Original Article

# Efficacy and safety of folfiri plus aflibercept in second-line treatment of metastatic colorectal cancer: Real-life data from Turkish oncology group

Cihan Erol, Mehmet Ali Nahit Sendur, Irem Bilgetekin[1], Duygu Bayir Garbioglu[2], Jamshid Hamdard[3], Sinem Akbas[4], Mutlu Hizal[5], Cagatay Arslan[6], Alper Sevinc[7], Ahmet Kucukarda[8], Dilek Erdem[9], Seda Kahraman, Emre Cakir[10], Aykut Demirkiran[11], Sercan On[12], Izzet Dogan[13], Atike Pinar Erdogan[14], Sinan Koca[15], Pinar Kubilay[16], Orhan Onder Eren[17], Ebru Cilbir[18], Emir Celik[19], Murat Araz[11], Deniz Tataroglu Ozyukseler[20], Mahmut Emre Yildirim[20], Aykut Bahceci[21], HalilTaskaynatan[22], Abdilkerim Oyman[23], Gulhan Ipek Deniz[24], Serkan Menekse[25], Engin Kut[25], Ahmet Gulmez[26], Abdullah Sakin[27], Erdinc Nayir[28], Ramazan Acar[29], Erdem Sen[30], Ali Inal[31], Serdar Turhal[32], Ali Osman Kaya[33], Semra Paydas[34], Didem Tastekin[13],

## ABSTRACT

**Aims:** The addition of aflibercept to the fluorouracil and irinotecan (FOLFIRI) regimen significantly improved clinical outcomes in patients with metastatic colorectal cancer (CRC) previously treated with oxaliplatin. We aimed to investigate the efficacy and safety of second-line FOLFIRI and aflibercept combination in patients with metastatic CRC in real-life experience.

**Materials and Methods:** Four hundred and thirty-three patients who treated with FOLFIRI and aflibercept in the second-line were included in the study. The clinical and pathological features of the patients were recorded retrospectively. Survival (overall and progression-free survival [PFS]), response rates, and safety data were analyzed.

**Results:** The median age was 61. Majority of patients (87.5%) received first-line bevacizumab and 10.1% of patients received anti-epidermal growth factor receptor agents. About 80% of patients had KRAS, 18.6% of patients had NRAS, and 6.4% of patients had BRAF mutations. The median OS was 11.6 months (95% confidence interval [CI], 10.6–12.6) and the median PFS was 6 months (95% CI, 5.5–6.5). About 4.6% of patients had complete response and 30.6% of patients had partial response as best tumor response. Grade 1–2 toxicities were seen in 33.4% of patients, while grade 3–4 toxicities were recorded in 27% of patients. Eight patients (2%) died due to treatment toxicity.

**Conclusions:** Overall and PFS were similar in routine clinical practice compared to phase III pivotal VELOUR trial. However, response rates were found to be higher. It was observed that there were fewer adverse events compared to the VELOUR trial.

**KEY WORDS:** Aflibercept, clinical practice, colorectal cancer, real-life data, second-line

## INTRODUCTION

Colorectal cancer (CRC) is the third-most common cancer in the world and also the second cause of cancer-related deaths.[1] The rate of CRC decreased approximately 3% per year between 2011 and 2015 and CRC mortality decreased by 35% from 1990 to 2007.[2] These improvements are natural results of cancer prevention strategy and early detection with better treatment through screening.

Systemic therapy is the main treatment modality in metastatic CRC (mCRC). The chemotherapy is usually based on combined therapy with infusional fluorouracil and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI).[3] Sometimes, both oxaliplatin and irinotecan (FOLFOXIRI regimen) are used with fluorouracil.[4] Monoclonal antibodies targeting vascular endothelial growth factor (VEGF)[5] and epidermal growth factor receptor (EGFR)[5,6] are also used in the treatment of patients with

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**Ilhan Hacibekiroglu[10], Irfan Cincin[8], Ahmet Bilici[3], Nil Molinas Mandel[4], Didem Sener Dede, Muhammed Bulent Akinci, Berna Oksuzoglu[1], Dogan Uncu[5], Bulent Yalcin, Mehmet Artac[11]**

Department of Medical Oncology, Faculty of Medicine, Ankara Yildirim Beyazit University, [1]Department of Medical Oncology, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, [5]Department of Medical Oncology, Ankara City Hospital, [16]Department of Medical Oncology, Faculty of Medicine, Ankara University, [18]Department of Medical Oncology, Diskapi Training and Research Hospital, [29]Department of Medical Oncology, Gulhane Education and Research Hospital, Ankara, [2]Department of Medical Oncology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, [3]Department of Medical Oncology, Faculty of Medicine, Istanbul Medipol University, [4]Department of Medical Oncology, Istanbul American Hospital, [13]Department of Medical Oncology, Istanbul University, Institute of Oncology, [15]Department of Medical Oncology, Goztepe Training and Research Hospital, Istanbul Medeniyet University, [19]Department of Medical Oncology, Cerrahpasa School of Medicine, Istanbul University, [20]Department of Medical Oncology, Kartal Dr. Lutfi Kirdar Training and Research Hospital, University of Health Sciences, [23]Department of Medical Oncology, Umraniye Education and Research Hospital, [24]Department of Medical Oncology, Sisli Hamidiye Etfal Education and Research Hospital, [33]Department of Medical Oncology, Faculty of Medicine, Biruni University, Istanbul, [6]Department of Medical Oncology, Izmir Medical Park Hospital, [12]Department of Medical Oncology, Faculty of Medicine, Ege University, Izmir, [7]Department of Medical Oncology, Gaziantep Medical Park Hospital, [21]Department of Medical Oncology, Dr. Ersin Arslan Education and Research Hospital, Gaziantep, [8]Department of Medical Oncology, Faculty of Medicine, Trakya University, Edirne, [9]Department of Medical Oncology, Samsun Medical Park Hospital, Samsun, [10]Department of Medical Oncology, Faculty of Medicine, Sakarya University, Sakarya, [11]Department of Medical Oncology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, [14]Department of Medical Oncology, Faculty of Medicine, Manisa Celal Bayar University, [25]Department of Medical Oncology Manisa City Hospital, Manisa, [17]Department of Medical Oncology, Faculty of Medicine, Selcuk University, Konya, [22]Department of Medical Oncology, Necip Fazil City Hospital, Kahramanmaras, [26]Department of Medical Oncology, Faculty of Medicine, Inonu University, Malatya, [27]Department of Medical Oncology, Faculty of Medicine, Van Yuzuncu Yil University, Van, [28]Department of Medical Oncology, Mersin Medical Park Hospital, [31]Department of Medical Oncology, Mersin City Hospital, Mersin, [30]Department of Medical Oncology, Mehmet Akif Ersoy Hospital, Canakkale, [32]Department of Medical Oncology, Anadolu Medical Center, Kocaeli, [34]Department of Medical Oncology, Faculty of Medicine, Cukurova University, Adana, Turkey

**For correspondence:** Dr. Cihan Erol,
Department of Medical Oncology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, 06100, Çankaya, Ankara, Turkey.
E-mail: chan_erol@hotmail.com

metastases, according to RAS (KRAS and NRAS) and BRAF mutation status.

Several studies have proven that the use of anti-VEGF agents (bevacizumab, aflibercept, and ramucirumab) combined with chemotherapy is beneficial for overall survival (OS).[7-11] Combining bevacizumab with FOLFOX4 benefits OS in mCRC patients. The Eastern Cooperative Oncology Group (ECOG) 3200 study, a second-line study that included patients who progressed on irinotecan-based chemotherapy, had 3 arms; single-agent bevacizumab, bevacizumab combined with FOLFOX4, and FOLFOX4.[12] This study demonstrated that the concomitant use of FOLFOX4 and bevacizumab provides a significant clinical benefit in patients with mCRC. With this study, it has been shown that bevacizumab is effective in those who had not treated with anti-VEGF in the first-line setting and anti-VEGF rationality in the second-line therapy. An irinotecan and fluoropyrimidine combined regimen (usually FOLFIRI) is the preferred treatment option for patients with mCRC who are progressed with an oxaliplatin-based treatment in the first-line treatment.[3]

Aflibercept is an anti-vascular fusion protein, which binds to PGF (placental growth factor), VEGF-A and VEGF-B, inhibits interactions with VEGF receptors.[13] The VELOUR trial is a phase 3, randomized study that investigated the efficacy and safety of FOLFIRI and aflibercept in the second-line setting in the patients with mCRC who progressed after oxaliplatin-based treatment.[11] In this study, approximately 1200 patients were randomized 1:1 to either aflibercept or placebo in combination with FOLFIRI. There was a benefit in both OS (13.5 vs. 12.1 months; hazard ratio [HR]: 0.82) and progression-free survival (PFS) (6.9 vs. 4.7 months; HR: 0.76) with aflibercept compared to placebo.[11] Based on this trial, aflibercept was approved for use with FOLFIRI in the second-line treatment of mCRC patients treated with oxaliplatin-based chemotherapy, regardless of the use of bevacizumab in the previous line.

Randomized controlled trials are indispensable for the evaluation of medications. However, the clinical practice may differ from randomized controlled trials. Clinical trials often exclude elderly patients or those with comorbidities due to their strict criteria. Therefore, the efficacy and safety of treatments at the population not included in clinical trials have been evaluated in observational studies, and ultimately these studies provide information reflecting routine clinical practice.

This study was aimed to evaluate the real-life characteristics, efficacy, and safety of the patients with mCRC who treated FOLFIRI and aflibercept as a second-line treatment after an oxaliplatin-based therapy in the Turkish population.

## MATERIALS AND METHODS

### Study design

This is a retrospective, based on medical records study that aimed to determine the efficacy and safety of aflibercept

combined with FOLFIRI treatment as second-line therapy in Turkey population. Patients who received aflibercept (4 mg/kg) and the FOLFIRI regimen (irinotecan 180 mg/m$^2$, leukovorin 400 mg/m$^2$, 5-FU 400 mg/m$^2$ bolus, and 5-FU 2400 mg/m$^2$ infusion over 46 h), on day 1 every 2 weeks, were included to this study retrospectively regardless of the progression time from first-line oxaliplatin-based treatment. This study is a Turkey Oncology Group study. Data were collected from medical oncology clinics across Turkey. This study was deemed ethically appropriate at the Ankara City Hospital Ethics Committee meeting on 16/09/2020. The study was carried out under the principles of the Declaration of Helsinki (1964) and all its subsequent amendments. All investigators gave signed and written informed consent before the study began.

### Data collection

Clinical, demographic, and pathological data were obtained retrospectively from patient files and hospital medical record systems. Disease characteristics included RAS and BRAF mutation status, whether or not to receive adjuvant treatment, primary tumor location, whether primary tumor surgery has been performed, the number and locations of metastases before aflibercept, the type of treatment in the first-line were recorded. The duration and number of cycles with FOLFIRI plus aflibercept, disease progression, and survival status were recorded. Delays in treatment due to dose reduction and toxicity were noted.

### Inclusion criteria

Patients with histopathologically diagnosed mCRC, who progressed during or after oxaliplatin-based chemotherapy (regardless of the time elapsed since the initiation of treatment) in first-line therapy, and those who received FOLFIRI combined with aflibercept therapy in second-line therapy were included. All patients who received at least one cycle of FOLFIRI and aflibercept between 2012 and 2020 were included, regardless of their RAS and BRAF mutation status.

### Outcomes

OS and PFS were the primary outcomes. OS was defined as the time between the beginning of second-line therapy and death by any reason, and PFS was defined as the time between the beginning of FOLFIRI plus aflibercept and radiologic progression or death by any reason. Other outcomes were also assessed such as objective response rate (ORR) and adverse events (AEs). ORR was defined as the proportion of patients with radiologically complete or partial responses according to RECIST 1.1 criteria. Treatment-related toxicity was recorded according to CTCAE v4.03.

### Statistical analysis

Statistical analyzes were carried out using the IBM SPSS Statistics Version 25 program (SPSS Inc., Chicago, IL, USA). Clinical, pathological, and demographic variables were compared using the Chi-square test. Values of continuous variables were given as median, mean, minimum, and maximum values. Categorical variables were given as percentages and absolute frequencies. The Kaplan–Meier model was used to predict survival outcomes and 95% confidence intervals (CI). Comparing of the differences between survival curves was used the log-rank test with a two-sided significance level of 0.05.

## RESULTS

### Patients and disease characteristics

A total of 433 patients data which collected from 35 centers across Turkey were analyzed. The general condition of the majority of patients was good (ECOG-Performance Status [PS] 0–1: 89.5%). The median age of the patients at the diagnosis was 61 (18–85 years) [Table 1]. Most patients (87.5%) received first-line bevacizumab and 10.1% of patients received anti-EGFR agents. The primary tumor was operated on in 58.9% of patients and 18.2% of patients had metachronous metastasis [Table 1].

Among patients with pathological mutational data, for KRAS ($n$ = 421), 80% of patients had KRAS gene mutation, for NRAS ($n$ = 290), 18.6% of patients had NRAS gene mutations and for BRAF gene mutation ($n$ = 250), 6.4% of patients had BRAF mutation [Table 2]. Of the 421 patients whose mutation data were obtained, 58 were detected RAS wild (13.8%). Median treatment of FOLFIRI and aflibercept was 6 cycles for both of them.

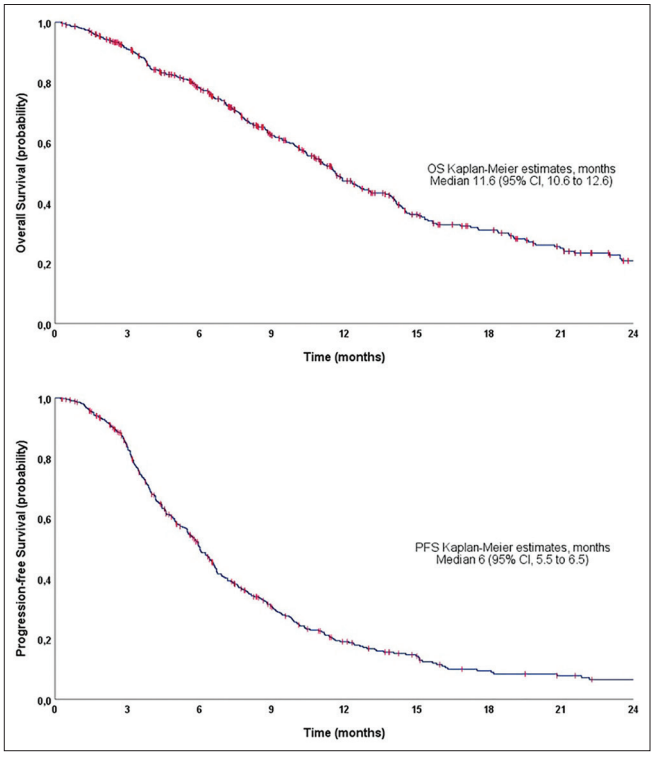


**Figure 1:** Kaplan–Meier curves of overall survival and progression-free survival (all population)

## Efficacy

The median PFS was 6 months (95% CI, 5.5–6.5) and median OS was 11.6 months (95% CI, 10.6–12.6) in all patients [Figure 1], with 23 months median follow-up. Similar to the whole population, median PFS was 6 months (95% CI, 5.5–6.5) and median OS was 11.6 months (95% CI, 10.2–13.1) in patients received bevacizumab in the first-line treatment and no significant difference compared to those who did not receive bevacizumab in first line ($P = 0.961$ and $P = 0.835$ for OS and PFS, respectively).

RAS mutation status had no effect on OS and PFS. The median OS in RAS mutant and wild patients were 11.9 months (95% CI, 10.2–13.7) and 11.5 months (95% CI, 9.8–13.2), respectively ($P = 0.369$). The median PFS in RAS mutant and wild patients were 6.2 (95% CI, 5.6–6.9) and 6.0 (95% CI, 4.7–7.2) months, respectively ($P = 0.289$). Similar to the whole population, RAS mutation status did not affect OS and PFS in patients who treated with bevacizumab in the first-line setting. In patients using bevacizumab in the first-line treatment, median OS in RAS mutant and wild patients were 11.7 (95% CI, 9.8–13.6) and 13.1 (95% CI, 0–27.6) months, respectively ($P = 0.424$). The median PFS in RAS mutant and wild patients were 6.1 (95% CI, 5.5–6.6) and 3.9 (95% CI, 1.3–6.6) months, respectively ($P = 0.362$).

As the best tumor response, 4.6% of the patients had a complete response, while 30.6% of the patients had a partial response [Table 3].

## Safety

AEs due to treatment were observed in 62.3% of patients. Grade 1–2 AEs were seen in 33.4% of patients, while Grade 3–4 AEs were reported in 27% of patients. AEs led to dose reduction of the treatment in 39.2% of patients and permanent discontinuation of therapy in 13.5% of patients. 2% of patients (8 patients) died due to the toxicity of treatment (Grade 5 AEs). The summary of the reported AEs is in Table 4.

The development of hypertension, a side effect of anti-VEGF therapy, was detected in 6.7% of patients, and the development of hypertension did not affect OS and PFS.

Discontinuation of treatment was most frequently due to disease progression (71.2%), and the second most common reason was toxicity (13.5%) [Table 5].

While 197 (51.2%) of 385 patients were receiving ≥3$^{rd}$ line treatment, the most common treatment given was regorafenib (38%). About 7.8% of patients received doublet treatment (fluoropyrimidine and oxaliplatin/irinotecan), 7% of patients received doublet plus bevacizumab, and 4.2% of patients received single-agent fluoropyrimidine treatment after FOLFIRI plus aflibercept. In patients who treated with ≥ third-line therapy, the median OS was

**Table 1: Patients demographics**

| | *n*=433, *n* (%) |
|---|---|
| Median age of diagnosis, years (range) | 61 (18-85) |
| Age <65 | 281 (64.9) |
| Male | 264 (61) |
| ECOG-PS before aflibercept | |
| 0-1 | 383 (89.5) |
| 2-3 | 45 (10.5) |
| Location of primary tumor | |
| Right colon | 96 (22.5) |
| Left colon | 331 (77.5) |
| Prior neoadjuvant/adjuvant chemotherapy | |
| Yes | 80 (18.5) |
| No | 353 (81.5) |
| Prior bevacizumab | |
| Yes | 379 (87.5) |
| No | 54 (12.5) |
| Number of metastatic sites before aflibercept | |
| 1 | 148 (34.3) |
| 2 | 171 (39.7) |
| 3 | 89 (20.6) |
| 4 | 19 (4.4) |
| 5 | 4 (0.9) |
| Metastasis sites before aflibercept | |
| Liver | 327 (75.9) |
| Lung | 215 (49.9) |
| Lymph nodes | 135 (31.3) |
| Peritoneum | 110 (25.5) |
| Brain | 4 (0.9) |
| Tumor presentation | |
| Synchronous | 354 (81.8) |
| Metachronous | 79 (18.2) |
| Primary tumor surgery | |
| Yes | 255 (58.9) |
| No | 178 (41.1) |
| First-line treatment | |
| mFOLFOX-6 plus bevacizumab | 314 (72.5) |
| XELOX plus bevacizumab | 50 (11.5) |
| mFOLFOX-6 plus cetuximab | 21 (4.8) |
| mFOLFOX-6 plus panitumumab | 20 (4.6) |
| XELOX plus cetuximab | 2 (0.5) |
| XELOX plus panitumumab | 1 (0.2) |
| Other | 25 (5.8) |
| The median cycle of first-line treatment | 12 |

ECOG-PS=Eastern Cooperative Oncology Group-Performance Status

**Table 2: Summary of RAS and BRAF mutation status***

| Mutation status | *n* (%) |
|---|---|
| KRAS | |
| Mutant | 338 (80.3) |
| Wild | 83 (19.7) |
| NRAS | |
| Mutant | 54 (18.6) |
| Wild | 236 (81.4) |
| BRAF | |
| Mutant | 16 (6.4) |
| Wild | 234 (93.6) |

*In patients with available biomarker data

**Table 3: Response rates**

| | *n* (%)* |
|---|---|
| ORR (complete and partial response) | 138 (35.2) |
| Complete response | 18 (4.6) |
| Partial response | 120 (30.6) |
| Stable disease | 106 (27) |
| Progressive disease | 148 (37.8) |

*In patients with available data. ORR=Objective response rate

**Table 4: The most common adverse events**

| Adverse event | All grades, *n* (%) | Grade 3-4, *n* (%) |
|---|---|---|
| Any | 263 (62.3) | 114 (27) |
| Neutropenia | 97 (22.4) | 36 (8.4) |
| Asthenia | 71 (16.4) | 26 (6) |
| Diarrhea | 68 (15.7) | 22 (5.1) |
| Hypertension | 29 (6.7) | 8 (1.9) |
| Stomatitis | 25 (5.8) | 5 (1.2) |
| Thrombocytopenia | 10 (2.3) | 2 (0.4) |
| Anemia | 8 (1.8) | 1 (0.2) |
| Proteinuria | 5 (1.1) | 1 (0.2) |
| GI perforation* | 3 (0.6) | 2 (0.4) |
| Other | 91 (21) | 26 (6.2) |

*Gastrointestinal perforation

**Table 5: Reasons for discontinuation of treatment***

| Reasons | *n* (%) |
|---|---|
| Progression | 289 (71.2) |
| Toxicity | 55 (13.5) |
| Continues | 40 (9.9) |
| Unknown | 10 (2.5) |
| Follow up without treatment | 6 (1.5) |
| Other | 4 (1) |
| Progression + toxicity | 2 (0.5) |

*In the available data

14.6 months (95% CI, 13.3–15.8), 7.3 months (95% CI, 6.1–8.4) for those who did not ($P \leq 0.001$).

## DISCUSSION

Randomized controlled trials are indispensable at determining the efficacy and safety of new treatments. However, clinical trials often have strict criteria and a narrow patient population. In routine clinical practice, many patient groups are not included in clinical trials. This retrospective study investigated effectiveness and safety in patients with mCRC who have treated with aflibercept in the second-line following after progressed prior oxaliplatin-based regimen in real-life in the Turkey population.

Similar to the cornerstone study of aflibercept, the VELOUR trial,[11] all patients treated with aflibercept and FOLFIRI in the second-line (as approved in Turkey) and required to be irinotecan-naïve. The median age and sex ratio is similar to the VELOUR trial. However, 87.5% of patients in our study were treated with bevacizumab before aflibercept, compared with only 30.4% in the VELOUR trial. In our study, the median OS and PFS were 11.6 and 6.0 months, respectively, in patients treated with bevacizumab in the first-line treatment. Similar to the VELOUR trial, there was no difference in OS and PFS compared with patients who did not treat with bevacizumab.

In our study, median OS (11.6 months) was slightly lower than the VELOUR trial (13.5 months) and PFS was similar (6 months vs. 6.9 in the VELOUR trial) which confirming the beneficial effect of aflibercept plus FOLFIRI in the second-line therapy in a real-world population. The lower OS can be explained, at least in part, by the slightly lower proportion of patients who received adjuvant therapy (indirectly primary operated) compared to the VELOUR trial in our study (18.5% vs. 26.5%). So we know, the prognosis of patients who received adjuvant therapy after primary surgery is better. Furthermore, while the proportion of patients with ECOG PS 0–1 was 89.5%, it was higher in the VELOUR study (97.8%). Moreover, the number of patients with single-site metastases in the VELOUR trial was higher than in our study (41.8% vs. 34.3%). Therefore, it can be said that our patients had a slightly worse clinical prognosis with higher tumor burden.

On the other hand, median OS is equivalent to real-world practices. In a study from the USA with 54 patients, the median OS was 11.9 months with FOLFIRI plus aflibercept in the second-line.[14] That study explores the real-life characteristics and treatment efficacy of patients receiving FOLFIRI plus aflibercept in the USA. They collected data of 218 patients who had disease progression after or on oxaliplatin-based therapy and treated with aflibercept as part of at least second-line treatment from the medical record. Similar to our study, majority of the patients were received bevacizumab (91.7%) before aflibercept, however, unlike our study, 59.6% of the patients were previously treated with irinotecan. Since no patient received irinotecan before aflibercept in our study. Similarly, in another study from Spain median OS was 12 months.[15] In this study, 78 mCRC patients who received FOLFIRI and aflibercept were analyzed. The patients progressed during oxaliplatin-based treatment in the first-line treatment or after oxaliplatin-based adjuvant therapy within <6 months, and the study was retrospective and observational.[15] This shows that real-life data are consistent with each other.

Median survival is also similar to other previously reported studies of other second-line anti-VEGF therapies used in patients with mCRC. Continuation of bevacizumab after disease progression has been shown to be beneficial in patients with mCRC as second-line therapy.[7,16] In the ML18147 randomized phase 3 trial, the median OS was 11.2 months.[7] Another phase 3 study (RAISE trial),[9] investigated the effect of the addition of ramucirumab to second-line chemotherapy on survival in patients with mCRC. In that study, patients progressed during or within 6 months after first-line combination therapy with bevacizumab and oxaliplatin-based chemotherapy. 83% of the patients had treated with bevacizumab at least 3 months in the first line. The median bevacizumab treatment duration was 6.9 months,[9] and the median OS was 13.3 months. 83% of patients in the RAISE trial treated with bevacizumab in the first line, while this rate was 87.5% in our study and 30% in the VELOUR trial. Although the usage of bevacizumab in first-line treatment did not statistically affect OS, in our study, the higher use of bevacizumab before aflibercept compared to the VELOUR trial may have led to a decrease in the benefit of aflibercept as it is possible to see resistance in anti-VEGF treatment for the second time.

In our study, the median PFS was almost equal to these three studies.[7,9,11] The median treatment cycle of our patients with aflibercept was also similar to the VELOUR trial (6 vs. 7 cycles).

In this analysis, ORR was 35.2% higher than the VELOUR trial (19.8%) and higher than those reported with other anti-angiogenic agents, the ML18147 trial (6%) and the RAISE trial (13.4%). The reason for the higher response rate may be that the patient, who is accepted as a partial response by clinicians, does not comply with the partial response criteria related to the RECIST criteria in clinical trials.

In our study, the treatment-related AEs rate was lower than reported in the VELOUR trial and real-world data.[14] In the VELOUR trial, the most reported AE was anemia (82.3%; Grade ≥3: 3.8%), and in the real-life experience,[14] the most common AEs were gastrointestinal (GI) origin (diarrhea, abdominal pain, stomatitis, 64.7%; Grade ≥3: 11.0%). In our study, the most common AEs were neutropenia (22.4%; Grade 3–4: 8.4%), asthenia (16.4%; Grade 3–4: 6%) and diarrhea (15.7%; Grade 3–4: 5.1%). Class-effect AEs were reported in only 6.7% of patients with newly developed hypertension, only 1.1% of proteinuria, and only 0.6% of patients with GI perforation.

These results should be evaluated carefully. Information obtained from clinical practices (observational studies) and randomized trials cannot be directly compared due to significant differences in patient selection. This study has several limitations. Some data may have been missed because the clinical data were obtained from hospital records and patient files retrospectively. These limitations may have caused the rate of AEs to be lower than expected. Furthermore, response assessment in clinical practice is not as stringent as in clinical trials. In this study, treatment response was evaluated by the patient's physician and the information was dependent on the physician. The higher response rate may be due to the flexibility that may be experienced in this process Finally, RAS and BRAF mutation status of the patients were not evaluated in the same center. This may have affected the results.

## CONCLUSIONS

The usage of anti-VEGF agents in combination with chemotherapy has provided a significant improvement in the treatment of mCRC. However, the superiority of aflibercept and other antiangiogenic agents over each other has not yet been clarified. There is a need to define predictive biomarkers. In this study, median OS was comparable to the VELOUR and other previously reported trials in the second-line of anti-VEGF treatment in mCRC. The rate of AEs in our study was lower than in other studies.

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### Conflicts of interest

There are no conflicts of interest.

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