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ORIGINAL RESEARCH

Feasibility and Tolerability of Anlotinib Plus PD-1 Blockades for Patients with Treatment-Refractory Metastatic Colorectal Cancer: A Retrospective Exploratory Study

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Objective: Therapeutic regimens are relatively scarce among patients with treatment-refractory metastatic colorectal cancer (CRC). This study aimed to determine the feasibility and tolerability of anlotinib plus PD-1 blockades in patients with treatment-refractory metastatic CRC retrospectively.

Methods: A total of 68 patients with previously treated metastatic CRC who received anlotinib plus PD-1 blockades in clinical practice were included in this study retrospectively. Demographic and clinical characteristics of the patients, therapeutic outcomes and safety profile during administration were collected and briefly analyzed. All subjects were followed up regularly. Therapeutic outcomes, including drug response and prognosis, were presented, and a safety profile was depicted to illustrate the adverse reactions.

Results: A total of 68 patients with treatment-refractory metastatic CRC who received anlotinib plus PD-1 blockades in clinical practice were included in the final analysis. Best therapeutic response during treatment indicated that partial response was observed in 11 patients, stable disease was noted in 41 patients, and progressive disease was found in 16 patients, producing an objective response rate of 16.2% (95% CI: 8.4%–27.1%) and a disease control rate of 76.5% (95% CI: 64.6%–85.9%). Prognostic analysis suggested that the median progression-free survival (PFS) of the 68 patients was 5.3 months (95% CI: 3.01–7.59), and the median overall survival (OS) was 12.5 months (95% CI: 9.40–15.60). Of the 11 patients who responded, the median duration of response was 6.7 months (95% CI: 2.89–10.53). Safety profile during treatment showed that patients experienced adverse reactions regardless of grade, and grade ≥3 adverse reactions were found in 61 patients (89.7%) and 41 patients (60.3%), respectively. Common adverse reactions were hypertension, myelosuppression (including leukopenia, neutropenia, thrombocytopenia, and anemia), fatigue, and hand-foot syndrome.

Conclusion: Anlotinib plus PD-1 blockades demonstrated encouraging efficacy and acceptable safety profile in patients with treatment-refractory metastatic CRC preliminarily in clinical practice. This conclusion should be confirmed in prospective clinical trials.

Keywords: colorectal cancer, anlotinib, PD-1 blockades, efficacy, safety

Introduction

Colorectal cancer (CRC) was one of the most common gastrointestinal cancer globally, and the incidence of CRC increased dramatically. It was estimated that there were approximately 1.88 million new cases and 0.92 million new deaths each year worldwide in 2020.[1] Currently, it was estimated that about 0.56 million new cases and 0.29 new deaths of CRC were observed in China in 2020.[2] Although surgical resection was the only way to cure patients with early-stage CRC, approximately a quarter of the patients were diagnosed with distant metastases, when curative resection was unachievable, rendering systemic therapy or best supportive care as the only available therapeutic options.[3] Metastatic CRC was still a major global health concern, and the development of innovative therapeutic strategies was essential to improve patient outcomes. Fortunately, recent years had witnessed great progress in the treatment of metastatic CRC in terms of molecular

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and targeted therapy, thus rendering the mCRC as one of the most successful types of cancer in precision medicine.[4] For metastatic or unresectable CRC, standard first-line or second-line treatments involved a combination of fluorouracil-based chemotherapy (5-Fu plus either oxaliplatin or irinotecan) and molecular targeted drugs such as anti-VEGF monoclonal antibody (bevacizumab) or anti-EGFR monoclonal antibody (cetuximab).[5] These combination regimens were proved to improve the progression-free survival (PFS) and overall survival (OS) with a steady elevation in median OS to approximately 30 months in numerous clinical trials during the last two decades.[6] Amazingly, recent years had witnessed outstanding research progress in the field of metastatic CRC who were mismatch repair deficient (dMMR) status in terms of first-line treatment, the Keynote-177 trial achieved significantly superior clinical outcomes of pembrolizumab single-agent compared with chemotherapy [objective response rate (ORR): 45.1% vs 33.1%, median PFS: 16.5 vs 8.2 months, median OS: NR vs 36.7 months].[7] However, many patients might progress of the first-line therapy and switch to other combined chemotherapy regimens as second-line treatment, achieving survival benefits consecutively.[8] Still and all, a certain amount of patients were able to receive the third-line treatment; to our knowledge, the FRESCO and CONCUR trials convinced that the antiangiogenic small-molecule tyrosine kinase blockades (TKIs) fruquintinib and regorafenib might further bring survival benefits for patients with CRC and were approved by guidelines as the third-line treatment for patients with metastatic CRC in China, respectively.[9,10] However, the disappointing ORR of fruquintinib and regorafenib (4.7% and 4.0%, respectively) highlighted that novel therapeutic options were still needed to be explored to provide patients with promising efficacy and acceptable safety profile in clinical practice.[11]

Anlotinib was also a novel oral small-molecule multi-target TKI with the inhibition of VEGFR2~3, FGFR1~4, PDGFRα~β, c-Kit and Ret,[12] and preclinical and clinical studies suggested that anlotinib monotherapy demonstrated potential anti-tumor activity and acceptable adverse reactions in patients with treatment-refractory metastatic CRC according to the Phase III clinical trial (ALTER0703).[13] In spite of the fact that anlotinib might significantly prolong the PFS in patients with CRC, the ORR was disappointing (ORR = 4.3%), suggesting that a combination therapeutic strategy was needed to improve the therapeutic outcomes clinically.

Notably, although the Keynote-177 study confirmed that pembrolizumab demonstrated encouraging therapeutic activity in patients with dMMR mCRC, which only accounted for approximately 4–5% of all metastatic CRC,[14] almost 95% of CRC patients with mismatch repair-proficiency (pMMR) status were cold tumors and ineffective in immunotherapy single-agent therapy.[15] A previous study found that the ORR of pembrolizumab monotherapy in patients with pMMR CRC was 0%.[16] Fortunately, recent accumulating basic research evidence highlighted that immunotherapy resistance might be partially relieved by combining antiangiogenic targeted drug treatment, and emerging evidence showed that appropriate antiangiogenic administration might switch the tumor immune environment from immune-suppressive to immune-active status.[17] Preclinical studies using mouse models of CRC provided compelling evidence for the synergistic action of combining antiangiogenic agents and programmed cell death protein 1 (PD-1) blockades, which demonstrated improved tumor regression, prolonged survival, and enhanced immune cell infiltration into the tumor microenvironment. Furthermore, the combination therapy was observed to promote the formation of high endothelial venules, specialized blood vessels that facilitated immune cell trafficking into tumors.[18] Therefore, the combination of antiangiogenic agents and PD-1 blockades was deemed as a promising treatment approach for metastatic CRC who were pMMR status according to REGONIVO trial.[19] Nevertheless, several challenges were still needed to be addressed for the optimal implementation of this combination therapy: exploring predictive biomarkers that might guide patient selection and therapeutic response assessment was crucial. Additionally, identifying the mechanisms of resistance to combination therapy and managing potential toxicities are ongoing areas of research currently.[20]

Therefore, this study aimed to determine the feasibility and tolerability of anlotinib combined with PD-1 blockades in patients with treatment-refractory metastatic CRC in real-world clinical practice.

Patients and Methods

Study Design and Eligibility Criteria

Since anlotinib and PD-1 blockade were licensed in China for over four years, a certain number of patients with metastatic CRC with pMMR status had received anlotinib plus PD-1 blockade in clinical practice; therefore, our

exploration was conducted as a retrospective study. As a result, patients with metastatic CRC who were heavily treated with at least two previous systemic regimens in the Department of Oncology of the People's Hospital of Zhengzhou from August 2018 to December 2022 were screened and consecutively enrolled in this study. Inclusion criteria included: (1) histologically confirmed colon cancer or rectal cancer with distant metastatic state; (2) older than 18 years; (3) eastern cooperative oncology group (ECOG) performance status (PS) score ranged from 0 to 2, indicating the well functional status of the individual; (4) The patients included in the study had received at least two prior lines of systemic standard therapy that included fluoropyrimidine, oxaliplatin, and irinotecan with or without anti-vascular endothelial growth factor or epidermal growth factor receptor monoclonal antibodies; (5) patients were administered with anlotinib combined with PD-1 blockades in clinical practice; (6) patients were mismatch repair-proficiency (pMMR) or the mismatch repair status was not available; (7) to assess the anticancer activity, it was required that the patients had at least one measurable target lesion, in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).[21] Furthermore, exclusion criteria manifested as: (1) patients with a history of autoimmune diseases or those who were currently receiving steroids or other immunosuppressive drugs; (2) patients had concomitant presence of more than one tumor or other serious diseases that might potentially compromise their survival; (5) response assessment data were not available; however, patients who were lost to follow-up during subsequent treatment were still deemed as eligible for inclusion in this study. Ultimately, our study included 68 patients; the study profile is presented in Figure 1 for reference.

In this study, the primary endpoint was PFS. The secondary endpoints included ORR, disease control rate (DCR), duration of response (DoR), OS, and safety profile. All participants provided written informed consent following the principles of the Declaration of Helsinki and the study was approved by the ethics committee of the People's Hospital of Zhengzhou.

Administration of Anlotinib and PD-1 Blockades and Assessment of Efficacy and Safety

All patients with CRC in this study were treated with anlotinib plus PD-1 blockades in clinical practice. PD-1 blockades included camrelizumab, sintilimab, tislelizumab and pembrolizumab, all the PD-1 blockades were licensed in China. The dosage of the four PD-1 blockades was 200 mg, administered intravenously on day 1, and every three weeks was

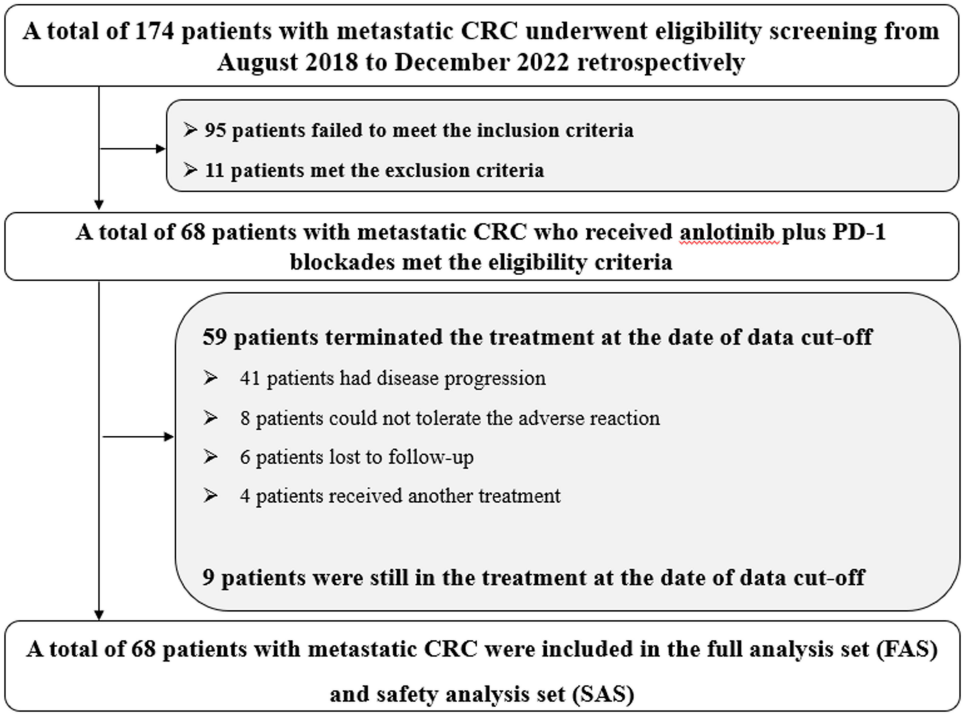

Figure 1 The study profile of this retrospective research regarding anlotinib plus PD-1 blockades for patients with treatment-refractory metastatic colorectal cancer.

considered as one cycle. Anlotinib monotherapy was administered orally at an initial dosage of 12mg or 10mg (determined by the investigator) daily with warm water for two weeks on and one week off; every three weeks was deemed as one cycle. The combined treatment was continued until disease progression or intolerable adverse reactions were observed. The option of selecting a single-drug treatment in cases of intolerance to the two-drug treatment regimen was permitted until disease progression. Additionally, anlotinib dosage reduction was adjusted according to patient's tolerance.

Therapeutic response was assessed according to the RECIST version 1.1 criteria, investigator's judgement. Computed tomography (CT) scans were used to evaluate target lesions in the lungs and liver, while CT or magnetic resonance imaging (MRI) scans were used for the target lesions in other positions. These evaluations were performed both before and after the administration of anlotinib plus PD-1 blockade therapy in each patient with CRC. The radiological assessment of target lesions was performed every two cycles or when necessary, such as when the clinical symptoms of the patients worsened. The ORR and DCR calculations in this study were defined in a previous study.[22]

With regard to the adverse reactions of the combined regimen during the treatment, the safety profile was recorded by severity during the treatment to present the overall adverse reactions according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.[23]

In addition, OS analysis was performed in this retrospective study. The clinical demographic characteristics, adverse reactions, and progression status of each patient were collected from the electronic medical record system during hospitalization. Subsequent follow-ups were performed primarily via telephone calls. Patients were followed up monthly to inquire about their mortality status. The data cut-off date for this study was May 15, 2023.

Statistical Analysis

All analyses were performed using SPSS version 25.0. Continuous and discrete variables were expressed as median (range) and number of patients (percentage), respectively. Survival endpoints (PFS and OS) were analyzed according to the previous study, DoR was defined as the duration from the date of first assessment of the tumor as CR or PR to the date of first assessment of PD or death from any cause.[24] Stata 14.0 software was adopted to generate survival curves for presenting PFS and OS data. The Log rank test was performed to analyze the differences in survival. For PFS, a multivariate Cox regression analysis was conducted, including variables that showed significance in the univariate analysis. A P-value of less significance was set at $P<0.05$.

Results

Demographic and Clinical Characteristics of the 68 Patients with Metastatic CRC

The demographic and clinical characteristics of 68 patients with treatment-refractory metastatic CRC are shown in Table 1. All the 68 patients included in this study had CRC in the clinical practice. Notably, 53 patients had left-sided cancer, and 15 patients had right-sided colon cancer. Additionally, the majority of patients had a pMMR status (86.8%), while nine patients were not available for MMR status. Furthermore, initial dosages of 12 and 10 mg of anlotinib were observed in 44 and 24 patients, respectively. Four PD-1 blockades (camrelizumab, sintilimab, tislelizumab, and pembrolizumab) were administered to 21, 19, 17, and 11 patients, respectively.

Therapeutic Outcomes of the 68 Patients with Treatment-Refractory Metastatic CRC

The results of radiographic assessment of each patient using CT or MRI were collected and recorded. The best overall response of the 68 patients during anlotinib plus PD-1 blockades administration suggested that PR was observed in 11 patients, SD in 41 patients, and PD in 16 patients, which yielded an ORR of 16.2% [95% confidence interval (CI): 8.4%–27.1%] and a DCR of 76.5% (95% CI: 64.6%–85.9%). Briefly, the waterfall plot for the best percentage change in target lesions among the 68 patients with metastatic CRC who received anlotinib plus PD-1 blockade therapy is illustrated in Figure 2. More than half of the patients experienced varying degrees of reduction in target lesions. Interestingly, the CT scan of the target lesions in the liver of a patient with PR before and after the administration of anlotinib plus PD-1 blockade is illustrated in Figure 3, where the tumor in the liver shrank significantly after two cycles of treatment with anlotinib plus tislelizumab.

Table 1 Demographic and Clinical Characteristics of the 68 Patients with Treatment-Refractory Metastatic CRC

Characteristics	Total Patients (N = 68)	Percentage
Age (Years)		
Median (range)	57 (25–79)	
≥60	27	39.7%
<60	41	60.3%
Gender		
Male	45	66.2%
Female	23	33.8%
ECOG performance status score		
0–1	49	72.1%
2	19	27.9%
Tumor location		
Left-sided colorectal cancer	53	77.9%
Right-sided colon cancer	15	22.1%
Previous lines of treatment		
<3rd line	16	23.5%
≥3rd line	52	76.5%
History of surgery		
Yes	39	57.4%
No	29	42.6%
MMR status		
pMMR	59	86.8%
Unknown	9	13.2%
Number of metastases sites		
≤3	47	69.1%
>3	21	30.9%
Previous anti-VEGF therapy		
Yes	39	57.4%
No	29	42.6%
Previous anti-EGFR therapy		
Yes	18	26.5%
No	50	73.5%
Live metastasis		
Yes	51	75.0%
No	17	25.0%
Initial dosage of anlotinib (mg)		
12	44	64.7%
10	24	35.3%
PD-1 blockades		
Camrelizumab	21	30.9%
Sintilimab	19	27.9%
Tislelizumab	17	25.0%
Pembrolizumab	11	16.2%

Abbreviations: CRC, Colorectal Cancer; ECOG, Eastern Cooperative Oncology Group; pMMR, mismatch repair proficiency.

Prognosis of the 68 Patients with Treatment-Refractory Metastatic CRC

The last follow-up date of the present study was May 15, 2023, producing a median follow-up duration in the 68 patients with a metastatic CRC of 10.5 months (follow-up range: 0.4–28.5 months). A total of 48 progression or death events were detected in the PFS analysis, which yielded a PFS maturity rate of 70.6%. As shown in Figure 4, the median PFS of

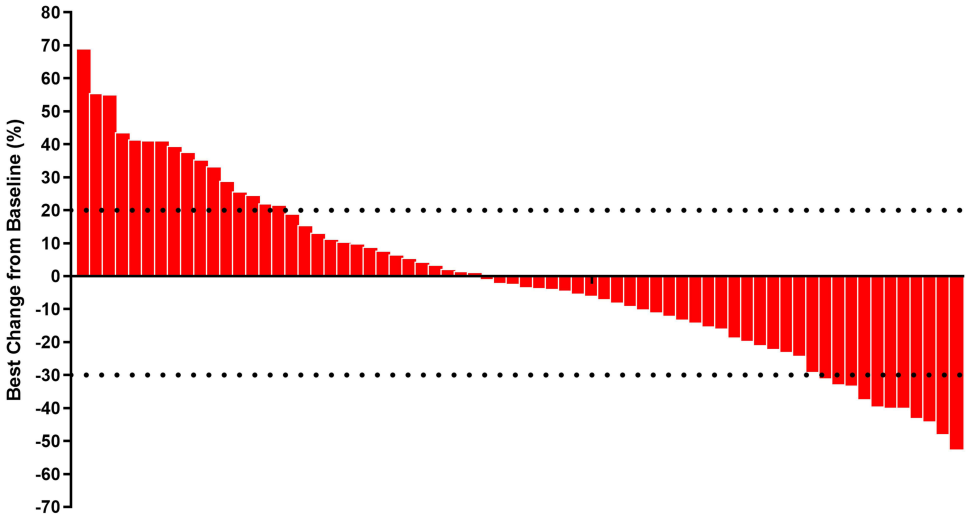

Figure 2 Waterfall plot for the best percentage change in target lesion of the 68 patients with treatment-refractory metastatic colorectal cancer who received anlotinib plus PD-1 blockades.

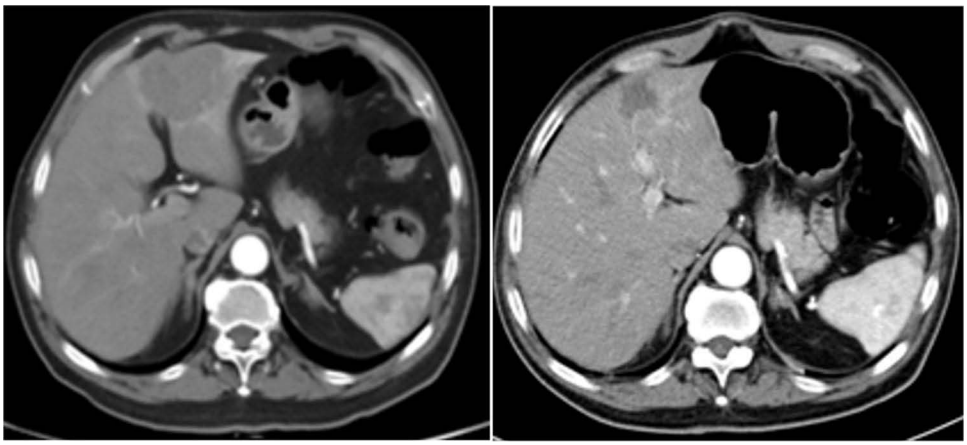

Figure 3 The CT scan results of the changes for target lesions in liver sites of one patient with metastatic colorectal cancer before and after the administration of anlotinib plus tislelizumab.

the 68 patients treated with anlotinib plus PD-1 blockades was 5.3 months (95% CI: 3.01–7.59). Furthermore, the 6-month PFS and 12-month PFS rates were 46.6% (95% CI: 34.1%–58.2%) and 25.2% (95% CI: 14.1%–37.9%), respectively.

Furthermore, we noticed that a total of 11 patients achieved PR in this study; as a result, the DoR data among the 11 PR patients was analyzed and illustrated in Figure 5. Accordingly, the median DoR among the 11 patients was 6.7 months (95% CI: 2.89–10.53). Furthermore, the 6-month and 12-month DoR rates were 54.6% (95% CI: 22.9%–78.0%) and 36.4% (95% CI: 11.2%–62.7%), respectively.

Correlation between PFS and baseline characteristics was identified using median PFS and 95% CI (Table 2). It seemed that all patients might benefit from anlotinib combined with PD-1 blockades uniformly, regardless of their demographic and clinical characteristics. Unfortunately, the univariate analysis indicated that patients with ECOG performance status 2 score and right-sided colon cancer conferred a relatively shorter PFS than those with 0–1 score and left-sided colorectal cancer (median PFS: 4.2 vs 5.8 months, P=0.013 and 3.8 vs 5.8 months, P=0.008). Interestingly, it seemed that patients with liver metastasis showed a trend for worse PFS compared to those without liver metastasis (median PFS: 4.5 vs 5.8 months), although the difference was not statistically significant (P=0.095).

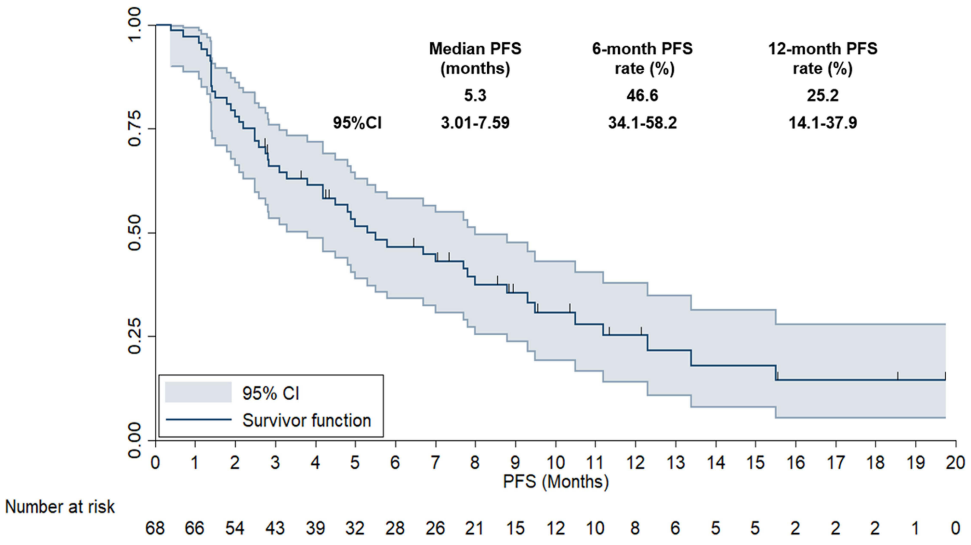

Figure 4 Progression-free survival curve of the 68 patients with treatment-refractory metastatic colorectal cancer who received anlotinib plus PD-1 blockades.

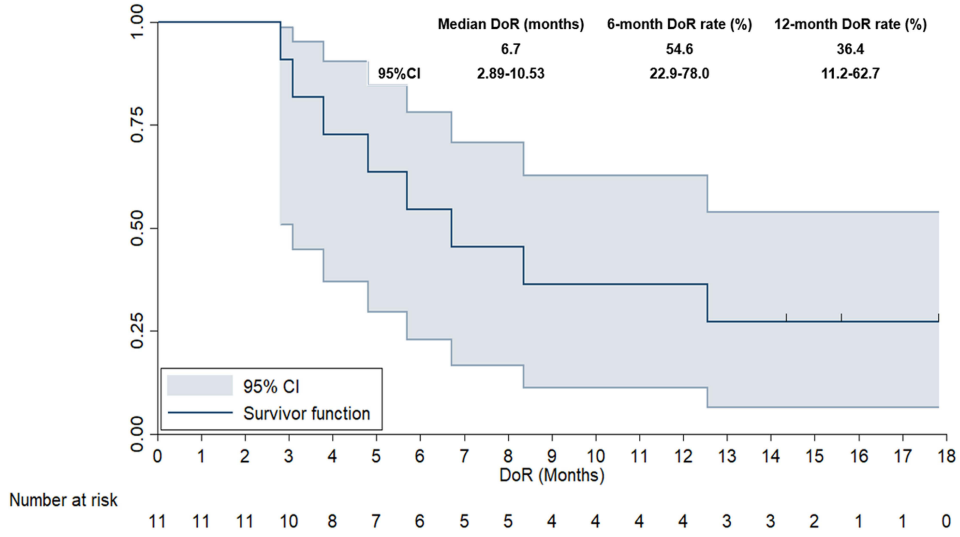

Figure 5 Duration of response of the 11 patients with treatment-refractory metastatic colorectal cancer who received anlotinib plus PD-1 blockades and achieved partial response.

Furthermore, given that the follow-up duration of this study was sufficiently long, OS was also analyzed. A total of 49 death events were observed at the date of the data cut-off, producing an OS maturity of 72.1%. As illustrated in Figure 6, the median OS of 68 patients administered with anlotinib plus PD-1 blockades was 12.5 months (95% CI: 9.40–15.60). The 12-month and 24-month OS rates were 50.3% (95% CI: 37.7%–61.6%) and 18.6% (95% CI: 8.8%–31.2%), respectively.

Safety Profile

As described in the Methods section, the maximum adverse reactions among the 68 patients with metastatic CRC observed during anlotinib plus PD-1 blockade therapy were presented, and adverse reactions, regardless of grade, were detected in 61 patients (89.7%), including a total of 41 patients with grade ≥3 adverse reactions (60.3%). One female patient (1.5%) with liver

Table 2 Univariate and Multivariate Analysis Between PFS and Baseline Characteristics of the 68 Patients with Treatment-Refractory Metastatic CRC

Characteristics	Median PFS (95% CI)	*P* (Univariate Analyses)	Multivariate Analyses	
			HR (95% CI)	*P*
Age (Years)				
≥60	5.3 (3.15–7.45)	0.512		
<60	5.5 (4.11–6.89)			
Gender				
Male	4.9 (3.04–6.76)	0.387		
Female	5.5 (3.89–7.11)			
ECOG performance status score				
0–1	5.8 (4.12–7.48)	0.013	0.71 (0.49–0.92)	0.028
2	4.2 (2.88–5.52)			
Tumor location				
Left-sided colorectal cancer	5.8 (3.91–7.69)	0.008	0.66 (0.41–0.89)	0.011
Right-sided colon cancer	3.8 (2.11–5.49)			
Previous lines of treatment				
<3rd line	5.3 (3.53–7.07)	0.616		
≥3rd line	5.0 (3.76–6.24)			
History of surgery				
Yes	5.5 (4.48–6.52)	0.538		
No	5.0 (3.76–6.24)			
MMR status				
pMMR	5.3 (3.27–7.33)	0.631		
Unknown	5.5 (4.11–6.89)			
Number of metastases sites				
≤3	5.8 (4.09–7.51)	0.318		
>3	5.0 (3.19–6.81)			
Previous anti-VEGF therapy				
Yes	5.0 (3.91–6.09)	0.478		
No	5.3 (3.11–7.49)			
Previous anti-EGFR therapy				
Yes	5.3 (4.14–6.46)	0.536		
No	5.5 (3.78–7.22)			
Liver metastasis				
Yes	4.5 (3.03–5.97)	0.095		
No	5.8 (4.09–7.51)			
Initial dosage of anlotinib (mg)				
12	5.5 (4.03–6.97)	0.438		
10	5.0 (3.86–6.14)			
PD-1 blockades				
Camrelizumab	4.8 (3.13–6.3)	0.448		
Sintilimab	5.0 (3.67–6.33)			
Tislelizumab	4.9 (3.25–6.55)			
Pembrolizumab	5.8 (4.56–7.04)			

Abbreviations: CRC, Colorectal Cancer; ECOG, Eastern Cooperative Oncology Group; pMMR, mismatch repair proficiency.

metastasis of colon cancer died of liver failure after two cycles of treatment with anlotinib plus camrelizumab. As shown in Table 3, common adverse reactions manifested as hypertension, myelosuppression (including leukopenia, neutropenia, thrombocytopenia, and anemia), fatigue, and hand-foot syndrome, with an incidence of >30% in this study. The most common grade ≥3 adverse reactions were myelosuppression (17.6%), hypertension (16.2%), hepatotoxicity (10.3%), fatigue (5.9%), diarrhea (5.9%), and nausea and vomiting (5.9%).

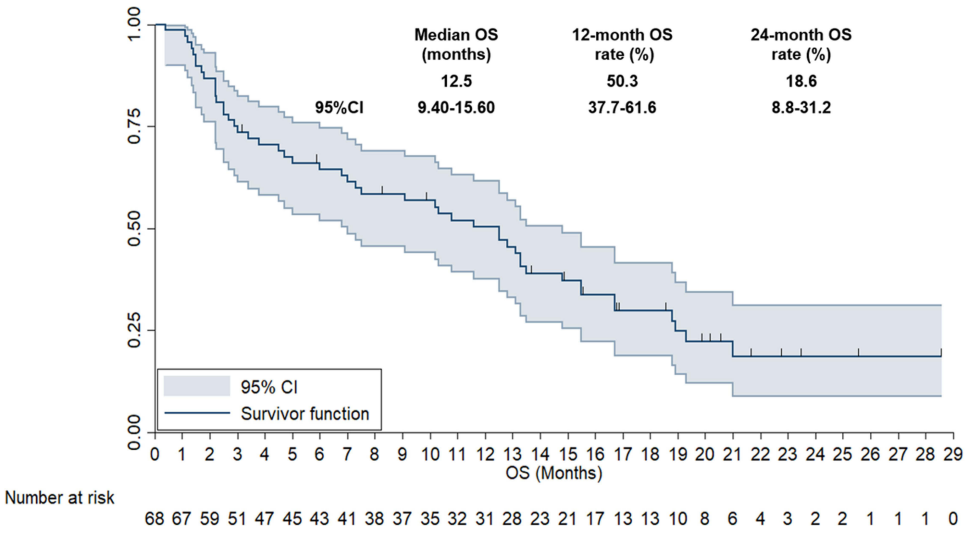

Figure 6 Overall survival curve of the 68 patients with treatment-refractory metastatic colorectal cancer who received anlotinib plus PD-1 blockades.

Discussion

In our opinion, the present study identified real-world evidence for the feasibility and tolerability of combination treatment with anlotinib and PD-1 blockade therapy in patients with treatment-refractory metastatic CRC. Univariate and multivariate analyses of PFS and baseline characteristics showed that patients with an ECOG performance status of 0–1 score and left-sided CRC exhibited superior PFS outcomes. Collectively, the administration of anlotinib plus PD-1 blockades might be a promising and encouraging regimen for patients with treatment-refractory metastatic CRC in clinical practice.

Colorectal cancer (CRC) is a heterogeneous malignant tumor that affects the digestive system. However, the progress in breakthrough research for subsequent therapies among patients with metastatic CRC was relatively limited in the past few decades.[25] Consequently, there was an urgent need for efficacious therapeutic options to significantly extend the survival of these patients.[26] Currently, immunotherapy was gradually enhancing the treatment options for various types

Table 3 The Safety Profile of the 68 Patients with Metastatic CRC Who Received Anlotinib Plus PD-1 Blockades Treatment

Adverse Reactions	Total (N, %)	Grade 1–2 (N, %)	Grade ≥3 (N, %)
Any adverse reactions	61 (89.7)		41 (60.3)
Hypertension	35 (51.5)	24 (35.3)	11 (16.2)
Myelosuppression	30 (44.1)	18 (26.5)	12 (17.6)
Fatigue	26 (38.2)	22 (32.3)	4 (5.9)
Hand-foot syndrome	21 (30.9)	18 (26.5)	3 (4.4)
Diarrhea	18 (26.5)	14 (20.6)	4 (5.9)
Nausea and vomiting	17 (25.0)	13 (19.1)	4 (5.9)
Hepatotoxicity	15 (22.1)	8 (11.8)	7 (10.3)
Rash	13 (19.1)	12 (17.6)	1 (1.5)
Pneumonia	11 (16.2)	10 (14.7)	1 (1.5)
Oral mucositis	10 (14.7)	10 (14.7)	0 (0.0)
Proteinuria	8 (11.8)	7 (10.3)	1 (1.5)
RCCEP	6 (8.8)	6 (8.8)	0 (0.0)

Abbreviation: RCCEP, Reactive cutaneous capillary endothelial proliferation.

of tumors. Despite promising efficacy was observed in digestive system tumors, the benefits of immunotherapy were currently limited to a small proportion of CRC patients.[27] Currently, it seemed that only patients with dMMR metastatic CRC might benefit from pembrolizumab single agent according to Keynote-177 trial.[7] Patients with pMMR metastatic CRC, accounted for approximately 95% of all the metastatic CRC, commonly referred to as "cold tumors", demonstrated a low rate of tumor immune response to immunotherapy.[28] Converting these "cold tumors" into "hot tumors" by altering the tumor immune microenvironment presented a significant challenge in the field of immunotherapy for metastatic CRC.[29] A previous study concluded combination therapy as a potential solution to overcome this limitation, particularly through the administration of antiangiogenic drugs, which might potentially provide amazing survival benefits for patients with metastatic CRC.[30] Notably, antiangiogenic drugs not only conferred the ability to enhance the tumor immune microenvironment but also suppressed the development of tumor neovascularization, thereby achieving a synergistic action with immunotherapy.[31] As a result, a previous study confirmed that the combination of bevacizumab and atezolizumab (PD-L1 blockade) demonstrated remarkable research breakthroughs in the treatment of unresectable hepatocellular carcinoma (HCC), which contributed to the establishment of this combination therapy as the current standard treatment option for HCC patients.[32] Mechanistically, by targeting immature blood vessels and inducing vascular normalization, anlotinib was found to enhance the infiltration of immune cells and reduce tumor immune tolerance.[33] Additionally, previous phase III clinical trial indicated that anlotinib exhibited promising PFS compared to placebo as a third-line treatment for patients with metastatic CRC clinically.[13] Therefore, anlotinib combined with PD-1 blockades might be a promising therapeutic option for patients with pMMR metastatic CRC and warranted to be explored.

A total of 68 patients with metastatic CRC who had undergone at least two lines of previous systemic treatment were included in this study. The majority of patients were pMMR status (86.8%) and the remaining 9 patients failed to detect the MMR status (13.2%), suggesting almost all patients were pMMR metastatic CRC, which was consistent with the previous study regarding antiangiogenic drugs plus PD-1 blockades for patients with previously treated metastatic CRC.[20] Additionally, the demographic and clinical characteristics of the 68 patients with treatment-refractory metastatic CRC indicated that patients participated in this study were common CRC patients clinically, which was in line with the CRC cohort of REGONIVO trial,[19] suggesting that the patients included in this study were of representative.

With regard to the therapeutic outcomes of anlotinib plus PD-1 blockades, in this study, the 68 patients with metastatic CRC who were treated with a combination of anlotinib and PD-1 blockades produced an ORR of 25.6%, a DCR of 72.1% and a median PFS of 5.8 months. Noteworthily, it seemed that the efficacy results in our study outperformed the results of anlotinib monotherapy or PD-1 blockades monotherapy numerically among patients with treatment-refractory metastatic CRC according the ALTER0703 trial (anlotinib arm: ORR = 4.3%, DCR = 75.9% and median PFS = 4.1 months) and Keynote-028 trial (pembrolizumab arm: ORR = 4.3%, DCR = 21.7% and median PFS = 1.8 months), respectively.[13,34] Therefore, this finding suggested that anlotinib combined with PD-1 blockades demonstrated a synergistic activity in vivo among patients with metastatic CRC preliminarily, and appropriate anlotinib administration might switch tumor immune microenvironment from immune-suppressive to immune-supportive status in clinical practice.[35] Similarly, we noticed that some retrospective studies reported recently also investigated another antiangiogenic TKI (fruquintinib and regorafenib) combined with PD-1 blockades among patients with treatment refractory metastatic CRC.[22,36,37] ORR of the combination regimen in these studies ranged from 7.1% to 11.8%, DCR ranged from 56.5% to 89.3%, and median PFS varied from 3.9 months to 6.4 months, which were basically consistent with the ORR, DCR and median PFS in our study. Furthermore, some prospective clinical trials have been performed to identify the feasibility of antiangiogenic TKI combined with PD-1 blockades in patients with previously treated metastatic CRC. A previous study initiated by Ma SC and colleagues explored the efficacy and toxicity of fruquintinib plus toripalimab (PD-1 inhibitor) as a third-line treatment in 19 patients with refractory metastatic CRC with MSS status.[20] After a median follow-up duration of over 10 months, this regimen produced an ORR of 21.1%, a DCR of 73.7%, and a median PFS of 5.98 months, which was also in concert with the efficacy in our study despite the limited sample size of Ma's work. Certainly, the most amazing finding regarding the efficacy of antiangiogenic TKI combined with PD-1 blockades among patients with MSS metastatic CRC was the REGONIVO trial, which was initiated by Shota Fukuoka and colleagues, they recruited 25 patients with treatment-refractory metastatic CRC and treated with regorafenib

plus nivolumab.[19] REGONIVO study yielded an ORR of 33.3%, a DCR of 88.0% and a median PFS of 7.9 months among the 25 patients with metastatic CRC. The therapeutic outcomes in our study were inferior to those in the REGONIVO study numerically. We speculated that the incongruity might be attributed to two aspects: first, patients included in REGONIVO were different from those in our study in terms of ethnicity and baseline characteristics, which might contribute to the discrepancy in efficacy.[38] Secondly, the retrospective design of our study might result in inferior patient management and compliance compared to the prospective clinical trial, thus deteriorating the therapeutic outcomes to some extent, which was also confirmed in a previous retrospective study.[39] Nevertheless, the observed synergistic activity of PD-1 blockades in combination with anlotinib suggested that anlotinib had the potential to augment the microenvironment of MSS tumor tissues and increased the immune response to PD-1 blockades.[40] However, further investigation was required to fully understand the underlying mechanisms involved. Additionally, it should be noted that a total of 11 patients responded to anlotinib plus PD-1 blockades durably and achieved PR response during the combination therapy. The median DoR of the 11 patients with PR was 6.7 months, which was consistent with a previous study and suggested that this regimen might produce durable therapeutic activity when patients responded.[20]

Furthermore, the exploration analysis between PFS and baseline characteristics was also identified in our study simultaneously. Apparently, it seemed that patients with treatment-refractory metastatic CRC might benefit from anlotinib plus PD-1 blockade therapy uniformly regardless of the baseline characteristic subgroups, which was consistent with a previous study that investigated the efficacy of anlotinib plus PD-1 blockades in patients with metastatic CRC.[36] However, it should be emphasized that patients with an ECOG performance status of 0–1 score and tumor location of left-sided CRC exhibited a significantly longer PFS than those with ECOG 2 score and tumor location of right-sided colon cancer in the univariate analysis (ECOG median PFS: 5.8 vs 4.2 months, P=0.013; tumor location median PFS: 5.8 vs 3.8 months, P=0.008). Consequently, our study suggested that a performance status of 2 score and right-sided colon cancer location might serve as useful biomarkers to predict the inferior prognosis of anlotinib plus PD-1 blockades. However, caution should be exercised when interpreting the results. According to our current understanding, patients with a higher ECOG score tended to exhibit a correlation with a poorer prognosis irrespective of the specific therapeutic regimens employed.[41] Besides, patients with right-sided colon cancer are usually associated with worse prognosis compared to left-sided CRC regardless of systemic therapeutic regimens.[42] Consequently, the use of ECOG performance status and tumor location as potential biomarkers to predict the efficacy of anlotinib plus PD-1 blockades for patients with metastatic CRC should be further validated in prospective clinical trials, which might provide more reliable evidence to confirm its effectiveness in predicting prognosis. Interestingly, we also observed that patients with liver metastasis showed a trend for worse PFS than those without liver metastasis, although the difference was not statistically significant (median PFS: 4.5 vs 5.8 months, P=0.095). To our knowledge, the liver was reported to be associated with a comparatively high fraction of immunosuppressive cells, and patients with liver metastasis were associated with a lower CD8 Treg ratio and decreased amount of activated PD-1$^+$/CTLA-4$^+$ CD8 cells in vitro,[43] which might explain the low response and worse PFS observed among patients with liver metastasis when receiving PD-1 blockade-related regimens in our study. Additionally, the analysis in the REGONIVO study showed that patients with liver metastasis demonstrated a decreased ORR, which is in line with the results of our study.[19]

Additionally, the study's findings revealed that among the 68 patients with metastatic CRC who received anlotinib plus PD-1 blockades, the median OS was 12.5 months, which was higher compared to patients who received either anlotinib monotherapy (median OS of 8.6 months) or PD-1 blockade monotherapy (median OS of 5.3 months).[13,34] We speculated that one possible reason for the improved OS observed in the study might be related to the fact that targeted drugs with different mechanisms of action, such as other antiangiogenic TKIs and TAS-102, were approved for use in China since 2018. Patients with metastatic CRC in the study could receive these additional targeted drugs after experiencing disease progression of anlotinib plus PD-1 blockade regimen, which might contribute to sustained survival benefits for the patients consecutively.[44] Another potential explanation we assumed was that considerable patients in our study had metastatic sites below three (number of metastases sites ≤3 accounted for 69.1% in our study), which suggested that a certain number of patients might have oligometastatic disease and low volume disease in our study. A recent publication on oligometastatic disease in CRC found that oligometastatic disease was described as an intermediate clinical state between localized cancer and systemically metastasized disease, and prolonged

survival might be achieved when aggressive locoregional approaches were added to systemic therapies for patients with oligometastatic disease in CRC.[45] Although the definition of oligometastatic disease in CRC remained controversial currently, it seemed that the most widely accepted definition of oligometastatic CRC manifested as up to 5 lesions in no more than 3 metastatic sites which typically involve the liver, lung and lymph nodes and absence of ascites and peritoneal, bone and central nervous system metastases in clinical practice currently.[46] Oligometastatic CRC might achieve superior prognosis if all metastatic lesions were resected or destructed using techniques such as surgery, radiofrequency ablation, stereotactic radiotherapy or TACE, especially when patients were live or lung metastasis.[47] Interestingly, we also found that patients with a number of metastases sites ≤3 conferred a trend for superior OS compared with that of a number of metastases sites >3 (median OS: 13.1 vs 7.5 months), even the difference was marginally significant (P=0.057). We speculated that patients with oligometastatic CRC conferred a better prognosis and helped to contribute to the superior OS of patients with number of metastases sites ≤3 to some extent. Therefore, we thought some patients might be deemed as oligometastatic disease and low volume disease among the 47 patients with a number of metastases sites ≤3, who might confer a superior prognosis even treated with anlotinib plus PD-1 blockades. In patients with oligometastatic CRC, the PFS and OS values might be somewhat lower than excepted cause they could have other useful therapeutic options (locoregional approaches) even after the treatment of anlotinib plus PD-1 blockades, and the previous study also suggested that locoregional approaches should be highly considered in patients with oligometastatic CRC mainly during the first-line therapy but also at later stages of treatment history in selected cases.[48]

Safety profile of anlotinib plus PD-1 blockades suggested that the common adverse reactions among the 68 patients with treatment-refractory metastatic CRC were hypertension, myelosuppression, fatigue, hand-foot syndrome, diarrhea, nausea and vomiting, hepatotoxicity, rash, pneumonia, oral mucositis, proteinuria and Reactive cutaneous capillary endothelial proliferation (RCCEP), which was basically consistent with the previous results of anlotinib plus PD-1 blockades in the treatment of patients with previously treated small cell lung cancer.[49] Noteworthily, it was important to consider that the incidence of grade ≥3 adverse reactions in our study was 60.3%, which was slightly higher compared to that of anlotinib monotherapy (52.5%) or PD-1 blockade monotherapy (56%) among patients with metastatic CRC.[13,14] This highlighted that the combination administration might augment the occurrence of grade ≥3 adverse reactions. Careful monitoring and management of these toxicities are crucial when adopting this therapeutic approach. Additionally, it should be noted that although the overall incidence of hepatotoxicity in this study was relatively low (22.1%), more than 10% of patients were hepatotoxicity of grade ≥3 (10.3%), and one patient died of liver failure after two cycles of treatment with anlotinib plus camrelizumab among the 68 patients with metastatic CRC (1.5%), suggesting that patients with liver metastasis and liver dysfunction should be extremely careful when using anlotinib plus PD-1 blockades in clinical practice, and it is necessary to monitor the patient's liver function in a timely manner when treated with anlotinib plus PD-1 blockades. Additionally, grade 5 adverse reactions occurred in one patient (1.5%) in our study, which was lower than that observed in the pembrolizumab group according to the Keynote-177 trial (4%). As a result, the safety profile of anlotinib plus PD-1 blockades in patients with treatment-refractory metastatic CRC was tolerable and manageable in clinical practice.

From an objective perspective, it is important to acknowledge the limitations of this study. First, the sample size in our study is limited, and the feasibility and safety of combination regimens as a subsequent line treatment for patients with treatment-refractory metastatic CRC needs to be confirmed in more patients. Second, it is important to recognize that our study is designed as a retrospective analysis, which inherently carries certain biases that are difficult to completely avoid. While retrospective studies may provide valuable insights, they are susceptible to selection bias, confounding factors, and limitations in data collection. Therefore, future prospective trials with well-designed protocols and rigorous methodologies are required to validate and strengthen the conclusions of this retrospective analysis. Despite the limitations of our study, treatment with anlotinib plus PD-1 blockades demonstrated promising efficacy in providing further benefits to patients with treatment-refractory metastatic CRC. The conclusion of our study provides potential guidance for subsequent treatment of patients with treatment-refractory metastatic CRC in clinical practice. Collectively, it is important to conduct further research

and clinical trials to validate these findings and to establish the feasibility and tolerability of this combination regimen.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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