Original Article

Efficacy observation of sequential TAS-102 following regorafenib as a later-line treatment in patients with metastatic colorectal cancer: a cohort study

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Background: Metastatic colorectal cancer (mCRC) is associated with poor prognosis and limited options for later-line treatment. Regorafenib and TAS-102 have shown significant benefit and are recommended as later-line treatment for mCRC. This study aimed to investigate the progression-free survival (PFS) and overall survival (OS) of patients with mCRC treated with TAS-102 sequentially after regorafenib progression.

Methods: This population-based cohort study retrospectively collected data of 30 patients with mCRC treated with TAS-102 sequentially after regorafenib at the Harbin Medical University Cancer Hospital and the Cancer Hospital Affiliated to Shanxi Medical University from January 1, 2020, to October 1, 2023. PFS and OS were considered to be the endpoints of this study. Kaplan-Meier analysis, log-rank test, and Cox proportional hazards regression analysis were used to analyze the OS, PFS, and risk factors.

Results: Among the 30 patients included in the study, the median PFS (mPFS) for all patients was 3.83 months [95% confidence interval (CI): 3.09–5.59]. OS was divided into two categories: OS_1, the time from regorafenib initiation to death; OS_2, the time from TAS-102 initiation to death. The median OS_1 (mOS_1) was 18.7 months [95% CI: 16.3–not available (NA)], and the median OS_2 (mOS_2) was 16.1 months (95% CI: 8.08–NA). The mPFS was 3.65 and 3.83 months (P=0.68) in the regorafenib monotherapy group and combination therapy group, respectively, while the mOS_1 was unreached in the regorafenib monotherapy group and was 18.7 months in the regorafenib combination therapy group (P=0.64). Meanwhile, the mOS_1 was 17.5 and 20.7 months in the TAS-102 monotherapy group and TAS-102 combination therapy group,

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respectively (P=0.53). Univariate and multivariate Cox analyses revealed that curative surgery was an independent predictive factor for PFS.

Conclusions: Our study demonstrated that the availability of sequential treatment options including regorafenib followed by TAS-102 prolongs the OS of patients compared to conventional monotherapy approaches. During the sequential treatment, regorafenib or TAS-102 combined with other therapeutic agents did not significantly differ from monotherapy, further investigation is required through large-scale trials.

Keywords: Metastatic colorectal cancer (mCRC); later-line treatment; regorafenib; TAS-102; sequential

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Introduction

Colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality among all cancers worldwide (1). The number of patients with CRC in China was estimated to be 590,000 in 2022, with 300,000 of these cases resulting in death, representing a high rate of mortality (2). Although the overall prognosis of patients with CRC has improved in recent years with the development of antitumor agents, the 5-year survival rate for patients with metastatic colorectal cancer (mCRC) is only about 14% (3). The available therapeutic agent options are particularly limited for patients with mCRC in the setting of third-line-or-ater treatment due to the poor physical condition of patients and drug resistance. Therefore, it is crucial to optimize treatment regimens by combining or sequencing therapeutic agents to improve the survival outcomes of patients in later lines of treatment.

According to the Chinese Society of Clinical Oncology (CSCO) guidelines, regorafenib and TAS-102 monotherapy are recommended as third-line palliative treatment options for patients with mismatch repair–proficient (pMMR) mCRC (4). Regorafenib, a small-molecule multi-kinase inhibitor, suppresses tumor cell proliferation through blockade of MAPK signaling pathway while exerting anti-angiogenic effects by targeting vascular endothelial growth factor receptors (VEGFRs) (5). The CORRECT study is a global multicenter, randomized controlled phase III clinical trial that enrolled 760 patients with CRC who had failed first-line and second-line standard therapies. The study successfully met its primary endpoint as the median overall survival (mOS) in the regorafenib group was significantly longer than that in the placebo group (6.4 *vs.* 5.0 months, P=0.0052). Subsequently, the efficacy of regorafenib was further confirmed in the CONCUR study. The CONCUR study is a randomized controlled phase III clinical trial conducted in Asia. Patients in the regorafenib group also achieved significantly extended mOS (8.8 *vs.* 6.3 months, P=0.00016) and median progression-free survival (mPFS) (3.2 *vs.* 1.7 months, P<0.0001) (6,7). In clinical practice, there is a growing preference for the sequential application of third-line therapeutic agents. As a classic drug for the third-line treatment of CRC, regorafenib has also been a focus of

Highlight box

Key findings

- The use of sequential treatment with regorafenib and TAS-102 prolonged overall survival in patients as compared to that reported in previous studies, which applied regorafenib or TAS-102 only. Additionally, combination therapy with regorafenib or TAS-102 along with other therapeutic agents during sequential therapy had no significant survival benefits compared to monotherapy.

What is known and what is new?

- Patients with metastatic colorectal cancer (mCRC) have limited options for later-line treatment, regorafenib and TAS-102 are recommended as later-line therapeutic agents in the Chinese Society of Clinical Oncology guidelines. In clinical practice, a sequential regimen of these two therapeutic agents can be applied in the later-line treatment of patients with mCRC. However, their efficacy remains uncertain.
- This study aimed to explore the survival outcomes of the sequential treatment regimen of regorafenib and TAS-102 in the later-line treatment of patients with mCRC.

What is the implication, and what should change now?

- Application of sequential treatment with regorafenib and TAS-102 was found to be able to prolong overall survival in patients compared to the survival observed in previous monotherapy studies; however, large-scale randomized controlled trials are needed to validate these findings.

the research in sequential treatment. The REVERCE and FRESCO-2 studies have shown that in later-line mCRC, the use of regorafenib followed by sequential targeted therapeutic agents such as cetuximab or fruquintinib can significantly prolong overall survival (OS) (8-11). These findings collectively support the use of regorafenib in a sequential approach in the treatment of mCRC.

Apart from the aforementioned sequential approach, TAS-102 can also be sequentially used with regorafenib in the third-line-or-later treatment of mCRC to potentially further improve the survival benefits for patients with mCRC. TAS-102 is a chemotherapy agent that targets nucleotide metabolism to overcome the resistance to 5-fluorouracil (5-FU) (12). The global phase III RECOURSE and Asian-specific TERRA trials reported significant survival benefits yielded by TAS-102, compared to the placebo group, with the OS being extended by 1.8 and 0.7 months, respectively (13,14), suggesting it as another alternative for patients with mCRC in the third-line-and-beyond setting. The order administration of multiple therapeutic agents in clinical practice has not been informed by well-established evidence and is often based on patient preferences and physician guidance (15). However, in recent years, numerous clinical studies have examined the efficacy of sequential treatment with regorafenib and TAS-102. Signorelli *et al.* conducted a retrospective study on the sequential treatment of the two therapeutic agents, in which that both the sequence from regorafenib to TAS-102 and the sequence from TAS-102 to regorafenib extended survival, but only the former could stabilize tumor growth and provided a relatively greater survival benefit (16). However, some studies have indicated that the sequence of these two therapeutic agents does not significantly impact survival outcomes (17,18).

To clarify the efficacy of sequential treatment consisting of regorafenib followed by TAS-102 in Chinese patients with mCRC, we collected data from 30 patients in two centers, which was then subjected to retrospective and subgroup analyses. We present this article in accordance with the STROBE reporting checklist (19) (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-47/rc).

Methods

Patients

This retrospective study accessed the electronic medical records from the Harbin Medical University Cancer Hospital and the Cancer Hospital Affiliated to Shanxi Medical University, two cancer research centers in China, to collect the clinical information, including the demographic characteristics, of 80 patients with mCRC who had received regorafenib and TAS-102 between January 1, 2020, and October 1, 2023. The survival status of all patients was obtained using a follow-up system or telephone interviews, with data collected until October 31, 2023. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was reviewed and approved by the Ethics Committee of Harbin Medical University Cancer Hospital (Ethics No. KY2022-63) and the Cancer Hospital Affiliated to Shanxi Medical University was informed and agreed with this study. Individual consent for this retrospective analysis was waived. All patient data were kept confidential.

The specific inclusion criteria were as follows: (I) histologically confirmed diagnosis of CRC; (II) presence of at least one measurable metastatic lesion that could be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; (III) previous treatment with two or more systemic therapies [including oxaliplatin, fluoropyrimidines, and irinotecan, with or without combination with targeted or immune therapeutic agents such as bevacizumab, cetuximab, and programmed cell death 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors, among others] and disease progression; (IV) use of TAS-102, with or without other therapeutic agents, after disease progression following treatment with regorafenib with or without other therapeutic agents; (V) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1; (VI) All patients had previously received the following medications: (i) First-line therapy: oxaliplatin-based regimens (e.g., FOLFOX or CAPOX) combined with fluoropyrimidines (5-FU or capecitabine). (ii) Second-line therapy: irinotecan-based regimens (e.g., FOLFIRI) ± targeted agents (e.g., bevacizumab or cetuximab), depending on RAS/BRAF mutation status.

Meanwhile, the exclusion criteria were as follows: (I) use of other therapeutic agents for transition during the sequential process of regorafenib and TAS-102, (II) presence of two or more primary tumors, and (III) inability to obtain survival-related data regarding both progression-free survival (PFS) and OS due to loss to follow-up.

Treatment criteria

(I) Regorafenib: 80 mg/day, orally administered once

daily from days 1 to 21, repeated every 28 days.

(II) TAS-102: Initiated upon disease progression during regorafenib monotherapy or regorafenib-based combination therapy. Dosage: 35 mg/m^2/dose, orally administered twice daily from days 1 to 5 and 8 to 12, repeated every 28 days.

(III) Combination therapy regimens:
  (i) Immune checkpoint inhibitors:
    - Camrelizumab: 200 mg via intravenous drip ivgtt on day 1, repeated every 21 days.
    - Cindilimab: 200 mg ivgtt on day 1, repeated every 21 days.
    - Toripalimab: 240 mg ivgtt on day 1, repeated every 21 days.
    - Tislelizumab: 200 mg ivgtt on day 1, repeated every 21 days.
  (ii) Chemotherapeutic agents:
    - Raltitrexed: 3 mg/m^2 ivgtt on day 1, repeated every 21 days.
    - S-1: 40 mg orally administered twice daily from days 1 to 14, repeated every 21 days.
  (iii) Targeted therapeutic agents:
    - Bevacizumab: 7.5 mg/kg ivgtt on day 1, repeated every 21 days.
    - Fruquintinib: 5 mg orally administered once daily from days 1 to 21, repeated every 28 days.

Efficacy evaluation and follow-up

According to RECIST 1.1, the treatment response of the enrolled patients was evaluated based on the results of each follow-up examination [including computed tomography (CT) scans, magnetic resonance imaging, ultrasound, and other imaging modalities capable of clearly displaying assessable lesions] after patients received the regorafenib and TAS-102 regimen. To minimize recall bias, the survival status of all patients was obtained through a combination of a follow-up system and telephone interviews, with data collected until October 31, 2023. The primary endpoints were PFS and OS. PFS was defined as the time from the initiation of regorafenib treatment, with or without combination with other therapeutic agents, to the date of first observed disease progression or death due to any causes, whichever occurred first. OS was divided into two categories: OS_1, which was defined as the time from the initiation of regorafenib treatment, with or without the combination with other therapeutic agents, to the date of death; and OS_2, which was defined as the time from the initiation of TAS-102 treatment, with or without the combination with other therapeutic agents, to the date of death. All 30 patients had PFS data available; however, five of them were lost to follow-up for OS, and were therefore excluded from the OS analysis.

Variables

The variables examined in this study were as follows: gender (male or female); age (<65 or ≥65 years); primary tumor location, including the left-sided colon (including splenic flexure, descending colon, and sigmoid colon), right-sided colon (the cecum, ascending colon, and the right two-thirds of the transverse colon), and bilateral involvement/rectum; metastatic tumor site, including the liver, lungs distant lymph nodes, peritoneum, and others (e.g., the bone, pelvic region, uterus); metastatic numbers of sites, 1, 2, ≥3; surgical treatment and approach, including no surgery, curative surgery, and palliative surgery; prior regimens, including targeted therapy [anti-vascular endothelial growth factor therapy (VEGF) agents or tyrosine kinase inhibitors (TKIs)] and immune therapy (anti-PD-1/PD-L1 agents); treatment line, (the line of treatment at which the regorafenib–TAS-102 regimen was administered sequentially); and the individual or combined use of regorafenib and TAS-102 (the administration of regorafenib with or without other therapeutic agents and the administration of TAS-102 with or without other therapeutic agents). The records for these variables were sourced from the electronic medical record databases of the Harbin Medical University Cancer Hospital and Cancer Hospital Affiliated to Shanxi Medical University.

Statistical analysis

The sample size of this study was determined based on the number of eligible patients between January 1, 2020, and October 1, 2023. The categorical variables were compared using the Chi-squared test or Fisher exact test. Survival analysis, including PFS and OS, was conducted using Kaplan-Meier curve analysis and the log-rank test. Death and disease progression were considered as the endpoint events. Cox regression models were used to estimate hazard ratio (HR) and 95% confidence interval (CI), which were evaluated using the Wald test. Univariate and multivariate Cox regression analyses were performed to assess factors associated with PFS and OS. All tests were two-sided, and

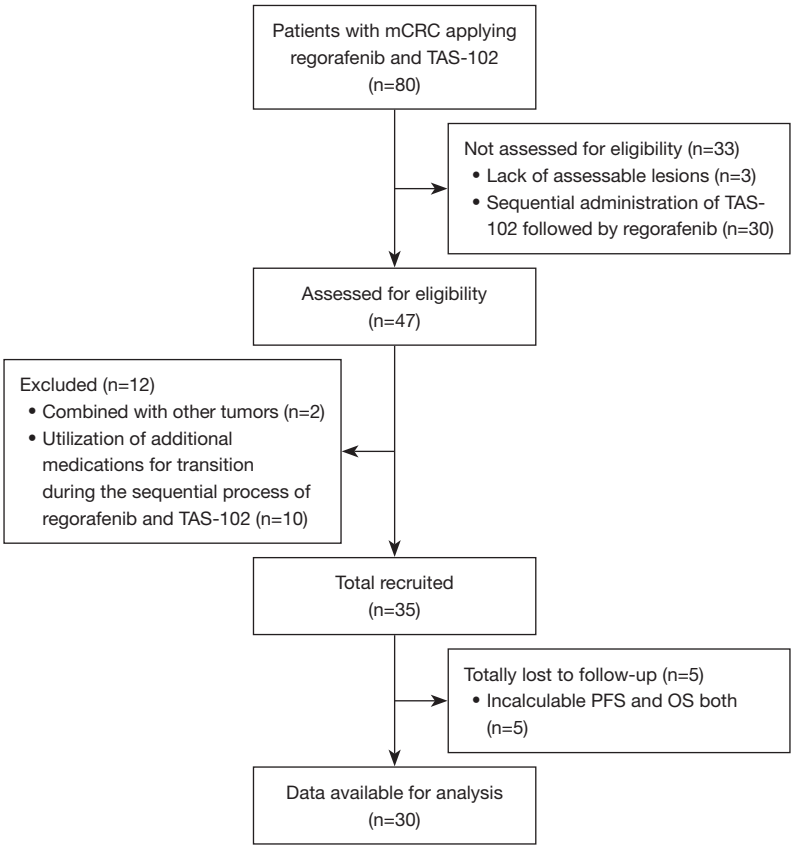

Figure 1 Flowchart of patient inclusion. mCRC, metastatic colorectal cancer; PFS, progression-free survival; OS, overall survival.

a P value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 26 (IBM Corp., Armonk, NY, USA) and R software version 4.3.2 (The R Foundation for Statistical Computing).

Results

Patient characteristics

A total of 80 patients with mCRC who had received regorafenib and TAS-102 between January 1, 2020, and October 1, 2023, were initially screened at the Harbin Medical University Cancer Hospital and Cancer Hospital Affiliated to Shanxi Medical University. Among them, 33 individuals did not meet the inclusion criteria and were excluded, including three patients with unassessable lesions and 30 patients who received TAS-102 before subsequent regorafenib treatment. Additionally, 12 patients met the exclusion criteria including having primary tumors other than CRC (two patients) and transitioning to other medications between the regorafenib and TAS-102 regimens (10 patients). Five patients were excluded due to both PFS and OS data being unavailable. Finally, 30 patients were included for statistical analysis. *Figure 1* presents the flowchart of patient inclusion.

The baseline characteristics of the included patients are presented in *Table 1*. The age of the patients ranged from 33 to 73 years, with a median age of 57 years. Among them, 6 (20.0%) patients were aged ≥65 years, and 18 were male patients (60.0%). Regarding the primary tumor location, 9 (30.0%) patients had tumors located in the left-sided colon, 7 (23.3%) patients in the right-sided colon, 1 (3.4%) patient in both the left and right-sided colon, and 13 (43.3%) patients in the rectum. The metastatic sites were not mutually exclusive, with 18 (60.0%) patients with liver metastasis, 22 (73.3%) with lung metastasis, 13 (43.3%) with distant lymph node metastasis, 4 (13.3%) with peritoneal metastasis, and 9 (30.0%) with metastasis in other locations. Analysis of

Table 1 Baseline demographic and clinical characteristics of 30 patients with mCRC

Characteristic	Values
Age (years)	
Median [range]	57 [33–73]
≥65, n (%)	6 (20.0)
<65, n (%)	24 (80.0)
Gender, n (%)	
Male	18 (60.0)
Female	12 (40.0)
Site of primary disease, n (%)	
Left-sided	9 (30.0)
Right-sided	7 (23.3)
Both left and right sided	1 (3.4)
Rectum	13 (43.3)
Site of metastases, n (%)	
Liver	18 (60.0)
Lung	22 (73.3)
Lymph node	13 (43.3)
Peritoneum	4 (13.3)
Other	9 (30.0)
Number of metastatic sites, n (%)	
1	8 (26.7)
2	8 (26.7)
≥3	14 (46.7)
MMR status, n (%)	
pMMR	20 (66.7)
dMMR	0 (0.0)
Unknown	10 (33.3)
Gene mutation status, n (%)	
RAS/*BRAF* wild type	13 (43.3)
RAS mutant	13 (43.3)
BRAF mutant	1 (3.4)
Unknown	3 (10.0)
Surgery, n (%)	
No	4 (13.3)
Radical resection	25 (83.3)
Palliative surgery	1 (3.4)
Prior regimens, n (%)	
Angiogenesis inhibitors	28 (93.3)
Anti–PD-1/PD-L1	2 (6.7)
Treatment line of regorafenib, n (%)	
Second line	3 (10.0)
Third line	13 (43.3)
Fourth line or later	14 (46.7)
Regorafenib regimen, n (%)	
Regorafenib alone	8 (26.7)
Regorafenib combination[#]	22 (73.3)
TAS-102 regimen, n (%)	
TAS-102 alone	11 (36.7)
TAS-102 combination[#]	19 (63.3)

[#], the detailed combination treatment regimen is provided in Table S1. dMMR, mismatch repair deficient; mCRC, metastatic colorectal cancer; MMR, mismatch repair; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; pMMR, proficient mismatch repair.

number of metastatic sites revealed distinct distribution patterns: 8 patients (26.7%) each exhibited one or two metastatic sites, while 14 cases (46.7%) demonstrated involvement of ≥3 anatomical locations. Data on (mismatch repair) MMR status was available for 20 patients (66.7%), all of whom exhibited pMMR. In terms of gene mutation testing, 13 (43.3%) patients had wild-type *RAS/BRAF*, 13 (43.3%) had *RAS* mutations, 1 (3.4%) had a *BRAF* mutation, and three (10%) were not tested. Regarding the surgical history of the primary tumor, 4 (13.3%) patients did not undergo surgery, 25 (83.3%) had previously undergone curative surgery and 1 (3.4%) underwent palliative surgery before recurrence or metastasis. Regorafenib was administered as the second-, third-, fourth- and later line of treatment in 3 (10%), 13 (43.3%), and 14 (46.7%) patients, respectively. During the sequential treatment process, regorafenib and TAS-102 were administered in combination with other therapeutic agents as following: regorafenib monotherapy was applied in 8 (26.7%) patients, and regorafenib was combined with other therapeutic agents in 22 (73.3%) patients. TAS-102 monotherapy was applied in 11 (36.7%) patients, and TAS-102 was combined with other therapeutic agents in 19 (63.3%) patients.

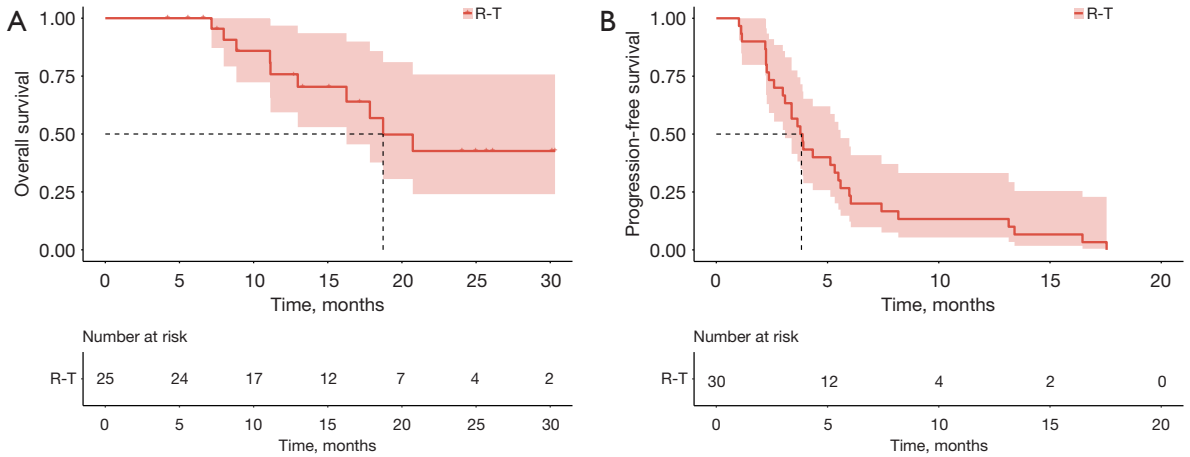

Figure 2 Kaplan-Meier survival analysis for OS_1 (A) and PFS (B) of R-T regimen. OS, overall survival; OS_1, the time from the initiation of the regorafenib regimen to the date of death; PFS, progression-free survival; R-T, sequential therapy with regorafenib followed by TAS-102.

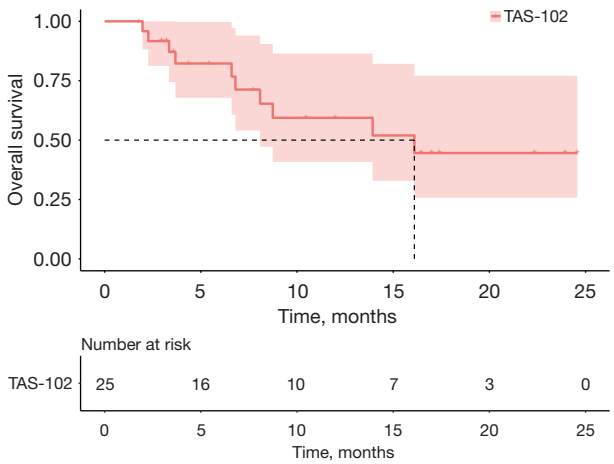

Figure 3 Kaplan-Meier survival analysis for OS_2. OS, overall survival; OS_2, the time from the initiation of the TAS-102 regimen to the date of death.

Efficacy and survival

As of the follow-up date of October 31, 2023, all 30 patients experienced progression after receiving the regorafenib regimen, thus reaching the PFS endpoint. By the follow-up date, a total of 10 patients had reached the OS endpoint, while the remaining 20 patients had not reached the OS endpoint. Among them, 15 patients were alive and five were lost to follow-up, and the last follow-up date of October 31, 2023, was used as the event date for calculating the OS of these 15 alive patients; patients who were lost to follow-up were excluded from the OS analysis. The median follow-up time was 21.13 months, with an average follow-up time of 24.05 months.

The Kaplan-Meier curves and log-rank tests showed that the median OS_1 (mOS_1) with the use of regorafenib was 18.7 months [95% CI: 16.3–not available (NA)] (*Figure 2A*). The mPFS was 3.83 months (95% CI: 3.09–5.59) (*Figure 2B*). The median OS_2 (mOS_2) with the use of TAS-102 was 16.1 months (95% CI: 8.08–NA) (*Figure 3*).

Although all the patients that we examined received sequential treatment with regorafenib followed by TAS-102, these patients were also concurrently treated with other therapeutic agents while being treated with regorafenib or TAS-102. Therefore, we divided the patients, based on whether regorafenib or TAS-102 was used in combination with other therapeutic agents, into a regorafenib monotherapy group (n=8) and a regorafenib combination therapy group (n=22) as well as a TAS-102 monotherapy group (n=11) and a TAS-102 combination therapy group (n=19). Survival analysis was performed by stratifying the patients. First, a stratified comparison was conducted between the regorafenib monotherapy group and the combination therapy group in terms of PFS, with the mPFS being 3.65 and 3.83 months, respectively. There was no significant difference between the regorafenib monotherapy group and the combination therapy group (HR 0.841, 95% CI: 0.369–1.916; P=0.68) (*Figure 4*). Second, a stratified comparison was conducted between the regorafenib monotherapy group and the combination therapy group in terms of OS_1, with the mOS_1 being not reached and 18.7 months, respectively. There was no significant

difference between the regorafenib monotherapy group and the combination therapy group (HR 1.442, 95% CI: 0.305–6.812; P=0.64) (*Figure 5A*). Finally, a comparison was made between the TAS-102 monotherapy group and the combination therapy group in terms of OS_1, with the mOS_1 being 17.5 and 20.7 months, respectively. There was no significant difference between the TAS-102 monotherapy group and the combination therapy group (HR 0.664, 95% CI: 0.187–2.366; P=0.53) (*Figure 5B*).

Univariate and multivariate Cox regression analyses showed that previous curative surgery was a significant independent factor of PFS (HR 0.189, 95% CI: 0.048–0.745; P=0.02) (*Table 2*). Univariate Cox regression analyses showed that having 1 metastatic site was associated with a better prognosis compared to 2 (HR 4.122, 95% CI: 1.075–15.810; P=0.04) or ≥3 sites (HR 3.805, 95% CI: 1.043–13.873; P=0.04) of OS_1 (Table S2). Moreover, MMR status and *RAS/RAF* status from baseline information were not included in the Cox analysis because they contained unknown or missing information.

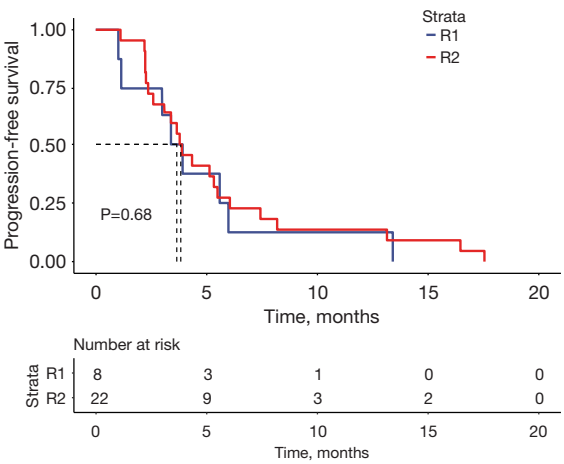

Figure 4 Kaplan-Meier survival analysis for PFS (R1 *vs.* R2). PFS, progression-free survival; R1, monotherapy with regorafenib; R2, regorafenib in combination with other therapeutic agents.

Treatment-related adverse events (TRAEs)

The incidence of TRAEs for regorafenib (R) and TAS-102 (T) in sequential therapy is summarized in *Table 3*. In the R group, the most frequent TRAE was bilirubin elevation (13.33%), followed by hypoproteinemia (6.67%), leukopenia (3.33%), and fatigue (3.33%). No cases of anemia, aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation, hand-foot skin reaction (HFSR), anorexia, nor nausea/vomiting were observed in the R cohort. In contrast, the T group exhibited higher rates of fatigue (20.00% *vs.* 3.33%, P=0.10), anorexia (16.67% *vs.* 0%, P=0.052), and nausea/vomiting (13.33% *vs.* 0%, P=0.11), though these differences did not reach statistical significance. Hypoproteinemia occurred at identical rates in both groups (6.67% each, P>0.99), while anemia (3.33% *vs.* 0%), AST elevation (3.33% *vs.* 0%), ALT elevation (3.33% *vs.* 0%), and HFSR (3.33% *vs.* 0%) were exclusively reported in the T group. Notably, no grade ≥3 TRAEs were observed in either treatment arm. Overall, the safety profiles of both

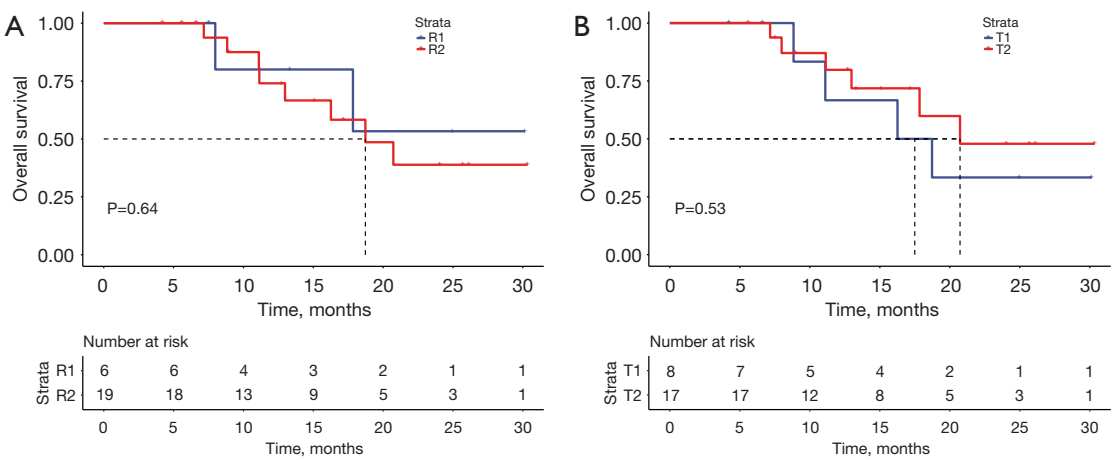

Figure 5 Kaplan-Meier survival analysis for OS_1. (A) R1 *vs.* R2; (B) T1 *vs.* T2. OS, overall survival; OS_1, the time from the initiation of the regorafenib regimen to the date of death; R1, monotherapy with regorafenib; R2, regorafenib in combination with other therapeutic agents; T1, monotherapy with TAS-102; T2, TAS-102 in combination with other therapeutic agents.

Table 2 Univariate and multivariate Cox analyses of PFS

Characteristics	Univariate Cox		Multivariate Cox	
	P value	HR (95% CI)	P value	HR (95% CI)
Gender				
Male	Ref	Ref		
Female	0.44	1.342 (0.632–2.850)		
Age				
<65 years	Ref	Ref		
≥65 years	0.58	1.304 (0.511–3.328)		
Site of primary disease	0.10		0.22	
Left-sided	Ref	Ref	Ref	Ref
Right-sided	0.51	0.714 (0.263–1.936)	0.78	0.859 (0.299–2.465)
Both left and right sided	0.92	1.119 (0.137–9.110)	0.64	1.696 (0.191–15.083)
Rectum	0.02*	0.296 (0.109–0.803)	0.057	0.376 (0.127–1.115)
Number of metastatic sites, n (%)	0.16			
1	Ref	Ref		
2	0.06	2.955 (0.952–9.175)		
≥3	0.13	2.268 (0.784–6.562)		
Site of metastases				
Liver (no/yes)	0.11	1.952 (0.854–4.463)		
Lung (no/yes)	0.09	0.473 (0.201–1.113)		
Lymph node (no/yes)	0.38	1.404 (0.658–2.998)		
Peritoneum (no/yes)	0.48	1.490 (0.499–4.451)		
Other (no/yes)	0.84	0.917 (0.405–2.075)		
Surgery	0.01*		0.057	
No	Ref	Ref	Ref	Ref
Radical resection	0.003*	0.141 (0.038–0.522)	0.02*	0.189 (0.048–0.745)
Palliative surgery	0.27	0.273 (0.028–2.708)	0.23	0.243 (0.024–2.451)
Prior regimens				
Angiogenesis inhibitors (no/yes)	0.90	0.881 (0.117–6.647)		
Anti–PD-1/PD-L1 (no/yes)	0.67	1.379 (0.316–6.017)		
Treatment line of regorafenib	0.15			
Second line	Ref	Ref		
Third line	0.058	0.257 (0.063–1.048)		
Fourth line or later	0.07	0.268 (0.066–1.086)		
Regorafenib regimen				
Regorafenib alone	Ref	Ref		
Regorafenib combination	0.68	0.841 (0.369–1.916)		

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	Univariate Cox		Multivariate Cox	
	P value	HR (95% CI)	P value	HR (95% CI)
TAS-102 regimen				
TAS-102 alone	Ref	Ref		
TAS-102 combination	0.25	1.560 (0.726–3.351)		

*, P<0.05. CI, confidence interval; HR, hazard ratio; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Table 3 Summary of treatment-related adverse events in all treated patients

TRAEs	Regorafenib, n (%)	TAS-102, n (%)	P value
Anemia	0 (0)	1 (3.33)	>0.99
Leukopenia	1 (3.33)	1 (3.33)	0.75
AST increased	0 (0)	1 (3.33)	>0.99
ALT increased	0 (0)	1 (3.33)	>0.99
Bilirubin increased	4 (13.33)	1 (3.33)	0.35
HFSR	0 (0)	1 (3.33)	>0.99
Fatigue	1 (3.33)	6 (20.00)	0.10
Anorexia	0 (0)	5 (16.67)	0.052
Nausea/vomiting	0 (0)	4 (13.33)	0.11
Hypoproteinemia	2 (6.67)	2 (6.67)	>0.99

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HFSR, hand-foot skin reaction; TRAEs, treatment-related adverse events.

agents were manageable, with no statistically significant disparities in TRAEs incidence (all P>0.05), supporting their tolerability in sequential use for advanced CRC.

Discussion

The third-line-and-beyond treatment of mCRC is an urgent clinical issue, and efforts to improve patients' survival are needed. In this cohort study, we applied data collected from two cancer research centers of 30 pathologically diagnosed patients with mCRC treated with a sequential regimen of regorafenib followed by TAS-102.

The REGOMUNE study investigates the combination of the PD-L1 inhibitor avelumab and regorafenib for the treatment of third-line or higher microsatellite stable (MSS) mCRC (20). In our study, the overall population had an mPFS of 3.83 months with the use of regorafenib, which is similar to the mPFS reported in the REGOMUNE study (3.6 months) and a study combining PD-1 inhibitors (113 days to 3.1 months) (20,21). The TERRA study enrolled 406 patients with mCRC who had previously received at least second-line standard chemotherapy regimens. The results demonstrated that TAS-102 significantly prolonged OS and PFS. The mOS was 7.8 *vs.* 7.1 months in the treatment versus placebo groups (HR 0.79, 95% CI: 0.62 to 0.99; P=0.035) (14). In our study the mOS with the use of TAS-102 was 16.1 months, which is significantly higher than the mOS reported in the TERRA study (7.8 months), providing some evidence for the efficacy of TAS-102 following regorafenib in improving patient survival. The prolonged OS observed in our cohort may stem from the sequential application of regorafenib followed by TAS-102, which leverage their distinct mechanisms to delay therapeutic resistance. Furthermore, stringent patient selection (ECOG PS 0–1 and high rates of curative surgery) likely contributed to improved baseline survivorship. Regional clinical practices, such as early regorafenib initiation under insurance coverage, may have optimized disease control prior to TAS-102 administration. While combination regimens showed numerical superiority, their statistical non-significance underscores the need for biomarker-driven trials to identify synergistic subgroups. In clinical practice, combination therapy can be considered for the third-line treatment of mCRC due to the lack of standardized treatment options. For instance, the REGONIVO study (22) demonstrated the potential advantages of combining immune checkpoint inhibitors with small-molecule targeted therapies, of which objective response rate (ORR) was over 30%. The combination of regorafenib with dual immune therapy was found to provide a further survival benefit, with a mOS of 19.6 months and a mPFS of 4 months in the overall population (23).

In the stratified analysis of our study, although there was no statistically significant difference in mPFS or mOS between the regorafenib monotherapy group and the combination therapy group or in mOS between the TAS-102 monotherapy group and the combination therapy group due to the small number of patients analyzed, the numerical values favored both the regorafenib and TAS-102 combination therapy group, and this regimen should be further investigated in future large-sample studies.

Regarding the monotherapy of regorafenib and TAS-102 in the treatment of third-line mCRC, some large-scale studies have shown comparable efficacy between these agents (17). However, the results are inconsistent as it pertains to the sequential treatment of these two agents. A study indicates that beginning with regorafenib may have advantages (16), while others indicate that the sequential order of the two agents does not result in significant differences (17,18). Moreover, a large-sample retrospective study demonstrated that the OS derived from the sequential use of TAS-102 was numerically superior to that of regorafenib followed by TAS-102 (24). These discrepancies in results are likely attributable to the different patient populations examined. For example, subgroup analyses based on age in studies of monotherapy with regorafenib or TAS-102 showed more significant benefits in patients younger than 65 years and older than 65 years, respectively (25,26). In our study, prior resection of the primary tumor was identified as an independent prognostic factor for PFS in patients treated with regorafenib (HR 0.141, 95% CI: 0.038–0.522; P=0.003), indicating that those who have undergone curative surgery and achieved a period of disease-free survival may have greater survival benefit from regorafenib treatment as compared to those who have not undergone curative surgery, which corresponds with previous study that surgical resection of the primary tumor (SRPT) improves survival in patients with stage IV CRC, independent of other prognostic variables including age, performance status, comorbid illness and chemotherapy (27). While, univariable Cox proportional hazards analysis further identified the number of metastatic sites as an independent prognostic factor for OS_1. Specifically, patients with a single metastatic site (n=1) demonstrated significantly prolonged survival compared to those with multiple metastases [2 sites (HR 4.122, 95% CI: 1.075–15.810; P=0.04) or ≥3 sites (HR 3.805, 95% CI: 1.043–13.873; P=0.04)]. This observation aligns with fundamental oncological principles: increased metastatic burden generally reflects greater tumor heterogeneity, more aggressive phenotypes, and widespread dissemination of neoplastic cells, collectively contributing to organ dysfunction and diminished response to systemic therapies. The safety profiles of regorafenib (R) and TAS-102 (T) in sequential therapy were generally comparable, with no statistically significant differences observed in most TRAEs (*Table 3*). Fatigue (20.00% *vs.* 3.33%, P=0.10) and anorexia (16.67% *vs.* 0%, P=0.052) occurred more frequently in the T group compared to the R group, though these differences did not reach statistical significance. Notably, hypoproteinemia exhibited identical incidence rates in both groups (6.67% each), while bilirubin elevation was numerically higher in the R group (13.33% *vs.* 3.33%, P=0.35). The absence of grade ≥3 TRAEs in either cohort suggests acceptable tolerability for sequential R-T therapy. However, the small cohort size may limit statistical power to detect subtle differences in rare TRAEs. Future studies with larger populations are warranted to validate these safety patterns. Furthermore, it would be interesting to study whether dynamic changes in the patient's molecular profile after the first-line treatments could help select the optimal treatment sequence and guide clinical decision-making.

Although we demonstrated the efficacy of the sequential use of regorafenib followed by TAS-102 in our study population, certain limitations should be acknowledged. First, given the retrospective design of the study, the accuracy of data collection needs to be considered, and the sample size in our study is small, as well as that for the subgroups analyzed, which may impact the results of survival analysis. Secondly, due to missing relevant data, side effects were not studied or reported. Thirdly, we did not investigate the quality of life (QoL) of the patients. The inclusion of T-R (TAS-102 followed by regorafenib) versus R-T (regorafenib followed by TAS-102) sequences for comparative analysis was initially considered in this study. However, the T-R cohort exhibited critically limited data availability (n<10), precluding meaningful statistical evaluation. This limitation stemmed from two real-world clinical challenges: (I) Clinical trial prioritization: over 65% of patients who experienced third-line treatment failure opted to enroll in investigational therapeutic trials rather than pursuing sequential regimens. (II) Regional drug accessibility disparities: regorafenib's inclusion in national insurance coverage ensured broad accessibility, whereas TAS-102 faced significant utilization barriers due to out-of-pocket costs and procurement difficulties. These systemic constraints not only reduced the T-R cohort size but also underscored the

inherent complexities of conducting retrospective sequence comparisons in real-world oncology practice. Therefore, further experiments, including studies with larger sample sizes and prospective, randomized controlled trials, are warranted to truly identify the optimal sequence including assessing the optimal combination and where regorafenib and TAS-102 fit in future sequence options.

Conclusions

Our study demonstrated that the availability of sequential treatment options including regorafenib followed by TAS-102 prolongs the OS of patients compared to conventional monotherapy approaches. During the sequential treatment, regorafenib or TAS-102 combined with other therapeutic agents did not significantly differ from monotherapy, and the impact of toxicity on QoL needs to be considered. Further investigation is required through large-scale trials.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-47/rc
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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. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was reviewed and approved by the Ethics Committee of Harbin Medical University Cancer Hospital (Ethics No. KY2022-63) and the Cancer Hospital Affiliated to Shanxi Medical University was informed and agreed with this study. Individual consent for this retrospective analysis was waived.

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