Regorafenib combined with immune checkpoint inhibitors versus regorafenib monotherapy as a late-line treatment for metastatic colorectal cancer: a single-center, retrospective cohort study

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Background: Few data are available on metastatic colorectal cancer (mCRC) treated with late-line regorafenib monotherapy or combined with other therapies. This study thus aimed to examine regorafenib combined with immune checkpoint inhibitors (ICIs) compared with regorafenib monotherapy in patients with advanced CRC.

Methods: This single-center retrospective cohort study included patients with advanced CRC who experienced recurrence and progression after standard first- and second-line treatments treatment from November 2018 to December 2021. The patients received regorafenib plus ICIs or regorafenib monotherapy. Treatment response was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST). Overall survival (OS) and progression-free survival (PFS) were analyzed via multivariate analysis.

Results: The combined group and the monotherapy group included 30 and 43 patients, respectively. The median OS (13.7 *vs.* 10.1 months; P=0.10) and PFS (4 *vs.* 3.6 months; P=0.32) were not significantly different between the two groups. In males, the median OS was significantly longer in the combined group compared with the monotherapy group (not reached *vs.* 8.03 months; P=0.02), but the median PFS showed no significant difference (7.23 *vs.* 3.90 months; P=0.16). There was no significant difference in OS (P=0.71) or PFS (P=0.89) in females. Eastern Cooperative Oncology Group performance status (ECOG PS) 1 [*vs.* 0; hazard ratio (HR) =3.13, 95% confidence interval (CI): 1.61–6.10; P<0.001] was independently associated with PFS. ECOG PS 1 (*vs.* 0; HR =3.63, 95% CI: 1.54–8.56; P=0.003) and combined therapy (*vs.* monotherapy; HR =0.47, 95% CI: 0.22–0.99; P=0.048) were associated with OS.

Conclusions: Regorafenib combined with ICIs led to numerically longer PFS and significantly prolonged OS in patients with mCRC compared to regorafenib monotherapy, especially in male patients.

Keywords: Colorectal cancer (CRC); metastatic; immune checkpoint inhibitors (ICIs); regorafenib; prognosis

Introduction

Colorectal cancer (CRC) is a cancer of the colon or rectum, and there were an estimated 1,880,725 new cases of CRC and 915,880 CRC-related deaths in 2020 (1,2). CRC most commonly affects older adults (≥60 years old), and more men are affected than are women (2,3). The risk factors include hereditary syndromes, diet, lifestyle factors, and concurrent diseases (2,4-6). Nearly half of the patients with CRC have distant metastatic CRC (mCRC) at diagnosis (2,7). The prognosis of patients with advanced CRC is poor, with a 5-year survival rate of 71–90% for locoregional disease and 14% for distant-stage disease (8).

When progression or recurrence occurs during or after the standard first-line treatment, there are limited choices for late-line treatment, and the prognosis of the subsequent lines of therapy is poor (3,5-7). Regorafenib is a small-molecule multikinase inhibitor that provides survival benefits in those with mCRC whose disease has progressed after all standard therapies, and a study has shown that regorafenib monotherapy as a late-line treatment for mCRC is effective compared to placebo (9). Additionally, the CONCUR trial reported overall survival (OS) benefits with regorafenib treated compared with placebo in patients with treatment-refractory mCRC in Asian population (10). Immunotherapy is a novel treatment paradigm in solid tumors (11), including CRC (12,13). However, whether regorafenib combined with programmed cell death protein 1 (PD-1) is effective for treating patients with mCRC remains unclear (14,15).

Furthermore, the impact of sex on treatment efficacy remains poorly understood. It has been suggested that the prognosis of female patients is better than that of males (16), but results suggesting the opposite have been reported (17). In China, Xu *et al.* (18) retrospectively examined the benefits of regorafenib in patients with mCRC and reported a disease control rate of 41%. However, there are few reports on patients with mCRC undergoing late-line regorafenib monotherapy or regorafenib-combined therapies and no data regarding the impact of sex on prognosis after these treatments.

Therefore, this single-center, retrospective cohort study analyzed the effectiveness and adverse events (AEs) of regorafenib combined with immune checkpoint inhibitors (ICIs) compared with those of regorafenib monotherapy in treating patients with advanced CRC and examined whether there were differences in treatments and outcomes between males and females. The results of this study may serve as a basis for future clinical trials of late-line treatments in patients with mCRC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-468/rc).

Methods

Study design and patients

This single-center retrospective cohort study included patients with advanced CRC treated in The First Affiliated Hospital of the Army Medical University from November 2018 to December 2021. This study was approved by the ethics committee of The First Affiliated Hospital

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Highlight box

Key findings

- Compared with regorafenib monotherapy, regorafenib combined with immune checkpoint inhibitors (ICIs) provided numerically longer progression-free survival (PFS) and significantly prolonged median overall survival (OS) (13.7 *vs.* 10.1 months) in patients metastatic colorectal cancer (mCRC). Eastern Cooperative Oncology Group performance status (ECOG PS) was independently associated with PFS and OS, while combined therapy was independently associated with better OS.

What is known and what is new?

- Late-line treatment options for mCRC are limited. Previous studies have demonstrated the efficacy of regorafenib monotherapy as a late-line intervention, with favorable OS benefits from regorafenib compared to placebo in patients with treatment-refractory mCRC. The use of ICIs is a novel approach in solid tumors, including CRC. However, the magnitude of the survival benefit of regorafenib combined with ICIs in patients with mCRC remains to be truly defined in a randomized trial.
- We demonstrate combination therapy led to numerically longer PFS and significantly prolonged OS in patients with mCRC than did regorafenib monotherapy. There was a noticeable association of gender with treatment effectiveness. A significantly longer median OS in the combined therapy group compared to the monotherapy group was observed in males, but not in females. The study also identified ECOG PS as an independent factor associated with PFS and OS, emphasizing its relevance in treatment outcomes.

What is the implication, and what should change now?

- To address the need for personalized treatment, further investigation should consider the combined therapy approach for late-line treatment in mCRC, especially in male patients, and clarify the influence of sex on treatment outcomes.

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of the Army Medical University [approval number: (B) KY2022153]. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients underwent follow-up every eight weeks with computed tomography (CT) scans to assess tumor progression according to RECIST 1.1 criteria. Standardized imaging protocols were used across the cohort to ensure consistent assessment.

The inclusion criteria for patients were the following: (I) age between 18 and 80 years; (II) pathologically or histologically confirmed advanced CRC or mCRC with any recurrence and progression after standard first-line and second-line treatment; (III) received regorafenib monotherapy or regorafenib combined with ICIs as late-line treatment for more than one cycle; (IV) at least one measurable lesion according to RECIST 1.1. Exclusion criteria: incomplete data, severe uncontrolled comorbidities, or inability to comply with study protocol. Patients were excluded primarily due to incomplete data which could affect the study's generalizability.

Treatment

The patients with mCRC were divided into the combination and monotherapy groups according to whether they received regorafenib combined with ICIs or regorafenib alone. The dosage of regorafenib was 80, 120, or 160 mg. The ICIs used in the combination group included toripalimab, sintilimab, camrelizumab, and pembrolizumab. Adjustments or interruptions in therapy were made based on the occurrence of AEs or patient intolerance, with dose reductions to the next lower dose level or temporary discontinuation until AEs resolved to grade 1 or lower.

Outcomes

Treatment evaluation was based on RECIST version 1.1. OS was considered to be the time from when regorafenib was initiated to death from any cause. Progression-free survival (PFS) was considered to be the time from when regorafenib was initiated to disease progression of the tumor or death. For the safety evaluation, the AEs included any grade symptomatic or hematological events and were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0.

Statistical analysis

R 4.2.0 software (The R Foundation for Statistical Computing) was used for statistical analysis. The continuous variables conforming to the normal distribution are expressed as the mean ± standard deviation and were analyzed using the Student's t-test; otherwise, they are expressed as the median with the minimum and maximum and were analyzed with the Mann-Whitney test. The categorical data are expressed as numbers and percentages and were analyzed using the chi-squared test or Fisher exact test. OS and PFS were analyzed with the Kaplan-Meier method, and the log-rank test was used to compare groups. Multivariate Cox regression analysis was performed to adjust for potential confounding factors and to identify independent prognostic factors. Two-sided P values <0.05 were considered statistically significant.

Missing data were handled using complete case analysis. Participants with missing data for key variables were excluded from certain analyses to avoid bias. No imputation techniques were used.

Results

Baseline characteristics of the patients

Table 1 presents the baseline characteristics of the patients. The combined group included 30 patients, with a median age of 55.5 (range, 37–76) years and 57% being male. The monotherapy group included 43 patients, with a median age of 54 (range, 27–80) years and 60% being male. There were no significant differences in the other characteristics (all P values >0.05).

Survival

The median OS was 13.7 [95% confidence interval (CI): 10.3 to not available (NA)] months in the combined group and 10.1 (95% CI: 6.57–14.2) months in the monotherapy group, with no significant difference (P=0.10) (*Figure 1A*). The median PFS was 4.0 (95% CI: 2.77–10.90) and 3.6 (95% CI: 3.00–5.77) months in the combined group and the monotherapy group, respectively, with no significant difference (P=0.32) (*Figure 1B*).

In males, the median OS was significantly longer in the combined group compared with the monotherapy group (not reached *vs.* 8.03 months; P=0.02) (*Figure 2A*), but the median PFS showed no significant difference (7.23 *vs.*

Table 1 Patient characteristics

Characteristic	Total sample (n=73)	Monotherapy (n=43)	Combined therapy (n=30)	P
Age (years)				0.96
Mean (SD)	55.6 (11.5)	55.6 (12.6)	55.5 (9.8)	
Median [min, max]	55 [27, 80]	54 [27, 80]	55.5 [37, 76]	
Sex				0.93
Male	43 [59]	26 [60]	17 [57]	
Female	30 [41]	17 [40]	13 [43]	
Smoking status				0.37
No	48 [66]	26 [60]	22 [73]	
Yes	25 [34]	17 [40]	8 [27]	
ECOG				1
0	53 [73]	31 [72]	22 [73]	
1	20 [27]	12 [28]	8 [27]	
Tumor location				0.65
Left	59 [81]	36 [84]	23 [77]	
Right	14 [19]	7 [16]	7 [23]	
Liver metastasis				0.87
No	34 [47]	19 [45]	15 [50]	
Yes	38 [53]	23 [55]	15 [50]	
Not evaluated	1	1	0	
Lung metastasis				0.96
No	35 [48]	20 [47]	15 [50]	
Yes	38 [52]	23 [53]	15 [50]	
Bone metastasis				1
No	67 [92]	39 [91]	28 [93]	
Yes	6 [8]	4 [9]	2 [7]	
Peritoneal metastasis				0.34
No	63 [86]	39 [91]	24 [80]	
Yes	10 [14]	4 [9]	6 [20]	
KRAS, *NRAS*, or *BRAF* mutation				0.74
Mutant	21 [40]	14 [44]	7 [35]	
Wild type	31 [60]	18 [56]	13 [65]	
Not evaluated	21	11	10	
Previous systemic anticancer agents				0.36
Bevacizumab + chemotherapy	41 [56]	22 [51]	19 [63]	
Cetuximab + chemotherapy	14 [19]	10 [23]	4 [13]	
Bevacizumab + chemotherapy, or cetuximab + chemotherapy, at different treatment lines	12 [16]	6 [14]	6 [20]	
Chemotherapy	6 [8]	5 [12]	1 [3]	

Data are presented as n [%] unless otherwise specified. SD, standard deviation; min, minimum; max, maximum; ECOG, Eastern Cooperative Oncology Group.
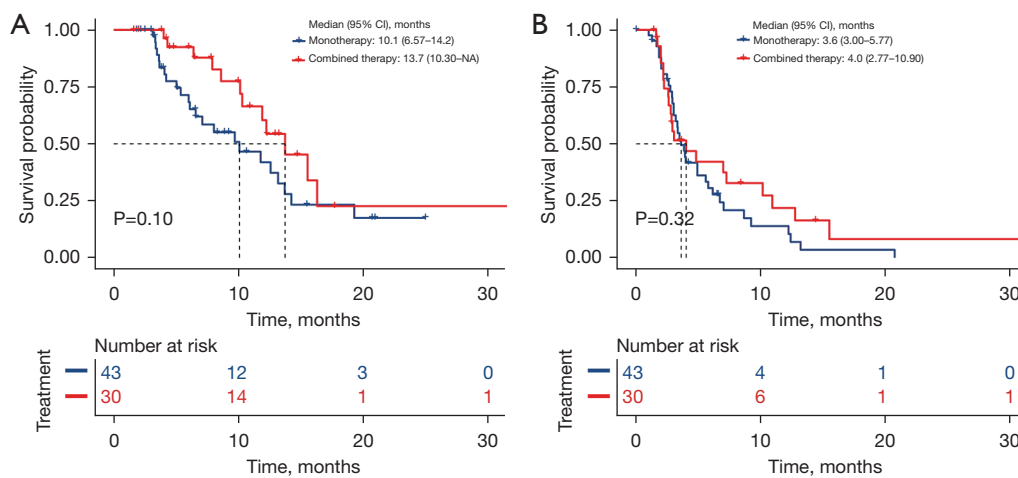
Figure 1 Survival of the monotherapy and combination therapy groups. (A) Overall survival. (B) Progression-free survival. CI, confidence interval; NA, not available.
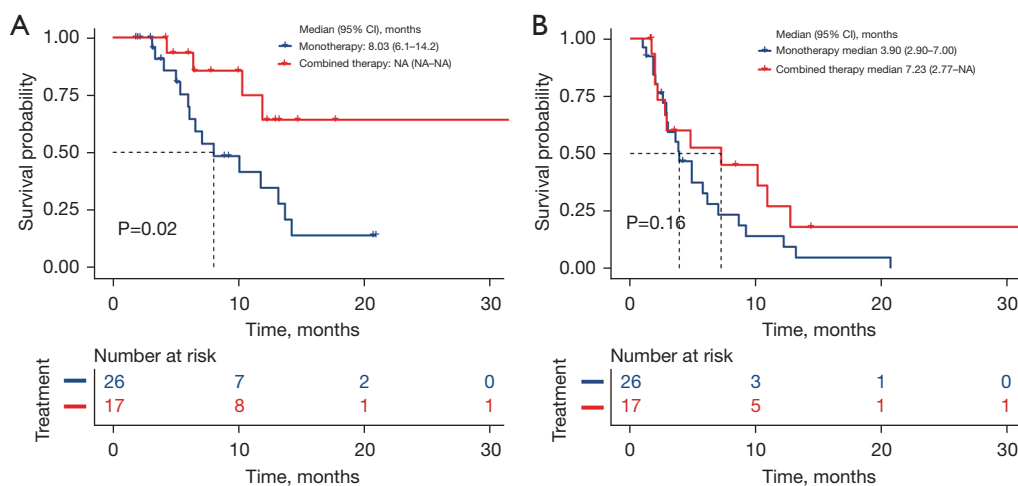

Figure 2 Survival of male patients in the monotherapy and combination therapy groups. (A) Overall survival. (B) Progression-free survival. CI, confidence interval; NA, not available.

3.90 months; P=0.16) (*Figure 2B*). In females, there was no significant difference in OS (P=0.71) or PFS (P=0.89). ECOG PS 1 [*vs.* 0; hazard ratio (HR) =3.13, 95% CI: 1.61–6.1; P<0.001] was independently associated with PFS, and ECOG PS 1 (*vs.* 0; HR =3.63, 95% CI: 1.54–8.56; P=0.003) and combined therapy (*vs.* monotherapy; HR =0.47, 95% CI: 0.22–0.99; P=0.048) were associated with OS (*Figure 3*).

Multivariate analysis

An Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 (*vs.* 0; (HR =3.63, 95% CI: 1.54–8.56; P=0.003) and combined therapy (*vs.* monotherapy;

HR =0.47, 95% CI: 0.22–0.99; P=0.048) were associated with OS (*Table 2*). This suggests that patient performance status should be a key consideration in treatment planning for mCRC. In addition, the multivariate analysis of PFS showed that only ECOG PS 1 (*vs.* 0; HR =3.13, 95% CI: 1.61–6.10; P<0.001) was independently associated with PFS (*Table 3*).

AEs

As shown in *Table 4*, all patients experienced AEs, with grade ≥3 AEs observed in 46.7% of the combined group and 25.6% of the monotherapy group. The most common
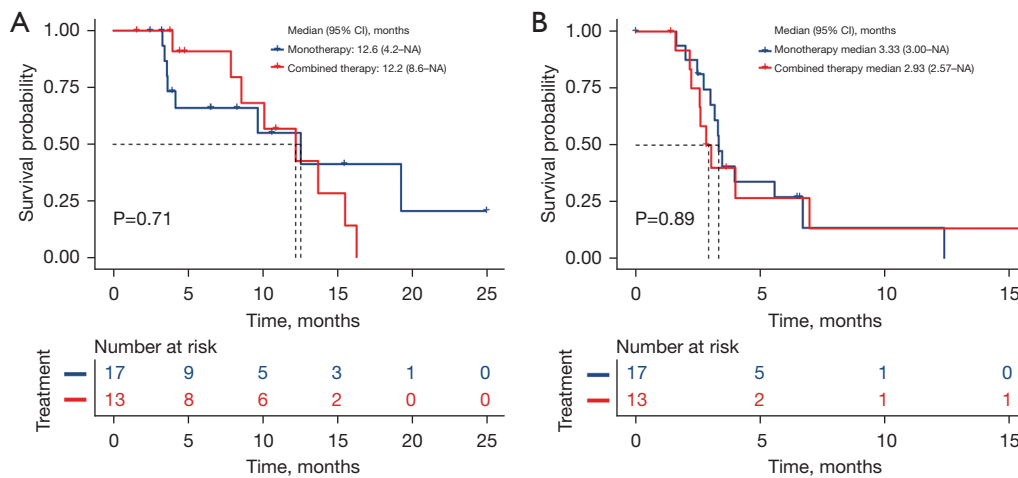
Figure 3 Survival of female patients in the monotherapy and combination therapy groups. (A) Overall survival. (B) Progression-free survival. CI, confidence interval; NA, not available.

AEs in the combined and monotherapy groups were hand-foot syndrome (76.7% and 60.5%, respectively), rash (63.3% and 51.1%, respectively), and hypertension (56.7% and 39.5%, respectively). Dose reductions were required in 30% of combined group patients and 15% of monotherapy group patients, while therapy discontinuation due to AEs occurred in 10% and 5% of patients, respectively.

Discussion

Few data are available on mCRC treated with late-line regorafenib monotherapy or combination with other therapies. This real-world study aimed to compare regorafenib combined with ICIs with regorafenib monotherapy for the treatment of patients with mCRC. An absolute benefit of patients in relation to OS and PFS was observed in the combination group indicating effectiveness of regorafenib plus ICIs in mCRC. Main clinical results indicated regorafenib combined with ICIs led to numerically longer PFS and significantly prolonged OS in patients with mCRC compared to regorafenib monotherapy, especially in male patients.

Among all patients, there was no significant difference in PFS. Therefore, the combination of regorafenib with an ICI did not appear to provide more benefits to the patients compared with regorafenib monotherapy. Xu et al. (18) reported that despite regorafenib-ICI combined therapy achieving longer PFS than regorafenib monotherapy for mCRC, there were no marked differences between the OS of these two therapies. In the multivariate analysis of our

study, combined treatment was associated with better OS but not better PFS. The PFS of the combination therapy group in our study was 4 months, which was shorter than that reported in the REGONIVO trial (7.9 months; regorafenib with nivolumab) (19) but longer than that reported in the REGOTORI trial (2.1 months; regorafenib with toripalimab) (20) and REGOMUNE trial (2.5 months; regorafenib with avelumab) (21). In a real-world study of patients with mCRC treated with regorafenib and ICIs in China, the median PFS was 3.1 months (22). Moreover, Chen et al. (23) reported a median PFS of 4.0 months in patients with mCRC treated with regorafenib and PD-1 inhibitors. However, all these studies, including our own, had small sample sizes that might have masked the benefits of regorafenib combined with ICIs.

Remarkably, analysis by subgroups suggested that among the female patients, there were no obvious differences in either PFS or OS between the combination and monotherapy groups, indicating that adding ICIs to regorafenib therapy might not provide further benefits to female patients with mCRC. On the other hand, although there were no differences in PFS among the male patients, the OS of the combination group was longer than that of the monotherapy group. Therefore, combining regorafenib with ICIs could be considered in male patients with mCRC. Regarding the differences in benefits between males and females, conflicting results have been reported, with some studies suggesting a better prognosis in females (16) and others a better prognosis in males (17). In one meta-analysis, sex was significantly associated with survival in

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Table 2 Multivariate analysis of the factors associated with OS

Characteristic	Univariable		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.01 (0.98–1.05)	0.38		
Smoking status		0.60		
No	Ref.			
Yes	0.82 (0.40–1.69)			
Sex		0.62		
Male	Ref.			
Female	1.18 (0.61–2.30)			
ECOG		0.01		0.003
0	Ref.		Ref.	
1	2.60 (1.23–5.51)		3.63 (1.54–8.56)	
Tumor location		0.36		
Left	Ref.			
Right	1.51 (0.62–3.66)			
Liver metastases		0.61		
No	Ref.			
Yes	1.19 (0.60–2.34)			
Lung metastasis		0.98		
No	Ref.			
Yes	1.01 (0.52–1.97)			
Bone metastasis		0.23		
No	Ref.			
Yes	1.71 (0.70–4.17)			
Peritoneal metastasis		0.59		
No	Ref.			
Yes	0.75 (0.26–2.14)			
Previous treatment		0.89		0.62
Bevacizumab + chemotherapy	Ref.		Ref.	
Cetuximab + chemotherapy	0.94 (0.37–2.36)		0.75 (0.29–1.97)	
Bevacizumab + chemotherapy, or cetuximab + chemotherapy, at different treatment lines	0.83 (0.31–2.23)		1.32 (0.47–3.72)	
Chemotherapy	1.35 (0.50–3.66)		1.74 (0.61–4.99)	
Treatment		0.11		0.048
Monotherapy	Ref.		Ref.	
Combined therapy	0.56 (0.28–1.14)		0.47 (0.22–0.99)	

OS, overall survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval; Ref., reference.

1504

Chen et al. Regorafenib plus ICIs for mCRC

Table 3 Multivariate analysis of the factors associated with PFS

Characteristic	Univariable		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.01 (0.99–1.03)	0.43		
Smoking status		0.59		
No	Ref.			
Yes	0.86 (0.49–1.50)			
Gender		0.25		
Male	Ref.			
Female	1.37 (0.80–2.36)			
ECOG		0.002		<0.001
0	Ref.		Ref.	
1	2.53 (1.38–4.63)		3.13 (1.61–6.10)	
Tumor location		0.87		
Left	Ref.			
Right	0.94 (0.47–1.88)			
Liver metastases		0.51		
No	Ref.			
Yes	1.2 (0.7–2.05)			
Lung metastasis		0.95		
No	Ref.			
Yes	0.98 (0.58–1.67)			
Bone metastasis		0.58		
No	Ref.			
Yes	0.77 (0.31–1.94)			
Peritoneal metastasis		0.44		
No	Ref.			
Yes	1.36 (0.61–3.03)			
KRAS, *NRAS*, or *BRAF* mutation		0.94		
Mutant	Ref.			
Wild type	0.98 (0.53; 1.83)			
Previous treatment		0.77		0.24
Bevacizumab + chemotherapy	Ref.		Ref.	
Cetuximab + chemotherapy	1.12 (0.55–2.25)		0.84 (0.4–1.76)	
Bevacizumab + chemotherapy, or cetuximab + chemotherapy, at different treatment lines	1.46 (0.72–2.95)		2.04 (0.98–4.28)	
Chemotherapy	1.03 (0.43–2.50)		1.36 (0.55–3.37)	
Treatment		0.32		0.09
Monotherapy	Ref.		Ref.	
Combined therapy	0.76 (0.44–1.31)		0.6 (0.34–1.09)	

PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval; Ref., reference.

Table 4 Adverse reactions

Characteristic	Total (n=73)		Combination therapy (n=30)		Monotherapy (n=43)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Total	73 (100.0)	25 (34.2)	30 (100.0)	14 (46.7)	43 (100.0)	11 (25.6)
Hand-foot syndrome	49 (67.1)	8 (11.0)	23 (76.7)	5 (16.7)	26 (60.5)	3 (7.0)
Hypertension	34 (46.6)	7 (9.6)	17 (56.7)	5 (16.7)	17 (39.5)	2 (4.6)
Rash	41 (56.2)	10 (13.7)	19 (63.3)	5 (16.7)	22 (51.1)	5 (11.6)
Fatigue	36 (49.3)	0	16 (53.3)	0	20 (46.5)	0
Fever	25 (34.2)	0	11 (36.7)	0	14 (32.5)	0
Proteinuria	16 (21.9)	5 (6.8)	7 (23.3)	3 (10.0)	9 (20.9)	2 (4.6)
Oral mucositis	11 (15.1)	1 (1.4)	5 (16.7)	1 (3.3)	6 (13.9)	0
Diarrhea	28 (38.4)	4 (5.5)	13 (43.3)	2 (6.7)	15 (34.9)	2 (4.6)
Decreased appetite	29 (39.7)	0	12 (40.0)	0	17 (39.5)	0
Liver dysfunction	11 (15.1)	1 (1.4)	5 (16.7)	1 (3.3)	6 (13.9)	0
Hyperthyroidism	6 (8.2)	0	4 (13.3)	0	2 (4.6)	0
Hypothyroidism	9 (12.3)	0	5 (16.7)	0	4 (9.3)	0

Data are presented as n (%).

patients with mCRC (24); however, any conclusion drawn from this comparison should be done with caution since this meta-analysis included studies published up to 2017, and immunotherapy data were only sparsely published before 2017. Nonetheless, sex should be considered in the selection of therapy for mCRC, as male sex has several covariates. For example, male sex is often associated with higher frequencies of smoking and alcohol drinking (25,26), and alcohol and tobacco affect the immune system and response to immunotherapy (27-29). Unfortunately, the sample size of our study was not sufficiently large to examine the covariates of sex. Furthermore, the male group showed discrepant results regarding OS and PFS. Interestingly, this is being increasingly observed within the context of targeted therapies and immunotherapies, which often show negligible improvements in PFS but substantial improvements in OS (30-33).

The incidence of grades ≥3 AEs in this study was lower than those reported in a previous retrospective study (18) and the CORRECT study (9). This might be explained by the retrospective design of our study and the fact that the included patients had received less previous treatment. Generally, there were slightly more adverse reactions in the combined group than in the monotherapy group, which is consistent with similar research (15,18,22,23). Among the AEs, hand-foot syndrome had the highest frequency in both groups, which is in line with the reported AE incidence in the literature (15,18,22,23).

This study had certain limitations. First, we employed a retrospective study design that was limited to the data available in the patient charts, including follow-up. Second, the sample size was relatively small.

Conclusions

In conclusion, although there was no significant difference in benefit between the combined group and the monotherapy group in the general population, an absolute benefit of patients in relation to OS and PFS was observed, with the patients in the combined group obtaining numerically longer OS and PFS than those in the monotherapy group. Besides the common AEs associated with tyrosine kinase inhibitors (TKIs), ICIs also lead to immune-related AEs. When combined, the incidence of AEs is significantly higher than in the monotherapy group. However, considering that AEs are manageable and patients can benefit more from combination therapy, this risk is acceptable. Hence, different treatment strategies should be considered for male and female patients, but additional studies are necessary to verify these results.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-468/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-468/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-468/prf

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of The First Affiliated Hospital of the Army Medical University [approval number: (B) KY2022153]. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study.

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