods

Study design

This retrospective study investigated the efficacy and safety of VEGFi as a second-line therapy in patients with mCRC that progressed after they had received bevacizumab combined with FOLFIRI as a first-line therapy. We collected the clinical outcomes of treatment, and the information obtained was from the review of actual charts and medical records. The enrolled patients were divided into two groups: a no-VEGFi group and a VEGFi group; mFOLFOX6 was selected as the second-line therapy in the no-VEGFi group, and mFOLFOX6 plus VEGFi (bevacizumab or aflibercept) was selected as the second-line therapy in the VEGFi group. The physicians determined all aspects of patients’ treatments over time, including specific chemotherapy agents and combinations. VEGFis (bevacizumab or aflibercept) were not supplied by a sponsor. All clinical samples were obtained with informed consent from each patient, and the study protocol was approved by the institutional review board of Kaohsiung Medical University Hospital under approval number KMUHIRB-
PFS was selected as the primary endpoint, and the secondary endpoints were OS, ORR, DCR, and safety.

**Patient eligibility**

Patients were considered eligible for this study if they exhibited mCRC with progression confirmed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (13) and if they had received bevacizumab plus FOLFIRI as a first-line treatment. The time to first disease progression had to be at least 3 months. An age of ≥20 years, life expectancy of >3 months, and Eastern Cooperative Oncology Group performance status of 0–2 were other inclusion criteria. In addition, the study patients were required to have adequate hematologic (absolute neutrophil count >1,500/µL, hemoglobin >9.0 g/dL, and platelet count >75,000/µL), hepatic (bilirubin <2.0 mg/dL and transaminase value <3-times the upper normal limit), and renal (creatinine <1.5 mg/dL and urinary excretion <500 mg of protein per day) function.

The exclusion criteria were (I) other malignancies in the preceding 2 years; (II) presence of clinically significant cardiovascular disease, uncontrolled hypertension, or central nervous system metastasis; (III) major surgery within the preceding 6 weeks; (IV) pregnancy or lactation; nonhealing wounds; (V) bleeding diatheses; (VI) regular use of aspirin (>325 mg/day) or other nonsteroidal anti-inflammatory agents; (VII) pre-existing coagulopathies; and need for full-dose anticoagulation.

**Treatment**

Among the 73 patients enrolled in this study, 48 patients who received mFOLFOX6 were assigned to the no-VEGFi group and 25 patients who received mFOLFOX6 plus bevacizumab or aflibercept were assigned to the VEGFi group. Right-sided colon cancer was defined as primary lesions located at the cecum, ascending colon, or transverse colon; a left-sided lesion was defined as that at the descending colon, sigmoid colon, rectosigmoid colon, or rectum. For each patient, we examined the genotyping of the RAS gene.

In the no-VEGFi group, the mFOLFOX6 regimen consisted of oxaliplatin (85 mg/m² as a 4-hour intravenous [IV] infusion) on day 1 followed by leucovorin (200 mg/m² as a 2-hour IV infusion) and 5-FU (2,800 mg/m² as a 46-hour IV infusion); this regimen was performed biweekly. In the VEGFi group, the regimen of mFOLFOX6 plus bevacizumab or aflibercept consisted of bevacizumab (5 mg/kg as a 2-hour IV infusion) or aflibercept (4 mg/kg as a 2-hour IV infusion) on day 1 followed by oxaliplatin (85 mg/m² as a 4-hour IV infusion), leucovorin (200 mg/m² as a 2-hour IV infusion), and 5-FU (2,800 mg/m² as a 46-hour IV infusion); this regimen was performed biweekly.

AEs were assessed using the National Cancer Institute’s Common Terminology Criteria for Adverse Events v4.02 (CTCAE v4.02) (14).

**Assessment**

The present study evaluated the PFS, OS, ORR, and toxicity of VEGFi in patients with mCRC for whom prior bevacizumab-containing treatment had failed. Failure of prior bevacizumab-containing treatment as the first-line regimen (FOLFIRI plus bevacizumab) was determined according to RECIST criteria (15). Tumor response was assessed using RECIST guidelines. Progression was defined as a 20% increase at the time of disease progression. PFS and OS were calculated using the Kaplan–Meier method. The day of introduction of second-line treatment was considered the starting point for the calculation of PFS and OS.

Toxicities were graded using the CTCAE v4.02. Radiographic assessments were performed at baseline (within 4 weeks prior to registration). For diagnostic assessment of efficacy, which was performed once every 12 weeks, computed tomography or magnetic resonance imaging was used to assess target and nontarget lesions and confirm the presence or absence of new lesions.

**Statistical analysis**

The means ± standard deviation was used as continuous variables, and dichotomous variables were expressed as numbers and percentages. All statistical analyses were performed using the Statistical Package for the Social Sciences, Version 19.0 (SPSS Inc., Chicago, IL, USA). Pearson’s chi-squared test was used to compare the clinicopathological characteristics of the two groups by using the Cox regression coefficients to estimate the hazard ratios for all independent variables in the model. The definitions of PFS were the time elapsed between the initiation of the study therapy and the date of disease progression, death, or the last follow-up. OS was defined as
the time elapsed between the initiation of the study therapy and the date of death from any cause or the final follow-up. The Kaplan-Meier method was used to evaluate the PFS and OS, and the log-rank test was used to compare time-to-event distributions. P<0.05 was considered statistically significant.

**Results**

**Patients’ characteristics**

Between May 2015 and February 2018, 73 patients were enrolled in this study; all 73 were included in the efficacy and safety analysis set. The baseline characteristics of the enrolled patients are presented in Table 1. The median age was 60 years (range, 25–87 years). The median follow-up period was 11.0 months (range, 3.2–34.4 months). Overall, 61 patients (83.6%) had left-sided mCRC and 12 (16.4%) had right-sided mCRC. Moreover, 25 patients (34.2%) exhibited mutant-type RAS and 48 (65.8%) exhibited wild-type RAS. Liver metastasis was more common in the no-VEGFi group (47.9%), whereas combined liver-lung metastasis was more common in the VEGFi group. The presence of multiple metastatic sites was more common in the VEGFi group than in the no-VEGFi group (48.0 vs. 27.1%; P=0.074).

**Efficacy for all 73 enrolled patients with mCRC**

During the median follow-up of 11.0 months (range, 3.2–34.4 months), 13 patients (27.1%) and 18 patients (72.0%) achieved disease control in the no-VEGFi and VEGFi groups, respectively (P<0.001, Table 1). Five patients had partial responses, resulting in ORRs of 20% in the VEGFi group and 0% in the no-VEGFi group (P=0.001, Table 1). The median PFS was 9.5 and 3.5 months in the VEGFi and no-VEGFi groups, respectively [P<0.001; Table 1]. The median OS was 15.5 and 10.5 months in the VEGFi and no-VEGFi groups, respectively (P=0.003; HR: 0.345; 95% CI: 0.162–0.736; Figure 2A); the median OS did not differ significantly between the two groups (15.5 vs. 13.5 months; P=0.137; HR: 0.567; 95% CI: 0.264–1.217; Figure 2B). For the 25 patients with mutant-type RAS mCRC, the median PFS was 12.0 and 3.5 months and median OS was 10.0 and 8.3 months in the VEGFi and no-VEGFi groups, respectively. Thus, PFS differed significantly between the two groups (P=0.006; HR: 0.245; 95% CI: 0.080–0.753; Figure 3A) but OS did not (P=0.631; HR: 0.745; 95% CI: 0.231–2.400; Figure 3B).

**Efficacy from the perspective of the RAS gene**

In total, 48 patients (65.8%) had wild-type RAS and 25 patients (34.2%) had mutant-type RAS. Regardless of whether the RAS gene was wild-type or mutant-type (Table 2), the ORR of the VEGFi group was superior to that of the no-VEGFi group (P=0.011 and 0.049, respectively), and the DCR of the VEGFi group was superior to that of the no-VEGFi group (P=0.004 and 0.017, respectively). In the VEGFi group, of the 16 patients with wild-type RAS mCRC, 3 (18.8%) and 12 (75.0%) achieved ORRs and DCRs, respectively. In comparison, of the nine patients with mutant-type RAS mCRC, 2 (22.3%) and 6 (66.7%) achieved ORRs and DCRs, respectively (Table 2). The effects of the RAS genotype on ORRs and DCRs did not differ significantly in the VEGFi group (ORR: P=0.835; DCR: P=0.656).

**Efficacy according to primary lesion location**

Of the patients with mCRC, 61 (83.6%) had primary left-sided colon lesions; the other patients (16.4%) had primary right-sided colon lesions. The ORRs and DCRs in patients with left-sided mCRC in the VEGFi group were superior to those of the corresponding patients in the no-VEGFi group (P=0.011 and P<0.001, respectively; Table 3). However, the ORRs and DCRs did not differ significantly between

In the VEGFi group, 6 patients (24.0%) developed grade 3 or 4 toxicities, namely neutropenia in two patients, diarrhea in one patient, proteinuria in one patient, and liver function impairment in two patients. A nonsignificant difference was observed in the incidence of severe AEs between the two groups (P=0.133; Table 1).
Table 1 Baseline clinical characteristics of 73 mCRC patients undergoing second-line treatment

| Baseline information     | N     | mFOLFOX6, N=48 (%) | mFOLFOX6 + VEGFi, N=25 (%) | P value |
|-------------------------|-------|---------------------|----------------------------|---------|
| Gender                  |       |                     |                            |         |
| Male                    | 41    | 28 (58.3)           | 13 (52.0)                  | 0.605   |
| Female                  | 32    | 20 (41.7)           | 12 (48.0)                  |         |
| Age (years)             |       |                     |                            | 0.064   |
| ≥65                     | 25    | 20 (41.7)           | 5 (20.0)                   |         |
| <65                     | 48    | 28 (58.3)           | 20 (80.0)                  |         |
| EGOG PS                 |       |                     |                            | 0.641   |
| 0                       | 48    | 31 (64.6)           | 17 (68.0)                  |         |
| 1                       | 25    | 17 (35.4)           | 8 (32.0)                   |         |
| Location                |       |                     |                            | 0.553   |
| R’t-sided colon         | 12    | 7 (14.6)            | 5 (20.0)                   |         |
| L’t-sided colon         | 61    | 41 (85.4)           | 20 (80.0)                  |         |
| mCRC                    |       |                     |                            | 0.097   |
| Synchronous             | 50    | 36 (75.0)           | 14 (56.0)                  |         |
| Metachronous            | 23    | 12 (25.0)           | 11 (44.0)                  |         |
| RAS gene                |       |                     |                            | 0.802   |
| WT                      | 48    | 32 (66.7)           | 16 (64.0)                  |         |
| Mut                     | 25    | 16 (33.3)           | 9 (36.0)                   |         |
| Metastatic sites        |       |                     |                            | 0.024   |
| Liver only              | 28    | 23 (47.9)           | 5 (20.0)                   |         |
| Lungs only              | 11    | 4 (8.4)             | 7 (28.0)                   |         |
| Liver + lungs           | 19    | 10 (20.8)           | 9 (36.0)                   |         |
| Others                  | 15    | 11 (22.9)           | 4 (16.0)                   |         |
| No. of metastatic sites |       |                     |                            | 0.074   |
| 1 site                  | 48    | 35 (72.9)           | 13 (52.0)                  |         |
| ≥2 sites                | 25    | 13 (27.1)           | 12 (48.0)                  |         |
| Treatment outcome       |       |                     |                            | < 0.001 |
| Response                |       |                     |                            |         |
| CR                      | 0     | 0 (0)               | 0 (0)                      |         |
| PR                      | 5     | 0 (0)               | 5 (20.0)                   |         |
| SD                      | 26    | 13 (27.1)           | 13 (52.0)                  |         |
| PD                      | 42    | 35 (72.9)           | 7 (28.0)                   |         |
| Responder               |       |                     |                            | 0.001   |
| Yes                     | 5     | 0 (0)               | 5 (20.0)                   |         |
| No                      | 68    | 48 (100.0)          | 20 (80.0)                  |         |

Table 1 (continued)
Table 1 (continued)

| Baseline information | N | mFOLFOX6, N=48 (%) | mFOLFOX6 + VEGFi, N=25 (%) | P value |
|----------------------|---|--------------------|---------------------------|---------|
| **Disease control rate** |   |                    |                           | <0.001  |
| Yes                  | 31| 13 (27.1)          | 18 (72.0)                 |         |
| No                   | 42| 35 (72.9)          | 7 (28.0)                  |         |
| **Grade 3/4 AE**      |   |                    |                           |         |
| Total                | 16| 10 (20.8)          | 6 (24.0)                  | 0.133   |
| Neutropenia           | 3 | 3                   | 2                         |         |
| Diarrhea              | 2 | 2                   | 1                         |         |
| Mucositis             | 5 | 5                   | 0                         |         |
| Proteinuria           | 0 | 0                   | 1                         |         |
| Liver function impaired| 0| 0                   | 2                         |         |

mCRC, metastatic colorectal cancer; VEGFi, vascular endothelial growth factor inhibitors (aflibercept and bevacizumab); R’t-sided colon, cecum + ascending colon + transverse colon; L’t-sided colon, descending colon + sigmoid colon + rectosigmoid colon + rectum; Wt: wild type; Mut, mutation type; others, included peritoneal seeding, para-aortic lymph nodes, neck lymph nodes; No. of metastatic sites, number of metastatic sites; response, best response during treatment; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; responder, CR + PR; DCR, CR + PR + SD; AE, adverse events.

Figure 1 Cumulative survival rates of the 73 enrolled patients with mCRC, obtained using the Kaplan-Meier method. The difference in survival rates was analyzed using the log-rank test. (A) PFS was significantly longer in the VEGFi group than in the no-VEGFi group (9.5 vs. 3.5 months; P<0.001); (B) OS did not differ significantly between the two groups (15.5 vs. 10.5 months; P=0.083). mCRC, metastatic colorectal cancer; PFS, progression-free survival; VEGFi, vascular endothelial growth factor inhibitor; OS, overall survival.
Table 2 Comparison of ORRs and DCRs between 48 mCRC patients with wild-type \textit{RAS} and 25 mCRC patients with mutant-type \textit{RAS} in the two groups of second-line treatment

| Variable      | Wild type of RAS gene | Mutant type of RAS gene | P value |
|---------------|------------------------|-------------------------|---------|
|               | mFOLFOX6, (N=32) (%)   | mFOLFOX6 + VEGFi, (N=16) (%) |         |
| Response      |                        |                        |         |
| PR            | 0 (0)                  | 3 (18.8)                | 0.003   |
| SD            | 10 (31.3)              | 9 (56.2)                |         |
| PD            | 22 (68.7)              | 4 (25.0)                |         |
| Responder     |                        |                        | 0.011   |
| Yes           | 0 (0)                  | 3 (18.8)                |         |
| No            | 32 (100.0)             | 13 (81.2)               |         |
| DCR           |                        |                        | 0.004   |
| Yes           | 10 (31.3)              | 12 (75.0)               |         |
| No            | 22 (68.7)              | 4 (25.0)                |         |

ORR, objective response rate; DCR, disease control rate; mCRC, metastatic colorectal cancer; VEGFi, vascular endothelial growth factor inhibitors (aflibercept and bevacizumab); PR, partial response; SD, stable disease; PD, progressive disease. Responder: yes, partial response; no, stable disease + progressive disease.

A

| No. of patients | Median PFS (ms) |
|-----------------|-----------------|
| mFOLFOX6 only   | 32              | 3.5            |
| mFOLFOX6 + VEGFi| 16              | 9.5            |

B

| No. of patients | Median OS (ms) |
|-----------------|----------------|
| mFOLFOX6 only   | 32              | 13.5           |
| mFOLFOX6 + VEGFi| 16              | 15.5           |

Figure 2 Cumulative survival rates of the 48 enrolled patients with wild-type \textit{RAS} mCRC, obtained using the Kaplan-Meier method. The difference in survival rates was analyzed using the log-rank test. (A) PFS was significantly longer in the VEGFi group than in the no-VEGFi group (9.5 vs. 3.5 months; \( P=0.003 \)); (B) OS did not differ significantly between the two groups (15.5 vs. 13.5 months; \( P=0.137 \)). mCRC, metastatic colorectal cancer; PFS, progression-free survival; VEGFi, vascular endothelial growth factor inhibitor; OS, overall survival.
Figure 3 Cumulative survival rates of the 25 enrolled patients who had mCRC with mutant-type RAS, obtained using the Kaplan-Meier method. The difference in survival rates was analyzed using the log-rank test. (A) PFS was significantly longer in the VEGFi group than in the no-VEGFi group (12.0 vs. 3.5 months; P=0.006); (B) OS did not differ significantly between the two groups (10.0 vs. 8.3 months; P=0.631).

mCRC, metastatic colorectal cancer; PFS, progression-free survival; VEGFi, vascular endothelial growth factor inhibitor; OS, overall survival.

Table 3 Comparison of ORRs and DCRs between 61 Left-Sided mCRC patients and 12 right-sided mCRC patients in the two groups of second-line treatment

| Variable | Left-sided mCRC | Right-sided mCRC | P value | P value |
|----------|-----------------|-----------------|---------|---------|
|          | mFOLFOX6, (N=41) (%) | mFOLFOX6 + VEGFi, (N=20) (%) | mFOLFOX6, (N=7) (%) | mFOLFOX6 + VEGFi, (N=5) (%) |
| Response |                 |                 |         |         |
| PR       | 0 (0)           | 3 (15.0)        | 0 (0)   | 2 (40.0) |
| SD       | 10 (24.4)       | 12 (60.0)       | 3 (42.9) | 1 (20.0) |
| PD       | 31 (75.6)       | 5 (25.0)        | 4 (57.1) | 2 (40.0) |
| Responder |                 |                 |         |         |
| Yes      | 0 (0)           | 3 (15.0)        | 0 (0)   | 2 (40.0) |
| No       | 41 (100.0)      | 17 (85.0)       | 7 (100.0) | 3 (60.0) |
| DCR      |                 |                 |         |         |
| Yes      | 10 (24.4)       | 15 (80.0)       | 3 (42.9) | 3 (60.0) |
| No       | 22 (75.6)       | 5 (20.0)        | 4 (57.1) | 2 (40.0) |

ORR, objective response rate; DCR, disease control rate; mCRC, metastatic colorectal cancer; VEGFi, vascular endothelial growth factor inhibitors (aflibercept and bevacizumab); PR, partial response; SD, stable disease; PD, progressive disease. Responder: yes, partial response; no, stable disease + progressive disease.
the two groups among patients with right-sided mCRC (P=0.067 and 0.558, respectively; Table 3).

The median PFS was 11.5 months in patients with left-sided mCRC and 3.5 months in patients with right-sided mCRC; the difference was significant (P<0.001; HR: 0.263; 95% CI: 0.130–0.532; Figure 4A). However, no significant difference was observed in median OS between the two groups (20.0 vs. 11.0 months; P=0.062; HR: 0.497; 95% CI: 0.245–1.008; Figure 4B). Nonsignificant differences were observed in median PFS (7.2 vs. 3.5 months; P=0.696; HR: 0.946; 95% CI: 0.250–3.587; Figure 5A) and median OS (9.7 vs. 10.3 months; P=0.543; HR: 1.534; 95% CI: 0.382–6.154; Figure 5B) in patients with right-sided mCRC.

The 73 patients were further divided into four subgroups according to the primary mCRC location and whether continued use of VEGFi was applied in the second-line therapy. The results indicated that patients with primary left-sided lesions and continued use of VEGFi exhibited the most marked effect in PFS compared with patients in the other three subgroups (P=0.001; Figure 6).

**Discussion**

The present study evaluated treatment patterns and clinical outcomes in patients with mCRC who had been administered FOLFIRI and bevacizumab as a first-line treatment. We demonstrated that the continued use of VEGFi outperformed mFOLFOX6 alone as a second-line regimen in terms of its effects on PFS, ORR, and DCR in patients with the wild-type or mutant-type RAS gene or with primary left-sided mCRC. This study also revealed that the toxicities were not significantly different between the two groups. To date, few randomized clinical studies have evaluated the effect of BBP continuation in patients with mCRC for the purpose of examining the clinical benefits of sustained VEGF suppression.

Disease progression generally represents resistance to therapy and guides changes in therapy regimens. The genetic instability inherent in cancer renders mutant cells insensitive to primary and secondary cytotoxic drugs and results in resistance. The appearance of tumor cells that are resistant to cytotoxic regimens does not...

![Figure 4](image.png) Cumulative survival rates of the 61 enrolled patients with left-sided mCRC, obtained using the Kaplan-Meier method. The difference in survival rates was analyzed using the log-rank test. (A) PFS was significantly longer in the VEGFi group than in the no-VEGFi group (11.5 vs. 3.5 months; P<0.001); (B) OS did not differ significantly between the two groups (20.0 vs. 11.0 months; P=0.062). mCRC, metastatic colorectal cancer; PFS, progression-free survival; VEGFi, vascular endothelial growth factor inhibitor; OS, overall survival.
definitively indicate that the disease is no longer partially or significantly dependent on VEGF-mediated endothelial cell mitogenesis and survival. One theory is that sustained VEGF suppression alongside secondary and tertiary cytotoxic regimens may result in sustained clinical benefits. The results of BBP survival analyses in the BRiTE (10) and ARIES (11) studies provide powerful evidence to support this hypothesis.

VEGF is the most influential mediator of angiogenesis and the sole angiogenic factor that has been shown to be expressed not only in the initial stages of tumor growth but also throughout the entire tumor life cycle (16). The development of resistance to bevacizumab is believed to be attributable to the apparent attenuation of its effects on other angiogenic factors, such as basic fibroblast growth factor and platelet-derived growth factor, and not to the attenuation of its effects on VEGF; this suggests that the continued use of VEGFi has partial or supplemental efficacy (17). In 2012, Tsutsumi et al. reported results that provide further evidence to support this assertion (18).

The present study showed that the VEGFi group treatment was active, with an ORR of 20% and overall DCR of 72%. Response and survival data in the present study seem more favorable than those reported in other studies. Efficacy data reported in other phase II studies vary considerably, with most studies reporting a median PFS of ≤ 5 months and median OS of < 13 months in second-line treatment settings (19-22). According to our data, the PFS was 9.5 months and the OS was 15.5 months in the VEGFi group. Notably, the PFS and OS values observed in the present study are similar to those reported in E3200 (6).

The effects of long-term exposure to VEGFis in patients who have received BBP are a concern. The results of the BRiTE study indicated no significant increase in serious AEs (SAEs) in the BBP group compared with those in the no-BBP group; these findings are similar to those of the present study. As described in previous reports (3,6), SAEs are believed to be controllable through similar management approaches. Regarding safety, the incidence of SAEs due to the long-term use of VEGFi was not higher in the no-VEGFi group. The observation of selected SAEs (i.e., any SAE assumed to be related to VEGFi, including
gastrointestinal perforation, arterial thromboembolic events, bleeding, and hypertension) revealed no such difference between the two groups in the present study. However, the higher cumulative incidence of grade 1 or 2 hypertension in the VEGFi group was expected given that the risk of developing bevacizumab-associated hypertension appeared to be constant over time (23) and that the VEGFi group had substantially longer bevacizumab exposure. Our study obtained similar outcomes for the cumulative incidence of grade 1 or 2 hypertension, namely 23.5% and 18.3% in the VEGFi and no-VEGFi groups, respectively.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study and study 181 serve as examples of phase III clinical studies assessing second-line therapy. In the EPIC study (24), the response rate for cetuximab plus irinotecan was 16.4%, and in study 181, the response rates for panitumumab plus FOLFIRI were 35% in patients with wild-type RAS and 13% in patients with mutant-type RAS (19). In the present study, the response rate for mFOLFOX6 plus VEGFi as a second-line regimen was 18.8% in patients with wild-type RAS and 22.3% in patients with mutant-type RAS. The response rates for mFOLFOX6 plus VEGFi in this study, which applied BBP, are comparable to those in patients with mutant-type RAS in study 181.

In 1990, Bufill described CRC according to primary tumor locations (25). Different origins lead to tumors with different gene expression and mutation profiles. In particular, right-sided tumors exhibit a higher frequency of BRAF mutation and microsatellite instability and occur more often in patients with a genetic predisposition to CRC (e.g., Lynch syndrome). By contrast, left-sided tumors are characterized by chromosomal instability and a gene expression profile that involves activation of the epidermal growth factor receptor pathway (26,27). These differences result in different prognoses for the two tumor types, and right-sided tumors are associated with poorer clinical outcomes (26-28). In another study, patients with
right-sided mCRC who underwent second-line treatments exhibited low ORRs, especially those in the FOLFIRI arm (29). In this study, left-sided patients with mCRC and BBP who had continued use of VEGFi as a second-line treatment exhibited favorable ORRs and DCRs; patients with right-sided mCRC experienced no such benefits. Furthermore, the 73 patients enrolled were divided into four subgroups according to primary tumor location and VEGFi administration mode; the left-sided VEGFi group had significantly longer PFS than did the other subgroups.

Several limitations of this study must be considered. All OCSs have inherent limitations resulting largely from the nonrandom assignment of patients to the treatment groups being compared. Second, only 25 patients with mCRC were included in the VEGFi group in this study. In a subgroup analysis with a small number of patients, no statistical significance is not meaningful. Third, the median follow-up duration was only 11.0 months. Nevertheless, this real-world study provides insights into the effects of VEGFi combined with a range of chemotherapy regimens commonly used in patients who experience disease progression after first-line therapy.

**Conclusions**

In conclusion, this study demonstrates a survival benefit associated with the continuation of VEGFi treatment beyond disease progression in patients with mCRC who have received bevacizumab-containing chemotherapy as a first-line therapy. The results support the hypothesis that continued suppression of the VEGF pathway may maximize the clinical benefits of bevacizumab in patients with mCRC, especially patients with left-sided mCRC, irrespective of RAS mutation.

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_Footnote_

_Conflicts of Interest:_ All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.09.59). The authors have no conflicts of interest to declare.

_Ethical Statement:_ The authors are accountable in all respects for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All clinical samples were obtained with informed consent from each patient, and the study protocol was approved by the institutional review board of Kaohsiung Medical University Hospital under approval number KMUHIRB-2012-03-02(II).

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