Scientific Research Publishing

Open Journal of Gastroenterology, 2025, 15(4), 204-214
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Combining Bevacizumab with FOLFIRI Improves Progression Free Survival as a Second-Line Treatment in Metastatic Colorectal Cancer Patients

Marvellous Okeke[1], Lin Liu[1*], Zanga Sensenta[2], Deo Kabula D. Pharm[3]

[1]Department of Oncology, School of Medicine, Southeast University, Nanjing, China
[2]Department of Gastroenterology, School of Medicine, Southeast University, Nanjing, China
[3]Department of Pharmaceutics, China Pharmaceutical University, Nanjing, China
Email: *101012478@seu.edu.cn, wenyu811@126.com

How to cite this paper: Okeke, M., Liu, L., Sensenta, Z. and Pharm, D.K.D. (2025) Combining Bevacizumab with FOLFIRI Improves Progression Free Survival as a Second-Line Treatment in Metastatic Colorectal Cancer Patients. *Open Journal of Gastroenterology*, **15**, 204-214.
https://doi.org/10.4236/ojgas.2025.154020

Received: February 27, 2025
Accepted: April 22, 2025
Published: April 25, 2025

Abstract

Introduction: Clinical trials have shown that bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor is effective in treating metastatic colorectal cancer (mCRC). Available evidence suggests that it is more effective in combination with chemotherapy acting in synergy. In this study, we assessed the efficacy and safety of bevacizumab combined with capeOX/FOLFOX or FOLFIRI emphasizing which combination therapy is best as a first, second, or third-line treatment for mCRC. Material and method: We reanalyzed secondary data from the DRYAD database that contained follow-up information on the combination use of bevacizumab with either capeOX/FOLFOX or FOLFIRI to treat mCRC. 147 mCRC patients were involved and the data was collected until December 30, 2019. Kaplan-Meier survival curves, Log-Rank tests, and Cox proportional hazards models were employed for analysis. All analyses were conducted using SPSS version 27. **Results**: From univariate analyses, higher ECOG status (HR 1.411, 95% CI: 1.137-1.977, p = 0.019), radical surgery of the primary organ (HR 0.649, 95% CI: 0.348-0.909, p = 0.033), the presence of ≥2 metastatic sites (HR 1.638, 95% CI: 1.189-1.907, p = 0.014), and the type of chemotherapy used (HR 0.563, 95% CI: 0.316-0.971, p = 0.036) were significantly associated with overall survival (OS). Multivariate analysis showed type of chemotherapy used (HR 0.463, 95% CI: 0.216-0.992, p = 0.048) as an independent predictor of OS. Kaplan-Meier survival analysis showed that patients receiving bevacizumab plus FOLFIRI as a second-line

therapy had better progression-free survival (PFS) **Conclusion:** Type of chemotherapy combined with bevacizumab independently influences overall survival (OS) in mCRC patients. Bevacizumab showed greater efficacy in extending progression-free survival (PFS) when paired with FOLFIRI rather than capeOX or FOLFOX.

Keywords

Bevacizumab, PFS, FOLFIRI, capeOX, FOFOX, Colorectal Cancer

1. Introduction

Colorectal cancer (CRC) ranks as the third most prevalent cancer and the second leading cause of cancer-related mortality worldwide [1]. In China advanced or metastatic CRC (mCRC), constitute about 20% of the total CRC cases, majority of which are often diagnosed at stage III or IV [2]. Despite advancements in survival rates, mCRC continues to be a fatal condition, with a 5-year survival rate of about 15.7% [3]. Over the last two decades, substantial progress has been made in CRC treatment. The median survival for patients with mCRC undergoing multimodal therapy now exceeds 25 months, yet the prognosis for these patients remains suboptimal [3] [4].

Metastatic colorectal cancer (mCRC) treatment varies globally based on healthcare resources and access to modern therapies, but systemic therapy remains the standard approach. First-line treatment typically involves chemotherapy regimens like FOLFOX (folinic acid, 5-FU, oxaliplatin) or FOLFIRI (folinic acid, 5-FU, irinotecan) [5], often combined with targeted biologics. Bevacizumab, an anti-VEGF agent, is commonly used in RAS-mutant tumors at 5 mg/kg biweekly or 7.5 mg/kg every 3 weeks. For RAS wild-type tumors, especially left-sided ones [6], anti-EGFR drugs like cetuximab (400 mg/m^2 loading, then 250 mg/m^2 weekly) or panitumumab (6 mg/kg biweekly) are used. In advanced settings, molecular profiling enables personalized treatments—BRAF V600E mutations are treated with BRAF inhibitors (e.g., encorafenib) plus EGFR inhibitors [7], while MSI-high or mismatch repair-deficient tumors respond to immune checkpoint inhibitors like pembrolizumab or nivolumab [8].

Currently, the standard treatment for mCRC remains a combination chemotherapy regimen, mostly either FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, and irinotecan), with the anti-VEGF antibody bevacizumab as the targeted therapy [9]. Bevacizumab functions by inhibiting VEGF, a protein that acts as an endothelial growth factor, facilitating the formation of new blood vessels that tumors rely on to sustain their growth [10]. The combination of bevacizumab with either CapeOX/FOLFOX or FOLRIRI is the most widely used regimen to date due to availability and

affordability. Despite this wide spread use hoverer, a pivotal question persists: Does the continued administration of bevacizumab as a second or third line therapy following disease progression provide any discernible clinical advantage? While certain studies suggest its effectiveness as a second or third-line treatment for mCRC, particularly in enhancing progression-free survival (PFS) [11] [12], the existing evidence remains insufficient to draw definitive conclusions.

In this retrospective study, we investigated and compared the efficacy of bevacizumab combined with capeOX/FOLFOX or FOLFIRI as first, second, or third-line treatment for mCRC. We evaluated the outcomes of bevacizumab combined with either of these two chemotherapy regimens in terms of overall survival (OS) and progression-free survival (PFS).

2. Materials and Methods

This was a secondary data analysis conducted on dataset obtained from the publicly accessible DRYAD database (https://datadryad.org/) whose policy states that the data can be used, modified, shared, and redistributed for both commercial and non-commercial purposes without the need for permission, as long as the original author is cited accordingly. Since the data was secondary and publicly available, there was no requirement for ethical approval. The dataset, pertaining to treatment of colorectal cancer using bevacizumab in combination with either capeOX/FOLFOX or FOLFIRI is freely available for download and reuse with proper citation from the Dryad Digital Repository https://doi.org/10.5061/dryad.ft5sk66. One hundred and fifty four metastatic colorectal cancer patients who underwent bevacizumab-based chemotherapy were initially screened for eligibility. Excluded were those with no pathological diagnosis, no measurable metastatic tumors, and missing drug prescription data. Based on these criteria, seven patients were excluded, leaving 147 participants **(Figure 1).** Eligible patients received bevacizumab in combination with capeOX/FOLFOX or FOLFIRI regimens, administered as a first, second, or third-line treatment. Bevacizumab was administered intravenously (IV) at a dose of either 5 mg/kg or 7. mg/kg over a 90-minute period every 2 or 3 weeks, prior to the initiation of chemotherapy. capeOX regimen involved oxaliplatin administered at a dose of 130 mg/m^2 through a 2 - 6 hour infusion on day 1, alongside Xeloda at a dose of 1 g/m^2 taken twice daily from day 1 to day 14, repeated every 3 weeks. The FOLFOX regimen consisted of oxaliplatin (85 mg/m^2) IV over 2 hours, leucovorin (400 mg/m^2) IV over 2 hours, and an IV bolus of 5-FU (400 mg/m^2), followed by 46 hours of continuous 5-FU IV (2,400 mg/m^2). While, the FOLFIRI regimen comprised irinotecan (180 mg/m^2) administered via IV infusion over 2 hours, followed by leucovorin (400 mg/m^2) IV over 2 hours. This was succeeded by an IV bolus of fluorouracil (5-FU) (400 mg/m^2), followed by continuous 5-FU IV (2,400 mg/m^2) over 46 hours.

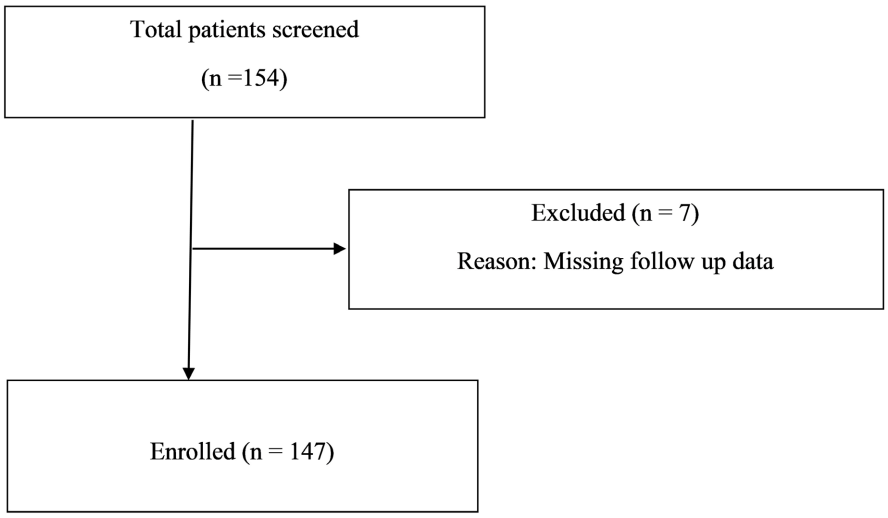

Figure 1. Patients' selection criteria.

2.1. Definition of Terms

For the purposes of this study, left-sided colorectal cancer (CRC) was defined as rectal, sigmoid, and left transverse colon cancers, while right-sided CRC was defined as right transverse colon, ascending colon, and appendiceal cancers. Data were gathered on demographics, treatment outcomes, and adverse events. Overall survival (OS) was defined as the time from the initiation of bevacizumab treatment to death from any cause or the last outpatient visit, while progression free survival (PFS) was defined as the time from when the patient started treatment to when they got a relapse. Since the data were anonymous, informed consent was not required.

2.2. Adverse Event

Hypertension was classified according to the Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v4.03), as follows: Grade 1, prehypertension (systolic blood pressure (BP) between 120 - 139 mm Hg or diastolic BP between 80 - 89 mm Hg); Grade 2, stage 1 hypertension (systolic BP between 140 - 159 mm Hg or diastolic BP between 90 - 99 mm Hg), with medical intervention recommended for recurrent or persistent increases lasting more than 24 hours, or for symptomatic increases exceeding 20 mm Hg (diastolic) or reaching > 140/90 mm Hg if previously within normal limits, necessitating monotherapy; Grade 3, stage 2 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥ 100 mm Hg), requiring medical intervention and possibly the use of multiple drugs or more intensive therapy than previously administered; Grade 4, life-threatening consequences (such as malignant hypertension, transient or permanent neurological deficits, or hypertensive crisis), demanding urgent intervention; Grade 5, death.

2.3. Statistical Analysis

The baseline characteristics between the two groups were compared using the chi-

square test for categorical variables and the Kruskal-Wallis test for continuous variables. The Kaplan-Meier method was employed to assess the relationship between chemotherapy used and overall survival (OS), with comparisons between the two groups made using the log-rank test. Univariate and multivariate analyses of the patients' baseline characteristics and chemotherapy were conducted using Cox proportional hazards models. The results were expressed as hazard ratios (HR) along with 95% confidence intervals (95% CI). A two-tailed P-value of less than 0.05 was considered statistically significant for all analyses. All statistical procedures were carried out using SPSS version 27.

3. Results

3.1. Baseline Characteristics and Clinical Outcomes

Between January 2018 and December 2019, a total of 154 consecutive patients were screened through the electronic health record system, with 147 cases ultimately included. The final data collection date was December 30, 2019, by which time 57 patients (38.7%) had been reported as deceased. The median follow-up duration for deceased patients was 11.2 months (range, 0.2 to 60 months), while for censored patients, it was 6.8 months (range, 0.1 to 58 months). Seven patients were excluded due to missing follow-up data. A comparison of the baseline characteristics between the included patients is presented in Table 1.

Table 1. Baseline characteristics of included patients.

Variables	Combination chemotherapy		P value
	capeOX/FOLFOX (n = 75)	FOLFIRI (n = 72)	
Mean age ± SD, years	55.2 ± 11.3	56.2 ± 13.5	0.804
Mean BMI ± SD, kg/m^2	22.7 ± 4.2	21.7 ± 4.1	0.653
Sex (%)			0.638
Male	45 (59.2)	38 (53.9)	
Female	30 (40.8)	34 (46.1)	
WHO performance status (%)			0.007*
0 - 1	37 (59.2)	32 (35.5)	
2 - 4	38 (40.8)	40 (64.5)	
Differentiation (%)			0.751
No/low	15 (19.7)	13 (18.4)	
Middle/High	60 (67.6)	59 (64.5)	
Primary site (%)			0.296
Right	21 (22.5)	19 (31.6)	
Left	54 (77.5)	53 (68.4)	
Surgery of primary organ (%)			0.057

Continued

None	30 (32.4)	09 (21.1)	
Palliative	21 (26.8)	12 (18.4)	
Radical	24 (40.8)	51 (60.5)	
No. of metastatic sites (%)			0.076
1	33 (45.1)	26 (35.5)	
≥2	42 (33.8)	46 (26.3)	

Note: BMI = body mass index. SD: Standard deviation. capeOX = capecitabine + oxaliplatin. FOLFOX = oxaliplatin + fluorouracil + calcium folinate. FOLFIRI = Irinotecan + fluorouracil + calcium folinate.

3.2. Outcomes

We conducted both univariate and multivariate Cox regression analyses to investigate the relationship between baseline characteristics, chemotherapy used, and patient survival. The results are presented in Table 2. In the univariate analyses, a higher ECOG performance status (HR 1.411, 95% CI: 1.137 - 1.977, p = 0.019), radical surgery of the primary organ (HR 0.649, 95% CI: 0.348 - 0.909, p = 0.033), the presence of ≥2 metastatic sites (HR 1.638, 95% CI: 1.189 - 1.907, p = 0.014), and the type of chemotherapy used (HR 0.563, 95% CI: 0.316 - 0.971, p = 0.036) were found to be significantly associated with overall survival. These variables were subsequently included in the multivariate analysis, which identified the type of chemotherapy used (HR 0.463, 95% CI: 0.216 - 0.992, p = 0.048) as an independent predictor of overall survival. Kaplan-Meier survival analysis further indicated that patients receiving bevacizumab plus FOLFIRI as a second-line therapy had better progression-free survival (PFS) (Figure 2).

Table 2. Adverse events of bevacizumab therapy between capeOX/FOLFOX and FOLRIRI chemotherapy use.

Variables	capeOX/FOLFOX (n = 75)	FOLFIRI (n = 72)	P value
Hypertension (CTC), n (%)			0.314
Normal	30 (40.0)	28 (38.9)	
CTC 1-2	34 (45.3)	36 (50.0)	
CTC 3-4	11 (14.7)	8 (11.1)	
Proteinuria, n (%)			0.198
No	70 (93.3)	69 (95.8)	
Yes	5 (6.7)	3 (4.2)	
Bleeding, n (%)			0.811
No	73 (97.3)	71 (98.6)	
Yes	2 (2.7)	1 (1.4)	
Thrombosis, n (%)			0.118
No	74 (98.7)	72 (100)	
Yes	1 (1.3)	0 (0.0)	

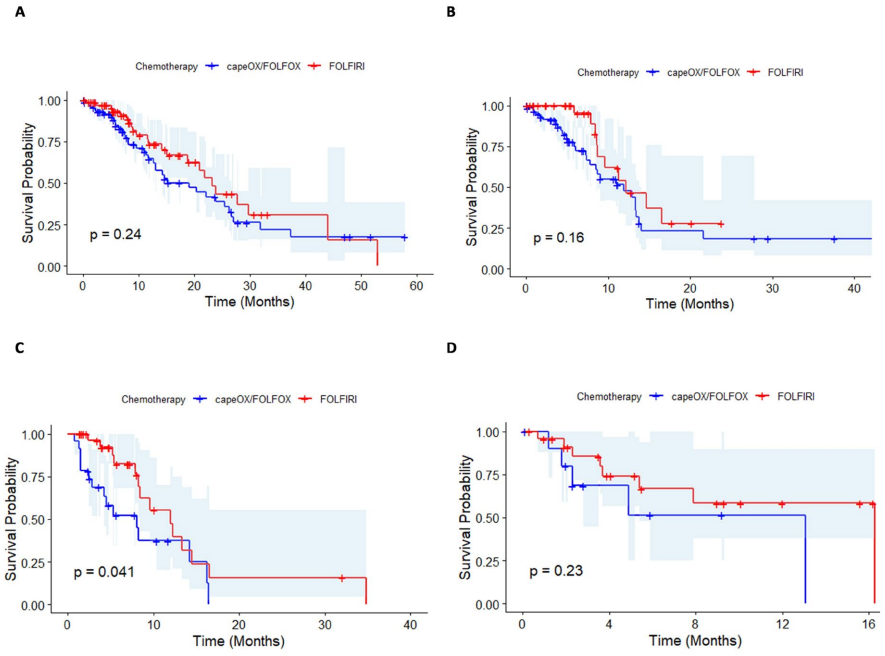

Figure 2. Kaplan-Meier survival analysis. A: Overall survival; B: Progression free survival as a first line; C: Progression free survival as a second line; D: Progression free survival as a third line or more.

3.3. Adverse Events

The median duration of chemotherapy was 8.1 months (range, 0.2 to 58 months). For patients receiving first-line bevacizumab-based treatment (n = 71), the median duration was 6.6 months (range, 0.2 to 58). The median durations for those who received second-line (n = 21) and subsequent-line therapies (n = 31) were 8.2 months (range, 1.3 to 53) and 5.1 months (range, 0.1 to 27), respectively. Hypertension was the primary adverse event associated with bevacizumab, and no statistically significant difference in adverse events was observed between the capeOX/FOLFOX and FOLFIRI groups (Table 3).

Table 3. Cox regression analysis of patients' characteristics as predictors of survival.

		Univariate analyses			Multivariate analyses		
Variable	Subgroup	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	<60	1			1		
	≥60	1.332	0.772 - 2.298	0.303	1.011	0.513 - 2.997	0.491
Gender	Female	1			1		
	Male	1.099	0.649 - 1.859	0.726	1.134	0.365 - 3.112	0.613
ECOG	0 - 1	1			1		
	2 - 4	1.411	1.137 - 1.977	0.019*	0.981	0.299 - 1.882	0.189
Differentiation	No/low	1			1		
	Middle/high	0.716	0.388 - 1.322	0.286	0.871	0.422 - 1.672	0.712

Continued

Primary site	Right	1			1		
	Left	0.938	0.512 - 1.718	0.836	1.009	0.489 - 2.131	0.799
Surgery of primary organ	None	1			1		
	Palliative	0.747	0.636 - 1.537	0.428	0.898	0.511 - 1.872	0.543
	Radical	0.649	0.348 - 0.909	0.033*	0.911	0.478 - 1.323	0.096
No. of metastatic sites	1	1			1		
	≥2	1.638	1.189 - 1.907	0.014*	1.219	0.498 - 3.112	0.239
Chemotherapy used	capeOX/FOLFOX	1			1		
	FOLFIRI	0.563	0.316 - 0.971	0.036*	0.463	0.216 - 0.992	0.048*
Line of treatment	1st line	1			1		
	≥2nd line	0.841	0.618 - 1.752	0.081	0.899	0.324 - 1.311	0.072

4. Discussion

Bevacizumab is a monoclonal antibody used in the treatment of metastatic colorectal cancer (mCRC) due to its ability to inhibit angiogenesis, the process by which tumors develop new blood vessels to support their growth. By binding to and neutralizing vascular endothelial growth factor (VEGF), a protein responsible for promoting blood vessel formation, bevacizumab effectively reduces the tumor's ability to grow and spread. In this retrospective cohort study, we compared the efficacy and adverse effects of bevacizumab combined with capeOX/FOLFOX, versus bevacizumab combined with FOLFIRI in treating mCRC across the different lines of therapy (1st, 2nd and 3rd line or above).

Our findings revealed that bevacizumab was more effective in prolonging PFS among mCRC patients when combined with FOLFIRI than with capeOX/FOLFOX (HR 0.463 [95% CI: 0.216 - 0.992], $p = 0.048$). Multivariate Cox regression analysis showed that the combination of bevacizumab and FOLFIRI significantly improved PFS (HR 0.463 [95% CI: 0.216 - 0.992], $p = 0.048$) compared to bevacizumab and capeOX/FOLFOX. This result is consistent with those of Yamazaki *et al.* [13] who compared the two regimens in a randomized open label phase III trial and found the median PFS for FOLFIRI + Bevacizumab (n = 197) and mFOLFOX6 + Bevacizumab (n = 198) to be 12.1 and 10.7 months, respectively [HR, 0.905; 95% confidence interval (CI) 0.723 - 1.133; $p = 0.003$ for non-inferiority]. Similarly, Aranda *et al.* [14] compared the two regimens and found that Median PFS was 12.4 months (95% CI 11.2 to 14.0) with FOLFIRI-Bevacizumab and 9.3 months (95% CI 8.5 to 10.7) with FOLFOX-Bevacizumab (stratified HR, 0.64; 95% CI 0.49 to 0.82; $p = 0.0006$).

Why the combination of bevacizumab and FOLFIRI (fluorouracil, leucovorin, and irinotecan) has been shown to improve progression-free survival (PFS) in metastatic colorectal cancer (mCRC) patients more effectively than bevacizumab and FOLFOX (fluorouracil, leucovorin, and oxaliplatin) could be due to the distinct mechanisms of action of irinotecan and oxaliplatin, the key drugs in FOLFIRI and

FOLFOX respectively. Irinotecan, a topoisomerase inhibitor [15], is particularly effective against tumors with specific genetic mutations and has demonstrated a better synergy with bevacizumab in targeting the tumor microenvironment, particularly in reducing vascular endothelial growth factor (VEGF) signaling, which is crucial for tumor growth [16] [17]. Additionally, irinotecan can induce more significant tumor cell apoptosis and enhance chemotherapy efficacy [18]. This combination, therefore, may be more potent in inhibiting tumor progression compared to FOLFOX, where oxaliplatin's mechanisms may not always align as efficiently with bevacizumab's action on angiogenesis in mCRC. In this study, this synergistic effect was only significant when the combination of bevacizumab and FOLFIRI were used as a second line drug. The reason for this remains unknown.

In this study, the rate of all adverse events monitored were not significant between the two groups. Bevacizumab therapy is often associated with increased rate of hypertension [19], however, its combination with either capeOX/FOLFOX or FOLFIRI did not significantly increase the rate of hypertension in one group more than the other.

Our study had a few important limitations. Firstly, it was a small, single-centre study, which could introduce bias due to unaccounted and unmeasured confounding factors. Secondly, the sample size was limited, even with the extended follow-up period and broad inclusion criteria. To better understand why the bevacizumab-FOLFIRI combination is more effective in improving PFS in mCRC patients as a second-line treatment, larger-scale prospective studies are needed in the future.

5. Conclusion

In conclusion, our findings indicate that type of chemotherapy used in combination with bevacizumab is an independent predictor of OS when managing mCRC patients. Furthermore, bevacizumab was more effective in prolonging progression-free survival (PFS) in mCRC patients when combined with FOLFIRI compared to capeOX or FOLFOX. This may be due to the superior synergy between irinotecan, the primary drug in FOLFIRI, and bevacizumab, as opposed to oxaliplatin, the main drug in FOLFOX. This effect was particularly pronounced when used as a second-line treatment. Larger-scale prospective studies are required to confirm these results.

Ethical Consideration

Since the data was secondary and publicly available, there was no requirement for ethical approval.

Conflict of Interest

All authors declare no conflict of interest.

References

[1] Siegel, R.L., Wagle, N.S., Cercek, A., Smith, R.A. and Jemal, A. (2023) Colorectal Can-

cer Statistics, 2023. *CA*: *A Cancer Journal for Clinicians*, **73**, 233-254. https://doi.org/10.3322/caac.21772

[2] Yu, Y., Ma, L., Wang, W., Zhao, Y., Xu, H., Cao, J., *et al.* (2022) Health-Related Quality of Life in Advanced Colorectal Cancer Patients in China: A Nationwide Hospital-Based Survey. *Annals of Translational Medicine*, **10**, 328-328. https://doi.org/10.21037/atm-22-991

[3] Zeineddine, F.A., Zeineddine, M.A., Yousef, A., Gu, Y., Chowdhury, S., Dasari, A., *et al.* (2023) Survival Improvement for Patients with Metastatic Colorectal Cancer over Twenty Years. *npj Precision Oncology*, **7**, Article No. 16. https://doi.org/10.1038/s41698-023-00353-4

[4] Popescu, I., Dudău, A., Dima, S., Herlea, V., Croitoru, V.M., Dinu, I.M., *et al.* (2024) Multimodal Treatment of Metastatic Rectal Cancer in a Young Patient: Case Report and Literature Review. *Medicina*, **60**, Article 696. https://doi.org/10.3390/medicina60050696

[5] Aparicio, J., Esposito, F., Serrano, S., Falco, E., Escudero, P., Ruiz-Casado, A., *et al.* (2020) Metastatic Colorectal Cancer. First Line Therapy for Unresectable Disease. *Journal of Clinical Medicine*, **9**, Article 3889. https://doi.org/10.3390/jcm9123889

[6] Dinu, I.M., Mihăilă, M., Diculescu, M.M., Croitoru, V.M., Turcu-Stiolica, A., Bogdan, D., *et al.* (2023) Bevacizumab Treatment for Metastatic Colorectal Cancer in Real-World Clinical Practice. *Medicina*, **59**, Article 350. https://doi.org/10.3390/medicina59020350

[7] Martinelli, E., Cremolini, C., Mazard, T., Vidal, J., Virchow, I., Tougeron, D., *et al.* (2022) Real-World First-Line Treatment of Patients with Brafv600e-Mutant Metastatic Colorectal Cancer: The CAPSTAN CRC Study. *ESMO Open*, **7**, Article 100603. https://doi.org/10.1016/j.esmoop.2022.100603

[8] Margalit, O., Stemmer, A., Chapin, W.J., Shacham-Shmueli, E., Kopetz, S., Andre, T., *et al.* (2024) Duration of Immunotherapy in dMMR/MSI-H Metastatic Colorectal Cancer Patients. *European Journal of Cancer*, **212**, Article 114336. https://doi.org/10.1016/j.ejca.2024.114336

[9] Morris, V.K., Kennedy, E.B., Baxter, N.N., Benson, A.B., Cercek, A., Cho, M., *et al.* (2023) Treatment of Metastatic Colorectal Cancer: ASCO Guideline. *Journal of Clinical Oncology*, **41**, 678-700. https://doi.org/10.1200/jco.22.01690

[10] Gerriets, V. and Kasi, A. (2025) Bevacizumab. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK482126/

[11] Cervantes, A. and Martinelli, E. (2024) Updated Treatment Recommendation for Third-Line Treatment in Advanced Colorectal Cancer from the ESMO Metastatic Colorectal Cancer Living Guideline. *Annals of Oncology*, **35**, 241-243. https://doi.org/10.1016/j.annonc.2023.10.129

[12] Yang, Q., Yin, C., Liao, F., Huang, Y., He, W., Jiang, C., *et al.* (2015) Bevacizumab Plus Chemotherapy as Third or Later-Line Therapy in Patients with Heavily Treated Metastatic Colorectal Cancer. *OncoTargets and Therapy*, **8**, 2407-2413. https://doi.org/10.2147/ott.s88679

[13] Yamazaki, K., Nagase, M., Tamagawa, H., Ueda, S., Tamura, T., Murata, K., *et al.* (2016) Randomized Phase III Study of Bevacizumab Plus FOLFIRI and Bevacizumab Plus Mfolfox6 as First-Line Treatment for Patients with Metastatic Colorectal Cancer (WJOG4407G). *Annals of Oncology*, **27**, 1539-1546. https://doi.org/10.1093/annonc/mdw206

[14] Aranda, E., Viéitez, J.M., Gómez-España, A., Gil Calle, S., Salud-Salvia, A., Graña, B., *et al.* (2020) FOLFOXIRI Plus Bevacizumab versus FOLFOX Plus Bevacizumab for

Patients with Metastatic Colorectal Cancer and ≥3 Circulating Tumour Cells: The Randomised Phase III VISNÚ-1 Trial. *ESMO Open*, **5**, e000944. https://doi.org/10.1136/esmoopen-2020-000944

[15] Reyhanoglu, G. and Smith, T. (2025) Irinotecan. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK554441/

[16] Cainap, C., Ungur, R.A., Bochis, O., Achimas, P., Vlad, C., Havasi, A., *et al.* (2021) Partnering Bevacizumab with Irinotecan as First Line-Therapy of Metastatic Colorectal Cancer Improves Progression Free Survival-A Retrospective Analysis. *PLOS ONE*, **16**, e0248922. https://doi.org/10.1371/journal.pone.0248922

[17] Chai, Y., Liu, J., Zhang, S., Li, N., Xu, D., Liu, W., *et al.* (2024) The Effective Combination Therapies with Irinotecan for Colorectal Cancer. *Frontiers in Pharmacology*, **15**, Article 1356708. https://doi.org/10.3389/fphar.2024.1356708

[18] Rudolf, E., John, S. and Cervinka, M. (2012) Irinotecan Induces Senescence and Apoptosis in Colonic Cells *in Vitro*. *Toxicology Letters*, **214**, 1-8. https://doi.org/10.1016/j.toxlet.2012.08.004

[19] Li, M. and Kroetz, D.L. (2018) Bevacizumab-Induced Hypertension: Clinical Presentation and Molecular Understanding. *Pharmacology & Therapeutics*, **182**, 152-160. https://doi.org/10.1016/j.pharmthera.2017.08.012