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Comparative Efficacy of Second-line Anti-VEGF Continuation and Anti-EGFR Switch Strategies in RAS Wild-type Metastatic Colorectal Cancer Patients Progressing on First-line Anti-VEGF Therapy: A Retrospective Single-center Study

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ABSTRACT

Objective: The optimal selection of second-line biological therapy remains unclear in patients with RAS wild-type metastatic colorectal cancer (mCRC) who develop disease progression following first-line anti-vascular endothelial growth factor (VEGF)-based treatment. This study aimed to compare the efficacy and safety outcomes of continuation of second-line anti-VEGF therapy versus switching to anti-epidermal growth factor receptor (EGFR) therapy.

Material and Methods: This retrospective single-center study included 38 patients with RAS wild-type mCRC who were treated between January 2015 and December 2025. All patients received bevacizumab-based chemotherapy in the first-line setting and subsequently developed disease progression. Patients were divided into two groups according to the second-line biological therapy administered concomitantly with chemotherapy: anti-VEGF continuation (n=20) and anti-EGFR switch (cetuximab/panitumumab; n=18). The primary endpoints were second-line progression-free survival (PFS2) and overall survival (OS).

Results: Median PFS2 was 7.1 months in the anti-VEGF group and 10.0 months in the anti-EGFR group (p=0.404). Median OS were 28.2 months and 25.5 months, respectively (p=0.752). No significant differences were observed between the groups in survival outcomes. Left-sided colon tumors were more frequent in the anti-EGFR group, whereas right-sided colon tumors were more frequent in the anti-VEGF group. Skin rash was significantly more common with anti-EGFR therapy (22.2%; p=0.041), while other toxicities were manageable.

Conclusion: In patients with RAS wild-type mCRC progressing after first-line anti-VEGF therapy, second-line anti-VEGF continuation and anti-EGFR switch strategies demonstrated comparable survival outcomes. Treatment selection should be individualized based on tumor sidedness, prior treatment response, toxicity profile, and patient characteristics.

Keywords: Metastatic colorectal cancer; RAS wild-type; second-line treatment; progression-free survival; real-world data

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide and the second leading cause of cancer-related mortality.[1] Approximately 25% of patients present with metastatic disease at initial diagnosis, and nearly half develop metastases during the course of the disease.[2] Metastatic CRC (mCRC) continues to represent a substantial global clinical burden due to its aggressive disease biology and limited therapeutic options.[3] In the management of mCRC, systemic therapies supported by randomized clinical trials and meta-analyses constitute the cornerstone of treatment.[4] With the widespread implementation of extended

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molecular testing and genomic profiling, contemporary mCRC treatment has become increasingly personalized. Despite these scientific advances, determining the most effective treatment sequence and defining the optimal therapeutic strategy remain major unresolved clinical challenges.[5]

Precision oncology approaches in patients with RAS wild-type mCRC require the integration of molecular biomarkers, primary tumor location, and patient-related characteristics into the therapeutic decision-making process.[6] Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR), including panitumumab and cetuximab, currently represent important first-line treatment options with demonstrated survival benefit.[7] In parallel, the addition of antibodies targeting the vascular endothelial growth factor (VEGF) signaling pathway to chemotherapy has been shown to improve response rates across all molecular subgroups, regardless of RAS mutation status.[8] Current guidelines identify primary tumor sidedness as a key determinant of treatment selection, recommending anti-EGFR agents preferentially for left-sided tumors and anti-VEGF agents for right-sided tumors.[9] Nevertheless, national registry data suggest that anti-EGFR-based therapies may provide advantages in progression-free survival (PFS) and overall survival (OS) compared with bevacizumab-based regimens in real-world practice.[10] Therefore, the selection of the optimal biological agent and treatment combination in the RAS wild-type population represents a multidimensional decision-making process requiring comprehensive evaluation of efficacy, clinical pharmacology, and toxicity profiles.[2,5]

In routine clinical practice, anti-VEGF agents, such as bevacizumab, when combined with cytotoxic chemotherapy, constitute one of the most frequently used biological strategies in the first-line treatment of mCRC because of their efficacy irrespective of RAS mutation status.[1,2,11] However, the optimal therapeutic approach for patients with RAS wild-type disease who experience progression during first-line anti-VEGF therapy remains unclear.[5,11,12] This uncertainty creates a critical clinical gap in optimizing treatment sequencing to maximize survival outcomes in patients with RAS wild-type mCRC.[5]

Among second-line treatment strategies, the potential of anti-EGFR agents to improve response rates and the rationale for continued anti-VEGF inhibition have yielded conflicting results in the literature.[5,11] The PRODIGE-18 study suggested a numerical survival advantage with bevacizumab continuation compared with switching to anti-EGFR therapy, whereas the SPIRITT trial demonstrated no significant differences in PFS or OS between the two approaches.[13,14] Such heterogeneity in available data complicates the translation of guideline recommendations into real-world practice and highlights the need to evaluate local treatment patterns in light of national registry data. Consequently, there is an increasing need for additional real-world evidence directly comparing these two biological strategies in patients with RAS wild-type mCRC who progress following first-line anti-VEGF therapy.

In the present study, using real-world clinical data, we aimed to compare the efficacy of continuing anti-VEGF as second-line therapy versus switching to anti-EGFR therapy in patients with RAS wild-type mCRC who developed disease progression after receiving first-line anti-VEGF-based chemotherapy. The primary endpoints were second-line PFS (PFS2) and OS, while secondary endpoints included treatment response rates and toxicity profiles. We anticipate that the findings of this study will address the current clinical uncertainty and strengthen the evidence base regarding optimal second-line biological agent selection in patients with RAS wild-type mCRC.

MATERIAL AND METHODS

Study Design and Patient Selection

This study was designed as a single-center, retrospective, observational analysis. The study protocol was approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval number: 2026/136, date: 06.02.2026), and all procedures were conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Patients diagnosed with mCRC and with histopathologically confirmed colorectal adenocarcinoma between January 2015 and December 2025 were included in the study. The inclusion criteria were defined as follows: (1) confirmed RAS wild-type and BRAF wild-type molecular status, (2) receipt of a standard first-line chemotherapy regimen containing bevacizumab, (3) radiological disease progression following first-line therapy with subsequent initiation of second-line systemic treatment, and (4) an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients with unknown RAS/BRAF mutation status, those with BRAF-mutant tumors, those who died before initiation of second-line therapy, or those with insufficient follow-up data were excluded from the study.

Eligible patients were categorized into two groups according to the biological agent administered during second-line treatment: the anti-VEGF group (bevacizumab-based regimen, n=20) and the anti-EGFR group (cetuximab- or panitumumab-based regimen, n=18).The selection of biological therapy was determined by the treating oncologist based on the patient's clinical condition, first-line chemotherapy regimen, and individual patient characteristics.

Assessment of Clinical and Treatment Characteristics

Clinical, demographic, and treatment-related data were retrospectively collected from the institutional electronic medical record system. The evaluated parameters included age at diagnosis, sex, body mass index (BMI), ECOG performance status, presence of comorbidities, primary tumor localization and clinical stage, histological subtype, status and intent of primary tumor surgery, type of metastasis (synchronous/metachronous), interval from diagnosis to metastatic disease, number of metastatic organs and their sites, number of liver metastases, RAS/BRAF mutation status and microsatellite instability (MSI) status, serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels, chemotherapy protocol administered, type of biological agent, number of treatment cycles, treatment response according to RECIST version 1.1, and reasons for treatment discontinuation. Toxicity data were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Follow-up and Study Endpoints

The primary endpoints of the study were PFS2 and OS. PFS2 was defined as the interval between the date of radiological progression following first-line treatment and the date of progression during second-line therapy or death from any cause. Radiologically confirmed first-line progression was selected as the starting point because it represented the predefined clinical event prompting the initiation of second-line treatment in all eligible patients. OS was defined as the interval from the initiation of first-line treatment for metastatic disease to death from any cause. This definition was chosen to evaluate the OS associated with the complete treatment strategy, rather than the isolated effect of second-line biological therapy. Patients without documented progression or death during follow-up were censored on the date of the last clinical evaluation.

The secondary endpoints included first-line PFS (PFS1) and toxicity profiles associated with each treatment group.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software, version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), whereas categorical variables were presented as frequencies and percentages (%). Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Survival analyses were conducted using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using univariable Cox proportional hazards models. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

The patient selection process is illustrated in Figure 1. A total of 38 patients with confirmed RAS- wild-type and BRAF- wild-type mCRC who met the study eligibility criteria and were followed at our center between January 2015 and December 2025 were retrospectively analyzed. Of these patients, 20 continued anti-VEGF therapy in the second-line setting, whereas 18 switched to anti-EGFR therapy. Baseline patient characteristics are summarized in Table 1.

TABLE 1: Baseline demographic and clinical characteristics of patients according to second-line biological treatment strategy.

Variable	Anti-VEGF (n=20)	Anti-EGFR (n=18)	p-value
Demographic characteristics			
Age (years)			
Mean ± SD	60.4±10.7	59.4±11.7	0.682[1]
Median (min-max)	61 (37-77)	58 (36-78)	
Age group			
<65 years	12 (60.0%)	13 (72.2%)	0.652[2]
≥65 years	8 (40.0%)	5 (27.8%)	
Sex			
Female	3 (15.0%)	8 (44.4%)	0.074[2]
Male	17 (85.0%)	10 (55.6%)	
BMI (kg/m²)			
Mean ± SD	25.0±5.1	29.1±6.7	0.034[1]
Median (min-max)	24.6 (15.6-36.6)	29.7 (15.1-41.1)	

TABLE 1: Continued.			
Variable	**Anti-VEGF (n=20)**	**Anti-EGFR (n=18)**	**p-value**
ECOG performance status			
ECOG 0	18 (90.0%)	14 (77.8%)	0.450[2]
ECOG 1	2 (10.0%)	3 (16.7%)	
ECOG 2	0 (0.0%)	1 (5.6%)	
Smoking status			
Never	7 (35.0%)	5 (27.8%)	1.000[2]
Ever	10 (50.0%)	8 (44.4%)	
Pack-years (mean ± SD)	29.4±12.0	31.2±8.3	0.622[1]
Comorbidity	15 (75.0%)	6 (33.3%)	0.024[2]
Family history			
None	8 (40.0%)	8 (44.4%)	0.598[2]
Family history of CRC	3 (15.0%)	2 (11.1%)	
Family history of non-CRC cancer	5 (25.0%)	2 (11.1%)	
Unknown	3 (15.0%)	5 (27.8%)	
Second primary malignancy	2 (10.0%)	0 (0.0%)	0.488[2]

[1]: Independent samples Mann-Whitney U test, [2]: Pearson chi-square test/Fisher's exact test, p<0.05 was considered statistically significant.
VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; SD: Standard deviation; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; CRC: Colorectal cancer.

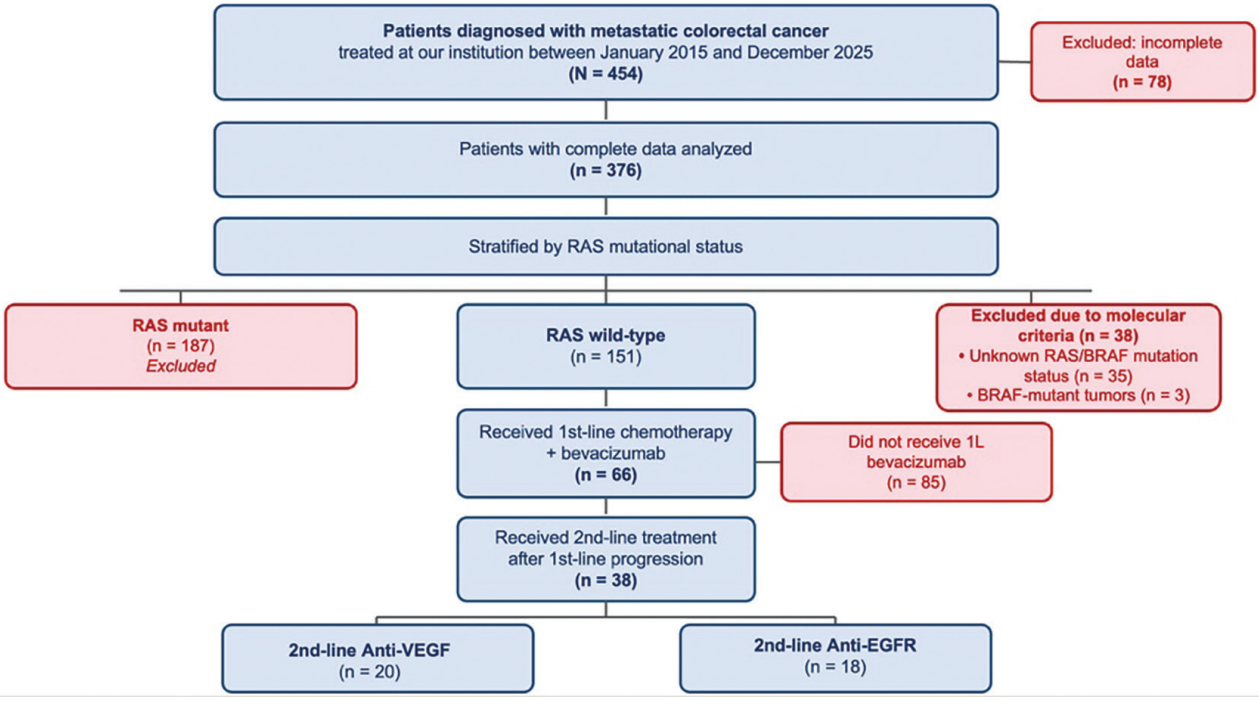

FIGURE 1: Flow diagram of patient selection.

VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor

No statistically significant differences were observed between the groups in demographic characteristics, including age, sex, ECOG performance status, smoking history, height and weight (Table 1). However, BMI was significantly higher in the anti-EGFR group compared with the anti-VEGF group (29.1±6.7 vs. 25.0±5.1 kg/m^2; p=0.034). The presence of comorbidities was more frequent in the anti-VEGF group than in the anti-EGFR group (75.0% vs. 33.3%; p=0.024), whereas no other significant differences in baseline clinical characteristics were identified.

Regarding primary tumor localization, right-sided colon tumors were more common in the anti-VEGF group (70.0%), whereas left-sided colon and rectal tumors predominated in the anti-EGFR group (77.8%). Detailed localization analysis demonstrated a statistically significant difference in tumor distribution between the groups (p=0.024). In terms of metastatic disease characteristics, liver metastasis was the most common metastatic site in both groups. Although lung and peritoneal metastases were observed more frequently in the anti-VEGF group, the differences did not reach statistical significance (both p=0.067) (Table 2).

TABLE 2: Tumor and metastatic disease characteristics according to second-line biological treatment strategy.

Variable	Anti-VEGF (n=20)	Anti-EGFR (n=18)	p-value
Clinical and pathological characteristics			
Clinical stage at initial diagnosis			
Stage 4A	7 (35.0%)	8 (44.4%)	0.559[2]
Stage 4B	4 (20.0%)	4 (22.2%)	
Stage 4C	6 (30.0%)	1 (5.6%)	
Stage 3C	1 (5.0%)	2 (11.1%)	
Stage 3B	1 (5.0%)	1 (5.6%)	
Stage 3A	0 (0.0%)	1 (5.6%)	
Stage 2A	1 (5.0%)	1 (5.6%)	
Tumor localization (general)			
Right colon	14 (70.0%)	4 (22.2%)	
Left colon	6 (30.0%)	14 (77.8%)	
Both sides	0 (0.0%)	0 (0.0%)	
Tumor localization (detail)			
Cecum	6 (30.0%)	2 (11.1%)	0.024[2]
Ascending colon	8 (40.0%)	1 (5.6%)	
Transverse colon	3 (15.0%)	2 (11.1%)	
Descending colon	1 (5.0%)	1 (5.6%)	
Sigmoid colon	3 (15.0%)	1 (5.6%)	
Rectum	1 (5.0%)	7 (38.9%)	
Rectosigmoid	1 (5.0%)	4 (22.2%)	
Primary tumor surgery			
Performed	10 (50.0%)	12 (66.7%)	0.478[2]
Not performed	10 (50.0%)	6 (33.3%)	
Surgical intent			
Curative	4 (20.0%)	5 (27.8%)	1.000[2]
Palliative	6 (30.0%)	7 (38.9%)	
Surgical procedure			
Right hemicolectomy	6 (30.0%)	2 (11.1%)	0.219[2]
Anterior resection	1 (5.0%)	1 (5.6%)	
Laparoscopic anterior resection	0 (0.0%)	2 (11.1%)	
Abdominoperineal resection	0 (0.0%)	1 (5.6%)	
Total colectomy	0 (0.0%)	2 (11.1%)	
Segmental resection	3 (15.0%)	4 (22.2%)	
Time from diagnosis to metastasis (months)			
Mean ± SD	2.2±5.7	7.1±12.4	0.176[1]
Median (min-max)	0 (0-20)	0 (0-40)	

TABLE 2: Continued.			
Variable	**Anti-VEGF (n=20)**	**Anti-EGFR (n=18)**	**p-value**
Metastasis type			
Synchronous	17 (85.0%)	12 (66.7%)	0.260[2]
Metachronous	3 (15.0%)	6 (33.3%)	
Number of metastatic sites			
Mean ± SD	1.6±0.9	1.3±0.5	0.318[1]
Median (min-max)	1 (1-4)	1 (1-2)	
Metastatic sites			
Liver	14 (70.0%)	14 (77.8%)	0.719[2]
Lung	8 (40.0%)	2 (11.1%)	0.067[2]
Peritoneum	8 (40.0%)	2 (11.1%)	0.067[2]
Bone	1 (5.0%)	1 (5.6%)	1.000[2]
Distant lymph node	2 (10.0%)	4 (22.2%)	0.395[2]
Liver metastasis count (among patients with liver metastases)			
Mean ± SD	1.9±1.1	2.2±1.8	0.940[1]
Median (min-max)	1 (1-4)	2 (1-7)	
Multiple (≥4)	4 (20.0%)	3 (16.7%)	1.000[2]
Baseline CEA (ng/mL)			
Mean ± SD	211.1±641.3	122.6±231.8	0.855[1]
Median (min-max)	14.1 (0.8-2834.0)	6.0 (1.2-658.0)	
Baseline CA 19-9 (U/mL)			
Mean ± SD	122.6±229.9	107.4±340.1	0.293[1]
Median (min-max)	30.8 (0.6-820.0)	7.8 (0.6-1418.0)	

[1]: Independent samples Mann-Whitney U test, [2]: Pearson chi-square test/Fisher's exact test, log-rank test, p<0.05 was considered statistically significant. Clinical stage refers to the stage at the time of the initial colorectal cancer diagnosis, before the development of metastatic disease in patients with metachronous metastases.
VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; SD: Standard deviation; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9.

All patients in both groups received bevacizumab-based treatment in the first-line setting. FOLFOX was the most commonly administered chemotherapy regimen. The number of first-line treatment cycles was comparable between the groups (8.3±4.1 vs. 9.7±3.5; p=0.500). A statistically significant difference was observed in first-line treatment response rates between the groups (p=0.047). The anti-VEGF group demonstrated a higher rate of partial response (40.0% vs. 5.6%), whereas progressive disease was more frequent in the anti-EGFR group (66.7% vs. 30.0%) (Table 3).

In the second-line setting, all patients in the anti-VEGF group continued bevacizumab therapy, while 66.7% of patients in the anti-EGFR group received cetuximab and 33.3% received panitumumab. Significant differences were observed between the groups in the second-line chemotherapy regimens administered (p=0.031), with FOLFIRI more frequently used in the anti-EGFR group (77.8%). No statistically significant difference was found between the groups in second-line treatment response (p=0.483) (Table 3).

Evaluation of treatment-line transitions revealed a numerically higher rate of progression to third-line therapy in the anti-VEGF group compared with the anti-EGFR group (65.0% vs. 50.0%); however, this difference was not statistically significant (p=0.544).

Survival analyses are presented in Table 4 and Figures 2-4. The median PFS1 was 12.3 months in the anti-VEGF group versus 9.1 months in the anti-EGFR group; the difference was not statistically significant (HR: 0.68; 95% CI: 0.32-1.44; p=0.311) (Figure 2). The median PFS2 durations were 7.1 months and 10.0 months in the anti-VEGF and anti-EGFR groups, respectively (HR: 1.42; 95% CI: 0.62-3.23; p=0.404) (Figure 3). Median OS durations were 28.2 months in the anti-VEGF group and 25.5 months in the anti-EGFR group (HR: 1.12; 95% CI: 0.54-2.32; p=0.752) (Figure 4). At the end of follow-up, mortality rates were 80.0% and 88.9% in the anti-VEGF and anti-EGFR groups, respectively.

TABLE 3: Treatment characteristics and response outcomes according to second-line biological treatment strategy.			
Variable	**Anti-VEGF (n=20)**	**Anti-EGFR (n=18)**	**p-value**
1st line treatment characteristics			
1st line chemotherapy regimen			
XELOX	7 (35.0%)	8 (44.4%)	0.363[2]
FOLFOX	11 (55.0%)	7 (38.9%)	
FOLFIRI	2 (10.0%)	1 (5.6%)	
FOLFIRINOX	0 (0.0%)	2 (11.1%)	
1st line anti-VEGF agent			
Bevacizumab	20 (100.0%)	18 (100.0%)	
Number of 1st line cycles			
Mean ± SD	8.3±4.1	9.7±3.5	0.500[1]
Median (min-max)	8 (1-14)	10 (3-18)	
1st line treatment response			
CR	2 (10.0%)	3 (16.7%)	0.047[2]
PR	8 (40.0%)	1 (5.6%)	
Stable disease	1 (5.0%)	2 (11.1%)	
PD	6 (30.0%)	12 (66.7%)	
2nd line treatment characteristics			
2nd line chemotherapy regimen			
XELOX	2 (10.0%)	0 (0.0%)	0.031[2]
XELIRI	6 (30.0%)	1 (5.6%)	
FOLFOX	5 (25.0%)	3 (16.7%)	
FOLFIRI	5 (25.0%)	14 (77.8%)	
FOLFIRINOX	1 (5.0%)	0 (0.0%)	
XELOXIRI	1 (5.0%)	0 (0.0%)	
2nd line biological agent			
Bevacizumab	20 (100.0%)	0 (0.0%)	<0.001[2]
Panitumumab	0 (0.0%)	6 (33.3%)	
Cetuximab	0 (0.0%)	12 (66.7%)	
Number of 2nd line cycles			
Mean ± SD	6.0±3.6	7.8±4.4	0.162[1]
Median (min-max)	5 (1-12)	6 (2-18)	
2nd line treatment response			
CR	1 (5.0%)	0 (0.0%)	0.483[2]
PR	1 (5.0%)	2 (11.1%)	
Stable disease	0 (0.0%)	1 (5.6%)	
PD	14 (70.0%)	12 (66.7%)	
Treatment line transition summary			
Received 1st line treatment	20 (100.0%)	18 (100.0%)	
Proceeded to 2nd line	20 (100.0%)	18 (100.0%)	1.000[2]
Proceeded to 3rd line	13 (65.0%)	9 (50.0%)	0.544[2]

[1]: Independent samples Mann-Whitney U test, [2]: Pearson chi-square test/Fisher's exact test, log-rank test, p<0.05 was considered statistically significant.
VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; SD: Standard deviation; CR: Complete response; PR: Partial response; PD: Progressive disease.

TABLE 4: Survival outcomes according to second-line biological treatment strategy.			
Variable	**Anti-VEGF (n=20)**	**Anti-EGFR (n=18)**	**p-value**
PFS1			
Definition: from 1st line start to 1st line progression			
Evaluable patients	20	18	0.311[3]
Events (progression/death)	12	15	
Censored patients	8	3	
Median PFS1 (months)	12.3	9.1	
95% CI	8.7-13.6	4.5-11.5	
HR (95% CI)	0.68 (0.32-1.44)	—	
Mean PFS1 (months)	10.8±7.3	10.2±7.1	
6-month PFS1 rate	94.4%	61.1%	
12-month PFS1 rate	52.5%	37.0%	
24-month PFS1 rate	16.4%	14.8%	
PFS2			
Definition: from 1st line progression to 2nd line progression			
Evaluable patients	20	18	0.404[3]
Events (progression/death)	13	10	
Censored patients	7	8	
Median PFS2 (months)	7.1	10.0	
95% CI	4.5-8.3	6.8-11.0	
HR (95% CI)	1.42 (0.62-3.23)	—	
Mean PFS2 (months)	6.1±3.8	6.8±3.7	
6-month PFS2 rate	67.0%	70.6%	
12-month PFS2 rate	8.4%	30.9%	
24-month PFS2 rate	8.4%	15.4%	
OS			
Definition: from 1st line start to death from any cause			
Evaluable patients	20	18	0.752[3]
Events (deaths)	16	16	
Censored patients	4	2	
Median OS (months)	28.2	25.5	
95% CI	21.3-31.4	19.5-32.6	
HR (95% CI)	1.12 (0.54-2.32)	—	
Mean OS (months)	27.1±11.8	28.0±17.2	
12-month OS rate	90.0%	88.9%	
24-month OS rate	54.2%	51.4%	
36-month OS rate	34.4%	25.7%	
60-month OS rate	0.0%	6.4%	
Survival status			
Alive	4 (20.0%)	2 (11.1%)	0.663[2]
Deceased	16 (80.0%)	16 (88.9%)	

[2]: Pearson chi-square test/Fisher's exact test, [3]: Kaplan-Meier survival analysis, log-rank test, $p<0.05$ was considered statistically significant.
VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; SD: Standard deviation; OS: Overall survival; CI: Confidence interval; PFS: Progression-free survival; HR: Hazard ratio.

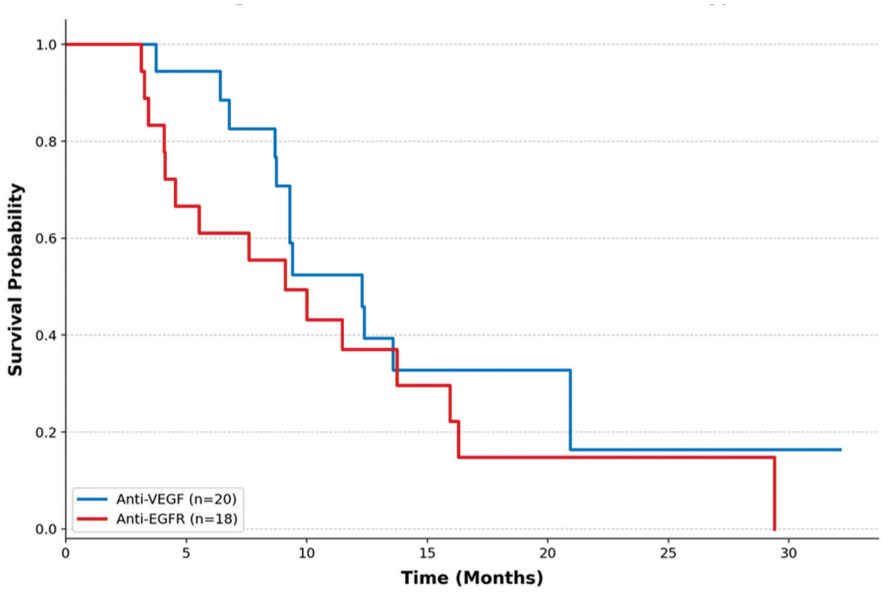

FIGURE 2: Kaplan-Meier analysis of first-line progression-free survival according to second-line biological treatment strategy.

VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor

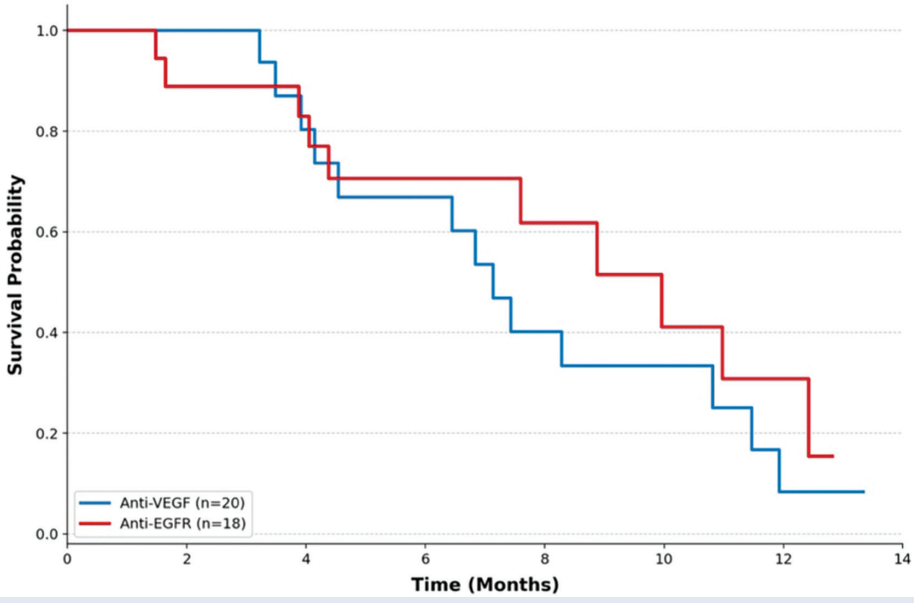

FIGURE 3: Kaplan-Meier analysis of second-line progression-free survival according to second-line biological treatment strategy.

VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor

Toxicities related to first-line treatment were summarized to provide clinical context for treatment tolerability prior to the initiation of second-line therapy. In the first-line toxicity analysis, the incidence of any adverse event was 50.0% in the anti-VEGF group and 33.3% in the anti-EGFR group, with no statistically significant difference (p=0.478) (Table 5). Peripheral neuropathy was the most common chemotherapy-related toxicity and tended to occur more frequently in the anti-VEGF group (30.0% vs. 5.6%; p=0.093).

In the second-line toxicity analysis, the overall incidence of adverse events was comparable between the groups (40.0% vs. 61.1%; p=0.330). Biologic agent-related skin rash was significantly more common in the anti-EGFR group than in the anti-VEGF group (22.2% vs. 0.0%; p=0.041). Apart from this finding, no significant differences were observed between the groups in chemotherapy-related or biologic agent-related toxicities (Table 5).

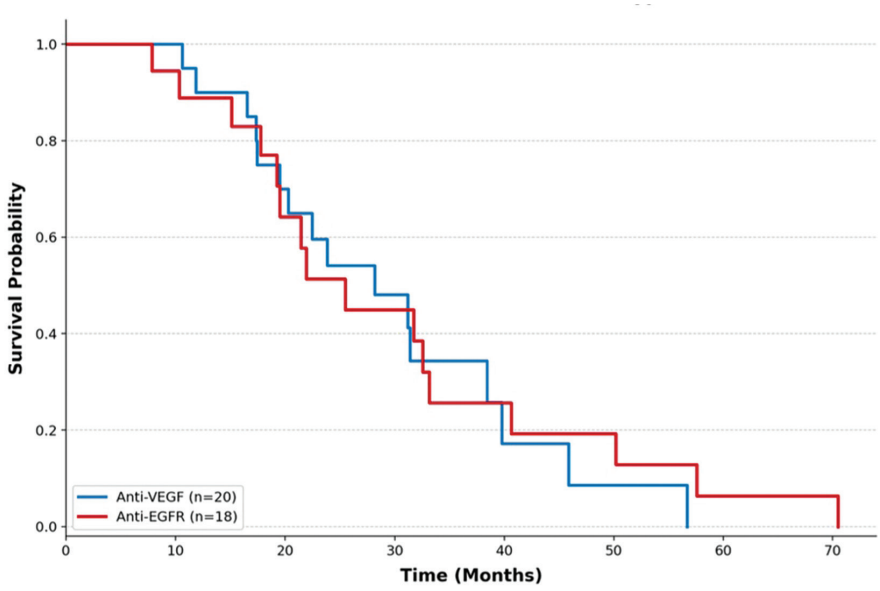

FIGURE 4: Kaplan-Meier analysis of overall survival according to second-line biological treatment strategy.

VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor

TABLE 5: First- and second-line treatment-related toxicities according to second-line biological treatment strategy.

Variable	Anti-VEGF (n=20)	Anti-EGFR (n=18)	p-value
1st line treatment toxicities			
Patients with adverse events	10 (50.0%)	6 (33.3%)	0.478[2]
Chemotherapy-related toxicities (1st line)			
Peripheral neuropathy	6 (30.0%)	1 (5.6%)	0.093[2]
Diarrhea	0 (0.0%)	2 (11.1%)	0.218[2]
Neutropenia	2 (10.0%)	1 (5.6%)	1.000[2]
Thrombocytopenia	4 (20.0%)	2 (11.1%)	0.663[2]
No chemotherapy toxicity	11 (55.0%)	12 (66.7%)	
Anti-VEGF agent-related toxicities (1st line)			
Hypertension	0 (0.0%)	1 (5.6%)	0.474[2]
Thromboembolic event	1 (5.0%)	0 (0.0%)	1.000[2]
Perforation	1 (5.0%)	0 (0.0%)	1.000[2]
Diarrhea	0 (0.0%)	2 (11.1%)	0.218[2]
No biological agent toxicity	19 (95.0%)	16 (88.9%)	
Maximum grade of biological agent toxicity			
Grade 1	0 (0.0%)	0 (0.0%)	
Grade 2	0 (0.0%)	1 (5.6%)	
Grade 3	1 (5.0%)	1 (5.6%)	
Grade 4	0 (0.0%)	0 (0.0%)	
2nd line treatment toxicities			
Patients with adverse events	8 (40.0%)	11 (61.1%)	0.330[2]
Chemotherapy-related toxicities (2nd line)			
Peripheral neuropathy	3 (15.0%)	2 (11.1%)	1.000[2]
Diarrhea	1 (5.0%)	4 (22.2%)	0.170[2]
Neutropenia	2 (10.0%)	0 (0.0%)	0.488[2]

TABLE 5: Continued.			
Variable	**Anti-VEGF (n=20)**	**Anti-EGFR (n=18)**	**p-value**
Thrombocytopenia	3 (15.0%)	0 (0.0%)	0.232[2]
Infusion reaction	1 (5.0%)	0 (0.0%)	1.000[2]
Nausea/vomiting	1 (5.0%)	1 (5.6%)	1.000[2]
Constipation	0 (0.0%)	1 (5.6%)	0.474[2]
No chemotherapy toxicity	11 (55.0%)	11 (61.1%)	
Anti-EGFR/anti-VEGF agent-related toxicities (2nd line)			
Proteinuria	0 (0.0%)	1 (5.6%)	0.474[2]
Bleeding	1 (5.0%)	1 (5.6%)	1.000[2]
Skin rash	0 (0.0%)	4 (22.2%)	0.041[2]
Diarrhea	0 (0.0%)	2 (11.1%)	0.218[2]
No biological agent toxicity	19 (95.0%)	10 (55.6%)	
Maximum grade of biological agent toxicity			
Grade 1	0 (0.0%)	1 (5.6%)	
Grade 2	1 (5.0%)	5 (27.8%)	
Grade 3	0 (0.0%)	2 (11.1%)	
Grade 4	0 (0.0%)	0 (0.0%)	

[2]: Pearson chi-square test/Fisher's exact test, log-rank test, $p<0.05$ was considered statistically significant.
VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor.

DISCUSSION

In this retrospective, real-world study, we compared continuation of anti-VEGF therapy as second-line treatment with switching to anti-EGFR therapy in patients with RAS wild-type mCRC who developed disease progression during first-line anti-VEGF-based treatment. The principal finding of our study was that there was no statistically significant difference between the two treatment strategies for second-line PFS2 and OS. Similarly, first-line PFS outcomes were comparable between the groups. These findings suggest that the optimal sequencing of biological agents in patients with RAS wild-type mCRC remains undefined, and they further support the ongoing debate in the current literature regarding the most effective treatment sequence. Because the objective of the present study was to compare alternative second-line biological treatment strategies rather than the isolated efficacy of individual second-line biological agents, survival endpoints were intentionally defined to reflect the clinical outcome of the entire treatment sequence. Accordingly, OS was calculated from initiation of first-line metastatic treatment. We acknowledge that this definition may be influenced by the duration of first-line treatment and by treatment response; however, we consider this approach more appropriate for evaluating the long-term outcomes associated with alternative second-line treatment strategies following first-line anti-VEGF-based therapy. Particularly in light of the heterogeneous results observed across randomized clinical trials and real-world studies, our findings underscore the importance of individualized treatment selection based on patient- and tumor-specific characteristics.

In our cohort, median PFS2 was 7.1 months in the anti-VEGF group and 10.0 months in the anti-EGFR group, while median OS was 28.2 months in the anti-VEGF group and 25.5 months in the anti-EGFR group. These results indicate no significant survival advantage for either continuing second-line anti-VEGF therapy or switching to anti-EGFR therapy. Our findings are consistent with those of the SPIRITT trial, which compared panitumumab-based and bevacizumab-based second-line strategies and reported no significant differences in PFS or OS between the two strategies.[14] In contrast, the PRODIGE-18 study demonstrated a numerically longer OS with continuation of bevacizumab than with switching to cetuximab following disease progression (15.8 vs. 10.4 months).[13] Although a numerically longer PFS2 was observed in the anti-EGFR arm in our cohort, this difference did not reach statistical significance. This discrepancy may be attributable to the limited sample size, selection bias inherent to the retrospective design, clinical and molecular heterogeneity of the patient population, and differences in treatment sequencing strategies.

One of the most notable clinical differences in our study was the distribution of primary tumor sidedness between the treatment groups. While the majority of patients in the anti-VEGF group had right-sided primary tumors (70.0%),

left-sided colon and rectal tumors predominated in the anti-EGFR group (77.8%). Primary tumor location is recognized as one of the most important prognostic and predictive factors guiding the selection of biological agents in RAS wild-type mCRC. Large meta-analyses and randomized studies have consistently demonstrated that anti-EGFR-based strategies confer a substantial survival advantage in left-sided RAS wild-type tumors, whereas anti-VEGF-based strategies may represent a more appropriate option for right-sided tumors.[15] In this context, the predominance of left-sided tumors in the anti-EGFR group may partially explain the numerically longer PFS2 observed in this cohort.

The higher rate of partial response achieved during first-line therapy in the anti-VEGF group may also support the clinical rationale for the "bevacizumab beyond progression" strategy. Previous studies have shown that continued VEGF inhibition after disease progression may provide an additional survival benefit for patients who derived clinical benefit from first-line bevacizumab therapy.[5]

Despite a higher rate of progressive disease during first-line treatment in the anti-EGFR group, the achievement of a median PFS2 of 10.0 months in the second-line setting is noteworthy. This finding suggests that targeting an alternative biological pathway following first-line angiogenesis inhibition may restore tumor sensitivity, particularly in molecularly selected subgroups. The potential benefit associated with switching from anti-VEGF to anti-EGFR therapy may be related to dynamic alterations in the tumor microenvironment and signaling networks induced by treatment pressure. Therefore, biologic-agent crossover may represent a rational therapeutic strategy to improve second-line treatment efficacy in selected patients with RAS wild-type disease.[5,15,16]

In the second-line treatment setting for mCRC, careful evaluation of toxicity profiles is as important as efficacy outcomes. Particularly in patients receiving palliative treatment, maintaining quality of life and treatment adherence are critical considerations influencing biological agent selection. In our study, skin rash was significantly more common in the anti-EGFR group (22.2%), consistent with the literature identifying cutaneous toxicity as the most characteristic class-specific adverse event associated with EGFR inhibitors.[2,10] Although anti-EGFR-related dermatologic toxicities are generally manageable, they may adversely affect daily activities and treatment compliance. Accordingly, patient education, early dermatologic assessment, and proactive supportive care strategies should be implemented at treatment initiation.[17]

In contrast, the higher incidence of peripheral neuropathy observed in the anti-VEGF group was likely attributable to the accompanying cytotoxic chemotherapy, particularly exposure to oxaliplatin. The absence of a substantial increase in severe toxicities related to biologic agents during continued anti-VEGF therapy suggests that this approach maintains a manageable safety profile. In patients with limited performance status or frailty, continuation of anti-VEGF therapy may represent a clinically preferable option because of its lower burden of cutaneous toxicity.[9,11]

Study Limitations

Several limitations of our study should be acknowledged. First, the retrospective single-center design inherently introduces the possibility of selection bias and incomplete registry-based data collection. The relatively limited sample size reduced the statistical power of the study and may have prevented clinically meaningful differences between the treatment strategies from reaching statistical significance. In addition, because biological agent selection was determined by physician preference rather than by randomization, heterogeneity in patient characteristics and treatment sequencing was unavoidable. The marked imbalance in primary tumor sidedness distribution and the heterogeneity of second-line chemotherapy regimens may have been confounding factors influencing survival outcomes. Because different chemotherapy backbones were used across the treatment groups, the observed clinical outcomes cannot be attributed solely to the biological agents; the potential contribution of the accompanying chemotherapy regimens should also be considered when interpreting the results. Because of the limited sample size, additional multivariable adjustments or subgroup analyses stratified by primary tumor sidedness were not considered statistically reliable, as these analyses would have led to substantial model instability and a high risk of overfitting. Therefore, the observed survival outcomes should be interpreted with caution, and the potential influence of tumor sidedness cannot be excluded. Comprehensive molecular profiling data, including MSI status, human epidermal growth factor receptor 2 amplification, neurotrophic tyrosine receptor kinase fusions, and detailed RAS submutation analyses, were not systematically available because molecular testing reflected routine clinical practice during the study period, thereby limiting a more refined evaluation of biologically distinct subgroups. Importantly, the absence of statistically significant differences between treatment groups should not be interpreted as evidence of therapeutic equivalence, as the study was not powered to detect or exclude clinically meaningful differences between the treatment strategies. Accordingly, our findings should be considered exploratory and hypothesis-generating, and require validation in larger prospective studies.

Nevertheless, the real-world nature of our study and the fact that it represents one of the limited analyses directly comparing second-line biological strategies following first-line anti-VEGF therapy enhance the clinical relevance of our findings.

CONCLUSION

In patients with RAS wild-type mCRC who developed disease progression during first-line anti-VEGF-based therapy, no significant differences in PFS or OS were observed between continuing anti-VEGF as second-line therapy and switching to anti-EGFR therapy. However, these findings should not be interpreted as evidence of therapeutic equivalence, given the study's retrospective design and limited sample size. Treatment decisions should therefore be individualized according to primary tumor sidedness, molecular characteristics, prior treatment response, toxicity profile, and patient-related factors. Although a numerically longer PFS2 was observed in the anti-EGFR group, this finding should be considered exploratory and hypothesis-generating. Larger prospective randomized studies are warranted to determine the optimal second-line biological treatment strategy in patients with RAS wild-type mCRC.

Ethics

Ethics Committee Approval: The study protocol was approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval number: 2026/136, date: 06.02.2026).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç., Concept: S.Ç., H.U.B., D.T., S.K., Design: S.Ç., H.U.B., D.T., S.K., Data Collection or Processing: S.Ç., E.N.S., İ.S.B., M.Ş., H.U.B., Analysis or Interpretation: S.Ç., E.N.S., İ.S.B., M.Ş., D.T., S.K., Literature Search: S.Ç., E.N.S., İ.S.B., M.Ş., D.T., S.K., Writing: S.Ç.

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