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ORIGINAL ARTICLE

A retrospective analysis on first-line bevacizumab, cetuximab, and panitumumab-containing regimens in patients with RAS-wild metastatic colorectal cancer: A Collaborative Study by Turkish Oncology Group (TOG)

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Summary

Purpose: *To compare the efficacy and adverse effect profiles of the first-line treatment of patients with KRAS wild type metastatic colorectal cancer (CRC) in Turkey who were treated based on regimens including bevacizumab, cetuximab and panitumumab.*

Methods: *This retrospective multicenter observational study involved a total of 238 patients who received chemotherapy in combination with either bevacizumab or cetuximab or panitumumab as first-line therapy for KRAS wild-type metastatic colorectal cancer. Patients with full medical records having pathological diagnosis of CRC adenocarcinoma were included in the study. The demographic, laboratory, histopathological and clinical characteristics of the patients were determined, and three groups were compared based on the study variables.*

Results: *The mean age of the entire sample (n=238) was 58±11 years, 64% of which were male. The most frequent tumor localization was the rectum (37%) and G2 was the most common tumor grade (59.7%). About 63% of the patients had metastatic disease at diagnosis, with the most common site of metastasis being lung (14.7%) and liver (52.5%). Overall survival (OS) was 63.9%, while 1-, 3- and 5-year survival rates were 91.7, 56.6 and 36.9%, respectively. The expected mean survival was 49.1 months (95% CI, 42.9-55.3). The 1-, 3- and 5-year progression-free survival (PFS) rates following first-line treatment were 65.3, 26.1 and 5.6%, respectively, while disease free survival (DFS) in patients without metastasis at diagnosis was 68.5%. An analysis carried out disregarding which treatment the patients received (FOLFOX or FOLFIRI) revealed that a panitumumab-containing combination resulted in poorer prognosis compared to bevacizumab or cetuximab-containing combination (p<0.001). With regard to the adverse effect profile, the most common adverse effects were neuropathy and neutropenia in patients receiving FOLFOX-bevacizumab; neutropenia and perforation in patients receiving FOLFIRI-bevacizumab; rash and pustular infection in patients receiving FOLFIRI-cetuximab; and diarrhea in patients who received FOLFIRI-panitumumab combination.*

Conclusion: *is the first multicenter study performed in Turkey evaluating the response to treatment and adverse effects in patients with KRAS wild-type metastatic colorectal cancer.*

Key words: *bevacizumab, cetuximab, colorectal cancer, KRAS, metastatic, panitumumab*

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Introduction

The prognosis of patients with advanced stage colorectal cancer (CRC) is still poor, despite developments in surgical interventions and the subsequently applied chemotherapy modalities. CRC still ranks 2nd worldwide in terms of cancer-related mortality [1]. In Turkey, CRC, with an incidence of 8%, ranks 4th following lung (30%), breast (25%), and thyroid (12%) cancers, according to the Republic of Turkish Ministry of Health 2014 basic cancer data [2]. The largest study of CRC epidemiology in Turkey was published in 2015 by the Turkish Oncology Group following an evaluation of 968 cases [3].

The application of the monoclonal antibody bevacizumab, which is effective against vascular endothelial growth factor A (VEGF-A), independently of the KRAS mutation, in combination with fluoropyrimidine derivatives and irinotecan or oxaliplatin has been shown to offer a survival advantage [4,5]. Combining FOLFIRI and FOLFOX with the epidermal growth-factor antibodies (anti-EGFR) cetuximab and panitumumab, respectively, whose efficacy has been defined only in KRAS and NRAS wild-type cases, has also shown survival benefit [6,7]. Responses to anti-VEGF and anti-EGFR agents in KRAS-wild mCRC patients raised the question of which agent should be used as a priority, given that the different toxicity profiles of the three targeted agents change the risk/benefit ratio of the treatment. The efficacy of these three agents has never been evaluated prospectively before in a single study, although some head-to-head studies on the efficacy of bevacizumab (BEV), cetuximab (CET), and panitumumab (PAN) have been carried out for the reason stated above [8-10].

There is a lack of a large multicenter database in our country, despite the development of mCRC treatment modalities based on mutation analysis of KRAS, NRAS and BRAF. The purpose of this study was to evaluate the preferences made depending on whether the treatment options are met by our health care system and the treatments used by clinics and medical oncologists, and to compare the adverse effect profiles and duration of survival in patients with KRAS wild-type mCRC receiving regimens including BEV, CET, and PAN.

Methods

This was a retrospective multicenter observational study including a total of 238 mCRC patients, who had been diagnosed pathologically as CRC adenocarcinoma with KRAS wild-type and who received chemotherapy in combination with either BEV or CET or PAN as a first-line therapy and whose medical records could be obtained from 18 different centers.

Statistics

The analyses were carried out using SPSS v21 and $p<0.05$ was accepted as significant. Descriptive studies were analyzed using chi-square test, Student's t-test, and Mann-Whitney U-test, depending on group numbers. Univariate and multivariate analyses were carried out using Spearman's correlation analysis, while PFS and OS were evaluated with Kaplan-Meier method. In addition, since the number of patients and their duration of follow-up in PAN group was less than the other groups, comparisons among the groups were made using Bonferroni corrections, with $p<0.017$ accepted as significant.

Results

The patients were divided into 3 groups as BEV, CET and PAN groups. The regimens accepted by the centers were determined as standard when selecting the study patients. Anti-VEGF (bevacizumab) or

Table 1. Demographics and clinical characteristics of the cases

Characteristics	*n=238* *n (%)*
Age, years, mean±SD	58.0±10.9
Range	27-85
Gender	
Male	153 (64.3)
Female	85 (35.7)
Tumor location	
Cecum	13 (5.5)
Ascending colon	28 (11.8)
Descending colon	26 (10.9)
Rectosigmoid colon	66 (27.7)
Rectum	89 (37.4)
Transverse colon	16 (6.7)
Metastasis at diagnosis	150 (63.0)
Lung	35 (14.7)
Liver	125 (52.5)
Peritoneal carcinomatosis	32 (13.4)
Other (Bone,brain,ovary)	10 (4.2)
Chemotherapy regimen	
FOLFIRI	136 (57.1)
FOLFOX	102 (42.9)
Monoclonal antibody	
Bevacizumab	114 (47.9)
Panitumumab	32 (13.4)
Cetuximab	92 (38.7)
Kras status	
Wild	200 (84.0)
Codon 13 wild	8 (3.4)
Codon 12 and 13 wild	30 (12.6)

Table 2. Adverse effects profile by standard therapy

Adverse effects	*FOLFIRI (n=136)* *n (%)*	*FOLFOX (n=102)* *n (%)*	*p value*
Nausea-vomiting	65 (47.8)	40 (39.2)	0.187
Neutropenia	62 (45.6)	41 (40.2)	0.406
Diarrhea	53 (39.0)	34 (33.3)	0.371
Rash	56 (41.2)	30 (29.4)	0.062
Mucositis	46 (33.8)	29 (28.4)	0.376
Anemia	41 (30.1)	18 (17.6)	**0.027**
Neuropathy	21 (15.4)	28 (27.5)	**0.023**
Trombocytopenia	18 (13.2)	17 (16.7)	0.459
Hand-foot syndrome	11 (8.1)	9 (8.8)	0.840
Ileus	2 (1.5)	12 (11.8)	**<0.001**
Nail disorders	11 (8.1)	1 (1.0)	**0.013**
Febrile neutropenia	3 (2.2)	8 (7.8)	0.059
Constipation	4 (2.9)	3 (2.9)	0.371
Arrhythmia	6 (4.4)	0 (0.0)	**0.039**
Deep vein thrombosis	6 (4.4)	0 (0.0)	**0.039**
Subileus	5 (3.7)	1 (1.0)	0.242
Blood transfusion	2 (1.5)	4 (3.9)	0.406
Malignant hypertension	5 (3.7)	0 (0.0)	0.073
Acute renal failure	0 (0.0)	4 (3.9)	**0.033**
Bowel perforation	0 (0.0)	4 (3.9)	**0.033**

Bold numbers denote statistical significance

Table 3. Adverse effects profile by monoclonal antibody

Adverse effects	*Bevacuzimab (n=114)* *n (%)*	*Panitumumab (n=32)* *n (%)*	*Cetuximab (n=92)* *n (%)*	*p value*
Nausea-vomiting	54 (47.4)	10 (31.3)	41 (44.6)	0.266
Neutropenia	51 (44.7)†	4 (12.5)†‡	48 (52.2)‡	**<0.001**
Diarrhea	30 (26.3)†¶	16 (50.0)†	41 (44.6)¶	**0.006**
Rash	10 (8.8)†¶	20 (62.5)†	56 (60.9)¶	**<0.001**
Mucositis	37 (32.5)	8 (25.0)	30 (32.6)	0.695
Anemia	29 (25.4)	6 (18.8)	24 (26.1)	0.693
Neuropathy	25 (21.9)	3 (9.4)	21 (22.8)	0.238
Trombocytopenia	20 (17.5)	3 (9.4)	12 (13.0)	0.436
Hand-foot syndrome	6 (5.3)	2 (6.3)	12 (13.0)	0.121
İleus	8 (7.0)	3 (9.4)	3 (3.3)	0.348
Nail disorders	4 (3.5)	2 (6.3)	6 (6.5)	0.577
Febrile neutropenia	1 (0.9)¶	2 (6.3)	8 (8.7)¶	**0.016**
Dehydration	2 (1.8)	0 (0.0)	5 (5.4)	0.124
Constipation	5 (4.4)	0 (0.0)	2 (2.2)	0.241
Arrhythmia	6 (5.3)¶	0 (0.0)	0 (0.0)¶	**0.011**
Deep vein thrombosis	2 (1.8)	3 (9.4)	1 (1.1)	0.085
Subileus	1 (0.9)	0 (0.0)	5 (5.4)	0.058
Blood transfusion	1 (0.9)	0 (0.0)	5 (5.4)	0.058
Malignant hypertension	3 (2.6)	0 (0.0)	2 (2.2)	0.471
Acute renal failure	0 (0.0)¶	0 (0.0)	4 (4.3)¶	**0.021**
Bowel perforation	1 (0.9)†	3 (9.4)†‡	0 (0.0)‡	**0.010**
Pustular infection	0 (0.0)†	4 (12.5)†‡	0 (0.0)‡	**<0.001**
Epistaxis	3 (2.6)	0 (0.0)	0 (0.0)	0.108
Proteinuria	1 (0.9)	0 (0.0)	1 (1.1)	0.740
Pulmonary embolism	2 (1.8)	0 (0.0)	0 (0.0)	0.227

†Bevacizumab vs Panitumumab (p<0.05), ‡Panitumumab vs Cetuximab (p<0.05), ¶Bevacizumab vs Cetuximab (p<0.05). Bold numbers denote statistical significance

anti-EGFR (cetuximab/panitimumab) were added to either FOLFIRI or FOLFOX combinations. The demographic, laboratory and clinical characteristics of the patients were determined and the study variables were compared for the three groups.

The clinical and demographic characteristics of the patients are shown in Table 1. The median age and gender distribution of the patients and the rates of rectal cancer were compatible with the previous study performed in this country [3].

Standard FOLFOX and FOLFIRI combinations and the targeted monoclonal antibodies were evaluated for adverse effects (Tables 2 and 3, respectively).

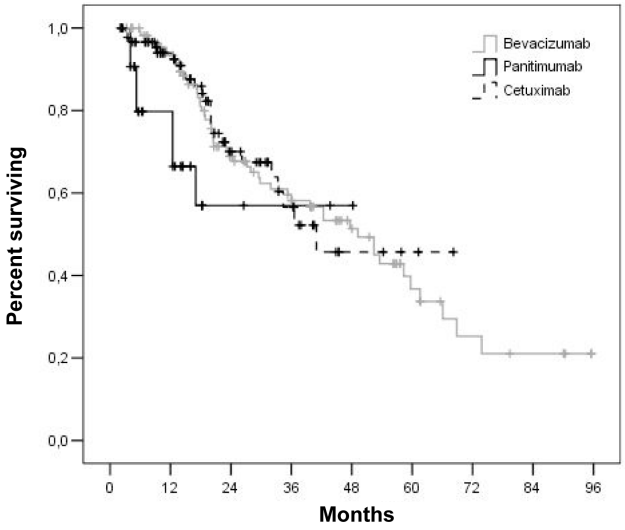

Figure 1. Kaplan-Meier overall survival of the BEV, CET and PAN groups (p=0.033).

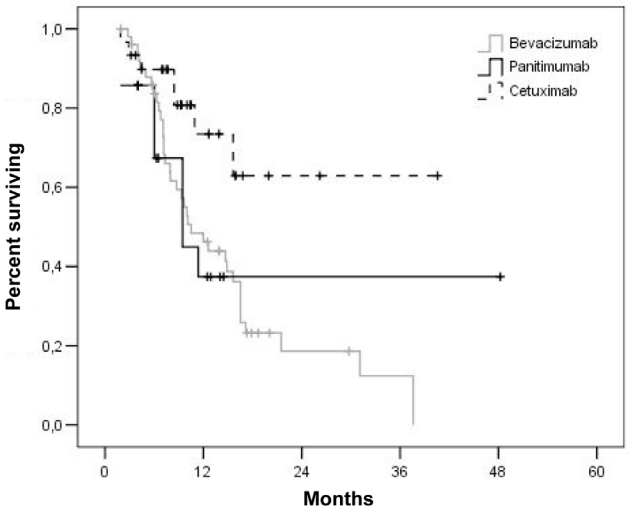

Figure 2. Kaplan-Meier progression-free survival curves of the FOLFOX-BEV, FOLFOX-CET and FOLFOX-PAN groups (p=0.016).

Table 4. Evaluation of the effects of categorical variables on overall survival using Kaplan-Meier survival analysis

Variables	*Number of cases*	*Event*	*Survival*	*Survival rates (%)*			*Survival time*	*Log - Rank*	*p value*
	(n)	*(n)*	*(n)*	1 year	3 years	5years			
Gender								1.109	0.292
Male	153	56	63.4	91.1	53.1	34.5	47.7 (39.8-55.7)		
Female	85	30	64.7	92.6	62.7	43.2	51.1 (42.1-60.1)		
Metastasis at diagnosis								20.854	**<0.001**
No	88	27	69.3	96.6	77.1	62.3	59.4 (50.9-67.9)		
Yes	150	59	60.7	88.2	36.6	16.8	37.7 (30.3-45.1)		
Lung met diagosis								18.144	**<0.001**
No	203	66	67.5	93.3	63.5	41.4	52.8 (46.0-59.5)		
Yes	35	20	42.9	81.6	15.1	-	22.5 (18.1-26.9)		
Liver met diagnosis								21.570	**<0.001**
No	113	33	70.8	96.3	73.8	57.8	57.6 (49.6-65.6)		
Yes	125	53	57.6	87.2	34.6	16.2	36.4 (28.6-44.3)		
Treatment								6.819	**0.033**
Bevacuzimab $^{\$\$}$	114	52	54.4	93.4	58.2	36.7	50.0 (42.7-57.2)		
Panitumumab $^{\$\$\ \#\#}$	32	10	68.8	79.8	57.0	-	31.7 (23.2-40.2)		
Cetuximab $^{\#\#}$	92	24	73.9	93.9	56.6	45.7	44.5 (37.2-51.7)		
1st line treatment response								3.048	0.081
Other	225	83	63.1	91.2	55.4	33.9	46.3 (40.3-52.2)		
Complete response	13	3	76.9	100.0	77.8	77.8	73.2 (52.7-93.8)		
Total	238	86	63.9	91.7	56.6	36.9	49.1 (42.9-55.3)	-	-

$^{\$\$}$ Bevacizumab vs Panitumumab (p=0.017), $^{\#\#}$ Panitumumab vs Cetuximab (p=0.039). Bold numbers denote statistical significance

The more notable adverse effects were compatible with findings in literature when the treatment combinations were analyzed. The main adverse effects were neutropenia and perforation in patients receiving FOLFIRI-BEV [4]; neuropathy and neutropenia in patients receiving FOLFOX-BEV [5]; rash, pustular infections, and diarrhea in patients receiving FOLFIRI-CET [8]; and diarrhea in patients receiving FOLFIRI-PAN [9].

The OS rate was 63.9% for all patients, with 1-, 3- and 5-year overall survival rates being 91.7, 56.6 and 36.9%, respectively. The expected mean survival was 49.1 months (95% CI, 42.9-55.3, Table 4). In all cases, the 1-, 3- and 5-year PFS rates

Table 5. Evaluation of the monoclonal agents and treatment regimens on progression-free survival

	Number of cases (n)	*Event (n)*	*Survival time months (95% CI)*	*Log rank*	*p value*
Bevacizumab				1.379	0.240
FOLFIRI	63	49	18.4 (14.6-22.3)		
FOLFOX	51	38	15.0 (11.6-18.4)		
Panitumumab				1.747	0.186
FOLFIRI	11	2	31.4 (17.5-45.3)		
FOLFOX	21	10	22.4 (12.2-32.6)		
Cetuximab				7.042	**0.008**
FOLFIRI	62	39	18.0 (11.7-24.3)		
FOLFOX	30	7	29.1 (21.6-36.5)		
FOLFIRI				4.447	0.108
Bevacizumab	63	49	18.4 (14.6-22.3)		
Panitumumab	11	2	31.4 (17.5-45.3)		
Cetuximab	62	39	18.0 (11.7-24.3)		
FOLFOX				7.698	**0.016**
Bevacizumab	51	38	15.0 (11.6-18.4)		
Panitumumab	21	10	22.4 (12.2-32.6)		
Cetuximab	30	7	29.1 (21.6-36.5)		
Total	238	145	19.8 (16.8-22.9)	-	-

Bold numbers denote statistical significance

Table 6. Evaluation of the monoclonal agents and treatment regimens on overall

Variables	*Number of cases*	*Event*	*Survival*	*Survival rates (%)*			*Survival time*	*Log - Rank*	*p value*
	(n)	*(n)*	*(n)*	1 year	3 years	5years			
Bevacizumab								2.466	0.116
FOLFIRI	63	28	55.6	95.1	64.5	42.9	54.6 (45.1-64.1)		
FOLFOX	51	24	52.9	91.2	48.6	27.9	39.1 (31.8-46.4)		
Panitumumab								5.306	**0.021**
FOLFIRI	11	0	100.0	100.0	100.0	-	-		
FOLFOX	21	10	52.4	70.6	42.4	-	26.8 (16.0-35.5)		
Cetuximab								4.835	**0.028**
FOLFIRI	62	15	75.8	96.4	65.8	52.3	48.2 (40.0-56.3)		
FOLFOX	30	9	70.0	88.7	26.6	-	26.0 (19.9-32.0)		
Folfiri								1.463	0.481
BEVACIZUMAB	63	28	55.6	95.1	64.5	42.9	54.6 (45.1-64.1)		
PANITUMUMAB	11	0	100.0	100.0	100.0	-	-		
CETUXIMAB	62	15	75.8	96.4	65.8	52.3	48.2 (40.0-56.3)		
Folfox								10.369	0.006
BEVACIZUMAB †	51	24	52.9	91.2	48.6	27.9	39.1 (31.8-46.4)		
PANITUMUMAB †	21	10	52.4	70.6	42.4	-	26.8 (16.0-35.5)		
CETUXIMAB	30	9	70.0	88.7	26.6	-	26.0 (19.9-32.0)		
Total	238	145	39.1	53.4	19.6	13.1	19.8 (16.8-22.9)	-	-

† Bevacizumab vs Panitumumab was statistically significant (p=0.003). Bold numbers denote statistical significance

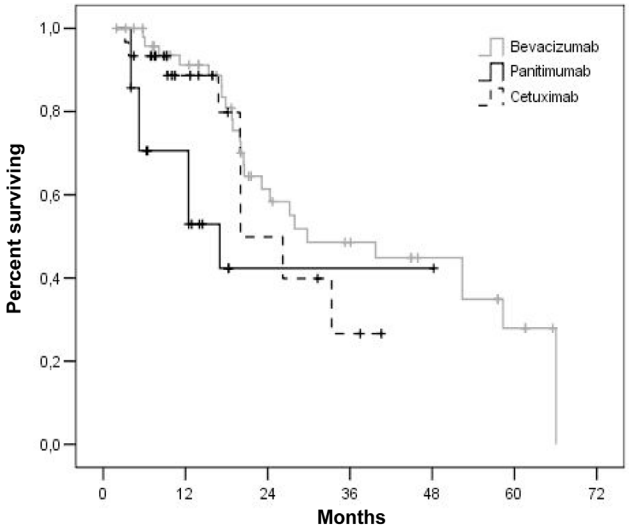

Figure 3. Kaplan-Meier overall survival curves of the FOLFOX-BEV, FOLFOX-CET and FOLFOX-PAN groups (p=0.006).

following first-line treatment were 65.3, 26.1 and 5.6%, respectively, and DFS in patients without initial metastasis was 68.5%. That said, the prognosis was found to be poor in terms of OS in patients who received the PAN combination compared to the patients receiving BEV or CET containing combinations (p=0.017 and p=0.039, respectively, Table 4, Figure 1). Univariate analysis revealed that the presence of initial metastasis, lung metastasis, and liver metastasis at the time of diagnosis had a negative effect on prognosis (p<0.001) (Table 4).

Among the targeted agents, patients who received FOLFOX-BEV showed better PFS than those receiving FOLFOX-PAN (p=0.016), with a similar PFS in those treated with FOLFOX-CET (p=0.148; Table 5; Figure 2). OS was found to be higher in the group receiving FOLFOX-BEV than those treated with FOLFOX-PAN or FOLFOX-CET treatments (p=0.006, survival was 39.1 months, 26.8 months and 26.0 months, respectively) (Table 6; Figure 3). No differences in PFS or OS were observed among the BEV, CET, and PAN groups in combination with FOLFIRI (p=0.108 and p=0.481, respectively) (Tables 5 and 6).

FOLFOX-CET provided better PFS in left colon tumors (p=0.042), while no difference was observed in terms of OS (p=0.205).

Discussion

Demonstration of survival advantages of anti-VEGF (bevacizumab)-containing chemotherapy regimens in patients with mCRC a decade ago, and the subsequent FDA approval of both irinotecan and oxaliplatin combinations have enlightened the way of the use of new targeted agents [4,11] and anti-EGFR agents cetuximab and panitumumab also received approval following bevacizumab in the treatment of mCRC [7,12].

Treatment with only 5-fluorouracil in cases of mCRC results in less than one year of OS, while the addition of anti-VEGF or anti-EGFR agents to oxaliplatin- or irinotecan-based treatment regimens provides an increased survival of up to 30 months [7,8,10].

KRAS exon 2-4 and NRAS exon 2-4 mutations, which are present in 50% of patients with mCRC, prevent the application of anti-EGFR agents [8,13,14]. The negative effect of the presence of KRAS and NRAS mutations on PFS and OS has been demonstrated in a meta-analysis [15]. Changes in tumor characteristics due to KRAS mutations can turn KRAS mutations into a prognostic factor, while the use of anti-EGFR regimens prior or subsequent to the anti-VGEF treatments in the treatment of KRAS-wild type metastatic patients may increase the survival rates. Furthermore, the addition of anti-EGFR agents to KRAS and NRAS mutant cases has been shown to have potential effect to shorten the duration of survival [7].

In the FIRE-3 trial comparing FOLFIRI-BEV versus FOLFIRI-CET as first-line treatments against mCRC, the median OS was 25 and 28.7 months, respectively [8], although no significant difference was found between these two groups in the present study. In the PEAK study, the highest OS of 43.4 months was achieved with FOLFOX-PAN treatment in left colon tumors, while the median OS was 34.2 months in all cases including both right- and left-colon tumors treated with FOLFOX-PAN compared to 26 months in the present study [9]. The reason for this difference in results may be the inadequate number of cases in PAN group.

Right- and left-colon carcinomas are deemed to be heterogeneous diseases and their prognosis is thought to be different due to their embryological development independent of histological type and differences in the microsatellite stability and tumorigenesis pathways [16]. In a meta-analysis evaluating KRAS wild-type mCRC patients, right-colon tumors were reported to have lower OS, PFS, and ORR than left-colon tumors [17] and the same meta-analysis revealed that anti-EGFR agents provided OS and PFS benefit in left-colon tumors. The factors that were found to be most predictive of PFS were determined using a multivariate Cox proportional hazards regression analysis in the present study. When other risk factors were corrected, primary tumors in the right colon showed increased progression rates by 1.869-fold (95%

CI:1.014-3.446), which was statistically significant (p=0.045). Furthermore, the better PFS provided by FOLFOX-cetuximab in left-colon tumors was found to be compatible with the findings of previous studies [10,17].

Limitations and Conclusions

The limitations of the present study include its retrospective nature, the inadequate numerical determination of BRAF and NRAS mutations, the low number of patients receiving panitumumab and their shorter duration of follow-up, and the low rate of expected events. This is the first multicenter study to be carried out in Turkey, evaluating treatments, responses to treatment, and adverse effects in patients with KRAS wild-type mCRC. Besides, the authors were also unable to identify any prospective study comparing these three monoclonal antibodies in the international body of literature, although there have been previous studies comparing anti-EGFR and anti-VEGF agents.

Conflict of interests

The authors declare no conflict of interests.

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