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Bevacizumab versus aflibercept with FOLFIRI after FOLFOX and bevacizumab in RAS mutant metastatic colon cancer a Turkish oncology group study

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We aimed to compare FOLFIRI and bevacizumab with FOLFIRI and aflibercept in terms of overall survival (OS), progression-free survival (PFS) and safety in patients with RAS-mutant metastatic colon cancer who progressed after first-line FOLFOX or XELOX and bevacizumab treatment. This retrospective study included 243 patients from 15 different centres in Turkey. The endpoints of the study were OS, PFS and safety and side effect outcomes. The median age of the patients included in the study was 60 (21–85) years. Of the patients enrolled in the study, 114 patients (46.9%) received aflibercept and 129 patients (53.1%) received bevacizumab. Median OS was 11.2 (95% CI: 9.1–13.2) months in patients receiving FOLFIRI + aflibercept and 14.1 (95% CI: 11.2–17.1) months in patients receiving FOLFIRI + bevacizumab. The median PFS was 5.7 (95% CI: 4.9–6.5) months in the aflibercept arm and 7.7 (95% CI: 7.1–8.3) months in the bevacizumab arm. Grade 3–4 side effects were observed in 58 (50.9%) patients in the aflibercept arm and 33 (25.6%) patients in the bevacizumab arm. As a result of our study, in patients with metastatic RAS-mutant colon cancer who progressed after first-line oxaliplatin-based doublet chemotherapy and bevacizumab, better OS and PFS results were obtained in patients receiving bevacizumab with FOLFIRI compared to patients receiving aflibercept with FOLFIRI. In addition, the side effect profile was more tolerable in the bevacizumab arm.

Keywords Metastatic colon cancer, Aflibercept, Bevacizumab, Real-life data

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide[1]. One of the most important factors in determining the prognosis of CRC is the stage of the disease and approximately 20% of patients with CRC at the time of diagnosis are metastatic[2,3].

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Fluoropyrimidines (fluorouracil [FU], capecitabine), oxaliplatin and irinotecan are the most preferred chemotherapies in the first-line treatment of metastatic CRC (mCRC). In the first-line treatment, fluorouracil and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (XELOX) or fluorouracil and irinotecan (FOLFIRI) doublet therapy is generally used, and fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI) triplet therapy may be preferred in some patient groups[4–7]. In addition to chemotherapy, monoclonal antibodies inhibiting vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) are used in the treatment of mCRC depending on the localisation of the primary tumour (right or left sided), RAS and BRAF mutations[8,9].

The frequency of KRAS or NRAS mutations in patients with mCRC is approximately 40–45%[10]. The frequency of BRAF mutation is around 6.5%[11]. In patients with these mutations, the addition of bevacizumab, a humanised monoclonal antibody that targets VEGF, to chemotherapy in first-line treatment has been shown to increase both overall survival (OS) and progression-free survival (PFS)[12]. In RAS-mutant patients, bevacizumab treatment was observed to be superior to anti-EGFR therapies[13]. In RAS-mutant patients, bevacizumab or aflibercept, another VEGF inhibitor, can be used again in case of progression after the use of bevacizumab in first-line treatment[14,15]. There is no randomised study comparing these two anti-VEGF drugs. In a retrospective study by Torregrosa et al. involving patients with both colon and rectal cancer and 81% had a RAS mutation, bevacizumab was found superior to aflibercept in terms of both OS and PFS[16].

In this study, we aimed to compare FOLFIRI and bevacizumab (FOLFIRI-B) with FOLFIRI and aflibercept (FOLFIRI-A) in terms of OS, PFS and safety in patients with RAS-mutant metastatic colon cancer who progressed after first-line FOLFOX or XELOX and bevacizumab treatment.

Methods

This retrospective study included 243 patients from 15 different centres in Turkey. Patients who applied to the centres between June 2012 and September 2023, who were over 18 years of age, who were diagnosed with RAS or BRAF-mutant metastatic colon cancer, who received bevacizumab treatment with FOLFOX or XELOX in first-line treatment, and who received aflibercept (First day 4 mg/kg) or bevacizumab (First day 5 mg/kg) treatment with FOLFIRI (First day irinotecan 180 mg/m², leucovorin 400 mg/m², fluorouracil 400 mg/m², then fluorouracil 2400 mg/m² continuous infusion over 46 h, every 2 weeks, 12 applications) after progression were included in the study. The physicians' choice of aflibercept or bevacizumab treatment was based on their clinical experience. Patients under 18 years of age, patients without RAS or BRAF mutations, non-metastatic patients, patients who did not receive bevacizumab treatment with XELOX or FOLFOX in first-line treatment, and patients who did not receive aflibercept or bevacizumab treatment with FOLFIRI in second-line treatment were excluded from the study. Clinical features, pathological features and laboratory results of the patients were obtained retrospectively from hospital files.

The primary endpoint of the study was OS, and secondary endpoints were PFS, safety and side effect outcomes. Accordingly, OS was defined as the time from the start of second-line treatment until death from any cause. PFS was considered as the time from the start of second-line treatment until progression or death from any cause. The time from the start of first-line treatment until progression was considered as PFS-1. Patients were evaluated every three months with the imaging modalities preferred by their physicians. Radiological treatment responses of the patients were recorded. Objective response rate (ORR) was defined as complete radiological response and partial radiological response. Disease control rate (DCR) was defined as patients who did not progress in post-treatment evaluations. Side effects of the patients during treatment were examined in detail. Common Terminology Criteria for Adverse Events (CTCAE) version 5 was used to evaluate the side effects of patients.

IBM SPSS version 25 was used for all statistical analyses. Histograms and the Shapiro-Wilk test were used to determine normal distribution. Normally distributed continuous variables were expressed as mean ± standard deviation, while non-normally distributed variables were expressed as median (min - max). Two group comparisons of continuous variables were performed using the Mann-Whitney U test. For categorical comparisons, the chi-square or Fisher exact test was used. Kaplan-Meier survival curves and Cox regression analysis were used for survival and prognostic factors. p value < 0.05 was considered significant.

Results

The median age of the patients included in the study was 60 (21–85) years. The median follow-up time from the time of diagnosis was 30.6 (95% confident interval [CI]: 27.2–34.0) months. Of the patients who participated in the study, 145 (59.7%) were male and 98 (40.3%) were female. Denovo metastatic disease was present in 87.2% of the patients. KRAS, NRAS and BRAF mutation was present in 88.1%, 9.5% and 2.4% of the patients, respectively. Of the patients enrolled in the study, 114 patients (46.9%) received aflibercept and 129 patients (53.1%) received bevacizumab. Baseline characteristics of the patients are shown in Table 1.

Patients in the FOLFIRI-A and FOLFIRI-B arms were compared according to age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, histological type of tumour, stage at diagnosis, mutation status, albumin levels and progression time on first-line treatment (PFS-1). According to this, no statistically significant difference was observed between the two groups (Table 2)

In the FOLFIRI-A group, 40 (35.1%) patients had metastasis in a single site and 74 (64.9%) patients had metastasis in multiple sites, while in the FOLFIRI-B group, 45 (34.9%) patients had metastasis in a single site and 84 (65.1%) patients had metastasis in multiple sites. There was no significant difference between the two groups ($p = 0.414$). The most common sites of metastasis in the FOLFIRI-A group were liver (74.5%), lung (44.7%) and peritoneum (28.7%), while similarly, the most common sites of metastasis in the FOLFIRI-B group were liver (61.2%), lung (43.7%) and peritoneum (32.0%).

Variables	*n* (%)
Age, years, median	60 (21–85)
≤60 years	124 (51.0%)
>60 years	119 (49.0%)
Sex	
Male	145 (59.7%)
Female	98 (40.3%)
Stage at diagnosis	
II	14 (5.8%)
III	17 (7.0%)
IV	212 (87.2%)
Histology	
Adenocarcinoma	215 (88.5%)
Mucinous adenocarcinoma or signet ring cell	28 (11.5%)
Surgery, primary ± metastasectomy	
Yes	138 (56.8%)
No	105 (43.2%)
Mutation	
K-RAS	214 (88.1%)
N-RAS	23 (9.5%)
BRAF	6 (2.4%)
MSI-H	12 (4.9%)
Adjuvant therapy	
Yes	31 (12.8%)
No	212 (87.2%)
PFS-1	
≤3 months	48 (19.8%)
>3 months	195 (80.2%)
2nd line treatment	
FOLFIRI + aflibercept	114 (46.9%)
FOLFIRI + bevacizumab	129 (53.1%)

Table 1. Baseline characteristics of the patients. *MSI-H* microsatellite instability-high, *PFS-1* progression-free survival-1.

When the responses of the patients to FOLFIRI-A or FOLFIRI-B treatments were evaluated, it was observed that 0.9% of the patients had a complete radiological response in the aflibercept arm and 3.9% of the patients had a complete radiological response in the bevacizumab arm. ORR was 41.1% in the aflibercept arm and 45.0% in the bevacizumab arm. DCR was 61.5% in the aflibercept arm and 71.3% in the bevacizumab arm (Table 3). When the reasons for discontinuation of the treatment of the patients were analysed, it was observed that 13.2% patients in the aflibercept arm completed treatment, 69.3% patients progressed, and 13.2% patients could not continue treatment due to toxicity. In the bevacizumab arm, 24.8% of the patients completed their treatment, 58.1% progressed, and 9.3% discontinued treatment due to toxicity (Table 4).

When treatment-related side effects were evaluated, neutropenia (26.3%), diarrhea (24.5%) and fatigue-asthenia (14.0%) were the most frequently observed side effects in the aflibercept arm. Similarly, the most frequently observed side effects in the bevacizumab arm were neutropenia (25.6%), diarrhea (23.3%) and fatigue-asthenia (17.1%). Grade 3–4 side effects were observed in 58 (50.9%) patients in the aflibercept arm and 33 (25.6%) patients in the bevacizumab arm. The side effects developed in patients are detailed in Table 5.

In the FOLFIRI-A group, 56 (45.9%) of the patients received treatment in the third-line or more, whereas in the FOLFIRI-B group, 66 (54.1%) of the patients received treatment in the third-line or more. There was no significant difference between the two groups ($p=0.798$). The most commonly used drug in third-line treatment was regorafenib. When the patients who received third-line treatment were analysed, 87.7% of the patients in the FOLFIRI-A group and 85.2% in the FOLFIRI-B group received regorafenib as third-line treatment. Other treatments used in the third line and the following lines were capecitabine monotherapy, capecitabine + temozolomide, FOLFOX or FOLFIRI rechallenge.

When the patients were analysed for OS, age ($p=0.759$), sex ($p=0.828$), histological type of tumour ($p=0.806$), presence of metastasis at the time of diagnosis ($p=0.167$), KRAS mutation ($p=0.341$), NRAS mutation ($p=0.554$), BRAF mutation ($p=0.446$), microsatellite instability (MSI) ($p=0.101$) and PFS-1 ($p=0.258$) did not affect OS. Localisation of the tumour (right-left) ($p=0.017$), albumin value ($p=0.004$) and aflibercept or bevacizumab in the second-line treatment ($p=0.006$) were statistically significantly affected OS. Multivariable analysis showed that tumour localisation ($p=0.037$), albumin value ($p=0.003$) and treatment ($p=0.031$) were

Variables	Aflibercept ($n=114$)	Bevacizumab ($n=129$)	p value
Age			
≤60 years	57 (50%)	67 (51.9%)	0.798
60 years	57 (50%)	62 (48.1%)	
Sex			
Male	70 (61.4%)	75 (58.1%)	0.694
Female	44 (38.6%)	54 (41.9%)	
ECOG			
0–1	97 (85.1%)	103 (79.8%)	0.315
2–4	17 (14.9%)	26 (20.2%)	
Histological type			
Adenocarcinoma	101 (88.6%)	114 (88.4%)	0.999
Non-adenocarcinoma	13 (11.4%)	15 (11.6%)	
At time of diagnosis			
Local	7 (6.1%)	18 (14.0%)	0.057
Metastatic	107 (93.9%)	111 (86.0%)	
Metastatic sites before treatment			
Single metastatic site	40 (35.1%)	45 (34.9%)	0.414
Multiple metastatic sites	74 (64.9%)	84 (65.1%)	
Primary tumor site			
Right	25 (22.5%)	40 (31.7%)	0.144
Left	86 (77.5%)	86 (68.3%)	
K-RAS mutation			
Yes	100 (87.7%)	114 (88.4%)	0.572
No	14 (12.3%)	15 (11.6%)	
N-RAS mutation			
Yes	10 (8.8%)	13 (10.1%)	0.381
No	104 (91.2%)	116 (89.9%)	
BRAF mutation			
Yes	4 (3.5%)	2 (1.6%)	0.423
No	110 (96.5%)	127 (98.4%)	
MSI status			
MSS	87 (94.6%)	92 (92.9%)	0.769
MSI-H	5 (5.4%)	7 (7.1%)	
No data	22	30	
Albumin			
≤4.0	47 (47.0%)	64 (51.2%)	0.423
>4.0	53 (53.0%)	61 (48.8%)	
No data	14	4	
PFS-1			
≤3 months	17 (14.9%)	31 (24.0%)	0.079
>3 months	97 (85.1%)	98 (76.0%)	

Table 2. The features of aflibercept and bevacizumab groups. *ECOG* Eastern Cooperative Oncology Group, *MSI* microsatellite instability, *MSI-H* microsatellite instability-high, *MSS* microsatellite stable, *PFS-1* progression-free survival-1.

independent risk factors affecting OS. When the same variables were analysed for PFS, it was observed that only the second-line treatment ($p=0.003$) was the independent risk factor affecting PFS. Multivariable analysis was not performed since it was the only factor statistically different for PFS (Table 6).

According to this analysis, median OS was 11.2 (HR: 0.68, 95% CI: 9.2–13.3) months in patients receiving FOLFIRI-A and 14.2 (95% CI: 11.2–17.2) months in patients receiving FOLFIRI-B (Fig. 1). The median PFS was 5.7 (HR: 0.66, 95% CI: 4.9–6.6) months in the aflibercept arm and 7.7 (95% CI: 7.1–8.3) months in the bevacizumab arm (Fig. 2).

Discussion

In our retrospective study, FOLFIRI-A treatment was compared with FOLFIRI-B in second line treatment in patients with RAS-mutant metastatic colon cancer who progressed after FOLFOX and bevacizumab treatment. As a result of our multicentric study, it was observed that OS and PFS results of bevacizumab were better than

Response	Aflibercept ($n=114$)	Bevacizumab ($n=129$)
Complete response	1 (0.9%)	5 (3.9%)
Partial response	39 (34.2%)	53 (41.1%)
Stable disease	29 (25.4%)	34 (26.3%)
Progressive disease	45 (39.5%)	37 (28.7%)
Objective response rate	40 (41.1%)	58 (45.0%)
Disease control rate	69 (61.5%)	92 (71.3%)

Table 3. Radiological treatment responses of aflibercept and bevacizumab groups.

Reasons	Aflibercept ($n=114$)	Bevacizumab ($n=129$)
End of treatment	15 (13.2%)	32 (24.8%)
Progression	79 (69.3%)	75 (58.1%)
Toxicity	15 (13.2%)	12 (9.3%)
Continues	5 (4.4%)	10 (7.8%)

Table 4. Reasons for discontinuation of treatment.

	Aflibercept ($n=114$)		Bevacizumab ($n=129$)	
Adverse event	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Anemia	11 (9.6%)	2 (1.8%)	15 (11.6%)	2 (1.6%)
Neutropenia	10 (8.8%)	20 (17.5%)	28 (21.7%)	5 (3.9%)
Thrombocytopenia	8 (7.0%)	4 (3.5%)	15 (11.6%)	4 (3.1%)
Nausea, vomiting	8 (7.0%)	5 (4.4%)	15 (11.6%)	4 (3.1%)
Diarrhea	20 (17.5%)	8 (7.0%)	20 (15.5%)	10 (7.8%)
Fatigue, asthenia	8 (7.0%)	8 (7.0%)	20 (15.5%)	2 (1.6%)
Neuropathy, myalgia	4 (3.5%)	2 (1.8%)	2 (1.6%)	2 (1.6%)
Constipation	2 (1.8%)	–	–	–
Hypertension	–	2 (1.8%)	–	2 (1.6%)
Mucositis	3 (2.6%)	–	2 (1.6%)	–
Rash	2 (1.8%)	–	–	–
Elevated liver function test	5 (4.4%)	–	–	–
Febrile neutropenia		1 (0.9%)		–
Gastrointestinal fistula		2 (1.8%)		
Acute kidney injury	–	–	–	1 (0.8%)
Pneumonia	–	–	–	1 (0.8%)
Pulmonary thromboembolism	–	2 (1.8%)	–	–
Sepsis	–	2 (1.8%)	–	–

Table 5. Treatment related adverse events.

aflibercept. Both ORR and DCR were higher in the bevacizumab arm. Fewer grade 3–4 side effects were observed with bevacizumab, and treatment discontinuation due to toxicity was more common in aflibercept arm.

Both the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines state that bevacizumab or aflibercept can be used in the second-line treatment of RAS-mutant colorectal cancer[3,17]. Therefore, the treatments received by the patients were selected by their physicians according to their clinical experience.

In the VELOUR study, the use of aflibercept with FOLFIRI was superior to the use of FOLFIRI alone in second-line treatment of patients who received oxaliplatin-based chemotherapy, 30% of whom received bevacizumab in the first-line setting[18]. In this study, median OS was 13.5 months and median PFS was 6.9 months. In our study, OS and PFS were shorter in patients using aflibercept in combination with FOLFIRI. The major factors in this difference are that the VELOUR study was a clinical trial and most of the patients did not receive bevacizumab treatment. In a retrospective study of 366 patients based on real life data conducted by Buchler et al. in the Czech Republic, median PFS was 5.6 months and median OS was 14.2 months in patients receiving chemotherapy and aflibercept in progression after chemotherapy and bevacizumab[19]. Ivanova et al. evaluated median OS and

Univariate analysis	*p* value	
Variables	**OS**	**PFS**
Age, ≤ 60 years vs. > 60 years	0.759	0.547
Sex, male vs. female	0.828	0.421
Histological type, adenocarcinoma vs. non-adenocarcinoma	0.806	0.078
At time of diagnosis, local vs. metastatic	0.167	0.180
Primary tumor site, right vs. left	**0.017**	0.150
KRAS mutation, yes vs. no	0.341	0.181
NRAS mutation, yes vs. no	0.554	0.268
BRAF mutation, yes vs. no	0.446	0.919
MSI status, MSS vs. MSI-H	0.101	0.585
Albumin, ≤ 4.0 vs. > 4.0	**0.004**	0.803
PFS-1, ≤ 3 months vs. > 3 months	0.258	0.842
FOLFIRI + bevacizumab vs. FOLFIRI + aflibercept	**0.006**	**0.003**
Multivariable analysis for OS		
Variables	**p value**	**HR (95% CI)**
Primary tumor site, right vs. left	**0.037**	**1.57 (1.03–2.41)**
Albumin ≤ 4.0 vs. > 4.0	**0.003**	**1.48 (1.04–2.10)**
FOLFIRI + bevacizumab vs. FOLFIRI + aflibercept	**0.031**	**0.59 (0.42–0.84)**

Table 6. Prognostic factors of overall survival and progression-free survival in patients. Significant values are in bold. *CI* confidence interval, *FOLFIRI* folinic acid + fluorouracil + irinotecan, *HR* hazard ratio, *MSI* microsatellite instability, *MSI-H* microsatellite instability-high, *MSS* microsatellite stable, *OS* overall survival, *PFS* progression-free survival, *PFS-1* progression-free survival-1.

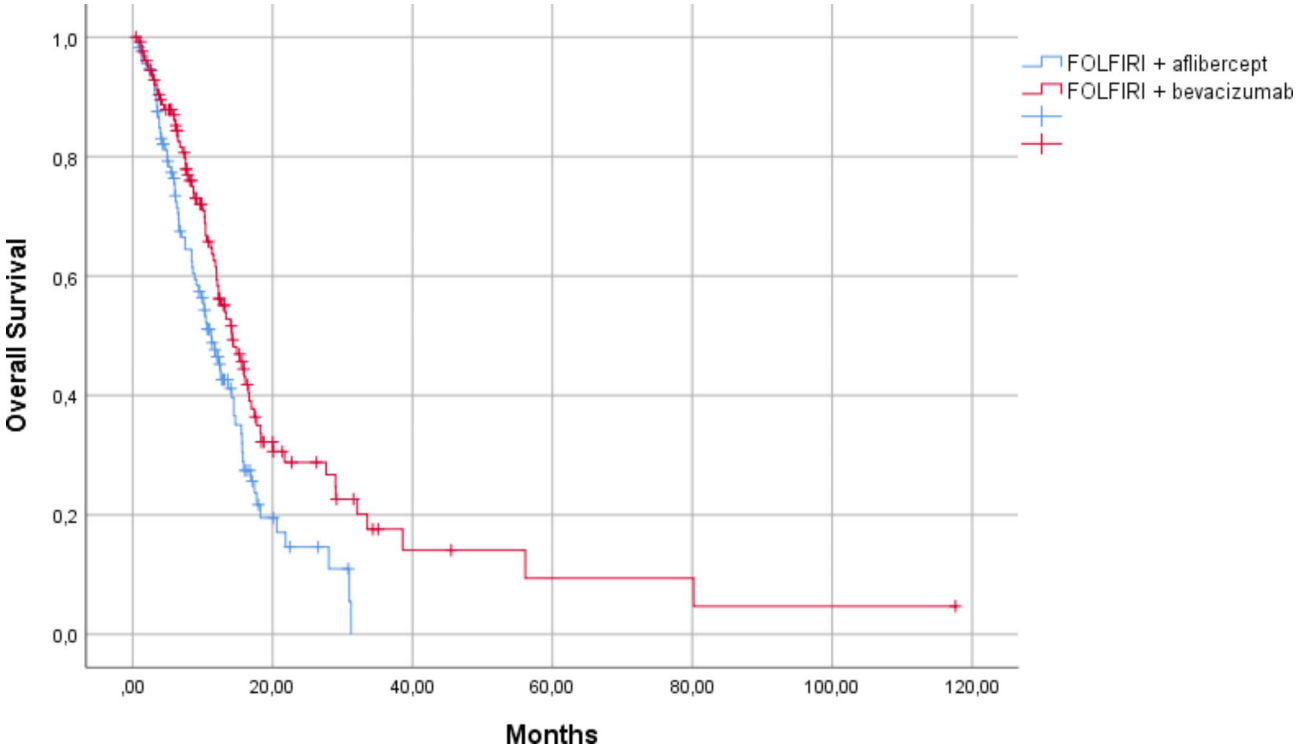


Fig. 1. Overall survival rates of aflibercept and bevacizumab groups.

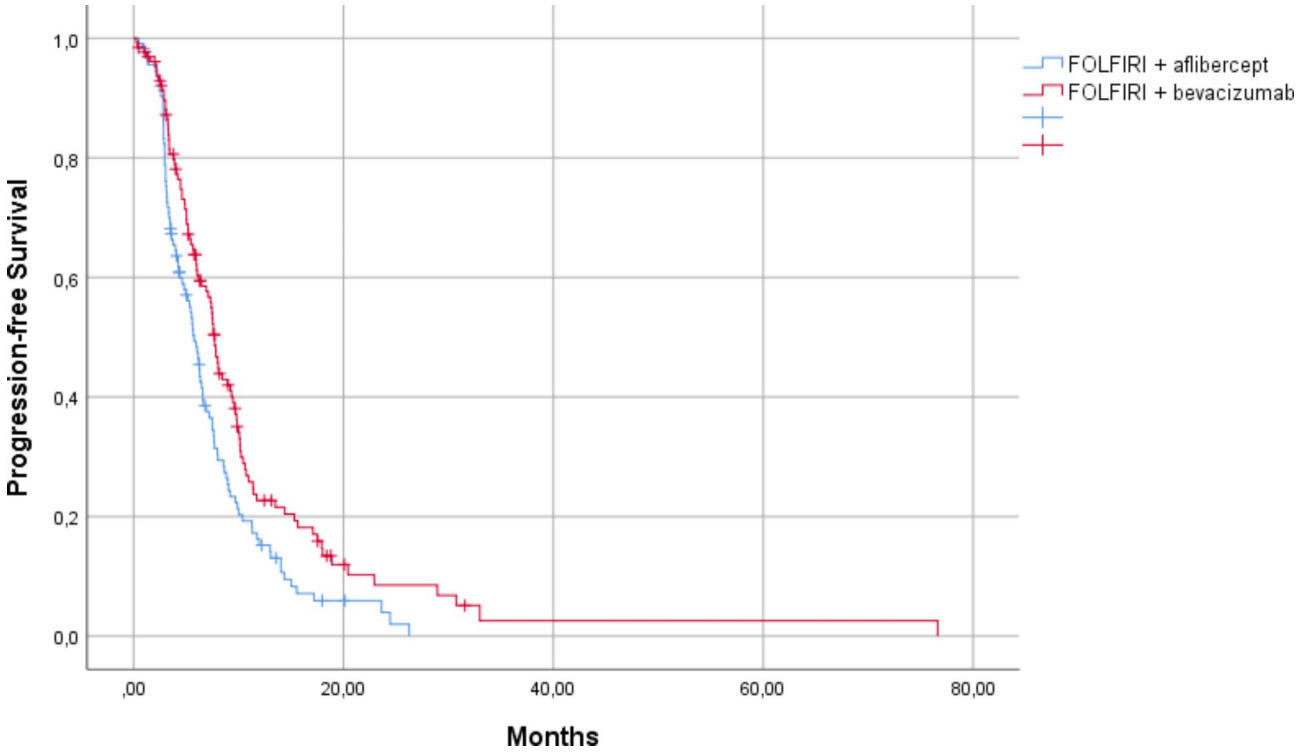


Fig. 2. Progression-free survival rates of aflibercept and bevacizumab groups.

PFS as 11.9 months and 4.4 months, respectively, in aflibercept real-life data of 218 patients in which 90% of the patients received bevacizumab in their previous treatment, and the results are more compatible with our study[20].

In the TML study, in which 820 patients participated, patients who progressed after receiving chemotherapy and bevacizumab in first-line treatment were compared with those who received chemotherapy alone or chemotherapy and bevacizumab[14]. As a result of this study, median OS was 11.2 months and PFS was 5.2 months in the bevacizumab arm, which was better than the group receiving chemotherapy alone. In our study, OS and PFS results were slightly higher compared to the TML study.

While ORR was 19% in the VELOUR study, ORR was 6% in the TML study. In our study, the ORR was 41.1% in the aflibercept arm and 45.0% in the bevacizumab arm. We think that such a difference occurred because our study was retrospective and the evaluations were made by the patient's personal physician and not evaluated with RECIST criteria as in clinical studies.

In our study, more grade 3–4 side effects were observed in the aflibercept arm and more patients discontinued treatment due to toxicity. When the side effect profiles of the patients were analysed, it was observed that there were fewer side effects than in the VELOUR and TML studies. It is thought that the main reason for this may be that our study was retrospective and not every side effect was recorded in the file records.

There is no large-scale randomised clinical trial on this subject. In a study by Yamazaki et al. in Japan comparing several angiogenesis inhibitors with FOLFIRI in patients who progressed after FOLFOX and bevacizumab treatment, a higher time to treatment failure (time from initiation of second-line chemotherapy to termination by any cause or death) was obtained with bevacizumab compared to aflibercept and ramicurumab[21]. In the Russian study by Fedyanin et al. no statistically significant difference in PFS or ORR was observed in patients receiving FOLFIRI-A or FOLFIRI-B in the second-line treatment of metastatic colon cancer. However, almost 40% of patients in both arms of this study were RAS or BRAF-mutant[22]. The largest study designed similarly to our study is the BEFLICO study, a multicentric retrospective study conducted by Torregrosa et al. in France[16]. In this study, similar to our study, OS, PFS, ORR and DCR results were better in patients using bevacizumab. Side effects were higher in the aflibercept arm. The differences of our study from this study are that all patients were RAS or BRAF-mutant, all patients received doublet therapy as first-line chemotherapy (in the BEFLICO study, approximately 10% patients received triplet therapy as first-line chemotherapy), and only patients with colon cancer were included in the study and patients with rectal cancer were excluded from the study.

The strength of our study is that it is a multicentric study and patients were recruited from many different parts of Turkey. The limitation of our study is that it is a retrospective study, side effects may not have been recorded regularly since screening was performed from file records.

Conclusion

As a result of our retrospective study, in patients with metastatic RAS-mutant colon cancer who progressed after first-line oxaliplatin-based doublet chemotherapy and bevacizumab, better OS, PFS, ORR and DRR results were obtained in patients receiving FOLFIRI-B compared to patients receiving FOLFIRI-A. In addition, the side effect

profile was more tolerable in the bevacizumab arm. Further randomised, prospective clinical trials are needed in this field.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to ethical reasons but are available from the corresponding author on reasonable request. Corresponding author SS has to be contacted in case of any queries or requirement of data.

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References

1. Sung, H. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**(3), 209–249 (2021).
2. Ciardiello, F. et al. Clinical management of metastatic colorectal cancer in the era of precision medicine. *CA Cancer J. Clin.* **72**(4), 372–401 (2022).
3. Benson, A. B. et al. Colon cancer, version 3.2024, NCCN clinical practice guidelines in oncology. *J. Natl. Compr. Cancer Netw.* **22**(2 d), e240029 (2024).
4. Goldberg, R. M. et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J. Clin. Oncol.* **22**(1), 23–30 (2004).
5. Colucci, G. et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J. Clin. Oncol.* **23**(22), 4866–4875 (2005).
6. Díaz-Rubio, E. et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. *J. Clin. Oncol.* **25**(27), 4224–4230 (2007).
7. Hurwitz, H. I. et al. Phase II randomized trial of sequential or concurrent FOLFOXIRI-bevacizumab versus FOLFOX-bevacizumab for metastatic colorectal cancer (STEAM). *Oncologist* **24**(7), 921–932 (2019).
8. Van Cutsem, E. et al. Cetuximab plus Irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J. Clin. Oncol.* **29**(15), 2011–2019 (2011).
9. Venook, A. P. et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA* **317**(23), 2392–2401 (2017).
10. Peeters, M. et al. Prevalence of RAS mutations and individual variation patterns among patients with metastatic colorectal cancer: a pooled analysis of randomised controlled trials. *Eur. J. Cancer* **51**(13), 1704–1713 (2015).
11. Yokota, T. et al. BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. *Br. J. Cancer* **104**(5), 856–862 (2011).
12. Hurwitz, H. et al. Bevacizumab plus Irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* **350**(23), 2335–2342 (2004).
13. Yin, J. et al. Prognostic and predictive impact of primary tumor sidedness for previously untreated advanced colorectal cancer. *J. Natl. Cancer Inst.* **113**(12), 1705–1713 (2021).
14. Bennouna, J. et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol.* **14**(1), 29–37 (2013).
15. Tabernero, J. et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur. J. Cancer.* **50**(2), 320–331 (2014).
16. Torregrosa, C. et al. FOLFIRI plus BEvacizumab or aFLIbercept after FOLFOX-bevacizumab failure for COlorectal cancer (BEFLICO): an AGEO multicenter study. *Int. J. Cancer* **151**(11), 1978–1988 (2022).
17. Cervantes, A. et al. Metastatic colorectal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* **34**(1), 10–32 (2023).
18. Van Cutsem, E. et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J. Clin. Oncol.* **30**(28), 3499–3506 (2012).
19. Buchler, T. et al. Sequential treatment with bevacizumab and aflibercept for metastatic colorectal cancer in real-world clinical practice. *Target Oncol.* **15**(2), 193–201 (2020).
20. Ivanova, J. I. et al. Real-world treatment patterns and effectiveness among patients with metastatic colorectal cancer treated with ziv-aflibercept in community oncology practices in the USA. *Med. Oncol.* **34**(12), 193 (2017).
21. Yamazaki, K. et al. Real-world evidence on second-line treatment of metastatic colorectal cancer using fluoropyrimidine, Irinotecan, and angiogenesis inhibitor. *Clin. Colorectal Cancer*. **20**(3), e173–e184 (2021).
22. Fedyanin, M. Y. et al. Efficacy and toxicity of aflibercept and bevacizumab in combination with FOLFIRI in second-line therapy for metastatic colon cancer: a retrospective multicenter study. *Surg. Oncol.* **11**(3–4), 11–17 (2022).

Author contributions

SS: Contributions to the conception, revising, final approval of the version to be published, agree to be accountable for all aspects of the workSNOC, DB, CE, FTK, MANS, YEA, TT, SY, SB, MMK, EB, NM, IVB, MA, KB, SA, AA, AB, FA, ES, OYB, AZB, SS, EA, YE: Contributions to the drafting the work, final approval of the version to be published, agree to be accountable for all aspects of the work.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

Ethical approval was obtained for the multicentric study from Ankara Bilkent City Hospital's Clinical Research Ethics Committee (Date: 03.07.2024 / No:24–349). All methods were performed in accordance with the relevant guidelines and regulations for this approval. Our Hospital's Clinical Research Ethics Committee decided that informed consent is waived due to retrospective study design.

Additional information

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