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Prognostic Factors Influencing the Efficacy of Regorafenib in the Treatment of Metastatic Colorectal Cancer

Metastatik Kolorektal Kanser Tedavisinde Regorafenib Etkinliğini Etkileyen Prognostik Faktörler

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ABSTRACT

Aim: Metastatic colorectal cancer (mCRC) remains a significant clinical challenge for patients who have exhausted standard treatment options. Regorafenib, an oral multikinase inhibitor, is approved for use in refractory with mCRC patients; however, its real-world efficacy continues to be an area of ongoing research. This study aimed to evaluate the efficacy and clinical outcomes of regorafenib in mCRC patients.

Materials and Methods: This retrospective study assessed the efficacy of regorafenib in mCRC patients who had progressed after at least two lines of systemic therapy. A total of 120 patients were included in the study. Univariate and multivariate analyses of factors affecting survival were conducted using the Cox regression models.

Results: Of the patients, 46 (38.3%) were female and the median age was 58 years. The median progression-free survival (PFS) was 3.38 months and the median overall survival (OS) was 8.01 months. Age and BRAF mutation status were determined as important prognostic factors for PFS. Patients under 65 years of age had a shorter PFS compared to patients aged 65 years and older (p=0.045). Patients with BRAF mutations exhibited significantly shorter PFS compared to those without the mutation (1.84 vs. 3.41 months, p=0.014). In OS analysis, ECOG score (p=0.022), regorafenib dose reduction (p=0.005) and carbohydrate antigen 19-9 (CA19-9) level (p=0.004) were independent prognostic factors. KRAS and NRAS mutations, primary tumor localization and prior targeted therapies combined with chemotherapy did not significantly affect PFS or OS.

Conclusion: Regorafenib is an effective option for the treatment of mCRC in third-line and beyond. ECOG performance status, regorafenib dose adjustment and CA19-9 levels are significant factors influencing survival.

Keywords: Regorafenib, metastatic colorectal cancer, survival

ÖZ

Amaç: Metastatik kolorektal kanser (mCRC), standart tedavi seçeneklerini tüketmiş hastalarda önemli bir klinik zorluk olmaya devam etmektedir. Oral bir multikinaz inhibitörü olan regorafenib, refrakter mCRC hastalarında kullanım için onaylanmıştır, ancak gerçek yaşamdaki etkinliği hala araştırılmaktadır. Bu çalışmanın amacı, regorafenibin mCRC hastalarındaki etkinliğini ve klinik sonuçlarını değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışma, en az iki sıra sistemik tedaviden sonra progresyon gösteren mCRC hastalarında regorafenibin etkinliğini değerlendirmektedir. Çalışmaya toplam 120 hasta dahil edilmiştir. Sağkalımı etkileyen faktörlerin tek değişkenli ve çok değişkenli analizleri Cox regresyon modelleri kullanılarak oluşturulmuştur.

Bulgular: Hastaların 46'sı (38,3) kadındı ve ortanca yaş 58 bulundu. Medyan progresyonsuz sağkalım (PFS) 3,38, medyan genel sağkalım (GS) ise 8,01 ay olarak bulundu. Yaş ve BRAF mutasyon durumu PFS için önemli prognostik faktörler olarak belirlendi. 65 yaş altı hastalarda PFS 65 yaş ve üstü hastalara kıyasla daha kısaydı (p=0,045). BRAF mutasyonu olan hastalar, mutasyonu olmayanlara göre anlamlı derecede daha kısa PFS gösterdi (1,84 vs. 3,41 ay, p=0,014). GS analizinde, ECOG skoru (p=0,022), regorafenib dozunun azaltılması (p=0,005) ve karbonhidrat antijen 19-9 (CA19-9)

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düzeyi (p=0,004) bağımsız prognostik faktörlerdi. KRAS ve NRAS mutasyonları, primer tümör lokalizasyonu ve kemoterapi ile kombine edilen önceki hedefe yönelik tedaviler, PFS veya GS'yi anlamlı şekilde etkilemedi.

Sonuç: Regorafenib üçüncü basamak ve sonrasında mCRC tedavisinde etkili bir seçenektir ve ECOG performans skoru, regorafenib doz ayarlamaları ve CA19-9 düzeyleri sağkalımı belirleyen önemli faktörlerdir.

Anahtar Kelimeler: Regorafenib, metastatik kolorektal kanser, sağkalım

INTRODUCTION

Colorectal cancer (CRC) is a widespread malignancy and a high contributor to cancer-related mortality[1-2]. Although the incidence is increasing, mortality is decreasing, probably due to earlier diagnosis, surgical success and treatment options[3]. Fluoropyrimidine-based therapies combined with oxaliplatin or irinotecan have been the backbone of metastatic colorectal cancer (mCRC) treatment for many years[4]. However, there is a burgeoning clinical demand for efficient tertiary and beyond therapeutic choices for patients who have exhausted standard first- and second-line treatment alternatives. In mCRC patients with good performance status (PS) and potential to respond to treatment, resistance development and exhaustion of effective options in earlier lines complicate disease management in third-line and beyond. Regorafenib is a tyrosine kinase inhibitor and is a treatment option used in line 3 and beyond for this purpose[5]. Clinical trials, in particular the REFLECT and CONCUR studies, have shown a clear survival advantage of regorafenib[6]. Although its efficacy has been demonstrated in phase 3 trials, the prognostic and predictive factors determining the clinical efficacy of regorafenib have not been fully clarified. Age, gender, tumor localization (right or left colon), and molecular mutation profiles such as KRAS, NRAS, and BRAF are among the factors that may influence treatment response. In particular, due to biological differences between right and left colon tumors, whether the efficacy of regorafenib is different in these groups is not yet clear.

We investigated the role of regorafenib in overall survival (OS) and progression-free survival (PFS) in mCRC patients in the third-line setting and beyond. Given the limited real-world data on regorafenib use beyond second-line treatment in mCRC, this study seeks to provide clinically relevant observations regarding patient characteristics that may influence survival outcomes.

MATERIALS AND METHODS

Patients diagnosed with colorectal adenocarcinoma by the pathology unit and seen in the medical oncology outpatient clinic between January 2017 and November 2024 were retrospectively analyzed. Patients over 17 years of age were included. The project was approved by Marmara University Faculty of Medicine Ethical Committee for Non-Pharmaceutical and Non-Medical Device Research Ethics Committee (decision no: 09.2024.1591, date: 24.12.2024). All patients received regorafenib in any line during the metastatic period. In this study, regorafenib was selected as a third-line or later therapy in patients with treatment potential who had exhausted chemotherapy options. The choice of third-line treatment was based on prior response to chemotherapy. Specifically, in patients who had achieved remission for more than six months with chemotherapy, chemotherapy rechallenge was preferred as the initial third-line option. However, in patients who experienced rapid progression under chemotherapy, regorafenib was prioritized in the third-line setting. These selection criteria ensured that treatment decisions were tailored to disease dynamics and individual patient response patterns.

Radiologic imaging methods were used to evaluate response to treatment. Response to regorafenib was defined according to radiological assessment. Patients achieving complete response (CR), partial response (PR), or stable disease (SD) were classified as responders, whereas those with progressive disease (PD) were categorized as non-responders. Clinicopathologic and demographic characteristics and laboratory parameters of the patients were obtained from patient files and the electronic database of the hospital. The association of parameters such as age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), tumor location, targeted therapies used in combination with chemotherapy, presence of RAS and BRAF mutations with OS and PFS in patients receiving regorafenib was analyzed. Although dose reductions were recorded in the dataset, detailed documentation of adverse events was not consistently available in-patient records due to the retrospective nature of the study. Therefore, a comprehensive analysis of toxicity profiles could not be conducted. However, based on available notes, the most frequently reported reasons for regorafenib dose modification were anorexia, fatigue, and dermatologic toxicity, such as hand-foot skin reaction.

Statistical Analysis

Statistical analysis was performed using SPSS software program version 26.0. Continuous variables were summarized as median interquartile range (IQR), while categorical variables were presented as frequencies and percentages. The comparison of continuous variables between groups was performed using the Mann-Whitney U test (for two groups) or the Kruskal-Wallis test (for three or more groups), depending on the number of categories. Categorical variables were analyzed using chi-

square or Fisher's exact tests as appropriate. Survival curves for each subgroup were constructed using the Kaplan-Meier method with 95% confidence intervals (CI). Between-group survival differences were evaluated using the log-rank test. Prognostic factors were initially assessed by univariate analysis and factors with a value of p less than 0.05 were then included in the multivariate analysis. Hazard ratios (HRs) were calculated using the Cox proportional hazards model. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

Population Characteristics: Demographic and Clinical Insights

The study included a total of 120 mCRC patients who received regorafenib in third-line or later lines. The median age was 58 years (IQR: 50.2-65.7). 74 (61.7%) of 120 patients were male. The ECOG-PS indicated that 101 (84.2%) of patients had a score of 0-1. 80 (66.7%) had a body mass index (BMI) of ≥25 kg/m^2. Most patients had left-sided primary tumors (75%) and synchronous metastases (58.3%). Liver-limited metastases were present in 20% of patients. KRAS mutation was detected in 50%, NRAS mutation in 16.7%, and BRAF mutation in 3.3% of cases. Regarding targeted therapies, 38.3% of patients received anti-epidermal growth factor receptor (EGFR) therapy in combination with chemotherapy at any step, while 80% received anti-vascular endothelial growth factor (VEGF) therapy. Regorafenib was administered as third-line treatment in 71.7% of patients and required dosage decrement in 70.8%. The best response to regorafenib was PR in 11.7% of patients, SD in 17.5% and PD in 70.8%. No CR was observed in any patient (Table 1).

Table 1. Population characteristics: demographic and clinical insights

Age, year Median (IQR)	**58 (50.2-65.7)**
Age group, n (%)	
<65	84 (70)
≥65	36 (30)
Gender, n (%)	
Female	46 (38.3)
Male	74 (61.7)
ECOG-PS, n (%)	
0/1	101 (84.2)
≥2	19 (15.8)
BMI group, n (%)	
<25 kg/ m^2	40 (33.3)
≥25 kg/m^2	80 (66.7)
Type of tumor, n (%)	
Colon	84 (70)
Rectum	36 (30)
The side of primary tumor	
Right side	30 (25)
Left side	90 (75)
Metastatic status*, n (%)	
Metachronous	50 (41.7)
Synchronous	70 (58.3)
Metastatic site, n (%)	
Single site	29 (24.2)
Multiple sites	91 (75.8)
Liver metastasis only&, n (%)	
Yes	24 (20)
No	96 (80)
Surgery for primary tumor, n (%)	
Yes	97 (82.2)
No	21 (17.8)
KRAS mutation, n (%)	
Yes	60 (50)
No	60 (50)
NRAS mutation, n (%)	
Yes	20 (16.7)
No	100 (83.3)
BRAF mutation, n (%)	
Yes	4 (3.3)
No	116 (96.7)
Anti-EGFR treatment, n (%)	
Yes	46 (38.3)
No	74 (61.7)
Anti-VEGF treatment, n (%)	
Yes	96 (80)
No	24 (20)
Line of regorafenib treatment, n (%)	
3rd	86 (71.7)
4th or above	34 (28.3)

Analysis of Survival

In the whole population, median PFS was 3.38 months, while median OS was 8.01 months, respectively (Figure 1).

Progression-Free Survival Outcomes and Analysis

Age was found to be a significant factor for PFS, with patients aged <65 years having a slightly shorter PFS compared to those aged ≥65 years (3.35 vs. 3.41 months, p=0.045). Patients with BRAF-mutated tumors had significantly worse PFS compared to those without the mutation (1.84 vs. 3.41 months, p=0.014). Furthermore, responders to regorafenib demonstrated a significantly longer PFS compared to non-responders (4.96 vs. 3.02 months, p<0.001), reinforcing the clinical relevance of achieving disease control with regorafenib. Other factors, including gender (0.496), ECOG-PS (0.390), BMI (0.718), primary tumor location (0.299), metastatic status at diagnosis (0.460), prior targeted therapies (anti-VEGF

Table 1. Continued	
Age, year Median (IQR)	**58 (50.2-65.7)**
Regorafenib dose reduction, n (%)	
Yes	85 (70.8)
No	35 (29.2)
Best response to regorafenib, n (%)	
Partial response	14 (11.7)
Stable disease	21 (17.5)
Progressive disease	85 (70.8)

IQR: Interquartile range, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, BMI: Body mass index, EGFR: Epidermal growth factor receptor, VEGF: Vascular endothelial growth factor

p=0.682, anti-EGFR p=0.692), regorafenib dose reduction (p=0.423), carcinoembryonic antigen (CEA) level (p=0.145) and carbohydrate antigen 19-9 (CA19-9) level (p=0.496) did not significantly impact PFS (Table 2).

Overall Survival Outcomes and Analysis

Results of univariate analysis revealed that ECOG-PS 1-2 (p=0.022), regorafenib dose reduction (p=0.005), CEA level (p=0.005) and CA19-9 level (p=0.004) were significantly associated with OS. Additionally, responders to regorafenib had significantly longer OS compared to non-responders (10.84 vs. 6.47 months, p<0.001). Although patients with BRAF mutations showed numerically worse OS compared to non-mutated cases (2.43 vs. 7.95 months), this difference was not statistically significant (p=0.242). Other clinical and molecular characteristics, including age (p=0.240), gender (p=0.856), tumor location (p=0.245), metastatic site (p=0.096), prior anti-EGFR (p=0.644) or anti-VEGF therapies (0.762) and treatment line (p=0.530) were not significantly associated with OS (Table 2). In multivariate analysis, the results indicate that ECOG-PS (HR: 1.82; 95% CI: 1.08-3.06), regorafenib dose reduction (HR: 1.58; 95% CI: 1.04-2.41), CA19-9 level (HR: 2.14; 95% CI: 1.43-3.22), and regorafenib response (HR: 0.38; 95% CI: 0.24-0.60, p<0.001) remained significant predictors of OS (Table 3).

DISCUSSION

This study evaluated the real-life efficacy of regorafenib for mCRC in settings in tertiary care and beyond, and explored the clinical and molecular factors that influence treatment outcomes. Our findings demonstrated a median PFS of 3.38 months and a median OS of 8.01 months, which are consistent with previously reported data. In particular, while age and BRAF mutation were prognostic factors for PFS, ECOG-PS, regorafenib dose reduction and CA19-9 levels have been determined as prognostic factors for OS. Additionally, our analysis revealed that patients who responded to regorafenib had significantly longer PFS and OS compared to non-responders, further supporting the clinical significance of achieving disease control with regorafenib. These findings support the role of regorafenib as a viable treatment option in the later lines of therapy for mCRC.

The pivotal CORRECT study evaluating regorafenib in heavily treated mCRC patients reported a median PFS of 1.9 and median OS of 6.4 months, reinforcing its therapeutic benefit in this challenging patient population[7]. Similarly, the CONCUR trial conducted in Asian patients found comparable results, with regorafenib improving PFS and OS over placebo[6]. Notably, the median OS observed in our study was longer compared to the CORRECT (6.4 months) and CONCUR (8.4 months) trials[6,7]. Several factors may explain this difference. First, our cohort predominantly consisted of patients with an ECOG-PS of

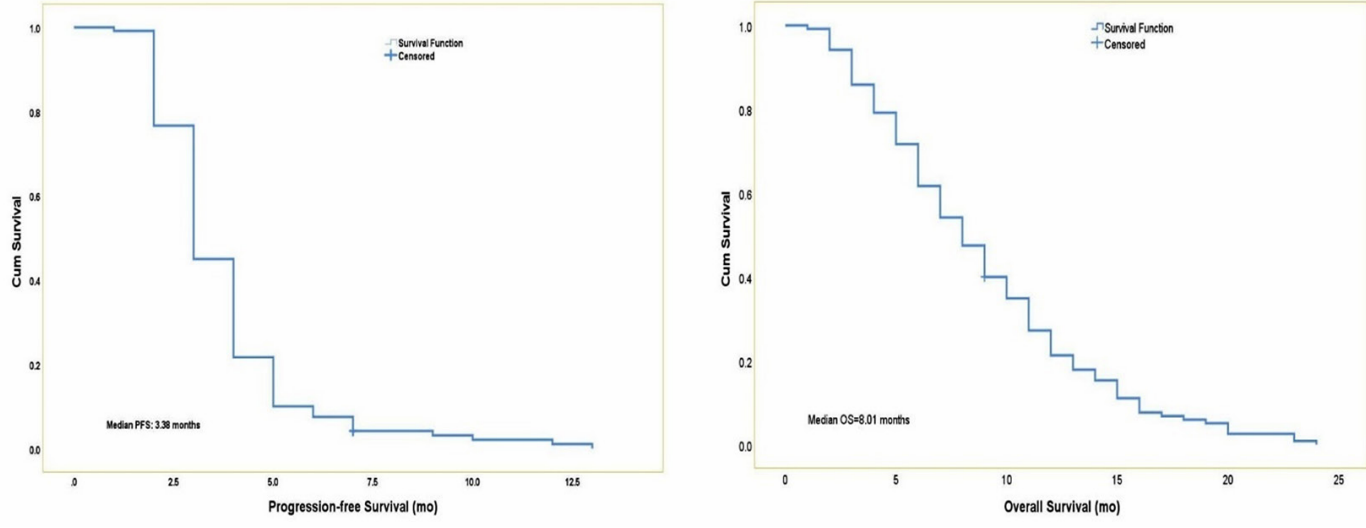

Figure 1. Survival outcomes: Kaplan-Meier estimates for PFS and OS
PFS: Progression-free survival, OS: Overall survival

Table 2. Univariate analysis of determinants for progression-free survival and overall survival

	Median PFS (months)	HR (95% CI)	p	Median OS (months)	HR (95% CI)	p-value
Age						
<65	3.35 (3.08-3.62)	0.66 (0.44-0.99)	0.045	7.75 (6.36-9.14)	0.78(0.52-1.17)	0.240
≥65	3.41 (2.69-4.14)			9.03 (6.13-11.93)		
Gender						
Male	3.41 (3.10-3.72)	0.88 (0.60-1.27)	0.496	7.82 (6.00-9.63)	1.03 (0.71-1.50)	0.856
Female	3.31 (3.06-3.56)			8.08 (7.02-9.14)		
ECOG-PS						
0/1	3.41 (3.24-3.60)	1.23 (0.75-2.02)	0.390	8.70 (7.65-9.75)	1.78 (1.08-2.96)	0.022
≥2	2.92 (2.22-3.62)			5.81 (4.18-7.45)		
BMI group						
<25 kg/ m^2	3.58 (3.11-4.05)	1.07 (0.71-1.62)	0.718	7.36 (5.81-8.90)	0.71 (0.47-1.08)	0.114
≥25 kg/m^2	3.31 (3.01-3.62)			8.90 (7.31-10.50)		
Type of tumor, n (%)						
Colon	3.35 (3.02-3.67)	0.80 (0.54-1.21)	0.299	8.08 (6.46-9.70)	0.78 (0.51-1.18)	0.245
Rectum	3.34 (3.04-3.66)			7.82 (5.84-9.8)		
The side of primary tumor						
Right side	3.35 (2.75-3.95)	1.07 (0.95-1.21)	0.375	6.37 (4.39-8.35)	1.10 (0.97-1.24)	0.129
Left side	3.35 (3.15-3.54)			8.77 (7.58-9.96)		
Metastatic status						
Metachronous	3.41 (3.14-3.68)	1.14 (0.79-1.66)	0.460	7.95 (6.16-9.73)	1.43 (0.97-2.11)	0.068
Synchronous	3.35 (3.12-3.57)			7.75 (6.07-9.43)		
Metastatic site						
Single site	3.48 (3.02-3.94)	1.18 (0.77-1.81)	0.426	7.65 (5.75-9.56)	1.43 (0.93-2.20)	0.096
Multiple sites	3.35 (3.12-3.57)			8.34 (7.03-9.65)		
Liver metastasis only						
Yes	3.48 (2.81-4.15)	1.10 (0.70-1.72)	0.676	7.65 (5.9-9.35)	1.28 (0.81-2.01)	0.283
No	3.35 (3.15-3.55)			8.14 (6.72-9.56)		
Surgery for primary tumor						
Yes	3.35 (3.15-3.54)	1.17 (0.72-1.90)	0.719	8.08 (6.90-9.26)	0.87 (0.53-1.42)	0.582
No	3.41 (2.80-4.03)			9.59 (4.62-14.56)		
RAS mutation						
Yes	3.48 (3.24-3.72)	0.92 (0.663-1.32)	0.648	8.70 (7.05-10.35)	0.95 (0.66-1.38)	0.819
No	3.28 (3.06-3.51)			7.65 (6.82-8.49)		
BRAF mutation						
Yes	1.84 (0.74-2.93)	3.26 (1.18-8.96)	0.014	2.43 (1.10-9.12)	1.80 (0.66-4.92)	0.242
No	3.41 (3.23-3.60)			7.95 (6.76-9.13)		
Anti-EGFR treatment						
Yes	3.48 (3.26-3.70)	0.93 (0.64-1.35)	0.692	7.89 (6.50-9.26)	1.09 (0.75-1.59)	0.644
No	3.22 (2.87-3.56)			8.14 (6.17-10.12)		
Anti-VEGF treatment						
Yes	3.41 (3.18-3.64)	1.13 (0.62-2.07)	0.682	8.14 (6.83-9.46)	1.09 (0.60-2.01)	0.762
No	3.31 (3.20-3.43)			7.82 (3.80-11.83)		
Line of regorafenib treatment						
3rd	3.31 (3.10-3.53)	0.84 (0.56-1.26)	0.394	7.81 (6.14-9.45)	1.05 (0.75-1.47)	0.530
4th or above	3.64 (3.36-3.92)			8.08 (6.62-9.53)		

Table 2. Continued

	Median PFS (months)	HR (95% CI)	p	Median OS (months)	HR (95% CI)	p-value
Regorafenib dose reduction						
Yes	3.35 (3.14-3.56)	1.17 (0.78-1.76)	0.423	7.65 (6.17-9.14)	1.78 (1.18-2.70)	0.005
No	3.41 (2.94-3.89)			9.59 (7.31-11.88)		
Regorafenib response						
Non-responders	3.02 (2.78-3.26)	0.05 (0.02-0.10)	<0.001	6.47 (5.48-7.46)	0.40 (0.26-0.62)	<0.001
Responders	4.96 (4.61-5.31)			10.84 (9.46-12.22)		
CEA						
<58	3.48 (3.26-3.70)	1.31 (0.90-1.90)	0.145	8.77 (6.82-10.72)	1.72 (1.17-2.53)	0.005
≥58	3.08 (2.79-3.38)			6.73 (4.99-8.48)		
CA19-9						
<74	3.35 (3.13-3.57)	1.14 (0.77-1.67)	0.496	9.03 (7.12-10.95)	1.75 (1.19-2.58)	0.004
≥74	3.48 (2.85-4.11)			6.37 (4.18-8.57)		

PFS: Progression-free survival, HR: Hazard ratio, CI: Confidence interval, OS: Overall survival, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, BMI: Body mass index, EGFR: Epidermal growth factor receptor, VEGF: Vascular endothelial growth factor, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen 19-9

0-1 (84.2%), indicating a relatively better functional status, whereas the CORRECT and CONCUR trials included a broader range of ECOG-PS scores, which could negatively impact survival. Second, a higher proportion of our patients had received prior targeted therapies, particularly anti-VEGF agents, which may have contributed to improved OS. Additionally, as a real-world study, flexible dosing strategies and individualized patient management may have led to better tolerability and prolonged treatment duration, ultimately enhancing survival. Lastly, advancements in supportive care over time could also be a contributing factor to the improved OS observed in our study. In a different large randomized trial, mCRC patients receiving regorafenib as treatment had a median OS of 5.6 months and a 12-month survival rate of 22%[8]. Our study demonstrated aligns with these findings, further validating regorafenib's effectiveness in this patient group. Notably, our results also highlight the impact of factors, such as ECOG-PS and regorafenib dose reduction, on survival outcomes, suggesting the potential for more personalized treatment strategies in mCRC management.

Table 3. Multivariate analysis of predictors for overall survival

	HR (95% CI)	p-value
ECOG-PS		
0-1	Ref	0.025
≥2	1.82 (1.08-3.06)	
Regorafenib dose reduction		
No	Ref	0.030
Yes	1.58 (1.04-2.41)	
CEA		
<58	Ref	0.225
≥58	1.29 (0.85-1.97)	
CA19-9		
<74	Ref	<0.001
≥74	2.14 (1.43-3.22)	
Regorafenib response		
Non-responders	Ref	<0.001
Responders	0.38 (0.24-0.60)	

HR: Hazard ratio, CI: Confidence interval, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen 19-9

To date, there are no biomarkers to predict the response to regorafenib in mCRC, but evidence suggests that prior exposure to targeted therapies is associated with worse outcomes. In particular, in the CORRECT trial, all patients had previously received bevacizumab, and 52% of patients had been exposed to anti-EGFR therapy. In the CONCUR trial, these rates were 41% and 35%, respectively[9]. The better OS observed in the CONCUR trial may have been influenced by these results. Similar results were reported in a single-arm, phase 2b study evaluating regorafenib in patients with chemotherapy-resistant, antiangiogenic-naive mCRC[10], consistent with the CONCUR findings. Similarly, in our study, 80% of patients had prior anti-VEGF therapy, while 38.3% had received anti-EGFR therapy at some point during their treatment course. Despite this high rate of prior targeted therapy exposure, our findings demonstrated a median OS of 8.01 months, which is numerically longer than that reported in CORRECT and CONCUR. This suggests that patient selection, treatment sequencing, and additional prognostic factors may influence survival outcomes with regorafenib.

Dose modification is a critical aspect of regorafenib treatment, as adverse events often necessitate dose reductions to maintain tolerability without compromising efficacy. In our study, 70.8% of patients required dose reduction, and multivariate analysis identified it as an independent predictor of OS. These findings are consistent with real-world data from the REBECCA study, a large observational cohort evaluating regorafenib in routine

clinical practice[8]. Starting at a lower dose and adjusting based on tolerance is a common approach in clinical practice to enhance treatment adherence. Furthermore, emerging evidence suggests that initiating regorafenib at a reduced dose with subsequent titration, as explored in the ReDOS trial, can improve tolerability and overall treatment success[11]. These findings highlight the importance of personalized dosing strategies to enhance the clinical benefit of regorafenib in heavily treated mCRC patients.

The role of molecular alterations in the efficacy of regorafenib remains controversial. In the CORRECT trial, KRAS, NRAS, and BRAF mutation statuses were not significantly associated with treatment outcomes, indicating that regorafenib exerts its antitumor effects independently of RAS mutation status[7]. The subgroup analysis of the CONCUR study also found no significant difference in OS between RAS mutant and wild-type tumors[6]. However, smaller retrospective studies have associated BRAF mutations with worse outcomes in patients treated with regorafenib, likely reflecting the inherently poor prognosis of BRAF mutant mCRC[12]. In our study, the results were consistent with the literature, with KRAS and NRAS mutations not significantly affecting PFS or OS. Nevertheless, this lack of statistical significance should be interpreted with caution, as these mutations represent only a limited aspect of tumor biology. Other factors-such as pathway crosstalk, epigenetic regulation, and tumor-stroma interactions-may contribute to therapeutic resistance and response variability, especially in real-world settings where patient heterogeneity is high. However, in our cohort, patients with BRAF mutations had a trend toward shorter OS, but the difference was not statistically significant, potentially due to the limited sample size. Moreover, the prognostic significance of tumor markers like CEA and CA19-9 continues to be a contention of discussion in clinical practice. Studies have shown that elevated CA19-9 levels may be associated with poor prognosis[13]. Associations between treatment outcomes and various laboratory parameters have also been documented in the literature, with elevated platelet counts and high neutrophil-to-lymphocyte ratios being linked to poorer OS, while higher lymphocyte counts have been associated with improved OS[14,15]. In our study, elevated CA19-9 levels were found to be an independent predictor of regorafenib efficacy, whereas CEA levels were not significantly associated with survival outcomes. CA19-9 is a sialylated Lewis antigen expressed on epithelial cells and secreted by mucin-producing adenocarcinomas. Its elevation may reflect not only higher tumor burden or biliary tract involvement, but also a more biologically aggressive phenotype characterized by enhanced mucin production, desmoplastic reaction, and increased metastatic capacity. Prior studies in gastrointestinal malignancies have demonstrated that elevated CA19-9 is associated with reduced treatment responsiveness and inferior survival outcomes. Accordingly, in the context of regorafenib therapy, baseline CA19-9 levels may reflect both tumor burden and biological aggressiveness, potentially contributing to the observed differences in survival outcomes. These findings suggest that CA19-9 could be considered a prognostic biomarker in clinical practice. Identifying reliable predictive biomarkers for regorafenib could enable more personalized treatment strategies and warrants further investigation.

Our findings highlight the importance of patient selection in regorafenib treatment for mCRC, as ECOG-PS and CA19-9 levels were significant prognostic factors for survival. The high rate of dose reductions emphasizes the need for careful toxicity management to improve treatment adherence. Although BRAF-mutant tumors showed a trend toward worse outcomes, the limited sample size precludes definitive conclusions, warranting further investigation. Future studies should focus on identifying biomarkers predictive of regorafenib response, optimizing treatment sequencing, and evaluating its role in combination strategies to enhance clinical benefit.

Study Limitations

Some limitations of this study need to be acknowledged. The retrospective design introduces the potential for selection bias, as patients were not randomly assigned to treatment groups. This may have led to an overrepresentation of patients with better PS or those who tolerated treatment longer, while patients with poorer prognosis may have been underrepresented. Additionally, our analysis lacked detailed data on adverse events, which is a critical aspect of regorafenib treatment. While dose reductions were recorded in our dataset, the specific reasons, severity grading, and timing of these modifications were not systematically documented. This limits our ability to assess the direct relationship between adverse events and dose adjustments, as well as their impact on treatment adherence and clinical outcomes. Given that a significant proportion of patients required dose reduction, it is likely that toxicity played a crucial role in treatment modifications. However, the absence of detailed adverse event profiles prevents us from determining whether specific toxicities had a greater influence on survival outcomes. The relatively small sample size may also limit the applicability of the results. Although the data were retrieved from medical records, detailed information on dose reduction and patient tolerance was not comprehensively collected. Dose reductions are a critical aspect of regorafenib therapy, and the lack of detailed information on the reasons and timing of dose adjustments may limit our understanding of how these factors affect treatment outcomes. Although we were able to assess OS and PFS, other relevant factors such as adverse event profiles could not be assessed. Furthermore, our dataset does not include treatment regimens after regorafenib in detail. Since most patients did not receive further treatment due to disease progression or clinical deterioration, and the available data on chemotherapy rechallenge in those who

underwent retreatment were insufficient for a comprehensive analysis, we were unable to assess the impact of subsequent therapies on survival outcomes.

CONCLUSION

Regorafenib is an efficient therapeutic choice for heavily pretreated mCRC patients and improves both OS and PFS. Our findings, consistent with prior studies, emphasize the importance of patient selection and dose modification in optimizing treatment outcomes. Despite the absence of definitive predictive biomarkers, our results suggest that factors such as ECOG-PS, treatment dose and CA19-9 levels may influence survival outcomes in patients treated with regorafenib. Given the limited evidence on genetic mutations and their impact on regorafenib efficacy, further investigation into molecular profiling and the role of specific biomarkers is warranted. Future prospective studies should focus on integrating clinical and molecular profiling to better elucidate why established prognostic factors such as ECOG PS and CA19-9 levels remain predictive of regorafenib outcomes, while common mutational markers fail to demonstrate consistent associations.

Ethics

Ethics Committee Approval: The project was approved by Marmara University Faculty of Medicine Ethical Committee for Non-Pharmaceutical and Non-Medical Device Research Ethics Committee (decision no: 09.2024.1591, date: 24.12.2024).

Informed Consent: Patients diagnosed with colorectal adenocarcinoma by the pathology unit and seen in the medical oncology outpatient clinic between January 2017 and November 2024 were retrospectively analyzed. Patients over 17 years of age were included.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.S., Concept: N.S., İ.V.B., Design: N.S., İ.V.B., Data Collection or Processing: N.S., Analysis or Interpretation: N.S., İ.V.B., Literature Search: N.S., İ.V.B., Writing: N.S.

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