Uludağ Üniversitesi Tıp Fakültesi Dergisi
Journal of Uludağ University Medical Faculty
52, 1776017, 2026
DOI: https://doi.org/10.32708/uutfd.1776017

ORIGINAL RESEARCH

Efficacy and Safety of Aflibercept Treatment in Patients with Metastatic Colorectal Cancer: A Single-Center Experience*

N. Gül ADA TAK[1], Erdem ÇUBUKÇU[2], Ahmet Bilgehan ŞAHİN[2]

[1] Department of Internal Medicine, Bursa Buyukorhan Integrated State Hospital, Bursa, Türkiye.
[2] Department of Medical Oncology, School of Medicine, Bursa Uludag University, Bursa, Türkiye.

ABSTRACT

Colorectal cancer is one of the most common malignancies worldwide, and new treatment options are continually emerging. This study aimed to assess the effects and side effects of aflibercept, one of the current treatment options for the condition. We included fifty-two patients diagnosed with colorectal cancer at the Bursa Uludağ University Medical Oncology Department between January 2014 and December 2020. These patients either presented with metastasis at the time of diagnosis or developed it during follow-up and were subsequently treated with aflibercept. Two patients were excluded from the study due to irregular follow-up. Among the patients included, 74% had metastatic disease at diagnosis, and 70% had tumors located in the left colon. KRAS mutations were identified in 56% of the patients. Aflibercept was the most commonly preferred second-line treatment. The median progression-free survival (PFS) after treatment with aflibercept was 5.13 months, while the median overall survival (OS) was 11.9 months. No significant difference was observed in overall survival between patients receiving aflibercept as second-line treatment and those receiving it as later lines. The frequency of side effects was consistent with existing literature; notably, significant proteinuria was observed during treatment.

Keywords: Metastatic colorectal cancer. Aflibercept. VEGF inhibitors. Proteinuria. Side effects.

Metastatik Kolorektal Kanserli Hastalarda Aflibercept Tedavisinin Etkinliği ve Güvenliği: Tek Merkez Deneyimi

ÖZET

Kolorektal kanser, dünya çapında en sık görülen malignitelerden birisidir ve sürekli olarak yeni tedavi seçenekleri ortaya sunulmaktadır. Bu çalışma, mevcut tedavi seçeneklerinden birisi olan aflibercept tedavisinin etki ve yan etkilerini göstermeyi amaçlamaktadır. Çalışmamıza Ocak 2014 ve Aralık 2020 tarihleri arasında Bursa Uludağ Üniversitesi Tıbbi Onkoloji Anabilim Dalı'nda kolorektal kanser tanısı almış 52 hasta dahil edildi. Bu hastaların tamamında tanı anında veya takiplerde gelişen metastaz mevcuttu. 2 hasta takip aralıklarının düzensiz olması nedeni ile çalışmadan çıkartıldı. Dahil edilen hastaların %74'ünde tanı anında metastaz mevcuttu ve %70'inde tümör sol kolon yerleşimliydi. Çalışma grubunun %56'sında KRAS mutasyonu saptandı. İkinci basamak tedavide en sık tercih edilen tedavi ajanı aflibercept olarak bulundu. İkinci ve sonraki basamaklarda aflibercept tedavisi almak arasında genel sağkalımda anlamlı fark izlenmedi. Yan etki profili ve sıklığı literatür ile uyumluydu, özellikle proteinüri açısından anlamlı fark saptandı.

Anahtar Kelimeler: Metastatik kolorektal kanser. Aflibercept. VEGF inhibitörleri. Proteinüri. Yan etki.

Date Received: 1.September.2025
Date Accepted: 3.January.2026

* **If the article has been previously presented, information of the related meeting:** Presented as an Oral Presentation at the "Uludag Internal Medicine Congress" (06-09 March 2025, Bursa, Türkiye).

Dr. N. Gül Ada TAK
Department of Internal Medicine,
Bursa Buyukorhan State Hospital, Bursa, Turkey
16980, Buyukorhan, Bursa, Turkey
E-mail: ngada@uludag.edu.tr

AUTHORS' ORCID INFORMATION
N. Gül ADA TAK: 0000-0002-0449-2482
Erdem ÇUBUKÇU: 0000-0002-0070-0889
Ahmet Bilgehan ŞAHİN: 0000-0002-7846-0870

Colorectal cancer (CRC) is the second most common type of cancer in women and the third most common in men[1]. It ranks as the third most common cause of cancer-related deaths in both sexes[2]. The treatment approach for CRC typically depends on the stage of the disease, pathological features, microsatellite instability (MSI) status, potential side effects of treatments, patient performance status, and comorbidities[3]. In cases of localized CRC, the therapeutic approach primarily relies on curative surgical procedures, which may be complemented by adjuvant chemotherapy when indicated[4]. For patients diagnosed with metastatic CRC, the survival expectation, previously 5-6 months with supportive care, has now increased to an average of 30 months.

Currently, the five-year survival rate has reached approximately 60%[5].

Aflibercept, also referred to as AVE0005, VEGF-Trap, and Ziv-Aflibercept in the USA, is a recombinant fusion protein[6]. It is a 97-kDa homodimeric glycoprotein[7] that received FDA approval in 2012 for use in combination with FOLFIRI (5-FU, leucovorin, and irinotecan) in patients whose disease has progressed despite prior oxaliplatin-based therapy. In addition to being an inhibitor of the vascular endothelial growth factor (VEGF) pathway, aflibercept comprises the extracellular portions of both VEGFR-1 and VEGFR-2, binding to the Fc portion of human IgG1[9]. Its design allows it to block VEGF-A with high affinity. Patients undergoing aflibercept treatment have exhibited antiangiogenic side effects, such as hypertension, embolism, and thrombosis, as well as diarrhea, stomatitis, proteinuria, and myelosuppression[10].

Our study aims to examine the efficacy and the side effect profile of the received aflibercept in patients with metastatic CRC.

Material and Method

Study Population

We conducted a retrospective review of electronic medical records for patients admitted to the Department of Medical Oncology at Bursa Uludag University between January 2014 and December 2020 due to metastatic colorectal cancer (CRC). As shown in Table I, a patient flow diagram is included. Patients who were under 18 years of age or had incomplete follow-up data were excluded from the study.

Treatment Regimen

Aflibercept was administered in combination with standard chemotherapy regimens following routine clinical practice. The most commonly used regimen included FOLFIRI, which consists of irinotecan, 5-fluorouracil and leucovorin, along with aflibercept. Aflibercept was given intravenously at a dosage of 4 mg/kg every two weeks.

Data Collection

Demographic and clinical data were collected from electronic medical records, including age, sex, tumor location, surgical history, and laboratory parameters. Hematologic parameters, including hemoglobin levels, white blood cell count, neutrophil count, and platelet count, were recorded before the initiation of aflibercept treatment and during routine clinical follow-up visits. Spot urine protein measurements were taken prior to treatment initiation and during follow-up to monitor for treatment-related proteinuria. Genetic mutation profiles were assessed for KRAS and NRAS mutations, and, when available, BRAF mutations and MSI/MMR status were also evaluated.

Statistical Analysis

Progression-free survival (PFS) was defined as the duration from the start of aflibercept treatment until documented disease progression or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from initial diagnosis to death from any cause. Statistical evaluations were performed using IBM SPSS software (version 22). Continuous variables were summarized as medians, along with their corresponding minimum and maximum values, while categorical variables were presented as frequency distributions. Survival probabilities were estimated using the Kaplan-Meier method, and a p-value of less than 0.05 was considered statistically significant. These were compared between groups using the log-rank test.

Results

In this study, a total of fifty-two patients were evaluated, with two individuals excluded due to inadequate follow-up intervals. The demographic and clinical features of the remaining cohort are summarized in Table I. The median age at diagnosis was 62.25 years, with a broad range from 22 to 76 years, and 72% were male. Notably, 74% (n = 37) of the patients presented with metastatic disease at the time of initial diagnosis. Among the included cases, left-sided colon involvement was observed in 70% (n = 35), whereas right-sided involvement was identified in 26% (n = 13). Additionally, two patients (4%) exhibited tumors affecting both sides of the colon. The liver was identified as the most frequent site of visceral metastasis, highlighting the aggressive clinical behavior of the condition.

Upon examining the genetic data available for our cohort (Table I), we found that 56% (n = 28) of patients harbored KRAS mutations. Among those evaluated for microsatellite instability (MSI) and mismatch repair (MMR), 34% (n=17) were classified as microsatellite stable (MSS), while 4% (n=2) were identified with high microsatellite instability (MSI-H). For the cohort with right colon tumors, an alarming 53.8% (n=7) had metastases at diagnosis; of those initially non-metastatic, 15.4% (n=2) developed metastases during treatment. Conversely, in the left colon group, 82.9% (n = 29) were diagnosed with metastases, with 11.4% (n = 4) developing metastases during treatment, and 5.7% (n = 2) experiencing metastases without treatment. The differential distribution of disease at diagnosis, based on tumor location, was statistically significant (p = 0.048).

Table I. Clinicopathological characteristics

Parameter		N	%
Age	*Median (range), years*	62.25 (22-76)	
Gender	Female	14	28
	Male	36	72
BMI	*Mean (±sd), (kg/m2)*	26.70±5.02	
Metastasis status	*De novo metastatic*	37	74
	Non-metastatic > adjuvant therapy > metastatic	6	12
	Non-metastatic > follow-up without treatment > metastatic	6	12
	Missing data	1	2
Tumor localization	*Left colon*	35	70
	Right colon	13	26
	Left and right colon	2	4
Metastasis sites	*Liver*	44	88
	Lymph node	29	58
	Lung	26	52
	Bone	14	28
	Omentum	13	26
	Adrenal	2	4
	Ovary	2	4
KRAS	*Mutant*	28	56
	Wild	19	38
	Missing data	3	6
NRAS	*Wild*	39	68
	Mutant	5	10
	Missing data	6	12
MSI/ MMR	*MSS*	17	34
	MSI-H	2	4
	Missing data	31	62
BRAF	*Negative*	25	50
	Observation	25	50

BMI:body mass index. SD:standard deviation. KRAS:kristen rat sarcoma. NRAS: neuroblastoma rat sarcoma. MSI: microsatellite instability. MMR:mismatch repair. MSS:microsatellite stability. MSI-H:microsatellite instability high. BRAF:V-raf murine sarcoma viral oncogene homolog B

In the first-line setting, patients received standard chemotherapy regimens according to routine clinical practice, most commonly oxaliplatin-based combinations, such as FOLFOX or XELOX, with or without targeted agents including bevacizumab, cetuximab, and panitumumab. Aflibercept was most commonly administered as second-line therapy, predominantly in combination with FOLFIRI (54%), followed by third-line treatment (36%), with use extending up to the sixth treatment line (Table II).

Table II. Aflibercept treatment lines

Line	N =50	(%)
First	0	0
Second	27	54
Third	18	36
Fourth	1	2
Fifth	3	6
Sixth	1	2

Data are given as n%.

The median progression-free survival (PFS) time following aflibercept treatment was 5.13 months (Figure 1), while overall survival was 11.9 months (Figure 2). Survival analysis revealed no significant differences between patients receiving Aflibercept as a second-line treatment and those receiving it in subsequent lines (p = 0.084) (Figure 3). When assessing PFS by tumor location, patients with left colon involvement exhibited a survival time of 6.38 months, compared to 5.01 months in the right colon group; however, this difference did not achieve statistical significance (p>0.05) (Figure 4). Furthermore, a comparative analysis of RAS mutations revealed no significant differences in OS or PFS between the RAS mutant group (4.83 months) and the RAS wild group (5.5 months) (p>0.05) (Figure 5).

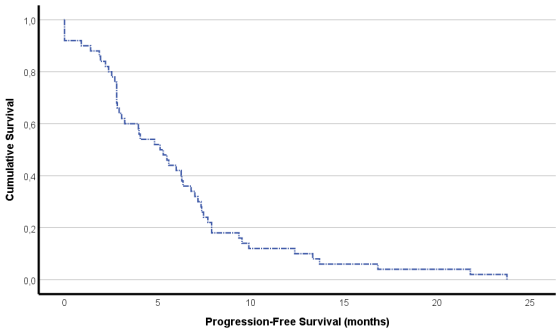

Figure 1.
Kaplan-Meier curve of progression-free survival

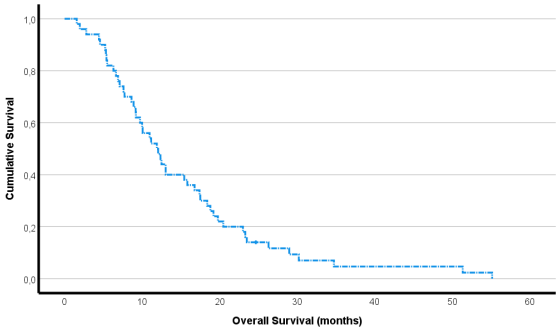

Figure 2.
Kaplan-Meier curve of overall survival

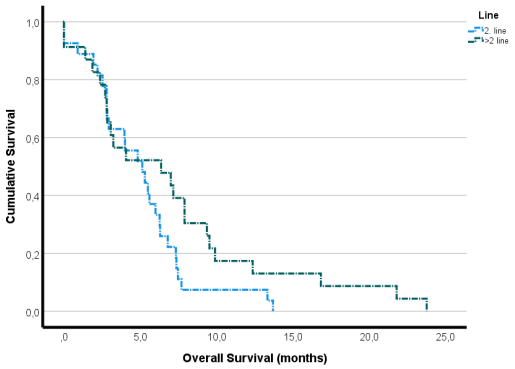

Figure 3.
Kaplan-Meier curve of overall survival according to lines of aflibercept treatment

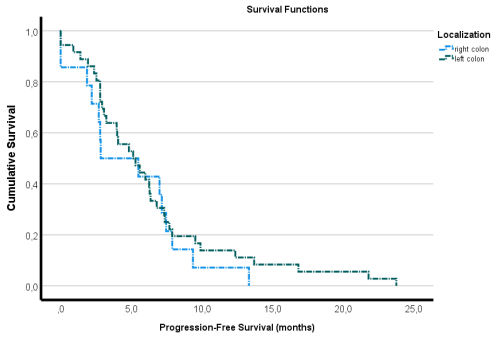

Figure 4.
Kaplan-Meier curve of progression-free survival according to tumor localization

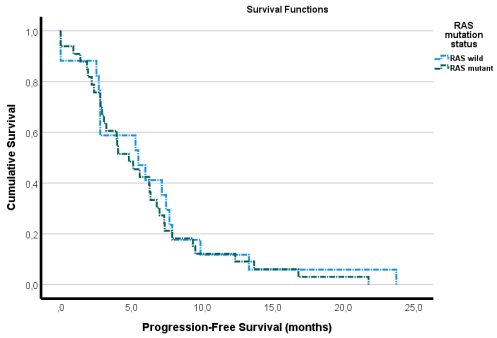

Figure 5.
Kaplan-Meier curve of progression-free survival according to RAS status

While 36% (n=18) of patients treated with aflibercept reported no drug-related side effects, 64% (n=32) experienced at least one adverse effect. Notably, neutropenia (neutrophils < 1.500) was identified in 40% (n = 20) of patients (Table III). A statistically significant difference was observed in the spot urine protein values of patients before and after aflibercept treatment, as determined by the McNemar test (p = 0.012) (Table IV).

Table III. Adverse events of aflibercept treatment

		N (50)	(%)
All adverse events		32	64
Side Effects	*Neutropenia*	20	40
	Stomachache	14	28
	Elevated LFT	10	20
	Diarrhea	10	20
	DVT	5	10
	Rectal bleeding	4	8
	Skin rash	3	6
	Perianal abscess	2	4
	Febrile neutropenia	2	4
	Hematuria	2	4
	Fournier gangrene	1	2
	Ventricular hemorrhage	1	2
	Allergy	1	2
	Gastrointestinal bleeding	1	2
	Psychiatric symptom	1	2
	Ileus	1	2
	Liver abscess	1	2

LFT: Liver function tests. DVT: Deep vein thrombosis. Data are given as n%.

Table IV. Proteinuria in aflibercept treatment

N=36	Before treatment (n)	After treatment (n)	
Spot urine protein negative	35	26	***P=0.012***
Spor urine protein positive	1	10	

Discussion and Conclusion

This study investigated the real-life data, efficacy, and side effect profiles of the aflibercept treatment group. Research has shown that treatments like aflibercept, which inhibit VEGF, can negatively affect hypertension management due to endothelial cell dysfunction, potentially leading to podocyte loss and resulting in proteinuria[11]. In our patient group, a significant difference was noted when comparing proteinuria levels before and during/after treatment.

A review of the existing literature indicated that PFS and OS were generally longer for patients receiving aflibercept as a second- or third-line therapy[12] although no significant differences were noted.

Upon examining both the VELOUR study and the ASQoP study, we found that various side effects, such as hypertension (HT), proteinuria, thromboembolic events, and hemorrhage associated with VEGF inhibition, were reported at rates higher than those associated with a placebo.[13] In addition, patients experienced diarrhea, neutropenia, stomatitis, and palmar-plantar skin reactions. Our evaluation of the treatment protocol concerning side effects revealed that 64% of the patient group reported complaints and findings during physical examinations after treatment with aflibercept. Neutropenia was the most frequently observed side effect, affecting 40% of patients. Severe neutropenia led to febrile neutropenia in two patients. Other commonly reported side effects included abdominal pain, elevated liver function tests (LFTs), diarrhea, and deep vein thrombosis (DVT). The frequencies of these side effects were consistent with those reported in the existing literature. We also noted occurrences of hemorrhage, gastrointestinal bleeding, hematuria, and DVT, all common complications following VEGF inhibition.

When our study group was analyzed by location, no significant difference was observed in PFS between patients with tumors in the right and left colon. However, PFS was determined to be 6.38 months for patients with left colon tumors and 5.01 months for those with right colon tumors. Existing literature also indicates that patients with tumors in the left colon generally have longer PFS and OS[14], with significant differences noted in some studies.

The VELOUR study demonstrated that adding aflibercept to FOLFIRI in the second-line treatment of patients with metastatic colorectal cancer significantly

improved both PFS and OS, especially for patients who had not previously received irinotecan-based treatment[15]. Among the participants in our study, the most commonly used regimen in the second-line treatment was FOLFIRI with aflibercept, accounting for 54%. In our patient group, aflibercept-containing regimens were utilized as a minimum for second-line and a maximum for sixth-line treatment options.

When comparing patients by RAS mutation status, we found that survival was shorter in the mutant group, as expected; however, this difference was not statistically significant. A review of the literature revealed mixed findings regarding mutation status, with some studies indicating longer overall survival in the mutant group, a finding similar to our own outcomes[14]. Nonetheless, our study did not reveal any significant differences. Among participants, aflibercept was administered as a second to a maximum of sixth-line treatment option. No significant differences were found between patients receiving aflibercept as their second treatment compared to those receiving it later in their treatment course.

The PFS time after aflibercept was 5.13 months, while the OS time was 11.9 months. In the VELOUR study on aflibercept, the PFS was reported to be 6.9 months, and the OS was 13.5 months[16]. Additionally, a multicenter study conducted in Turkey involving 433 patients showed a PFS of 6 months and an OS of 11.6 months[17], which is comparable to the results of our study. Our patient group exhibited a survival rate similar to that of the VELOUR study. Furthermore, in another multicenter study in the USA and Spain that included patients who had not previously received irinotecan-containing treatments, the OS for patients receiving aflibercept combined with FOLFIRI in the second line was reported as 11.9 and 12 months, aligning with our findings[12].

Our study has several limitations. These include its retrospective design, being conducted at a single center, a limited patient population, and the challenges of accurately assessing treatment-related adverse events using electronic medical records. Additionally, we were unable to systematically evaluate objective response rates because there was no standardized method for radiological response assessments in this retrospective cohort. Therefore, further prospective and multicenter studies are needed to validate and expand upon our findings.

Upon examining real-life data from a group of patients diagnosed with colorectal cancer, we found that many developed metastases either at diagnosis or during follow-up. Our analysis revealed that the effects of aflibercept treatment on efficacy, side effects, overall survival, and progression-free survival were comparable to those reported in the literature.

Aflibercept is a significant treatment option for both RAS-mutant and RAS-wild-type patients in second-line and later treatment settings. It is essential to monitor patients for proteinuria, a specific side effect, throughout their treatment.

Researcher Contribution Statement:
Idea and design: N.G.A.T., A.B.S.; Data collection and processing: N.G.A.T.; Analysis and interpretation of data: N.G.A.T., A.B.S., E.Ç.; Writing of significant parts of the article: N.G.A.B.T., A.B.S., E.Ç.
Support and Acknowledgement Statement:
Funding: No funding was received.
Acknowledgments: Not applicable.
Conflict of Interest Statement:
The authors declare that they have no competing interests.
Ethics Committee Approval Information:
Approving Committee: The clinical research ethics committee of Bursa Uludag University Faculty of Medicine
Approval Date : 21.02.2023
Decision No: 2023-4/15

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of ıncidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145–64.
3. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.
4. Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. Signal Transduct Target Ther. 2020;5(1).
5. Van Cutsem E, Cervantes A, Nordlinger B, et al. The ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(September):iii1–9.
6. Patel A, Sun W. Ziv-afibercept in metastatic colorectal cancer. Biol Targets Ther. 2013;8:13–25.
7. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15(2):171–85.
8. Ciombor KK, Berlin J, Chan E. Aflibercept. Clin Cancer Res. 2013;19(8):1920/5
9. Teng LS, Jin KT, He KF,et al. Clinical applications of VEGF-Trap (Aflibercept) in cancer treatment. J Chinese Med Assoc. 2010;73(9):449–56.
10. Van Cutsem E, Tabernero J, Lakomy R, 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. 2012;30(28):3499–506.
11. Piscitani L, Sirolli V, Di Liberato L, et al. Nephrotoxicity associated with novel anticancer agents (Aflibercept, dasatinib, nivolumab): Case series and nephrological considerations. Int J Mol Sci. 2020;21(14):1–18.
12. Ivanova JI, Saverno KR, Sung J, 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. 2017;34(12):1–10.
13. Syed YY, McKeage K. Aflibercept: A Review in Metastatic Colorectal Cancer. Drugs. 2015;75(12):1435–45.

14. Fernández MA, Martínez LN, Covela RM, et al. Efficacy and safety of FOLFIRI/aflibercept in second-line treatment of metastatic colorectal cancer in a real-world population: prognostic and predictive markers. Cancer Med. 2019;8(3):882–9.
15. Giordano G, Febbraro A, Venditti M, et al. Targeting angiogenesis and tumor microenvironment in metastatic colorectal cancer: role of aflibercept. Gastroenterol Res Pract. 2014;2014.
16. Riechelmann RP, Srimuninnimit V, Bordonaro R, et al. Aflibercept plus FOLFIRI for second-line treatment of metastatic colorectal cancer: observations from the global aflibercept safety and health-related quality-of-life program (ASQoP). Clin Colorectal Cancer. 2019;18(3):183-191.e3.
17. Erol C, Nahit Sendur MA, Bilgetekin I, et al. Efficacy and safety of folfiri plus aflibercept in second-line treatment of metastatic colorectal cancer: Real-life data from Turkish oncology group. J Can Res Ther 2022;18:S347-53